NDA 20665

Food and Drug Administration
Rockville MD 20857

NDA 20-665

DEC 23 1996

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
Attention: Mr. Adrian L. Birch
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Birch:

Please refer to your December 28, 1995 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) 80 and 160 mg Capsules.

We acknowledge receipt of your amendments and correspondence dated December 28, 1995, March 7, 8, 21, 22 and 27, April 3, 9, 22 and 25, May 7, 13, 29, 30 and 31, June 24, July 3, 5, 9, 10 and 31, August 13 and 19, September 5, 6, 9, 23 and 24, October 3, 18, 22, 29 and 30, and November 5, 13 and 14, and December 11 and 19, 1996.

This new drug application provides for the use of Diovan (valsartan) Capsules for the treatment of hypertension.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling included in the December 19, 1996 submission. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling included in the December 19, 1996 submission. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-665. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We note that in a telephone conversation on December 10, 1996, with Ms. Kathleen Bongiovanni of the Division of Cardio-Renal Drug Products, Ms. Nancy Price of your firm confirmed that you have agreed to an interim dissolution specification of Q not less than at 30 minutes. A final dissolution specification will be determined after review of the 3-year stability data on the first three production batches.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

RHPM NDA Overview
December 20, 1996

1S NDA 20-665 Diovan (valsartan) 80 and 160 mg Tablets

Sponsor: Ciba Pharmaceuticals Division, Ciba-Geigy Corporation

Date of Application: December 28, 1995
Date of Receipt: December 28, 1995
Date of Receipt of User Fee: December 15, 1995
User Fee Goal Date: December 28, 1996

Meetings:
January 13, 1994 End-of-Phase II Meeting (IND)
September 20, 1995 Meeting to discuss comparative efficacy trials (IND
February 7, 1996 Filing Meeting (internal)

STATUS:

Medical Review
Medical Reviewer: Charles Ganley, M.D.
Labeling: Revisions made to draft.
Conclusion (from review #1, page 1): Single daily oral doses of 80-160 mg were effective in decreasing diastolic blood pressure. Comparably effective in subgroups based on age and sex. The data are unclear whether this is an effective monotherapy for black patients. One safety issue regarding decreases in absolute neutrophil counts was resolved to Dr. Ganley's satisfaction (see MOR 11-5-96).

Biopharmaceutics Review:
Reviewer: Pamian Zia-amirhosseini, Ph.D. and Ameeta Parekh, Ph.D.
Dissolution specifications: Acceptable, except that the dissolution specification should be set at Q= instead of the proposed Q= I relayed this in a telecon on October 16, 1996. Firm to respond in writing to suggestion with counterproposal for Q= in 30 min. We are asking for an interim spec of Q= at 30 min, with a final spec set after we see 3-year stability data from the first three production batches (see AParekh 11-13-96 review and RWolters 11-8-96 review). This recommendation is included in the letter.

Dr. Collins completed his review of in vitro metabolism question. See Dr. Parekh's October 22, 1996 review.

Labeling: see pg. 22 of July 3, 1996 review. (Revisions made to draft.)
Conclusion: Approvable.

Statistics (clinical)
Reviewer: Walid Nuri, Ph.D.
Labeling: None
Conclusion: approvable

Chemistry- Christopher Coughlin, Ph.D.:
Carton & container labeling: acceptable.
Labeling: acceptable.
cGMP Inspections: EER Acceptable 10/9/96

Methods validation: not completed. Noted in approval letter.
Conclusion: approvable

Environmental Assessment: Completed December 3, 1996.

Pharmacology-
Anthony Proakis, Ph.D.: Rodent Carcinogenicity Studies: were presented to the CAC September 17, 1996; additional questions were posed to firm in telecon on September 19, 1996. Firm responded with amendment dated October 3, 1996. CAC agreed in meeting on October 22, 1996 that the studies were adequate.
Labeling: see page 28 of August 28, 1996 review for recommended changes. (Revisions made to draft.)
Conclusion: approvable.

G. Jagadeesh, Ph.D.: Pharmacology and Toxicology Data
Labeling: see pages 131-132 of review for recommended changes (Revisions made to draft.)
Conclusion: approvable

Statistics (preclin):
Reviewer: Walid Nuri, Ph.D.: Review completed.

Safety Update: Requested October 7, 1996; in November 13, 1996 submission.

Patent info: included in package

Debarment Certification: included in package

DSI Inspections- Antoine El Hage, Ph.D. : Six of six inspections complete (according to COMIS, 10/30/96); 4-VAI; 2-NAI.

CDER Labeling & Nomemclature Committee: May 23, 1996: conclusion: no reason to find Diovan unacceptable.

Kathleen F. Bongiovanni
12·20·96

cc:
NDA 20-665
HFD-110
HFD-111/SBenton
HFD-111/KBongiovanni
kb/10/9/96; 10/30/96; 11/6/96; 11/20/96; 12/20/96.

DEPARTMENT OF H.. .LTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-665

JAN 14 1997

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
Attention: Mr. Adrian L. Birch
556 Morris Avenue
Summit, NJ 07901

Dear Mr. Birch:

We acknowledge the receipt of your January 2, 1997 submission containing final printed labeling in response to our December 23, 1996 letter approving your new drug application (NDA) for Diovan (valsartan) 80 and 160 mg Capsules.

We have reviewed the labeiing that you have submitted in accordance with our December 23, 1996 letter, and we find it acceptable.

At the time of your next printing, please replace the word "have" in the second sentence of the **PRECAUTIONS, Impaired Renal Function** subsection with the word "has."

If you have any questions, please contact:

Ms. Kathleen Bongiovanni
Regulatory Health Project Manager
Telephone: (301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA No: [illegible] Rec'd. [illegible]

Reviewed by: Kingan

Diovan™

valsartan

C96-70 (Rev. 12/96)
666750

Capsules

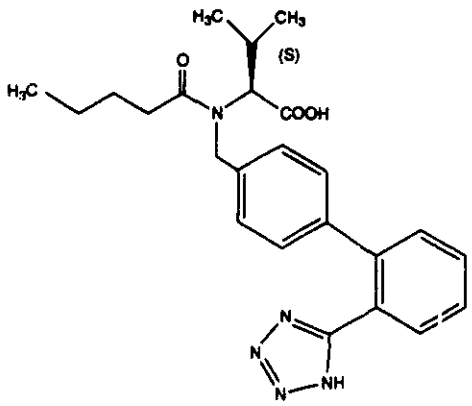
Prescribing Information

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Diovan (valsartan) is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT_1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2'-(1*H*-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as capsules for oral administration, containing either 80 mg or 160 mg of valsartan. The inactive ingredients of the capsules are cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one 200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for the capsule formulation is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination

Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations

Pediatric: The pharmacokinetics of valsartan have not been investigated in patients <18 years of age.

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min) or patients undergoing dialysis, and it is not known whether valsartan is removed by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease (see DOSAGE AND ADMINISTRATION).

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Pharmacodynamics and Clinical Effects

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

The antihypertensive effects of Diovan were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

INDICATIONS AND USAGE

Diovan is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

Diovan is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, valsartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation

and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hypotension in Volume- and/or Salt-Depleted Patients
Excessive reduction of blood pressure was rarely seen (0.1%) in patients with uncomplicated hypertension. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

PRECAUTIONS

General

Impaired Hepatic Function: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan to these patients.

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists have been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Diovan would be expected to behave similarly.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions
No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glibenclamide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility
There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers
It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
In the controlled clinical trials of valsartan, 1214 (36.2%) of patients treated with valsartan were ≥ 65 years and 265 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS
Diovan has been evaluated for safety in more than 4000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

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increase in the incid
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Diovan has been
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Other adverse ex
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cannot be determine
Body as a Whole: Al
Cardiovascular: Palp
Dermatologic: Pruriti
Digestive: Constipat
Musculoskeletal: Ba
Neurologic and Psyc
Respiratory: Dyspne
Special Senses: Ver
Urogenital: Impotenc

Other reported event
syncope, anorexia, v

Clinical Laboratory
In controlled clinical t
parameters were rare
Creatinine: Minor ele
Diovan and 0.6% give
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OVERDOSAGE
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It is not known whe
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mg/m^2 basis). (Calcul
patient.)

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p<0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

Body as a Whole: Allergic reaction and asthenia
Cardiovascular: Palpitations
Dermatologic: Pruritus and rash
Digestive: Constipation, dry mouth, dyspepsia, and flatulence
Musculoskeletal: Back pain, muscle cramps, and myalgia
Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence
Respiratory: Dyspnea
Special Senses: Vertigo
Urogenital: Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver function tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

Serum Potassium: Greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. No patient treated with valsartan discontinued therapy for hyperkalemia.

OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

It is not known whether valsartan or its active metabolite can be removed by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 37 times, respectively, the maximum recommended human dose on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

DOSAGE AND ADMINISTRATION

The recommended starting dose of Diovan is 80 mg once daily when used as monotherapy in patients who are not volume-depleted. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once-a-day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required, the dosage may be increased to 160 mg or 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

HOW SUPPLIED

Diovan is available as capsules containing valsartan 80 mg or 160 mg. Both strengths are packaged in bottles of 100 capsules and 4000 capsules and unit dose blister packages. Capsules are imprinted as follows:

80 mg Capsule - Light grey/light pink opaque, imprinted CG FZF
- Bottles of 100 ..... NDC 0083-4000-01
- Bottles of 4000 ..... NDC 0083-4000-41
- Unit Dose (blister pack) ..... NDC 0083-4000-61
  - Box of 100 (strips of 10)

160 mg Capsule - Dark grey/light pink opaque, imprinted CG GOG
- Bottles of 100 ..... NDC 0083-4001-01
- Bottles of 4000 ..... NDC 0083-4001-41
- Unit Dose (blister pack) ..... NDC 0083-4001-61
  - Box of 100 (strips of 10)

Store below 30°C (86°F). Protect from moisture. Dispense in tight container (USP).

/50 C96-70 (Rev. 12/96)

ciba

Dist. by:
Ciba-Geigy Corporation
Pharmaceuticals Division
Summit, NJ 07901

EXCLUSIVITY SUMMARY for NDA # 20-665 SUPPL # _____

Trade Name Diovan **Generic Name** valsartan
Applicant Name Ciba-Geigy **HFD-** 110

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Catherine J. Gorman 10-14-96
Signature Date
Title: Regulatory Health Project Manager

Ray Lipicky 11/18/96
Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

8/8/95

PATENT INFORMATION
VALSARTAN (CGP 48933) CAPSULES
21 CFR 314.50 (h)

Patent Number:	U.S. 5,399,578
Patent Expiration Date:	March 21, 2012
Type of Patent:	Drug
Name of Patent Owner:	CIBA-GEIGY Corporation

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-665 Trade (generic) names Diovan (valsartan) Capsules

Check any of the following that apply and explain, as necessary, on the next page:

#1 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

10/30/96
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

Ciba Pharmaceuticals Division

Ciba-Geigy Corporation

New Drug Application for

Tradename

(valsartan / CGP 48933)

CERTIFICATION STATEMENT (21 U.S.C. 335a)

Ciba-Geigy Corporation hereby certifies that, to the best of its knowledge, it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act, in connection with this application.

Signed Nancy A. Price for Adrian Birch Date 12/15/95

Executive Director

Drug Regulatory Affairs

NDA #: 20-665/BM
NDA Volume:
Drug Name: valsartan
Sponsor: Ciba Geigy
Type of Document: Response to request for information
Correspondence Date: 10/18/96
Date Received: 10/23/96

In a previous submission, the sponsor provided a listing of all patients who had an absolute neutrophil count (ANC) < 1000 x 10^6/L. The event rate for valsartan patients was similar to that of ACEI treated patients. The placebo incidence rate was zero. The sponsor was asked to provide the incidence rate for the valsartan and ACEI treated patients as a function of exposure. In this submission, the sponsor does not provide an incidence rate as a function of exposure because "the summary would have reflected the spacing of the lab tests, rather than the actual time to onset of the abnormality". Instead, they have provided a summary for each patient identified with post-randomization neutrophil counts less than 1000 x 10^6/L.

Table 1 list the patients treated with valsartan with low ANCs.

Table 1. Valsartan Patients with ANC < 1000 x 10^6/L

Protocol	Patient #	ANC Outcome	Comment
27	1049	ANC low @ 2 visits, last visit	
27	1051	ANC low @ 2 visits, last visit	
10	18	Last Visit	
19	882	Last Visit	
19	975	Last Visit	
21	1227	Last Visit	? due to incorrect storage & shipment
21	1230	Last Visit	? due to incorrect storage & shipment
21	1233	Last Visit	? due to incorrect storage & shipment
51	1048	Last Visit	Bronchitis at time of low ANC
23	5164	low baseline	
21	1016	low baseline, RTN	
5	1018	RTN	Flu symptoms prior to visit
9	18	RTN	
11	16	RTN	
11	10	RTN	Pharyngitis 2 weeks prior and 2 months after low ANC
27	1062	RTN	
31	668	RTN	normal 2 days later

RTN = return to normal despite continued therapy with valsartan
Last Visit = low ANC observed on last visit, no repeat

Only one patient had evidence of an infection at the time of the low ANC. Two were low at baseline. Six patient's ANC returned to normal despite continued valsartan therapy. Seven patients had the low ANC at their last visit with no repeat measurement.

Impression

It appears unlikely that the low ANC counts observed during treatment with valsartan are attributable to valsartan. Counts returned it normal in six patients despite continued therapy with valsartan. Other low ANC counts on the last visit appear to be confined to certain centers or protocols.

Action

No labeling regarding low ANCs is warranted at this time.

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY/R..Fenichel

DONGLOUANNE

MEDICAL OFFICER REVIEW

NDA #: 20-665
DRUG NAME: Valsartan
SPONSOR: Ciba-Geigy
TYPE OF DOCUMENT: New NDA
DATE RECEIVED: 3/21/96
DATE REVIEW COMPLETED: 10/4/96
MEDICAL OFFICER: Charles J. Ganley, M.D.

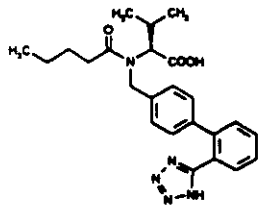
Submissions

Date Received	File # (volume)	Information
12/28/95	20-665	NDA
5/8/96	20-665	report on protocol 46
5/13/96	20-665 (4.1)	urinalysis data on disk
5/17/96	40,704 (40.1)	additional information on death in protocol 20
7/8/96	20-665 (4.1)	Revised CANDA submitted
9/25/96	20-665	Subjects with absolute neutrophil counts lass than 1.0 x 10 ^{9}/L

In addition to the archival copies of the NDA, the clinical trial reports and data (SAS data files) for the placebo controlled trials were provided on CD-ROM.

General Information

Name of Drug
Generic: valsartan
Trade: DIOVAN®
Chemical: (S)-N-Valeryl-N-([1H-tetrazol-5-yl) biphenyl-4-yl] methyl)- valine



M.W. = 435.5

Pharmacologic Category: Angiotensin II Receptor Antagonist (AT_1 subtype)
Proposed Indication: Hypertension
Dosage Form: 80 mg and 160 mg capsule
Route of Administration: oral
Related Drugs: losartan

Resume

Valsartan is an angiotensin II receptor antagonist. It has a chiral center and will be marketed as only the S-enantiomer. It has good solubility at neutral and alkaline pH but is poorly soluble at acid pH which may contribute to the absolute bioavailability of approximately 23%. Approximately two-thirds of the bioavailable dose is excreted by the biliary tract with the remainder excreted in the urine as metabolites or valsartan. Approximately 40% of the bioavailable dose is metabolized. An inactive hydroxylated metabolite is the major metabolite. Unidentified metabolites account for approximately 15% of the bioavailable dose. The pathways responsible for metabolism have not been identified.

Single daily oral doses of valsartan 80 - 160 mg were effective in decreasing diastolic blood pressure. Valsartan appeared to comparably effective in subgroups based on age and sex. The data is unclear whether this is an effective monotherapy for Black patients. There is one safety issue regarding decreases in absolute neutrophil counts that needs to be resolved before a final decision regarding approval is made.

Table of Contents

Study Location.

SUMMARY

Patient Exposure

A total of 67 clinical trials evaluating valsartan have been initiated in different patient populations. Open label extensions of controlled trials are counted as separate trials. The NDA contains information on 53 trials: 51 completed and 2 ongoing trials with interim reports. Fourteen trials are ongoing and limited information from these trials are not included. The trials have been sponsored and monitored by Ciba Geigy. The 53 trials reported in the NDA include the following:

- 27 biopharmaceutical trials (01, 02, 03, 04, 06, 07, 12, 13 ,14, 15, 16, 30, 36, 37, 38, 39, 40, 42, 43, 47,48, 52, 53, ANG-001, ANG-002, ANG-003, ANG-007) ;
- 18 controlled trials in hypertensive patients (Protocols 05, 08, 09, 10, 11, 17, 23, 31, 50, 51, 19, 20, 21, 22, 27, 28, 33, 25) ;
- 3 controlled trials evaluating valsartan in glaucoma (CH-91-07, CH-92-01, CH-92-07) ;
- 1 controlled trial in patients with congestive heart failure (102) ;
- 4 uncontrolled trials in hypertensive patients (11 1st year Extension, ANG-004, ANG-006, ANG-006).

The total number of patients with essential hypertension randomized to valsartan in the ten double-blind, placebo-controlled trials was 2330. The dose of valsartan in these studies ranged from 10 mg to 320 mg. The duration of double-blind therapy ranged from 4 days to 12 weeks. An additional 1380 patients with essential hypertension were randomized to valsartan or valsartan/HCTZ in positive controlled trials. The open label extension of study 11 and the double-blind portion of study 28 provide safety information for patients with greater than 12 weeks of valsartan exposure. Table S.1 lists the number of patients exposed to valsartan in each type of trial.

Table S.1. Listing of Studies and the Number of Patients Randomized in Each Study.

Category	Protocol Numbers	No. of Trials	Valsartan	All Treatments
Placebo Controlled *, Multi-Dose	05, 08, 09, 10, 11, 17, 23, 31, 50, 51	10	2330	3517
Positive Controlled *, Multi-Dose	19, 20, 21, 22, 27, 28, 33	7	1380***	1936 [a]
Placebo Controlled**, Multi-Dose	25	1	9	11
Controlled Trials Total		**18**	**3719 [f] 3366 [g]**	**5464**
Biopharmaceutic Trials	01, 02, 03, 04, 06, 07, 12, 13 ,14, 15, 16, 30, 36, 37, 38, 39, 40, 42, 43, 47, 48, 52, 53, ANG-001, ANG-002, ANG-003, ANG-007	27	385	398
CHF Placebo Controlled	102	1	21	25
Glaucoma Controlled	CH-91-07, CH-92-01, CH-92-07	3	20	20
Long Term Open Label (Uncontrolled) Valsartan	11 1st year extension [c]	1	399 [e]	399 [e]
Short Term Open Label	19 run-in, ANG-004, ANG-005, ANG-006	4 [b]	1008 [d]	1008 [d]
Total Exposed to Valsartan in NDA		**53**	**4543 [f] 4190 [g]**	**6208**

* Essential Hypertension Patients; ** Renovascular Hypertension Patients; *** includes 353 patients randomized to valsartan/HCTZ in protocol 19 (1027 randomized to valsartan monotherapy); a = does not include patients exposed to lisinopril during the lisinopril run-in and not randomized in study 33. ; b = 19 run-in counted in positive controlled trials also; c = extension counted as separate trial ; d = includes 708 patients counted previously; e = 301 patients were previously exposed to valsartan in the double-blind portion of the study (98 newly exposed).; f = randomized to monotherapy or combination therapy; g = randomized to monotherapy

Note: Trials starting with ANG are Japanese trials. Trials starting with CH are performed in patients with glaucoma with valsartan solution. Trial reports for study 27 and 28 includes only interim data.

Table S.2 outlines the number of patients exposed to valsartan and other therapies in all controlled and uncontrolled trials as a function of duration of exposure. The treatment groupings are not mutually exclusive. Thus, if a patient started valsartan monotherapy and eventually was titrated to valsartan/HCTZ

combination therapy, the patient would be counted in both the monotherapy and combination therapy group. A majority of patients had exposure for less than 60 days. Four hundred and twenty-three patients had at least 6 months of valsartan monotherapy.

Table S.2. Duration of Exposure

	Treatment					
Duration of Exposure	Valsartan N (%)	Valsartan/ Diuretics N (%)	Valsartan/ Other N (%)	HCTZ N (%)	ACEI N (%)	Placebo N (%)
≥ 1 day	4004 (100)	693 (100)	40 (100)	131 (100)	793 (100)	900 (100)
≥ 2 days	3987 (99.6)	683 (98.6)	40 (100)	131 (100)	793 (100)	899 (99.9)
≥ 8 days	3931 (98.2)	679 (98.0)	40 (100)	131(100)	783 (98.7)	875 (97.2)
≥ 30 days	3261 (81.4)	618 (89.2)	4 (10.0)	121 (92.4)	654 (82.5)	801 (89.0)
≥ 60 days	1825 (45.6)	318 (45.9)		68 (51.9)	439 (55.4)	289 (32.1)
≥180 days	423 (10.6)	203 (29.3)			97 (12.2)	
≥365 days	166 (4.1)	58 (8.4)			9 (1.1)	

Protocols included: 05, 08,09,10,11, 11 Ext. 1, 17, 19-23, 25, 27, 28, 31, 33, 50 and 51.

In the sponsor's safety database for the placebo controlled trials, safety data was available on 2316 patients. The demographics of the patients randomized in these trials is listed in Table S.3. The demographics of the treatment groups is similar. Approximately 87% of the patients were Caucasian and 8% black. Fifty-seven percent of the patients were male.

Table S.3. Demographics of Patients Randomized to Placebo Controlled Trials.

	Treatment		
Patient Data	Valsartan N (%)	ACEI N (%)	Placebo N (%)
Total patients	2316 (100)	330 (100)	888 (100)
Sex			
Male	1341 (57.9)	176 (53.3)	502 (56.5)
Female	975 (42.1)	154 (46.7)	386 (43.5)
Race			
White	2005 (86.6)	288 (87.3)	771 (86.8)
Black	183 (7.9)	30 (9.1)	65 (7.3)
Other	128 (5.5)	12 (3.6)	52 (5.9)
Age (years)			
Mean	57.3	57.7	56.8
STD	12.3	12.5	12.5
Range	20-92	28-92	22-89
Duration of Htn. (yr.)			
Mean	8.8[1]	8.1	8.7[1]
STD	8.4[1]	8.0	7.9[1]
Range	0-55[1]	0-44	0-52[1]

Protocols included : 05, 08, 09, 10, 11, 17, 23, 31, 50, 51.

[1] Duration of hypertension not available for 13 patients and 2 patients in the valsartan and placebo treatment groups respectively.

Table S.4 lists the reasons patients discontinued prematurely from controlled clinical trials. Approximately 8% of valsartan patients discontinued from controlled trails. Adverse events accounted for the primary reason patients were discontinued. A listing of all patients discontinued from the placebo controlled trails for reasons other than adverse events are listed in the appendix (pages xxxii - xxxv).

Table S.4 . Summary of Reasons for Premature Discontinuation from All Controlled Trials.

	Treatment					
	Valsartan N (%)	Valsartan/ Diuretic N (%)	Valsartan/ Other N (%)	HCTZ N (%)	ACEI N (%)	Placebo N (%)
Principal reason						
- Total Patients -	3350 (100)	508 (100)	40 (100)	131 (100)	675 (100)	900 (100)
Adverse Experience	103 (3.1)	17 (3.3)	0 (0.0)	4 (3.1)	49 (7.3)	36 (4.0)
Abnormal Laboratory Value	9 (0.3)	1 (0.2)	0 (0.0)	1 (0.8)	2 (0.3)	5 (0.6)
Unsatisfactory Therapeutic Effect	54 (1.6)	26 (5.1)	0 (0.0)	4 (3.1)	4 (0.6)	21 (2.3)
Death	4 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Other	95 (2.8)	18 (3.5)	1 (2.1)	7 (5.3)	27 (4.0)	31 (3.4)
Total	265 (7.9)	62(12.2)	1 (2.1)	16 (12.2)	84 (12.4)	93 (10.3)

The term "other" includes the following reasons for termination: administrative problems, lost to follow-up, patient withdrew consent, patient non-compliance, patient does not meet protocol criteria, patient's condition longer requires trial treatment and abnormal test procedure results.

Safety

Deaths

Twelve patients died in all clinical trials as of March 31, 1995. Eight patients received valsartan and one received valsartan/HCTZ. Table SS. 1 lists the patients who died and the cause of death. A narrative summary for each death is provided in the appendix (pages viii - x) . Valsartan does not appear to be directly responsible for the demise of any of the patients.

Table SS. 1. Deaths in Clinical Trials

Protocol	Center/Patient	Treatment	Age/Sex	Cause of Death
11E2	010/510/Ellison	Valsartan 40 mg	50/M	Accidental Drowning
28	1282/Gallage	Valsartan 80 mg	88/M	Bronchopneumonia
28	1214/Deering	Valsartan 80 mg	70/M	Carcinoma of kidney
11E2	011/5[illegible]	Valsartan 20 mg	49/M	Cardiac arrest
31	Serfer/0489/5506	Valsartan 20 mg	46/M	Cardiac arrest
20	1189/Halmenschlager	Valsartan 80 mg	71/F	Cardiac arrest
11E1	016/515/Garrett	Valsartan 20 mg	74/F	Cardiovascular collapse
28	1184/Collins	Valsartan 80 mg	82/F	Myocardial infarction
11E1	012/509/Grimm	Valsartan 80 mg/HCTZ 12.5 mg	62/M	Arteriosclerotic heart disease
28	1338/Jaiswal	Lisinopril 2.5 mg	66/M	Bronchopneumonia
28	1889/Blagden	Lisinopril 20 mg	75/F	Cerebrovascular accident
50	274/5197/Ginsberg	Placebo	77/M	Cerebrovascular accident

11E1 = 1st year extension of protocol 11; 11E2 = 2nd year extension of protocol 11

Adverse Events

The incidence of the commonly (> 1%) reported adverse events in the placebo controlled trials are listed in table SS.2. The percentage of patients complaining of at least one adverse event was about 42% in all of the treatment groups. The most common adverse event was headache and dizziness. Cough occurred in 7.9% of ACEI treated patients and in 2.3% of valsartan treated patients. A complete listing of adverse events incidence rates in the placebo controlled trials is provided in the appendix (pages ii - vii). The incidence rates for patients in all controlled (placebo and active) trials is similar to the placebo controlled trial data. Approximately 2% of valsartan patients had adverse events that were categorized as serious.

Table SS.2. Adverse Events Occurring In >1% Of The Patients In Placebo Controlled Trials.

	Valsartan n (%)	ACEI n (%)	Placebo n (%)
Total Patients	2316 (100)	330 (100)	888 (100)
Total Patients with AE's	977 (42.2)	143 (43.3)	378 (42.6)
Adverse Experience			
Headache	226 (9.8)	26 (7.9)	120 (13.5)
Dizziness	83 (3.6)	11 (3.3)	31 (3.5)
Infection Viral	72 (3.1)	6 (1.8)	17 (1.9)
Upper Respiratory Tract Infection	58 (2.5)	12 (3.6)	21 (2.4)
Coughing	54 (2.3)	26 (7.9)	13 (1.5)
Diarrhea	48 (2.1)	7 (2.1)	16 (1.8)
Fatigue	48 (2.1)	7 (2.1)	11 (1.2)
Rhinitis	47 (2.0)	7 (2.1)	20 (2.3)
Sinusitis	44 (1.9)	10 (3.0)	14 (1.6)
Pain Back	37 (1.6)	9 (2.7)	12 (1.4)
Pain Abdominal	36 (1.6)	4 (1.2)	9 (1.0)
Nausea	35 (1.5)	7 (2.1)	18 (2.0)
Pharyngitis	27 (1.2)	6 (1.8)	6 (0.7)
Arthralgia	24 (1.0)	7 (2.1)	9 (1.0)

Protocols included: 05, 08, 09, 10, 11 Core, 17, 23, 31 Core, 50, and 51.

Table SS.3 lists the incidence of adverse events by body system for each treatment group in the placebo controlled trials. There is no relevant differences between the treatments. For most body systems the incidence rates are similar between treatment groups. The notable exception is the incidence rates for respiratory symptoms in ACEI treated patients (17.3%) compared to both valsartan (10.3%) and placebo (9.8%) patients.

Table SS.3. Incidence Of Adverse Experiences By Body System (> 1% In The Valsartan Group) All Adverse Experiences (Placebo Controlled Trials)

	Valsartan n (%)	ACEI n (%)	Placebo n (%)
Total Patients	2316 (100)	330 (100)	2316 (100)
Total Patients with AE's	977 (42.2)	143 (43.3)	378 (42.6)
Body System			
Nervous System	363 (15.7)	42 (12.7)	170 (19.1)
Respiratory System	238 (10.3)	57 (17.3)	87 (9.8)
Digestive System	191 (8.2)	33 (10.0)	76 (8.6)
Body As A Whole	179 (7.7)	23 (7.0)	57 (6.4)
Musculoskeletal System	159 (6.9)	30 (9.1)	54 (6.1)
Infections And Infestations	87 (3.8)	8 (2.4)	22 (2.5)
Endocrine System	2 (.1)	0	0
Hematopoetic System	4 (.2%)	0	5 (.6%)
Metabolic	13 (.6)	0	6 (.7)
Special Senses	81 (3.5)	8 (2.4)	18 (2.0)
Skin And Appendages	68 (2.9)	12 (3.6)	21 (2.4)
Urogenital System	57 (2.5)	15 (4.5)	31 (3.5)
Cardiovascular System	51 (2.2)	5 (1.5)	23 (2.6)

Protocols included: 05, 08, 09, 10, 11 Core, 17, 23, 31 Core, 50, and 51.

Two patients developed hypothyroidism on valsartan therapy (patient # 186/5135 in protocol 50; Patient # 384/5276 in protocol 50). It is unlikely that these events can be attributed to valsartan.

Table SS.4 - SS.7 lists the most commonly reported adverse events (> 1%) based on sex, age, race and valsartan dose in placebo controlled trials. There do not appear to be relevant differences in the

incidence of adverse events based on sex and age. Cough occurred in 2.6% of white patients and in .5% of black patients. Both dizziness and cough appear to increase with increasing dose.

Table SS.4. Most Commonly Reported Adverse Events (> 1%) Based On Sex In Placebo Controlled Trials

	Valsartan		ACEI		Placebo	
	Male n (%)	Female n (%)	Male n (%)	Female n (%)	Male n (%)	Female n (%)
Total Patients	1341 (100)	975 (100)	176 (100)	154 (100)	502 (100)	386 (100)
Total Patients with AE's	559 (41.7)	418 (42.9)	72 (40.9)	71 (46.1)	211 (42.0)	167 (43.3)
Adverse Experience						
Headache	125 (9.3)	101 (10.4)	13 (7.4)	13 (8.4)	68 (13.5)	52 (13.5)
Dizziness	49 (3.7)	34 (3.5)	8 (4.5)	3 (1.9)	11 (2.2)	20 (5.2)
Infection Viral	46 (3.4)	26 (2.7)	5 (2.8)	1 (0.6)	12 (2.4)	5 (1.3)
Upper Respiratory Tract Infection	37 (2.8)	21 (2.2)	7 (4.0)	5 (3.2)	10 (2.0)	11 (2.8)
Coughing	26 (1.9)	28 (2.9)	16 (9.1)	10 (6.5)	8 (1.6)	5 (1.3)
Diarrhea	23 (1.7)	25 (2.6)	3 (1.7)	4 (2.6)	12 (2.4)	4 (1.0)
Fatigue	31 (2.3)	17 (1.7)	3 (1.7)	4 (2.6)	5 (1.0)	6 (1.6)
Rhinitis	34 (2.5)	13 (1.3)	4 (2.3)	3 (.9)	9 (1.8)	11 (2.8)
Sinusitis	23 (1.7)	21 (2.2)	5 (2.8)	5 (3.2)	8 (1.6)	6 (1.6)
Pain Back	21 (1.6)	16 (1.6)	4 (2.3)	5 (3.2)	6 (1.2)	6 (1.6)
Pain Abdominal	22 (1.6)	14 (1.4)	1 (0.6)	3 (1.9)	7 (1.4)	2 (0.5)
Nausea	13 (1.0)	22 (2.3)	3 (1.7)	4 (2.6)	11 (2.2)	7 (1.8)
Pharyngitis	16 (1.2)	11 (1.1)	3 (1.7)	3 (1.9)	2 (0.4)	4 (1.0)
Arthralgia	14 (1.0)	10 (1.0)	2 (1.1)	5 (3.2)	6 (1.2)	3 (0.8)

Protocols included: 05, 08, 09, 10, 11 Core, 17, 23, 31 Core, 50 and 51.

Table SS.5. Most Commonly Reported Adverse Events (> 1%) Based On Age In Placebo Controlled Trials

	Valsartan		ACEI		Placebo	
	< 65 n (%)	≥ 65 n (%)	< 65 n (%)	≥ 65 n (%)	< 65 n (%)	≥ 65 n (%)
Total Patients	1571 (100)	745 (100)	213 (100)	117 (100)	596 (100)	292 (100)
Total Patients with AE's	711 (45.3)	266 (35.7)	104 (48.8)	39 (33.3)	268 (45.0)	110 (37.7)
Adverse Experience						
Headache	181 (11.5)	45 (6.0)	23 (10.8)	3 (2.6)	95 (15.9)	25 (8.6)
Dizziness	59 (3.8)	24 (3.2)	9 (4.2)	2 (1.7)	21 (3.5)	10 (3.4)
Infection Viral	61 (3.9)	11 (1.5)	5 (2.3)	1 (0.9)	16 (2.7)	1 (0.3)
Upper Respiratory Tract Infection	48 (3.1)	10 (1.3)	11 (5.2)	1 (0.9)	19 (3.2)	2 (0.7)
Coughing	37 (2.4)	17 (2.3)	19 (8.9)	7 (6.0)	5 (0.8)	8 (2.7)
Diarrhea	38 (2.4)	10 (1.3)	5 (2.3)	2 (1.7)	10 (1.7)	6 (2.1)
Fatigue	41 (2.6)	7 (0.9)	7 (3.3)	0 (0.0)	6 (1.0)	5 (1.7)
Rhinitis	36 (2.3)	11 (1.5)	6 (2.8)	1 (0.9)	16 (2.7)	4 (1.4)
Sinusitis	37 (2.4)	7 (0.9)	10 (4.7)	0 (0.0)	11 (1.8)	3 (1.0)
Pain Back	28 (1.8)	9 (1.2)	8 (3.8)	1 (0.9)	10 (1.7)	2 (0.7)
Pain Abdominal	27 (1.7)	9 (1.2)	3 (1.4)	1 (0.9)	6 (1.0)	3 (1.0)
Nausea	29 (1.8)	6 (0.8)	5 (2.3)	2 (1.7)	12 (2.0)	6 (2.1)
Pharyngitis	19 (1.2)	8 (1.1)	6 (2.8)	0 (0.0)	4 (0.7)	2 (0.7)
Arthralgia	16 (1.0)	8 (1.1)	4 (1.9)	3 (2.6)	8 (1.3)	1 (0.3)

Protocols included: 05, 08, 09, 10, 11 Core, 17, 23, 31 Core, 50 and 51.

Table SS.6. Most Commonly Reported Adverse Events (> 1%) Based On Race In Placebo Controlled Trials

	Valsartan			Placebo		
	White n (%)	Black n (%)	Other n (%)	White n (%)	Black n (%)	Other n (%)
Total Patients	2005 (100)	183 (100)	128 (100)	771 (100)	65 (100)	52 (100)
Total Patients with AE's	846 (42.2)	82 (44.8)	49 (38.3)	327 (42.4)	29 (44.6)	22 (42.3)
Adverse Experiences						
Headache	187 (9.3)	28 (15.3)	11 (8.6)	102 (13.2)	11 (16.9)	7 (13.5)
Dizziness	69 (3.4)	8 (4.4)	6 (4.7)	25 (3.2)	2 (3.1)	9 (7.7)
Infection Viral	65 (3.2)	5 (2.7)	2 (1.6)	13 (1.7)	2 (3.1)	2 (3.8)
URI	51 (2.5)	5 (2.7)	2 (1.6)	16 (2.1)	3 (4.6)	2 (3.8)
Coughing	52 (2.6)	1 (0.5)	1 (0.8)	12 (1.6)	1 (1.5)	0 (0.0)
Diarrhea	38 (1.9)	4 (2.2)	6 (4.7)	16 (2.1)	0 (0.0)	0 (0.0)
Fatigue	42 (2.1)	3 (1.6)	3 (2.3)	9 (1.2)	2 (3.1)	0 (0.0)
Rhinitis	42 (2.1)	5 (2.7)	0 (0.0)	18 (2.3)	2 (3.1)	0 (0.0)
Sinusitis	38 (1.9)	2 (1.1)	4 (3.1)	13 (1.7)	1 (1.5)	0 (0.0)
Pain Back	34 (1.7)	3 (1.6)	0 (0.0)	10 (1.3)	1 (1.5)	1 (1.9)
Pain Abdominal	33 (1.6)	1 (0.5)	2 (1.6)	9 (1.2)	0 (0.0)	0 (0.0)
Nausea	29 (1.4)	4 (2.2)	2 (1.6)	17 (2.2)	1 (1.5)	0 (0.0)
Pharyngitis	25 (1.2)	1 (0.5)	1 (0.8)	6 (0.8)	0 (0.0)	0 (0.0)
Arthralgia	18 (0.9)	5 (2.7)	1 (0.8)	9 (1.2)	0 (0.0)	0 (0.0)

Protocols included: 05, 08, 09, 10, 11 Core, 17, 23, 31 Core, 50 and 51.

Table SS.7. Most Commonly Reported Adverse Events (> 1%) Based On Dose In Placebo Controlled Trials

	Valsartan						Placebo
	10 mg n (%)	20 mg n (%)	40 mg n (%)	80 mg n (%)	160 mg n (%)	320 mg n (%)	n (%)
Total Patients	25 (100)	385 (100)	423 (100)	1281 (100)	660 (100)	185 (100)	888 (100)
Patients with AE's	11 (44.0)	141 (36.6)	131 (31.0)	465 (36.3)	251 (38.0)	75 (40.5)	378 (42.6)
Adverse Experiences							
Headache	2 (8.0)	39 (10.1)	28 (6.6)	106 (8.3)	54 (8.2)	11(5.9)	120 (13.5)
Dizziness	1 (4.0)	9 (2.3)	12 (2.8)	33 (2.6)	14 (2.1)	15 (8.1)	31 (3.5)
Infection Viral	0 (0.0)	11 (2.9)	7 (1.7)	34 (2.7)	18 (2.7)	3 (1.6)	17 (1.9)
URI	2 (8.0)	4 (1.0)	1 (0.2)	22 (1.7)	21 (3.2)	9 (4.9)	21 (2.4)
Coughing	1 (4.0)	6 (1.6)	5 (1.2)	21 (1.6)	15 (2.3)	6 (3.2)	13 (1.5)
Diarrhea	1 (4.0)	8 (2.1)	4 (0.9)	21 (1.6)	11 (1.7)	4 (2.2)	16 (1.8)
Fatigue	0 (0.0)	7 (1.8)	7 (1.7)	23 (1.8)	10 (1.5)	2 (1.1)	11 (1.2)
Rhinitis	0 (0.0)	6 (1.6)	4 (0.9)	25 (2.0)	9 (1.4)	3 (1.6)	20 (2.3)
Sinusitis	1 (4.0)	3 (0.8)	9 (2.1)	17 (1.3)	9 (1.4)	6 (3.2)	14 (1.6)
Pain Back	0 (0.0)	5 (1.3)	3 (0.7)	19 (1.5)	11 (1.7)	0 (0.0)	12 (1.4)
Pain Abdominal	0 (0.0)	5 (1.3)	5 (1.2)	16 (1.2)	6 (0.9)	4 (2.2)	9 (1.0)
Nausea	0 (0.0)	3 (0.8)	2 (0.5)	22 (1.7)	6 (0.9)	2 (1.1)	18 (2.0)
Pharyngitis	0 (0.0)	5 (1.3)	2 (0.5)	8 (0.6)	8 (1.2)	4 (2.2)	6 (0.7)
Arthralgia	0 (0.0)	2 (0.5)	2 (0.5)	14 (1.1)	5 (0.8)	1 (0.5)	9 (1.0)

Protocols included: 05, 08, 09, 10, 11 Core, 17, 23, 31 Core, 50 and 51.

All serious adverse events not resulting in discontinuation in the study are listed in the appendix (pages xxvi - xxx)

Adverse Event in Open Label Studies

Protocol 28 (interim data) and protocol 11 Extension provide long term safety data. Protocol 28 was studied valsartan 40 - 80 mg and lisinopril 2.5 - 20 mg in a randomized, double-blind, parallel dose trial with a 52 week treatment period. Protocol 11 extension is a open label extension of protocol 11. Adverse events incidence rates (interim data) for all adverse events in protocol 28 are listed in the appendix (pages xi - xvi). There does not appear to be a significant difference between valsartan and lisinopril. The one exception is the incidence of back pain. Less than 1% of lisinopril patients and 7.5% of valsartan patients complained of back pain. The clinical relevance of this is unclear.

Discontinuations due to Adverse Events

Two-hundred and eighty-five patients were discontinued due to adverse events from controlled and uncontrolled trials. One-hundred and eighty-nine received valsartan or valsartan/HCTZ. This accounts for approximately 4% of valsartan treated patients. A complete listing of patients discontinued and the adverse events responsible for withdrawal are listed in the appendix (page xvii - xxv). Table SS.8 lists the adverse events causing the highest incidence of premature withdrawal in valsartan and placebo patients. Headache and dizziness caused .8% and .4% of valsartan patients to discontinue.

Table SS.8. Most Common Adverse Events and Premature Discontinuation Incidence (Controlled and Uncontrolled Trials)

	Valsartan [n(%)]		Placebo [n(%)]	
	Overall AE Incidence	Premature Discontinuation.	Overall AE Incidence	Premature Discontinuation.
Total Patients	4004 (100)	4004 (100)	900 (100)	900 (100)
With Reactions	1864 (46.6)	157 (3.9)	381 (42.3)	36 (4.0)
Adverse Experiences				
Headache	441 (11.0)	32 (0.8)	121 (13.4)	12 (1.3)
Dizziness	156 (3.9)	16 (0.4)	31 (3.4)	5 (0.6)
Diarrhea	121 (3.0)	8 (0.2)	16 (1.8)	0 (0.0)
Fatigue	102 (2.5)	7 (0.2)	11 (1.2)	2 (0.2)
Pain Abdominal	70 (1.7)	9 (0.2)	9 (1.0)	2 (0.2)
Chest Pain	40 (1.0)	7 (0.2)	10 (1.1)	2 (0.2)

Protocols included: 05, 08, 09, 10, 11 Core, 11 Ext. 1, 17, 19, 20, 21, 22, 23, 25, 27, 28, 31 Core, 33, 50 and 51.

Orthostatic Hypotension

Symptomatic orthostatic hypotension was rare with valsartan therapy.

Angioedema

There is at least one case of angioedema reported in the valsartan NDA. In protocol 50, patient # 795/5571/Ryan; valsartan 80 mg) experienced a mild case of lip and tongue swelling presumably due to a seafood allergy which the investigator termed angioedema on the case report form. There are other adverse reports that are described as facial swelling or eye edema that may represent angioedema. Angioedema is a rare event.

Angioedema has been associated with ACEI use. The experience with the only approved angiotensin receptor antagonist is not dissimilar to that of ACEI. There have been many post-marketing reports of angioedema for losartan despite only a few reports in the extensive losartan database. The angioedema labeling for valsartan should be similar to losartan.

Cough

Protocol 33 evaluated the incidence of cough in patients with a history of ACEI induced cough. In this study, 24% of valsartan patients, 29% of HCTZ patients and 69% of lisinopril patients experienced cough during the double blind treatment period. There was a significant difference between the lisinopril and valsartan groups. This is the only controlled study included in the NDA specifically designed to evaluate cough.

Six placebo or active control, double blind trials included an ACEI as a treatment regimen. Table SS.10 lists the percentage of patients in each treatment group that complained of cough. In all studies, the incidence rate of cough in the ACEI groups were numerically greater than the valsartan groups.

Table SS.10. Incidence of Cough in Protocols 20, 23, 27, 28, 50 and 51.

Protocol	Treatment	N	% with Cough
20	valsartan 80 mg	94	2.1
	enalapril 20 mg	95	3.2
23	placebo	144	4.2
	valsartan 40 mg	148	2.7
	valsartan 80 mg	142	1.4
	valsartan 160 mg	144	5.6
	lisinopril 10 mg	74	8.1
27 [1]	valsartan 40 --> 80 mg	36	0
	lisinopril 2.5 --> 10 mg	38	2.6
28	valsartan 40 --> 80	334	8.1
	lisinopril 2.5 --> 20 mg	167	19.2
50	placebo	183	1.6
	valsartan 80 --> 160 mg	363	3.3
	lisinopril 10 --> 20 mg	187	9.1
51	placebo	142	0
	valsartan 80 mg	137	.7
	enalapril 20 mg	69	4.3

[1] based on a subsequent submission to the IND for the renal insufficiency development program the incidecn of cough was 0% for valsartan and 1% for lisinopril

In protocol 28, patients completed a visual analogue scale (100 mm) for the frequency of cough, nocturnal cough and the severity of cough at week 0, 26 and 52. Data at the follow-up visits was incomplete since only 80% of randomized patients had data for visit 26. Only 40% of randomized patients had data at visit 52. The median analogue score for frequency of cough changed by 6 mm (6 mm --> 12 mm) in the lisinopril group and by -1 mm (6 mm --> 5 mm) in the valsartan group at week 26. In conclusion, the analogue scores go in the right direction for valsartan but not much else can be said.

There is only one piece of information that associates valsartan with cough. The adverse event rate for cough in all placebo controlled trials combined suggests an increased incidence of cough with increasing valsartan dose (table SS.11). The major limitation with this analysis is the limited exposure at the highest dose where even a single event can change the incidence rate an appreciable amount. It may be that the cough dose response curve for valsartan differs considerably from angiotensin converting enzyme inhibitors (i.e. valsartan cough dose response curve shifted to the right of ACEI response curve).

Table SS.11. Incidence of Cough in Placebo Controlled Trials as a Function of Dose.(Placebo Controlled Trials)

	Valsartan						Placebo
	10 mg n (%)	20 mg n (%)	40 mg n (%)	80 mg n (%)	160 mg n (%)	320 mg n (%)	n (%)
Total Patients	25 (100)	385 (100)	423 (100)	1281 (100)	660 (100)	185 (100)	888 (100)
Coughing	1 (4.0)	6 (1.6)	5 (1.2)	21 (1.6)	15 (2.3)	6 (3.2)	13 (1.5)

Renal Failure

There were no cases of acute renal failure in valsartan patients. There were rare cases of elevations in creatinine above baseline. Based on the post-marketing experience with losartan, some patients who receive valsartan will develop acute renal failure. This is consistent with drugs that block the renin-angiotensin system. In some cases, it will not be completely reversible and possibly be life-threatening without appropriate intervention (i.e. discontinuation of therapy, dialysis). The valsartan labeling should be similar to losartan's label with regard to the risk of developing renal dysfunction.

Several studies in patients with renal dysfunction in single dose (protocol 12) and multiple dose studies (protocol 27 - only preliminary information provided) were performed and the drug appears to be tolerated in patients with renal insufficiency. This information, however, does not preclude the risk of renal failure that is expected with drugs that affect the Renin Angiotensin System.

Hepatitis

There were no cases of symptomatic hepatitis reported in valsartan treated patients. There were several patients who experienced elevations of SGOT/SGPT not associated with symptoms. These are described under the section on abnormal liver function tests.

Laboratory

There were no significant change in mean laboratory parameters with valsartan treatment. There are some differences between valsartan and placebo in the number of patients who had abnormal terminal labs compared to baseline. Table SS.12. lists the incidence of high or low labs in patients for all controlled trials. It is difficult to assess the clinical relevance of the differences between treatments. Uric acid is the only lab parameter that showed at least double the incidence of high values in valsartan patients compared to placebo patients. Low absolute neutrophil counts occurred with a frequency of 2.0% which was comparable to ACEI patients (2.2%) but more than placebo patients (1.1%). Table SS.13 lists the incidence of patients increasing or decreasing a lab parameter from baseline by a specified amount. Valsartan is not much different than ACEI treated patients. Compared to placebo patients, the results observed with valsartan in table SS.12. are similar.

Table SS.12. Number of patients with laboratory test values outside the normal range: all controlled trials, baseline vs terminal lab

Laboratory Test	Valsartan		Valsartan/Diuretic		ACEI		Placebo	
	High n (%)	Low n (%)	High n (%)	Low n (%)	High n (%)	Low n (%)	High n (%)	Low n (%)
Hematocrit	89 (2.8)	142 (4.5)	21 (4.6)	6 (1.3)	25 (4.0)	24 (3.8)	24 (2.8)	19 (2.2)
Hemoglobin	36 (1.1)	141 (4.5)	10 (2.2)	12 (2.6)	10 (1.6)	32 (5.1)	12 (1.4)	26 (3.1)
WBC	87 (2.7)	58 (1.8)	11 (2.4)	7 (1.5)	26 (4.1)	17 (2.7)	19 (2.3)	15 (1.8)
Abs. Neutrophils	88 (2.8)	64 (2.0)	13 (2.8)	9 (2.0)	31 (5.0)	14 (2.2)	23 (2.8)	9 (1.1)
Alk. Phosphatase	60 (1.9)	16 (0.5)	15 (3.3)	0 (0.0)	29 (4.6)	5 (0.8)	15 (1.8)	1 (0.1)
Total Bilirubin	79 (2.5)	4 (0.1)	11 (2.4)	0 (0.0)	19 (3.0)	1 (0.2)	12 (1.4)	0 (0.0)
Calcium	3 (0.1)	12 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	9 (1.6)
Total Cholesterol	154 (5.0)	46 (1.5)	27 (5.9)	2 (0.4)	48 (8.0)	11 (1.8)	45 (5.4)	6 (0.7)
Creatinine	81 (2.6)	33 (1.0)	19 (4.1)	3 (0.7)	27 (4.3)	19 (3.0)	15 (1.8)	2 (0.2)
CPK	90 (7.1)	0 (0.0)	38 (11.3)	0 (0.0)	11 (5.0)	0 (0.0)	32 (10.7)	0 (0.0)
Glucose	188 (6.7)	79 (2.8)	33 (9.2)	8 (2.2)	35 (7.5)	6 (1.3)	65 (7.7)	24 (2.9)
Potassium	100 (3.2)	35 (1.1)	4 (0.8)	27 (5.8)	30 (4.8)	8 (1.3)	15 (1.8)	11 (1.3)
Sodium	65 (2.0)	25 (0.8)	6 (1.3)	9 (1.9)	15 (2.4)	6 (1.0)	14 (1.7)	4 (0.5)
SGOT	78 (2.5)	83 (2.6)	17 (3.7)	22 (4.8)	21 (3.4)	48 (7.7)	32 (3.8)	0 (0.0)
SGPT	110 (3.5)	36 (1.1)	17 (3.7)	2 (0.4)	19 (3.0)	16 (2.5)	35 (4.2)	2 (0.2)
Uric Acid	134 (4.2)	25 (0.8)	52 (11.3)	1 (0.2)	46 (7.3)	1 (0.2)	15 (1.8)	4 (0.5)

Protocols included : 05, 08, 09, 10, 11 Core, 17, 19, 20, 21, 22, 23, 25, 27, 28, 31 Core, 33, 50, and 51.
"High" - Low or normal at baseline vs. high at Terminal Visit.
"Low" - High or normal at baseline vs. low at Terminal Visit.

Table SS.13. Percentage of patients with specified percent change from baseline for selected laboratory tests: all controlled trials

	Valsartan n (%)	Valsartan/ Diuretic n (%)	Placebo n (%)	ACEI n (%)	ACEI/ Diuretic n (%)
Laboratory Test					
Hematology					
Hematocrit	3184 (100)	458 (100)	853 (100)	629 (100)	78(100)
> 50% increase	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
> 20% decrease	24 (0.8)	5 (1.1)	1 (0.1)	6 (1.0)	5 (6.4)
Hemoglobin	3172 (100)	458 (100)	841 (100)	629 (100)	78 (100)
> 50% increase	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
> 20% decrease	12 (0.4)	0 (0.0)	1 (0.1)	1 (0.2)	1 (1.3)
Absolute Neutrophils	3149 (100)	457 (100)	835 (100)	626 (100)	77 (100)
> 50% increase	216 (6.9)	29 (6.4)	48 (5.8)	58 (9.3)	6 (7.8)
> 50% decrease	26 (0.8)	3 (0.7)	3 (0.4)	7 (1.1)	0 (0.0)
Chemistry					
Alkaline Phosphatase	3148 (100)	460 (100)	833 (100)	625 (100)	79 (100)
> 100% increase	201 (6.4)	69 (15.0)	3 (0.4)	104 (16.6)	37 (46.8)
Total Bilirubin	3133 (100)	459 (100)	833 (100)	627 (100)	79 (100)
> 100% increase	187 (6.0)	45 (9.8)	9 (1.1)	81 (12.9)	26 (32.9)
Calcium	1968 (100)	337 (100)	544 (100)	223 (100)	0 (0.0)
> 10% increase	40 (2.0)	12 (3.6)	14 (2.6)	5 (2.2)	-
> 10% decrease	11 (0.6)	1 (0.3)	6 (1.1)	0 (0.0)	-
Cholesterol	3101 (100)	458 (100)	839 (100)	600(100)	74 (100)
> 50% increase	8 (0.3)	1 (0.2)	5 (0.6)	2 (0.3)	0 (0.0)
> 25% decrease	50 (1.6)	1 (0.2)	8 (1.0)	13 (2.2)	2 (2.7)
Creatinine	3148 (100)	459 (100)	848(100)	629 (100)	79 (100)
> 50% increase	25 (0.8)	7 (1.5)	5 (0.6)	10 (1.6)	3 (3.8)
CPK	1269 (100)	337 (100)	299 (100)	220 (100)	0 (0.0)
> 300% increase	10 (0.8)	7 (2.1)	3 (1.0)	4 (1.8)	-
Glucose	2815 (100)	359 (100)	840 (100)	469 (100)	30 (100)
> 50% increase	73 (2.6)	8 (2.2)	20 (2.4)	15 (3.2)	2 (6.7)
> 50% decrease	10 (0.4)	0 (0.0)	7 (0.8)	3 (0.6)	0 (0.0)
Potassium	3131 (100)	468 (100)	839 (100)	626 (100)	79 (100)
> 20% increase	137 (4.4)	11 (2.3)	24 (2.9)	40 (6.4)	3 (3.8)
> 20% decrease	49 (1.6)	16 (3.4)	14 (1.7)	5 (0.8)	3 (3.8)
Sodium	3179 (100)	472 (100)	848 (100)	631 (100)	79 (100)
> 7% increase	5 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (1.3)
> 5% decrease	25 (0.8)	5 (1.1)	3 (0.4)	6 (1.0)	6 (7.6)
SGOT	3145 (100)	459 (100)	836 (100)	627(100)	79 (100)
> 150% increase	24 (0.8)	3 (0.7)	7 (0.8)	9 (1.4)	1 (1.3)
SGPT	3148 (100)	460 (100)	836 (100)	627 (100)	79 (100)
> 150% increase	62 (2.0)	12 (2.6)	16 (1.9)	17 (2.7)	2 (2.5)
Uric Acid	3185 (100)	459 (100)	852 (100)	632 (100)	80 (100)
> 50% increase	31 (1.0)	18 (3.9)	8 (0.9)	11 (1.7)	3 (3.8)

Valsartan patients with significant change in hemoglobin or hematocrit are listed in table SS.14. Patient 177/5128/Chrysant (valsartan 160 mg) had decreases in both hemoglobin and hematocrit that were related to vaginal bleeding. This patient was referred by the investigator to a gynecologist for follow-up of this problem. Patient 85/5057/Marbury (valsartan 20 mg) had a decrease in hemoglobin secondary to a hemorrhaging renal cyst. Patient 22/1131(valsartan 80 mg) had a decrease in both hemoglobin and hematocrit that was diagnosed as microcytic anemia by the investigator. Valsartan patients 6/5024,

202/1017, 202/1021, and 267/1812 had decreases in hematocrit and/or hemoglobin considered clinically relevant by the investigator. These patients had no symptoms or adverse events related to these findings.

Table SS.14. Patients with significant changes in hemoglobin and hematocrit

Protocol	Patient	Treatment	Sex	Age	Baseline	Week 8	Week 12	Week 26
20	22/1131	valsartan 80 mg	M	61	HCT 39.1 HGB 12.3	40 13	22.8 6.5	
23	6/5024	valsartan 80 mg	M	70	HCT 41.2 HGB 14.5	31.8 10.8		
28	202/1017	valsartan	F	69	HCT 48		37.7	35.5
28	202/1021	valsartan	F	75	HCT 45		40.9	34.1
28	267/1812	valsartan	F	77	HCT 35.3		31.3	28.1
31	85/5057/ Marbury	valsartan 20 mg	M	57	HGB 14.4	10.1		
50	177/5128/ Ch[illegible]	valsartan 160 mg	F	47	HCT 41.9 HGB 13.8		31.9 10.5	

Normal ranges: Protocols 20 & 23 HCT 38-52%, HGB 13-18 g/dL; Protocol 28 HCT (F) 36.1-46.1%; Protocols 31 & 50 HCT (F) 34-44%, (M) 36-50%, HGB (F) 11.5-15.0 g/dL, (M) 12.5-17.0 g/dL.

Three patients on valsartan had significant changes in creatinine. Table SS.16. lists the patients and the changes. It is possible that valsartan contributed to these changes.

Table SS.16. Patients with significant changes in creatinine

						Week					
Protocol	Patient	Treatment	Sex	Age	Bsln.	1	5	8	9	12	13
27	1/1038	valsartan	F	66	1.61	2.93	3.18		3.11		2.62
31	232/5158	valsartan 320 mg	M	50	0.9			1.9			
50	632/5449	valsartan 80 mg	M	30	1.1					1.7	

Normal ranges: Protocol 23 0.5-1.50 mg/dL; Protocol 27 0.7-1.2 mg/dL; Protocols 31 & 50 0.6-1.5 mg/dL.
Bsln. = baseline.

Table SS.17 lists several valsartan treated patients had elevations in CPK to levels greater than 1000u/L. In some of the cases, the elevations were associated with exercise. There are no symptoms associated with the increases.

Table SS.17. Patients with Significant Increases in CPK

Patient	Treatment	Age	Sex	Baseline	Terminal	Possible Explanation
209/5567/Hilty (11)	160 mg	45	F	140	1844	Exercise Related
175/5115/Drehobl (11)	320 mg	38	M	163	1002	None.
444/5295 (19)				384	2733	Weight Lifting
138/5095 (19)				167	1362	None. Repeat 1 month after trial was 337 U/L.
799/5720 (19)				122	1119	None
569/5409/Graff (50)	valsartan 160 mg	M	54	110	1328	None.

Note: Normal range = 0 - 174 u/L (male) 0 - 140 u/L (female)
( ) = protocol

Several patients on valsartan experienced asymptomatic increases in SGPT and SGOT > 200 U/L. At least one placebo patient (574/5409/Fagan in protocol 11), experienced similar changes. One valsartan patient in protocol 50 (1129/5829), was discontinued from the study due to increases in SGPT and SGOT. This patient had an elevated SGPT at baseline (97 U/L). SGPT increased to 118 U/L which resulted in discontinuation from the trial. Patient 476/5321 in protocol 19 was a 51 year old female who had increases in SGOT (22 --> 289 U/L) and SGPT (15 --> 247 U/L) during week 8 of valsartan therapy. The

abnormality was attributed to ETOH cirrhosis, however, there is no mention of cirrhosis in the patient's past medical history. Patient 207/1027 (valsartan) in protocol 28 was discontinued due to asymptomatic abnormal liver function tests. SGOT and SGPT increased to 208 U/L and 227 U/L at visit 6 from a normal baseline and visit 4 values. Valsartan was discontinued and repeat labs one month later were normal. Patient 017/512 in protocol 11E was a 62 year old male who had normal baseline SGOT (11 U/L) and SGPT (13 U/L). (Normal Range: SGOT = 0 - 40 U/L, SGPT = 0 - 45 U/L) Terminal visit SGOT (219 U/L) and SGPT (338 U/L) were increased. Total bilirubin increased from .9 mg/dl at baseline to 3 mg/dl at the terminal visit. The patient remained asymptomatic. The relationship to therapy is unclear. Patient 207/1058 (valsartan) in protocol 28 had an increase in SGOT (12 - 208 U/L) and SGPT (5 - 227 U/L) at week 12.

Absolute Neutrophil Counts

Five valsartan treated patients had absolute neutrophil counts decline to less than 1.0 10^9/L while on therapy. Table SS.15 lists the absolute neutrophil counts for these patients. All were enrolled in foreign studies. The patients in study 21 received valsartan 80 mg and all were patients at center #7. One additional patient at this center (patient # 1238) had a neutrophil count as low as 1.0 10^9/L but it returned to normal while on therapy. Total WBC counts were decreased in these patients. Total lymphocyte counts were less than 1.0 10^9/L in patients 1230 and 1233. The patients in study 27 also appear to be enrolled at the same center (center 1). The total WBC count for these patients was decreased (absolute lymphocytes were decreased; differentials for neutrophils and lymphocytes were normal).

The fact that these cases all occurred at the two centers suggest that other factors may be involved. The sponsor was asked to provide a listing of all patients that developed absolute neutrophil counts less than 1.0 10^9/L.

Table SS.15. Absolute Neutrophil Counts for Patients with Counts < 1.0 10^9/L.

Protocol	Patient #	Visit 1	Visit 4 (week 7)	Visit 5 (week 12)
21	1227	1.93		.37
21	1230	3.29	2.09	.75
21	1233	4.11	3.36	.63
		Visit 2	Visit 6 (week 9)	Visit 7 (week 13)
27	1049	2.72	.83	.59
27	1051	4.59	.81	.83

Urinalysis

Individual patient data was included in the archival copy of the NDA. Summary information for urinalysis was included. In response to a request, the sponsor submitted summary data. Data from protocols 9, 10, 11, 17, 19, 31, 33 and 50 were included in their analysis (only USA controlled trials). There was no difference between valsartan and placebo in the percentage of patients who had a shift from a normal to high value for RBCs, glucose, protein and WBCs.

Efficacy

Diastolic Blood Pressure

The sponsor performed ten placebo controlled trials in patients with essential hypertension. The double-blind treatment period ranged in duration from 1 week to 12 weeks. The doses ranged from 10 mg to 320 mg. The studies can be divided into either dose titration studies (05, 08, 09, 50) or parallel dose studies (10, 11, 17, 23, 31, 51). The primary evidence of efficacy (i.e. decreases siDBP or suDBP) is provided by the 6 parallel dose trials. Data from the week 4 blood pressure measurement prior to dose titration in protocol 50 is also supportive. Table SE.1 lists the changes in siDBP or suDBP in the parallel dose trials.

Table SE.1. Mean Changes (mm Hg) In siDBP or suDBP At Endpoint [1] In Placebo Controlled ≥ 4 Weeks Duration

					valsartan			
Protocol		placebo	10 mg	20 mg	40 mg	80 mg	160 mg	
10 [2, 7]	N	25	25		24	22	24	
week 4	Mean	-4.57	-5.41		-6.69	-7.56	-9.36	
	s.d.	5.17	7.95		6.23	7.24	6.86	
	Rel.Mean		-.84		-2.12	-2.99 *[6]	-4.79 *[6]	
11 [5]	N	111		105	113	112		
Week 6	Mean	-4.61		-7.49	-8.48	-8.01		
	s.d.	7.05		7.03	7.23	6.76		
	Rel.Mean	-		-2.88 *[6]	-3.87 *[6]	-3.4 *[6]		
17	N	57				119 [fed]		
fed	Mean	-0.48				-7.34		
week 8	s.d.	12.48				13.95		
	Rel.Mean	-				-6.86*		
	N	57				109 [fast]		
fasted	Mean	-0.48				-6.05		
week 8	s.d.	12.48				15.22		
	Rel.Mean	-				-5.57 *		
23 [4, 8]	N	141			145	139	139	
week 8	Mean	-8.6			-10.2	-11.2	-12.4	
	s.d.							
	Rel.Mean	-			-1.6 [6]	-2.6 [6]	-3.8 [6]	
31	N	145		139		148	147	150
week 8	Mean	-2.28		-4.98		-7.37	-7.71	-8.65
	s.d.	7.56		7.96		7.82	7.18	8.70
	Rel.Mean	-		-2.70 *		-5.09 *	-5.43 *	-6.37 *
50 [3]	N	183				364		
week 4	Mean	-3.13				-7.10		
	s.d.	6.49				7.03		
	Rel.Mean					-3.97 *		
51 [8]	N	142				136		
week 8	Mean	-4.5				-9.5		
	s.d.							
	Rel.Mean					-5.0 *		

Rel.Mean = endpoint - baseline; * = statistically significant difference compared to placebo

[1] = except for study 50. Study 50 measurements at week 4 prior to dose titration (monotherapy endpoint was at week 4)

[2] = suDBP, all other trials were siDBP, [3] = measurements prior to optional dose titration

[4] = all patients ≥ 65 years of age; [5] = Caucasian only

[6] = results of the pairwise comparisons, with the adjustment for multiple comparisons using Dunnett's procedure

[7] = predominately < 65 years of age and Caucasian; [8] = ≤ 1% black patients

See p41 these are systolic values

There were three placebo controlled trials that also included an ACEI as an active treatment group. Table SE.2 lists the results from these studies comp

Table SE.2. Mean Changes (mm Hg) In siDBP or suDBP At Endpoint [1] In Placebo and Active Controlled Trials of ≥ 4 Weeks Duration

Protocol		placebo	40 mg	80 mg	160 mg	20 mg	10 mg
23 [3,4]	N	141	145	139	139		73
week 8	Mean	-8.6	-10.2	-11.2	-12.4		-12.4
	s.d.						
	Rel.Mean	-	-1.6	-2.6	-3.8		-3.8
50 [2]	N	183		364			187
week 4	Mean	-3.13		-7.10			-7.80
	s.d.	6.49		7.03			6.72
	Rel.Mean			-3.97			-4.67
51 [4]	N	142		136		69	
week 8	Mean	-4.5		-9.5		-9.4	
	s.d.						
	Rel.Mean			-5.0		-4.9	

Rel.Mean = endpoint - baseline;
[1] = except for study 50. Study 50 measurements at week 4 prior to dose titration (monotherapy endpoint was at week 4)
[2] = measurements prior to optional dose titration
[3] = all patients ≥ 65 years of age
[4] = 99% Caucasian

Sitting Diastolic Blood Pressure - Subgroup Analysis

The change in DBP in placebo controlled trials was evaluated among subgroups based on demographic variables. There are limitations in most of the studies such that each study may not be useful for each analysis. Protocol 10 randomized predominately patients < 65 years of age, few blacks and only about 25 per treatment group. Protocol 10 is not used in any of the descriptive analysis. Protocols 11, 23 and 51 randomized few if any black patients and are not used in the analysis based on race. Protocol 23 randomized only patients ≥ 65 years of age and is not used in the analysis based on age.

Table SE.3 lists the placebo subtracted change in siDBP at endpoint as a function of sex. In studies 31, 50 and 51, female patients had greater changes than males by 1.5 - 3 mm Hg at each dose. In study 17 (fasted), female patients had only a slightly greater change in siDBP (.6 mm Hg). In study 11 and 23, female patients had a smaller change in siDBP than males. It is difficult to explain the discrepancy between studies. Study 23 randomized more females than males but they were all greater than 65 years of age. Study 11 randomized the smallest number of females per treatment. In the end, the only conclusion can be that both male and female patients respond to valsartan therapy.

Table SE.3. Placebo Subtracted Change in siDBP (Placebo Controlled Trials) Based on Sex

		valsartan										lisinopril		enalapril	
Protocol		N	20 mg	N	40 mg	N	80 mg	N	160 mg	N	320 mg	N	10 mg	N	20 mg
11	M	76	-3.54	76	-4.74	86	-4.22								
	F	30	-1.7	37	-1.09	26	-1.94								
17 (fast)	M					73	-4.8								
	F					47	-5.4								
23 [1]	M			46	3.3	49	-3.2	55	-5.8						
	F			102	-0.9	93	-2.3	89	-2.9						
31	M	92	-2.27			87	-3.98	93	-4.65	95	-6.18				
	F	47	-3.55			61	-6.64	54	-6.77	55	-6.68				
50	M					220	-3.2					112	-4.08		
(week 4)	F					144	-5.2					75	-5.62		
51	M					64	-3.8							40	-2.6
	F					72	-6.1							29	-8.0

M = male; F = female. [1] = all patients ≥ 65 years of age.

Table SE.4 lists the placebo subtracted change in siDBP at endpoint as a function of age. There does not appear to be a consistent age related effect.

Table SE.4. Placebo Subtracted Change in siDBP (Placebo Controlled Trials) Based on Age

		Valsartan										lisinopril		enalapril	
Protocol		N	20 mg	N	40 mg	N	80 mg	N	160 mg	N	320 mg	N	10 mg	N	20 mg
11	< 65	89	-3.9	94	-4.7	84	-5								
	≥ 65	17	0.3	19	-1.5	28	1.3								
17 (fast)	< 65					96	-4.9								
	≥ 65					24	-4.8								
31	< 65	118	-3.08			120	-5.34	129	-5.49	125	-6.57				
	≥ 65	21	-0.73			28	-4.03	18	-5.32	25	-5.45				
50	< 65					303	-4.5					155	-4.03		
(week 4)	≥ 65					61	-5.4					32	-7.67		
51	< 65					113	-5.4							57	-5.6
	≥ 65					23	-3.3							12	-1.9

Table SE.5 lists the placebo subtracted change in siDBP at endpoint as a function of race. In all studies, the change in siDBP for blacks is comparable to white patients. In study 31, blacks show a greater change in blood pressure than white patients (which is similar to the change in the group defined as 'other') particularly at 80 and 160 mg. This observation is somewhat inconsistent with the belief that drugs affecting the renin angiotensin system are less effective in blacks than whites. This is the case in the losartan NDA database (i.e. blacks were less responsive than whites). The active control studies that included an ACE inhibitor are not helpful. Protocols 20 and 28 are double-blind, ACEI controlled studies but they were performed in Europe and randomized only a handful of black patients

It is worthwhile noting that in study 50 the response to lisinopril in black patients was comparable to white patients (similar to what is observed with valsartan). The lisinopril label states that lisinopril is less effective in black patients than Caucasians. Because of the small number of blacks randomized in most of valsartan trials, there is not a lot of confidence that a blacks patient's response to valsartan is any different than what would be observed with ACE inhibitors or with losartan. Valsartan should not receive labeling that differs from the ACE inhibitors and angiotensin receptor antagonists with regard to the effect in blacks.

Table SE.5. Placebo Subtracted Change in siDBP (Placebo Controlled Trials) Based on Race

		Valsartan								lisinopril	
Protocol		N	20 mg	N	80 mg	N	160 mg	N	320 mg	N	10 mg
17 (fast)	White			95	-5.0						
	Black			20	-4.1						
	Other				-						
31	White	105	-1.99	113	-4.45	102	-4.63	114	-6.24		
	Black	12	-2.41	18	-7.11	25	-7.91	17	-6.83		
	Other	22	-6.39	17	-7.27	20	-8.73	19	-6.84		
50	White			301	-3.7					148	-4.67
(week 4)	Black			48	-4.74					27	-5.19
	Other			15	-4.94					12	-4.36

Protocols 10, 11, 23 and 51 excluded because of few black patients randomized.

Sitting Systolic Blood Pressure

Table SE.6 lists the mean changes in siSBP at endpoint in placebo controlled trials.

Table SE.6. Mean Changes (mm Hg) In siSBP or suSBP At Endpoint [1] In Placebo Controlled Trials Of ≥ 4 Weeks Duration

			Valsartan					
Protocol		placebo	10 mg	20 mg	40 mg	80 mg	160 mg	320 mg
10 [2,7]	N	25	25		24	22	24	
week 4	Mean Δ		-1.3		-2.3	-6.6	-9.9	
11 [5]	N	111		105	113	112		
Week 6	Mean Δ			-6.8	-8.2	-9.9		
17 fed	N	57				119 [fed]		
week 8	Mean Δ					-5.6		
17 fasted	N	57				109 [fast]		
week 8	Mean Δ					-6.9		
23 [4,8]	N	141			145	139	139	
week 8	Mean Δ				-5.3	-4.5	-7.2	
31	N	145		139		148	147	150
week 8	Mean Δ			-4.6		-7.4	-7.2	-9.0
50 [3]	N	183				364		
week 4	Mean Δ					-7.4		
51 [9]	N	142				136		
week 8	Mean Δ					-6.7		

Mean Δ = placebo subtracted change

Response Rate

A successful response was defined as DBP < 90 mm Hg or ≥ 10 mm Hg change from baseline. Table SE.6 list the response rates at endpoint for the placebo controlled trials that did not have a dose titration. In studies with multiple valsartan dose groups (protocols 10, 11, 23, 31), there is generally an increase in response with increases in dose. In study 11, the response rate is fairly flat.

Table SE.6. Response Rates at Endpoint in Parallel Dose Placebo Controlled Trials

		Valsartan					
Protocol	placebo	10 mg	20 mg	40 mg	80 mg	160 mg	320 mg
10 [3]	16	24		33	45	54	
11 [1]	30		41	50	45		
17 (fed)	-				37		
17 (fast)	26				44		
23 [2]	48			59	60	68	
31	20		28		42	44	52
51	20				54		

Successful Response is defined as the mean supine diastolic blood pressure <90 mm Hg or a ≥ 10 mm Hg decrease compared to baseline. [1] = Caucasian only; [2] = all patients ≥ 65 years of age; [3] = majority are ≥ 65 and Caucasian

Twice a Day Dosing

The only study to compare twice a day dosing with once a day dosing was protocol 50. Protocol 50 is a randomized, double-blind, placebo controlled trial. Patients with siDBP ≥ 95 mm Hg and ≤ 115 mm Hg at baseline were randomized to placebo, valsartan 80 mg (2 separate treatment groups) or lisinopril 10 mg. After 4 weeks of once a day therapy, patients who continued to have elevated blood pressure had the dose doubled. The valsartan patients were randomized to one of two groups at the start of the trial. In one group, if titration was necessary, the dose was doubled as once a day therapy (i.e. 160 mg once a day). In the other group, the dose was doubled but as a twice a day dose regimen (i.e. 80 mg twice a day). To

compare the effectiveness of once a day dosing versus twice a day dosing, only patients who actually had dose titration are included. Approximately 65% of the valsartan patients required dose titration compared to 78% of the placebo group and 64% of the lisinopril group. Table SE.7 lists the mean change in siDBP at endpoint for these patients. There is no significant difference between once a day and twice a day dosing of valsartan.

Unclear

① What week is visit 3.

② Should be plbo sub'd

Table SE.7. Mean Change In siDBP For Patients Who Had The Dose Titrated in Protocol 50

	Visit 3		Visit 4		Visit 5		Endpoint	
	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	142	-1.5	141	-3.4	129	-2.53	142	-2.01
Valsartan 80 --> 160 OD	114	-3.67	112	-7.44	104	-7.52	114	-7.1
Valsartan 80 OD --> 160 BID	124	-4.02	124	-7.87	116	-7.71	124	-7.30
Lisinopril 10/20 OD	120	-4.95	119	-8.66	116	-8.6	120	-8.39

Food Effect

During the development of valsartan, it was observed that food decreased the AUC and Cmax of valsartan by 41% and 53% respectively. Protocol 17 was undertaken to determine whether this difference resulted in a difference in the pharmacodynamics in hypertensive patients. Patients were randomized to placebo, valsartan 80 mg fasted or valsartan 80 mg fed. After 8 weeks of treatment, both fed and fasted valsartan groups had a significant effect on siDBP compared to placebo. The change from baseline in the fasted group was 1.7 mm Hg greater than in the fed group. Although this was not statistically significant, it is consistent with the pharmacokinetic observations.

Is this what

Table SE.8. Summary of Mean Decreases in Trough Mean Sitting Diastolic Blood Pressure (mm Hg)

	Endpoint		Visit 7 (week 3)	
	N	Mean Change from Baseline (S.D.)	N	Mean Change from Baseline (S.D.)
Placebo	57	-3.6 (7.54)	48	-4.03 (7.51)
Valsartan 80 mg, fasted	119	-8.55 (7.62)* 4.95	108	-8.88 (7.76)
Valsartan 80 mg, fed	109	-6.87 (7.92)** 3.27	102	-7.23 (7.40)

* p = .001, fasted vs. placebo; p = 0.046, fed vs. placebo; based on the least squares mean and between-treatment comparison of change from baseline (prefasted measurement at Visit 3) derived from the two-way analysis of covariance.

why are these #'s different from

Trough Peak Effect

Protocols 09, 10 and 31 (ABPM) collected blood pressure measurements at trough and at time points other than trough. In protocol 09 and 10, blood pressure measurements were collected at 2, 4 and 6 hours post-dosing. In protocol 11, 24 hours ABPM was performed in a subset of patients.

In protocol 09, the maximum decline in siDBP occurred at 6 hours post dosing (compared to trough baseline). The trough/peak ratio at week 10 was .55 (-8.2 mm Hg/ -15.0 mm Hg; not placebo subtracted)[1] compared to a ratio of .3 for placebo[based on data in volume 1.69, p. 174].

In protocol 10, the maximum decline in suDBP occurred at 6 hours post dosing (compared to trough baseline). The trough/peak ratio at week 6 for placebo and the valsartan treatment groups are listed in table SE.9. Valsartan 80 and 160 mg dose groups have trough/peak ratios of .6 or greater

Table SE.9. Change in Peak and Trough suDBP at Week 6 Endpoint Visit. (mm Hg)

Treatment	Peak Change	Trough Change	Trough/Peak Ratio
placebo	-9.13	-4.57	.5
valsartan 10 mg	-11.9	-5.4	.45
valsartan 40 mg	-13.7	-6.7	.49
valsartan 80 mg	-11.3	-7.6	.67
valsartan 160 mg	-15.0	-9.4	.63

must do plbo subtracted

The data provided for protocol 31 does not permit an assessment of the trough/peak ratio.

[1] If placebo results are subtracted, the ratio is 1.06 (- 5.2 mm Hg/ - 4.9 mm Hg).

CLINICAL PHARMACOLOGY

The clinical pharmacology studies were reviewed by Dr. Zia-Amirhosseini. This summary was obtained from information included in her review.

Twenty-seven clinical pharmacology studies were completed. Six of the studies were performed in the USA with the remainder being conducted in Europe and Japan. Nine protocols involved the evaluation of valsartan pharmacokinetic interactions with HCTZ, furosemide, amlodipine, atenolol, digoxin, warfarin, cimetidine, indomethacin or glibenclamide. Protocols ANG-002 and 6 evaluated the effect of food on valsartan absorption. Protocol 15 evaluated the absolute bioavailability of valsartan. Protocol 16 studied the pharmacokinetics of radiolabeled valsartan. Protocols 4 and 30 evaluated the effect of valsartan on the blood pressure response to the infusion of angiotensin II. Protocol 12 and 13 assessed the pharmacokinetics of valsartan in patients with differing physiologic or demographic characteristics (renal function, age, sex)[2]. Protocol 47 assessed the bioequivalence of the final formulation with the formulation used in clinical trials. Three hundred and eighty-five subjects were exposed to valsartan. All were healthy subjects except for those with renal impairment enrolled in protocol 12.

Valsartan has a chiral center and will be marketed as only the S-enantiomer. It has good solubility at neutral and alkaline pH but is poorly soluble at acid pH [pKa = 4.73 (tetrazole group) and 3.9 (carboxylic acid group)]. Based on an N of 1 (subject in protocol 40), there was no conversion to the R-enantiomer in vivo.

Pharmacokinetics and Metabolism

In protocol 16, radiolabeled (C^{14}) valsartan was administered to 6 healthy male subjects. Table CP.1 shows the radioactivity measurements as a function of time. After 7 days, 99% of the radioactivity was recovered, 13% from the urine and 86% from the feces. Eighty percent was recovered as unchanged drug. Three metabolite peaks were observed. Only an hydroxylated metabolite (designated M1) has been identified (see figure CP.1.). The radioactivity and valsartan concentration curves are superimposable during the first two hours after dosing. This suggests little first pass metabolism. Table CP.1a lists the amounts of valsartan and metabolites collected in the feces and urine.

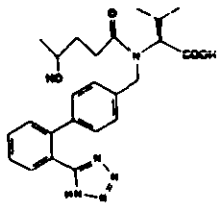
Table CP.1. Radioactivity in Urine and Feces

Time Interval	Excretion of Radioactivity (% of Dose)		
	Urine	Feces	Total
0 - 48	12.9 ± 3.6	48.6 ± 18.6	61.4 ±16.5
0 - 96	13.1 ± 3.8	80.3 ± 11.4	93.4 ± 8.1
0 - 168	13.2 ± 3.8	85.7 ± 4.5	98.9 ± 1.0

Table CP.1a. Valsartan and Metabolite Distribution in the Feces and Urine

HPLC Peaks	Excretion [% of dose]		
	Urine (0 - 48 hr.)	Feces (12 - 72 hr.)	Total
M1 metabolite	1.1 ± .6	8.0 ± 3.0	9.1 ± 3.4
unidentified	.3 ± .1	1.9 ± .7	2.1 ± .7
unidentified	.3 ± .1	.9 ± .3	1.2 ± .3
valsartan	9.8 ± 2.5	70.8 ± 6.5	80.6 ± 5.0
Total	11.5 ± 3.2	81.5 ± 4.0	93.0 ± 1.4
Other Unidentified	1.4 ± .9	1.5 ± .3	2.9 ± 1.1
Total Excretion	12.9 ± 3.6	83.1 ± 4.0	95.6 ± 1.6

Figure CP.1. M1 Metabolite



[2] Protocol 46 is an ongoing study that assesses the effect of liver dysfunction on valsartan pharmacokinetics.

The volume of distribution is 16.9 ± 6.9 L. Ninety-five percent of valsartan is protein bound in plasma.

Protocol 15 evaluated single doses of valsartan 20 mg (i.v.), valsartan 80 mg capsules (oral) and valsartan 80 mg buffered solution. Table CP.2. lists the pharmacokinetic parameter obtained with each dose form.

Table CP.2. Pharmacokinetic Parameters for Various Dose Forms

Parameter	20 mg i.v.	80 mg clinical capsule	80 mg buffered solution
Cmax (uM)		3.77 ± 1.45	7.47 ± 1.96
Tmax (hr.)		2	1
AUC $_{(0-24)}$ (umol.h/L)	21.55 ± 3.91	19.62 ± 5.99	32.88 ± 8.1
Bioavailability	1.0	.23 ± .07	.39 ± .07
CL (L/h)	2.19 ± .39		
Vss (L)	16.91 ±6.90		
MRT (h)	7.82 ± 3.32		
$T_{1/2a}$	1.01 ± .13		
$T_{1/2b}$ (h)	9.45 ± 3.83	7.05 ± 1.58	7.50 ± 1.73
Urinary Excretion (% of dose over 24 hours)	28.95 ± 5.82	7.34 ± 3.02	12.55 ± 3.10
CL_R (L/h)	.62 ± .12		

The capsule formulation had a lower absolute bioavailability than the buffered solution. This may be a consequence of the solubility of valsartan in acid solutions. The absolute bioavailability for the capsule was 23%. The elimination half-life of the capsule is approximately 7 hours. With the IV formulation, approximately 29% of the dose was recovered in the urine.

Dose Proportionality

There are proportional increase in Cmax and AUC with single doses of 80 mg, 160 mg and 320 mg. There was no significant accumulation of valsartan with multiple doses compared to single doses.

Effect of Age and Sex

Protocol 13 evaluated the effect of age and sex on pharmacokinetics. Twelve males (6 younger[3], 6 older) and 12 females (6 younger, 6 older) ingested a single dose of valsartan 80 mg. Table CP.3 lists the AUC and Cmax for as a function of age and sex. The AUC and Cmax for females was greater than males for both age groups. The elimination $t_{1/2}$ was 5.1 hours for the younger group and 7.4 hours for the older group. The AUC for older males and older females was greater than younger subjects [Note: Two older subjects were receiving carbamazepine. It is unclear whether this would effect the metabolism of valsartan.].

Not so younger M ✗ for Cmax

Table CP.3. Pharmacokinetic Parameters for Younger and Older Subjects in Protocol 13.

	Younger			Older		
Parameter	Men	Women	All	Men	Women	All
AUC 0 - δ (umol.h/L)	34.82 ± 9.41	39.08 ± 14.34	36.95 ± 11.78	54.52 ± 29.51	69.52 ± 31. 59	62.7 ± 30.15
Cmax (umol/L)	6.09 ± 1.31	5.22 ± 4.40	6.88 ± 3.20	5.98 ± 2.62	11.13 ± 3.78	8.55 ± 4.11
$T_{1/2}$ (h)	6.27 ± 1.87	5.22 ± .89	5.23 ± .70	5.25 ± .53	7.74 ± 2.04	7.07 ± 2.0

Food Effect

Food (FDA standard breakfast) slowed the rate of absorption (Tmax increased with food from 2.5 hours -->6.1 hours), decreased Cmax by 53% (8.26 umol/L --> 3.89 umol/L) and decreased AUC by 41% (51.9 umol.h/L --> 30.5 umol.h/L).

[3] younger = 18 - 45 years of age; older = ≥ 65 years of age

Renal Dysfunction

In protocol 12, patients with mild (creatinine clearance 61 - 90 ml/minute) and moderate (creatinine clearance 30 - 60 ml/minute) renal impairment do not appear to have different pharmacokinetic parameters compared to a population with normal creatinine clearance. Patients with severe (creatinine clearance < 30 ml/minute) renal dysfunction had variable results. Two subjects had AUC and C_{max} values that were comparable to the control group and two had marked increases in C_{max} and AUC. Table CP.4 lists the Pharmacokinetic parameters and baseline creatinine clearance of the subjects enrolled in protocol 12.

Table CP.4. Pharmacokinetic Parameters for Individual Patients from Protocol 12.

Subject #	Sex	Age	Bsl. Cr. Cl. (ml/min)	C_{max} (ng/ml)	T_{max} (hr)	AUC (0 - δ)	$T_{1/2}$
101	m	30					
102	m	30					
103	m	53					
104	f	62					
105	f	26					
106	m	63					
107	f	41					
201	f	65					
202	f	67					
203	m	62					
301	f	50					
302	m	55					
303	m	54					
304	f	62					
401	f	70					
402	m	68					
403	m	72					
404	m	69					
405	m	75					

[1] = baseline creatinine clearance
[2] = AUC_{0-48}

Liver Dysfunction

Interim data was provided from study 46 (ongoing study). In patients with mild or moderate[4] impaired liver function, the AUC after valsartan 160 mg was 2 - 4 times greater than that of a healthy control group. C_{max} was increased to a lesser extent. This is consistent with the role of biliary excretion in the elimination of valsartan.

Effect on Renin Angiotensin System

Valsartan induced an increase in plasma renin activity and plasma angiotensin II after 10 to 400

[4] mild = Grade A and moderate = Grade B of Pugh's modification of Child's classification
Grade A = 5 - 6 points, Grade B = 7 - 9 points

Pugh's Modification of Child's classification

	Points		
	1	2	3
Encephalopathy	nil	slight	mod - severe
Ascites	nil	slight	mod - severe
Bilirubin (umol/l)	< 34	34 - 51	> 51
Albumin (g/l)	> 35	28 - 35	< 28
Prothrombin	< 1.3	1.3 - 1.5	> 1.5

mg doses. Plasma angiotensin II levels peaked at 4 - 8 hours after dosing and levels were greater on day 8 compared to day 1. Valsartan blocked the blood pressure response of exogenous angiotensin II (40 mg and 80 mg studied). Based on this information, it is clear that valsartan blocks the angiotensin II receptor and does impair the conversion of angiotensin I to angiotensin II (ACE mediated).

Pharmacodynamics

Blood pressure measurements were obtained from healthy subjects after dosing with valsartan. This data contributes little to the interpretation of the dose response in hypertensive patients. Concentration effect data from 5 trials (protocol 9, 10, 17, 27 and 31) in hypertensive patients was fitted to an E_{max} model. There are limitations for the interpretation of this data because 82% of the concentration data points were greater than the EC50 (see Biopharm review for details).

Drug Interaction Studies

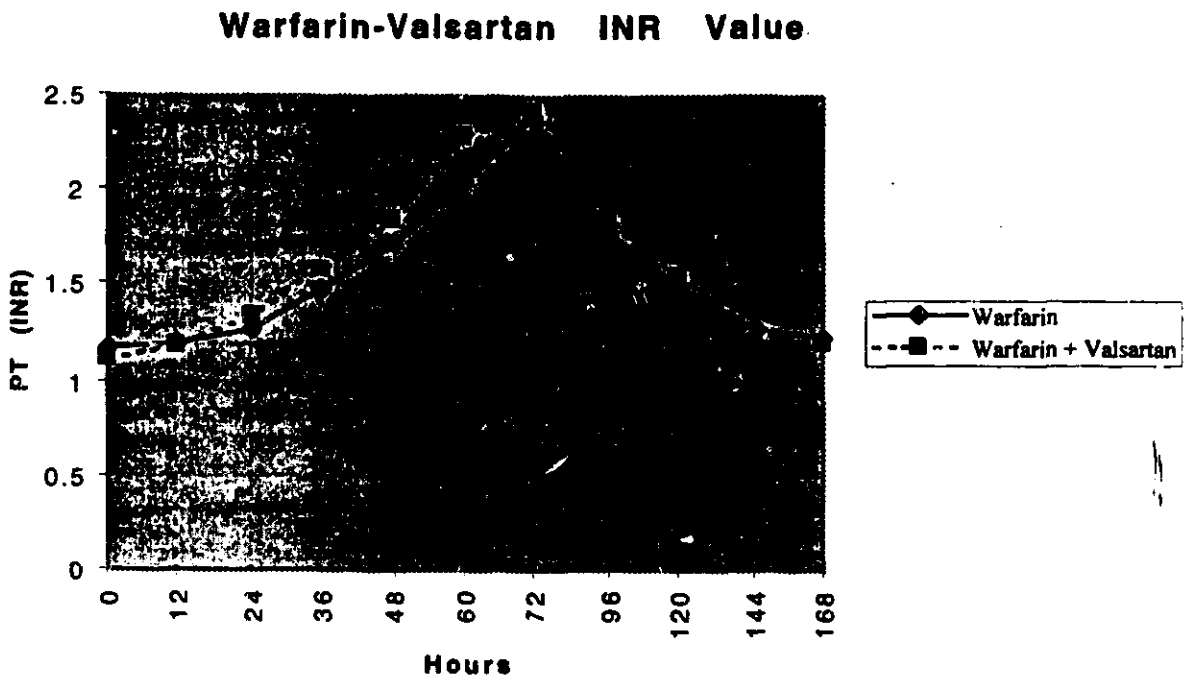
Nine drug interaction studies were performed. There do not appear to be clinically significant Pharmacokinetic interactions with valsartan except for cimetidine. The valsartan C_{max} after cimetidine pre-treatment was 33% greater than after valsartan alone. The AUC, however, increased by only 14%. In protocol 4C, warfarin 10 mg was administered for 3 days with and without valsartan 160 mg. Plots of the PT (INR) were similar with either therapy (see Figure CP.1).

Table CP.5. Pharmacokinetic Parameters of Valsartan and Valsartan + Drug.

Protocol #/ Interaction Drug		Valsartan [1]	Valsartan + Drug	Drug	Drug + Valsartan
7 HCTZ	C_{max} (umol/L)	7.6 (2.3)	6.4 (2.3)	.46 (.14)	.34 (.9)
	AUC_{0-8} (umol.h/L)	60.0 (24.3)	53.0 (23.7)	3.7 (.9)	2.6 (.91)
36 furosemide	C_{max} (umol/L)	6.38 (2.39)	7.37 (2.96)	3.8 (1.9)	2.4 (1.1)
	AUC_{0-24} (umol.h/L)	40.0 (16.8)	44.5 (19.3)	8.6 (3.0)	6.2 (1.9)
37 amlodipine	C_{max} (ng/ml)	2307 (1024)	2269 (1571)	3.37 (.94)	3.54 (.55)
	AUC_{0-8} (ng.h/ml)	18063 (9775)	19614 (14084)	213 (54.4)	226 (79.9)
38 atenolol	C_{max} (umol/L)	7.18 (4.1)	8.48 (3.8)	2.1 (.58)	1.89 (.54)
	AUC_{0-8} (umol.h/L)	40.9 (22.9)	43.3 (20.4)	18.1 (4.4)	16.5 (4.7)
39 digoxin	C_{max} (ng/ml)	2632 (1115)	2297 (1022)	.93 (.28)	.94 (.29)
	AUC_{0-8} (ng.h/ml)	15260 (7160)	15472 (7573)	8.54 (3.3)	8.6 (3.1)
40 warfarin	C_{max} (umol/L)	7.8 (3.54)	7.75 (2.6)		
	AUC_{0-24} (umol.h/L)	45.7 (15.0)	41.9 (9.8)		
42 cimetidine	C_{max} (ng/ml)	2248 (48) [1]	3352 (60) [1]	4010 (19) [1]	3868 (20) [1]
	AUC_{0-48} (ng.h/ml)	14023 (44) [1]	16341 (60) [1]	16670 (16) [1]	14791 (18) [1]
43 indomethacine	C_{max} (ng/ml)	2844 (1279)	2554 (976)	5439 (1661)	5018 (1982)
	AUC_{0-48} (ng.h/ml)	17505 (10398)	19573 (8167)	16430 (3286)	17252 (4440)
52 glibenclamide	C_{max} (umol/L)	7.24 (4.5)	5.3 (2.9)	.223 (.072)	.223 (.071)
	AUC_{0-8} (umol.h/L)	38.5 (17.2)	28.6 (12.0)	.61 (.15)	.60 (.16)

[1] coefficient of variation; ( ) = s.d. unless specified

Figure CP. 1. PT (INR) plot after Treatment with Warfarin Alone or Warfarin + Valsartan



Warfarin = Warfarin 10 mg administered for 3 days. Warfarin + Valsartan = Warfarin 10 mg administered for 3 days and Valsartan 160 mg administered for 7 days.

PLACEBO CONTROLLED TRIALS

Index 1. lists the completed placebo controlled trials included in the NDA

Index 1. Placebo Controlled Trials in Patients with Hypertension

Study #	Design	Measure of Efficacy	Treatment Groups	N
05	- r, db, pc, Europe, 4 week Rx period, forced titration weekly 20 mg --> 40 mg --> 80 mg --> 160 mg - hypertensive patients with sitting diastolic blood pressure ≥ 90 mmHg and ≤ 115 mmHg	Primary - no endpoint specified - supine and standing DBP and SBP measured	- placebo - valsartan 20 mg --> 160 mg	18 72
08	- r, db, pc, sc (Italy), 1 week Rx period, forced titration 20 mg --> 40 mg --> 80 mg - hypertensive patients with sitting diastolic blood pressure ≥ 95 mmHg and ≤ 115 mmHg	Primary - no endpoint specified - supine and standing DBP and SBP measured	- placebo - valsartan 20 mg --> 80 mg	2 9
9	- r, db, pc, 5 centers (USA), 10 week Rx period, optional dose titration - hypertensive patients (mean supine trough diastolic blood pressure was ≥ 95 mg and ≤ 115 mmHg) - dose titrated (doubled from previous dose) every 2 weeks based on blood pressure response	Primary - change in trough supine DBP every 2 weeks Secondary - change in trough supine SBP every 2 weeks - change in supine DBP at 2, 4 6 hours post-dosing at each visit - angiotensin II and renin level at trough, 2, 4, 6 hours post-dosing - pharmacokinetics	- placebo - valsartan 20 mg --> 320 mg	61 60
10	- r, db, pc, p, mc (USA), 4 week Rx period - hypertensive patients (mean supine trough diastolic blood pressure was ≥ 95 mg and ≤ 115 mmHg)	Primary - change in trough mean suDBP at 2 and 4 weeks Secondary - 16 endpoints including measuring renin, aldosterone, AII after the first dose	- placebo - valsartan 10 mg - valsartan 40 mg - valsartan 80 mg - valsartan 160 mg	25 25 25 23 24
11	- r, pc, 6 wk db Rx period, USA - 98 week optional open label period - hypertensive patients (mean sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg). - Caucasian only	Primary - change in trough mean sitting DBP from baseline at endpoint Secondary - change in trough mean sitting DBP from baseline at endpoint at 2 and 4 weeks - change in trough mean sitting SBP from baseline at endpoint at 2, 4 and 6 weeks	- placebo - valsartan 20 mg - valsartan 40 mg - valsartan 80 mg	111 106 113 112
17	- r, db, pc, 8 week Rx period - hypertensive patients with a mean sitting diastolic blood pressure ≥ 100 mmHg and ≤ 114 mmHg	Primary - the change in trough mean sitting diastolic blood pressure (compare placebo vs valsartan and valsartan fasted versus valsartan fed) at week 8 (endpoint) - change in trough mean siDBP after 2, 4, and 6 weeks of dosing - change in trough mean siSBP after 2, 4, 6 and 8 weeks of dosing	- placebo - valsartan 80 mg (fasted) - valsartan 80 mg (fed)	59 120 118

OD = once a day; BID = twice a day; r = randomized; db = double-blind; pc = placebo controlled; Rx = treatment period; sc = single center; co = crossover; p = parallel dose; ac = active control

Index 1. Placebo Controlled Trials in Patients with Hypertension (con't)

Study #	Design	Measure of Efficacy	Treatment Groups	N
23	- r, db, pc, 8 week Rx period, Europe, patients ≥ 65 years of age - hypertensives with sitting diastolic blood pressure (siDBP) > 95 mm Hg and < 115 mm Hg	Primary - change in siDBP and siSBP Secondary - change in siPulse, stSBP, stDBP, stPulse	- placebo - valsartan 40 mg - valsartan 80 mg - valsartan 160 mg - lisinopril 10 mg	144 143 142 144 74
25	- r, sc (Italy), pc, 2 period co, 4 day Rx period each treatment - hypertensives with siDBP > 95 mmHg and < 120 mmHg and with unilateral renal artery stenosis	Primary - GFR, renal function parameters Secondary	- placebo - valsartan	12
31	- r, 8 week db Rx period, pc, parallel dose, USA - hypertensive patients (mean sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg). - 52 week open label extension	Primary - change in trough mean sitting DBP from baseline Secondary - population clearance - 24 hour ABPM	- placebo - valsartan 20 mg - valsartan 80 mg - valsartan 160 mg - valsartan 320 mg	148 140 150 148 150
50	- r, 12 week db Rx, pc, parallel dose, optional titration at 4 weeks, USA - hypertensive patients (mean sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg).	Primary - change in trough mean sitting DBP from baseline Secondary	- placebo - valsartan 80 mg OD----> 160 mg OD - valsartan 80 mg OD-----> 80 mg BID - lisinopril 10 mg OD --> 20 mg OD	183 177 187 187
51	- r, db, mc (Europe), 8 week Rx, pc, ac - hypertensive patients (mean sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg).	Primary - change in siDBP Secondary - change in siSBP, stDBP, stSBP at endpoint	- placebo valsartan 80 mg - enalapril 20 mg	142 137 69

OD = once a day; BID = twice a day; r = randomized; db = double-blind; pc = placebo controlled; Rx = treatment period; sc = single center; co = crossover; p = parallel dose; ac = active control

Protocol 05. Double-Blind, Multi-center, Multiple Dose, Forced Titration Study In Patients With Mild To Moderate Essential Hypertension
(September 1992 - October 1992)

Protocol

This was a double-blind, multiple doses, forced titration trial in patients with mild to moderate essential hypertension to obtain information on the tolerability of valsartan 20 mg, 40 mg, 80 mg and 160 mg, administered once daily in the treatment of essential hypertension.

Patients with mild to moderate hypertension (sitting diastolic blood pressure ≥ 90 mmHg and ≤ 115 mmHg) were randomised into the study (visit 2). After a 2 week placebo run-in phase (visit 1 and 2), patients received valsartan 20 mg or placebo in an unbalanced manner (4: 1 ratio). After one double-blind treatment week on 20 mg, patients received valsartan or placebo 40 mg for one week, then valsartan or placebo 80 mg for one week and then valsartan or placebo 160 mg for one week (visits 3 - 6). Blood pressure and pulse rate measurements were taken in the supine (after 5 min. resting) and standing (after 1 min. resting) position after morning drug intake (1 - 6 hours post dose).

No primary or secondary endpoints are listed in the protocol. The study was performed in Europe.

Results

Disposition and Demographic

Ninety patients at 6 centers were randomized at visit 2, 72 to valsartan and 18 to placebo. Three patients discontinued prematurely. Table 5.1 lists the patient disposition.

Table 5. 1. Patient Disposition

	Placebo	Valsartan	total
Enrolled			94
Randomized	18	72	90
Discontinued Prematurely	1	2	3
Completed Study	17	70	87
Reason Discontinued			
Adverse Event	1	0	1
Unsatisfactory Response	0	0	1
Withdrew Consent	0	1	1

Seventy-six percent of these patients (n=71) were male and all patients were Caucasian. The age of the patients ranged from 30 to 74 years. Median duration of hypertension was 4.2 years.

Blood Pressure

Changes in blood pressure reflect measurements obtained 1 - 6 hours post-dosing. Ten patients did not follow the scheduled dosage titration (n= 9 / 72 valsartan and n=1/18 placebo). Table 5.2 and 5.3 list the mean change in supine DBP and supine SBP 1 - 6 hours post dosing at visits 3, 4, 5, and 6.

Table 5. 2. Mean Change From Baseline For Supine DBP (1 - 6 hours post-dose).

	Visit 3	Visit 4	Visit 5	Visit 6
Valsartan	- 7	-10.8	- 14.5	- 15.2
Placebo	-4.2	- 5.6	- 5.6	- 4.9

Visit 3 = 20 mg dosing; Visit 4 = 40 mg dosing; Visit 5 = 80 mg dosing; Visit 6 = 160 mg dosing;

Table 5. 3. Mean Change From Baseline For Supine SBP (1 - 6 hours post-dose).

	Visit 3	Visit 4	Visit 5	Visit 6
Valsartan	- 6.7	- 13.5	- 18 .3	- 20.3
Placebo	- 1.4	- 4.9	- 9.3	- 4.6

Visit 3 = 20 mg dosing; Visit 4 = 40 mg dosing; Visit 5 = 80 mg dosing; Visit 6 = 160 mg dosing;

Since the blood pressure changes reflect measurements obtained at various time points after dosing, few conclusions can be made other than noting that the changes with valsartan therapy are greater than with placebo (no statistical analysis planned).

Safety

No death occurred in this trial in either treatment group.

Discontinuations due to Adverse Event

Patient 1075/56 was a 63 year old female (placebo) who discontinued after experiencing abdominal pain/obstipation/increased diuresis of moderate severity two days after the starting active treatment. Patient 1096/84 was a 59 year old male (valsartan) who discontinued from the trial due to a hypertensive crisis. Supine blood pressures on entry were 162/103 and 159/101 mmHg. On day 22 of treatment, after the first dose of valsartan 160 mg, the patient complained of headache, cough and rhinitis. Supine blood pressure was 196-200/105-108 mm Hg and standing blood pressure was 190/115 mm Hg. Physical examination was normal and there were no significant changes in safety laboratory tests. The patient was withdrawn from the trial, hospitalized, and treated with nifedipine; blood pressure was controlled the next day. This was listed as an adverse event but could also be counted as an unsatisfactory therapeutic response.

Adverse Events

During the double-blind treatment period, 40.3% of valsartan and 22.2% of placebo patients reported at least one adverse experience. Table 5.4 list the incidence of adverse events report during double-blind treatment.

Table 5.4. Adverse Event Incidence* During Double-Blind Treatment.

Adverse Event	Valsartan (N = 72)	Placebo (N = 18)
Asthenia	8.3%	0
Fatigue	5.6%	0
Hypertension	1.4%	0
Hypotension	4.2%	0
Postural Hypotension	2.8%	0
Ataxia	1.4%	0
Dizziness	5.6%	0
Headache	1.4%3	11.1%
Neuralgia	1.4%	0
Somnolence	6.9%	0
Sialoadenitis	1.4%	0
Vertigo	8.3%	0
Tachycardia	1.4%	0
Back Pain	1.4%	0
Musculoskeletal Pain	1.4%	0
Sprains/Strains	1.4%	0
Agitation	1.4%	0
Libido Decreased	1.4%	0
Viral Infection	6.9%	5.6%
Coughing	1.4%	0
Rhinitis	1.4%	0
Taste Perversion	1.4%	0
Polyuria	1.4%	5.6%
Conjunctivitis	1.4%	0
Migraine	0	5.6%
Tinnitus	0	0
Palpitations	0	0
Constipation	0	0
Abdominal Pain	0	0
Vision Abnormal	0	5.6%
Skin Disorder	0	5.6%

* Patients can have more than one adverse event reported.

Laboratory Abnormalities

There were no significant laboratory abnormalities.

Protocol 08. Double-Blind, Single Center, Multiple Dose, Placebo-Controlled, Forced Titration One Week Pilot Trial In Patients With Mild To Moderate Essential Hypertension
(May 12, 1993 - October 5, 1993)

This is a double-blind, single center, multiple doses, forced titration trial in patients with mild to moderate essential hypertension to obtain preliminary information on the tolerability of valsartan 20 mg, 40 mg, and 80 mg administered once daily in the treatment of essential hypertension. Thirteen patients with mild to moderate hypertension (sitting diastolic blood pressure $\geq$ 95 mmHg and $\leq$ 115 mmHg) were entered into the study. After a 2 week placebo run-in phase, eleven patients(7M:4F, 11 white:0 black) received valsartan or placebo for 1 week, with a forced titration from Day 1 to 3. Patients received valsartan 20 mg on Day 1, valsartan 40 mg on Day 2 and valsartan 80 mg on Days 3-7, or placebo.

There were no significant adverse events nor laboratory abnormalities. The blood pressure changes contribute little to the overall NDA data base due to the short duration of treatment, the small number of patients and the limited dose range studied.

Protocol 09. A Double-Blind, Placebo-Controlled, Forced Titration, Parallel Trial In Patients With Mild To Moderate Hypertension
(December 9, 1992 - August 6, 1993)

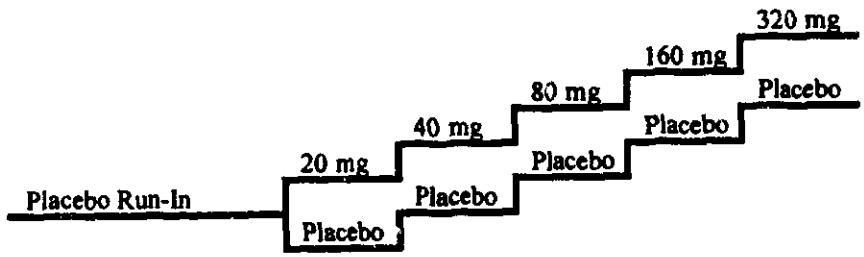
Protocol

This was a multi-center, double-blind, placebo-controlled, forced titration, randomized, parallel design trial in mild to moderate hypertensives. The trial consists of a 4-week placebo run-in period, followed by a 10-week double-blind treatment period where patients are titrated to the next highest dose every 2 weeks with valsartan, 20 mg to 320 mg, or placebo, according to tolerability.

The following diagram outlines the trial design:

Figure 9.1. Study Outline.

Period	**Placebo Run-in**				**Double-Blind Treatment**					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Treatment Week	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**



During the study, trough supine blood pressures were obtained after the patients lay recumbent for 30 minutes. At visit 5, patients were randomized to the placebo or valsartan treatment groups if mean trough supine diastolic blood pressure (suDBP) was ≥ 95 mg and ≤ 115 mmHg at both Visits 4 and 5, the mean supine diastolic blood pressure between visits 4 and 5 did not vary by more than ± 5 mmHg and there was no evidence of orthostatic hypotension (after 2 minutes standing from the supine position, defined by a decrease in mean diastolic blood pressure of > 10 mmHg). At each visit, blood pressure measurement were also obtained in the 2, 4 and 6 hours after dose administration. Blood samples for plasma renin activity, plasma angiotensin II, plasma aldosterone, and valsartan drug levels were obtained prior to each blood pressure measurement.

At each post-randomization 2 week visit, the dose of valsartan or placebo was titrated by a single dose level if the mean supine diastolic blood pressure was > 85 mmHg and there were no symptoms of orthostatic hypotension (e.g., syncope, near-syncope, lightheadedness or dizziness) on changing position from supine to standing, or a decrease in mean diastolic blood pressure of > 10 mmHg in the standing position, after 2 minutes equilibrium. If the patient has a mean supine diastolic blood pressure 85 mmHg and/or symptoms of orthostatic hypotension and ***no evidence*** of volume depletion, the patient may be maintained on the current dose level or ***back-titrated***, at the discretion of the investigator.

Table 9.1 lists the procedures performed during the study.

Table 9.1. Study Procedures.

	Run-in				Double-Blind Treatment					
Visit	1	2	3	4	5	6	7	8	9	10[a]
Treatment Week	0	1	2	3	4	6	8	10	12	14
Complete History/ Physical Examination	x									
Interim/Final Physical Examination		x	x	x	x	x	x	x	x	x
Blood Pressure, Pulse Rate	x	x	x	x	x	x	x	x	x	x
Randomization					x					

Table 9.1. Study Procedures.

	Run-in				Double-Blind Treatment					
12-Lead ECG	x									x
Chest X-Ray	x									
Safety Laboratory Tests	x				x		x			x
Adverse Experiences		x	x	x	x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x	x	x	x
Dispense Trial Medication	x	x	x	x	x	x	x	x	x	
Plasma Renin Activity [b]					x	x	x	x	x	x
Plasma Angiotensin II [b]					x	x	x	x	x	x
Plasma Aldosterone [b]					x	x	x	x	x	x
Valsartan Levels [b]					x á	x	x	x	x	x
6-Hour Observation										
After Dosing					x	x	x	x	x	x
Termination Sheet										x

[a] Trial termination information will be completed at the last visit or whenever a patient terminates prematurely.
[b] Obtained at baseline and 2, 4, and 6 hours after dosing.

The primary measure of efficacy is the change in trough mean supine diastolic blood pressure after each 2 week interval compared to baseline. Secondary measures of efficacy included the change in trough mean supine systolic blood pressure after each 2 week interval compared to baseline, the change in mean supine diastolic blood pressure at 2, 4 and 6 hours after dosing, pharmacokinetics and pharmacokinetic/pharmacodynamic information.

Results

Disposition

Five centers enrolled one hundred and forty-one patients (visit 1). Of these, 121 patients were randomized at Visit 5 into the double-blind treatment phase, and 106 completed the trial. The number randomized at each center ranged from 15 to 43. The frequency distribution of randomized patients and completed patients by treatment is listed in table 9.2. Fifteen patients withdrew secondary to adverse events.

Table 9.2. Patient Disposition

	Placebo	Valsartan	Total
Enrolled			141
Randomized	61	60	121
Completed	51	55	106
Withdrew Prematurely	10	5	15
Reasons Discontinued			
Adverse Event	1	2	3
Abnormal Lab	0	0	0
Unsatisfactory Response	1	0	1
Administrative Problems	1	1	2
Lost to Follow-up	1	0	1
Withdrew Consent	4	2	6
Non-Compliance	1	0	1
Does meet protocol Criteria	1	0	1

Demographics

There was a fairly equal distribution of males and females in each treatment group. The majority of patients randomized were white. Blacks accounted for 12% and other races accounted for 37% of the patients randomized. The mean supine diastolic blood pressure at baseline was similar in both treatment groups. Tables 9.3 and 9.3a lists the demographics of each treatment group.

Table 9.3. Demographics of Treatment Groups

Treatment	# Of Patients	Sex		Race		
		Male	Female	White	Black	Other
Placebo	61	33 (54.10%)	28 (45.90%)	29 (47.54%)	6 (9.84%)	26 (42.62%)
Valsartan	60	34 (56.67%)	26 (43.33%)	32 (53.33%)	9 (15.00%)	19 (31.67%)
Total	121	67 (55.37%)	54 (44.63%)	61 (50.41%)	15 (12.40%)	45 (37.19%)

Table 9.3a. Demographics of Treatment Groups

Treatment	Number Of Patients	Age (Years)	Baseline Mean (+ s.d.) Trough Supine Diastolic Blood Pressure
Placebo	61	54.36 (±9.06)	102.56 (±5.48)
Valsartan	60	55.33 (±9.46)	101.87 (±5.24)
Total	121	54.84 (±9.23)	-

Efficacy

The dose titration design of the study allowed for incremental increases (doubling of dose) at each visit. As a consequence, blood pressure measurements after visit 6 would reflect the effect of various doses of placebo and valsartan. Table 9.4 lists the number of patients at each dose level at each visit. For example, after blood pressure measurement at visit 6, 49 valsartan patients were sent home on level 2 and 9 were sent home on dose level 1. The blood pressure measurement at visit 6, however, reflects the effect of level 1 dosing

Table 9.4. Dose Administered During Double-Blind Treatment

	Placebo Visit						Valsartan Visit					
Dose Level[1]	5	6	7	8	9	10[2]	5	6	7	8	9	10[2]
1	61	4	1	1	1	1	60	9	4	1	1	1
2		51	8	4	2	2		49	12	9	5	5
3			43	6	3	3			42	10	6	6
4				41	5	5				38	9	9
5					40	40					35	35

[1] For valsartan, 1 = 20 mg, 2 = 40 mg, 3 = 80 mg, 4 = 160 mg, and 5 = 320 mg. Some patients were dosed inappropriately in violation of the protocol. See Section 6.2 for more information on these patients.
[2] The dose level at Visit 10 is the dose level prescribed at Visit 9.

Table 9.5 lists the mean change from baseline in trough supine diastolic blood pressure. There is a progressive increase in the decline in suDBP with valsartan therapy but not with placebo therapy. The change in suDBP with valsartan at visit 9 and 10 was significantly different from placebo

Table 9.5. Mean Decreases in Trough Mean Supine Diastolic Blood Pressure (mmHg) at the Visit Endpoints

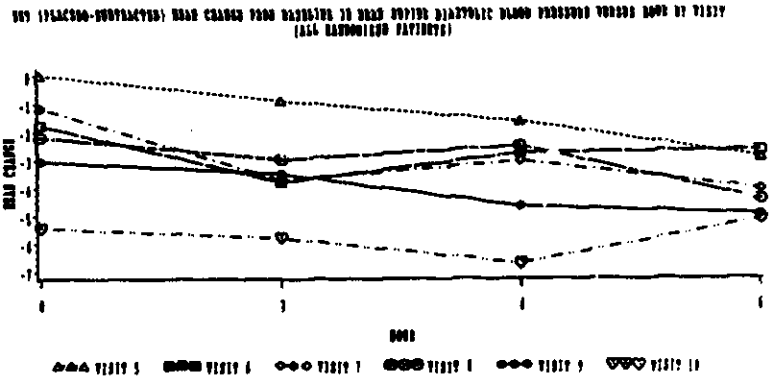
	Placebo (N=57)	Valsartan (N=59)
	Change From Baseline	Change From Baseline
Week 2	-2.53 (±5.83)*	-4.31 (±6.19)**
Week 4	-4.08 (±8.69)**	-5.53 (±7.87)**
Week 6	-4.21 (±8.30)**	-6.62 (±8.20)**
Week 8	-3.94 (±7.70)**	-7.22 (±6.95)**[1]
Week 10	-2.60 (±8.29)*	-7.72 (±7.40)**[2]

Within treatment comparison: * P < .05. ** P < .001. Between treatment comparison: [1] P = .01 comparing valsartan to placebo; [2] P < .001 comparing valsartan to placebo

The changes in mean trough standing DBP were similar to change in sitting DBP results [vol. 1.69, p. 147].

Supine diastolic blood pressure measurements was obtained at 2, 4 and 6 hours post-dosing at each visit. Figure 9.2 plots the change in suDBP at each visit as a function of hours post-dosing. With each visit, the effect of valsartan therapy is increased because patients with inadequate responses had the dose titrated.

Figure 9.2. Mean change from baseline in supine DBP at trough, 2, 4 and 6 hours post-dosing. [volume 1.69, p. 448; see volume 1.69, p 173 and 191 for additional summary data]



The change in supine SBP at each visit is provided in table 9.6. There was a significant difference in suSBP at visit 10 endpoint between treatment groups (p = .004).

Table 9.6 Mean Decreases in Trough Mean Supine Systolic Blood Pressure (mmHg) at the Visit Endpoints [from volume 1.69, p. 144]

	Placebo (N=57)	Valsartan (N=59)
	Change From Baseline	Change From Baseline
Week 2	.08 (±10.93)	-6.93 (±12.76)
Week 4	-2.54 (±16.58)	-6.64 (±12.63)
Week 6	-3.49 (±14.96)	-9.86 (±13.53)
Week 8	-2.07 (±14.43)	-9.36 (±14.71)
Week 10	-2.15 (±16.09)	-9.75 (±15.06)

There was no statistically significant decreases from baseline in trough supine pulse seen in either group at the Visit 10 Endpoint The mean trough change in supine pulse at visit 10 end point was 1.33 beats per minute for placebo and - 1.61 beats per minute for valsartan.

The response rate [defined as a mean supine diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline (pre-dose measurement at the randomization visit)] at endpoint was 23% for placebo and 49% for valsartan. The response rate for valsartan is somewhat surprising in that all patients were titrated to effect and a higher response rate would be expected. At least half of the patients would require additional anti-hypertensive therapy to maintain a DBP less than 90 mmHg.

Analysis based on demographic variables were performed but are limited for age and race because of the small numbers of black patients and patients ≥ 65 years of age. The mean change from baseline in black patients treated with valsartan is less than white or other subgroups. The placebo effect in black

patients is also markedly different than in the other racial subgroups. Patients ≥ 65 years of age had a marked effect on placebo such that the net effect of valsartan therapy (i.e. placebo subtracted) is less than that observed in patients < 65 years of age. Tables 9.7a - c list the change in suDBP by subgroup.

Table 9.7a. Mean Changes from Baseline in Mean Supine Diastolic Blood Pressure (mmHg) at Visit 10 Endpoint by Age

	Age < 65 N = 102 (84.3%)			Age ≥ 65 N = 19 (15.7%)		
Treatment Group	N	Mean	Mean Change from Baseline	N	Mean	Mean Change from Baseline
Placebo	53	100.59	-2.07	8	94.29	-6.38
Valsartan	49	94.54	-7.43	11	91.39	-8.97

Table 9.7b. Mean Changes from Baseline in Mean Supine Diastolic Blood Pressure (mmHg) at Visit 10 Endpoint by Sex

	Male N = 67 (55.4%)			Female N = 54 (44.6%)		
Treatment Group	N	Mean	Mean Change from Baseline	N	Mean	Mean Change from Baseline
Placebo	33	99.98	-2.84	28	99.62	-2.31
Valsartan	34	93.11	-7.76	26	95.03	-7.67

Table 9.7c. Mean Changes from Baseline in Mean Supine Diastolic Blood Pressure (mmHg) at Visit 10 Endpoint by Race

	White N = 61 (50.4%)			Black N = 15 (12.4%)			Other N = 45 (37.2%)		
Treatment Group	N	Mean	Mean Change from Baseline	N	Mean	Mean Change from Baseline	N	Mean	Mean Change from Baseline
Placebo	29	99.63	-2.54	6	108.40	3.73	26	98.29	-3.92
Valsartan	32	91.94	-8.52	9	96.59	-4.96	19	96.22	-7.67

Safety

Discontinuations due to Adverse Events

There were no deaths during the trial. Three patients were discontinued secondary to adverse events. Table 9.8 lists the patients and the reason for discontinuation.

Table 9.8. Patients Discontinued due to Adverse Events

Treatment	Investigator	Patient	Sex	Age	Day*	Medical Problem
Placebo	Zuschke	024/519	M	70	7	Cerebrovascular Accident
Valsartan	Holtzman	020/518	M	69	54	Intermittent Headaches
Valsartan	Chrysant	004/505	F	49	62	Atypical Chest Pain

* Onset Day During Double-Blind Period

Patient 004/505 (Chrysant) was a 49 year old female who on day sixty-two after randomization (valsartan) was admitted to the hospital after presenting at the emergency room with a complaint of atypical chest pain of 6-8 hours duration. Her Visit 1 ECG was normal and the baseline mean supine blood pressure was 151/105. The patient had taken hormone replacement therapy and famotidine 20 mg bid for gastritis throughout the trial. During the placebo run-in period the patient had complained of moderate chest tightness, which resolved after ten minutes. While in the hospital, serial EKGs and cardiac enzymes ruled out an acute MI, however, the ECG showed non-specific ST-T changes in the inferolateral leads. A coronary arteriogram did not show obstruction of major coronary arteries, but did show that the left ventricle was dilated and had increased left ventricular end diastolic pressure of 35 mmHg. The most likely cause for the ST-T changes and ventricular enlargement are microvascular disease due to hypertension and obesity. At the last trial visit, the patient's mean supine blood pressure was 167/109.

The percentage of patients reporting adverse experiences was 50.8% in the placebo group and 55.0% in the valsartan group. Headache was the most common adverse event in both treatment groups (23% vs. 18%, placebo vs. valsartan). Cough occurred in only one valsartan patient.

One patient experienced symptomatic orthostatic hypotension. Patient 005/505 , had experienced orthostatic hypotension at two separate visits, both at 2-hours post-dose. The first episode occurred at Visit 6, after standing for two minutes from the supine position, his standing systolic blood pressure had decreased by 29 mmHg, his diastolic blood pressure decreased by 20 mmHg, and he had experienced dizziness. The symptoms resolved after 20 minutes. The next episode occurred at Visit 8, after standing for two minutes from the supine position, this patient's systolic blood pressure decreased by 34 mmHg, his diastolic blood pressure decreased by 32 mmHg and he was dizzy and pale. The symptoms resolved after 10 minutes.

There were no significant mean changes in lab parameters from baseline to the terminal visit. Patients with laboratory values outside of the normal range for laboratory parameters were of no clinical significance.

Eleven valsartan patients had an abnormal urine albumin at some time during double-blind treatment compared with 4 placebo patients (vol. 1.69, p. 330 and 332). At the terminal visit, four valsartan and four placebo patients had abnormal urine protein (vol. 1.69, p. 321). It is not clear that this is clinically relevant.

Pharmacokinetics

Table 9.9 summarizes the mean trough plasma concentrations and net effect of valsartan in 33 patients following 20, 40, 80, 160, and 320 mg once-a-day for 2 weeks. There appears to be a dose proportional increase in mean trough concentration.

Table 9.9. Mean Trough Valsartan Concentrations

Dose (mg)	Mean trough conc. ± S.D. (ng/ml)
20	52.7 ± 90
40	117.5 ± 243
80	187.9 ± 299
160	376.1 ± 653
320	565.0 ± 986

Angiotensin II and Renin

At 2, 4, and 6 hours post-dose, the valsartan treatment group had increased angiotensin II levels compared to the placebo group. The change from baseline at trough for angiotensin II did not increase appreciably as the trial progressed, but varied from visit to visit (see volume 1.69, p. 209).
The trough levels of plasma renin, after each visit, and 2, 4, and 6 hours post-dose, increased in the valsartan treatment group compared to the placebo group (see volume 1.69, p. 212).

Protocol 10. A Double-Blind, Placebo-Controlled, Fixed-Dose, Parallel Trial In Patients With Mild To Moderate Hypertension
(December 11, 1992 - June 29, 1993)

Protocol

This was a multi-center, double-blind, placebo-controlled, fixed dose, randomized, parallel design trial in mild to moderate hypertensives. The trial consisted of a 4-week placebo run-in period, followed by a 4-week double-blind treatment period with patients receiving valsartan 10, 40, 80, and 160 mg, or placebo once a day. This trial was one of two studies performed to ascertain preliminary dose range information for valsartan, to be utilized in determining the dose range for the definitive dose-response and pivotal efficacy trials.

During the placebo baseline period, patients were evaluated on a weekly basis (visits 1 - 5). After 4 weeks of placebo therapy (visit 5), patients were randomized if the mean supine diastolic blood pressure was $\geq$ 95 mmHg and $\leq$ 115 mmHg at both Visits 4 and 5, the mean supine diastolic blood pressure between Visits 4 and 5 did not vary by more than $\pm$ 5 mmHg and the patients had no evidence of orthostatic hypotension, after 2 minutes standing from the supine position, defined by a decrease in mean diastolic blood pressure of > 10 mmHg.

Blood pressure was measured at each visit prior to drug administration with the patient resting for a minimum of 30 minutes in the supine position. After a minimum of 30 minutes, three supine blood pressures and one pulse rate measurement were taken. Immediately after supine measurements were taken, the patient changed to the standing position, and remained in that position for a minimum of 2 minutes.

Patients remained in the office for a minimum of 6 hours after drug administration. At 1 hours, 3 hours, and 5 hours after drug had been administered, all procedures for blood drawing, blood pressure, and pulse were repeated (except for safety laboratory tests, which are only done at the baseline time point).

Table 10.1. Schedule of Procedures

	Single-Blind Placebo Run-in Period				Double-Blind Rx Period		
					randomization		
Visit	1	2	3	4	5	6	7
Rx Week	0	1	2	3	4	6	8
Complete H + P	x						
Interim/Final Physical Exam		x	x	x	x	x	x
Blood Pressure/Pulse [3]	x	x	x	x	x	x	x
12 lead ECG	x						x
Chest X-ray	x						
Safety Lab Tests [2]	x				x		x
Plasma Renin Activity [1]					x	x	x
Plasma Angiotensin II [1]					x	x	x
Plasma Aldosterone [1]					x	x	x
Valsartan Levels [1]					x	x	x
6 hour observation after dosing					x	x	x

[1] 30 minutes prior to drug administration and 2, 4 and 6 hours post-drug
[2] CBC, Chemistries and Urinalysis prior to dosing
[3] Patients rested in the supine position for a minimum of 30 minutes. After a minimum of 30 minutes, three supine blood pressures and one pulse rate measurement were taken. Immediately after supine measurements were taken, the patient changed to the standing position, and remained in that position for a minimum of 2 minutes. At this point, one standing blood pressure and one pulse rate measurement was taken.

The primary endpoint is the change in trough mean supine diastolic blood pressure (24 hours after dosing) after 2 a. d 4 weeks of dosing compared to baseline supine diastolic blood pressure at Visit 5.

Secondary endpoints include the following:

- Change in mean supine diastolic blood pressure at 2, 4, and 6 hours after the first dose of valsartan 10 mg, 40 mg, 80 mg, 160 mg, or placebo as compared to the baseline mean supine diastolic blood pressure at Visit 5.
- Change in mean supine diastolic blood pressure at 2, 4, and 6 hours after the first dose of CGP 48933 10 mg, 40 mg, 80 mg, 160 mg, or placebo as compared to the baseline mean supine diastolic blood pressure at Visit 5.
- Comparison of anti-hypertensive effect at 2 and 4 weeks to determine if additional effect is observed > 2 weeks.
- Calculation of the trough/peak ratio of change in mean supine diastolic blood pressure at 2 and 4 weeks.
- By comparison of these anti-hypertensive effects at each dose level, preliminary dose-ranging information will be obtained.
- Change in plasma renin activity, plasma angiotensin II, and plasma aldosterone after the first dose of CGP 48933.
- Change in plasma renin activity, plasma angiotensin II and plasma aldosterone at 2, 4, and 6 hours after the final dose of valsartan and at the 2 and 4 week dosing interval compared to pre-dose levels on day of assessment.
- Change in trough plasma renin activity, plasma angiotensin II, and plasma aldosterone at 2 and 4 weeks of dosing.
- Change in plasma level of valsartan after initial dose of 10, 40, 80, and 160 mg.
- Trough plasma level after 2 and 4 weeks of dosing.
- Comparison of trough plasma levels at each dose to determine if higher plasma levels are achieved with > 2 weeks of dosing.

• Change in plasma levels valsartan at 2, 4, and 6 hours after the final dose of the 2 and 4 week dosing interval, compared to trough measurement on day of assessment.
• Relationship of trough blood level to change in mean supine diastolic blood pressure after 2 and 4 weeks of dosing.
• Relationship of plasma levels at 2, 4, and 6 hours to change in mean supine diastolic blood pressure at 2, 4, and 6 hours after dosing with first dose and after 2 and 4 weeks.
• Relationship of trough/peak plasma levels to change in plasma renin activity, plasma angiotensin II, and plasma aldosterone.
• Relationship of plasma level to presence of orthostatic hypotension (defined as greater than 10 mmHg decrease in mean diastolic blood pressure after changing from supine to standing position, with 2 minute equilibrium) after the first dose, and after 2 and 4 weeks of dosing.

The projected sample size in the protocol was 100 patients.

Results

Disposition

One hundred forty-six patients were enrolled at Visit 1. Of these, 122 patients were randomized at Visit 5 into the double-blind treatment phase. Five centers randomized from 9 to 32 patients. The number of patients randomized to each treatment ranged from 23 to 25. Eight patients discontinued prematurely. One placebo patient and one valsartan 40 mg patient discontinued due to adverse experiences. Table 10.2 outlines the patient disposition in the study.

Table 10.2. Patient Disposition

	Placebo	Valsartan				Total
		10 mg	40 mg	80 mg	160 mg	
# Randomized	25	25	25	23	24	122
# Completing	24	23	22	22	23	114
Discontinued Prematurely	1	2	3	1	1	8
Reasons Discontinued:						
Adverse Experience	1	0	1	0	0	2
Abn. Lab Value	0	0	0	0	0	0
Unsatisfactory Response	0	2	1	0	0	3
Other	0	0	1	1	1	3

Demographics

There was a significant difference in the distribution of p. .its based on sex between treatment groups (p = .04). The 80 mg group randomized only 4 females while the placebo group randomized 13. The majority of patients were white (only 10 black patients randomized) and under 65 years of age.

Table 10.3. Demographics

	Placebo	Valsartan				Total
		10 mg	40 mg	80 mg	160 mg	
# Randomized	25	25	25	23	24	122
Sex						
Male	12	19	17	19	12	79 (65%)
Female	13	6	8	4	12	43 (35%)
Race						
White	20	21	18	19	20	98 (80%)
Black	2	1	2	3	2	10 (8%)
Other	3	3	5	1	2	14 (12%)
Mean Age	53.0	54.3	52.4	52.3	52.7	52.9
≥ 65	3	4	2	4	2	15
< 65	22	21	23	19	22	107
Trough Mean Supine DBP	101.7	102.6	101.8	100.7	101.0	

Endpt not defined

P is the 80 mg dose is too

Efficacy

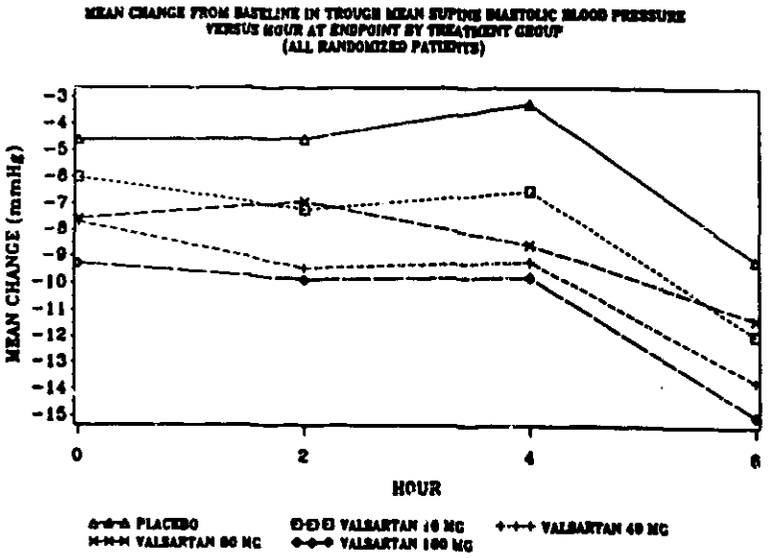
Table 10.4 lists the mean change in trough supine diastolic blood pressure at endpoint. There is a progressive decrease in supine DBP with increasing doses of valsartan. Comparison of the treatment effect of each valsartan group versus placebo, adjusting for multiple testing, suggests that only valsartan 160 mg was significantly different from placebo. An analysis looking at only those patients with blood pressure measurements at visit 7 yielded similar results as the endpoint analysis.

Table 10.4. Mean Change In Trough Supine Diastolic Blood Pressure At Endpoint (calculated from data).

Treatment Group	N	Mean (s.d.)	Maximum Increase/ Decrease	Placebo Subtracted
Placebo	25	- 4.57 (5.17)	3.33/- 16.67	-
Valsartan 10 mg	25	- 5.41 (7.95)	8.67/ - 23.33	- .84
Valsartan 40 mg	24	- 6.69 (6.23)	6.0/ - 20.67	- 2.12
Valsartan 80 mg	22	- 7.56 (7.24)	2.67/ - 22.0	- 2.99
Valsartan 160 mg	24	- 9.36 (6.86)	5.33/ - 24.67	- 4.79

Figure 10.1 plots the change in suDBP at 2, 4 and 6 hours post-dosing for the endpoint visit. The treatment effect increases with increasing dose.

Figure 10.1. [vol. 1.75, p. 493]



The mean change in trough standing diastolic blood pressure were less pronounced than supine changes in DBP. Table 10.4a lists the mean change in trough standing blood pressures at endpoint. Compare the results in table 10.4a to table 10.4. The difference between the standing and supine results observed in this study is not consistent with the standing and supine results in Protocol 9 (the only other study to measure supine DBP as a primary endpoint). In studies that measured sitting DBP as the primary measure of efficacy, the sitting and standing results were similar.

Table 10.4a. Mean Change In Trough Standing Diastolic Blood Pressure At Endpoint [vol. 1.75, p. 134]

Treatment Group	N	Mean (s.d.)	Placebo Subtracted
Placebo	25	- 3.84 (8.24)	-
Valsartan 10 mg	25	- 4.16 (6.48)	- .32
Valsartan 40 mg	24	- 4.08 (4.92)	- .24
Valsartan 80 mg	22	- 5.73 (9.80)	- 1.89
Valsartan 160 mg	24	- 6.08 (6.25)	- 2.24

Due to the homogeneity of the treatment groups with regard to age and race, subgroup analysis based on age and race provide little information. The mean change in supine DBP based on sex is listed in table 10.4b. The effect of valsartan in males and females was similar.

Table 10.4b. Mean change from baseline in trough supine diastolic blood pressure at endpoint (mmHg).

Treatment Group	Males (N=99)	Females (N=43)
Placebo	-3.53	-5.54
Valsartan 10 mg	-4.84	-7.22
Valsartan 40 mg	-7.42	-5.25
Valsartan 80 mg	-7.24	-9.00
Valsartan 160 mg	-8.06	-10.67

There was no significant difference in the mean change in trough pulse rate between treatments [vol. 1.75, p. 112].

Table 10.5 list the mean change in trough supine systolic blood pressure at endpoint. As with diastolic blood pressure, there is a progressive decrease in systolic blood pressure with increasing dose.

Table 10.5. Mean Change In Trough Supine Systolic Blood Pressure At Endpoint

Treatment Group	N	Mean (s.d.)	Maximum Increase	Maximum Decrease
Placebo	25	- 3.44 (11.56)	16.67	- 32.0
Valsartan 10 mg	25	- 4.69 (12.51)	29.33	- 28.67
Valsartan 40 mg	24	- 5.71 (13.43)	35.33	- 30.67
Valsartan 80 mg	22	- 10.09 (13.18)	16.67	- 39.33
Valsartan 160 mg	24	- 13.35 (16.89)	34.0	- 51.33

Hormonal Levels

Plasma angiotensin II levels, renin levels and aldosterone levels were obtained at visits 5, 6 and 7 at 30 minutes prior to dosing, 2, 4 and 6 hours post-dosing. Angiotensin II levels increased during the 6 hours post-dosing in the valsartan treatment groups compared to placebo [vol. 1.75, p. 150]. Renin levels increased during the 6 hours post-dosing in the valsartan treatment groups compared to placebo[vol. 1.75, p. 151]. Aldosterone levels decreased during the 6 hours post dosing for all treatment groups[vol. 1.75, p. 152].

Safety

There were no deaths during the trial.

The percentage of patients reporting adverse experiences, whether or not trial drug-related, ranged from 44.0% (in placebo and valsartan 10 mg groups) to 20.8% in the valsartan 160 mg group. Adverse experiences reported by > 3% of patients are presented in Table 10.6. Diarrhea was the most common adverse event in the valsartan treatment group.

Table 10.6. Incidence Of Most Frequently Reported (In ≥ 3% Of Patients) Adverse Experiences Regardless Of Relationship To Trial Drug.

	N (%)				
	Placebo	Valsartan			
		10 mg	40 mg	80 mg	160 mg
Total Patients	25 (100.0)	25 (100.0)	25 (100.0)	23 (100.0)	24 (100.0)
Patients with Adverse Experiences	11 (44.0)	11 (44.0)	9 (36.0)	5 (21.7)	5 (20.8)
Diarrhea	0 (0.0)	1 (4.0)	2 (8.0)	1 (4.3)	1 (4.2)
Headache	3 (12.0)	2 (8.0)	1 (4.0)	0 (0.0)	1 (4.2)
Dizziness	1 (4.0)	1 (4.0)	1 (4.0)	1 (4.3)	1 (4.2)
Upper Respiratory Tract Infection	1 (4.0)	2 (8.0)	1 (4.0)	0 (0.0)	1 (4.2)

One placebo and one valsartan 40 mg patient discontinued due to adverse events. Table 10.7 list the reason for discontinuation. Patient 008/507/Norton (placebo) completed the placebo run-in uneventfully and was randomized to double-blind treatment (placebo), at which time her average supine blood pressure was 171/105. On day 12 of double-blind treatment, the patient reported that she awoke with a severe

headache and could not stand without losing her balance. She reported that she took her blood pressure at home and it was 178/130. At this time, patient took herself off trial drug and resumed her nifedipine and reported that her symptoms completely resolved. At the onset of these symptoms, the patient had been off active anti-hypertension medication for a total of 41 days. Three days after the patient resumed taking nifedipine, she reported to the clinic and her average supine blood pressure was 177/101. The patient was discontinued from the trial.

Table 10.7. Patients discontinued due to adverse events

Treatment Group	Investigator	Patient	Sex	Age	Day*	Medical Problem
Placebo	Norton	008/507	F	59	12	Headache & Equilibrium Dysfunction
Valsartan 40 mg	Pool	031/526	M	47	12	Gouty Arthritis

* Onset Day During Double-Blind Period

None of the valsartan patients experienced symptomatic orthostatic changes in blood pressure.

There were no significant changes in the mean values for laboratory parameters from baseline to the terminal visit. There was no significant difference in the number of outliers between valsartan treatment groups and placebo.

Pharmacokinetics

Average plasma valsartan concentrations and the net effect at 0 hour (pre-dose), 2, 4, and 6 hours following 10 mg, 40 mg, 80 mg and 160 mg doses on Days 1, 14, and 28 are presented in the table 10.8.

Table 10.8. Valsartan concentrations pre-dose, 2, 4 and 6 hours post-dosing.

		Concentration (ng/ml)			
Dose (mg)	Day	Pre-dose	2 hr	4 hr	6 hr
10	1	0	440	269	172
	14	0	351	271	180
	28	0	393	296	199
40	1	0	930	802	463
	14	80	969	709	412
	28	75	950	778	452
80	1	0	1334	1258	809
	14	156	1395	1382	907
	28	148	1488	1358	862
160	1	0	1683	1755	1009
	14	215	1831	1995	1140
	28	213	2222	2168	1378

Protocol 11. A Double-Blind, Randomized, Placebo-Controlled, Fixed-Dose, Parallel Design Trial Of 10 Weeks Duration In Caucasian Patients With Mild To Moderate Hypertension Followed By An Open-Label Extension Of 98 Weeks Duration.
(January 28, 1993 - September 9, 1993)

Protocol

Design

This is a randomized, double-blind, placebo controlled, multi-center, parallel dose trial in Caucasian patients with essential hypertension. There was a four week placebo run-in period (visits 1 - 5) followed by a 6 week double-blind treatment (visits 6 - 8) period and a optional 98 week open label period (visit 9 - 21). Patients completing the placebo run-in period were required to have a mean siDBP ≥ 95 and ≤ 115 mmHg at visits 4 and 5 in order to be randomized to one of four treatment group: placebo, valsartan 20 mg OD, valsartan 40 mg OD or valsartan 80 mg OD. Table 11.1 is a flowchart outlining the procedures performed during the study.

Table 11.1. Flowchart Of Procedures.

	Placebo Run-in Period		Double-Blind Treatment Period		
Visit (Trial Week)	(0)	(1, 2 and 3)	Randomization (4)	(6 and 8)	(10)
Complete History and Physical Examination	x				
Interim/Final Physical Examination		x	x	x	x
Blood Pressure and Pulse Rate [a]	x	x	x	x	x
12-Lead ECG	x				x
Chest X-ray [b]	x				
Safety Laboratory Tests [c]	x		x		x
Adverse Experiences		x	x	x	x
Concomitant Medications	x	x	x	x	x
Dispense Trial Medication	x	x	x	x	x [d]
Collect Unused Trial Medication		x	x	x	x
Termination Sheet					x [e]

[a] Blood pressure measurement took place between 7:00 AM and 10:00 AM (i.e., 23 to 26 hours after the last dose of trial medication).
[b] Within one year prior to Visit 1.
[c] Blood was drawn and urine obtained following a 12-hour fast (hematology, blood chemistry, and urinalysis).
[d] One bottle of open-label trial medication.
[e] Visit 8 or sooner if patient terminated early from the double-blind treatment period.

The primary endpoint is the change in trough mean siDBP from baseline at six weeks. The last post-baseline blood pressure measurement during the double-blind period is the endpoint measurement. Secondary endpoints included the change in trough mean siDBP from baseline at 2 and 4 weeks and the change in trough mean siSBP from baseline at 2, 4 and 6 weeks.

A sample size of 328 patients completing double-blind therapy was calculated based on the primary efficacy variable, mean sitting diastolic blood pressure, and the fact that Dunnett's multiple comparison technique will be used in the analysis of this variable. The primary null hypothesis being tested is that all doses of valsartan (20 mg, 40 mg, or 80 mg) are equal to placebo versus the alternative hypothesis that at least one dose is not equal to placebo. The treatment difference of 4 mmHg in mean sitting diastolic blood pressure was utilized as the minimum treatment difference to be detected to be statistically significant with 80% power at the two-sided overall significance level of 0.05, assuming a standard deviation of 8 mmHg.

Results - Efficacy

Disposition

Four hundred and forty-two patients were randomized at 22 centers. The number of patients randomized at each center ranged from 11 to 28. The number of patients randomized to each treatment group ranged from 106 to 113. Eighteen patients discontinued prematurely. Table 11.2 lists the patient disposition by treatment group.

Table 11.2. Patient Disposition

		valsartan			Total
	placebo	20 mg	40 mg	80 mg	
Randomized	111	106	113	112	442
Completed	105	102	107	110	424
Discontinued Prematurely	6	4	6	2	18

Table 11.3 lists the number and reasons patients discontinued from the study prematurely. Nine patients discontinued for adverse events or abnormal laboratory values.

Table 11.3. Patients Discontinuing Prematurely During the Double-Blind Treatment Period

Treatment Group	Total	Adverse Experience	Abnormal Lab	Unsatisfactory Therapeutic Response	Other
Placebo	6	1	1	1	3
Valsartan 20 mg	4	2	0	0	2
Valsartan 40 mg	6	4	0	1	1
Valsartan 80 mg	2	1	0	0	1
Total	18	8	1	2	7

Demographics

Of the 442 patients who were randomized to receive treatment, 312 (71%) were male and 130 (29%) were female. The patients ranged in age from 25 to 79 years (mean age = 55 years) and, with the exception of one patient (004/505/Chaudhery) who was Egyptian, **all patients were Caucasian.** No statistically significant differences were observed at baseline for sex, age, height, weight, significant past medical history and/or concomitant diagnosis, duration of hypertension, or anti-hypertensive medications taken within the previous three months.

Endpoints

Table 11.4 list the mean change in trough siDBP at endpoint and at visit 8. Only one valsartan 20 mg patient did not have a post-randomization measurement of siDBP. All treatments groups exhibited significant mean changes from baseline. All valsartan treatment groups were significantly different from placebo. The results for standing DBP change were similar to the results for siDBP.

Table 11.4. Summary of Mean Decreases in Trough Mean Sitting Diastolic Blood Pressure (mmHg)

	Endpoint			Visit 8		
	N	Mean Change from Baseline (S.D.)	P-value†	N	Mean Change from Baseline (S.D.)	P-value†
Placebo	111	-4.61 (7.05)		105	-4.68 (7.08)	
Valsartan 20 mg	105	-7.49 (7.03)	0.0021‡	102	-7.66 (6.98)	0.0014‡
Valsartan 40 mg	113	-8.48 (7.23)	0.0001‡	107	-8.83 (6.62)	0.0001‡
Valsartan 80 mg	112	-8.01 (6.76)	0.0006‡	110	-7.84 (6.69)	0.0019‡

‡ The adjusted p-value for Dunnett's multiple comparison procedure indicates a statistically significantly greater reduction in trough mean sitting diastolic blood pressure as compared to placebo (Based on least square mean change).

† P-Value is based on the t-test without adjustment for multiple comparisons

A subgroup analysis as a function of race is not feasible (only Caucasians enrolled). Analysis based on sex and age are shown in table 11.5a and 11.5b. Both female and patients greater than 65 years of age had minimal treatment effect for all doses of valsartan compared to placebo.

Table 11.5a . Mean Change from Baseline in Mean Sitting Diastolic Blood Pressure (mmHg) at Endpoint by Age

	Age <65† years		Age ≥65† years	
	Endpoint Mean	Mean Change from Baseline	Endpoint Mean	Mean Change from Baseline
Placebo	97.52	-3.74	90.59	-7.21
Valsartan 20 mg	92.96	-7.60	91.21	-6.94
Valsartan 40 mg	92.07	-8.44	91.29	-8.68
Valsartan 80 mg	91.62	-8.70	94.29	-5.96

† At Endpoint, the number of patients in each treatment group ranged from 83 to 94 for patients aged <65 years and from 17 to 28 for patients aged ≥65 years.

Table 11.5b. Mean Change from Baseline in Mean Sitting Diastolic Blood Pressure (mmHg) at Endpoint by Sex

	Male		Female	
	Endpoint Mean	Mean Change from Baseline	Endpoint Mean	Mean Change from Baseline
Placebo	96.46	-3.66	94.47	-6.52
Valsartan 20 mg	93.24	-7.20	91.29	-8.21
Valsartan 40 mg	91.68	-8.90	92.48	-7.61
Valsartan 80 mg	92.45	-7.88	91.75	-8.46

The number of patients in each treatment group ranged from 74 to 86 for males and from 26 to 37 for females.

Table 11.6 lists the mean change from baseline for siSBP. All valsartan groups had a significant change from baseline compared to placebo.

Table 11.6. Summary of Mean Decreases in Trough Mean Sitting Systolic Blood Pressure (mmHg)

	Endpoint			Visit 8		
	N	Mean Change from Baseline (S.D.)	P-value	N	Mean Change from Baseline (S.D.)	P-value
Placebo	111	-0.59 (12.39)		105	-1.09 (12.30)	
Valsartan 20 mg	105	-7.36 (13.34)	0.0001‡	102	-7.45 (13.49)	0.0001‡
Valsartan 40 mg	113	-8.83 (12.71)	0.0001‡	107	-9.48 (11.58)	0.0001‡
Valsartan 80 mg	112	-10.49 (13.47)	0.0001‡	110	-10.05 (13.07)	0.0001‡

† P-Value is based on the t-test without adjustment for multiple comparisons.
‡ The adjusted p-value for Dunnett's multiple comparison procedure indicates a statistically significantly greater reduction in trough mean sitting systolic blood pressure as compared to placebo. (Based on least square mean change).

There was no significant difference in the mean change in pulse between treatments. The percent of responders (siDBP ≤ 90 mmHg or ≥ 10 mmHg decrease compared to baseline) ranged from 41% to 50 % in the valsartan groups compared to 29% in the placebo group.

Figure 11.1 plots the mean change in siDBP from baseline for each treatment group by visit.

Figure 11.1. Mean Trough siDBP By Visit. [volume 1.81, p. 509]

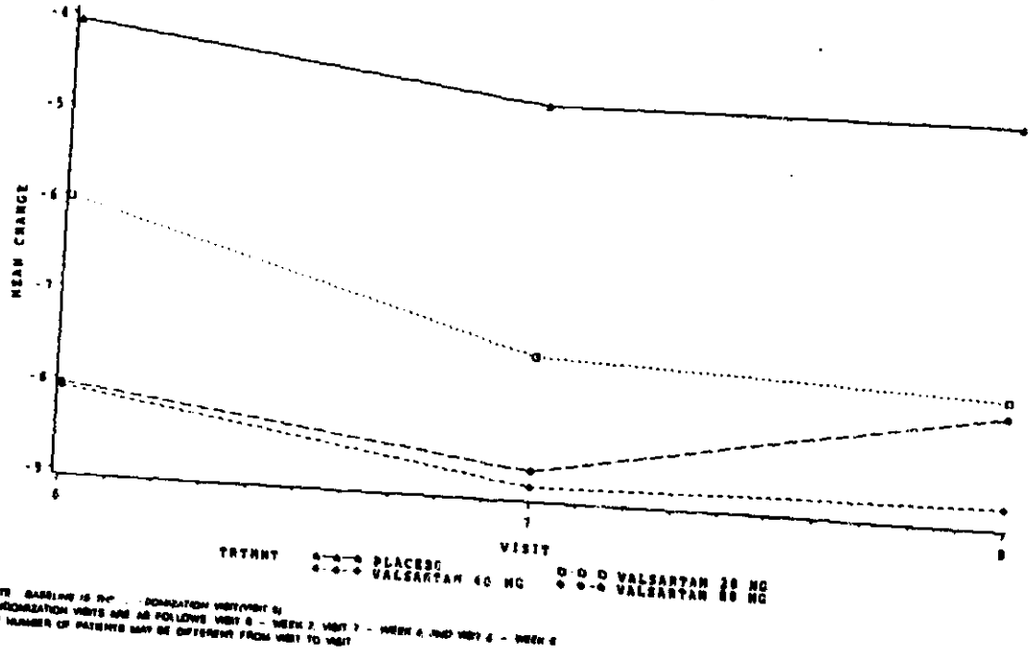
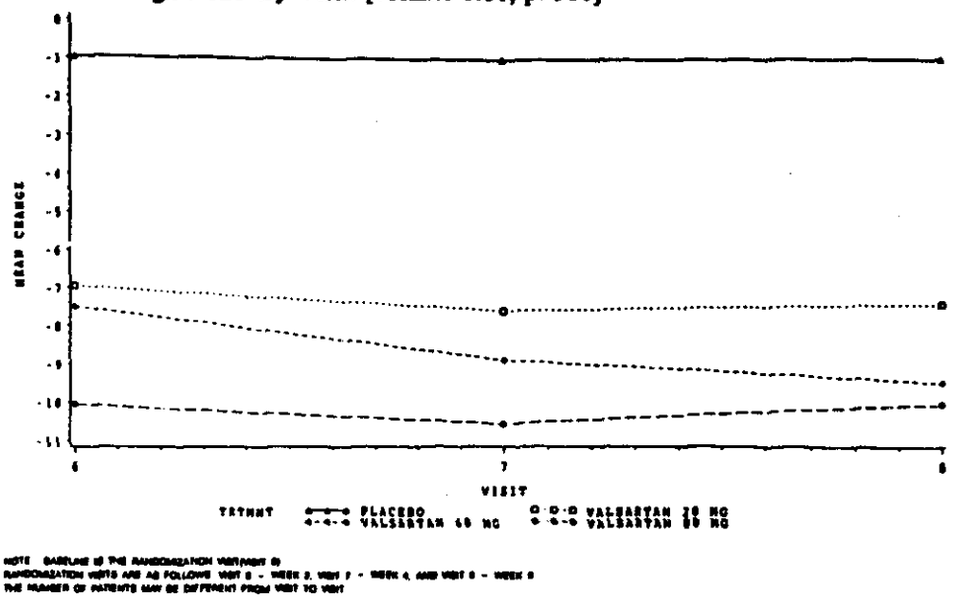


Figure 11.2 plots the mean change in siSBP from baseline for each treatment group by visit.

Figure 11.2. Mean Trough siSBP By Visit. [volume 1.81, p. 511]



Safety

Deaths

There were no deaths during the study.

Patients Discontinued for Adverse Events

Table 11.7 list nine patients who discontinued prematurely from the study for adverse events or abnormal laboratory values.

Table 11.7. Patients With Serious Adverse Experience and/or Who Discontinued Prematurely Due to an Adverse Experience or Laboratory Abnormality

Treatment	Investigator	Patient #	Sex	Age	[illegible]	Medical Problem
Placebo	Lasseter	015/512	F	56	[illegible]	Poor glucose control
	Wombolt	001/503	F	51	[illegible]	[illegible]vated blood pressure, lightheaded, difficulty breathing, hot flashes, ringing in right ear, and pain in back of head; orthostatic hypotension
Valsartan 20 mg	Gray	027/526	F	61	6*	[illegible]ctive cholecystectomy
	Oparil	031/524	M	61	[illegible]	[illegible]est tightness not accompanied by shortness of breath, nausea, or diaphoresis
Valsartan 40 mg	Ansari	008/508	M	77	6	Hospitalization due to spondylolisthesis and a compression fracture
	Ellison	023/520	F	62	6	Spontaneous detached retina of the right eye
	Kraus	009/504	F	38	7	Hospitalization due to hepatomegaly and secondarily to congestive heart failure
	Oparil	030/526	M	29	6	Depression
	Sugimoto	013/507	M	61	6*	Dizzy/lightheaded and elevated blood pressure throughout the trial

* Experience began during the placebo run-in period and continued into the double-blind treatment period.

Patient 009/504 (valsartan 40 mg) was a 38 year old female who was admitted to the hospital for evaluation of hepatomegaly and elevated liver enzymes on day 32 of double-blind treatment. The patient had been seen in the emergency room one week earlier with complaints of acute abdominal pain. Lab work and an x-ray of the kidney, urethra, and abdomen were performed. The diagnosis was to rule out hepatitis. She was treated with butorphanol tartrate and ranitidine hydrochloride and was discharged home with instructions to follow up with her physician. Of note, the patient had entered the active treatment phase of

the trial on 5/25/93 (Visit 5). Liver function tests performed at this visit and 4 weeks earlier at Visit 1 were normal. Because of little improvement in her condition, the patient returned to the hospital where she was hospitalized for evaluation of hepatomegaly and elevated liver enzymes. Trial medication had been discontinued 3 days prior to hospitalization. At the time, the relationship to study medication was not known. While in the hospital, the patient was being cared for by another physician. However, a follow-up report received by Dr. Kraus one week later indicated that the patient had been diagnosed with congestive heart failure. An echocardiogram performed in the hospital revealed an ejection fraction of 30%. Of interest was the fact that a baseline chest x-ray performed prior to trial entry revealed borderline cardiomegaly with mild increased lung markings. The patient was treated with diuretics and digoxin with some improvement in her condition. The investigator considered the hepatomegaly to be due to congestive heart failure. Cardiac catheterization results indicated a final diagnosis of idiopathic dilated cardiomyopathy.

Clinical Adverse Events

Table 11.8 list the most commonly reported adverse events in the study. The overall incidence of adverse experiences was similar in all treatment groups. Headache was the most common complaint for all groups.

Table 11.8. Incidence of Most Frequently Reported (≥3% of Patients) Adverse Experiences Whether or Not Related to Treatment [N (%)]

		Valsartan		
Total Patients	Placebo N=111	20 mg N=105	40 mg N=113	80 mg N=112
Total Patients with an Adverse Experience	49 (44.1%)	39 (36.8%)	45 (39.8%)	41 (36.6%)
Headache	21 (18.9%)	17 (16.0%)	11 (9.7%)	7 (6.3%)
Dizziness	3 (2.7%)	5 (4.7%)	3 (2.7%)	2 (1.8%)
Rhinitis	2 (1.8%)	3 (2.8%)	2 (1.8%)	4 (3.6%)
Sinusitis	1 (0.9%)	2 (1.9%)	4 (3.5%)	3 (2.7%)
Diarrhea	3 (2.7%)	4 (3.8%)	0 (0.0%)	2 (1.8%)
Constipation	1 (0.9%)	0 (0.0%)	4 (3.5%)	0 (0.0%)

Patient 523 (Center M7871T; Placebo) developed swelling under the right ear which extended to the throat during visit 5.

Laboratory Results

There was no difference between treatment groups for the mean change in laboratory parameters from baseline to the terminal visit.

Outliers were evaluated by looking at the number of patients who had terminal visit lab values outside of the normal range and at the number of patients who exceeded a specified percentage increase or decrease above baseline. There were no outliers identified with clinically relevant changes.

Protocol 17. Double-Blind, Randomized, Placebo-Controlled, Parallel Design Trial Of Twelve To Fourteen Weeks Duration To Determine The Effect Of Food On The Anti-hypertensive Response Of Valsartan 80 Mg In Patients With Mild To Moderate Essential Hypertension
(May 17, 1993 to January 26, 1994)

Protocol

This was a multi-center, double-blind, randomized, placebo-controlled, parallel design trial to determine the effect of food on the anti-hypertensive response of valsartan 80 mg in patients with mild to moderate hypertension. The trial consisted of a 2 - 4 week placebo run-in phase followed by 8 week double-blind treatment phase. Hypertensive patients with a mean sitting diastolic blood pressure ≥ 100 mmHg and ≤ 114 mmHg were randomized to valsartan 80 mg (fasted[5]), 80 mg (fed) or placebo in a ratio of 2:2:1. Table 17.1 lists the procedures performed during the study.

[5] 10 hours since last meal and 2 hours before next meal

Table 17.1. Schedule of Procedures

Visit (Trial Week)	Single-Blind Placebo Run-in (0)	(2)	Double-Blind Treatment (4)	(6, 8, and 10)	(12)
Complete History and Physical Examination	x				
Interim/Final Physical Examination		x	x	x	x
Blood Pressure and Pulse Rate[c,g]	x	x	x	x	x
Randomization		x[a]	x		
12-Lead ECG	x				x
Chest X-ray[d]	x				
Safety Laboratory Tests[e]	x	x[a]	x		x
Valsartan Levels		x[a]	x	x[f]	x
Adverse Experiences		x	x	x	x
Concomitant Medications	x	x	x	x	x
Dispense Trial Medication	x	x	x	x	
Termination Sheet					x

[a] If patient satisfied the criteria for randomization at Visit 2, the indicated Visit 3 procedures were performed and the Visit 3 CRFs were completed.
[b] Trial termination information was completed at the last visit or whenever a patient terminated prematurely.
[c] Blood pressure measurement took place before 9:00 AM (i.e., 24 to 26 hours after the previous day's fasted dose). Blood pressure measurements were also obtained prior to breakfast.
[d] Within one year prior to Visit 1.
[e] Blood was drawn and urine obtained following a 10-hour fast (hematology, blood chemistry, and urinalysis).
[f] Valsartan levels were determined at Visit 5 only.
[g] Patients sit for 5 minutes prior to blood pressure measurement; standing blood pressures were obtained after 2 minutes of standing

The primary measure of efficacy is the change in trough mean sitting diastolic blood pressure (24 to 26 hours after dosing) from baseline sitting diastolic blood pressure at week 8. Secondary measures of efficacy included: change in trough mean sitting diastolic blood pressure (24 to 26 hours after dosing) after 2, 4, and 6 weeks of dosing, change in trough mean sitting systolic blood pressure (24 to 26 hours after dosing) after 2, 4, 6 and 8 weeks of dosing and comparison of trough plasma levels of valsartan in the fed and fasted groups at 4 and 8 weeks of dosing.

The sample size was estimated based on detecting a 3 mmHg difference with 80% power at the two-sided significance level of 0.05 (does not take multiple comparison into account), assuming a standard deviation of 8 mmHg. A sample size of 280 was calculated with a 2:2:1 (valsartan fed, valsartan fasted, placebo) randomization distribution.

Results - Efficacy

The study was conducted at eighteen centers in the USA. . hundred and ninety-seven patients were randomized. Forty-one patients discontinued prematurely leaving 256 patients completing the study. Table 17.2 outlines the patient disposition in the study.

Table 17.2 Patient Disposition

	Placebo	Valsartan (fasted)	Valsartan (fed)	Total
Randomized	59	120	118	297
Completed	47	107	102	256
Premature Discontinuation	12	13	16	41
Reason Discontinued				
Did not meet protocol criteria	1	0	0	1
Withdrew Consent	2	4	0	6
Non-compliant	1	0	0	1
Improper Dosing	1	1	5	7
Study site discontinued †	0	1	0	1
Lost to follow up	0	0	2	2
Adverse experience	4	4	5	13
Abnormal Lab	1	0	1	2
Poor therapeutic response	2	1	2	5
Protocol Violation	0	1	1	2
Unable to keep appointment.	0	1	0	1

† participation of Dr. Joseph Liotti, the principal investigator for Future Healthcare Research Center in West Orange, New Jersey was terminated because of serious deficiencies uncovered during an audit of the study site

Of the 297 patients who were randomized to receive treatment, 179 (60%) were male and 118 (40%) were female. Patients ranged in age from 22 to 75 years (mean age = 54 years). Seventy-nine percent of the patients were white.

Table 17.3. Frequency Distribution of Sex and Race N (%)

Treatment Group	# of Patients	Sex		Race		
		Male	Female	White	Black	Other †
Placebo	59	34 (58)	25 (42)	47 (80)	12 (20)	0 (0)
Valsartan 80 mg, fasted	120	73 (61)	47 (39)	95 (79)	20 (17)	5 (4)
Valsartan 80 mg, fed	118	72 (61)	46 (39)	93 (79)	25 (21)	0 (0)
Total	297	179 (60)	118 (40)	235 (79)	57 (19)	5 (2)

† Other category includes three Hispanic patients, one Asian patient, and one Indian patient.

All treatments showed a significant change from baseline in sitting diastolic blood pressure at endpoint. Table 17.4 lists the mean change in sitting diastolic blood pressure at endpoint and visit 7. Both valsartan treatment groups were significantly different from placebo (not corrected for multiple comparison). The valsartan groups were not significantly different from each other (p = .082) though the fed group decrease was 1.68 mmHg less than the fasted group at endpoint .

Table 17.4. Summary of Mean Decreases in Trough Mean Sitting Diastolic Blood Pressure (mmHg)

	Endpoint		Visit 7	
	N	Mean Change from Baseline (S.D.)	N	Mean Change from Baseline (S.D.)
Placebo	57	-3.6 (7.54)	48	-4.03 (7.51)
Valsartan 80 mg, fasted	119	-8.55 (7.62)*	108	-8.88 (7.76)
Valsartan 80 mg, fed	109	-6.87 (7.92)**	102	-7.23 (7.40)

* p = .001, fasted vs. placebo; p = 0.046, fed vs. placebo; based on the least squares mean and between-treatment comparison of change from baseline (prefasted measurement at Visit 3) derived from the two-way analysis of covariance.

Table 17.5 list the mean changes in sitting systolic blood pressure from baseline at endpoint. Both valsartan treatments were significantly different from placebo. The valsartan groups were not significantly different from each other.

Table 17.5. Summary of Mean Decreases in Trough Mean Sitting Systolic Blood Pressure (mmHg)

	Endpoint		Visit 7	
	N	Mean Change from Baseline (S.D.)	N	Mean Change from Baseline (S.D.)
Placebo	57	- 0.48 (12.48)	48	-0.08 (12.14)
Valsartan 80 mg, fasted	119	- 7.34 (13.95)	108	- 8.4 (13.84)
Valsartan 80 mg, fed	109	- 6.05 (15.22)	102	-5.65 (15.33)

The number of responder (a successful response was defined as a mean sitting diastolic blood pressure <90 mmHg or a ≥10 mmHg decrease compared to baseline) at endpoint was 26.3%, 43.7% and 36.7% in the placebo, fasted and fed groups respectively.

Subgroup analysis based on race are provided in table 17.6. The treatment effect of valsartan in white patients is similar to that observed in black patients.

Table 17.6. Mean Change from Baseline in Trough Mean Sitting Diastolic Blood Pressure (mmHg) at Endpoint by Race [Results confirmed from electronic data submission]

	Black		Other		White	
	N	Mean Change	N	Mean Change	N	Mean Change
Placebo	12	-2.03	0		47	-3.98
Valsartan 80 mg, fasted	20	-6.13	5	-10.93	95	-8.94
Valsartan 80 mg, fed	25	-6.53	0	–	93	-6.96

There were three Hispanic patients, one Indian patient, and one Asian patient.

Results - Safety

No deaths occurred during the trial. Fifteen patients were discontinued prematurely from the trial due to adverse events or abnormal laboratory values. Table 17.7 lists these patients and the reason for discontinuation.

Table 17.7. Patients Who Discontinued Prematurely Due to an Adverse Experience or Laboratory Abnormality

Treatment	Center	Patient #	Sex/Age	Visit	Medical Problem
Placebo	Coalson	201/516	M/58	6	Unstable angina
	Denker	182/681	M/60	4	Headaches *
	Smucker	365/609	F/65	6	Headache, malaise, myalgia, dizziness, lightheadedness
	Smucker	412/864	M/52	4	Elevated serum glucose *
	Strauss	320/679	F/65	6	Tingling and grabbing in right arm and right leg
Valsartan 80 mg fasted	Bath	212/712	F/61	6	Weakness, dizziness, blurry vision
	Intile	164/667	M/71	6	Headache, diaphoresis, weakness
	Smucker	110/610	M/66	7	Transient ischemic attack
	Sugimoto	121/621	M/64	5	Extreme weakness, generalized joint pain

Table 17.7. (con't) Patients Who Discontinued Prematurely Due to an Adverse Experience or Laboratory Abnormality

Treatment	Center	Patient #	Sex/Age	Visit	Medical Problem
Valsartan 80 mg fed	Gaman	222/698	F/68	4	Peripheral edema, uncontrolled hypertension, headache
	Intile	078/670	F/67	4	Right chronic dacryocystitis, right dacryocystorhinostomy with silicone intubation, right nasolacrimal duct obstruction
	O'Reilly	097/600	M/75	6	Arthritis, pain in both knees
	Serfer	422/850	M/58	5	Impotence, funny feeling in head
	Smucker	368/608	M/32	4	Lightheadedness, chest pressure
	Sugimoto	260/758	M/51	4	Elevated serum glucose

* Experience began during the placebo run-in period and continued into the double-blind treatment period

On Trial Day 41 of double-blind treatment, patient 212/712/Bath (valsartan 80 mg fasted) was seen in the emergency room with complaints of mild vertigo, a staggering gait, and nausea. She was evaluated by the hospital emergency room and released. The investigator did not take any action and noted that all three adverse experiences were possibly related to trial medication. The patient recovered the same day. One day later (Trial Day 42), the patient reported moderate dizziness and blurred vision. Again, the investigator considered these adverse experiences to be possibly related to treatment and did not take any action. Subsequently on Trial Day 42, the patient complained of severe weakness, dizziness, and blurry vision. The investigator considered these adverse experiences to be possibly related to trial medication and discontinued the patient from the trial. At the time of discontinuation, the patient's sitting blood pressure was 132/90 mmHg; the patient's screening blood pressure was 150/100 mmHg. The investigator began treatment with hydroxyzine pamoate and noted that the adverse experiences abated the same day. Two days following discontinuation of treatment, the patient again reported mild weakness, dizziness, and blurred vision. No action was taken by the investigator and the patient recovered.

On Trial Day 33 of double-blind treatment, patient 164/667/Intile (Valsartan 80 mg, fasted) complained of mild headache, diaphoresis, and weakness. The investigator considered these adverse experiences to be possibly related to trial medication and three days later prematurely discontinued the patient from the trial. At discontinuation, the patient's sitting blood pressure was 181/98 mmHg; the screening visit value was 150/100 mmHg. The investigator initiated treatment with felodipine and noted that the patient recovered four days later. No significant past medical history was reported by the patient.

Patient 110/610/Smucker (Valsartan 80 mg, fasted) had a history of ST-T wave changes prior to entering the trial and the ECG at Visit 1 showed possible old interior wall M.I. and nonspecific ST-T wave changes. On Trial Day 49 of double-blind treatment, the patient experienced a transient ischemic attack. The patient stated that after working out on a stationary bicycle at a health club, he became confused and experienced short-term memory loss. He contacted his trainer who summoned an ambulance. An ECG showed some changes (not specified) and his blood pressure was noted to be 180/130 mmHg. The patient was transported to the emergency room via an ambulance. The patient stated that while en route he was given a nitroglycerin patch. Upon arrival at the emergency room, the patient underwent additional work-up including an ECG, blood work, chest x-ray, and CAT scan. The patient stated that all tests were within normal limits. Approximately three hours after arrival in the emergency room, the patient's blood pressure was 130/80 mmHg. The patient was discharged with no restriction of activities and told to follow-up with a neurologist the next day. The diagnosis was a transient ischemic attack. As a result of this adverse experience, the patient was discontinued from the trial. Two days later at the discharge visit, the patient's blood pressure was 150/108 mmHg, the ECG showed nonspecific ST-T wave changes, and hematology and blood chemistry parameters were normal with the exception of an elevated cholesterol (234 mg/dL). Chest x-ray showed plate-like atelectatic changes possibly fibrosis in the bilateral lower lung fields; otherwise, no infiltrates were identified. There was poor inspiration on both views of the chest; however, this was also present in the baseline chest x-ray and was considered not clinically significant. The patient was instructed to resume his regular medications with atenolol and terazosin HCl and to follow-up with his primary care physician and neurologist.

On Trial Day 1 of double-blind treatment, patient 121/621/Sugimoto (Valsartan 80 mg, fasted) complained of mild generalized fatigue and increased sleep. The investigator considered these experiences to be possibly related to trial medication; however, at this time he did not initiate any treatment. The generalized fatigue continued for 14 days at which time the patient recovered. The next day (Trial Day 15),

the patient reported extreme weakness and generalized joint pain. Both experiences were considered to be of moderate intensity and possibly related to trial medication by the investigator. The patient was prematurely discontinued from the trial and recovered 27 days la[illegible] The patient had a current medical history of arrhythmia, bilateral mild to moderate leg pain, and s[illegible]ss of breath with exercise. In addition, the patient was receiving acetaminophen 1000 mg as ne[illegible] to relieve muscle pain in the legs since the beginning of the placebo run-in period.

Four days prior to beginning double-blind treatment, patient 222/698/Gaman (Valsartan 80 mg, fed) experienced moderate generalized edema which was considered not related to treatment by the investigator. At the time, no action was taken and the adverse experience continued. Following the start of double-blind treatment (no onset time was recorded), the patient experienced peripheral edema. On Trial Day 2, the patient reported headache. This was followed by uncontrolled hypertension (241/137 mmHg) on Trial Day 5. The investigator noted that for all three of these adverse experiences, trial medication was prematurely discontinued and the events were ongoing at the time of discontinuation. Each of these events were considered to be of moderate intensity and related to trial medication. The patient was taking a diuretic (furosemide) for pedal edema prophylaxis and hypertension prior to the start of the trial. She had a history of right nephrectomy (donation) and obesity.

On Trial Day 9 of double-blind treatment, the patient 422/850/Serfer (Valsartan 80 mg, fed) experienced mild impotence which the investigator considered probably related to treatment. No action was taken and the event was noted to be ongoing. On Trial Day 21, the patient again reported impotence. In addition, the patient reported a "funny feeling" in the head. Both adverse experiences were considered to be of mild intensity by the investigator; the impotence was considered to have a highly probable relationship to trial medication and the "funny feeling" in the head was considered probably related to trial medication. The patient was prematurely discontinued from the trial and the adverse experiences were noted to be ongoing. No significant past medical history was reported by the patient, nor did the patient take any concomitant medications during the trial.

On Trial Day 4 of double-blind treatment, patient 368/608/Smucker (Valsartan 80 mg, fed) complained of moderate lightheadedness and chest pressure. The patient's standing blood pressure was 122/86 mmHg at this time. Both adverse experiences were considered probably related to trial medication and the patient was prematurely discontinued from the trial. The investigator began treatment with acetylsalicylic acid and noted that the patient recovered the same day. No significant past medical history was reported by the patient.

A similar proportion of patients in each of the three treatment groups reported adverse experiences: 25 (42.4%) placebo patients, 57 (47.5%) valsartan 80 mg fasted patients, and 51 (43.2%) valsartan 80 mg fed patients. Table 17.8 list the incidence of adverse events occurring in ≥ 3% of the patients randomized. The most frequently reported adverse event was headache in all treatment groups.

Table 17.8. Incidence of Most Frequently Reported (≥3% of Patients) Adverse Experiences Whether or Not Related to Treatment[N (%)]

		Valsartan 80 mg	
Total Patients	Placebo N=59	Fasted N=120	Fed N=118
Total Patients with an Adverse Experience	25 (42.4)	57 (47.5)	51 (43.2)
Headache	9 (15.3)	15 (12.5)	18 (15.3)
Nausea	1 (1.7)	9 (7.5)	1 (0.8)
Fatigue	0 (0.0)	6 (5.0)	1 (0.8)
Peripheral edema	0 (0.0)	3 (2.5)	4 (3.4)
Dizziness	1 (1.7)	3 (2.5)	4 (3.4)
Rhinitis	4 (6.8)	3 (2.5)	4 (3.4)
Viral infection	2 (3.4)	4 (3.3)	2 (1.7)
Sinusitis	0 (0.0)	4 (3.3)	2 (1.7)
Upper respiratory tract infection	1 (1.7)	4 (3.3)	1 (0.8)
Musculoskeletal pain	0 (0.0)	0 (0.0)	4 (3.4)
Dependent edema	0 (0.0)	4 (3.3)	0 (0.0)
Dyspepsia	3 (5.1)	1 (0.8)	0 (0.0)
Hypertonia	2 (3.4)	1 (0.8)	0 (0.0)

There were no significant changes in mean laboratory parameters. There were no clinically relevant laboratory abnormalities except for two patients. Patient 077/580/Intile (Valsartan 80 mg, fed) had a baseline BUN of 11 mg/dl and a terminal visit BUN of 41 mg/dl (Normal range: 7.0 to 25.0 mg/dL). Serum creatinine increased from 1.0 mg/dl to 1.3 mg/dl. Serum potassium increased from 4.7 mEq/L to 5.6 mEq/L. Patient 029/529/Denker (Valsartan 80 mg, fasted) had a baseline potassium of 4.8 mEq/L and a visit 7 potassium of 6.6 mEq/L. A repeat potassium at visit 7 was 4.8 mEq/L.

Pharmacokinetics

Table 17.9 summarizes the mean steady-state trough concentrations (ng/ml) of valsartan on Trial Days 28 (Visit 5) and 56 (Visit 7) following 80 mg once-a-day dosing under fed and fasted conditions in hypertensive patients.

Table 17.9. Trough valsartan concentration at visit 5 and 7.

Trial Day/Visit	Fed (N=91)		Fasted (N=87)	
	Mean (ng/ml)	S.D.	Mean (ng/ml)	S.D.
28/5	152	263	111	266
56/7	113	182	129	347

Based on the half-life (six hours) of valsartan, the trough concentrations on Trial Days 28 and 56 were considered steady-state. Steady state plasma trough levels were less than the quantifiable limit (<50 ng/mL) in approximately 25% of fed patients and in 40% of fasted patients. The difference in the trough concentrations are not different at visit 7. It is difficult to interpret these results since the Cmax and AUC are not provided.

It is interesting that the trough valsartan concentrations are similar in the fasted and fed treatment groups. Numerically (not statistically), the change in siDBP is greater in the fasted group compared to the fed group by 1.5 - 2 mmHg.

Protocol 23. Multinational, Randomized, Double Blind, Placebo And Active Controlled Trial Comparing The Efficacy And Tolerability Of Valsartan 160 Mg, Valsartan 80 Mg, Valsartan 40 Mg To Placebo And Lisinopril 10 Mg All Given Once Daily In Elderly Patients With Essential Arterial Hypertension (March 2, 1994 - March 16, 1995)

This is a multinational (France, Germany, Spain), randomized, double-blind, parallel group, placebo and active controlled trial to compare the efficacy and the tolerability of valsartan 160 mg, valsartan 80 mg, valsartan 40 mg to placebo and lisinopril 10 mg once daily for 8 weeks in elderly patients with essential arterial hypertension.

The trial included a one week wash-out period and a two-week placebo run-in period. Only patients 65 years and over, with a mean sitting diastolic blood pressure (siDBP) ≥ 95 mm Hg and ≤ 115 mm Hg were randomized to receive either valsartan 160 mg, valsartan 80 mg, valsartan 40 mg, placebo or lisinopril 10 mg (ratio 2:2:2:2:1) once daily for 8 weeks. Table 23.1 lists the procedures performed during the trial.

Table 23.1 Procedures

Procedure	Phase	Wash-out	Run-in	Trial Treatment Period		
	Day	-21	-14	0*	28	56
	Visit	1	2	3	4	5 or final
informed consent, personal data, physical exam, medical history, concomitant disease,. previous/current medication/non-drug therapy		x				
12-Lead ECG			x			
Check of inclusion and exclusion criteria		x	x	x		
Weight		x	x	x	x	x
Pulse rate, blood pressure **			x	x	x	x

Table 23.1 (con't) Procedures

Procedure	Phase	Wash-out	Run-in	Trial Treatment Period		
	Day	-21	-14	0*	28	56
	Visit	1	2	3	4	5 or final[1]
Adverse experiences, concomitant medication/non-drug therapy			x	x	x	x
Laboratory examinations[2] (hematology, blood chemistry, urine)				x		x

* randomization; ** two measurements were obtained in the sitting position after 5 minutes resting followed by one measurement in the standing position after at least 2 minutes of equilibration. All measurements should be to the nearest 2 mm Hg.

[1] or in the event of premature discontinuation

[2] Measurement of total creatine kinase activity were to be performed each time a patient complained of neck pain, back pain, myalgia or any other symptoms which could be related to myolysis. If the total creatine kinase activity increased above the upper limit of the normal range, creatine kinase isoenzyme fractions were also to be determined.

There were two primary endpoints, the change from baseline in mean sitting diastolic blood pressure (siDBP) and the change from baseline in mean sitting systolic blood pressure (siSBP). Secondary variables included changes from baseline in sitting pulse, weight, standing diastolic blood pressure , standing systolic blood pressure and standing pulse.

A sample size of 693 patients was calculated based on detecting a difference of at least 3.0 mm Hg in mean sitting diastolic blood pressure between any dose of valsartan and placebo with a power of 80%. The estimate of the standard deviation of siDBP was 8 mmHg. There are three main comparisons, each dose of valsartan versus placebo. Dunnett's procedure was used in order to allow for multiple comparisons. Each level of valsartan was compared to placebo, the null hypothesis being that all doses are equal to placebo versus the alternative that at least one dose is not equal to placebo.

It should be noted that randomized treatment was given to patients at various times of day depending on the country the center was located. In France, patients ingested therapy at 7 p.m. and blood pressure measurements occurred between 5 pm. and 8 pm. In Spain and Germany, randomized therapy was ingested in the morning.

Results - Efficacy

The results of this trial should be viewed with caution due to many irregularities that have been identified by the sponsor. These irregularities included:

- A total of 69 randomized patients were found to have major protocol violations as defined in the protocol resulting in their removal from one or more time points (i.e. either Visit 4 or Visit 5 or both) in the acceptable patient analysis.

Table 23.2. Protocol Violations by Treatment Group

Treatment	valsartan			placebo	lisinopril	total
Dose	160 mg	80 mg	40 mg		10 mg	
Number of Patients	N=144	N=142	N=148	N=144	N=74	N=652
Reason						
At randomization visit siDBP ≤ 95 mmHg	6	4	8	7	3	28
Time between last capsule taken and time of blood pressure measurements < 12 or > 30 hours	4	9	5	4	2	24
Use of any other anti-hypertensive medication during the trial	1	1	2	1	0	5
Interval between post-randomization visits > 36 days	4	4	2	3	0	13
Total	15	18	17	15	5	70

• In Center 1 in Spain a serious deviation from GCP was discovered for patients being treated by one of the investigators. It became obvious that 16 patients had not received any trial medication at all. The remaining 5 patients were under the care of another investigator and for these patients no irregularities were reported.
• It was also suspected that for Center 6 in Germany there had been some irregularities and inconsistencies with the reporting of the patients. Therefore it was decided that the 9 patients (5019 to 5027) should be excluded from the intention-to-treat analysis, and therefore the acceptable patient analysis, for efficacy but that a supplementary analysis should be carried out on the primary variables.
• In a number of centers the patients were not randomized in the correct order by being assigned to the lowest available randomization number for that center as described in the protocol. The centers involved in this were Centers 2, 3, 4, 5, 7, and 8 in France, Centers 9, 19, 20 and 22 in Germany and Center 2, 4, 5, 8, 12, 13, 14, 16, 17 and 18 in Spain.
• In France the trial treatments were stored by the main investigators. Therefore although some patients were randomized at Visit 3 they continued to take placebo for a few days until the randomized trial treatment was made available in the center.

Six hundred and fifty-two patients were randomized (305 patients were randomized in France, 108 in Germany and 239 in Spain). Table 23.3 lists the number of patients randomized to each treatment group.

Table 23.3. Patient Disposition

Number of Patients	placebo	valsartan 40 mg	valsartan 80 mg	valsartan 160 mg	lisinopril 10 mg	total
Enrolled *						730
Randomized *	144	148	142	144	74	652
Completed	136	135	131	134	68	604
Discontinued Prematurely	8	13	11	10	6	48
Reasons						
Adverse experience	3	4	6	2	1	16
Unsatisfactory therapeutic effect	0	3	1	1	0	5
Other	5	6	4	7	5	27
Abnormal laboratory values	1	0	0	1	0	2
Patient does not meet protocol criteria	2	5	2	2	3	14
Patient non-compliance	0	1	0	0	0	1
Patient withdrew consent	1	0	0	3	1	5
Lost to follow-up	1	0	1	1	1	4
Administrative problems	0	0	1	0	0	1

* the number of enrolled patients and the number of randomized patients include nine patients from German center 6 but exclude the 16 patients with irregularities from center 1 in Spain (5 patients under the supervision of another physician at the center were included)

Forty-eight patients were discontinued prematurely. The primary reason for discontinuation was adverse events. Table 23.4 lists the number of patients discontinued prematurely from each treatment group.

Table 23.4. Premature Discontinuation by Treatment Group

Treatment	placebo	valsartan			lisinopril	total
Dose		40 mg	80 mg	160 mg	10 mg	
Number of Patients	N=144	N=148	N=142	N=144	N=74	N=652
Reason						
Adverse experience	3	4	6	2	1	16
Abnormal laboratory values	1	0	0	1	0	2
Unsatisfactory therapeutic effect	0	3	1	1	0	5
Patient does not meet protocol criteria	2	5	2	2	3	14
Patient non-compliance	0	1	0	0	0	1
Patient withdrew consent	1	0	0	3	1	5
Lost to follow-up	1	0	1	1	1	4
Administrative problems	0	0	1	0	0	1

The group of 652 randomized patients included 224 males (34%) and 428 females (66%). Almost all of the patients (650) were Caucasian, with only 2 blacks. The patients ranged in age from 45 to 92 years with a mean of 72 years although the criterion gave the minimum age for inclusion as 65 years. Only 9 patients were less than 65 years of age. Table 23.5 list the demographic information for each treatment group.

Table 23.5. Demographic Information For Each Treatment Group At Baseline.

Treatment Group	N	Sex		Age (years)	siDBP	siSBP
		Male	Female			
placebo	144	50	94	71.6±6.0	100.8±4.5	171.8±14.8
valsartan 40 mg	148	46	102	72.0±6.0	100.5±4.6	174.7±15.5
valsartan 80 mg	142	49	93	71.9±6.1	101.1±4.8	173.4±15.2
valsartan 160 mg	144	55	89	72.6±6.4	101.7±4.9	172.5±14.4
lisinopril 10 mg	74	24	50	72.1±6.3	101.5±5.0	171.8±14.9
total	652	224	428			

The mean change in siDBP at endpoint for each treatment is listed in table 23.6.

Table 23.6. Change From Baseline In Mean Sitting Diastolic Blood Pressure At Endpoint * (mmHg) [All randomized patients]

	placebo	valsartan 40 mg	valsartan 80 mg	valsartan 160 mg	lisinopril 10 mg
Number of patients	141	145	139	139	73
Mean siDBP at baseline (Visit 3)	100.8	100.6	101.2	101.7	101.6
Mean siDBP at end point (Visit 5)	92.2	90.4	89.9	89.3	89.3
Mean change from baseline	- 8.6	- 10.2	- 11.2	- 12.4	- 12.4
Placebo Subtracted Change	-	- 1.6	- 2.6	- 3.8	- 3.8
Least squares mean **	-8.0	-9.6	-10.5	-11.6	-11.7

* The end point for the analysis is defined as Visit 5 with the last post-treatment measurement carried forward in the case of a premature discontinuation.; includes all 9 patients in Center 6 in Germany and excludes the 16 patients with irregularities in Center 1 in Spain;
** analysis excluding interaction terms

Based on an analysis of covariance model, none of the valsartan treatment group effects were significantly different from placebo ($p < .019$) required for significance based on adjustment for multiple comparison using Dunnett's procedure.

Table 23.7 list the mean change in siSBP at endpoint. There was a large decrease in siDBP in the placebo group.

Table 23.7. Change From Baseline In Mean Sitting Systolic Blood Pressure (mmHg) At Endpoint. (All randomized patients)

	placebo	valsartan 40 mg	valsartan 80 mg	valsartan 160 mg	lisinopril 10 mg
Number of patients	141	145	139	139	73
Mean siSBP at baseline (Visit 3)	171.6	174.9	173.5	172.7	172.1
Mean siSBP at end point (Visit 5)	162.4	160.4	159.8	157.0	155.7
Mean change from baseline	-9.2	-14.5	-13.7	-15.7	-16.4

The number of patients who had a decrease in siDBP to < 90 mmHg or ≥ 10 mm Hg change from baseline are listed in Table 23.8. Only the response rate for valsartan 160 mg and lisinopril were significantly different from placebo.

Table 23.8. Number Of Responders To Treatment At End Point (All randomized patients)

Responder N(%)	placebo	valsartan 40 mg	valsartan 80 mg	valsartan 160 mg	lisinopril 10 mg
Yes	68 (48)	86 (59)	83 (60)	94 (68)	45 (62)
No	73 (52)	59 (41)	56 (40)	45 (32)	27 (38)

Table 23.9 list the mean change in siDBP stratified by sex. Female patients had less of an effect than male patients with valsartan and lisinopril treatments. Similar results were observed for siSBP.

Table 23.9. Mean Change From Baseline In Sitting Diastolic And Systolic Blood Pressure By Sex

	Diastolic Blood Pressure (mmHg)			
Treatment Group	Males	Placebo Subtracted	Females	Placebo Subtracted
valsartan 160 mg	-12.7	- 5.8	-12.3	- 2.9
valsartan 80 mg	-10.2	- 3.3	-11.7	- 2.3
valsartan 40 mg	-10.2	- 3.3	-10.3	- .9
placebo	-6.9	-	-9.4	-
lisinopril 10 mg	-12.8	- 5.9	-12.2	- 2.8

Safety

There were no deaths in this trial.

Eighteen patients were discontinued prematurely from the trail due to adverse events or abnormal labs. Table 23.10 lists the patients discontinued prematurely and the reason for discontinuation.

Table 23.10. Premature discontinuations from the double-blind period of the trial due to adverse events or abnormal laboratory parameters

Patient #	Treatment	Country	Sex	Age	Visit	Medical problem
5122	valsartan 160 mg	Germany	M	85	4	Increased CK
7046	valsartan 160 mg	Spain	M	73	4	Headache/palpitations
6453	valsartan 160 mg	France	F	83	4	Orthostatic hypotension
7118	valsartan 80 mg	Spain	F	65	4	Hallucinations/headache/insomnia
6474	valsartan 80 mg	France	F	80	4	Nausea/abdominal pain
6385	valsartan 80 mg	France	F	69	5	Pyelonephritis *
6190	valsartan 80 mg	France	M	66	4	Headache/dizziness
6235	valsartan 80 mg	France	F	67	4	Abdominal pain
6282	valsartan 80 mg	France	F	70	4	Tinnitus, Headache
5195	valsartan 40 mg	Germany	F	81	4	Headache
6311	valsartan 40 mg	France	M	69	5	Disorientation, neurological changes *
6337	valsartan 40 mg	France	M	66	4	Abdominal pain

Table 23.10. Premature discontinuations from the double-blind period of the trial due to adverse events or abnormal laboratory parameters

Patient #	Treatment	Country	Sex	Age	Visit	Medical problem
6509	valsartan 40 mg	France	M	72	4	Fracture wrist
5118	placebo	Germany	M	64	4	Hypertensive crisis
7415	placebo	Spain	F	89	4	Hypertensive crisis/cerebral infarct *
6486	placebo	France	F	89	4	Abnormal Vision
6285	placebo	France	M	71	4	Increased glucose
6154	lisinopril 10 mg	France	M	69	4	Confusion

* serious adverse event

Patient 7415 (Placebo) with a 12 year history of essential hypertension, also had a history of vertebrobasilar insufficiency and arthrosis. Therapy with clobazam for anxiety was being concomitantly given. On Day 27, she suffered a severe hypertensive crisis (blood pressure 230/105 mmHg) and a cerebral infarct with left hemiplegia which led to hospitalization. She was discharged from hospital on Day 32 when her condition was improving.

Patient 6311 (valsartan 40 mg) had a 34 year history of essential hypertension. In addition, prostatic adenoma had been diagnosed in 1991 and he had a family history of stroke (father). Concomitant medications reported at entry were cycloteriam (hypertension), lorazepam (anxiety) and piascledine (arthrosis). Blood pressure was 176/92 mm Hg on Day 28. On Day 29, he presented with temporospatial disorientation with nervousness and inconsistent speech. As the disorientation increased, he was hospitalized one day later and the trial medication was stopped. A scan revealed a right frontal intracerebral hematoma. Further scans, performed on Days 42 and 58, showed reabsorption of the hematoma. One month later, this patient was discharged from hospital with sequelae of aggressiveness which lasted for 2 months.

Patient 6385 (valsartan 80 mg) had a 4 year history of essential hypertension which had not previously been treated. On Day 58, the patient was hospitalized for investigation of fever with pain on urination. *E. coli* was found in the urine and pyelonephritis was diagnosed which was treated with antibiotics. The patient stopped taking the trial medication on admission to hospital. A scan was performed due to abdominal pain and a benign pancreatic tumor was discovered (cystadenoma). The patient was discharged after 2 weeks when her condition was said to be improving.

Patient 5118 (placebo) presented with a moderate hypertensive crisis on Day 39. Mean supine blood pressure was 192/104 mmHg on Day 0 (randomization), 200/105 mmHg after 5 weeks of treatment and 210/110 mmHg when the patient presented with the hypertensive crisis. Treatment was given with clonidine and nitrendipine. The patient was withdrawn from the trial and subsequently made a complete recovery.

Patient 5122 (valsartan 160 mg) had a 5 year history of essential hypertension and a 6 year history of arthrosis. Therapy with indapamide had been previously given for essential hypertension and diclofenac gel was concurrently being used for arthrosis. One week prior to randomization, creatine kinase was measured and found to be high (4.47 ukat/l; normal range < 2.83 ukat/l). The investigator considered that this value was abnormal and clinically relevant. One month later (Visit 4), this parameter was measured again and was still high (4.47 ukat/l) thus this patient was withdrawn from the trial.

Patient 5195 (valsartan 40 mg) had a moderate headache which started one day prior to randomization. The patient returned after 6 days of taking the trial medication as the headache persisted and she was withdrawn from the trial.

This patient 7046 (valsartan 160 mg) with a 20 year history of essential hypertension, presented with moderate headache and mild palpitations on Day 2. The investigator considered that the headache was possibly related to the trial medication while the palpitations were unlikely to be related to the trial medication. Both experiences lasted for 1 day. The investigator withdrew the patient from the trial and he made a complete recovery.

Patient 7118 (valsartan 80 mg) presented with mild hallucinations, headache and insomnia on Day 23. No other medications were being taken and the investigator considered all 3 experiences to be possibly related to the trial medication. By the next visit (Day 28), the severity had increased to moderate and the patient requested that she be withdrawn from the trial.

Patient 6154 (lisinopril 10 mg) with a 6 year history of essential hypertension had previously experienced an ocular venous thrombosis (1985) and a single episode of visual disturbance with confusion in 1993. During the placebo run-in phase, he presented with a "subconfusional" state and associated memory loss, neither of which were considered to be related to the trial medication. As the symptoms improved, he was randomized as planned 5 days later. Ten days after the start of active treatment, a nuclear

magnetic resonance procedure showed cerebral lacunae and a probable parieto-occipital hematoma. The patient was then hospitalized for an arteriography, and a serious adverse experience report was completed although the experience had started prior to active treatment. Trial treatment was stopped and the patient made a full recovery.

Patient 6190 (valsartan 80 mg) presented with a severe headache starting on Day 1 and moderate dizziness starting on Day 2. The investigator considered that neither experience was related to the trial medication, however, he did note that the headaches and dizziness were being exacerbated by hypertension. The patient requested to be withdrawn from the trial and treatment with prazosin and enalapril was started.

Patient 6235 (valsartan 80 mg) had a 3 year history of essential hypertension which had not previously been treated. She also had a history of gastro-duodenal ulcer and hypercholesterolemia which required therapy with fenofibrate. On Day 15, this patient reported moderate abdominal pain, which had lasted for 7 days, required concomitant treatment with omeprazole and led to withdrawal from the trial.

Patient 6282 (valsartan 80 mg) had a 10 year history of essential hypertension which had been previously treated with hydrochlorothiazide, atenolol and amlodipine In addition, she had a 6 year history of hyperlipidemia for which she took ciprofibrate. The patient complained of severe headache and mild tinnitus starting on Day 2. The investigator withdrew the patient from the trial.

Patient 6337 (valsartan 40 mg) had a 7 year history of essential hypertension which had been previously treated with ramipril. In addition, she was taking clobazam and fluoxetine for depression (the latter stopped at randomization), fenofibrate for hyperlipidemia, molsidomine for angina and cyanocobalamin for anemia. At Visit 4, this patient informed the investigator she had suffered from a mild dry cough starting on Day 2 which had lasted for 2 days and mild abdominal pain starting on Day 7 which had lasted for 3 days. Treatment with the trial medication was stopped due to the abdominal pain and therapy was given with fenoverine and amoxapine.

Patient 6453 (valsartan 160 mg) had a 7 year history of essential hypertension which had been previously treated with captopril. In addition, she had a history of diabetes, arteritis and arthrosis which were treated with gliclazide, ifenprodil and oxaceprol. On Day 0, the mean supine BP was 198/103 mmHg. At Visit 4, the mean supine BP was 167/94 mmHg and the standing BP was 160/96 mmHg. However, the patient informed the investigator that she had suffered from an episode of orthostatic hypertension, lasting for one hour, on Day 6. The investigator noted that the patient had completely recovered from this episode.

Patient 6474 (valsartan 80 mg) had a 5 year history of essential hypertension which had previously been treated with benazepril. In addition, she was receiving treatment with bromazepam for anxiety, oxybutinin hydrochlorothiazide for a bladder disorder and simvostatin for hyperlipidemia. This patient started suffering from moderate nausea and mild abdominal pain from Day 3. The patient made a complete recovery from both adverse experiences.

Patient 6486 (placebo) with a 5 month history of essential hypertension presented with a moderate abnormality of vision on Day 5. Mean supine blood pressure at randomization was 189/99 mmHg and at the time of the adverse experience 181/92 mmHg. The investigator considered that this experience was possibly related to the trial medication. The patient requested that she be withdrawn from the trial and therapy with benazepril was prescribed.

Two valsartan treated patients had serious adverse events but did not require discontinuation from the study. Patient 5119 (Valsartan 40 mg) had a short history of essential hypertension (14 months) for which therapy with ramipril had been previously given. On entry, a left arterial subclavian stenosis was reported as a concomitant condition, along with hyperlipidemia which was treated with gemfibrozil. After approximately 7 weeks of treatment, this patient complained that his left eye had been producing tears which was followed by blurred vision. On investigation by an ophthalmologist, a left retinal vein thrombosis was diagnosed on Day 53. The next day, this patient was transferred to hospital for treatment with oxpentifylline infusion.

Patient 6388 (valsartan 80 mg) had an 8 year history of essential hypertension previously treated with enalapril. She was taking lorazepam for insomnia, infenprodil tartrate for arteritis, dihydroquinone for palpitations and simvostatin for hypercholesterolemia. She presented with thrombophlebitis on Day 1, which required hospitalization, and treatment with the trial medication was stopped.

Of the 652 randomized patients a total of 207 (32%) reported one or more adverse experience. Of these, 42 (29%) were from the valsartan 160 mg group, 44 (31%) were from the valsartan 80 mg group, 44 (30%) were from the valsartan 40 mg group, 52 (36%) from the placebo group and 25 (34%) from the lisinopril 10 mg group. Table 23.10 list the most commonly reported adverse events.

Table 23.10. Incidence of Most Frequently Reported (≥ 3%) Adverse Experience [N(%)]

	valsartan 160 mg	valsartan 80 mg	valsartan 80 mg	placebo	lisinopril 10 mg
Total Patients	144 (100.0)	142 (100.0)	148 (100.0)	144 (100.0)	74 (100.0)
Total Patients with an Adverse Experience	42 (29.2)	44 (31.0)	44 (29.7)	52 (36.1)	25 (33.8)
Headache	3 (2.1)	7 (4.9)	9 (6.1)	7 (4.9)	2 (2.7)
Coughing	8 (5.6)	2 (1.4)	4 (2.7)	6 (4.2)	6 (8.1))
Dizziness	5 (3.5)	4 (2.8)	2 (1.4)	4 (2.8)	1 (1.4)

Symptomatic orthostatic hypotension[6] occurred in 2 valsartan patients and 1 lisinopril patient.

Table 23.11 lists three valsartan 160 mg patients (vol. 1.143, p. 411) who experienced slight increases in serum creatinine outside the normal range at endpoint.

Patient #	Baseline Creatinine	Terminal Creatinine	Normal Range
5026/26	68 umol/L	138 umol/L	62 - 106 umol/L
6314/698	87.6 umol/L	154.9 umol/L	44.2 - 132.7 umol/L
6153/650	108 umol/L	176.1 umol/L	44.2 - 132.7 umol/L

Protocol 25. Single-Center, Randomized, Double-Blind, Within Patient Trial To Assess The Tolerability And Effect On Renal Function Of Valsartan 80 Mg Once Daily, In Comparison To Placebo, In Patients With Renovascular Arterial Hypertension Treated For Four Days
(4/21/94 - 12/21/94)

This was a single center (Italy), randomized, double-blind, placebo controlled, 2 period crossover trail in patients with hypertension (siDBP > 95 mmHg and < 120 mmHg) and a diagnosis of unilateral renal artery stenosis diagnosed by digital subtraction angiography awaiting renal vascular surgery. After initial screening (visit 1), the patients received one week of placebo. At randomization (visit 2), patients were randomized to one of two treatment sequences during which they received either placebo or valsartan 80 mg. Each treatment was administered for 4 days. There was no washout period between periods. The purpose of the study was to determine the effect of valsartan on renal function. At the end of the first treatment period (visit 3) and the second treatment period (visit 4), the patients had GFR (inulin infusion), effective renal plasma flow (PAH infusion), filtration fraction, renal blood flow, creatinine clearance, aldosterone, angiotensin II, renin, Ace Inhibitor Activity, blood pressure, sodium excretion and renal vascular resistance measured.

Twelve patients (10F, 2M; 12 Caucasian) with an average age of 41 years enrolled and completed the study. There were no significant differences in renal function observed for the two treatment groups. There were no significant adverse events reported during the trial.

Study 31. Randomized, Double-Blind, Placebo-Controlled Parallel Group Trial Comparing Valsartan 20 mg, 80 mg, 160 mg, and 320 mg to Placebo in Patients with Essential Hypertension Followed by an Open-Label Extension of 52 Weeks Duration
(March 29, 1994 - January 13, 1995)

Protocol

Design

This was a multi-center, randomized, double-blind, placebo controlled, parallel group trial in hypertensive patients (mean sitting diastolic blood pressure [siDBP] ≥ 95 and ≤ 115 mmHg). Patients were randomized to placebo, valsartan 20 mg, valsartan 80 mg, valsartan 160 mg or valsartan 320 mg for 8 weeks of double blind treatment. This study was performed to determine the useful dosing range of valsartan. The study outline is depicted in table 31.1.

[6] [a decrease in BP upon changing position from the supine or sitting position to the standing position after at least 2 minutes of equilibration i.e.a decrease in SBP of ≥ 20 mmHg and/or a decrease in DBP of ≥ 10 mmHg, and concomitant symptoms of cerebral hypoperfusion (e.g. lightheadedness, dizziness, presyncope etc.]

Table 31. 1. Study Outline.

Wash-Out		Single-Blind Placebo Run-In	Double-Blind Treatment		No Drug	Open-Label Extension						
			Randomization									
			⇩									
Visit	0	1	2	3	4	5*	6	7	8	9	10	11
Week		-4	0	4	8	8.5	12	16	24	36	48	60
			valsartan 20 mg OD									
			valsartan 80 mg OD									
		Placebo	valsartan 160 mg OD			valsartan 160 mg (± HCTZ 12.5 mg or 25 mg)						
			valsartan 320 mg OD									
			Placebo									

* All patients who completed Visits 1-4 were to be seen at Visit 5 to assess potential rebound effects of medication withdrawal. Those patients who continued into the open-label extension were dispensed open-label drug at Visit 5.

Inclusion/ Exclusion Criteria

The study enrolled male or female subjects, 21 - 80 years of age, with a diagnosis of essential hypertension. At both visits 1 and 2 patients had a mean siDBP ≥ 95 mmHg and ≤ 115 mmHg. The difference in siDBP between Visits 1 and 2 was ≤ 10 mmHg. Exclusion criteria included history of heart failure, malignant hypertension, renal impairment and significant cardiovascular disease. A complete list of exclusion criteria can be found in volume 1.104, page 13.

Study Description

The study consisted of a 2 week washout period, followed by a 2-4 week single-blind placebo run-in, followed by an 8 week double-blind treatment period where patients were randomized to receive either valsartan 20 mg once daily, valsartan 80 mg once daily, valsartan 160 mg once daily, valsartan 320 mg once daily or placebo once daily

Patients were completely withdrawn from their previous anti-hypertensive medication for at least 2 weeks prior to initiation of the placebo baseline period. Patients who met the eligibility were scheduled for visit 1. At visit 1 (screening visit), three blood pressure readings and one pulse rate were taken in the sitting position. After sitting measurements were taken, one standing blood pressure and pulse rate were measured. Patients had a mean sitting diastolic blood pressure ≥ 95 and ≤ 115 mmHg in order to be entered into the placebo run-in period.

Visit 2 (week 0 of double-blind Rx) took place 2 - 4 weeks ± 3 days after visit 1. Blood pressure and pulse measurements were performed in the sitting and standing positions. Before assigning a randomization number, patients were required to have mean sitting diastolic blood pressure ≥ 95 mmHg and ≤ 115 mmHg at visit 2. The difference in siDBP between Visits 1 and 2 was ≤ 10 mmHg. Patients meeting the above criteria were assigned a randomization number from the double-blind number series assigned to that center. The randomization was stratified for age.

Visit 3 (week 4 of double-blind Rx) took place 4 weeks ± 3 days after Visit 2. Blood pressure and pulse measurements were performed in the sitting and standing positions.

Visit 4 (week 8 of double-blind Rx) took place 4 weeks ± 3 days after Visit 3. Blood pressure and pulse measurements were performed in the sitting and standing positions.

Visit 5 took place 3 days after Visit 4. The purpose of this visit was to check patient's blood pressure for rebound hypertension. Patients at pre-designated centers who had completed all 5 visits of the core phase of this trial had the option of receiving open-label valsartan 160 mg daily for an additional 52 weeks. After enrollment into the open label extension, patients were evaluated at 4 and 12 weeks and then every 12 weeks. During the open label extension, open-label HCTZ 12.5 mg or 25 mg was added in those patients whose siDBP is > 90 mmHg.

Some centers participated in substudies of population pharmacokinetics and/or ambulatory blood pressure monitoring. In those patients participating in the pharmacokinetic study, blood samples for the measurement of valsartan concentrations were collected prior to visit 2 and at 3 to 5 hours or 6 to 8 hours

after dosing on any day between visit 3 and 4 (not on visit 4). For those patients participating in the ABPM, ambulatory blood pressure was measured on the day before visit 2 and visit 4.

Approximately 640 patients (minimum 20 patients per center) could be randomized in order to obtain the 575 required patients who meet all admission and randomization criteria and complete all visits of the core protocol (5 visits). A total of 200 patients at 10 selected centers (20 patients each) could have 24 hour ABPM assessed.

A total of 160 patients at 8 selected centers (20 patients each) could have 3 additional blood samples drawn during the trial for determination of population pharmacokinetics data. One of the timepoints took place between 3 and 8 hours post-dose (assigned randomly) prior to the last double-blind visit (Visit 4).

A total of 400 patients at 20 selected centers (20 patients each) were permitted to enter the open-label extension phase of the trial.

Primary Endpoint

The primary efficacy variable is the change in trough mean sitting diastolic blood pressure from baseline (Visit 2).

Secondary Endpoint

The secondary efficacy variable was the change in mean sitting systolic blood pressure. Other endpoints included standing diastolic and systolic blood pressures, sitting and standing pulse, and weight.

Statistical Analysis

Group comparability was examined using the Cochran-Matel-Haenszel chi-square test and F-test. Primary and secondary efficacy variables were analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and trial center as factors and baseline (pre-dose measurement at the randomization visit) as a covariate. Both treatment-by-center and treatment-by-baseline interactions were included in the model. Ambulatory blood pressure (ABP) was analyzed using a two-way analysis of variance for mean ABP over 24 hours and a repeated-measures (split-plot) analysis for daytime and nighttime ambulatory mean pressure. The Bonferroni procedure was used to maintain an overall two-sided significance level of $\leq$ 0.05 for the between treatment multiple comparisons versus placebo. For safety variables, descriptive evaluations were used.

For the primary efficacy variable, a successful reduction in blood pressure was defined as mean sitting diastolic blood pressure < 90 mmHg or a > 10 mmHg decrease compared to baseline (pre-dose measurement at Visit 2).

Study Flowchart

A flowchart of procedures performed during the study are listed in table 31.2.

Table 31.2. Flowchart

Wash-Out[1]	Run-In	Double-Blind Treatment		No Drug	Open-Label Extension						
Visit	1	2	3	4	5	6	7	8	9	10	11
Treatment Week	-4	0	4	8	8.5	12	16	24	36	48	60
Complete History/Physical Examination	x										
Interim/Final Physical Examination		x	x	x	x	x	x	x	x	x	x
Blood Pressure and Pulse Rate[2]	x	x	x	x	x	x	x	x	x	x	x
Randomization		x									
12-Lead ECG	x			x							
Chest X-Ray[3]	x										
Safety Laboratory Tests[4]	x	x		x		x		x			x
Serum Pregnancy Test	x	x	x	x		x	x	x[5]	x[5]	x[5]	x[5]
Blood Drawn for Population Pharmacokinetics		x	x[6]	x							

Table 31.2. Flowchart

Wash-Out[1]	Run-In	Double-Blind Treatment		No Drug	Open-Label Extension						
Visit	1	2	3	4	5	6	7	8	9	10	11
Treatment Week	-4	0	4	8	5	12	16	24	36	48	60
24 Hour ABPM[7]		x		x							
Adverse Experiences		x	x	x	x	x	x	x	x	x	x
Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x
Dispense Double-Blind Trial Medication		x	x								
Dispense Open-Label valsartan					x	x	x	x	x	x	x
Dispense Open-Label HCTZ[8]						x	x	x	x	x	x
Termination Sheet					x[9]						x[9]

1 A wash-out period for anti-hypertension medication a minimum of two weeks prior to Visit 1.

2 Should take place between 7 AM and 10 AM (i.e., 23 to 26 hours after the last dose of trial drug, except Visit 1)

3 X-Ray to be performed only if not done within one year prior to Visit 1

4 Blood will be drawn and urine obtained in the fasted state (hematology, blood chemistry, and urinalysis)

5 To be done at each visit, as well as at monthly intervals between scheduled visits.

6 This will occur between Visits 3 and 4

7 For those patients undergoing 24 hour ABPM, the apparatus will be applied the day prior to the actual Visit 2 and Visit 4 procedures are performed, the apparatus must be placed on the patient at the same time at both visits.

8 Only if siDBP not controlled on valsartan alone. Serum electrolytes to be drawn 2 weeks after HCTZ initiated.

9 Or sooner if premature termination occurs.

Results

Disposition

At 32 centers in the USA, there were 822 patients enrolled, 736 patients randomized to double-blind treatment, 668 who completed the double blind period (Visit 4), and also 668 with follow-up (Visit 5). The number of patients randomized to the centers ranged from 4 - 50. Table 31.5 outlines the patient disposition. Twenty-five patients were discontinued from therapy secondary to adverse experiences. Some patients with adverse experiences could have been classified as unsatisfactory therapeutic response (i.e. there was some inconsistency in the application of the dropout definitions).

Table 31.5. Patient Disposition

Number of patients	Placebo	Valsartan 20 mg	Valsartan 80 mg	Valsartan 160 mg	Valsartan 320 mg	Total
Enrolled (Visit 1)	-	-	-	-	-	822
Randomized (Visit 2)	148	140	150	148	150	736
Completed Double Blind (Visit 4)	128	125	140	136	139	668***
With Follow-Up (Visit 5)	128	125	140	136	139	668
Discontinued prematurely during double-blind						
Total	20	15	10	12	11	68
For adverse experience*	11	4	3	3	4	25
For unsatisfactory therapeutic response		6	3	2	4	19
Other**	5	5	4	7	3	24

* includes clinical or laboratory AE;

** includes 8 lost to follow-up, 7 non-compliant, 6 did not meet protocol criteria, 3 withdrew consent;

*** There were 30 randomized patients who discontinued at Visit 4 earlier than scheduled per protocol who are not included in the number of patients completing the double blind treatment period. (Of these 30 patients, 29 had Visit 4 efficacy measurements and 1 did not.)

Demographics

Table 31.3 and 31.4 provide the demographic information for each treatment group. For all randomized patients, the five treatment groups were comparable overall with respect to demographic and medical history characteristics, except that there was a statistically significant difference detected with respect to duration of hypertension (p=0.031). For all randomized patients, no statistically significant baseline treatment differences were found with respect to the primary, secondary, and other variables.

Table 31.3. Distributions For Sex And Race (All Randomized Patients)

Treatment	Number of patients	Sex		Race		
		Male	Female	White	Black	Other
Placebo	148	98 (66%)	50 (34%)	114 (77%)	19 (13%)	15 (10%)
Valsartan 20 mg	140	93 (66%)	47 (34%)	106 (76%)	12 (9%)	22 (16%)
Valsartan 80 mg	150	88 (59%)	62 (41%)	114 (76%)	19 (13%)	17 (11%)
Valsartan 160 mg	148	94 (64%)	54 (36%)	103 (70%)	25 (17%)	20 (14%)
Valsartan 320 mg	150	95 (63%)	55 (37%)	114 (76%)	17 (11%)	19 (13%)
All Treatments	736	468 (64%)	268 (36%)	551 (75%)	92 (13%)	93 (13%)

Table 31.4. Summary Statistics For Age, Weight, And Duration Of Hypertension (All Randomized Patients)

Treatment group	Number of patients	Age (Mean years ± SD)	Weight at Visit 1 (mean pounds ± SD)	Duration of Hypertension (mean years ± SD)
Placebo	148	53.64 (±11.60)	192.28 (±40.48)	9.93 (±7.76)
Valsartan 20 mg	140	53.81 (±10.40)	193.39 (±39.79)	10.30 (±8.57)
Valsartan 80 mg	150	53.59 (±10.90)	194.74 (±42.32)	7.71 (±7.88)
Valsartan 160 mg	148	51.97 (±10.47)	202.86 (±45.87)	8.34 (±7.32)
Valsartan 320 mg	150	53.74 (±10.35)	193.80 (±40.41)	9.69 (±9.43)
All Treatments	736	53.35 (±10.75)	195.44 (±41.92)	9.18 (±8.26)

Efficacy - Change in Blood Pressure

Seven hundred and twenty-nine patients were included in the endpoint analysis (had post-baseline siDBP measurements). Table 31.6a shows the trough mean changes in siDBP at endpoint and visit 5 (3 days after final dose)

Table 31.6a. Mean Change in Trough siDBP at Endpoint and Visit 5

	Endpoint		Visit 5	
	N	Mean Change	N	Mean Change
Placebo	145	-2.28 (7.56)	128	-3.35 (6.87)
Valsartan 20 mg	139	-4.98 (7.96)	125	-3.68 (6.91)
Valsartan 80 mg	148	-7.37 (7.82)	140	-4.82 (7.74)
Valsartan 160 mg	147	-7.71 (7.18)	136	-5.94 (6.89)
Valsartan 320 mg	150	-8.65 (8.70)	139	-6.64 (7.42)

The least square treatment means from the analysis of covariance for change from baseline to Endpoint and the results of the treatment comparisons are summarized in tables 31.6b and 31.6c. The mean change in siDBP was significantly different for all treatment groups compared to placebo.

Table 31.6b. Results Of Between-Treatment Comparisons For Change From Baseline In Trough Mean Sitting Diastolic Blood Pressure At Endpoint [Last Post-Randomization Measurement (Among Visits 3 And 4) Carried Forward For Each Patient].

Treatment Group	N	Least square mean change from baseline (mm Hg)
Placebo	145	-2.02
Valsartan 20 mg	139	-5.39
Valsartan 80 mg	148	-7.22
Valsartan 160 mg	147	-7.34
Valsartan 320 mg	150	-8.50

Table 31.6c. Statistical Comparison Of Each Treatment Group For Sitting DBP.

Treatment Comparison	Difference (mm Hg)	Confidence Interval (98.75%)	p-value
Valsartan 20 mg vs. placebo	-3.37	(-5.77, -0.96)	<0.001*
Valsartan 80 mg vs. placebo	-5.20	(-7.53, -2.86)	<0.001*
Valsartan 160 mg vs. placebo	-5.32	(-7.68, -2.95)	<0.001*
Valsartan 320 mg vs. placebo	-6.48	(-8.81, -4.14)	<0.001*

* indicates statistical significance at the level of 0.0125 ($p<0.0125$).

No statistically significant center-by-treatment or baseline-by-treatment interaction was observed. An analysis that included only patients who had blood pressure measurements at visit 4 and those that were clinically assessable [7] yielded similar results to the endpoint analysis.

For the 185 patients with evaluable eating habit diary data at 9 selected centers, there appeared to be general consistency within patients regarding whether trial medication was taken with or without food.

Table 31.7 lists the percentage of patients who were considered responders [defined as a post-baseline trough mean sitting diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline (Visit 2)]. Statistically significant treatment differences were observed in favor of valsartan 80 mg, valsartan 160 mg, and valsartan 320 mg versus placebo .

Table 31.7. Results Of Between -Treatment Comparisons For The Proportion Of Patients Achieving A Successful Response In The Control Of Trough Mean Sitting Diastolic Blood Pressure For All Randomized Patients At Endpoint And Visit 4 And For All Clinically Assessable Patients At Endpoint

Treatment Group	Proportion of Patients Achieving a Successful Response in the Control of Trough Mean Sitting Diastolic Blood Pressure		
	Endpoint (all randomized)	Visit 4 (all randomized)	Endpoint (clinically assessable)
Placebo	20.7%	19.3%	20.1%
Valsartan 20 mg	28.1%	29.5%	28.9%
Valsartan 80 mg	42.6%	43.2%	42.9%
Valsartan 160 mg	44.2%	45.3%	43.5%
Valsartan 320 mg	52.0%	51.7%	50.7%

Table 31.8a list the mean change in trough siSBP at endpoint and visit 5. Table 31.8b list the least square treatment means from the analysis of covariance for change from baseline to endpoint for sitting systolic blood pressure. Statistically significant treatment differences were observed in favor of all valsartan doses versus placebo (table 31.8a). No statistically significant center-by-treatment or baseline-by-treatment interaction was observed.

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[7] **Clinically assessable** patients were defined as randomized patients:

(1) with mean sitting diastolic blood pressure at baseline (pre-dose measurement at Visit 2) ≥ 95 mmHg,

(2) who did not take any antihypertensive drug other than trial drug at any time during the trial,

(3) for whom the number of hours between the "time of blood pressure measurements" at Endpoint and the "time of last dose of trial medication" at the corresponding visit was between 12 and 30 hours (inclusive), and

(4) for whom the total duration on trial medication was at least 25 days.

Table 31.8a. Mean Change in siSBP at Endpoint and at Visit 5.

	Endpoint		Visit 5	
	N	Mean Change	N	Mean Change
Placebo	145	-1.91 (15.04)	128	-2.00 (13.52)
Valsartan 20 mg	139	-6.51 (13.40)	125	-3.18 (12.12)
Valsartan 80 mg	148	-9.27 (12.27)	140	-4.17 (13.80)
Valsartan 160 mg	147	-9.10 (13.70)	136	-4.99 (12.95)
Valsartan 320 mg	150	-10.93 (15.56)	139	-6.64 (13.86)

Table 31.8b. Results Of Between-Treatment Comparisons For Change From Baseline In Trough Mean Sitting Systolic Blood Pressure At Endpoint (All Randomized Patients)

Treatment Group	N	Least square mean change from baseline (mm Hg)
Placebo	145	-1.33
Valsartan 20 mg	139	-6.33
Valsartan 80 mg	148	-8.60
Valsartan 160 mg	147	-8.96
Valsartan 320 mg	150	-10.59

Table 31.8c. Statistical Analysis Of Change In Mean Sitting Systolic Blood Pressure At Endpoint.

Treatment Comparison	Difference (mm Hg)	Confidence Interval (98.75%)	p-value
Valsartan 20 mg vs. placebo	-5.00	(-9.11, -0.90)	0.002*
Valsartan 80 mg vs. placebo	-7.27	(-11.3, -3.28)	<0.001*
Valsartan 160 mg vs. placebo	-7.63	(-11.7, -3.58)	<0.001*
Valsartan 320 mg vs. placebo	-9.26	(-13.3, -5.26)	<0.001*

* indicates statistical significance at the level of 0.0125 ($p<0.0125$).

Tables 31.9a - 31.9c lists the summary statistics for trough mean sitting diastolic blood pressure by age group, by sex and by race. Formal statistical analysis was not performed. There does not appear to be a difference in effect based on age. Female patients may have a greater response with a comparable dose of valsartan. Surprisingly, the response in black patients is comparable to white patients. These patterns of response should be confirmed in other studies.

Table 31.9a. Mean change from baseline in trough mean sitting diastolic blood pressure (mmHg) at Endpoint by age (all randomized patients)

	< 65 (years)		>= 65 (years)	
Treatment Group	N	Raw Mean	N	Raw Mean
Placebo	117	-2.18	28	-2.70
Valsartan 20 mg	118	-5.26	21	-3.43
Valsartan 80 mg	120	-7.52	28	-6.73
Valsartan 160 mg	129	-7.67	18	-8.02
Valsartan 320 mg	125	-8.75	25	-8.15
	N	Relative Mean Change*	N	Relative Mean Change*
Valsartan 20 mg	118	- 3.08	21	- 0.73
Valsartan 80 mg	120	- 5.34	28	- 4.03
Valsartan 160 mg	129	- 5.49	18	- 5.32
Valsartan 320 mg	125	- 6.57	25	- 5.45

* relative mean change = (treatment change - placebo change)

Table 31.9b. Mean change from baseline in trough mean sitting diastolic blood pressure (mmHg) at Endpoint by sex (all randomized patients)

	Male		Female	
Treatment Group	N	Raw Mean	N	Raw Mean
Placebo	96	-2.22	49	-2.40
Valsartan 20 mg	92	-4.49	47	-5.95
Valsartan 80 mg	87	-6.20	61	-9.04
Valsartan 160 mg	93	-6.87	54	-9.17
Valsartan 320 mg	95	-8.40	55	-9.08
	N	Relative Mean Change*	N	Relative Mean Change*
Valsartan 20 mg	92	- 2.27	47	- 3.55
Valsartan 80 mg	87	- 3.98	61	- 6.64
Valsartan 160 mg	93	- 4.65	54	- 6.77
Valsartan 320 mg	95	- 6.18	55	- 6.68

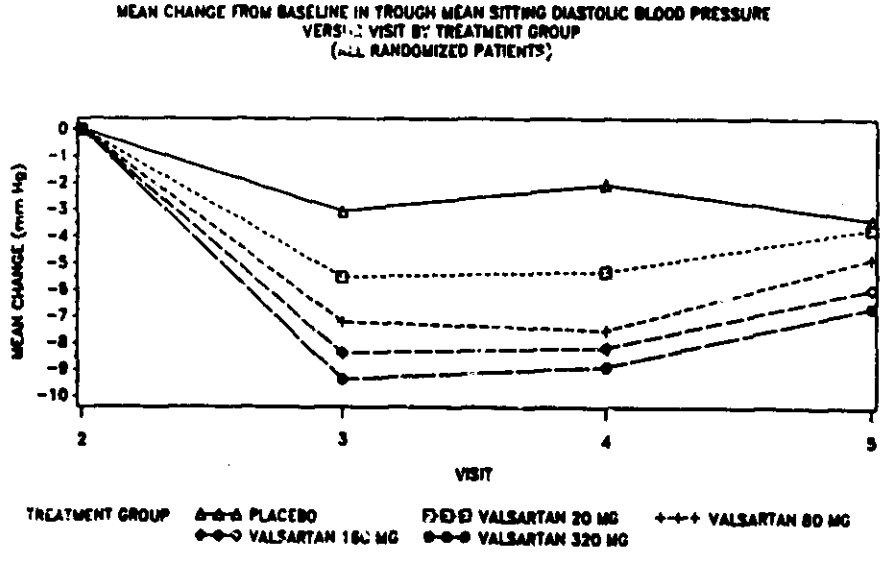
* relative mean change = (treatment change - placebo change)

Table 31.9c. Mean change from baseline in trough mean sitting diastolic blood pressure (mmHg) at Endpoint by race (all randomized patients)

	White		Black		Other	
Treatment Group	N	Raw Mean	N	Raw Mean	N	Raw Mean
Placebo	111	-3.31	19	+1.30	15	+0.80
Valsartan 20 mg	105	-5.30	12	-1.11	22	-5.59
Valsartan 80 mg	113	-7.76	18	-5.81	17	-6.47
Valsartan 160 mg	102	-7.94	25	-6.61	20	-7.93
Valsartan 320 mg	114	-9.55	17	-5.53	19	-6.04
	N	Relative Mean Change*	N	Relative Mean Change*	N	Relative Mean Change*
Valsartan 20 mg	105	- 1.99	12	- 2.41	22	- 6.39
Valsartan 80 mg	113	- 4.45	18	- 7.11	17	- 7.27
Valsartan 160 mg	102	- 4.63	25	- 7.91	20	- 8.73
Valsartan 320 mg	114	- 6.24	17	- 6.83	19	- 6.84

Figure 31.1 (volume 1.103, page 414) plots the mean change in trough sitting diastolic blood pressure for all patients randomized at each visit. At the first post-randomization visit (visit 3 @ 4 weeks), the treatment effect is maximal.

Figure 31.1



NOTE: BASELINE IS THE RANDOMIZATION VISIT (VISIT 2). TRIAL DRUG WAS NOT ADMINISTERED BETWEEN VISITS 4 AND 5.
POST-RANDOMIZATION VISITS OCCURRED IN THE FOLLOWING WEEKS: 4 (VISIT 3), 8 (VISIT 4), AND 8.5 (VISIT 5).
THE NUMBER OF PATIENTS MAY BE DIFFERENT FROM VISIT TO VISIT.

Figure 31.2a (volume 1.103, p. 431) and 31.2b (volume 1.103, p. 434) plots the mean change from baseline in ambulatory diastolic and systolic blood pressure over 24 hours at endpoint (visit 4) respectively. There appears to be a dose response for blood pressure change.

Figure 31.2a.

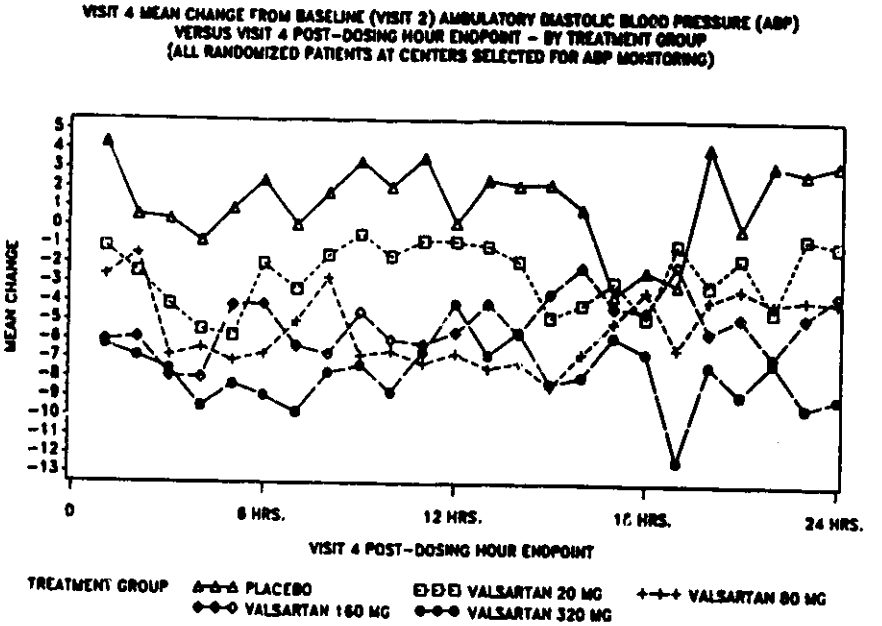
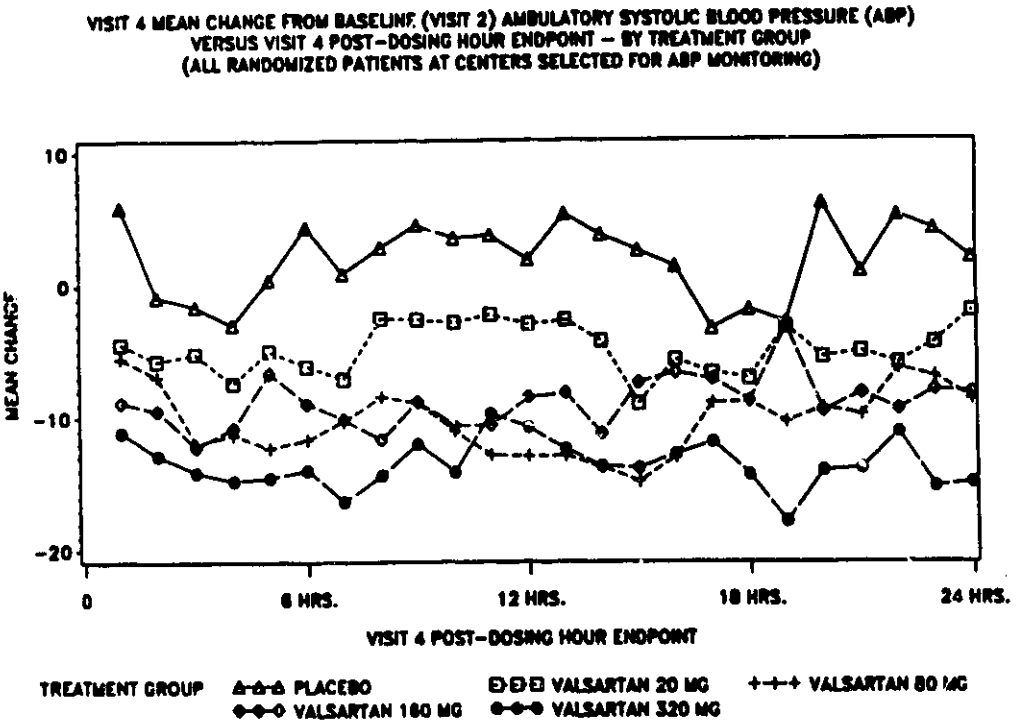


Figure 31.2b.



The number of patients with orthostatic blood pressure changes[8] was not significantly different between treatment groups.

Safety

The safety data base included adverse events evaluations for all patients randomized. Even though 668 patients had a visit 5, only 651 are included in the evaluation for rebound hypertension. Six hundred and ninety-seven patients had a visit 4 evaluation although it is not clear that blood for lab evaluations were collected. Only 687 patients are included in the analysis for lab safety. Table 31.10 lists the number of patients included in each safety evaluation.

Table 31.10. Number of Patients Included in Each Safety Evaluation

		Valsartan				
Number of patients	Placebo	20 mg	80 mg	160 mg	320 mg	Total
Randomized (Visit 2)	148	140	150	148	150	736
Completed Double Blind (Visit 4)	128	125	140	136	139	668
With Follow-Up (Visit 5)	128	125	140	136	139	668
Safety Analyses						
Adverse experience evaluations	148	140	150	148	150	736
Rebound evaluations	121	123	137	132	138	651
Laboratory evaluations	133	132	142	139	141	687

Deaths

There was one death in a patient in the valsartan 20 mg dose group. Patient 0489/5506 (Serfer) was a 46 year old male with a history of hypertension for twelve years. At Visit 1, his sitting BP was 158/101 mmHg (158/102 mmHg standing) and ECG and chest X-Ray results were normal. At randomization, his sitting BP was 149/101 mmHg (148/102 mmHg standing). Nine days after entering the double-blind treatment phase, while participating in scuba diving lessons, the patient sustained a cardiac arrest. Cardiopulmonary resuscitation was attempted but unsuccessful. The patient was pronounced dead on arrival after transport to an emergency facility. Autopsy findings revealed right ventricular hypertrophy, pulmonary congestion and edema. The report lists the cause of death as pulmonary hypertension.

Discontinuations Secondary to Adverse Clinical or Laboratory Events

Twenty-five patients who prematurely discontinued from the double-blind treatment period due to adverse experiences or laboratory abnormalities are listed table 31.11. The list includes 11 placebo patients, 4 valsartan 20 mg patients, 3 valsartan 80 mg patients, 3 valsartan 160 mg patients and 4 valsartan 320 mg patients.

Table 31.11 List of Patient Discontinued due to Clinical or Laboratory Adverse Events.

Treatment	Investigator	Patient	Sex/Age	Day*	Medical Problem
Placebo	Fagan	563/5403	M/60	7-11	Dizziness; fatigue; head pressure
Placebo	Hilty	725/5636	M/78	41-45	Dull headache; shortness of breath ,
Placebo	Marbury	84/5058	F/67	24	Dizziness ,
Placebo	Mieras	93/5063	F/36	3	Uncontrolled hypertension during surgery , **
Placebo	Oparil	282/5190	F/40	7	Abnormal SGOT
Placebo	Oparil	861/5728	M/66	2	Myocardial Infarction **

[8] a decrease of ≥ 10 mmHg in DBP and or a decrease of ≥ 20 mmHg in SP

Table 31.11 (con't) List of Patient Discontinued due to Clinical or Laboratory Adverse Events.

Treatment	Investigator	Patient	Sex/Age	Day*	Medical Problem
Placebo	Serfer	228/5153	M/45	32	Superficial Cellulitis dorsal area left foot **
Placebo	Serfer	488/5340	M/55	41	Right Upper Quadrant Pain **
Placebo	Serfer	493/5507	M/61	33	Abnormal BUN and Creatinine 2
Placebo	Sugimoto	802/5826	F/61	42	Colon Fistula **
Placebo	Weiss	154/5102	M/54	20	Cancer of Prostate **
Valsartan 20 mg	Drehobl	677/5505	F/70	4	Abdominal pain; diverticulitis
Valsartan 20 mg	Harris	553/5397	M/65	47	Angina **
Valsartan 20 mg	Serfer	0489/5506	M/46	9	Death **
valsartan 20 mg	Marbury	85/5057	M/57	13	Polycystic Kidney Disease **
valsartan 80 mg	Anger	145/5695	M/70	6	Difficulty voiding secondary to BPH
valsartan 80 mg	Lunde	217/5145	M/51		New LBBB on visit 4 ECG; asymptomatic
valsartan 80 mg	Sugimoto	803/5828	M/68	33	Dizziness; feeling faint; weakness
valsartan 160 mg	Lewis	295/5196	M/56	6	Depression; trouble sleeping
valsartan 160 mg	Velasquez	669/5493	F/47	40-43	Constipation; lower abdominal pain, nausea
valsartan 160 mg	Weiss	159/5104	F/43	2	Headache; nausea 1
valsartan 320 mg	Anger	141/5095	M/63	2-28	Anxiousness; diarrhea, cataract; nocturnal ringing in ears
valsartan 320 mg	Kief	857/5782	M/51	20	Dizziness
valsartan 320 mg	Oparil	279/5188	M/43	2	Impotency
valsartan 320 mg	Papademetrious	580/5419	M/76	32	Ataxia; confusion; lightheadedness; anxiousness; tinnitus

Complete list of Dropouts found in Volume 1.102, p. 200.

* Onset Day During Double-Blind Period; if a range is given it indicates the various start dates of the different AE's. ** = serious

1 = Should have been classified as unsatisfactory therapeutic response

2 = Had abnormal Bun and Creatinine that changed little with randomized therapy (vol. 1.117, p. 408)

Patient 580/5419 was a 76 year old male who received valsartan 320 mg. This patient had a history of headaches. Approximately one month into the double-blind treatment phase, the patient complained of ataxia, lightheadedness, anxiety, confusion, and tinnitus. The anxiety and confusion had resolved after two weeks, however, the ataxia, lightheadedness and tinnitus were ongoing. The patient was discontinued from the trial and follow-up information indicated that the ataxia, lightheadedness, and tinnitus were improving.

Clinical Adverse Events

Adverse experiences, whether or not trial drug related were reported by a total of 339 (46.1%) of the 736 randomized patients. There does not appear to be an increased incidence of adverse events with valsartan treatment based on body system analysis or by total adverse events. Table 31.11 lists all of the adverse events reported by at least 1% of the valsartan treated patients. There does not appear to be a treatment related difference in the incidence of adverse events. Cough occurred in .7% of placebo patients and in 2.4% of losartan patients.

Table 31.11 Incidence Of Most Frequently Reported Adverse Experiences (In ≥ 1% Of Valsartan Patients or of Clinical Interest for Drugs that Affect the Renin Angiotensin System) Whether Or Not Trial Drug Related

		Valsartan				
	Placebo N (%)	20 mg N(%)	80 mg N(%)	160 mg N(%)	320 mg N(%)	All Doses
Total Patients	148 (100.0)	140 (100.0)	150 (100.0)	148 (100.0)	150 (100.0)	588
Patients with Adverse Experiences	65 (43.9)	70 (50.0)	68 (45.3)	66 (44.6)	70 (46.7)	274 (46.6)
Headache	16 (10.8)	12 (8.6)	10 (6.7)	12 (8.1)	11 (7.3)	45 (7.7)
Dizziness	8 (5.4)	3 (2.1)	5 (3.3)	5 (3.4)	14 (9.3)	27 (4.6)
URI	6 (4.1)	4 (2.9)	5 (3.3)	6 (4.1)	9 (6.0)	24 (4.1)
Viral Infection	3 (2.0)	5 (3.6)	4 (2.7)	5 (3.4)	3 (2.0)	17 (2.9)
Cough	1 (0.7)	3 (2.1)	4 (2.7)	2 (1.4)	5 (3.3)	14 (2.4)
Diarrhea	4 (2.7)	3 (2.1)	5 (3.3)	0 (0)	4 (2.7)	12 (2.0)
Sinusitis	5 (3.4)	1 (0.7)	3 (2.0)	1 (0.7)	6 (4.0)	11 (1.9)
Nausea	4 (2.7)	2 (1.4)	3 (2.0)	5 (3.4)	1 (0.7)	11 (1.9)
Dyspepsia	6 (4.1)	4 (2.9)	0	0	2 (1.3)	6 (1.0)
Abdominal Pain	3 (2.0)	3 (2.1)	3 (2.0)	2 (1.4)	4 (2.7)	12 (2.0)
Thrombocytopenia	0	0	1 (.7)	1 (.7)	0	2 (.3)
Myalgia	2 (1.4)	2 (1.4)	0	1 (.7)	4 (2.7)	7 (1.2)
Myositis	0	0	1 (.7)	1 (.7)	0	2 (.3)
Back Pain	1 (.7)	3 (2.1)	2 (1.3)	3 (2.0)	0	8 (1.4)
Insomnia	0	1 (.7)	1 (.7)	4 (2.7)	2 (1.3)	8 (1.4)
Libido Decreased	0	1 (.7)	0	1 (.7)	1 (.7)	3 (.5)
Somnolence	3 (2.0)	0	3 (2.0)	4 (2.7)	2 (1.3)	9 (1.5)
Coughing	1 (.7)	3 (2.1)	4 (2.7)	2 (1.4)	5 (3.3)	14 (2.4)
Pharyngitis	1 (.7)	2 (1.4)	1 (.7)	2 (1.4)	4 (2.7)	9 (1.5)
Rhinitis	4 (2.7)	3 (2.1)	4 (2.7)	2 (1.4)	3 (2.0)	12 (2.0)
Eye Edema	1 (.7)	1 (.7)	0	0	0	1 (.2)
Vision Abnormal	0	1 (.7)	1 (.7)	2 (1.4)	2 (1.3)	6 (1.0)
Arthralgia	1 (0.7)	1 (0.7)	6 (4.0)	2 (1.4)	1 (0.7)	10 (1.7)

There does not appear to be sex or race related differences in the incidence of specific adverse events. Headache appeared to occur more frequently in patients < 65 years of age compared to patients > 65 years of age in all valsartan dose groups by approximately a 2:1 ratio.

Table 31.12 lists the patients who experienced serious adverse events but did not discontinue from double-blind therapy. There does not appear to be a causal relationship between treatment and the adverse event.

Table 31.12 List of Patients with Serious Clinical Adverse Events Not Leading to Discontinuation.

Treatment	Investigator	Patient	Sex	Age	Day*	Medical Problem
Placebo	Archer	422/5290	M	66	17 58	Shingles Atrial Flutter
Placebo	Archer	435/5581	M	72	1	Hematuria
Placebo	Fagan	574/5409	M	57	24	Basal Cell Carcinoma
valsartan 20 mg	Lewis	293/5194	M	64	45	Rectal bleeding
valsartan 80 mg	Lewin	265/5177	F	49	40	Chest Pain; Vomiting; Diarrhea
valsartan 160 mg	Archer	434/5582	M	75	28	Right Inguinal Hernia

* Onset Day During Double-Blind Period; if a range is given it indicates the various start dates of the different AE's.

Patient #5295 (valsartan 20 mg) had mild face swelling at visit 2 but not at subsequent visits. Patient #5607 (valsartan 20 mg) had puffiness under the eyes at visit 3 but not at subsequent visits despite continued therapy.

Laboratory Results

Laboratory evaluations (complete blood count, blood chemistry and urinalysis) were to be obtained at Visits 1, 2 and 4 following a 12-hour fast. There were no significant changes in the mean laboratory parameters within any treatment group (Table 9.6:3 in volume 1.103, p. 368). Table 31.13 lists several lab parameters and the number of patients with specified increases/decreases from baseline. CPK and potassium appear to be the only lab parameters that suggest there may be increased incidence of change from baseline with increasing dose.

Table 31.13. Number of Patients with Specified Changes from Baseline

		Valsartan			
Parameter	Placebo	20 mg	80 mg	160 mg	320 mg
BUN > 50% Increase N (%) =	133 9 (6.8)	132 3 (2.3)	142 4 (2.8)	137 9 (6.6)	141 7 (5.0)
Creatinine > 50% Increase N (%) =	133 2 (1.5)	132 0 (0)	142 0 (0)	137 1 (0.7)	141 1 (0.7)
Sodium > 5% Decrease N (%) =	133 0 (0)	132 0 (0)	142 1 (0.7)	137 0 (0)	141 1 (0.7)
Potassium: N (%) = > 20% Increase > 20% Decrease	 131 2 (1.5) 0 (0)	 128 1 (0.8) 1 (0.8)	 140 4 (2.9) 0 (0)	 131 5 (3.8) 3 (2.3)	 134 3 (2.2) 1 (0.8)
CPK > 300% Increase N (%) =	133 0 (0)	132 0 (0)	142 0 (0)	138 1 (0.7)	141 3 (2.1)

A >50% increase from baseline in creatinine was felt to represent a clinically significant change. Four patients exhibited such a change; two were within normal range while two were outside the normal range.

Table 31.13a. Patients with Increases in Creatinine Outside of Normal Range

Patient	Treatment	Age	Sex	Baseline Value	Terminal Value
059/5210/Harris	Placebo	66	F	1.0	1.7
232/5158/Serfer	320 mg	50	M	0.9	1.9

Note: Normal range = 0.6-1.5 mg/dL

Patient 59/5210/Harris had normal creatinine values at Visit 1 and at randomization. The terminal visit result was 1.7 mg/dL. Patient 232/5158/Serfer had normal creatinine values at Visit 1 and at randomization. At terminal visit, the creatinine was 1.9 mg/d . This change was not associated with an increase in BUN.

Twenty patients had a > 20% increase or decrease from baseline in potassium. Eighteen of the changes were within the normal range. Two changes were outside the normal range and are shown in Table 31.13b. The changes are not clinically relevant.

Table 31.13b. Patients with Increases in Potassium Outside of Normal Range

Patient	Treatment Group	Age	Sex	Baseline Value	Terminal Value
508/5517/Lewin	20 mg	61	M	4.4	3.2
448/5430/Neutel	160 mg	74	F	4.0	5.5

Note: Normal range = 3.5 - 5.3 mEq/L

Six patients (table 31.13c) exhibited a >150% increase in SGOT or SGPT from baseline and they were also outside the normal range. Changes occurred with both placebo and valsartan.

Table 31.13c. Patients with Increases in SGOT or SGPT Outside of Normal Range

Patient	Treatment Group	Age	Sex	Baseline Value	Terminal Value
574/5409/Fagan	Placebo	56	M	23 (SGOT) 14 (SGPT)	120 406
261/5223/Lewin	Placebo	41	F	34 (SGOT) 36 (SGPT)	122 134
686/5527/Serfer	80 mg	41	F	16 (SGOT) 15 (SGPT)	114 184
025/5019/Gray	160 mg	53	F	15 (SGOT) 14 (SGPT)*	51 38*
209/5567/Hilty	160 mg	45	F	16 (SGOT) 11 (SGPT)*	42 36*

Table 31.13c. (con't) Patients with Increases in SGOT or SGPT Outside of Normal Range

Patient	Treatment Group	Age	Sex	Baseline Value	Terminal Value
270/5225/Lewin	320 mg	47	M	19 (SGOT) 28 (SGPT)*	51 56*
569/5406/Fagan	320 mg	50	M	42 (SGOT)* 58 (SGPT)	71* 167

*Included for comparison only.
Note: Normal range = 0 - 40 u/L (SGOT); 0-45 u/L (SGPT)

Four patients exhibited a > 300% increase from baseline in CPK and these were also outside the normal range. All of the changes occurred in patients receiving valsartan as illustrated in table 31.13d. For patients #5567, #5354 and #5003, the investigator indicated that the increases were exercise related. For patient #5115, a repeat lab showed a much lower value (although this repeat lab was not included in the data).

Table 31.13d. Patients with Increases in CPK Outside of Normal Range

Patient	Treatment Group	Age	Sex	Baseline Value	Terminal Value
209/5567/Hilty	160 mg	45	F	140	1844
175/5115/Drehobl	320 mg	38	M	163	1002
003/5003/Elinoff	320 mg	41	M	55	420
500/5354/Lewin	320 mg	51	F	55	255

Note: Normal range = 0 - 174 u/L (male) 0 - 140 u/L (female)

Protocol 50. Randomized, Double-Blind, Placebo-Controlled, Optional Titration, Parallel Group Trial Comparing Valsartan to Lisinopril and Placebo in Patients with Essential Hypertension (April 26, 1994 - February 14, 1995)

Protocol

Design

This was a multi-center, randomized, double-blind, placebo controlled, optional titration, parallel-group trial in patient with a history of essential hypertension. The study included a 2 - 4 week single blind placebo followed by randomization to a 12 week double-blind treatment period. The primary objective was to determine the efficacy, safety, and tolerability of valsartan (80 mg OD potentially titrated to 80 mg BID or 160 mg OD) compared tc Lisinopril (10 mg OD potentially titrated to 20 mg OD) and placebo.

During visit 1 (week -4), patients with a mean siDBP $\geq$ 95 and $\leq$ 115 mmHg were eligible to enter the placebo run-in period. At visit 2 (week -2 or 0), patients were randomized to double blind treatment if they were 21 - 80 years of age, had mean siDBP $\geq$ 95 mmHg and $\leq$ 115 mmHg at visits 1 (screening) and 2 (randomization) and the difference in mean siDBP between visits 1 and 2 was $\leq$ 10 mmHg. Patients were excluded if they had a history of CHF, angina, pregnancy, malignant hypertension, 2° or 3° heart block, either MI or hypertensive encephalopathy or CVA within the previous 6 months, hepatic disease, renal disease, IDDM, poorly controlled NIDDM or any severe or life threatening disease (a complete list of exclusion criteria is in volume 1.122, page 283). Randomization was stratified by age. The treatment groups included: placebo, valsartan 80 mg once daily (2 different groups) and Lisinopril 10 mg once daily.

At visit 3 (week 4), patients with a mean siDBP < 90 mmHg or symptoms of orthostatic hypotension continued to receive their initial treatment for an additional eight weeks. Patients with a mean siDBP ≥ 90 mmHg and no symptoms of orthostatic hypotension were titrated in the following manner for an additional eight weeks:

valsartan 80 mg OD → titrate to → valsartan 160 mg OD
valsartan 80 mg OD → titrate to → valsartan 80 mg BID
Lisinopril 10 mg OD → titrate to → Lisinopril 20 mg OD
placebo OD → titrate to → placebo OD.

Patients had visits at weeks 8 (visit 4) and 12 (visit 5) post-randomization. At all visits, all blood pressure measurements were taken three times in the sitting position, and once standing. Table 50.1 lists the procedures performed during the study.

Table 50.1. Flowchart Of Procedures.

	Washout	Run-In	Double-Blind Treatment Period			
Visit	0	1	2	3	4	5
Treatment Week	-6/-4	-4/-2	0	4	8	12
Complete History/ Physical Examination		x				
Interim/Final Physical Examination			x	x	x	x
Blood Pressure and Pulse Rate[1]		x	x	x	x	x
Randomization			x			
Titration[2]				x		
12-Lead ECG		x				
Chest X-Ray[3]		x				
Safety Laboratory Tests[4]		x	x			x
Serum Pregnancy Test[5]		x	x	x	x	x
Adverse Experiences			x	x	x	x
Concomitant Medications		x	x	x	x	x
Dispense Trial Medication		x	x	x	x	
Termination Sheet						x[6]

[1]Took place between 7 am and 10 am (i.e., 11 to 14 hours after the last dose of trial drugs)

[2]Only if mean sitting DBP ≥ 90 mmHg and no signs or symptoms of orthostatic hypotension

[3]X-ray within 1 year prior to Visit 1

[4]Blood was drawn and urine obtained in the fasted state (hematology, blood chemistry, urinalysis)

[5]If patient was a female of child-bearing potential

[6]Or sooner if premature termination occurred

The primary efficacy variable is the change in mean sitting diastolic blood pressure mean siDBP from baseline at endpoint. The primary analysis is an intent-to-treat analysis. The secondary efficacy variable is the change in mean sitting systolic blood pressure from baseline. Other variables to be analyzed include the change in standing diastolic and systolic blood pressures, sitting and standing pulse and weight.

A total of 720 completed patients (180 per treatment arm) were planned in the protocol. The treatment difference of 3 mmHg in mean sitting diastolic blood pressure was utilized as the minimum treatment difference to be detected to be statistically significant with 90% power, assuming a standard deviation of 8 mmHg. Bonferroni's multiple comparison procedure was utilized to maintain an overall significance level ≤ 0.05.

Blood pressure and pulse were analyzed at visit 3 (Week 4 after randomization), and blood pressure, pulse, and body weight were analyzed at visit 5 (Week 12 after randomization) and at the endpoint by means of a two-way analysis of covariance model with treatment and trial center as factors and

the baseline (pre-dose measurement at the randomization visit) as a covariate. Both treatment-by-center and treatment-by-baseline interactions are included in the model. The set of patients to be analyzed at each timepoint consisted of all randomized patients at that timepoint. The last post-baseline measurement of each patient carried forward is the endpoint measurement of that patient. The analyses at the endpoint is the primary endpoint.

A successful response in the control of mean sitting diastolic blood pressure was defined as a mean sitting diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease from baseline.

Results - Efficacy

Disposition

A total of 842 patients were enrolled at 38 centers in this trial. Of the enrolled patients, 734 patients were randomized at Visit 2 into the double-blind treatment period and 644 patients completed the trial. Ninety patients were discontinued prematurely during the double-blind period. There were 734 patients included in the primary efficacy analysis at endpoint, 734 patients in the adverse experience evaluation, and 700 patients in the safety laboratory evaluation. Table 50.2 outlines the disposition of patients throughout the trial and the number of patients available for other types of analysis.

Table 50.2. Patient Disposition

Number of patients	Placebo	Valsartan 80/160 OD	Valsartan 80 OD/BID	Lisinopril 10/20 OD	Total
Enrolled (Visit 1)	-	-	-	-	842
Randomized (Visit 2)	183	177	187	187	734
Completed (Visit 5)	148	157	170	169	644
Discontinued prematurely during double-blind period					
Total	35	20	17	18	90
For adverse experience	14	3	8	7	32
For abnormal laboratory value	0	1	0	0	1
For unsatisfactory therapeutic response	12	8	6	3	29
Other	9	8	3	8	28
Primary efficacy analyses					
Endpoint	183	177	187	187	734
Visit 5†	153	162	172	172	659
Assessable patients	163	157	174	171	665
Safety analyses					
Adverse experience evaluation	183	177	187	187	734
Laboratory tests*	169	168	184	179	700

†: Fifteen prematurely discontinued patients who came to Visit 5 earlier than the scheduled visit designed in the protocol had blood pressure measurements at Visit 5. They were included in the visit 5 analysis.

*: The patients counted were those who had a valid baseline value and at least one valid post-baseline value.

Demographics

Tables 50.3a, 50.3b and 50.3c lists the demographic distribution of patients randomized in study 50. There is a similar distribution between treatment groups based on age, race and sex. Patient ages ranged from 24 to 83 years (mean age = 54 years). Approximately 80% were Caucasian and 60% male. No statistically significant treatment differences were found with respect to any of the demographic and medical history variables.

Table 50.3a. Demographic Distribution Of Patients In Each Treatment Group.

Treatment	N	Sex		Race		
		Male	Female	White	Black	Other
Placebo	183	114 (62%)	69 (38%)	148 (81%)	28 (15%)	7 (4%)
Valsartan 80/160 OD	177	106 (60%)	71 (40%)	148 (84%)	22 (12%)	7 (4%)
Valsartan 80 OD/BID	187	114 (61%)	73 (39%)	153 (82%)	26 (14%)	8 (4%)
Lisinopril 10/20 OD	187	112 (60%)	75 (40%)	148 (79%)	27 (14%)	12 (6%)
Total	734	446 (61%)	288 (39%)	597 (81%)	103 (14%)	34 (5%)

Table 50.3b. Summary Statistics Of Age, Weight, And Height (All Randomized Patients)

		Mean (±S.D.)		
Treatment	N	Age (years)	Weight (lbs.)	Height (inches)
Placebo	183	54.03 (±11.78)	204.10 (±39.48)	67.78 (±3.81)
Valsartan 80/160 OD	177	53.49 (±11.07)	199.02 (±43.12)	67.39 (±4.53)
Valsartan 80 OD/BID	187	53.43 (±11.06)	201.44 (±43.56)	67.84 (±4.23)
Lisinopril 10/20 OD	187	53.86 (±10.71)	198.50 (±45.20)	67.58(±4.27)
All	734	53.70 (±11.14)	200.77 (±42.88)	67.65 (±4.21)

Table 50.3c. Baseline Mean Blood Pressures

Treatment group	N	Mean siDBP	Mean siSBP
Placebo	183	100.93 (±4.37)	154.13 (±14.39)
Valsartan 80/160 OD	177	100.81 (±4.41)	153.64 (±14.95)
Valsartan 80 OD/BID	187	101.66 (±4.83)	154.27 (±14.95)
Lisinopril 10/20 OD	187	100.99 (±4.45)	153.93 (±14.94)

Primary Endpoint - Change in siDBP

Table 50.4 shows the change in mean siDBP at endpoint, visit 5 and visit 3. Table 50.4a shows the relative mean change from placebo. There is a significant difference in all of the active treatment groups compared to placebo.

Table 50.4. Change In siDBP At Visit 3, Visit 5 And Endpoint (all randomized patients). [from volume 1.121, p. 167]

VI. ALL RANDOMIZED PATIENTS (WITHIN-TREATMENT ANALYSIS FOR MEAN SITTING DIASTOLIC BLOOD PRESSURE)

			MEANS (S.D.)			
TIMEPOINT	TREATMENT	N	BASELINE	POST	CHANGE	P-VALUE
ENDPOINT	PLACEBO	183	100.93 (4.37)	98.01 (8.96)	-2.92 (7.96)	<0.001*
	VALSARTAN 80/160 OD	177	100.81 (4.41)	93.03 (8.29)	-7.77 (7.95)	<0.001*
	VALSARTAN 80 OD/BID	187	101.66 (4.83)	93.23 (8.90)	-8.43 (7.85)	<0.001*
	LISINOPRIL 10/20 OD	187	100.99 (4.45)	91.11 (8.68)	-9.88 (7.23)	<0.001*
VISIT 5	PLACEBO	153	100.85 (4.32)	97.32 (8.76)	-3.53 (7.82)	<0.001*
	VALSARTAN 80/160 OD	162	100.62 (4.50)	92.20 (7.35)	-8.42 (7.31)	<0.001*
	VALSARTAN 80 OD/BID	172	101.49 (4.67)	92.75 (8.43)	-8.74 (6.87)	<0.001*
	LISINOPRIL 10/20 OD	172	100.98 (4.32)	90.57 (8.28)	-10.35 (6.89)	<0.001*
VISIT 3	PLACEBO	183	100.93 (4.37)	97.81 (7.89)	-3.13 (6.49)	<0.001*
	VALSARTAN 80 OD	564	101.25 (4.64)	94.15 (8.42)	-7.10 (7.05)	<0.001*
	LISINOPRIL 10 OD	187	100.99 (4.45)	93.20 (7.97)	-7.80 (6.72)	<0.001*
ENDPOINT (TITRATED PATIENTS)	VALSARTAN 80 OD->160 OD	114	101.79 (4.68)	94.69 (7.89)	-7.10 (6.82)	<0.001*
	VALSARTAN 80 OD->80 BID	124	102.92 (5.14)	95.62 (9.28)	-7.30 (7.19)	<0.001*
ENDPOINT (ALL ASSESSABLE PATIENTS)	PLACEBO	163	100.88 (4.36)	97.57 (8.68)	-3.31 (7.83)	<0.001*
	VALSARTAN 80/160 OD	157	100.76 (4.15)	92.98 (7.78)	-7.88 (7.25)	<0.001*
	VALSARTAN 80 OD/BID	174	101.76 (4.83)	93.13 (8.96)	-8.63 (7.87)	<0.001*
	LISINOPRIL 10/20 OD	171	101.18 (4.44)	90.93 (8.72)	-10.26 (7.10)	<0.001*

* INDICATES STATISTICAL SIGNIFICANCE AT THE 0.05 LEVEL (p<0.05).

Table 50.4a. Relative Mean Change From Placebo At Endpoint For siDBP (placebo - active therapy).

Treatment	Placebo Subtracted Change in mean siDBP
Valsartan 80/160 OD	-4.85 mmHg
Valsartan OD/BID	-5.51 mmHg
Lisinopril	-6.96 mmHg

There was no significant difference between once a day and twice a day valsartan dosing (vol. 1.121, p. 165; 160 mg OD vs. 80 mg BID). At visit 3 (week 4 prior to titration), both valsartan treatment groups were combined in the analysis. There was a significant difference in mean change in siDBP between valsartan and placebo (vol. 1.121, p. 164; least square estimates $p < .001$) after 4 weeks of therapy.

Table 50.5 lists the mean change in siDBP at visit 3, 5 and endpoint based on demographic variables. At endpoint, the treatment effect of blacks was greater than whites, females was greater than males and patients > 65 was greater than patients < 65 years of age. Within a demographic group, OD versus BID dosing was not different.

Table 50.5. Relative Mean Change In siDBP (mmHg) Based On Demographic Variables. (active therapy - placebo) [from vol. 1.121, table 8.1:20]

siDBP (< 65)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	146	-3.06	140	-4.18	131	-4.8	146	-4.5
Valsartan 80/160 BID	157	-3.78	153	-5.17	145	-5.11	157	-5.31
Lisinopril	155	-4.03	147	-5.32	143	-6.45	155	-6.45
siDBP (≥ 65)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	31	-5.91	31	-6.74	31	-5.43	31	-6.47
Valsartan 80/160 BID	30	-7.15	28	-7.42	27	-5.85	30	-6.49
Lisinopril	32	-7.67	31	-9.6	29	-8.64	32	-9.37
siDBP (male)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	106	-2.26	103	-4.48	97	-4.15	106	-4.14
Valsartan 80/160 BID	114	-4.06	110	-5.32	102	-4.93	114	-5.03
Lisinopril	112	-4.08	106	-5.78	104	-6.5	112	-6.68
siDBP (female)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	71	-5.62	68	-4.88	65	-6.01	71	-5.91
Valsartan 80/160 BID	73	-4.83	71	-5.81	70	-5.61	73	-6.26
Lisinopril	75	-5.62	72	-6.46	68	-7.26	75	-7.38
siDBP (Caucasian)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	148	-3.49	144	-4.55	137	-4.02	148	-4.05
Valsartan 80/160 BID	153	-3.99	148	-5.42	143	-4.53	153	-4.94
Lisinopril	148	-4.42	143	-5.76	141	-5.82	148	-6.3
siDBP (Black)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	22	-3.27	20	-3.48	18	-8.23	22	-7.9
Valsartan 80/160 BID	26	-5.97	25	-5.26	23	-8.52	26	-8.09
Lisinopril	27	-6.33	24	-6.84	21	-11.24	27	-9.18
siDBP (Other)	N	Visit 3	N	Visit 4	N	Visit 5	N	Endpoint
Valsartan 80/160 OD	7	-4.67	7	-8.1	7	-9.05	7	-9.05
Valsartan 80/160 BID	8	-5.19	8	-7.83	6	-6.98	8	-6.98
Lisinopril	12	-4.36	11	-9.27	10	-10.92	12	-10.92

Table 50.6 shows the change in siDBP at each visit for those patients who had their dose titrated at visit 3. Doubling the dose resulted in an additional decrease of 3 - 4 mmHg in siDBP in the valsartan and Lisinopril treatment groups. In this group of patients, there was no difference in the effect of once a day dosing versus BID dosing. Approximately 65% of the valsartan patients had their dose titrated.

Table 50.6. Mean Change In siDBP For Patients Who Had The Dose Titrated

	visit 3		visit 4		visit 5		Endpoint	
	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	142	-1.5	141	-3.4	129	-2.53	142	-2.01
Valsartan 80 --> 160 OD	114	-3.67	112	-7.44	104	-7.52	114	-7.1
Valsartan 80 OD --> 160 BID	124	-4.02	124	-7.87	116	-7.71	124	-7.30
Lisinopril 10/20 OD	120	-4.95	119	-8.66	116	-8.6	120	-8.39

Table 50.7 shows the mean change in siSBP from baseline at visit 3, visit 5 and endpoint. Table 50.7a shows the relative mean change from placebo.

Table 50.7. Change In siSBP At Visit 3, Visit 5 And Endpoint (all randomized patients). (vol. 1.121, p. 173)

VI. ALL RANDOMIZED PATIENTS (WITHIN- ..EATMENT ANALYSIS FOR MEAN SITTING SYSTOLIC BLOOD PRESSURE)

			MEANS (S.D.)			
TIMEPOINT	TREATMENT	N	BASELINE	POST	CHANGE	P-VALUE
ENDPOINT	PLACEBO	183	154.13 (14.4)	153.*5 (17.7)	-0.77 (12.6)	0.489
	VALSARTAN 80/160 OD	177	153.64 (15.0)	14..,6 (16.4)	-9.08 (13.7)	<0.001*
	VALSARTAN 80 OD/BID	187	154.27 (14.9)	145.22 (19.2)	-9.05 (13.9)	<0.001*
	LISINOPRIL 10/20 OD	187	153.95 (14.9)	141.80 (16.3)	-12.15 (12.4)	<0.001*
VISIT 5	PLACEBO	151	153.81 (13.9)	152.26 (16.2)	-1.55 (12.1)	0.116
	VALSARTAN 80/160 OD	142	153.20 (14.9)	143.51 (15.2)	-9.69 (13.5)	<0.001*
	VALSARTAN 80 OD/BID	172	155.59 (14.5)	144.74 (18.2)	-9.44 (13.8)	<0.001*
	LISINOPRIL 10/20 OD	172	153.37 (14.3)	141.03 (15.5)	-12.33 (12.1)	<0.001*
VISIT 3	PLACEBO	183	154.13 (14.4)	153.35 (17.2)	-0.77 (12.5)	0.402
	VALSARTAN 80 OD	544	153.97 (14.9)	145.85 (14.9)	-8.12 (11.1)	<0.001*
	LISINOPRIL 10 OD	187	155.*' (14.9)	144.98 (17.2)	-8.96 (13.5)	<0.001*
ENDPOINT (TITRATED PATIENTS)	VALSARTAN 80 OD->160 OD	114	155.57 (14.7)	146.08 (16.6)	-9.49 (13.9)	<0.001*
	VALSARTAN 80 OD->80 BID	124	1.81 (14.9)	147.40 (19.1)	-8.68 (12.7)	<0.001*
ENDPOINT (ALL ASSESSABLE PATIENTS)	PLACEBO	163	154.19 (14.5)	153.50 (17.0)	-0.69 (12.4)	0.478
	VALSARTAN 80/160 OD	157	153.57 (14.8)	144.05 (15.4)	-9.52 (13.1)	<0.001*
	VALSARTAN 80 OD/BID	174	154.08 (14.7)	144.58 (18.3)	-9.50 (..3.5)	<0.001*
	LISINOPRIL 10/20 OD	171	153.42 (14.5)	141.17 (16.1)	-12.26 (12.5)	<0.001*

* INDICATES STATISTICAL SIGNIFICANCE AT THE 0.05 LEVEL (p<0.05).

Table 50.7a. Relative Mean Change From Placebo At Endpoint For siSBP (placebo - active therapy).

Treatment Group	Placebo Subtracted Change in mean siDBP
Valsartan 80/160 OD	-8.31 mmHg
Valsartan OD/BID	-8.28 mmHg
Lisinopril	-11.36 mmHg

The mean pulse at endpoint changed by 2.8, 1.45, 1.11 and .71 beats per minute from baseline for placebo, valsartan 80/160 OD, valsartan 80 OD/BID and Lisinopril 10/20 OD respectively. A between treatment analysis suggests a significant difference in mean change in pulse between placebo and valsartan OD/BID (vol. 1.121, p. 182; p = .033). This difference is not clinically relevant.

Table 50.8 lists the response rates for each treatment group at endpoint. There is no difference in response rates between active treatment groups. All active treatment groups showed a significant increase in response rate compared to placebo. The response rate for placebo was 21%. The active treatment response rates ranged from 44 - 57%.

Table 50.8. Response Rates (from volume 1.121, p. 193)

Summary Of The Results From Between-Treatment Analysis For The Proportion Of Patients Achieving A Successful Response In the Control Of Sitting Diastolic Blood Pressure For Various Populations (Endpoint, Visit 5, Visit 5, Titrated Patients, and Assessable Patients)

1. All Randomized Patients at Endpoint

Between-Treatment Comparison		Treatment 1			Treatment 2			P-Value
(Treatment 1	vs. Treatment 2)	n	N	%	n	N	%	(Between-Treatment)
VALSARTAN 80/160 QD	vs. PLACEBO	78	177	44.07	39	183	21.31	<0.001*
VALSARTAN 80 QD/BID	vs. PLACEBO	91	187	48.66	39	183	21.31	<0.001*
LISINOPRIL 10/20 QD	vs. PLACEBO	107	187	57.22	39	183	21.31	<0.001*
VALSARTAN 80/160 QD	vs. LISINOPRIL 10/20 QD	78	177	44.07	107	187	57.22	0.012*
VALSARTAN 80 QD/BID	vs. LISINOPRIL 10/20 QD	91	187	48.66	107	187	57.22	0.098
VALSARTAN 80 QD/BID	vs. VALSARTAN 80/160 QD	91	187	48.66	78	177	44.07	0.380

Note: N = Total Number of Patients Evaluated, n = The number of patients with a Successful Response, % = n/N.

A Successful Response is defined as a trough mean sitting diastolic blood pressure < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline.

* Indicates a statistical significance at the 0.025 level (P-value < 0.025).

Safety

The safety database includes all patients randomized. Both valsartan treatment groups, once a day dosing group and the BID dosing groups, start with valsartan 80 mg OD. In the summary of safety information, the valsartan 80 mg data included information from the OD and BID dosing groups. Both the valsartan and Lisinopril treatment groups include multiple dose regimens of active therapy.

Table 50.9 list the number of patients included in the clinical and laboratory safety analysis and the number of patients discontinued for adverse events.

Table 50.9. Patient Disposition

Number of patients	Placebo	Valsartan 80/160 QD	Valsartan 80 QD/BID	Lisinopril 10/20 QD	Total
Randomized (Visit 2)	183	177	187	187	734
Completed (Visit 5)	148	157	170	169	644
Discontinued prematurely during double-blind period					
For adverse experience	14	3	8	7	32
For abnormal laboratory value	0	1	0	0	1
Safety analyses					
Adverse experience evaluation	183	177	187	187	734
Laboratory tests*	169	168	184	179	700

†: Fifteen prematurely discontinued patients who came to Visit 5 earlier than the scheduled visit designed in the protocol had blood pressure measurements at Visit 5. They were included in the visit 5 analysis.

*: The patients counted were those who had a valid baseline value and at least one valid post-baseline value.

Deaths

There were no deaths during the double blind portion of the study. Patient 274/5197/Ginsberg (placebo) died 19 days after completing the study secondary to a CVA.

Patients Discontinued for Adverse Events

Table 50.10 list the patients discontinued secondary to adverse events.

Table 50.10. List Of Patients Discontinued Due To Adverse Events (clinical or laboratory).

Treatment	Investigator	Patient #	Sex	Age	Visit	Adverse Experience
Valsartan 80 mg OD	Bloom	126/5094	F	52	3	Bone metastases
	Burch	148/5108	F	48	5	Headache
	Burch	153/5114	F	48	3	Shortness of breath
	Foley	463/5330	M	47	5	Rash
	Hilliard	704/5519	M	65	3	Tiredness
	Lahvis	296/5209	M	42	4	Congestion Drainage Lightheadedness
	Ryan	804/5575	F	70	3	Headache
	Spangenthall	957/5693	M	47	3	Headache Tingling in arms
	Surath	1129/5829	M	43	5	Elevated SGOT/SGPT
	Surath	1140/5839	M	56	3	Exertional chest pain
Valsartan 160 mg OD	Stoltz	068/5050	M	51	4	Back pain
Valsartan 80 mg BID	Lahvis	294/5210	M	52	4	Headache
Lisinopril 10 mg OD	Blumenthal	1029/5751	M	72	3	Headache Shortness of breath Lightheadedness
	Carimini	008/5006	M	51	5	Dry cough
	Carr	443/5961	F	40	4	Chest pain
	Ginsberg	271/5190	F	52	3	Productive cough
	Lahvis	286/5204	F	43	4	Nausea Dizziness Flushing Fever/Chills Achy feeling
Lisinopril 20 mg OD	Graff	588/5646	F	46	4	Fatigue
	Surath	1133/5848	M	68	4	Dry cough
Placebo	Bloom	125/5093	M	60	3	Headache
	Blumenthal	694/5497	F	70	4	Headache
	Foley	459/5339	F	65	4	Vomiting
	Garland	236/5178	M	65	5	Pneumonia
	Garland	242/5174	M	55	3	Headache
	Graff	1221/5901	M	50	4	Pain flank
	Hilliard	728/5518	F	72	3	Fatigue Nausea
	Holtzman	397/5284	M	57	4	Headache
	Kirkegaard	031/5023	M	50	3	Inguinal hernia
	Kirkegaard	034/5027	F	43	4	Urticaria
	Mersey	597/5428	M	60	3	Headache
	McGuire	322/5233	M	52	5	Impotence
	Ryan	789/5564	F	47	4	Head pressure
	Sperling	512/5368	M	55	3	Chest pain Shortness of breath Tingling in left hands

Patient 153/5114 was a 48 year old female (valsartan 80 mg once daily) who on the day of randomization received double-blind medication at approximately 10:00 am. At approximately 14:00 she experienced feeling sedated and from approximately 17:00 to 18:00 she experienced shortness of breath and

a dry cough. By 21:00 she was recovered and took her evening dose without incident. The next morning she took a dose at 9:00 am and experienced shortness of breath which appeared and resolved within several hours of that dose. Her blood pressure was taken at the site, it was noted to be 130/80 mmHg (blood pressure at screening was 161/102 mmHg, and at randomization was 153/98 mmHg). At 18:00 she again experienced shortness of breath, this time accompanied by chest tightness. She took the evening dose at approximately 21:00 and at approximately midnight called the investigator complaining of asthma-like symptoms. She was seen at the site the next day, blood pressure was 130/86 mmHg. As a result of these events, the investigator discontinued the patient from the trial. The patient had no prior history of asthma. Concomitant medications consisted of simvastatin and estradiol. A chest x-ray report written approximately two months prior to the patient's screening for the trial noted the pulmonary vasculature as centrally congested and the presence of mild interstitial lung disease thought to represent interstitial edema. The investigator stated he had discussed the report with the patient's cardiologist and neither of them felt the patient had congestive heart failure. The investigator also noted the patient had a similar event when receiving therapy with enalapril.

Patient 1129/5829 was a 43 year old male (valsartan 80 mg OD) who entered the trial with screening SGOT and SGPT levels of 35 U/L and 76 U/L respectively (normal range: SGOT 0-40 U/L, SGPT 0-45 U/L). LDH and alkaline phosphatase levels were within the normal range. At randomization, SGOT and SGPT levels were 44 U/L and 97 U/L (randomization criteria: SGOT ≤ 80 U/L; SGPT ≤ 90 U/L). A repeat obtained approximately one month later at the next scheduled trial visit showed levels for SGOT and SGPT of 40 U/L and 92 U/L respectively. At the next scheduled trial visit levels for SGOT and SGPT were 52 U/L and 118 U/L respectively. As a result the investigator discontinued the patient and performed a hepatitis screen. The hepatitis screen was negative, repeat values obtained eight days after discontinuation showed SGOT and SGPT levels of 46 U/L and 113 U/L respectively. Repeat values obtained approximately six weeks later showed SGOT and SGPT levels of 50 U/L and 96 U/L respectively. LDH and alkaline phosphatase levels did not fluctuate significantly from screening values during the trial. The patient reported itching which resolved after five days of treatment with moisturizing cream and musculoskeletal rib pain for which he took acetaminophen during the double-blind period of the trial. No other concomitant medications were reported by the patient during the trial. The patient claimed he did not drink alcohol. No etiology was identified for the elevated SGOT and SGPT values.

Patient 459/5339 was a 65 year old female (placebo) who five days after starting double-blind treatment reported experiencing severe intermittent diarrhea. The diarrhea continued for approximately one month during which time the patient also reported an episode of vomiting which lasted for one day. Thirty-nine days after randomization she reported severe vomiting and was treated in an emergency room with an injection of prochlorperazine; diagnosis was esophageal spasm. Laboratory work conducted in the emergency room showed the patient's SGOT level as 83 U/L (range 15-37 U/L) and LDH as 192 U/L (range 100-192U/L). Laboratory values obtained by the investigator four days later showed levels for SGOT as 82 U/L (range 0-40), SGPT as 102 (range 0-45) and LDH as 203 U/L (range 0-240). Baseline values were: SGOT- 20 U/L, SGPT-15 U/L and LDH-196 U/L respectively. Niacin was taken concomitantly during the trial for hyperlipidemia. As a result of the patients adverse experiences, the investigator discontinued treatment with trial medication and niacin. The investigator commented that the patients symptoms were consistent with possible liver toxicity most likely caused by the niacin. He also noted the patient had a previous adverse experience with niacin therapy. Subsequent to discontinuation from the trial the patient revealed she was also taking fluoxetine, alprazolam and temazepam for anxiety and depression.

Patient 236/5178 was a 65 year old male (placebo) who fifty-seven days after randomization presented to an emergency room complaining of shortness of breath. A diagnosis of acute hypertensive crisis with blood pressure of 240/140 mmHg was made in the emergency room. Radiological evaluation done in the emergency room showed a left upper lobe process for which the patient was admitted to the hospital. The patient was treated with I.V. ceftrioxone and p.o. clonidine, and nifedipine. Blood pressure was controlled within 48 hours after admission. I.V. ceftrioxine was administered for four days as treatment for pneumonia, the patient was then discharged in stable condition.

Table 50.11 lists the patients who experienced serious adverse events but were not discontinued from the trial.

Table 50.11. Patients With Serious Adverse Events That Did Not Leads To Discontinuation.

Treatment	Investigator	Patient #	Sex	Age	Visit	Adverse Experience
Valsartan 80 mg BID	Ruff	347/5247	M	62	5	Sessile adenomatous polyp
	Waks	1197/5896	F	74	Post-trial	Overdose (carbamazepine)
Lisinopril 10 mg OD	McGuire	317/5227	F	44	5	Uterine fibroids
Placebo	Reed	490/5351	M	53	5	Umbilical hernia

Clinical Adverse Events

There did not appear to be an increased incidence of orthostatic blood pressure[9] changes in patients receiving valsartan compared to placebo (NOTE: Standing BP was measured after the patient stood for 2 minutes).

The overall incidence of adverse events ranged from 58.3% to 63.4% in the treatment groups (NOTE: no distinction is made between OD and BID valsartan dosing). When the incidence rate is broken down by low or high dose, the high dose of valsartan and Lisinopril had a greater incidence of adverse events (table 50.12.). Table 50.12 lists adverse events that occurred with a frequency greater than 3%.

Table 50.12. Incidence Of Most Frequently Reported (In ≥ 3% Of Patients) Adverse Experiences

	Valsartan			Lisinopril			Placebo
	80 mg	160 mg	All Doses	10 mg	20 mg	All Doses	All Doses
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total Patients	364 (100)	238 (100)	364 (100)	187 (100)	120 (100)	187 (100)	183 (100)
With AEs	165 (45.3)	117 (49.2)	228 (62.6)	85 (45.5)	60(50.0)	109 (58.3)	116 (63.4)
Headache	44 (12.1)	30 (12.6)	68 (18.7)	16 (8.6)	11 (9.2)	23 (12.3)	41 (22.4)
Infection Viral	19 (5.2)	8 (3.4)	26 (7.1)	2 (1.1)	3 (2.5)	5 (2.7)	8 (4.4)
URI	9 (2.5)	13 (5.5)	21 (5.8)	7 (3.7)	5 (4.2)	12 (6.4)	8 (4.4)
Fatigue	8 (2.2)	6 (2.5)	14 (3.8)	5 (2.7)	4 (3.3)	7 (3.7)	4 (2.2)
Pain Back	8 (2.2)	7 (2.9)	14 (3.8)	5 (2.7)	4 (3.3)	8 (4.3)	6 (3.3)
Diarrhea	8 (2.2)	6 (2.5)	13 (3.6)	3 (1.6)	5 (4.2)	7 (3.7)	5 (2.7)
Coughing	8 (2.2)	4 (1.7)	12 (3.3)	12 (6.4)	6. (5.0)	17 (9.1)	3 (1.6)
Dizziness	9 (2.5)	3 (1.3)	12 (3.3)	5 (2.7)	6 (5.0)	10 (5.3)	6 (3.3)
Sinusitis	6 (1.6)	7 (2.9)	12 (3.3)	8 (4.3)	2 (1.7)	10 (5.3)	5 (2.7)

Coughing occurred more frequently in the Lisinopril treatment group compared to valsartan and placebo. Table 50.13 lists the adverse events that occurred in ≥ 1% but ≤ 3% of the valsartan patients.

Table 50.13. Adverse Events With An Incidence Of ≥ 1% And ≤ 3% In The Valsartan Treated Patients.

Adverse Event	Valsartan N = 364	Lisinopril N = 187	Placebo N = 183
Allergic Reaction*	4 (1.1%)	0	0
Edema Dependent	4 (1.1%)	0	2 (1.1%)
Edema Peripheral	4 (1.1%)	4 (2.1%)	2 (1.1%)
Fatigue	14 (3.8%)	7 (3.7%)	2 (1.1%)
Injury	4 (1.1%)	1 (.5%)	2 (1.1%)
dyspepsia	6 (1.6%)	6 (3.2%)	3 (1.6%)
pain abdominal	9 (2.5%)	4 (2.1%)	4 (2.2%)
periodontitis	5 (1.4%)	2 (1.1%)	3 (1.6%)
infection viral	26 (7.1%)	5 (2.7%)	8 (4.4%)
arthralgia	5 (1.4%)	5 (2.7%)	4 (2.2%)
cramps muscle	4 (1.1%)	1 (.5%)	0
pain arm	8 (2.2%)	3 (1.6%)	2 (1.1%)

[9] Patients were judged to exhibit a clinically significant postural decrease in blood pressure as measured from the sitting to standing position by showing either a) a decrease of ≥ 10 mmHg in diastolic blood pressure and/or, b) a decrease of ≥ 20 mmHg in systolic blood pressure.

Table 50.13. Adverse Events With An Incidence Of ≥ 1% And ≤ 3% In The Valsartan Treated Patients.

Adverse Event	Valsartan N=364	Lisinopril N=187	Placebo N=183
pain back	14 (3.8%)	8 (4.3%)	6 (3.3%)
anxiety	4 (1.1%)	1 (.5%)	1 (.5%)
insomnia	4 (1.1%)	2 (1.1%)	2 (1.1%)
bronchitis	7 (1.9%)	3 (1.6%)	2 (1.1%)
pharyngitis	6 (1.6%)	6 (3.2%)	1 (.5%)
rhinitis	9 (2.5%)	7 (3.7%)	7 (3.8%)
pruritus	4 (1.1%)	4 (2.1%)	0
angioedema	1 (.3%)	0	0

(from vol. 1.121, table 9.1:2); * distinguished from allergy in the summary table

One patient (795/5571/Ryan) in the valsartan 80 mg dose group experienced a mild case of lip and tongue swelling presumably due to a seafood allergy which the investigator termed angioedema on the case report form. The patient was treated with a single dose of chlorpheniramine maleate. This event occurred at visit 5 and is not clear that the patient received an another dose of valsartan. As a result, it is not clear that this event was unrelated to valsartan therapy.

Table 50.14 lists the incidence within each treatment group by sex of all adverse events. The incidence of total adverse events is consistently higher in females regardless of treatment groups. Individual adverse events will be evaluated by sex in the overall summary of safety.

Table 50.14. Incidence Of Total Adverse Events By Sex And Treatment Group.

	Valsartan		Lisinopril		Placebo	
	All Doses		All Doses		All Doses	
	M	F	M	F	M	F
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total Patients	220 (100)	144 (100)	112 (100)	75 (100)	114 (100)	69 (100)
With AEs	127 (57.7)	101 (70.1)	58 (51.8)	51 (68.0)	67 (58.8)	49 (71.0)

The overall incidence of adverse events in valsartan treated patients was similar for black and white patients.

Laboratory Results

Laboratory evaluations consisting of a complete blood count, blood chemistry and urinalysis were done at Visits 1, 2 and 5 (Weeks -2/-4, 0 and 12) following a 12 hour fast. Repeat specimens obtained for safety purposes were excluded from the summaries. Repeat specimens obtained for verification of values possibly disrupted by improper handling of specimens were included in the summaries; improper specimens were excluded. Occasionally, repeat specimens were analyzed at a local laboratory. These values were obtained for safety purposes and were excluded from the summaries.

For all laboratory variables in all dose groups, the difference in group mean and median values from baseline to terminal laboratory did not exhibit any clinically significant trends except for CPK. The mean change in CPK from baseline to the terminal visit for all treatment groups are listed in table 50.15. The valsartan and Lisinopril groups are further divided by titrated dose. In patients who received valsartan 160 mg total daily dose (OD or BID), the mean CPK increased while the mean CPK decreased in the placebo and Lisinopril group. The valsartan 80 mg per day cohort has a mean CPK change consistent with the Lisinopril and placebo cohorts. If all valsartan dosing cohorts are combined, the mean change in CPK is 5.8 U/L.

Table 50.15. Mean Change In CPK From Baseline To Terminal Visit.

Treatment Group	Mean change in CPK from baseline (U/L)
Valsartan OD: 80 mg	-12.5
Valsartan BID: 80 mg	5.7
Valsartan OD: 160 mg	26.3
Lisinopril OD: 10 mg	-1.8
Lisinopril OD: 20 mg	-4.7
Placebo	-6.0

The laboratory data was also evaluated by the number of patients who were normal at baseline and had an abnormality (high or low) at endpoint. Table 50.16. list some lab parameters and the incidence of values outside the normal ranges at the terminal visit. This includes only patients who had normal values at baseline. Compared to placebo, valsartan did not appear to have an excess amount of lab values outside of the normal range.

Table 50.16. Percent Of Patients With Laboratory Values Outside The Normal Range.

	valsartan			placebo	
	N	high	low	N	high	low
hemoglobin	352	3.7%	1.7%	169	5.9%	0.6%
hematocrit	352	6.3%	0.6%	169	12.4%	0%
glucose	339	15.0%	2.9%	164	15.2%	4.3%
BUN	350	1.4%	0	168	0.6%	0
creatinine	350	1.4%	0.3%	168	0.6%	0.6%
sodium	350	0.9%	0.6%	168	0.6%	0.6%
potassium	339	0.6%	0.3%	163	0	1.2%
uric acid	350	2.3%	0.3%	168	1.8%	0.6%
SGOT	350	4.6%	0	168	8.3%	0
SGPT	350	8.0%	0	168	10.1%	0
CPK	350	26.6%	0	166	23.5%	0

Table 50.17 list the number of patients who had changes from baseline outside specified ranges. There does not appear to be a significant difference between treatment groups.

Table 50.17. Number Of Patients With Specified Percent Change From Baseline For Selected Laboratory Tests.

	Valsartan	Valsartan	Valsartan	Lisinopril	Lisinopril	Placebo
	80 mg OD	80 mg BID	160 mg OD	10 mg	20 mg	Total
Laboratory Tests	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
BUN - Total Patients	120	122	108	63	115	168
> 50 % increase	10 (8.33)	5 (4.10)	4 (3.70)	2 (3.17)	7 (6.09)	6 (3.57)
Creatinine - Total Patients	120	122	108	63	115	168
> 50 % increase	2 (1.67)	0 (0)	1 (0.93)	1 (1.59)	1 (0.87)	0 (0)
Sodium - Total Patients	120	122	108	63	115	168
> 7 % increase	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
> 5 % decrease	0 (0)	1 (0.82)	1 (0.93)	0 (0)	0 (0)	1 (0.60)
Potassium - Total Patients	114	119	106	63	112	163
> 20 % increase	3 (2.63)	4 (3.36)	1 (0.94)	3 (4.76)	6 (5.41)	6 (3.70)
> 20 % decrease	1 (0.88)	0 (0)	2 (1.89)	1 (1.59)	0 (0)	1 (0.62)
Calcium - Total Patients	120	122	108	63	115	168
> 10 % increase	5 (4.17)	2 (1.64)	2 (1.85)	1 (1.59)	3 (2.61)	4 (2.38)
> 10 % decrease	0 (0)	0 (0)	1 (0.93)	0 (0)	0 (0)	1 (0.60)
SGOT - Total Patients	120	122	108	63	115	168
> 150 % increase	0 (0)	1 (0.82)	0 (0)	0 (0)	1 (0.87)	1 (0.60)
SGPT - Total Patients	120	122	108	63	115	168
> 150 % increase	1 (0.83)	3 (2.46)	3 (2.78)	0 (0)	4 (3.48)	6 (3.57)
CPK - Total Patients	119	122	109	63	115	166
> 300 % increase	0 (0)	2 (1.64)	2 (1.83)	0 (0)	3 (2.61)	3 (1.81)

Patient 632/5449/Pruitt, a 30 year old male patient randomized to valsartan 80 mg OD, had a baseline creatinine of 1.1 mg/dL and a terminal visit value of 1.7 mg/dL. The patient had no relevant medical history and was asymptomatic at the time the change occurred. The patient was prematurely terminated at Visit 3 (31 days after randomization) for non-compliance; repeat laboratory was not obtained.

Patient 382/5274/Wright, a 63 year old male patient randomized to valsartan 80 mg BID, had a baseline SGOT of 22 U/L and a terminal visit value of 77 U/L. No repeat laboratory was obtained.

Twelve of the fifteen patients to exhibit a > 150% increase in SGPT, had terminal visit values which were within normal limits. The three patients with terminal visit values which fell outside the normal range are displayed in table 50.18. The increase in SGPT does not appear to be clinically significant.

Table 50.18. Patients With Abnormal SGPT.

Patient	Treatment Group	Age	Sex	Baseline Value	Terminal Value
007/5005/Carimi	Valsartan 80 mg OD	60	M	21	53
565/5404/Graff	Valsartan 80 mg BID	52	M	16	53
188/5137/Chryant	Placebo	57	M	27	70

Normal range = 0 - 45 U/L

Two patients demonstrated a > 150% increase in both SGOT and SGPT which fell outside the normal range post-baseline. These patients are displayed in table 50.19.

Table 50.19. Patients With Abnormal SGOT and SGPT.

				SGOT			SGPT		
Patient	Treatment	Age	Sex	Base	Interim	Term	Base	Interim	Term
589/5421/Mersey	Lisinopril 20 mg	69	M	30	101	41	26	69	34
459/5339/Foley	Placebo	65	F	20	*	82	15	*	102

Normal Range: SGOT = 0 - 40 U/L; SGPT = 0 - 45 U/L; * not done

Twenty-nine days after beginning treatment with Lisinopril, Patient 589/5421/Mersey developed abdominal pain. An interim laboratory was performed revealing an increase in SGOT and SGPT levels. Six days after the abdominal pain began, a hepatitis screen and repeat SGOT and SGPT values were obtained. The SGOT and SGPT values returned to within baseline range however, the hepatitis screen was positive for hepatitis B antigens. The patient was treated for fourteen days with omeprazole for the abdominal pain. The SGOT and SGPT values at terminal visit remained within baseline range.

Thirty-nine days after beginning treatment with placebo, Patient 459/5339/Foley experienced severe vomiting and was treated in an emergency room with prochlorperazine. Laboratory work conducted in the emergency room showed the patient's SGOT level as 83 U/L; SGPT value was not obtained. SGOT and SGPT levels at terminal visit are displayed above. Concomitant diagnosis at Visit 1 included hyperlipidema, anxiety and depression, and insomnia. Concomitant therapy included niacin, fluoxetine, alprazolam, and temazepam. In addition to the severe vomiting, the patient also reported experiencing severe intermittent diarrhea for approximately one month. Repeat laboratory, conducted after trial termination by a local laboratory, returned to within baseline range.

Protocol 51. Multinational, Randomized, Double-Blind, Placebo- And Active-Controlled, Between Patient Trial To Determine The Anti-hypertensive Effect And To Assess The Tolerability Of Valsartan 80 Mg Once Daily In Patients With Uncomplicated Essential Arterial Hypertension Treated For Eight Weeks. (Dates: September 1, 1994 - February 28, 1995)

This was a multinational, randomized, double-blind, placebo- and active-controlled trial to compare once-a-day oral administration of valsartan 80 mg, placebo or enalapril 20 mg in out-patients with uncomplicated essential arterial hypertension.

After completion of a 2-week, placebo run-in period, patients with a mean siDBP $\geq$ 95 mmHg and $\leq$ 115 mmHg were randomized to valsartan 80 mg, placebo or enalapril 20 mg in ratio of 2:2:1 respectively. The duration of the double-blind treatment was 56 days. Figure 51.1 shows the study outline.

Figure 51.1. Study Outline

	Wash-out Period	Single-blind placebo run-in	Double-blind treatment		
			Randomization ↓		
Visit	1	2	3	4	Final[2)]
Day	-21	-14	0	28[1)]	56
		Placebo	Valsartan 80 mg o.d.		
			Enalapril 20 mg o.d.		
			Placebo o.d.		

1) In case of mean siDBP ≥ 110 mmHg or mean sitting systolic blood pressure (siSBP) ≥ 180 mmHg, the patient could be prematurely discontinued from the trial if deemed necessary by the investigator

2) or on premature discontinuation.

The sample size was determined to detect a difference of at least 3.5 mmHg in mean siDBP between valsartan 80 mg once daily and placebo. In order to achieve this, allowing for a dropout rate of 5%, and a standard deviation of 8 mmHg and to ensure 90% power at the 5% level of significance, it was planned to randomize a total of 290 patients in a ratio of 2:2:1 to valsartan, placebo and enalapril respectively (i.e. 116, 116 and 58 patients respectively). It was planned that 43 centers from 3 countries (Italy, France and The Netherlands) would be involved.

The primary efficacy variable was the change from baseline in mean sitting diastolic blood pressure after 56 days of therapy. The secondary efficacy variable was the change from baseline in mean sitting systolic blood pressure after 56 days. The other efficacy variables were the change from baseline in standing diastolic blood pressure and standing systolic blood pressure.

Table 51.1 lists the procedures performed during the study.

Table 51.1. Study Procedures

	Phase	Wash-out	Run-in	Trial Treatment Period		
Procedure	Day	-21	-14	0	28	56
	Visit	1	2	3*	4	Final[3]
Informed consent, personal data, physical exam., medical history, concomitant diseases, previous/current medication/non-drug therapy		x				
Check of inclusion criteria		x		x		
Check of exclusion criteria		x	x	x		
Weight		x	x	x	x	x
Pulse rate, blood pressure			x	x	x[1]	x
Adverse experiences, concomitant medication/non-drug therapy			x	x	x	x
Laboratory examinations[2] (hematology, blood chemistry, urine)			x			x
Trial medication			d	cd	cd	c

Notes:

1 In cases of mean siDBP ≥ 110 mmHg or mean siSBP ≥ 180 mmHg, the patient may be prematurely discontinued from the trial if deemed necessary by the investigator

2 Measurements of total creatine kinase activity were to be performed each time a patient complained of neck pain, back pain, myalgia or any other symptoms which can be related to myolysis. If the total creatine kinase activity increased above the upper limit of the normal range, creatine kinase isoenzyme fractions were also to be determined

3 Or in the event of premature discontinuation. * Randomization

D Capsules dispensed

C Date/time last dose of trial medication taken and amount of trial medication returned.

Results

Disposition

Table 51.1 lists the number of patients randomized and completing the trial. Three hundred and forty-eight patients were randomized at 43 centers in France, Italy and the Netherlands. Three-hundred and thirty-five patients completed the study.

Table 51.2. Patient Disposition

Number of Patients	valsartan 80 mg	placebo	enalapril 20 mg	total
Enrolled				373
Randomized	137	142	69	348
Completed	133	137	65	335
Discontinued Prematurely				
Reasons Discontinued				
Adverse experience	1	3	0	4
Unsatisfactory therapeutic effect	1	1	1	3
Patient does not meet protocol criteria	1	1	1	3
Lost to follow-up	1	0	1	2
Abnormal laboratory values	0	0	1	1
Total	4	5	4	13

Table 51.3 list the demographic characteristics for each treatment group. There was an equal number of males and females with 181 males (52%) and 167 females (48%). The average age was approximately 53 years. Baseline siDBP was similar among treatment groups. There were only 5 non-Caucasian patients enrolled (3 Blacks, 1 Asian. 1 Other).

Table 51.3. Demographics

Treatment Group	N	Baseline siDBP	Sex		Age (years)
			Male	Female	
valsartan 80 mg	137	101.2±4.5	65	72	53.1±12.4
placebo	142	101.8±4.4	76	66	53.1±12.9
enalapril 20 mg	69	102.2±4.2	40	29	52.5±10.3
total	348		181	167	

Table 51.4 list the mean change in siDBP at endpoint for each treatment group. Based on the estimated differences of least square means from an ANCOVA model (with or without interaction terms for baseline and treatment-by-center), valsartan and enalapril treatment effects were significantly different form placebo.

Table 51.4. Change From Baseline to Mean Sitting Diastolic Blood Pressure (mmHg)
(All randomized patients)

	valsartan 80 mg	placebo	enalapril 20 mg
Number of patients	136	142	69
Mean siDBP at baseline (Visit 3)	101.2	101.8	102.2
Mean siDBP at end point (Visit 5)	91.7	97.3	92.7
Mean change from baseline	-9.5	-4.5	-9.4
Least squares mean*	-9.4	-5.3	-9.5
Difference vs placebo	-4.1	-	-3.2
p value	<0.001		0.003

* includes interaction terms

Table 51.5 lists the mean change in siSBP at endpoint.

Table 51.5 Change From Baseline In Mean Sitting Systolic Blood Pressure (mmHg)
(All randomized patients)

	valsartan 80 mg	placebo	enalapril 20 mg
Number of patients	136	142	69
Mean siSBP at baseline (Visit 3)	161.8	161.0	161.5
Mean siSBP at end point (Visit 5)	149.4	155.3	148.4
Mean change from baseline	-12.4	-5.7	-13.1

The response rate (patients with siDBP < 90 mmHg or if there had been a decrease of at least 10 mmHg from baseline) was 54%, 20% and 58% in the valsartan, placebo and enalapril groups respectively. The difference between the valsartan and placebo response rates was significant (chi square $p < .001$).

Females tended to have a slightly greater decline in siDBP compared to males for both valsartan and enalapril treatments.

Table 51.6. Mean Change From Baseline In Sitting Diastolic And Systolic Blood Pressure By Sex

	Diastolic Blood Pressure (mmHg)			Systolic Blood Pressure (mmHg)		
Treatment Group	Males	Females	Difference	Males	Females	Difference
valsartan 80 mg	-8.7	-10.2	1.5	-10.7	-14.0	3.3
placebo	-4.9	-4.1	-0.8	-5.5	-5.8	0.3
enalapril 20 mg	-7.5	-12.1	4.6	-11.7	-15.1	3.4

The change in siDBP for patients < 65 was not different from those ≥ 65 years (table 51.7).

Table 51.7. Mean Change From Baseline For Sitting Diastolic And Systolic Blood Pressure By Age

	Diastolic Blood Pressure (mmHg)				Systolic Blood Pressure (mmHg)			
	N	< 65 years	N	≥ 65 years	N	<65 years	N	≥ 65 years
valsartan 80 mg	113	-9.7	23	-8.7	113	-13.2	23	-8.7
placebo	57	-4.3	12	-5.4	57	-5.1	12	-7.7
enalapril 20 mg	113	-9.9	29	-7.3	113	-13.9	29	-9.3

Results - Safety

There were no deaths in this study.

Five patients withdrew prematurely due to adverse events. Table 51.8 lists the patients discontinued due to adverse events.

Table 51.8. Patient Discontinued Prematurely For Adverse Events Or Abnormal Labs.

Center # / Randomization #	Treatment	Sex	Age	Visit # /Day	Adverse Event
2/384	valsartan	F	30	5/55	Renal Colic
31/152	placebo	M	37	5/45	Nausea and dyspepsia
3/397	placebo	M	59	5/36	CVA
2/861	placebo	M	59	4/25	Dizziness
6/28	enalapril	M	51	4/28	Increased hepatic enzymes*

* increased at baseline also.

Patient 384 (valsartan) had a 6 year history of essential hypertension and had a mean sitting BP of 160/98 mmHg on starting randomized treatment. On Day 39, this patient complained of moderate renal colic which the investigator considered to be unrelated to the trial medication. The patient was hospitalized. Following treatment with ketoprofen and ciprofloxacin she had lithuresis. On Days 40 and 43, this patient experienced moderate hypertensive crises which the investigator considered to be of possible relationship to the trial medication. In both cases, treatment with one capsule of nifedipine was given. The trial medication was discontinued on Day 53 and the patient was discharged on enalapril. The investigator reported that this patient made a complete recovery.

A total of 53 patients (15%) reported one or more adverse experience. The incidence of adverse events ranged from 14.7% for valsartan, 13% for enalapril and 16.9% for placebo. No adverse experience occurring in patients in either the valsartan or enalapril groups was considered severe. There was no

clinically relevant difference in the incidence of any on adverse event. Patient 1350/343 experienced postural dizziness at visit 5 (v. 156, p. 136)

There were no significant change in the mean change in laboratory parameters between baseline and endpoint. There were no clinically significant changes in individual laboratory parameters.

ACTIVE CONTROL TRIALS

Index 2 lists the active controlled trials included in the NDA.

Index 2. Active Control Trials

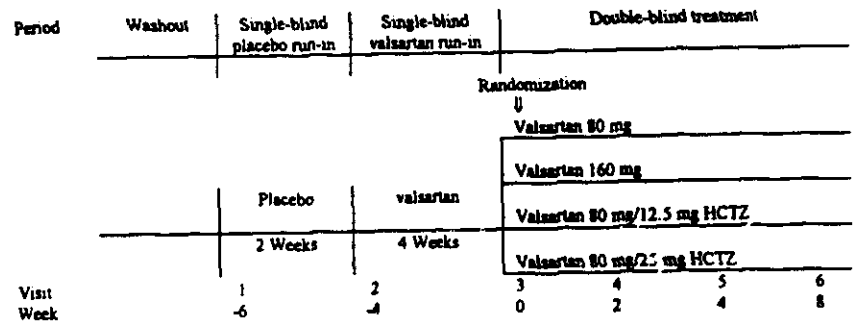
Study #	Design	Measure of Efficacy	Treatment Groups	N
19	- r, db, mc (USA), p, 8 wk Rx period - hypertensives with siDBP ≥ 95 mm Hg and ≤ 120 mm Hg after valsartan 80 mg - 2 wk placebo period then 4 week valsartan 80 mg sb period then 8 wk db Rx period	1° endpoint: change in trough siDBP at 8 weeks	- valsartan 80 mg - valsartan 160 mg - valsartan 80 mg/HCTZ 12.5 mg - valsartan 80 mg/HCTZ 25 mg	183 172 176 177
20	- r, db, mc (France), p, 12 wk Rx period - hypertensives with siDBP ≥ 95 mm Hg and ≤ 120 mm Hg - at wk 8 of db treatment, HCTZ 12.5 mg added based on response	1° endpoint: change in trough siDBP at 8 and 12 weeks 2° endpoint: change in trough siSBP at 8 and 12 weeks	- valsartan 80 mg - enalapril 20 mg	94 95
21	- r, db, mc (Italy), p, 12 wk Rx period - hypertensives with siDBP ≥ 95 mm Hg and ≤ 120 mm Hg - at wk 8 of db treatment, amlodipine 5 mg added based on response	1° endpoint: change in trough siDBP at 8 and 12 weeks 2° endpoint: change in trough siSBP at 8 and 12 weeks	- valsartan 80 mg - amlodipine 5 mg	84 85
22	- r, db, mc (Germany), p, 12 wk Rx period - hypertensives with siDBP ≥ 95 mm Hg and ≤ 115 mm Hg - at wk 8 of db treatment, atenolol 50 mg added based on response	1° endpoint: change in trough siDBP at 8 and 12 weeks 2° endpoint: change in trough siSBP at 8 and 12 weeks	- valsartan 80 mg - HCTZ 25 mg	82 85
27	- r, db, mc (Italy), p, 12 wk Rx period - hypertensives with siDBP ≥ 95 mm Hg and ≤ 115 mm Hg; creatinine clearance 20 - 70 ml/min. - at wk 8 of db treatment, furosemide added based on response	1° endpoint: change in trough siDBP at 12 weeks 2° endpoint: change in trough siDBP and GFR	- Valsartan 40 mg --> 80 mg - Lisinopril 2.5 or 5 mg --> 5 or 10 mg	36 38
28	- r, db, mc (United Kingdom), p, 52 wk Rx period, dose titration - hypertensives with siDBP ≥ 95 mm Hg and ≤ 115 mm Hg; creatinine clearance 20 - 70 ml/min. - at ≥ wk 2 of db treatment, HCTZ added based on response	1° endpoint: number of responders at 12 and 52 weeks	- Valsartan 40 mg --> 80 mg - Lisinopril 2.5 mg --> 20 mg	334 167
33	- r, db, mc (USA), 6 wk Rx period - all patients had a history of ACEI induced cough - 2 to 4 week placebo period then 4 week lisinopril challenge period then 2 week placebo period then 6 week db Rx period	1° endpoint: incidence of cough	- valsartan 80 mg - HCTZ 25 mg - lisinopril 10 mg	42 42 45

r = randomized; db = double-blind; Rx = treatment; sc = single center; p = parallel dose; mc = multi-center; wk = week;

Protocol 19. A Double-Blind, Randomized, Active Controlled, Parallel Design Trial Comparing The Efficacy Of The Combination Of HCTZ 12.5 Mg Or 25 Mg Plus Valsartan 80 Mg Once Daily To Valsartan 160 Mg Once Daily In Hypertensive Patients Inadequately Controlled With Valsartan 80 Mg Once Daily
(4/13/94 - 1/25/95)

This is a randomized, multi-center (USA), active control, double-blind, parallel trial in patients with essential hypertension (mean siDBP ≥ 95 and ≤ 115 mmHg). Patients with siDBP ≥ 95 and ≤ 120 mmHg were enrolled into a two week single blind placebo run-in period at visit 1. At visit 2, subjects with siDBP siDBP ≥ 95 and ≤ 120 mmHg received valsartan 80 mg for four weeks (single blind). At visit 3, patients with siDBP ≥ 95 and ≤ 115 mmHg were randomized to double-blind treatment with either valsartan 80 mg, valsartan 160 mg, valsartan 80 mg + HCTZ 12.5 mg or valsartan 80 mg + HCTZ 25 mg for 8 weeks. Patients were stratified by age. Figure 19.1 illustrates the study design.

Figure 19.1. Study Design [vol. 1.159, p. 8]



The primary endpoint was the change in trough siDBP at endpoint from baseline. The secondary endpoint was the change in trough siSBP at endpoint from baseline. The project sample size was 800 patients (to detect a treatment difference = 3 mm Hg, s.d. = 8 mm, power = 90%, $\alpha = .025$). A protocol amendment permitted enrollment to terminate prematurely to permit 450 completed patients.

Results

Valsartan 80 mg was initiated in 908 subjects. Twenty-one of these subjects withdrew during the valsartan run-in due to adverse events. Fifty-six centers randomized 708 patients. Six hundred and thirty-one patients completed the study. Seventy-seven patients discontinued prior to completion of the eight week double-blind treatment period. Table 19.1 list the patient disposition for the study.

Table 19.1. Patient Disposition

	Valsartan 80 mg	Valsartan 160 mg	Valsartan 80 mg / HCTZ 12.5 mg	Valsartan 80 mg / HCTZ 25 mg	Total
Enrolled	-	-	-	-	1938
Valsartan Run-in	-	-	-	-	908
Randomization	183	172	176	177	708
Completed	157	153	158	163	631
Withdrew	26	19	18	14	77

Table 19.2. lists the reason patients withdrew prematurely. Twenty-two patients withdrew treatment because of adverse events in the double-blind treatment period.

Table 19.2. Reasons Patients Withdrew Prematurely from Double-Blind Treatment

	Valsartan 80 mg	Valsartan 160 mg	Valsartan 80 mg / HCTZ 12.5 mg	Valsartan 80 mg / HCTZ 25 mg
Adverse Events	6	7	5	4
Abnormal Lab	2	0	0	0
Unsatisfactory Response	6	4	6	3
Did not fulfill protocol criteria	1	0	1	1
Non-compliant	2	4	3	0
Withdrew Consent	3	2	1	1
Lost to follow-up	4	0	0	3
Administrative Reasons	2	2	2	2
Total	26	19	18	14

The average age of randomized patients was 53.2 years. Two-thirds of the patients were male and 71% were Caucasian. Fifteen percent of the patients were black and another 14% were various other races. Table 19.3 list the demographics for each treatment group.

Table 19.3. Demographics (%)

	Valsartan 80 mg	Valsartan 160 mg	Valsartan 80 mg / HCTZ 12.5 mg	Valsartan 80 mg / HCTZ 25 mg
N	183	172	176	177
Male (%)	63	63	66	70
Caucasian (%)	72	72	69	71
Black (%)	15	13	16	15
Other race (%)	13	15	15	15
< 65	85	85	86	80

Table 19.4 lists the mean siDBP measurements at baseline and at endpoint. The change in siDBP for both combination therapy treatment groups were significantly different from both monotherapy groups. The monotherapy treatment groups were not significantly different from each other. The Valsartan 80 mg / HCTZ 25 mg had a significantly greater effect than Valsartan 80 mg / HCTZ 12.5 mg . If patients with visit 6 measurements were only included in the analysis, there is no difference in the conclusions.

Table 19.4. Mean Sitting DBP Measurements and Change from Baseline at Endpoint [vol. 1.159, p. 181]

	Valsartan 80 mg	Valsartan 160 mg	Valsartan 80 mg / HCTZ 12.5 mg	Valsartan 80 mg / HCTZ 25 mg
N*	179	171	176	176
Baseline**	100.21 (4.94)	99.83 (4.5)	99.89 (5.14)	100.6 (5.13)
Endpoint	94.95 (9.17)	94.12 (8.12)	92.04 (9.33)	90.22 (9.69)
Change	- 5.26 (7.72)	- 5.71 (7.19)	- 7.85 (7.96)	- 10.38 (8.04)

* the number of subjects with at least one post-baseline BP measurement; ** visit 3 measurement

Table 19.5 lists the mean siSBP measurements at baseline and at endpoint. The between treatment analysis yielded similar outcomes as observed with siDBP (i.e. combination significantly better than monotherapy, combinations significantly different from each other).

9.2
3.81
5.51

Table 19.5. Mean Sitting SBP Measurements and Change from Baseline at Endpoint [vol. 1.159, p. 183]

	Valsartan 80 mg	Valsartan 160 mg	Valsartan 80 mg / HCTZ 12.5 mg	Valsartan 80 mg / HCTZ 25 mg
N*	179	171	176	176
Baseline**	150.15 (15.3)	149.27 (15.3)	149.63 (14.1)	152.41 (15.2)
Endpoint	146.34 (16.2)	143.35 (16.9)	140.31 (16.9)	136.68 (16.6)
Change	- 3.81 (11.6)	- 5.92 (11.3)	- 9.32 (12.7)	- 15.74 (15.3)

* the number of subjects with at least one post-baseline BP measurement; ** visit 3 measurement

There was no significant difference between treatments for the change in pulse.

Table 19.6 shows the change in siDBP based on demographic variables of age, sex and race. In the monotherapy groups, black patients had less of a change in siDBP than white patients. In black patients, HCTZ 25 mg added little additional benefit compared to HCTZ 12.5 mg. Females patient and patients ≥ 65 years had greater changes in siDBP compared to males and patients < 65 years respectively for all treatment groups.

Table 19.6. Change in siDBP at Endpoint Based on Age, Sex and Race

Treatment	Subgroup	N	siDBP	siSBP
Valsartan 80 mg	< 65 years	152	- 5.23 (7.74)	- 3.64 (11.41)
	≥ 65 years	27	- 5.48 (7.76)	- 4.77 (13.04)
	Male	113	- 5.17 (7.45)	- 4.60 (11.53)
	Female	66	- 5.42 (8.22)	- 2.65 (11.79)
	Caucasian	127	- 5.58 (7.87)	- 4.12 (11.88)
	Black	28	- 4.45 (8.38)	- 0.38 (11.53)
	Other	24	- 4.53 (6.14)	- 6.17 (9.94)
Valsartan 160 mg	< 65 years	145	- 5.50 (7.07)	- 5.67 (11.20)
	≥ 65 years	26	- 6.90 (7.90)	- 7.31 (12.13)
	Male	109	- 4.80 (7.38)	- 4.48 (11.39)
	Female	62	- 7.31 (6.62)	- 8.45 (10.84)
	Caucasian	123	- 6.32 (6.79)	- 6.48 (11.07)
	Black	23	- 2.19 (7.32)	- 1.10 (10.84)
	Other	25	- 5.95 (8.30)	- 7.60 (12.26)
Valsartan 80 mg / HCTZ 12.5 mg	< 65 years	151	-7.76 (7.98)	- 9.16 (12.82)
	≥ 65 years	25	- 9.63 (7.78)	-10.32 (12.4)
	Male	117	- 7.79 (7.59)	- 9.76 (13.24)
	Female	59	- 7.97 (8.72)	- 8.45 (11.70)
	Caucasian	121	- 8.12 (7.42)	- 8.75 (12.68)
	Black	29	- 8.63 (9.39)	-12.54 (13.46)
	Other	26	- 5.72 (8.64)	- 8.38 (12.04)
Valsartan 80 mg / HCTZ 25 mg	< 65 years	141	-9.67 (7.98)	-15.01 (15.32)
	≥ 65 years	35	- 13.. 1 (7.77)	-18.67 (15.25)
	Male	123	- 9.40 (8.36)	- 14.40 (14.94)
	Female	53	-12.64 (6.80)	-18.83 (15.91)
	Caucasian	125	- 11.10 (7.52)	- 16.85 (15.05)
	Black	25	- 9.12 (8.98)	- 16.69 (18.40)
	Other	26	- 8.13 (9.25)	- 9.49 (12.20)

There were no deaths in the study. Fifty percent of the patients experienced at least one adverse event during the double-blind treatment period. There was no difference in the total incidence of adverse events in all treatment groups. The most common adverse events in all treatment groups were headache and upper respiratory infection. Cough was reported by 2% - 4% of the patients.

Table 19.7 lists the patients who discontinued from the study due to adverse events during the single blind valsartan treatment period. Table 19.8 lists the patients who discontinued from the study due to adverse events during the double-blind treatment period. Patients with serious adverse events but not requiring discontinuation are also included in these tables.

Table 19.7. Patients with Serious Adverse Events or Adverse Events Resulting in Discontinuation during the Single-Blind Valsartan Treatment Period [vol. 1.159, p. 59]

Patients with serious adverse experiences and/or who discontinued prematurely due to an adverse experience or laboratory abnormality during the single-blind valsartan treatment period

Treatment group: Single-blind valsartan 80 mg

Investigator	Patient number	Sex	Age	Last Visit	Medical Problem	Disc Yes/No	Serious Yes/No	Comments
Anderson	190	F	79	3	TIA, garbled speech	Yes	Yes	Adverse experience
Antonishen	482	F	53	3	Dizzy, red blotches on arms, water retention	Yes	No	Adverse experience
Chappel	382	M	56	3	Cardiac arrhythmia	Yes	Yes	Adverse experience
Carder	1088	F	44	3	Leg and stomach cramps	Yes	No	Adverse experience
Davis	39	M	63	3	Right lower lobe lung mass	Yes	Yes	Adverse experience
Dolene	216	M	59	3	Appetite loss, incontinence, bruises on throat, arms, chin, decreased libido	Yes	No	Adverse experience
Edmunds	770	F	53	3	Facial pain, numbness in finger, radiating shoulder pain	Yes	No	Adverse experience
Gann	220	F	51	3	Chest pain	Yes	Yes	Adverse experience
Hall	1229	M	51	3	Back pain	Yes	No	Adverse experience
Kerzner	885	F	71	3	Increased pedal edema, pain while walking	Yes	No	Adverse experience
Kerzner	1175	M	44	3	Increased headache	Yes	No	Adverse experience
Lewin	1055	F	51	3	Headache	Yes	No	Adverse experience
Marzec	580	F	54	3	Insomnia, headache	Yes	No	Adverse experience
Miller, C	1210	M	64	3	Right leg numbness	Yes	No	Adverse experience
Montoro	576	M	54	3	Head pressure	Yes	No	Adverse experience
Montoro	978	F	55	3	Migraine	Yes	No	Adverse experience
Montoro	984	M	49	3	Headache	Yes	No	Adverse experience
Neutel	873	M	49	3	Cold and tingling extremities, cramping in extremities, cough	Yes	No	Adverse experience
Offenberg	662	F	65	3	Amblyopia left eye	Yes	Yes	Adverse experience
Quadrucci	0369/5245	M	65	6	Fracture left distal humerus	No	Yes	Adverse experience
Sulit	1130	M	44	3	Blurry vision	Yes	No	Adverse experience
Williams, D	268	M	52	3	Constipation	Yes	No	Adverse experience
Weshler	256	F	46	3	Dizziness, headache	Yes	No	Adverse experience

Table 19.8. Patients with Serious Adverse Events or Adverse Events Resulting in Discontinuation during the Double-Blind Treatment Period [vol. 1.159, p. 60]

Patients with serious adverse experiences and/or who discontinued prematurely due to an adverse experience or laboratory abnormality during the double-blind treatment period

Treatment group: Valsartan 80 mg

Investigator	Patient number	Sex	Age	Last Visit	Medical Problem	Disc. Yes/No	Serious Yes/No	Comments
Andersen	0157/5105	F	60	5	Lack of energy	Yes	No	Adverse experience
Angelo	0108/5071	F	45	5	Proteinuria	Yes	No	Abnormal lab value
Delrane	0853/5545	M	63	6	Low platelet count	Yes	No	Abnormal lab value
Genn	0222/5148	M	58	6	Food poisoning	No	Yes	Adverse experience
Karzner	0868/5466	M	42	4	Fatigue	Yes	No	Adverse experience
McInroy	0451/5304	F	48	5	Muscle contraction headache	Yes	No	Adverse experience
Nolen	0314/5209	F	51	6	Bilat. contact dermatitis	Yes	No	Adverse experience
Stringer	1202/5616	M	66	6	Squamous cell carcinoma	No	Yes	Adverse experience
Warren	1097/5298	F	59	4	Hepatitis C	Yes	No	Adverse experience
Woehler	0234/5189	M	47	4	Bronchitis	Yes	No	Adverse experience

Treatment group: Valsartan 160 mg

Investigator	Patient number	Sex	Age	Last Visit	Medical Problem	Disc. Yes/No	Serious Yes/No	Comments
Fogel	0568/5403	F	39	4	Frontal headache	Yes	No	Adverse experience
Hall	1231/5434	M	51	5	Ankle sprain	Yes	No	Adverse experience
Jan	0476/5321	F	51	5	Poss alcoholic cirrhosis	Yes	No	Adverse experience
Jan	1027/5689	M	46	5	High anterolateral infarction	Yes	Yes	Adverse experience
Jan	1037/5693	F	60	4	Ischemic 3rd nerve palsy. Ptosis right upper eyelid	Yes	Yes	Adverse experience
Lewin	1057/5726	M	50	6	CVA	Yes	Yes	Adverse experience
McInroy	0453/5313	F	61	6	Osteoarthritis left knee, pain, swelling	No	Yes	Adverse experience
Rosen	0299/5373	M	32	4	Abdominal pain, diarrhea	Yes	No	Adverse experience
Weiss	0302/5202	M	50	6	Atypical chest pain	No	Yes	Adverse experience

Treatment group: Valsartan 80 mg + HCTZ 12.5 mg

Investigator	Patient number	Sex	Age	Last Visit	Medical Problem	Disc. Yes/No	Serious Yes/No	Comments
Caldwell	0195/5129	F	47	6	Ovarian cyst	No	Yes	Adverse experience
Carder	1068/5736	M	41	6	Abdomen pain right side	Yes	No	Adverse experience
Davis	0043/5031	F	66	5	Headaches, chest cold	Yes	No	Adverse experience
Jain	0746/5416	M	53	4	Shortness of breath, chest tightness	Yes	No	Adverse experience
Miller, C	0853/5641	M	51	6	Benign prostatic hypertrophy	No	Yes	Adverse experience
Rosen	0297/5196	F	74	4	Fatigue	Yes	No	Adverse experience
Woehler	0722/5173	M	51	5	Cerebral aneurysm	Yes	Yes	Adverse experience

Treatment group: Valsartan 80 mg + HCTZ 25 mg

Investigator	Patient number	Sex	Age	Last Visit	Medical Problem	Disc. Yes/No	Serious Yes/No	Comments
Carder	1072/5739	F	46	5	Dizziness	Yes	No	Adverse experience
Glatte	0883/5585	M	45	6	Basal cell cancer	No	Yes	Adverse experience
Littlejohn	0180/5457	M	75	6	Rash on buttocks, lower abdomen	Yes	No	Adverse experience
Miller, C	0408/5634	M	52	5	Myocardial infarction	Yes	Yes	Adverse experience
Weems, O	0883/5486	M	66	4	Fatigue	Yes	No	Adverse experience

A listing of patients who discontinued prematurely from the trial during the double-blind treatment period is displayed by principal reason in Table 6.1.3.

By patient reference Data Listing VI.1 Termination page and comments

Data Listing VI.11 Adverse experiences whether or not trial drug related

Patient 0106/5071 had proteinuria prior to the initiation of valsartan therapy (+2 by dipstick). Patient 0853/5546 had a low platelet count prior to valsartan therapy. Patient 476/5321 was a 51 year old female who had increases in SGOT and SGPT starting on day 29 (visit 3) of valsartan therapy. Table 19.9 list the values for this patient. The abnormalities were attributed to early ETOH cirrhosis. However, in the significant past medical history records on this patient there is no mention of ETOH abuse [vol. 1.166, p. 107].

Table 19.9. SGPT and SGOT Values for Patient 476/5321.

Visit	Treatment	SGOT (U/L) Normal : 0 - 40 U/L	SGPT (U/L) Normal : 0 - 45 U/L
1	-	22	15
3	valsartan 80 mg	63	31
4	valsartan 160 mg	253	
5	valsartan 160 mg	289	247

There was no significant mean change in laboratory parameters with valsartan therapy. It is difficult to assess shifts in individual patient labs since there is no placebo control group for comparison.

Eight patients had increases in CPK > 300% at the terminal visit compared to baseline. All eight were male. Three patients with values > 1000 U/L (Normal: 0 - 174 U/L) are listed in table 19.10. The relationship of CPK elevation to study therapy is not known.

Table 19.10. Patients with CPK > 1000 U/L.

Patient #	Baseline CPK (U/L)	Terminal CPK (U/L)	Possible Explanation
444/5295	384	2733	Weight Lifting
138/5095	167	1362	None. Repeat 1 month after trial was 337 U/L.
799/5720	122	1119	None.

Protocol 20. Multi-Center, Randomized, Double-Blind, Between Patient Trial Comparing The Efficacy Of Valsartan 80 Mg Once Daily To Enalapril 20 Mg Once Daily In Patients With Uncomplicated Essential Arterial Hypertension Treated For Eight Weeks And To Assess And Compare The Tolerability Of Both Drugs As Monotherapy And In Combination With HCTZ 12.5 Mg Once Daily
(2/22/94 - 9/6/94)

This was a randomized, double-blind, multi-center (France), placebo controlled, parallel group trial in hypertensive patients with a siDBP > 95 mm Hg and < 120 mm Hg at randomization. The trial consisted of a 1 week washout period, a 2 week single-blind placebo period and a 12 week double-blind treatment period. Patients were randomized to either valsartan 80 or enalapril 20 mg. After 8 weeks of double-blind treatment, if the patient's siDBP was ≥ 95 mm Hg, HCTZ 12.5 mg would be added to the randomized therapy. Patients with siDBP < 95 mm Hg remained on randomized monotherapy. The primary endpoint was the change in mean siDBP from baseline at the end of monotherapy (week 8) and 12 weeks of therapy (includes monotherapy and combined therapy patients) based on an intent to treat analysis. Secondary endpoints included the mean change in siSBP at week 8 and week 12.

The study was conducted at 40 centers in France [10]. Two-hundred and eleven subjects were enrolled of which 189 subjects were randomized. Ninety-four were randomized to valsartan and ninety-five to enalapril. One hundred and sixty-nine patients completed twelve weeks of therapy. Table 20.1 list the reasons patients were discontinued from the trial.

[10] Centers were numbered from 1 - 42. Center # 4 and # 39 are not listed. The reason for exclusion of these center numbers is not provided.

Table 20.1. Reasons for Premature Discontinuation from the Trial.

Reason Discontinued	Valsartan	Enalapril
Total Premature Discontinuations	8	12
Adverse Events	3	8
Death	1	0
Abnormal Lab	2	1
Lost to Follow-up	1	1
Administrative Problem	1	0
Non-Compliant	0	1
Protocol Eligibility Not Met	0	1

There were 94 men and 95 women randomized. The trial randomized predominately all Caucasians except for 3 blacks. 2 oriental and 2 of unspecified race.

Table 20.2 list the mean change in siDBP from baseline at week 8 (monotherapy) and week 12 (monotherapy or combination therapy). There was no significant difference between treatment groups.

Table 20.2. Mean Change in siDBP and siSBP (mm Hg)

Sitting Diastolic Blood Pressure	Valsartan [N=94] Mean (s.d.)	Enalapril [N=95] Mean (s.d.)
Baseline	102.1 (4.7)	102.1 (5.4)
Week 8 (monotherapy)	88.5 (9.0)	90.7 (8.9)
Change at week 8	-13.2 (8.8)	-12.0 (8.1)
Week 12 (monotherapy or combination therapy)	86.6 (8.8)	88.9 (9.1)
Change at week 12	-15.5 (8.2	-13.7 (9.2)
Sitting Systolic Blood Pressure		
Baseline	165 (11.1)	169.1 (14.5)
Week 8 (monotherapy)	147.8 (12.9)	151.4 (15.0)
Change at week 8	-17.2 (12.0)	-17.7 (12.1)
Week 12 (monotherapy or combination therapy)	145.3 (13.3)	148.7 (14.7)
Change at week 12	-19.7 (13.6)	-20.4 (14.5)

The number of patients who had a siDBP < 90 mm Hg or decreased siDBP by ≥ 10 mm Hg at week 8 was 61% and 53% in the valsartan and enalapril groups respectively. This was not significantly different.

There was no treatment effect difference based on age. Females on valsartan (n = 47) had a slightly greater decrease in siDBP versus males (N = 47), -14.2 (± 7.3) mm Hg versus -12.2 (±10.0) mm Hg.

There was one death. Patient 1189 (valsartan) died suddenly on day 15 of therapy with valsartan. The patient had a history of gastric ulcer, depression, and hypothyroidism. Medications at the time of death included levothyroxine, metanizole caffeine, paracetamol and iron sulfate. The patient was found dead by a neighbor. No autopsy was performed. No cause of death was determined.

The percentage of patients complaining of at least one adverse event was similar between treatments (26% in valsartan and 28% in enalapril). There were 6 valsartan patients with severe adverse events compared to seven in the enalapril group. Two valsartan and three enalapril patients complained of cough. Table 20.3 lists the patients who discontinued due to adverse events.

Table 20. 3. Discontinuations due to Adverse Events and Lab Abnormalities. (from vol. 185, p. 44)

Premature Discontinuations from the Double-Blind Period of the Trial - due to adverse experiences and laboratory abnormalities

	Treatment Group	Center	Patient Number	Sex	Age	Visit	Medical problem	Serious Yes/No
VALSARTAN	Mono therapy	13	1073	M	79	4	Edema low extremities	No
VALSARTAN	Mono therapy	16	1288	F	63	6	Dry cough	No
VALSARTAN	Mono therapy	22	1131	M	62	6	Mycrocytic anemia	Yes
VALSARTAN	Mono therapy	32	1189	F	71	4	Death	Yes
VALSARTAN	Mono therapy	34	1196	F	78	6	Hip joint replacement	Yes
VALSARTAN	+ HCTZ	16	1091	M	38	6	Creatine Kinase increased	Yes
ENALAPRIL	Mono therapy	05	1027	M	73	5	Pruritus generalized	No
ENALAPRIL	Mono therapy	18	1105	F	47	4	Dry cough	No
ENALAPRIL	Mono therapy	20	1116	F	64	4	Hypertensive crisis	No
ENALAPRIL	Mono therapy	22	1127	F	65	5	Thrombophlebitis leg deep	No
ENALAPRIL	Mono therapy	25	1149	M	73	5	Pulmonary edema	No
ENALAPRIL	Mono therapy	32	1190	F	71	5	Phosphatase alkaline increased	No
ENALAPRIL	Mono therapy	16	1288	M	44	4	Cramps muscle	No
ENALAPRIL	Mono therapy	29	1338	F	47	5	Dry cough	No
ENALAPRIL	Mono therapy	16	1344	M	60	5	Dry cough	No

A listing of patients who were prematurely discontinued from the trial is displayed by main reason in Table 6.1-2, Module I

A by-patient listing of all adverse experiences reported during the trial is presented by investigator in Module VI, Data Listing 11

Patient 1131 developed a microcytic anemia (hgb. = 65 g/L at week 12 from baseline = 123g/L [normal: 130 - 180 g/L]) associated with low iron levels. The patient refused a diagnostic work-up and was treated with iron therapy. Patient 1091 developed a markedly elevated creatine kinase level (3079 ui/L [normal: 35 - 120]) . The patient had experienced some leg cramps two weeks prior to the measurement. The patient had started weight lifting the week prior to testing. Valsartan was discontinued and within 2 months CK was normal. Patient 1073 developed leg swelling during the two week run-in period which was attributed to CHF.

There were no significant changes in mean laboratory parameters. Three patients were excluded for lab abnormalities. Patients 1131 had anemia and patient 1091 had an elevated creatine kinase. Patient 1190 (enalapril) had an alkaline phosphatase of 489 U/L [Normal: 30 - 90] at baseline and 1304 U/L at week 12.

The mean laboratory parameters for creatinine and potassium are provided in table 20.4. There are no differences between treatment groups. When HCTZ is added, the mean potassium decreases slightly.

Table 20 .4. Mean Creatinine and Potassium Values by Treatment Group at week 8 or 12

Laboratory Parameter	Valsartan		Enalapril	
	Baseline	week 8	Baseline	week 8
Creatinine (umol/L) [Normal: 44.2 - 132.7]	88.7	87.4	90.9	88.8
Potassium (mmol/L) [Normal: 3.5 - 5]	4.62	4.32	4.57	4.53

Table 20.4.(con't) Mean Creatinine and Potassium Values by Treatment Group at week 8 or 12

	Valsartan + HCTZ *		Enalapril + HCTZ *	
	Baseline	week 12	Baseline	week 12
Potassium (mmol/L) * [Normal: 3.5 - 5]	4.46	4.3	4.45	4.24

* N = 20 for each treatment group

Protocol 21. Multi-Center, Randomized, Double-Blind, Between Patient Trial Comparing The Efficacy Of Valsartan 80 Mg To Amlodipine 5 mg, Both Once Daily, In Patients With Uncomplicated Essential Arterial Hypertension Treated For Eight Weeks And To Assess And Compare The Tolerability Of Both Drugs As Monotherapy And In Combination With Amlodipine 5 mg Once Daily
(2/1/94 - 1/26/95)

This was a randomized, double-blind, multi-center (Italy), placebo controlled, parallel group trial in hypertensive patients with a siDBP > 95 mm Hg and < 120 mm Hg at randomization. The trial consisted of a 2 week single-blind placebo period and a 12 week double-blind treatment period. Patients were randomized to either valsartan 80 or amlodipine 5 mg. After 8 weeks of double-blind treatment, if the patient's siDBP was ≥ 95 mm Hg, amlodipine 5 mg would be added to the randomized therapy. Patients with siDBP < 95 mm Hg remained on randomized monotherapy. The primary endpoint was the change in mean siDBP from baseline at the end of monotherapy (week 8) and 12 weeks of therapy (includes monotherapy and combined therapy patients) based on an intent to treat analysis. Secondary endpoint included the mean change in siSBP at week 8 and week 12.

The study was conducted at 7 centers in Italy. One hundred and eighty-eight subjects were enrolled of which 168 subjects were randomized. Eighty-four were randomized to valsartan and eighty-one to amlodipine. One hundred and sixty-two patients completed twelve weeks of therapy. Table 21.1 list the reasons patients were discontinued from the trial.

Table 21.1. Reasons for Premature Discontinuation from the Trial.

Reason Discontinued	Valsartan	Amlodipine
Total Premature Discontinuations	3	3
Adverse Events	1	1
Unsatisfactory Response	0	1
Other	2*	1**

* patient 1001 was to start estroger/progesterone, patient 1137 did not meet protocol criteria
** patient 1240 withdrew consent at week 4.

There were 97 men and 71 women randomized. All patients were Caucasian. The average age was 52.8 years.

Table 21.2 list the mean change in siDBP from baseline at week 8 (monotherapy) and week 12 (monotherapy or combination therapy). Twenty-four valsartan and twenty-eight amlodipine patients had amlodipine 5 mg added at week 8. There was no significant difference between treatment groups with regard to change in siDBP.

Table 21.2. Mean Change in siDBP and siSBP (mm Hg)

Sitting Diastolic Blood Pressure	Valsartan [N = 84] Mean (s.d.)	Amlodipine [N = 83] Mean (s.d.)
Baseline	101.1 (3.7)	101.8 (4.5)
Week 8 (monotherapy)	89.6 (8.0)	90.8 (8.1)
Change at week 8	-11.5 (6.8)	-11.1 (7.6)
Week 12 (monotherapy or combination therapy)	87.6 (7.3)	87.1 (7.2)
Change at week 12	-13.5 (6.8)	14.8 (7.4)

Table 21.2.(con't) Mean Change in siDBP and siSBP (mm Hg)

Sitting Systolic Blood Pressure	Valsartan [N = 84] Mean (s.d.)	Amlodipine [N = 83] Mean (s.d.)
Baseline	157.5 (13.3)	161.5 (12.8)
Week 8 (monotherapy)	144.4 (16.0)	147.4 (14.2)
Change at week 8	-13.1 (12.2)	14.8 (12.0)
Week 12 (monotherapy or combination therapy)	141.0 (14.8)	142.8 (11.8)
Change at week 12	-16.5 (12.5)	-19.3 (12.7)

The number of patients who had a siDBP < 90 mm Hg or decreased siDBP by ≥ 10 mm Hg at week 8 was 67% and 60% in the valsartan and amlodipine groups respectively. This was not significantly different.

There were too few patients ≥ 65 years of age to perform an analysis. Males (N = 49) and females (N = 35) on valsartan had similar mean effects for siDBP, - 11.2 mm Hg versus - 12.0 mm Hg respectively.

Sixteen percent of patients in each treatment group had at least one adverse event. There were no deaths. Patient # 1054 (valsartan) withdrew because of headache and tachycardia.

There were no significant changes in mean laboratory parameters. Table 21.3 lists three valsartan patients who had a absolute neutrophil count less than 1000 x 10^9/L. None of the amlodipine treated patients had a neutrophil count less than 1000 x10^9/L. The relationship to valsartan is not known.

Table 21.3. Valsartan Patients with Absolute Neutrophil Count < 1000 x 10^9/L (x 10^9/L)

Patient #	Visit 1	Visit 4 (week 7)	Visit 5 (week 12)
1227	1.93		.37
1230	3.29	2.09	.75
1233	4.11	3.36	.63

Protocol 22. Multi-Center, Randomized, Double-Blind, Between Patient Trial Comparing The Efficacy Of Valsartan 80 Mg Once Daily To HCTZ 25 mg Once Daily In Patients With Uncomplicated Essential Arterial Hypertension Treated For Eight Weeks And To Assess And Compare The Tolerability Of Both Drugs As Monotherapy And In Combination With Atenolol 50 mg Once Daily
(3/11/94 - 1/30/95)

This was a randomized, double-blind, multi-center (Germany), placebo controlled, parallel group trial in hypertensive patients with a siDBP > 95 mm Hg and < 115 mm Hg at randomization. The trial consisted of a 2 week single-blind placebo period and a 12 week double-blind treatment period. Patients were randomized to either valsartan 80 or HCTZ 25 mg. After 8 weeks of double-blind treatment, if the patient's siDBP was ≥ 95 mm Hg, atenolol 50 mg would be added to the randomized therapy. Patients with siDBP < 95 mm Hg remained on randomized monotherapy. The primary endpoint was the change in mean siDBP from baseline at the end of monotherapy (week 8) and 12 weeks of therapy (includes monotherapy and combined therapy patients) based on an intent to treat analysis. Secondary endpoint included the mean change in siSBP at week 8 and week 12.

The study was conducted at 18 centers in Germany. One hundred and sixty-seven subjects were enrolled of which 167 subjects were randomized. Eighty-two were randomized to valsartan and eighty-five to HCTZ. One hundred and fifty-five patients completed twelve weeks of therapy. Table 22.1 list the reasons patients were discontinued from the trial.

Table 22.1. Reasons for Premature Discontinuation from the Trial.

Reason Discontinued	Valsartan	HCTZ
Total Premature Discontinuations	6	6
Adverse Events	1	2
Unsatisfactory Response	0	1
Withdrew Consent	1	0
Lost to Follow-up	0	2
Administrative Problems	3	0
Abnormal Lab	1	1

There were 91 men and 76 women randomized. All patients were Caucasian except for one black. The average age was 57.2 years.

Table 22.2 list the mean change in siDBP from baseline at week 8 (monotherapy) and week 12 (monotherapy or combination therapy). Sixteen valsartan and seventeen HCTZ patients had atenolol 50 mg added at week 8. There was no significant difference between treatment groups with regard to change in siDBP.

Table 22.2. Mean Change in siDBP and siSBP (mm Hg)

Sitting Diastolic Blood Pressure	Valsartan [N = 84] Mean (s.d.)	Amlodipine [N = 83] Mean (s.d.)
Baseline	103.8 (5.2)	103.4 (4.8)
Week 8 (monotherapy)	90.2 (6.5)	91.4 (8.2)
Change at week 8	-13.6 (6.2)	-12.0 (8.1)
Week 12 (monotherapy or combination therapy)	88.5 (6.7)	89.1 (7.5)
Change at week 12	-15.3 (6.?)	-14.3 (7.?)
Sitting Systolic Blood Pressure		
Baseline	165.2 (16.1)	165.3 (15.3)
Week 8 (monotherapy)	148.6 (16.0)	146.8 (16.8)
Change at week 8	-16.6 (11.3)	-18.5 (14.5)
Week 12 (monotherapy or combination therapy)	146.6 (14.1)	145.1 (16.0)
Change at week 12	-18.6 (12.?)	-20.3 (14.?)

The number of patients who had a siDBP < 90 mm Hg or decreased siDBP by ≥ 10 mm Hg at week 8 was 74% and 62% in the valsartan and HCTZ groups respectively. This was not significantly different.

Males (N = 43) and females (N = 39) on valsartan had similar mean effects for siDBP, - 14.2 mm Hg versus - 12.9 mm Hg respectively.

Twenty-three percent of valsartan patients and twenty-nine percent of HCTZ patients had at least one adverse event. There were no deaths. Two valsartan patients withdrew for either adverse events or for abnormal labs. Patient 1022 (valsartan) was a 73 year old who withdrew prematurely due angina pectoris requiring hospitalization and the initiation of medical therapy. Patient 1029 withdrew due to increased SGOT (99 U/L [normal: 8 - 38 U/L]) and SGPT (96 U/L [normal: 8 - 38 U/L]) that were actually elevated at baseline and remained elevated with therapy.

There were no significant changes in mean laboratory parameters. Three valsartan patients had decreased hematocrit or hemoglobin during treatment. Table 22.3 lists the hematocrit and hemoglobin results from these patients. No adverse events are reported with these decreases.

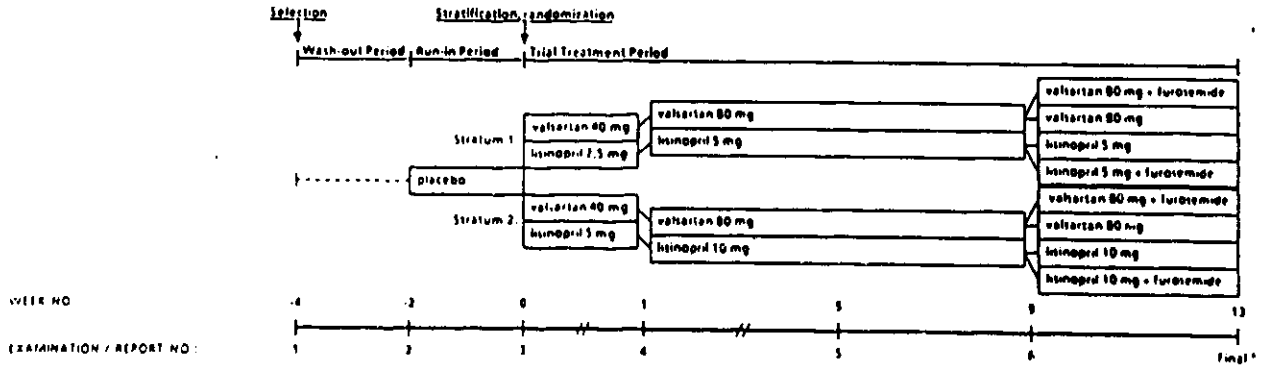
Table 22.3. Patients with Decreases in Hemoglobin [normal: 130 - 180 g/L]or Hematocrit [normal: 38 - 52 %]

Patient #	Test	Visit 1	Visit 4	Visit 5
1007	hemoglobin	151.0	120.	110.0
	hematocrit	46.2	34.9	31.9
1119	hemoglobin	130.0	101.0	116.0
	hematocrit	39.0	29.7	35.3
1094	hemoglobin	155.0	153.0	121.0
	hematocrit	45.3	42.9	37.4

Protocol 27. Multi-center, Randomized, Double-Blind, Between Patient Trial Comparing The Effect On Hypertension And Renal Function Of Valsartan 80 Mg With Lisinopril 5/10 Mg, Both Once Daily, In Patients With Arterial Hypertension And Stable Renal Insufficiency Treated For Eight Weeks And To Assess And Compare The Tolerability Of Both Drugs As Monotherapy And In Combination With Furosemide. (May 5, 1994 - March 7, 1995)

Protocol 27 was a multi-center (Italy), randomized, double-blind study to evaluate the effect of valsartan 80 mg compared to Lisinopril 5/10 mg once daily in hypertensive patients with stable renal insufficiency after 12 weeks of treatment. The trial consisted of a 2 week placebo run-in period followed by a 13 week double blind treatment period. For randomization, patients had a siDBP > 95 mm Hg and < 120 mm Hg and a stable creatinine clearance 20 - 70 ml/ min/1.73 m^2. Patients were randomized to valsartan 40 mg or Lisinopril 2.5 mg or 5 mg (stratified by renal function ; Stratum 1 = creatinine clearance 20 - 30 ml/min/1.73 m^2, Stratum 2 = creatinine clearance 31 - 70 ml/min/1.73 m^2) as outlined in figure 27.1. After 1 week of treatment, the dose was doubled and continued for 8 weeks. At week 9, lasix (dose determined by physician) could be added if siDBP > 95 mm Hg. The projected sample size was 208 patients based on 80% power to detect 4 mm Hg change in siDBP and 10 % difference in GFR at 5% significance). The primary endpoint was the change in mean siDBP at week 9. Secondary endpoints included change from baseline in mean siSBP and GFR.

Figure 27.1. Study Design and Procedures (vol. 198, p. 46; vol. 199, p. 284)



Procedure	Week / Visit	Single blind		Double-blind				
		-4 / 1	-2 / 2	0 / 3	1 / 4	5 / 5	9 / 6	13 / 7
Informed consent, personal data, physical examination, medical history, concomitant disease, previous/current medication/non-drug therapy		X						
Check of inclusion/exclusion criteria		X	X	X				
Weight, pulse rate, blood pressure, adverse experience, concomitant medication/non-drug therapy			X	X	X	X	X	X
Laboratory examinations:								
- Haematology, 24 hour urine			X				X	X
- Blood chemistry			X	X	X	X	X	X
- Urinalysis, urinary sediment, urine chemistry			X		X		X	X
- Renal function evaluation				X			X	X
- Other measurements*				X			X	
Trial medication dispense			X	X	X	X	X	X

*: in a subset of patients only; measurement of valsartan plasma concentration, plasma cGMP, urine cGMP; plasma nitric oxide; urinary endothelin excretion; urinary TxB_2 excretion, urinary 6 keto PGF1α excretion.

Results

The NDA includes an interim report of the data. Seventy-four of the projected 208 patients were randomized [11]. Table 27.1 provides the patient disposition. Only 2 valsartan patients failed to complete the study due to withdrawal of consent. Of note is that 80% of the patients violated the protocol as outlined in table 27.2.

Table 27.1. Patient Disposition

	Valsartan	Lisinopril
Randomized	36	38
Completed	34	38
Discontinued	2	0

Table 27. 2. Protocol Violations (vol. 197, p. 81)

	TREATMENT				ALL	
	Valsartan N	%	Lisinopril N	%	N	%
Total number of patients	36	100.0	38	100.0	74	100.0
Any Protocol violations	31	86.1	28	73.7	59	79.7
Age not between 18 and 80 years	0	0.0	0	0.0	0	0.0
Mean sitting DBP <=95 mmHg at visit 3 or at visit 2	5	13.9	3	7.9	8	10.8
Mean sitting DBP >=120 mmHg at visit 3 or at visit 2	1	2.8	0	0.0	1	1.4
Discordance between furosemide therapy and SDBP at visit 6	5	13.9	0	0.0	5	6.8
Creatinine clearance not between 20 and 70 mL/min/1.73m² (visit 2)	12	33.3	10	26.3	22	29.7
Wrong stratification	3	8.3	1	2.6	4	5.4
SGOT values >= 76 U/L (twice the upper limit) at visit 2	0	0.0	1	2.6	1	1.4
SGPT values >= 76 U/L (twice the upper limit) at visit 2	1	2.8	2	5.3	3	4.1
Blood glucose > 200 mg/dl (>11.1 mmol/L) at visit 2	2	5.6	3	7.9	5	6.8
Urine collection period is <22 or >26 hours at visit 2	0	0.0	0	0.0	0	0.0
Missing informed consent	0	0.0	0	0.0	0	0.0
Disallowed presence of medical condition	0	0.0	0	0.0	0	0.0
Disallowed previous concomitant medication	0	0.0	0	0.0	0	0.0
Visit 3 not in required time frame (>21 days)	0	0.0	0	0.0	0	0.0
Visit 4 not in required time frame (>14 days)	0	0.0	0	0.0	0	0.0
Visit 5 not in required time frame (>35 days)	0	0.0	0	0.0	0	0.0
Visit 6 not in required time frame (>35 days)	1	2.8	1	2.6	2	2.7
Visit 7 not in required time frame (>35 days)	0	0.0	1	2.6	1	1.4
Time interval between drug intake and visit 3 >28 or <12 hours	2	5.6	6	15.8	8	10.8
Time interval between drug intake and visit 4 >28 or <12 hours	1	2.8	2	5.3	3	4.1
Time interval between drug intake and visit 5 >28 or <12 hours	0	0.0	0	0.0	0	0.0
Time interval between drug intake and visit 6 >28 or <12 hours	0	0.0	0	0.0	0	0.0
Time interval between drug intake and visit 7 >28 or <12 hours	22	61.1	19	50.0	41	55.4

Table 27.3 lists the baseline demographic variables for the treatment groups. The valsartan group had a larger proportion of females compared to the Lisinopril group.

Table 27.3. Mean Baseline Variables

	Valsartan		Lisinopril	
Mean Age	59.4 (12.7)		58.1 (11.7)	
Females	55.6%		34.2%	
	Stratum 1	Stratum 2	Stratum 1	Stratum 2
Creatinine Clearance*	24.98 (6.53)	65.11 (23.45)	26.02 (3.77)	63.83 (27.28)
GFR (ml/min/1.73 m^2)*	31.0	56.5	27.6	56.8

* Median of visits 1 and 2

Table 27.4 lists the mean change in siDBP for each treatment at the end of monotherapy (week 9) and at endpoint. Female patients had a greater change in siDBP from baseline compared to males at week 9 (- 13.43 mm Hg vs. - 4.31 mm Hg).

[11] The number of centers involved in the study is not clear.

Table 27.4. Mean Change in siDBP. (vol. 197, p. 34)

	Valsartan 80 mg		Lisinopril	
	Endpoint Monotherapy	Endpoint Titration	Endpoint Monotherapy	Endpoint Titration
# of Patients	36	36	38	38
Change in siDBP (mmHg)	-9.38	-7.32	-10.64	-9.71
Change in siSBP (mmHg)	-11.04	-10.74	-8.21	-11.26

There was no difference between treatments in the mean change in GFR. Table 27.5 lists the mean and median change in GFR.

Table 27.5. Mean and Median Change in GFR. (vol. 197, p. 134)

		Valsartan			Lisinopril		
		Baseline	Post	Change	Baseline	Post	Change
Week 9	N	36	36	36	38	38	38
	Geom. Mean	50.9	47.8		53.84	52.3	
	Median	53.4	51.3	-1.66	56.8	54.7	-1.15
Week 13	N	34	34	34	38	38	38
	Geom. Mean	49.6	47.4		53.8	49.8	
	Median	53.0	50.6	-2.4	56.8	55.1	-1.9
Endpoint	N	36	36	36	38	38	38
	Geom. Mean	50.9	48.7		53.8	49.8	
	Median	53.4	52.1	-1.9	56.8	55.1	-1.9

There were no deaths in the study. Five valsartan patients complained of adverse events (hernia, URI, UTI). There two adverse laboratory results worth reporting. Patient 1049 had a decrease in neutrophil count from 2.72 10^9/L at visit 2 to .83 10^9/L at visit 6 and .59 10^9/L at visit 7. Patient 1051 had a decrease in neutrophil count from 4.59 10^9/L at visit 2 to .81 10^9/L at visit 6 and .83 10^9/L at visit 7.

Sixteen valsartan patient had valsartan blood levels measured. Table 27.6 lists the $t_{1/2}$ and AUC for these patients. In patients with GFR 30 - 70 ml/min/1.73 m^2, the $t_{1/2}$ averaged 6.6 hours.

Table 27.6. Pharmacokinetic Parameters (vol. 199, p. 298)

Group	Patient	C_{max} (μmol/L)	t_{max} (h)	AUC (0-10h) (μmol.h/L)	$t_{1/2}$ (h)	AUC (0-24h) (μmol.h/L)	GFR (mL/min/1.73 m^2)
I	1	6.16	3		5.66		94
	503	9.72	2	58.7	8.89	127	28
II	2	2.72	3	-	*	-	97
	501	6.04	7.5	39.0	7.54	81.9	55
	506	21.0	4	-	12.7	-	56
	508	1.98	4	12.5	5.61	19.7	46
	510	8.06	3	44.8	5.68	67.5	50
	512	5.16	3	32.2	6.16	52.5	46
	515	4.28	2	23.6	3.96	35.8	67
	516	9.52	2	61.9	4.59	82.7	58
	518	1.22	2	8.47	5.33	12.7	43
	519	3.08	2	15.5	6.42	22.6	85
	521	13.5	3	75.6	5.18	79.8	39
	522	4.20	4	33.2	11.3	62.1	53
	529	4.72	2	21.5	4.94	31.1	48
	Mean**	6.58	-	33.5	6.62	50.8	60.9
	SD	5.48	-	20.9	2.89	27.9	9.22
	CV (%)	83.3		62.5	40.7	55.0	18.1
	N	13	13	11	12	11	13
	Median	-	3	-	5.85	-	-
III	525	5.92	2	25.0	5.08	34.2	82

* : Not well defined.

** : Only for patients with GFR of 31-70 mL/min/1.73 m^2.

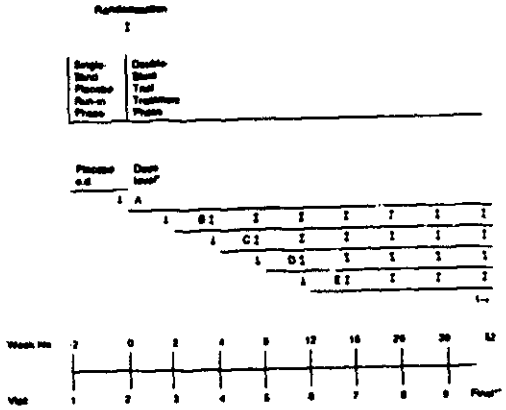
\- : Missing values.

Additional tests were performed in the study that were not reported. They include albumin fractional excretion, IgG fractional excretion, urine/plasma cGMP concentration, nitric oxide concentration, urinary endothelin excretion, urine TxB_2 excretion and urinary 6-keto $PGF_{1\alpha}$.

Protocol 28. Randomized, Double-Blind, Parallel Group Trial Comparing The Tolerability Of Titrated Doses Of Valsartan To Titrated Doses Of Lisinopril Both Given Once-Daily In Elderly Patients With Essential Arterial Hypertension Treated For 52 Weeks
(Dates of trial: 2/8/94 - 4/13/95; NOTE - INTERIM RESULTS ARE AVAILABLE)

This is a randomized, double-blind, multi-center (United Kingdom), dose titration, parallel dose trial in hypertensive patients ≥ 65 years of age who have a baseline siDBP ≥ 96 mmHg and ≤ 110 mmHg[12]. The trial consisted of a 2 week single-blind placebo period followed by a 52 week double-blind treatment period. Patients were randomized to either valsartan 40 mg or Lisinopril 2.5 mg in a 2:1 ratio. After 2 weeks of randomized treatment, medication was titrated to control blood pressure. The maximum titrated dose was 80 mg of valsartan and 20 mg of Lisinopril. HCTZ 12.5 mg or 25 mg could be added to control blood pressure. The primary endpoint was the percent of responders (siDBP < 90 mm Hg or change in siDBP ≥ 10 mm Hg) in each group at 12 and 52 weeks. The sample size was estimated based on recruitment capabilities rather than statistical considerations. Figure 28.1 depicts the study design.

Figure 28.1. Study Design [vol. 1.200, p. 8]



The NDA contains an interim report for this study. Since only interim results are available, only safety data will be summarized. Data was collected on the incidence and severity of cough. [NOTE: Only the final version of the protocol is provided.] It is premature to report findings since all patient data is not available. This study is not pivotal to the NDA from an efficacy viewpoint. It may prove important for the incidence of cough (as supportive evidence). Safety data from the study was reviewed. Sixty-seven centers in the United Kingdom enrolled 545 patients. Five hundred and one patients were randomized. At the time of the interim analysis, only 148 patients had completed 52 weeks of therapy. Another one hundred and eighteen discontinued prematurely. Table 28.1 lists the patient disposition for each treatment group.

Table 28.1. Patient Disposition

	Valsartan	Lisinopril	Total
Enrolled			545
Randomized	334	167	501
Completed	100	48	148
Discontinued Prematurely	69	49	118
Reasons Discontinued			
Adverse Event	35	28	63
Unsatisfactory Response	17	4	21
Abnormal Lab	2	1	3
Other	15	16	31

[12] All BP measurements are recorded to the nearest 2 mm Hg.

Four patients died during the study, two from each treatment group. Table 28.2 provides information on these patients.

Table 28.2. Listing of Patients Who Died During the Study

Center	Patient #	Treatment	Sex	Age	Day of Rx	Cause
223	1184	valsartan	F	82	101	MI
237	1282	valsartan	M	88	251	Pneumonia
210	1889	Lisinopril	F	76	118	CVA
244	1338	Lisinopril	M	66	185	Pneumonia

Table 28.3 lists the patients who discontinued therapy prematurely due to adverse experiences or laboratory abnormalities. Patient 1321 (valsartan) is noteworthy because of discontinuation due to left sided facial swelling that may be consistent with angioedema.

Table 28.3. Premature Discontinuations due to Adverse Events or Abnormal Labs [vol. 1.200, p. 50]

Treatment Group	Centre	Patient Number	Sex	Age	Visit	Medical Problem	Reason
Valsartan	201	1011	Female	79	5	Ankle Oedema	Adverse experience
Valsartan	201	1013	Female	73	3	Leg Weakness/Confusion	Adverse experience
Valsartan	201	1014	Female	70	6	Ankle Swelling	Adverse experience
Valsartan	202	1021	Female	75	9	Dizziness, Pain in Legs, URTI	Adverse experience
Valsartan	203	1025	Female	79	7	Headache/Dizziness on Standing	Adverse experience
Valsartan	206	1055	Female	77	6	Elevated Alkaline Phosphatase	Laboratory abnormality
Valsartan	210	1079	Female	86	10	Angina	Adverse experience
Valsartan	215	1113	Female	74	9	Nausea	Adverse experience
Valsartan	225	1753	Female	68	6	Vertigo	Adverse experience
Valsartan	225	1758	Male	73	8	Dry cough	Adverse experience
Valsartan	231	1235	Female	73	4	Frequency of Micturition	Adverse experience
Valsartan	235	1265	Male	69	3	Tiredness and Headache	Adverse experience
Valsartan	242	1321	Female	79	8	Left-sided Facial Swelling	Adverse experience
Valsartan	242	1324	Female	86	5	Anxiety State Exacerbation	Adverse experience
Valsartan	245	1348	Female	66	3	Depression	Adverse experience
Valsartan	251	1396	Female	65	3	Nausea/Headache/ Blurred Vision /Heaviness of Arms	Adverse experience
Valsartan	261	1473	Female	71	5	Dry cough	Adverse experience
Valsartan	269	1537	Female	66	6	Dizziness	Adverse experience
Valsartan	269	1538	Female	71	3	Light-headedness/ Malaise	Adverse experience
Valsartan	272	1556	Female	83	5	Multiple Adverse Experiences	Adverse experience
Valsartan	272	1559	Female	79	5	Angina of Effort	Adverse experience
Valsartan	272	1928	Female	74	3	Pain in Right Thigh	Adverse experience

Table 28.3.(con't) Premature Discontinuations due to Adverse Events or Abnormal Labs [vol. 1.200, p. 50]

Treatment Group	Centre	Patient Number	Sex	Age	Visit	Medical Problem	Reason
Valsartan	274	1573	Female	73	8	Dizziness	Adverse experience
Valsartan	276	1586	Male	81	10	Diarrhoea	Adverse experience
Valsartan	278	1804	Female	75	3	Severe Diarrhoea	Adverse experience
Lisinopril	200	1788	Female	70	8	Dry Cough	Adverse experience
Lisinopril	201	1010	Female	74	4	Heaviness in Limbs / Cerebral Hypoperfusion	Adverse experience
Lisinopril	201	1012	Female	73	7	Dry cough	Adverse experience
Lisinopril	203	1032	Female	74	5	Dry cough	Adverse experience
Lisinopril	212	1092	Female	82	6	Headache/Dizziness	Adverse experience
Lisinopril	214	1108	Female	65	6	Glycosuria / Hyperglycaemia	Laboratory abnormality
Lisinopril	215	1735	Female	68	8	Nausea	Adverse experience
Lisinopril	219	1145	Female	71	9	Cough	Adverse experience
Lisinopril	221	1163	Male	72	6	Dry Cough	Adverse experience
Lisinopril	224	1186	Female	65	4	Dry Cough	Adverse experience
Lisinopril	231	1234	Female	67	3	Dizziness/Fatigue/ Epistaxis/Rash	Adverse experience
Lisinopril	247	1363	Male	68	3	Dizzy Spells	Adverse experience
Lisinopril	251	1393	Female	68	7	Oedema/Nausea/ Dizziness	Adverse experience
Lisinopril	256	1434	Male	73	6	Weight Gain	Adverse experience
Lisinopril	261	1474	Female	79	6	Dry Cough	Adverse experience
Lisinopril	266	1515	Female	73	3	Cough	Adverse experience
Lisinopril	273	1562	Male	74	6	Nausea/Headache /Light-headedness	Adverse experience
Lisinopril	278	1766	Female	81	8	Dry cough	Adverse experience
Lisinopril	279	1828	Male	67	6	Depression	Adverse experience
Lisinopril	289	1689	Female	68	5	Haemorrhagic Rash over Varicose Vein	Adverse experience
Lisinopril	290	1700	Female	72	3	Cough	Adverse experience

One of 25 valsartan treated patients (Patient 206/1055) and 1 of 21 lisinopril treated patients (Patient 214/1108) withdrew due to a laboratory abnormality. The remaining patients withdrew due to non-serious adverse experiences. It should be noted that one of the lisinopril patients had previously had a serious adverse experience but was not withdrawn due to this (Patient 215/1735).

Two patients were discontinued due to laboratory abnormalities. Patient 207/1027 (valsartan) was discontinued due to asymptomatic abnormal liver function tests. SGOT and SGPT increased to 208 U/L and 227 U/L at visit 6 from a normal baseline and visit 4 values. Valsartan was discontinued and repeat labs one month later were normal. Patient 206/1055 (valsartan) had an elevated alkaline phosphatase. Alkaline phosphatase was 237, 8818 and 1345 U/L at visits 1, 4 and 6 respectively. It is not clear what relationship valsartan had on the changes in these labs.

Patient 242/1321 (valsartan/HCTZ) was discontinued due to left facial swelling. The patients had a history of sinus inflammation and had URI symptoms at the same time. It appears that the patient continued on medication for approximately 2 months after the first complaints of swelling. The relationship to valsartan therapy is unclear.

Table 28.4 lists the most frequently reported adverse events during double blind treatment. This is a composite of patients either on monotherapy or combination therapy. Of note, the incidence of cough is approximately double in the Lisinopril group compared to the valsartan group. Back pain occurred in only one Lisinopril patient but was reported by 24 valsartan patients. The clinical significance of this observation is unclear.

Table 28.4. Adverse Events Reported by ≥ 3% of the Patients [vol. 1.200, p. 38]

(N(%))

	valsartan	lisinopril
	N=	N=
Total Patients	204 (100.0)	107 (100.0)
Total Patients with an Adverse Experience	143 (70.1)	121 (72.8)
Arthralgia	12 (5.9)	4 (2.4)
Bronchitis	9 (2.7)	6 (3.6)
Coughing	27 (8.1)	22 (13.2)
Dizziness	24 (7.2)	9 (5.4)
Dizziness	29 (8.7)	12 (7.2)
Dyspepsia	15 (4.5)	6 (3.6)
Fatigue	12 (3.6)	5 (3.0)
Headache	29 (8.7)	14 (8.4)
Infection chest	10 (3.0)	8 (4.8)
Infection viral	11 (3.3)	4 (2.4)
Nausea	13 (3.9)	6 (3.6)
Pain back	24 (7.2)	1 (0.6)
Rhinitis	10 (3.0)	12 (7.2)
Upper respiratory tract infection	30 (9.0)	13 (7.8)
Urinary tract infection	7 (2.1)	6 (3.6)
Vomiting	4 (1.2)	7 (4.2)

For each laboratory parameter, there was no difference between treatment groups in the incidence of labs outside the pre-defined percent change from baseline. There was no difference between treatment groups in the changes in the mean lab values for each visit (e.g. mean alkaline phosphatase doubled post-baseline in both the valsartan and Lisinopril group).

Protocol 33. A Multiple Dose, Randomized, Double-Blind, Active Controlled, Parallel Trial Comparing Valsartan 80 mg PO OD vs. Lisinopril 10 mg OD vs. HCTZ 25 mg PO OD For The Occurrence Of Cough In Hypertensive Patients Age 18 - 80 With A History Of ACEI Induced Cough (5/13/94 - 2/1/95)

This a randomized, double-blind, multi-center, parallel dose, active control trial whose purpose was to compare the incidence rates of dry cough with valsartan and lisinopril treatment in patients with a history of ACEI induced cough. The trial consisted of a 2 - 4 week placebo period, a 4 week Lisinopril challenge period, a 2 week Lisinopril washout period and a 6 week double-blind treatment period as illustrated in Table 33.1.

Table 33.1. Study Design.

Period	Placebo Run-In	Lisinopril Challenge	Lisinopril Washout	Double-Blind Treatment		
Visit	1	2	3	4	5	6
Week	-10	- 6	- 2	0	3	6
Duration	2 - 4 weeks	up to 4 weeks	2 weeks	6 weeks		
Treatment	placebo	Lisinopril 10 mg	placebo	Lisinopril 10 mg valsartan 80 HCTZ 25 mg		

In order to be randomized to double-blind treatment, patients had to fulfill the following criteria:

- 18 - 80 years of age;
- have a history of ACEI induced cough;
- a mean siDBP ≥ 90 mm Hg and ≤ 115 mm Hg at visit 2;
- no cough present during the placebo run-in;
- dry cough must be present at visit 3;
- cough absent at visit 4.

Patients with a history of asthma, smoking history in past 2 years, current smoking, CHF and IDDM were excluded. Numerous medications as listed in the protocol (vol. 1.18, p. 12) resulted in exclusion.

The primary endpoint was the incidence of dry persistent cough at either visit 5 or 6. The secondary endpoint was the terminal visit mean siDBP and siSBP (baseline was calculated from visit 2 and 4 separately).

There is one limitation in the collection of data in this study. At visit 2 and 4, the case report form does not ask "Does the patient have a cough?" Thus, in the data there are no responses for these visits regarding cough unless the patient was discontinued prior to randomization.

Results

Table 33.2 lists the patient disposition for the study. Nineteen centers participated in the study. One-hundred and ninety-seven patients started the Lisinopril challenge period. One-hundred and twenty-nine patients were randomized. One-hundred and six patients completed the six week treatment period. Twenty-three patients discontinued prematurely.

Table 33.2. Patient Disposition.

	Valsartan 80 mg	Lisinopril 10 mg	HCTZ 25 mg	Total
Enrolled	-	-	-	203
Started Lisinopril Challenge	-	-	-	197
Started Post-Challenge Washout	-	-	-	141
Randomized	42	45	42	129
Completed	35	35	36	106
Discontinued Prematurely	7	10	6	23
Adverse Experience	3	10	2	15
Unsatisfactory Response	2	0	3	5
Withdrew Consent	0	0	1	1
Lost to Follow-up	2	0	0	2

There were no significant difference between the treatment groups with regard to major demographic variables. The majority of patient were men. Ninety-three percent of patients were white. Only 4 black patients were enrolled. Table 33.3 lists the demographic variables for each treatment group.

Table 33.3. Patient Demographics

	Valsartan 80 mg N = 42	Lisinopril 10 mg N = 45	HCTZ 25 mg N = 42	Total N = 129
Male	24 (57%)	25 (56%)	22 (52%)	71 (55%)
White	41 (98%)	41 (91%)	38 (90%)	120 (93%)
Mean Age	52.6	55.9	52.3	53.6
Mean Baseline siDBP (visit 4)	96.9 ± 6.9	96.1 ± 6.6	96.9 ± 8.2	

Twenty-three patients received prohibited medication during the trial (7 valsartan, 6 Lisinopril, 10 HCTZ). It is unlikely that this contributed significantly to the outcome.

Table 33.4 lists the number of patients with dry cough at either visit 5 or visit 6. There is a slight difference in the incidence as calculated by the sponsor and the medical reviewer. The difference in incidence between the valsartan and Lisinopril groups are significantly different ($P < .00004$; Chi-Square).

Table 33.4. Incidence Of Patients With Cough During Double-Blind Treatment.

	# of Patients	Sponsors Incidence	Medical Reviewer's Incidence
Valsartan	41*	8 (19.5%)	10 (24.3%)
Lisinopril	45	31 (68.9 %)	31 (68.9%)
HCTZ	42	8 (19.0 %)	12 (28.6%)

* One patient lost to follow-up with no post-randomization visit. [Note: The difference between the sponsor's count and the medical reviewer's count involves the inclusion of patients who had cough that was not deemed dry or persistent. The conclusion does not change.]

The mean change in siDBP at week 3 (visit 5) and week 6 (visit 6) of double-blind treatment are listed in table 33.5. There was no significant difference in the change in siDBP between treatments.

Table 33.5. Mean Change in siDBP at Visit 5 and 6.

	Valsartan		Lisinopril		HCTZ	
	N	Mean Change	N	Mean Change	N	Mean Change
Visit 5	41	- 5.07 (6.67)	45	- 6.56 (7.31)	42	- 4.67 (7.91)
Visit 6	36	- 4.54 (7.55)	37	- 5.32 (9.69)	39	- 4.80 (7.50)

Three valsartan patients discontinued due to adverse events. None were deemed top be serious. Table 33.6 lists the valsartan patients discontinued due to adverse events.

Table 33.6. Valsartan Patients Discontinued due to Adverse Events.

Patient Number	Sex	Age	Visit	Adverse Event
410/1201	f	60	5	Hives
165/1084	m	44	6	Dry Cough
210/1098	f	70	5	Headache

There were no clinically significant changes in laboratory values for valsartan treated patients.

Protocols CH-91-07, CH-92-01, CH-92-07.

Three trials were performed in which either a 1 or 2% valsartan solution was administered to the eyes of healthy subjects or patients with increased intraocular pressure. A total of 20 subjects completed the studies. There was no evidence of a pharmacodynamic effect. Minor keratopathies were reported and were thought to be secondary to repeated tonometry measurements.

Protocols ANG-004, ANG-005, ANG-006

Protocols ANG-004, ANG-005, ANG-006 were open-label, multi-center, dose titration studies in hypertensive patients. The studies were performed in Japan during 1993 or 1994. The doses studied ranged from 10 mg to 160 mg. All had a placebo run-in followed by a treatment period ranging from 4 days to 10 weeks. Ninety-five patient enrolled and 86 patients completed the studies. Valsartan was well tolerated.

The design of these studies limits the usefulness of the information obtained. There are more relevant studies in the NDA.

Protocol 102.

This was an open label, placebo controlled, dose ranging study to evaluate the central hemodynamic effects of valsartan in patients with stable CHF (EF < 35%). Patients received a single dose of valsartan (10, 20, 40, 80 or 160 mg) or placebo and central pressure measurements were performed for 24 hours post-dosing via Swan-Ganz catheter. The primary endpoint was the change in pulmonary capillary wedge pressure (PCWP) and cardiac output over time. Valsartan blood concentrations were also measured.

This study was reviewed for safety only. Efficacy will not be discussed because it does not pertain to the current indication being sought by the sponsor and the design of the study does not lend itself to assigning much relevance to the results. Twenty-five patients were randomized to either placebo (N = 4) or valsartan (N = 21). Ten patients (8 valsartan, 2 placebo) reported adverse events. There was one serious adverse event in a patient dosed with valsartan 160 mg (worsening CHF). Dizziness was the most common adverse event reported (3 valsartan patients).

Protocol 11 Open Label Extension (1st Year)
(4/6/93 - 1/20/95)

This is an open label, optional, uncontrolled trial in patients who completed protocol 11. Only information for the first year of extension therapy is included. The trial consisted of a 6 week titration phase during which patients initially received valsartan 20 mg. The dose was titrated to 40 mg and then 80 mg at 2 week intervals based on blood pressure response (titration if mean siDBP > 90 mmHg and there was < 10 mmHg decrease from baseline). Patients who needed additional therapy could receive HCTZ

12.5 mg or 25 mg. Following the titration phase, patients continued in a 102 week extension phase. During the extension phase, the dose of valsartan and HCTZ could be adjusted based on blood pressure response.

Results

Three hundred and ninety-nine patients entered the open label extension. The number of patients from each of the treatment groups in the double-blind portion of the protocol 11 ranged from 94 to 104. Two hundred and fourteen patients received only valsartan monotherapy during the open label study. One hundred and eighty-five received valsartan monotherapy and valsartan/HCTZ therapy at some during the extension phase. The exposure to therapy in patient years is listed in table 11E.1. After approximately 1 year of therapy, approximately 50% of the patients remained on monotherapy and 50% received combination therapy.

Table 11E.1. Patient Exposure.

Dose Level	Patients Exposed to Dose Level	Patient Years of Exposure
Valsartan 20 mg	399	93
Valsartan 40 mg	319	79
Valsartan 80 mg	252	82
Valsartan Monotherapy Total	399	254
Valsartan/HCTZ Exposure	185	134

One hundred and forty-six patients prematurely discontinued the extension phase. The reasons patients discontinued are listed in table 11E.2.

Table 11E.2. Reasons for Premature Discontinuation

Reason Discontinued	# Discontinued
Adverse Experience	46
Abnormal Lab	2
Administrative Problems	2
Death	2
Did not meet protocol criteria	3
Lost to Follow-up	7
Non-compliant	6
Withdrew Consent	30
Unsatisfactory Response	48
Total	146

The average age of the patients was 55.0 years. All were Caucasian and 70% were male.

Table 11E.3 lists the mean change in siDBP from baseline by week for all extension patients regardless of therapy. Since the means in the latter weeks do not include patients who discontinued in earlier weeks for any reason including failure to respond, the mean values are likely inflated.

Table 11E.3. Mean Change from Baseline* in siDBP

Visit	Extension Week	N	Mean (±S.D.)
9	2	394	- 7.5 (± 7.4)
10	4	389	- 9.6 (± 7.2)
11	6	379	- 10.5 (± 6.9)
12	10	364	- 11.9 (± 7.1)
13	14	355	- 11.9 (± 6.5)
14	22	343	- 11.7 (± 6.7)
15	30	321	- 11.8 (± 6.8)
16	38	297	- 12.3 (± 6.6)
17	46	278	- 13.5 (± 7.0)
18	58	264	- 12.7 (± 7.3)

* baseline = visit 5

Two patients died. Patient 016/515 was a 75 yo female (valsartan 20 mg) who was found dead after 6 months treatment in the extension period. No autopsy was performed. Death was attributed to cardiovascular disease. Patient 012/509 was a 64 yo male (valsartan 80 mg) who experienced an acute episode of chest pain and died. No autopsy was performed.

Seventy percent of the patients experienced adverse events on at least one occasion. Table 11E.4 list the most frequently reported adverse events (> 3% of patients) by the patients. The most common adverse event was headache reported in 19% of patients. Respiratory related adverse events were the next most commonly reported. Dizziness occurred in 7.5%. Coughing was reported in 6.3%. It should be kept in mind that exposure to valsartan in the double-blind period may have some effect on the event rates of adverse events in the open label since those adverse events occurring in the double blind portion of the study are not included. Adverse event rates were analyzed as a function of age and by sex [not by race since there were no black patients]. It is unclear whether any individual adverse events show a predilection for either sex or are age related. Tables 11E.5 and 11E.6 lists the incidence of the most commonly reported adverse events as a function of sex and age. The appendix (page xxxi) contains a listing of all adverse events reported by 1% of the patients.

Table 11E.4. Adverse Events Reported By At Least 3% Of The Patients [volume 1.212, p. 40].

	Valsartan N (%)	Valsartan/HCTZ N (%)
Total Patients	399 (100.0)	185 (100.0)
Total Patients with an Adverse Experience	281 (70.4)	127 (68.6)
Adverse Experience		
Headache	75 (18.8)	14 (7.6)
Sinusitis	44 (11.0)	15 (8.1)
Viral Infection	43 (10.8)	24 (13.0)
Upper Respiratory Tract Infection	34 (8.5)	18 (9.7)
Dizziness	30 (7.5)	10 (5.4)
Arthralgia	28 (7.0)	9 (4.9)
Coughing	25 (6.3)	12 (6.5)
Back Pain	25 (6.3)	5 (2.7)
Diarrhea	21 (5.3)	8 (4.3)
Dyspepsia	18 (4.5)	6 (3.2)
Pharyngitis	16 (4.0)	6 (3.2)
Arm Pain	16 (4.0)	5 (2.7)
Nausea	14 (3.5)	4 (2.2)
Leg Pain	13 (3.3)	6 (3.2)
Injury	13 (3.3)	3 (1.6)
Rash	13 (3.3)	3 (1.6)
Fatigue	12 (3.0)	6 (3.2)
Abdominal Pain	9 (2.3)	7 (3.8)
Respiratory Disorder	8 (2.0)	8 (4.3)
Sprains and Strains	7 (1.8)	6 (3.2)

Table 11E.5. Adverse Events Reported By At Least 3% Of The Patients by Age Groups [volume 1.212, p. 44].

	Valsartan		Valsartan/HCTZ	
	< 65 N (%)	≥ 65 N (%)	< 65 N (%)	≥ 65 N (%)
Total Patients	317 (100.0)	82 (100.0)	151 (100.0)	34 (100.0)
Total Patients with an Adverse Experience	224 (70.7)	57 (69.5)	102 (67.5)	25 (73.5)
Adverse Experiences				
Headache	64 (20.2)	11 (13.4)	11 (7.3)	3 (8.8)
Sinusitis	34 (10.7)	10 (12.2)	11 (7.3)	4 (11.8)
Viral Infection	36 (11.4)	7 (8.5)	20 (13.2)	4 (11.8)
Upper Respiratory Tract Infection	32 (10.1)	2 (2.4)	16 (10.6)	2 (5.9)
Dizziness	24 (7.6)	6 (7.3)	7 (4.6)	3 (8.8)
Arthralgia	19 (6.0)	9 (11.0)	5 (3.3)	4 (11.8)
Coughing	20 (6.3)	5 (6.1)	12 (7.9)	0 (0.0)
Back Pain	20 (6.3)	5 (6.1)	5 (3.3)	0 (0.0)
Diarrhea	19 (6.0)	2 (2.4)	7 (4.6)	1 (2.9)
Dyspepsia	15 (4.7)	3 (3.7)	6 (4.0)	0 (0.0)
Pharyngitis	12 (3.8)	4 (4.9)	4 (2.6)	2 (5.9)
Arm Pain	14 (4.4)	2 (2.4)	5 (3.3)	0 (0.0)
Nausea	9 (2.8)	5 (6.1)	2 (1.3)	2 (5.9)
Leg Pain	11 (3.5)	2 (2.4)	6 (4.0)	0 (0.0)
Injury	10 (3.2)	3 (3.7)	3 (2.0)	0 (0.0)
Rash	11 (3.5)	2 (2.4)	2 (1.3)	1 (2.9)
Fatigue	11 (3.5)	1 (1.2)	4 (2.6)	2 (5.9)
Abdominal Pain	8 (2.5)	1 (1.2)	6 (4.0)	1 (2.9)
Respiratory Disorder	7 (2.2)	1 (1.2)	7 (4.6)	1 (2.9)
Sprains and Strains	7 (2.2)	0 (0.0)	4 (2.6)	2 (5.9)

Table 11E.6. Adverse Events Reported By At Least 3% Of The Patients by Sex [volume 1.212, p. 46].

	Valsartan		Valsartan/HCTZ	
	Male N (%)	Female N (%)	Male N (%)	Female N (%)
Total Patients	281 (100.0)	115 (100.0)	138 (100.0)	47 (100.0)
Total Patients with an Adverse Experience	192 (68.3)	89 (75.4)	97 (70.3)	30 (63.8)
Adverse Experience				
Headache	44 (15.7)	31 (26.3)	9 (6.5)	5 (10.6)
Sinusitis	28 (10.0)	16 (13.6)	8 (5.8)	7 (14.9)
Viral Infection	30 (10.7)	13 (11.0)	17 (12.3)	7 (14.9)
Upper Respiratory Tract Infection	26 (9.3)	8 (6.8)	15 (10.9)	3 (6.4)
Dizziness	17 (6.0)	13 (11.0)	8 (5.8)	2 (4.3)
Arthralgia	22 (7.8)	6 (5.1)	5 (3.6)	4 (8.5)
Coughing	15 (5.3)	10 (8.5)	10 (7.2)	2 (4.3)
Back Pain	19 (6.8)	6 (5.1)	5 (3.6)	0 (0.0)
Diarrhea	14 (5.0)	7 (5.9)	4 (2.9)	4 (8.5)
Dyspepsia	11 (3.9)	7 (5.9)	4 (2.9)	2 (4.3)
Pharyngitis	10 (3.6)	6 (5.1)	3 (2.2)	3 (6.4)
Arm Pain	10 (3.6)	6 (5.1)	3 (2.2)	2 (4.3)
Nausea	7 (2.5)	7 (5.9)	4 (2.9)	0 (0.0)
Leg Pain	8 (2.8)	5 (4.2)	4 (2.9)	2 (4.3)
Injury	12 (4.3)	1 (0.8)	2 (1.4)	1 (2.1)
Rash	9 (3.2)	4 (3.4)	3 (2.2)	0 (0.0)
Fatigue	10 (3.6)	2 (1.7)	3 (2.2)	3 (6.4)
Abdominal Pain	8 (2.8)	1 (0.8)	5 (3.6)	2 (4.3)
Respiratory Disorder	6 (2.1)	2 (1.7)	6 (4.3)	2 (4.3)
Sprains and Strains	5 (1.8)	2 (1.7)	5 (3.6)	1 (2.1)

Forty-nine patients discontinued from the study due to adverse events or laboratory abnormalities. Forty-three patients had adverse experiences described as serious (of which 15 discontinued prematurely). Table 11E.7 lists the patients who discontinued due to adverse events, lab abnormalities and those with serious adverse events.

Table 11E.7. Patients With Serious Adverse Events Or Discontinued Due To Adverse Event Or Lab Abnormality. [vol. 1.212, p. 52]

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Sugimoto	11E1	Valsartan	20 mg	004/502	M	63	10	Diarrhea	Yes	No
							10	Impotence	Yes	No
Oparil	11E1	Valsartan/ HCTZ	80/25	004/502	M	50	15	Impotency	Yes	No
Ansari	11E1	Valsartan	20 mg	004/503	M	58	16	Low back pain	Yes	No
							16	Nightmares/frequent dreams	Yes	No
								Numbness leg and arms	Yes	No
McNeer	11E1	Valsartan	20 mg	005/504	M	64	10	Dyspepsia	Yes	No
							10	Atopic rhinitis	Yes	No
							10	Burning in eyes	Yes	No
							10	Headache	Yes	No
								Shakes in morning	Yes	No
McNeer	11E1	Valsartan	20 mg	008/507	F	55	9	Headache	Yes	No
							9	Blurred vision	Yes	No
Marbury	11E1	Valsartan	40 mg	009/505	M	44	10	Dry throat	Yes	No
							10	Delayed focusing of eyes	Yes	No
							10	Agitation	Yes	No
								Decreased libido	Yes	No
								Headache	Yes	No
								Involuntary twitch lower eyelid	Yes	No
								Nervousness	Yes	No
Kliger	11E1	Valsartan	40 mg	009/506	M	48	12	Hypotension	Yes	No
Kraus	11E1	Valsartan	20 mg	011/507	F	66	18	General fatigue	Yes	No
							18	Lethargy	Yes	No
Miller	11E1	Valsartan	80 mg	012/510	M	46	15	Increased fatigue	Yes	No
							15	Diarrhea/change in stools	Yes	No
							15	Difficulty in urination	Yes	No
Grimm	11E1	Valsartan	40 mg	013/510	M	55	16	Transient ischemic attack	Yes	Yes
							16	Confusion	Yes	Yes
Yarbrough	11E1	Valsartan	80 mg	014/510	M	31	18	Anxiety reaction	Yes	No
							16	Migraine	No	Yes
							18	Migraine equivalent	Yes	Yes
Davis	11E1	Valsartan	80 mg	015/514	M	71	11	Stomach upset	Yes	No
							11	Neck pain	Yes	No
							11	Dizzy spells	Yes	No
								Headaches	Yes	No
Cobler	11E1	Valsartan	80 mg	019/515	M	57	15	Fatigue	Yes	No
								Cracking fingernails	Yes	No
								Increased hair loss	Yes	No
Davis	11E1	Valsartan	40 mg	020/515	M	48	11	Intermittent headache	Yes	No
							11	Low sexual response	Yes	No
Marbury	11E1	Valsartan	80 mg	032/524	F	59	13	Feet swelling	Yes	No
								Finger swelling	Yes	No
								Hand swelling	Yes	No
								Shoulder swelling	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
								Soreness feet	Yes	No
								Soreness fingers	Yes	No
								Soreness hands	Yes	No
								Soreness knees	Yes	No
								Soreness shoulders	Yes	No
								Swelling knees	Yes	No
Kraus	11E1	Valsartan	20 mg	001/501	M	47	10	Dyspepsia	Yes	No
								Gastric pressure	Yes	No
Marbury	11E1	Valsartan	40 mg	002/502	M	76	16	Loose stools	Yes	No
Kliger	11E1	Valsartan	40 mg	002/502	M	35	10	Headaches	Yes	No
Wombolt	11E1	Valsartan	40 mg	005/505	M	65	10	Severe atherosclerosis left leg	Yes	Yes
Lasseter	11E1	Valsartan	40 mg	005/505	F	46	15	Low hemoglobin/ hematocrit	Yes	No
Serfer	11E1	Valsartan	20 mg	006/503	F	49	17	Syncope	Yes	No
Miller	11E1	Valsartan	20 mg	006/504	M	65	18	Cerebrovascular accident	No	Yes
								Transient ischemic attack	Yes	Yes
Cobler	11E1	Valsartan	20 mg	007/505	M	44	15	Impotence	Yes	No
Oparil	11E1	Valsartan	20 mg	007/506	M	50	14	Increased edema feet	Yes	No
								Increased edema legs	Yes	No
Davis	11E1	Valsartan	20 mg	008/508	F	63	14	Abnormal platelet count	Yes	No
								Abnormal WBC count	Yes	No
Cobler	11E1	Valsartan	80 mg	013/510	M	67	13	Leukemia	Yes	Yes
Miller	11E1	Valsartan	20 mg	013/511	M	46	9	Chest pain	Yes	Yes
Kliger	11E1	Valsartan	80 mg	015/511	M	59	16	Cervical radiculopathy	Yes	Yes
Sugimoto	11E1	Valsartan	20 mg	016/510	M	56	18	Impotence	Yes	No
Grimm	11E1	Valsartan	40 mg	016/513	M	71	17	Impotence	Yes	No
Davis	11E1	Valsartan	20 mg	017/517	F	71	10	Abdominal distention	Yes	No
Sugimoto	11E1	Valsartan	80 mg	018/512	M	60	15	Weight gain	Yes	No
Garrett	11E1	Valsartan	20 mg	019/518	M	66	9	Headache	Yes	No
Cobler	11E1	Valsartan	20 mg	024/518	M	67	17	Cardiomyopathy	Yes	No
Oparil	11E1	Valsartan	20 mg	025/521	M	35	16	Right and left flank pain	Yes	No
Davis	11E1	Valsartan	40 mg	026/523	F	55	12	Intermittent positional dizziness	Yes	No
Gray	11E1	Valsartan	40 mg	029/528	F	48	11	Headaches	Yes	No
Marbury	11E1	Valsartan	20 mg	030/521	F	49	17	Syncope	Yes	Yes
Ellison	11E2	Valsartan	40 mg	010/510	M	50	21	Accidental drowning	Yes	Yes
								Death	Yes	Yes
Ellison	11E2	Valsartan	20 mg	011/511	M	49	20	Cardiac arrest	Yes	Yes
								Death	Yes	Yes
Kliger	11E2	Valsartan	20 mg	014/510	F	59	20	Hives	Yes	No
Garrett	11E1	Valsartan/ HCTZ	80/12.5	007/506	M	54	13	Pulmonary embolism	Yes	Yes
Wombolt	11E1	Valsartan	80 mg	016/515	M	72	14	Atrial fibrillation	No	Yes
								Cerebrovascular disease	No	Yes
								Complete heart block	Yes	Yes
								Right ventricular myocardial infarction	Yes	Yes
Serfer	11E1	Valsartan/ HCTZ	80/12.5	001/501	M	40	17	Fracture left elbow	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Vaziri	11E1	Valsartan/ HCTZ	80/25	007/504	M	56	18	Cervical spondylosis Neck pain Right arm weakness Right leg weakness	Yes Yes No No	Yes Yes Yes Yes
Miller	11E1	Valsartan/ HCTZ	80/25	007/505	F	68	14	Muscular chest pain	Yes	Yes
Ellison	11E1	Valsartan/ HCTZ	80/25	008/507	F	67	18	Adenocarcinoma in situ Colon polyp Tubulovillous adenoma	Yes Yes Yes	Yes No Yes
Ansari	11E1	Valsartan/ HCTZ	80/12.5	012/509	M	72	14	Black stool	Yes	Yes
Grimm	11E1	Valsartan/ HCTZ	80/12.5	012/509	M	62	17	Arteriosclerotic heart disease Death	Yes Yes	Yes Yes
Chaudhery	11E1	Valsartan/ HCTZ	80/25	017/517	M	49	16	Cough Wheeze	Yes Yes	No No
Oparil	11E1	Valsartan HCTZ	80/25	021/517	F	57	15	Itching, chest, arms and neck	Yes	No
Grimm	11E1	Valsartan/ HCTZ	80/12.5	022/516	M	59	12	Decreased libido	Yes	No
Oparil	11E2	Valsartan/ HCTZ	80/25	003/501	M	65	19	Chest pain coronary artery disease	Yes	Yes
Chrysant	11E2	Valsartan/ HCTZ	80/12.5	002/502	M	66	21	Squamous cell carcinoma, larynx	Yes	Yes
Vaziri	11E2	Valsartan/ HCTZ	80/25	017/512	M	63	19	Bilateral flank pain	Yes	No
Cobler	11E2	Valsartan/ HCTZ	80/25	018/514	M	39	20	Decreased libido	Yes	No

Serious Adverse Events Not Prematurely Discontinued

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Miller	11E1	Valsartan	20 mg	013/511	M	46	9	Shortness of breath	No	Yes
Wombolt	11E1	Valsartan	80 mg	016/515	M	72	14	Worsening diabetes mellitus	No	Yes
Wombolt	11E1	Valsartan	80 mg	016/515	M	72	14	Osteoarthritis right knee	No	Yes
Gray	11E1	Valsartan	40 mg	021/518	F	57	11	Acute cholecytitis	No	Yes
Gray	11E1	Valsartan	40 mg	021/518	F	57	14	Retinal arteriolar occlusion	No	Yes
Vaziri	11E1	Valsartan	80 mg	028/520	F	48	16	Chest pain (gastric)	No	Yes
Vaziri	11E1	Valsartan	80 mg	028/520	F	48	16	Heartburn	No	Yes
Vaziri	11E1	Valsartan	80 mg	028/520	F	48	16	Anxiety attack	No	Yes
Pool	11E1	Valsartan	80 mg	003/503	M	60	16	Flank pain	No	Yes
Ellison	11E1	Valsartan	40 mg	003/504	F	70	18	Basal cell carcinoma nose	No	Yes
Cobler	11E1	Valsartan	80 mg	004/504	M	58	11	Bile duct stone	No	Yes
Grimm	11E1	Valsartan	40 mg	007/507	M	62	14	Exertional chest pain	No	Yes
Wombolt	11E1	Valsartan	80 mg	007/509	M	62	14	Osteoarthritis left knee	No	Yes
Serfer	11E1	Valsartan	80 mg	008/507	M	54	14	Basal cell carcinoma	No	Yes
McNeer	11E1	Valsartan	20 mg	009/508	F	74	18	Peripheral vascular disease	No	Yes
Vaziri	11E1	Valsartan	80 mg	010/506	F	53	15	Intermittent chest pain, cardiac	No	Yes
Yarbrough	11E1	Valsartan	80	012/512	F	55	18	Adenomatous hyperplasia with atypia, uterus	No	Yes
Vaziri	11E1	Valsartan	20 mg	020/514	F	79	14	Basal skin carcinoma	No	Yes

Serious Adverse Events Not Prematurely Discontinued

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Davis	11E1	Valsartan	20 mg	023/519	M	62	11	Amputation 3rd and 5th fingers left hand	No	Yes
Ansari	11E1	Valsartan/ HCTZ	80/12.5	001/501	F	78	18	Hypokalemia	No	Yes
Ansari	11E1	Valsartan/ HCTZ	80/12.5	001/501	F	78	18	Pneumonia	No	Yes
Oparil	11E1	Valsartan/ HCTZ	80/25	004/502	M	50	14	Worsening neck pain	No	Yes
Garrett	11E1	Valsartan/ HCTZ	80/12.5	007/506	M	54	13	Brain tumor	No	Yes
Chrysant	11E2	Valsartan/ HCTZ	80/25	001/501	M	41	20	Fractured scaphoid bone right wrist	No	Yes
Chaudhery	11E1	Valsartan/ HCTZ	80/12.5	003/503	F	53	16	Abdominal pain	No	Yes
Chrysant	11E1	Valsartan/ HCTZ	80/25	004/504	M	58	18	Basal cell carcinoma ear	No	Yes
McNeer	11E1	Valsartan/ HCTZ	80/12.5	007/505	M	62	16	Prostate cancer	No	Yes
Pool	11E1	Valsartan/ HCTZ	80/12.5	011/507	M	73	12	Basal cell carcinoma back	No	Yes
Chrysant	11E2	Valsartan/ HCTZ	80/25	016/516	M	59	20	Transient ischemic attack	No	Yes
Pool	11E1	Valsartan/ HCTZ	80/25	017/511	M	43	Post-trial	Stenosis of left common iliac vessel	No	Yes
Chrysant	11E1	Valsartan/ HCTZ	80/25	021/519	F	45	18	Fracture right ankle	No	Yes
Vaziri	11E1	Valsartan/ HCTZ	80/25	025/518	M	69	17	Cerebrovascular accident	No	Yes
Grimm	11E1	Valsartan/ HCTZ	80/25	027/520	M	48	15	Hydrocele recurred	No	Yes
Oparil	11E1	Valsartan/ HCTZ	80/12.5	027/525	M	54	12	Cyst left neck	No	Yes
Marbury	11E2	Valsartan/ HCTZ	80/25	036/527	M	58	19	Benign prostatic hypertrophy	No	Yes
Oparil	11E1	Valsartan	20 mg	020/518	M	65	18	Adenomatous polyps sigmoid colon Adenovillous polyps ascending colon	No No	Yes Yes
Kliger	11E1	Valsartan	40 mg	009/506	M	48	12	Malignant lymphoma Splenomegaly	No No	Yes Yes
Yarbrough	11E1	Valsartan	80 mg	014/510	M	31	16	Right arm weakness Right sided facial weakness	No No	Yes Yes
McNeer	11E1	Valsartan	40 mg	006/506	M	50	13	Angina - chest pain Coronary artery disease	No No	Yes Yes
Garrett	11E1	Valsartan	20 mg	016/515	F	74	15	Cardiovascular collapse Death	No No	Yes Yes
Oparil	11E1	Valsartan	20 mg	014/512	M	68	15	Heme positive stool Hiccups Nausea Vomiting	No No No No	Yes Yes Yes Yes

Serious Adverse Events Not Prematurely Discontinued

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Oparil	11E1	Valsartan/ HCTZ	80/25	010/510	M	60	14	Abdominal pain	No	Yes
								Cholelithiasis	No	Yes
							17	Abdominal pain	No	Yes
								Cholelithiasis	No	Yes
								Acute Cholelithiasis	No	Yes
								Nausea	No	Yes

Patient 008/508 was a 63 yo female who discontinued due to WBC count and platelet count abnormalities. Table 11E.8 lists the abnormalities. The patient did not have signs of infection or easy bruising. The WBC differential was normal.

Table 11E.8. Labs for Patient 008/508.

Visit	WBC (T/mm^3)	platelet (T/mm^3)
5		
6		
8		
11		
13		
13 R		
14		

R = repeat lab 3 days after visit 3

Patient 005/505 was a 46 yo female who experienced a decrease in hemoglobin and hematocrit as listed in table 11E.9. Other than noting that a GI series was negative there are no other labs performed to work-up the anemia. It appears that WBC and platelets tended to decrease also.

Table 11E.9. Labs for Patient 005/505.

Visit	hemoglobin (gm/dl)	hematocrit (%)	WBC (T/mm^3)	platelet (T/mm^3)
5				
8				
11				
13				
14				
15				

There were no significant changes in mean laboratory parameters for the terminal visit compared to the baseline visit. Seventeen patients did not have terminal visit labs. Mean serum potassium did not change in patients treated with monotherapy throughout the first year of the extension but it did decrease by .2 mEq/L for valsartan/HCTZ treated patients (4.5 mEq/L ----> 4.3 mEq/L). Some patients had isolated increases in potassium or phosphate but these resolved despite continued therapy (which suggests a lab error). None of the patients had creatinine values above the normal range at the terminal visit.

The lab results for two patients warrant further discussion.

- Patient 017/512 was a 62 yo male who had normal baseline SGOT (11 U/L) and SGPT (13 U/L). (Normal Range: SGOT = 0 - 40 U/L, SGPT = 0 - 45 U/L) Terminal visit SGOT (219 U/L) and SGPT (388 U/L) were increased. Total bilirubin increased from .9 mg/dl at baseline to 3 mg/dl at the terminal visit. The patient remained asymptomatic. The relationship to therapy is unclear.
- Patient 16/511 had multiple lab abnormalities at visit 10 (see table 11E.10.). The patient withdrew consent at visit 10. The relationship of the abnormalities to therapy are unclear.

Table 11E.10. Patient 16/511 Labs.

Visit	Creatinine (mg/dl)	Phosphate (mg/dl)	Potassium (mEq/L)	Sodium (mEq/L)
5				
8				
10				

Conclusions

Efficacy

- Valsartan is an effective therapy for lowering Diastolic Blood Pressure in the dose range of 80 - 160 mg once a day.
- Limited numbers of Black patients were randomized into clinical trials assessing efficacy. Consequently, subgroup analysis are underpowered. In the limited data available, the effect of valsartan in Black patients was comparable to the effect observed in Caucasians. The effect of valsartan in Black patients was comparable to the effect of lisinopril in Black patients. Any labeling regarding the effect in racial subgroups should be similar to the labeling found in Angiotensin Converting Enzyme Inhibitors and AII antagonists until definitive data is available.

Safety

- The incidence of cough with valsartan appears to be less than the incidence of cough with lisinopril. This was documented in patients with a history of ACEI induced cough in a single trial (protocol 33). The sponsor uses the incidence rate of cough in ACEI controlled trials as supportive data.
- Angioedema was a rare event. Labeling regarding angioedema should be similar to losartan's labeling.
- Occasional increases in serum creatinine were noted in valsartan treated patients. Acute renal failure or rapid increases in serum creatinine has been reported in a patient (1062/61) and patient (1030/29) in protocol 26 but the treatment of the patients has not been unblinded. Post-marketing reports with losartan indicate that acute renal failure will occur.
- The sponsor has provided information on the number of patients with decreases of the absolute neutrophil count to less than 1.0 x 10^9/L. Additional information is required before any conclusions can be made.

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY / R. LIPICKY

Appendix Attached

APPENDIX CONTENTS

Adverse Events Incidence in Protocol 28.

Adverse Event	Valsartan	lisinopril	Valsartan	lisinopril
N	334	167	334	167
coughing	28	28	8.38%	16.77%
upper resp tract	27	10	8.08%	5.99%
dizziness	26	10	7.78%	5.99%
pain back	25	1	7.49%	0.60%
headache	25	13	7.49%	7.78%
diarrhea	24	8	7.19%	4.79%
arthralgia	15	4	4.49%	2.40%
dyspepsia	14	7	4.19%	4.19%
fatigue	11	3	3.29%	1.80%
rhinitis	10	12	2.99%	7.19%
pharyngitis	10	5	2.99%	2.99%
infection viral	10	4	2.99%	2.40%
nausea	9	3	2.69%	1.80%
infection chest	9	6	2.69%	3.59%
bronchitis	9	4	2.69%	2.40%
pain abdominal	8	2	2.40%	1.20%
otitis externa	8	1	2.40%	0.60%
injury	8	5	2.40%	2.99%
vertigo	7	5	2.10%	2.99%
sprains and stra	7		2.10%	0.00%
pain leg	7	1	2.10%	0.60%
pain arm	7	1	2.10%	0.60%
hypotension post	7	1	2.10%	0.60%
edema dependent	7	3	2.10%	1.80%
palpitation	6	1	1.80%	0.60%
myalgia	6	1	1.80%	0.60%
ear disorder nos	6		1.80%	0.00%
conjunctivitis	6	6	1.80%	3.59%
urinary tract in	5	6	1.50%	3.59%
tendon disorder	5		1.50%	0.00%
neuralgia	5	1	1.50%	0.60%
insomnia	5		1.50%	0.00%
gastroenteritis	5	3	1.50%	1.80%
eczema	5	1	1.50%	0.60%
dyspnea	5		1.50%	0.00%
dermatitis	5		1.50%	0.00%
depression	5		1.50%	0.00%
pain	4	1	1.20%	0.60%
cramps muscle	4	1	1.20%	0.60%
vomiting	3	7	0.90%	4.19%
vision abnormal	3	1	0.90%	0.60%
trauma	3	1	0.90%	0.60%

Adverse Events Incidence in Protocol 28.

Adverse Event	Valsartan	lisinopril	Valsartan	lisinopril
N	334	167	334	167
somnolence	3	1	0.90%	0.60%
rash	3	2	0.90%	1.20%
purpura	3	1	0.90%	0.60%
procedure gastro	3	1	0.90%	0.60%
procedure eye	3	2	0.90%	1.20%
pain chest	3		0.90%	0.00%
micturition freq	3		0.90%	0.00%
influenza like s	3		0.90%	0.00%
hemorrhoids	3	2	0.90%	1.20%
hematuria	3		0.90%	0.00%
fracture	3		0.90%	0.00%
esophagitis	3	1	0.90%	0.60%
epistaxis	3	3	0.90%	1.80%
earache	3		0.90%	0.00%
cramps leg	3	1	0.90%	0.60%
constipation	3	3	0.90%	1.80%
arthrosis	3	1	0.90%	0.60%
angina pectoris	3	4	0.90%	2.40%
allergic reactio	3	2	0.90%	1.20%
vestibular disor	2		0.60%	0.00%
verruca	2	1	0.60%	0.60%
urinary incontin	2		0.60%	0.00%
tonsillitis	2		0.60%	0.00%
sputum increased	2		0.60%	0.00%
skin cold clammy	2		0.60%	0.00%
sinusitis	2	4	0.60%	2.40%
rigors	2		0.60%	0.00%
periodontitis	2		0.60%	0.00%
pain musculo-ske	2	1	0.60%	0.60%
otitis media	2	1	0.60%	0.60%
mouth dry	2	1	0.60%	0.60%
laryngitis	2		0.60%	0.00%
infection	2	1	0.60%	0.60%
herpes zoster	2	1	0.60%	0.60%
gout	2		0.60%	0.00%
gait abnormal	2		0.60%	0.00%
flushing	2		0.60%	0.00%
flatulence	2	1	0.60%	0.60%
conjunctival hem	2		0.60%	0.00%
cerebrovascular	2	1	0.60%	0.60%
cellulitis	2	1	0.60%	0.60%
asthma	2		0.60%	0.00%
arthritis	2		0.60%	0.00%

Adverse Events Incidence in Protocol 28.

Adverse Event	Valsartan	lisinopril	Valsartan	lisinopril
N	334	167	334	167
weight increase	1	1	0.30%	0.60%
vulva disorder	1	1	0.30%	0.60%
vitreous detachm	1		0.30%	0.00%
vein varicose	1	1	0.30%	0.60%
vaginitis atroph	1		0.30%	0.00%
uveitis	1		0.30%	0.00%
urticaria	1		0.30%	0.00%
urinary retentio	1		0.30%	0.00%
tremor	1	1	0.30%	0.60%
tracheitis	1		0.30%	0.00%
tongue discolora	1		0.30%	0.00%
tongue coated	1		0.30%	0.00%
tinnitus	1		0.30%	0.00%
tendinitis	1		0.30%	0.00%
taste perversion	1		0.30%	0.00%
syncope	1		0.30%	0.00%
sweating increas	1		0.30%	0.00%
stomatitis ulcer	1		0.30%	0.00%
sputum abnormal	1		0.30%	0.00%
skin dry	1		0.30%	0.00%
skin disorder	1	1	0.30%	0.60%
seborrhea	1		0.30%	0.00%
rheumatism	1		0.30%	0.00%
respiratory diso	1	1	0.30%	0.60%
rash maculopapul	1		0.30%	0.00%
rash erythematou	1		0.30%	0.00%
pruritus	1		0.30%	0.00%
prostatic disord	1		0.30%	0.00%
proctitis	1		0.30%	0.00%
procedure surgic	1		0.30%	0.00%
procedure muscul	1	1	0.30%	0.60%
polyuria	1	1	0.30%	0.60%
pneumonia	1	1	0.30%	0.60%
phlebitis	1		0.30%	0.00%
paronychia	1		0.30%	0.00%
paresthesia	1	1	0.30%	0.60%
paralysis	1		0.30%	0.00%
pain renal	1		0.30%	0.00%
pain perineal fe	1		0.30%	0.00%
paget's disease	1		0.30%	0.00%
nocturia	1	1	0.30%	0.60%
nervousness	1		0.30%	0.00%
nasal obstructio	1	1	0.30%	0.60%

Adverse Events Incidence in Protocol 28.

Adverse Event	Valsartan	lisinopril	Valsartan	lisinopril
N	334	167	334	167
nail disorder	1		0.30%	0.00%
muscle weakness	1		0.30%	0.00%
moniliasis	1		0.30%	0.00%
migraine	1		0.30%	0.00%
micturition diso	1		0.30%	0.00%
macula lutea deg	1	1	0.30%	0.60%
leukopenia	1		0.30%	0.00%
ischemia	1		0.30%	0.00%
intervertebral d	1		0.30%	0.00%
infection ocular	1	1	0.30%	0.60%
immobilization p	1		0.30%	0.00%
hyperuricemia	1		0.30%	0.00%
hypertonia	1		0.30%	0.00%
hyperkeratosis	1		0.30%	0.00%
hypercholesterol	1		0.30%	0.00%
hot flushes	1		0.30%	0.00%
high density lip	1		0.30%	0.00%
herpes ocular	1		0.30%	0.00%
hemoptysis	1		0.30%	0.00%
hemiparesis	1		0.30%	0.00%
hematemesis	1		0.30%	0.00%
hallucination	1		0.30%	0.00%
hair texture abn	1		0.30%	0.00%
glaucoma	1	1	0.30%	0.60%
gastritis	1		0.30%	0.00%
fibrillation atr	1	1	0.30%	0.60%
falling down nos	1	3	0.30%	1.80%
face edema	1	1	0.30%	0.60%
esophageal ulcer	1		0.30%	0.00%
enteritis	1		0.30%	0.00%
edema peripheral	1		0.30%	0.00%
edema legs	1		0.30%	0.00%
dysuria	1		0.30%	0.00%
dysphonia	1	1	0.30%	0.60%
duodenal ulcer	1		0.30%	0.00%
deformity skelet	1		0.30%	0.00%
deafness	1		0.30%	0.00%
cyst	1		0.30%	0.00%
cataract	1	1	0.30%	0.60%
carpal tunnel sy	1		0.30%	0.00%
cardiac failure	1		0.30%	0.00%
carcinoma renal	1		0.30%	0.00%
bronchospasm	1	2	0.30%	1.20%

Adverse Events Incidence in Protocol 28.

Adverse Event	Valsartan	lisinopril	Valsartan	lisinopril
N	334	167	334	167
blepharoconjunct	1		0.30%	0.00%
bladder calculus	1		0.30%	0.00%
bilirubinemia	1		0.30%	0.00%
asthenia	1		0.30%	0.00%
appendicitis	1		0.30%	0.00%
anxiety	1	1	0.30%	0.60%
anorexia	1		0.30%	0.00%
anemia hypochrom	1		0.30%	0.00%
amnesia	1		0.30%	0.00%
alopecia	1		0.30%	0.00%
adhesive capsuli	1		0.30%	0.00%
acne	1	1	0.30%	0.60%
abnormal stools	1		0.30%	0.00%
abnormal auscult	1		0.30%	0.00%
xerophthalmia		1	0.00%	0.60%
ulcer of extremi		1	0.00%	0.60%
ulcer		1	0.00%	0.60%
tooth ache		1	0.00%	0.60%
thrombocythemia		1	0.00%	0.60%
tachycardia		1	0.00%	0.60%
sprains and stra		1	0.00%	0.60%
skin ulceration		1	0.00%	0.60%
sepsis		1	0.00%	0.60%
retinal hemorrha		1	0.00%	0.60%
psoriasis		1	0.00%	0.60%
procedure female		1	0.00%	0.60%
nystagmus		1	0.00%	0.60%
neoplasm endomet		1	0.00%	0.60%
melena		1	0.00%	0.60%
malaise		1	0.00%	0.60%
lymphocytosis		1	0.00%	0.60%
intermenstrual b		1	0.00%	0.60%
infection skin		1	0.00%	0.60%
hyperuricemia		1	0.00%	0.60%
hyperesthesia		1	0.00%	0.60%
herpes simplex		2	0.00%	1.20%
hemorrhage rectu		1	0.00%	0.60%
hematuria		4	0.00%	2.40%
gastric ulcer		1	0.00%	0.60%
eye complaints		1	0.00%	0.60%
encephalopathy		1	0.00%	0.60%
dermatitis funga		1	0.00%	0.60%
cystitis		1	0.00%	0.60%

Adverse Events Incidence in Protocol 28.

Adverse Event	Valsartan	lisinopril	Valsartan	lisinopril
N	334	167	334	167
claudication int		1	0.00%	0.60%
bullous eruption		1	0.00%	0.60%
bone disorder		1	0.00%	0.60%
basal cell carci		1	0.00%	0.60%
atherosclerosis		1	0.00%	0.60%

Deaths in Valsartan Treated Patients.

Protocol	Center/Patient Treatment Age/Sex	Cause of Death
11E2	010/510/Ellison Valsartan 40 mg 50/M	**Accidental Drowning** This 50 year old male patient with a 15 year history of hypertension died due to accidental drowning approximately 90 weeks after beginning treatment with valsartan in the open-label extension phase. The patient had been fishing on a boat with relatives when the boat sank. The patient never made it to shore. His body was later recovered by divers. An autopsy was performed confirming that the death was accidental.
28	1282/Grillage Valsartan 80 mg 88/M	**Bronchopneumonia** This patient began the double-blind phase of the trial on 03/05/94, and progressed to Level B (valsartan 80 mg) medication on 16/05/94. He had a previous history of chronic bronchitis, but was not taking any medication. On 04/01/95 he became unconscious and was admitted to hospital where a diagnosis of bronchopneumonia was made. Trial medication was discontinued. The adverse experience commenced 246 days after starting Level B (valsartan 80 mg) medication. The patient died 5 days later on 09/01/95.
28	1214/Deering Valsartan 80 mg 70/M	**Carcinoma of kidney** This patient began the double-blind phase of the trial on 05/04/94, and progressed to Level B (valsartan 80 mg) medication on 19/04/94 and Level C (valsartan 80 mg) medication on 03/05/94. He had no previous history of urinary problems. On 15/09/94 he was admitted to hospital with bilateral groin pain, and was subsequently diagnosed as having chronic urinary retention secondary to prostatic enlargement, along with a urinary tract infection. This adverse experience began 149 days after starting Level C medication. Treatment with trial medication was stopped. He was discharged two days later on 17/09/94, having been prescribed trimethoprim. He was re-admitted on 01/ 0/94, after a blood urea sample taken during his follow-up out-patient clinic visit was found to be high. He was subsequently referred to an oncologist, who diagnosed kidney carcinoma. He was then referred for bilateral nephrostomy and radiotherapy treatment. This patient died on 22/10/94. In the investigator's opinion there was no relationship between the trial medication and the adverse experience.
11E2	011/511/Ellison Valsartan 20 mg 49/M	**Cardiac arrest** This 49 year old male patient with a 6 year history of hypertension presented in an emergency room with chest pain approximately 85 weeks after beginning treatment with valsartan in the open-label extension phase. Laboratory evaluations and ECG were normal. The patient was diagnosed with esophagitis, treated with cisapride, scheduled for a GI consultation and discharged. The patient was last seen by the investigator approximately 9 weeks prior to the onset of the chest pain for a routine trial visit. Physical examination at that time was unremarkable and the patient was without complaints. Eight days following the chest pain episode, the patient was reported to have complained to his spouse of difficulty breathing while sitting in a chair. The patient's wife called for an ambulance and on returning to the room found the patient blue and gurgling. The patient was transported to the emergency room and pronounced dead on arrival. Preliminary autopsy revealed severe gastroenteritis and 90% occlusion of the left anterior descending coronary artery. Final autopsy results revealed findings of CAD with 90% narrowing of the left anterior descending coronary artery and passive congestion of the liver and spleen with hemosiderin laden macrophages consistent with CHF. Cause of death was determined to be sudden cardiac arrest most likely due to arrhythmia.

Deaths in Valsartan Treated Patients.

Protocol	Center/Patient Treatment Age/Sex	Cause of Death
31	Serfer/0489/5506 Valsartan 20 mg 46/M	**Cardiac arrest** This patient had a history of hypertension for twelve years. At Visit 1, his MSBP was 158/101 mmHg (158/102 mmHg standing) and ECG and chest X-Ray results were normal. At randomization, his MSBP was 149/101 mmHg (148/102 mmHg standing). Nine days after entering the double-blind treatment phase, while participating in scuba diving lessons, the patient sustained a cardiac arrest. Cardiopulmonary resuscitation was attempted but unsuccessful. The patient was pronounced dead on arrival after transport to an emergency facility. Autopsy findings revealed right ventricular hypertrophy, pulmonary congestion and edema. The report lists the cause of death as pulmonary hypertension.
20	1189/Halmenschlager Valsartan 80 mg 71/F	**Cardiac arrest** After 15 days of exposure to the trial medication, the patient was found dead at home one morning. The investigator had seen her a few days before and no medical problem had been noticed. Her previous medical history included a depression since 1980, hypothyroidism since 1985 and a gastric ulcer in 1988. She was treated by levothyroxine, metanizole caffeine, paracetamol and iron sulfate. No autopsy was performed, causality of death was cardiac arrest.
11E1	016/515/Garrett Valsartan 20 mg 74/F	**Cardiovascular collapse** The patient entered the open-label treatment period on 8/17/93. The patient lived alone and was last seen on 2/20/94. When the neighbors did not see her on 2/21/94, they had the maintenance man check on her. She was found unresponsive in her apartment. The rescue company was called and she was declared dead on arrival at the hospital. The actual date of death (2/20 or 2/21) has not been determined. The family did not want an autopsy to be performed. The death was ruled due to cardiovascular collapse. The patient had a history of hypertension since 1986.
28	1184/Collins Valsartan 80 mg 82/F	**Myocardial infarction** This patient began the double-blind phase of the trial on 09/06/94, and progressed to Level B (valsartan 80 mg) medication on 08/09/94. She had a previous history of mild angina of effort, but was not taking any medication. On 17/09/94 she was hospitalized with chest pains, and a diagnosis of myocardial infarction was made. This adverse experience occurred 9 days after beginning Level B (valsartan 80 mg) medication. This patient died one day later on 18/09/94.
11E1	012/509/Grimm Valsartan 80 mg / HCTZ 12.5 mg 62/M	**Arteriosclerotic heart disease** This 64-year old male patient completed the double-blind phase of the trial on 6/30/93 and began the open-label phase at that time. His trial medication was titrated to 80 mg daily on 8/04/93. HCTZ 12.5 mg was initiated on 4/15/94. The patient was last seen by the investigator on 5/11/94 when he came in for an unscheduled visit for blood pressure monitoring post-initiation of HCTZ. At that time his blood pressure was 133/75 mmHg. On 6/23/94, the study coordinator received a voice mail message from a family member of the patient's indicating that he had died on 6/22/94. The patient was scheduled for an interim visit on 6/23/94, and the study coordinator had spoken to him on 6/21/94, confirming his appointment. The patient had experienced chest pain during the week, which he attributed to indigestion and did not seek medical intervention. At 2:00 A.M. on 6/22/94, the patient experienced an acute episode of chest pains and expired. No autopsy was performed. The investigator indicated that when the patient was last seen, he was in good condition and that he had a heart attack while sleeping. The investigator felt that this event was not related to trial drug. Throughout the study, the

Deaths in Valsartan Treated Patients.

Protocol	Center/Patient Treatment Age/Sex	Cause of Death
		patient experienced the following adverse events: gastrointestinal flu (10/02/93 - 10/10/93), abdominal pain right upper quadrant (12/03/93 - 12/05/93), cold sinusitis (3/30/94 - unknown). All were related to trial drug. An autopsy was not performed.
28	1338/Jaiswal Lisinopril 2.5 mg 66/M	**Bronchopneumonia** This patient began the double-blind phase of the trial on 03/05/94. He had a previous history of cervical spondylosis and cervical decompression, and had suffered a brainstem infarct. On 23/11/94 the patient was diagnosed as having a chest infection, and was admitted to hospital on 29/11/94. He died in hospital of bronchopneumonia on 30/11/94. The bronchopneumonia began 204 days after the start of treatment.
28	1889/Blagden Lisinopril 20 mg 75/F	**Cerebrovascular accident** This patient began the double-blind phase of the trial on 10/05/94, and progressed to Level B (lisinopril 10 mg) medication on 26/05/94 and Level C (lisinopril 20 mg) medication on 10/06/94. She had a previous history of CVA, having had an attack in 1991, and concomitant medications included omeprazole 20 mg daily, metoclopramide 10 mg tds and isosorbide mononitrate 60 mg daily. She also had a history of esophagitis treated with antacids. On 01/09/94 the patient stopped taking her trial medication because of dizziness. On 05/09/94 she attended her GP and confirmed this. Later that day, she died of a CVA. The CVA occurred 118 days after beginning treatment with Level C (lisinopril 20 mg) medication.
50	274/5197/Ginsberg Placebo 77/M	**Cerebrovascular accident** Nineteen days after successfully completing the trial, this patient suffered a left sided cerebrovascular accident with right sided paralysis and expressive and receptive aphasia. He expired nine days after onset of the CVA. Blood pressure at randomization was 171/103 mmHg and at the end of the trial was 173/101 mmHg. At the end of the trial the patient was started on diltiazem and enalapril. At the fourteen day post-trial follow-up blood pressure was 164/88 mmHg. His only reported adverse experience during the trial was a moderate headache which resolved prior to the end of the trial. The patient took no concomitant medications during the trial.

Adverse Events in Protocol 28.

Adverse Event	Valsartan	Lisinopril
N	334	167
coughing	8.38%	16.77%
URI	8.08%	5.99%
dizziness	7.78%	5.99%
pain back	7.49%	0.60%
headache	7.49%	7.78%
diarrhea	7.19%	4.79%
arthralgia	4.49%	2.40%
dyspepsia	4.19%	4.19%
fatigue	3.29%	1.80%
rhinitis	2.99%	7.19%
pharyngitis	2.99%	2.99%
infection viral	2.99%	2.40%
nausea	2.69%	1.80%
infection chest	2.69%	3.59%
bronchitis	2.69%	2.40%
pain abdominal	2.40%	1.20%
otitis externa	2.40%	0.60%
injury	2.40%	2.99%
vertigo	2.10%	2.99%
sprains and strain	2.10%	0.00%
pain leg	2.10%	0.60%
pain arm	2.10%	0.60%
hypotension postural	2.10%	0.60%
edema dependent	2.10%	1.80%
palpitation	1.80%	0.60%
myalgia	1.80%	0.60%
ear disorder nos	1.80%	0.00%
conjunctivitis	1.80%	3.59%
UTI	1.50%	3.59%
tendon disorder	1.50%	0.00%
neuralgia	1.50%	0.60%
insomnia	1.50%	0.00%
gastroenteritis	1.50%	1.80%
eczema	1.50%	0.60%
dyspnea	1.50%	0.00%
dermatitis	1.50%	0.00%
depression	1.50%	0.00%
pain	1.20%	0.60%
cramps muscle	1.20%	0.60%
vomiting	0.90%	4.19%
vision abnormal	0.90%	0.60%
trauma	0.90%	0.60%

Adverse Events in Protocol 28.

Adverse Event	Valsartan	lisinopril
N	334	167
somnolence	0.90%	0.60%
rash	0.90%	1.20%
purpura	0.90%	0.60%
procedure GI	0.90%	0.60%
procedure eye	0.90%	1.20%
pain chest	0.90%	0.00%
frequent micturition	0.90%	0.00%
influenza like syndrome	0.90%	0.00%
hemorrhoids	0.90%	1.20%
hematuria	0.90%	0.00%
fracture	0.90%	0.00%
esophagitis	0.90%	0.60%
epistaxis	0.90%	1.80%
earache	0.90%	0.00%
cramps leg	0.90%	0.60%
constipation	0.90%	1.80%
arthrosis	0.90%	0.60%
angina pectoris	0.90%	2.40%
allergic reaction	0.90%	1.20%
vestibular disorder	0.60%	0.00%
verruca	0.60%	0.60%
urinary incontinence	0.60%	0.00%
tonsillitis	0.60%	0.00%
sputum increased	0.60%	0.00%
skin cold clammy	0.60%	0.00%
sinusitis	0.60%	2.40%
rigors	0.60%	0.00%
periodontitis	0.60%	0.00%
pain musculo-skeletal	0.60%	0.60%
otitis media	0.60%	0.60%
mouth dry	0.60%	0.60%
laryngitis	0.60%	0.00%
infection	0.60%	0.60%
herpes zoster	0.60%	0.60%
gout	0.60%	0.00%
gait abnormal	0.60%	0.00%
flushing	0.60%	0.00%
flatulence	0.60%	0.60%
conjunctival hemorrhage	0.60%	0.00%
cerebrovascular	0.60%	0.60%
cellulitis	0.60%	0.60%
asthma	0.60%	0.00%
arthritis	0.60%	0.00%

Adverse Events in Protocol 28.

Adverse Event	Valsartan	Lisinopril
N	334	167
weight increase	0.30%	0.60%
vulva disorder	0.30%	0.60%
vitreous detachment	0.30%	0.00%
vein varicose	0.30%	0.60%
atrophic vaginitis	0.30%	0.00%
uveitis	0.30%	0.00%
urticaria	0.30%	0.00%
urinary retention	0.30%	0.00%
tremor	0.30%	0.60%
tracheitis	0.30%	0.00%
tongue discoloration	0.30%	0.00%
tongue coated	0.30%	0.00%
tinnitus	0.30%	0.00%
tendinitis	0.30%	0.00%
taste perversion	0.30%	0.00%
syncope	0.30%	0.00%
sweating increase	0.30%	0.00%
stomatitis ulcer	0.30%	0.00%
sputum abnormal	0.30%	0.00%
skin dry	0.30%	0.00%
skin disorder	0.30%	0.60%
seborrhea	0.30%	0.00%
rheumatism	0.30%	0.00%
respiratory disorder	0.30%	0.60%
rash maculopapular	0.30%	0.00%
rash erythematous	0.30%	0.00%
pruritus	0.30%	0.00%
prostatic disorder	0.30%	0.00%
proctitis	0.30%	0.00%
procedure surgical	0.30%	0.00%
procedure muscular	0.30%	0.60%
polyuria	0.30%	0.60%
pneumonia	0.30%	0.60%
phlebitis	0.30%	0.00%
paronychia	0.30%	0.00%
paresthesia	0.30%	0.60%
paralysis	0.30%	0.00%
pain renal	0.30%	0.00%
pain perineal	0.30%	0.00%
paget's disease	0.30%	0.00%
nocturia	0.30%	0.60%
nervousness	0.30%	0.00%
nasal obstruction	0.30%	0.60%

Adverse Events in Protocol 28.

Adverse Event	Valsartan	Lisinopril
N	334	167
nail disorder	0.30%	0.00%
muscle weakness	0.30%	0.00%
moniliasis	0.30%	0.00%
migraine	0.30%	0.00%
micturition disorder	0.30%	0.00%
macular degeneration	0.30%	.60%
leukopenia	0.30%	0.00%
ischemia	0.30%	0.00%
intervertebral disc	0.30%	0.00%
infection ocular	0.30%	0.60%
immobilization p	0.30%	0.00%
hyperuricemia	0.30%	0.00%
hypertonia	0.30%	0.00%
hyperkeratosis	0.30%	0.00%
hypercholesterol	0.30%	0.00%
hot flushes	0.30%	0.00%
high density lip	0.30%	0.00%
herpes ocular	0.30%	0.00%
hemoptysis	0.30%	0.00%
hemiparesis	0.30%	0.00%
hematemesis	0.30%	0.00%
hallucination	0.30%	0.00%
hair texture abnormality	0.30%	0.00%
glaucoma	0.30%	0.60%
gastritis	0.30%	0.00%
atrial fibrillation	0.30%	0.60%
falling down nos	0.30%	1.80%
face edema	0.30%	0.60%
esophageal ulcer	0.30%	0.00%
enteritis	0.30%	0.00%
edema peripheral	0.30%	0.00%
edema legs	0.30%	0.00%
dysuria	0.30%	0.00%
dysphonia	0.30%	0.60%
duodenal ulcer	0.30%	0.00%
deformity skeletal	0.30%	0.00%
deafness	0.30%	0.00%
cyst	0.30%	0.00%
cataract	0.30%	0.60%
carpal tunnel syndrome	0.30%	0.00%
cardiac failure	0.30%	0.00%
carcinoma renal	0.30%	0.00%
bronchospasm	0.30%	1.20%

Adverse Events in Protocol 28.

Adverse Event	Valsartan	lisinopril
N	334	167
blepharoconjunctivitis	0.30%	0.00%
bladder calculus	0.30%	0.00%
bilirubinemia	0.30%	0.00%
asthenia	0.30%	0.00%
appendicitis	0.30%	0.00%
anxiety	0.30%	0.60%
anorexia	0.30%	0.00%
hypochromic anemia	0.30%	0.00%
amnesia	0.30%	0.00%
alopecia	0.30%	0.00%
adhesive capsulitis	0.30%	0.00%
acne	0.30%	0.60%
abnormal stools	0.30%	0.00%
abnormal auscultation	0.30%	0.00%
xerophthalmia	0.00%	0.60%
ulcer of extremity	0.00%	0.60%
ulcer	0.00%	0.60%
tooth ache	0.00%	0.60%
thrombocythemia	0.00%	0.60%
tachycardia	0.00%	0.60%
sprains and strain	0.00%	0.60%
skin ulceration	0.00%	0.60%
sepsis	0.00%	0.60%
retinal hemorrhage	0.00%	0.60%
psoriasis	0.00%	0.60%
procedure female	0.00%	0.60%
nystagmus	0.00%	0.60%
neoplasm endometrial	0.00%	0.60%
melena	0.00%	0.60%
malaise	0.00%	0.60%
lymphocytosis	0.00%	0.60%
intermenstrual bleeding	0.00%	0.60%
infection skin	0.00%	0.60%
hyperuricemia	0.00%	0.60%
hyperesthesia	0.00%	0.60%
herpes simplex	0.00%	1.20%
hemorrhage rectum	0.00%	0.60%
hematuria	0.00%	2.40%
gastric ulcer	0.00%	0.60%
eye complaints	0.00%	0.60%
encephalopathy	0.00%	0.60%
fungal dermatitis	0.00%	0.60%
cystitis	0.00%	0.60%

Adverse Events in Protocol 28.

Adverse Event	Valsartan	lisinopril
N	334	167
claudication intermittent	0.00%	0.60%
bullous eruption	0.00%	0.60%
bone disorder	0.00%	0.60%
basal cell carcinoma	0.00%	0.60%
atherosclerosis	0.00%	0.60%

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Klein	05	Valsartan	160 mg	Q1096/84	M	59	6	Hypertonic crisis	Yes	Yes
Klein	05	Valsartan	160 mg	Q1096/84	M	59	6	Headache	Yes	Yes
Chrysant	09	Valsartan	320 mg	Q004/505	F	49	10	Atypical chest pain	Yes	Yes
Chrysant	09	Valsartan	320 mg	Q004/505	F	49	10	Inferolateral ischemia	Yes	Yes
Holtzman	09	Valsartan	160 mg	020/518	M	69	9	Intermittent headaches	Yes	No
Pool	10	Valsartan	40 mg	031/526	M	47	6	Gouty arthritis	Yes	No
Kraus	11	Valsartan	40 mg	Q009/504	F	38	8	Congestive heart failure	Yes	Yes
Ansari	11	Valsartan	40 mg	008/508	M	77	6	Spondylolisthesis	Yes	Yes
Sugimoto	11	Valsartan	80 mg	013/507	M	61	6	Dizziness	Yes	No
Ellison	11	Valsartan	40 mg	023/520	F	62	6	Detached retina	Yes	Yes
Gray	11	Valsartan	20 mg	027/526	F	61	6	Abdominal pain Nonfunctioning gallbladder	Yes Yes	Yes Yes
Oparil	11	Valsartan	40 mg	030/526	M	29	7	Depression	Yes	No
Oparil	11	Valsartan	20 mg	031/524	M	61	7	Chest tightness	Yes	No
Sugimoto	11E1	Valsartan	20 mg	Q004/502	M	63	10	Diarrhea	Yes	No
Sugimoto	11E1	Valsartan	20 mg	Q004/502	M	63	10	Impotence	Yes	No
Ansari	11E1	Valsartan	20 mg	Q004/503	M	58	16	Low back pain	Yes	No
Ansari	11E1	Valsartan	20 mg	Q004/503	M	58	16	Nightmares/frequent dreams Numbness leg and arms	Yes Yes	No No
McNeer	11E1	Valsartan	20 mg	Q005/504	M	64	10	Dyspepsia	Yes	No
McNeer	11E1	Valsartan	20 mg	Q005/504	M	64	10	Atopic rhinitis	Yes	No
McNeer	11E1	Valsartan	20 mg	Q005/504	M	64	10	Burning in eyes	Yes	No
McNeer	11E1	Valsartan	20 mg	Q005/504	M	64	10	Headache Shakes in morning	Yes Yes	No No
McNeer	11E1	Valsartan	20 mg	Q008[illegible]7	F	55	9	Headache	Yes	No
McNeer	11E1	Valsartan	20 mg	Q00[illegible]7	F	55	9	Blurred vision	Yes	No
Marbury	11E1	Valsartan	40 mg	Q009/505	M	44	10	Dry throat	Yes	No
Marbury	11E1	Valsartan	40 mg	Q009/505	M	44	10	Delayed focusing of eyes	Yes	No
Marbury	11E1	Valsartan	40 mg	Q009/503	M	44	10	Agitation Decreased libido Headache Involuntary twitch lower eyelid Nervousness	Yes Yes Yes Yes Yes	No No No No No
Kliger	11E1	Valsartan	40 mg	Q009/506	M	48	12	Hypotension	Yes	No
Kraus	11E1	Valsartan	20 mg	Q011/507	F	66	18	General fatigue	Yes	No
Kraus	11E1	Valsartan	20 mg	Q011/507	F	66	18	Lethargy	Yes	No
Miller	11E1	Valsartan	80 mg	Q012/510	M	46	15	Increased fatigue	Yes	No
Miller	11E1	Valsartan	80 mg	Q012/510	M	46	15	Diarrhea/change in stools	Yes	No
Miller	11E1	Valsartan	80 mg	Q012/510	M	46	15	Difficulty in urination	Yes	No
Grimm	11E1	Valsartan	40 mg	Q013/510	M	55	16	Transient ischemic attack	Yes	Yes
Grimm	11E1	Valsartan	40 mg	Q013/510	M	55	16	Confusion	Yes	Yes
Yarbrough	11E1	Valsartan	80 mg	Q014/510	M	31	18 16 18	Anxiety reaction Migraine Migraine equivalent	Yes No Yes	No Yes Yes
Davis	11E1	Valsartan	80 mg	Q015/514	M	71	11	Stomach upset	Yes	No
Davis	11E1	Valsartan	80 mg	Q015/514	M	71	11	Neck pain	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Davis	11E1	Valsartan	80 mg	015/514	M	71	11	Dizzy spells	Yes	No
								Headaches	Yes	No
Cobler	11E1	Valsartan	80 mg	019/515	M	57	15	Fatigue	Yes	No
Cobler	11E1	Valsartan	80 mg	019/515	M	57	15	Cracking fingernails	Yes	No
								Increased hair loss	Yes	No
Davis	11E1	Valsartan	40 mg	020/515	M	48	11	Intermittent headache	Yes	No
Davis	11E1	Valsartan	40 mg	020/515	M	48	11	Low sexual response	Yes	No
Marbury	11E1	Valsartan	80 mg	032/524	F	59	13	Feet swelling	Yes	No
								Finger swelling	Yes	No
								Hand swelling	Yes	No
								Shoulder swelling	Yes	No
Marbury	11E1	Valsartan	80 mg	032/524	F	59	13	Soreness feet	Yes	No
								Soreness fingers	Yes	No
								Soreness hands	Yes	No
								Soreness knees	Yes	No
								Soreness shoulders	Yes	No
								Swelling knees	Yes	No
Kraus	11E1	Valsartan	20 mg	001/501	M	47	10	Dyspepsia	Yes	No
								Gastric pressure	Yes	No
Marbury	11E1	Valsartan	40 mg	002/502	M	76	16	Loose stools	Yes	No
Kliger	11E1	Valsartan	40 mg	002/502	M	35	10	Headaches	Yes	No
Wombolt	11E1	Valsartan	40 mg	005/505	M	65	10	Severe atherosclerosis left leg	Yes	Yes
Lasseter	11E1	Valsartan	40 mg	005/505	F	46	15	Low hemoglobin/ hematocrit	Yes	No
Serfer	11E1	Valsartan	20 mg	006/503	F	49	17	Syncope	Yes	No
Miller	11E1	Valsartan	20 mg	006/504	M	65	18	Cerebrovascular accident	No	Yes
								Transient ischemic attack	Yes	Yes
Cobler	11E1	Valsartan	20 mg	007/505	M	44	15	Impotence	Yes	No
Oparil	11E1	Valsartan	20 mg	007/506	M	50	14	Increased edema feet	Yes	No
								Increased edema legs	Yes	No
Davis	11E1	Valsartan	20 mg	008/508	F	63	14	Abnormal platelet count	Yes	No
								Abnormal WBC count	Yes	No
Cobler	11E1	Valsartan	80 mg	013/510	M	67	13	Leukemia	Yes	Yes
Miller	11E1	Valsartan	20 mg	013/511	M	46	9	Chest pain	Yes	Yes
Kliger	11E1	Valsartan	80 mg	015/511	M	59	16	Cervical radiculopathy	Yes	Yes
Sugimoto	11E1	Valsartan	20 mg	016/510	M	56	18	Impotence	Yes	No
Grimm	11E1	Valsartan	40 mg	016/513	M	71	17	Impotence	Yes	No
Davis	11E1	Valsartan	20 mg	017/517	F	71	10	Abdominal distention	Yes	No
Sugimoto	11E1	Valsartan	80 mg	018/512	M	60	15	Weight gain	Yes	No
Garrett	11E1	Valsartan	20 mg	019/518	M	66	9	Headache	Yes	No
Cobler	11E1	Valsartan	20 mg	024/518	M	67	17	Cardiomyopathy	Yes	No
Oparil	11E1	Valsartan	20 mg	025/521	M	35	16	Right and left flank pain	Yes	No
Davis	11E1	Valsartan	40 mg	026/523	F	55	12	Intermittent positional dizziness	Yes	No
Gray	11E1	Valsartan	40 mg	029/528	F	48	11	Headaches	Yes	No
Marbury	11E1	Valsartan	20 mg	030/521	F	49	17	Syncope	Yes	Yes
Ellison	11E2	Valsartan	40 mg	010/510	M	50	21	Accidental drowning	Yes	Yes
								Death	Yes	Yes
Ellison	11E2	Valsartan	20 mg	011/511	M	49	20	Cardiac arrest	Yes	Yes
								Death	Yes	Yes
Kliger	11E2	Valsartan	20 mg	014/510	F	59	20	Hives	Yes	No
Intile	17	Valsartan	80 mg	078/670	F	67	4	Dacryocystorhinostomy	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient#	Sex	Age	Visit	Adverse Experience	DC	SAE
Intile	17	Valsartan	80 mg	Q078/670	F	67	4	Chronic dacryocystitis Nasolacrimal duct obstruction	Yes Yes	No No
Sugimoto	17	Valsartan	80 mg	Q121/621	M	64	5	Extreme weakness	Yes	No
Sugimoto	17	Valsartan	80 mg	Q121/621	M	64	5	Generalized joint pain	Yes	No
Intile	17	Valsartan	80 mg	Q164/667	M	71	6	Weakness	Yes	No
Intile	17	Valsartan	80 mg	Q164/667	M	71	6	Headache	Yes	No
Intile	17	Valsartan	80 mg	Q164/667	M	71	6	Diaphoresis	Yes	No
Bath	17	Valsartan	80 mg	Q212/712	F	61	6	Weakness	Yes	No
Bath	17	Valsartan	80 mg	Q212/712	F	61	6	Dizziness	Yes	No
Bath	17	Valsartan	80 mg	Q212/712	F	61	6	Blurred vision	Yes	No
Gaman	17	Valsartan	80 mg	Q222/698	F	68	4	Peripheral edema	Yes	No
Gaman	17	Valsartan	80 mg	Q222/698	F	68	4	Uncontrolled hypertension	Yes	No
Gaman	17	Valsartan	80 mg	Q222/698	F	68	4	Headache	Yes	No
Smucker	17	Valsartan	80 mg	Q368/608	M	32	4	Chest pressure	Yes	No
Smucker	17	Valsartan	80 mg	Q368/608	M	32	4	Lightheadedness	Yes	No
Serfer	17	Valsartan	80 mg	Q422/850	M	58	5	Funny feeling in head	Yes	No
Serfer	17	Valsartan	80 mg	Q422/850	M	58	5	Impotence	Yes	No
O'Reilly	17	Valsartan	80 mg	097/600	M	75	6	Arthritis pain both knees Psoriatic arthritis	Yes Yes	No No
Smucker	17	Valsartan	80 mg	110/610	M	66	7	Transient ischemic attack	Yes	No
Sugimoto	17	Valsartan	80 mg	260/758	M	51	4	Elevated serum glucose	Yes	No
Corder	19	Valsartan	160 mg	Q1066	F	44	3	Stomach cramps	Yes	No
Corder	19	Valsartan	80 mg	Q1066	F	44	3	Leg cramps	Yes	No
Anderson	19	Valsartan	80 mg	Q160	F	79	3	Transient ischemic attack	Yes	Yes
Anderson	19	Valsartan	80 mg	Q160	F	79	3	Garbled speech	Yes	Yes
Delans	19	Valsartan	80 mg	Q216	M	59	3	Loss of appetite	Yes	No
Delans	19	Valsartan	80 mg	Q216	M	59	3	Decreased libido	Yes	No
Delans	19	Valsartan	80 mg	Q216	M	59	3	Bruises on arms, chin and throat	Yes	No
Antonishen	19	Valsartan	80 mg	Q482	F	53	3	Water retention	Yes	No
Antonishen	19	Valsartan	80 mg	Q482	F	53	3	Dizziness	Yes	No
Antonishen	19	Valsartan	80 mg	Q482	F	53	3	Red blotches on arms	Yes	No
Edmunds	19	Valsartan	80 mg	Q770	F	53	3	Parietal facial pain	Yes	No
Edmunds	19	Valsartan	80 mg	Q770	F	53	3	Pain radiating to shoulder	Yes	No
Edmunds	19	Valsartan	80 mg	Q770	F	53	3	Numbness left index finger	Yes	No
Neutel	19	Valsartan	80 mg	Q873	M	49	3	Cramping of extremities	Yes	No
Neutel	19	Valsartan	80 mg	Q873	M	49	3	Tingling of extremities	Yes	No
Neutel	19	Valsartan	80 mg	Q873	M	49	3	Cough	Yes	No
Neutel	19	Valsartan	80 mg	Q873	M	49	3	Cold extremities	Yes	No
Davis	19	Valsartan	80 mg	039	M	63	3	Right pleural effusion	Yes	Yes
Jain	19	Valsartan	160 mg	1027/5689	M	46	5	High anteriolateral myocardial infarction	Yes	Yes
Jain	19	Valsartan	160 mg	1037/5693	F	60	4	Ischemic third nerve palsy Ptosis upper right eyelid	Yes Yes	Yes Yes
Lewin	19	Valsartan	80 mg	1055	F	51	3	Headache	Yes	No
Lewin	19	Valsartan	160 mg	1057/5726	M	50	6	Cerebrovascular accident	Yes	Yes
Angelo	19	Valsartan	80 mg	106/5071	F	45	5	Proteinuria	Yes	No
Corder	19	Valsartan	80	1069/5736	M	41	6	Right abdominal pain	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Vranian	19	Valsartan	80 mg	1097/5298	F	59	4	Hepatitis C	Yes	No
Sufit	19	Valsartan	80 mg	1130	M	44	3	Blurry vision	Yes	No
Kerzner	19	Valsartan	80 mg	1175	M	44	3	Headache	Yes	No
Miller, C.	19	Valsartan	80 mg	1210	M	64	3	Numbness right leg	Yes	No
Hall	19	Valsartan	80 mg	1229	M	51	2	Back pain	Yes	No
Hall	19	Valsartan	160 mg	1231/5434	M	51	5	Ankle sprain	Yes	No
Anderson	19	Valsartan	80 mg	157/5105	F	60	5	Lack of energy	Yes	No
Gann	19	Valsartan	80 mg	220	F	51	3	Chest pain	Yes	Yes
Woehler	19	Valsartan	80 mg	234/5169	M	47	4	Bronchitis	Yes	No
Woehler	19	Valsartan	80 mg	256	F	48	3	Dizziness Headache	Yes Yes	No No
Williams, D.	19	Valsartan	80 mg	268	M	52	3	Bloating Constipation	Yes Yes	No No
Rosen	19	Valsartan	160 mg	299/5373	M	32	4	Abdominal pain Diarrhea	Yes Yes	No No
Nolen	19	Valsartan	80 mg	314/5209	F	51	6	Contact dermatitis	Yes	No
Chappel	19	Valsartan	80 mg	382	M	56	3	Cardiac arrhythmia	Yes	Yes
McInroy	19	Valsartan	80 mg	451/5304	F	48	5	Muscle contraction headache	Yes	No
Jain	19	Valsartan	160 mg	476/5321	F	51	5	Alcoholic cirrhosis	Yes	No
Marzec	19	Valsartan	80 mg	560	F	54	3	Headache Insomnia	Yes Yes	No No
Fogel	19	Valsartan	160 mg	568/5403	F	39	4	Increased frequency frontal headaches	Yes	No
Montoro	19	Valsartan	80 mg	576	M	54	3	Head pressure	Yes	No
Offenberg	19	Valsartan	80 mg	662	F	65	3	Amblyopia left eye	Yes	Yes
Kerzner	19	Valsartan	80 mg	665	F	71	3	Pedal edema Pain while walking	Yes Yes	No No
Kerzner	19	Valsartan	80 mg	668/5466	M	42	4	Fatigue	Yes	No
Detrano	19	Valsartan	80 mg	853/5546	M	63	6	Low platelet count	Yes	No
Montoro	19	Valsartan	80 mg	978	F	55	3	Migraine	Yes	No
Montoro	19	Valsartan	80 mg	984	M	49	3	Headache	Yes	No
Kronek	20	Valsartan	80 mg	1131	M	61	-	Microcytic anemia	Yes	Yes
Kronek	20	Valsartan	80 mg	1131	M	61	-	Microcytic anemia	Yes	Yes
Decobert	20	Valsartan	80 mg	1073	M	79	-	Edema lower extremities	Yes	No
Halmenschlager	20	Valsartan	80 mg	1189	F	71	-	Cardiac arrest Death	Yes Yes	Yes Yes
Lavot	20	Valsartan	80 mg	1199	F	78	-	Hip joint replacement	Yes	Yes
Gricourt	20	Valsartan	80 mg	1269	F	62	-	Dry cough	Yes	No
Cardoni	21	Valsartan	80 mg	1054	F	57	-	Tachycardia	Yes	No
Cardoni	21	Valsartan	80 mg	1054	F	57	-	Headache	Yes	No
Hebbeln	22	Valsartan	80 mg	1022	M	73	-	Chest pain - angina	Yes	Yes
Hebbeln	22	Valsartan	80 mg	1022	M	73	-	Arrhythmia Coronary disease	Yes Yes	Yes Yes
Lemme	22	Valsartan	80 mg	1029	M	37	-	Increased SGOT/SGPT	Yes	No
Dutilleul	23	Valsartan	80 mg	6282	F	70	-	Headache	Yes	No
Dutilleul	23	Valsartan	80 mg	6282	F	70	-	Tinnitus	Yes	No
Payeras	23	Valsartan	160 mg	7046	M	73	-	Palpitations	Yes	No
Payeras	23	Valsartan	160 mg	7046	M	73	-	Headache	Yes	No
Michel	23	Valsartan	160 mg	5122	M	85	-	Increased creatine kinase	Yes	No
Schneider	23	Valsartan	40 mg	5195	F	81	-	Headache	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Godde	23	Valsartan	80 mg	6190	M	66	-	Dizziness	Yes	No
								Headache	Yes	No
Fournier	23	Valsartan	80 mg	6235	F	67	-	Abdominal pain	Yes	No
Richard	23	Valsartan	40 mg	6311	M	69	-	Disorientation	Yes	Yes
								Neurological changes	Yes	Yes
Diss	23	Valsartan	40 mg	6337	M	66	-	Abdominal pain	Yes	No
Cazals	23	Valsartan	80 mg	6385	F	69	-	Pyelonephritis	Yes	Yes
Meridjen	23	Valsartan	160 mg	6453	F	83	-	Orthostatic hypotension	Yes	No
Jacquier	23	Valsartan	80 mg	6474	F	80	-	Abdominal pain	Yes	No
								Nausea	Yes	No
Meridjen	23	Valsartan	40 mg	6509	M	72	-	Fractured right wrist	Yes	No
Guzman	23	Valsartan	80 mg	7118	F	65	-	Hallucinations	Yes	No
								Headache	Yes	No
								Insomnia	Yes	No
Greiber	26	Unknown	?	1013/12	M	72	-	Renal function deteriorated	Yes	No
Stein	26	Valsartan	80 mg	1030/29	F	59	-	Rapid increase serum creatinine	Yes	No
Baldamus	26	Unknown	?	1041/40	F	65	-	Increased creatinine	Yes	No
Wanner	26	Unknown	?	1056/56	M	60	-	Nausea	Yes	No
								Salivation	Yes	No
Frei	26	Unknown	?	1062/61	M	27	-	Renal failure	Yes	Yes
Frei	26	Unknown	?	1066/66	M	67	-	Inguinal hernia repair	Yes	Yes
Meyer	26	Unknown	?	1079/19	F	40	-	Hypertension	Yes	Yes
Orpen	28	Valsartan	80 mg	Q1513	M	67	-	Rash	Yes	No
Allin	28	Valsartan	40 mg	Q1013	F	73	-	Leg weakness	Yes	No
Allin	28	Valsartan	40 mg	Q1013	F	73	-	Confusion	Yes	No
Anand	28	Valsartan	80 mg	Q1021	F	76	-	Pain in legs	Yes	No
Anand	28	Valsartan	80 mg	Q1021	F	76	-	Dizziness	Yes	No
Anand	28	Valsartan	80 mg	Q1021	F	76	-	Upper respiratory infection	Yes	No
Gough	28	Valsartan	40 mg	Q1265	M	69	-	Tiredness	Yes	No
Gough	28	Valsartan	40 mg	Q1265	M	69	-	Headache	Yes	No
Kirby	28	Valsartan	80 mg	Q1379	F	77	-	Atrial fibrillation	Yes	Yes
Kirby	28	Valsartan	80 mg	Q1379	F	77	-	Dizziness	Yes	Yes
Laws	28	Valsartan	40 mg	Q1396	F	65	-	Nausea	Yes	No
Laws	28	Valsartan	40 mg	Q1396	F	65	-	Heaviness in arms	Yes	No
Laws	28	Valsartan	40 mg	Q1396	F	65	-	Headache	Yes	No
Laws	28	Valsartan	40 mg	Q1396	F	65	-	Blurred vision	Yes	No
Orpen	28	Valsartan	80 mg	Q1513	M	67	-	Anti-synthetase syndrome	Yes	Yes
Orpen	28	Valsartan	80 mg	Q1513	M	67	-	Breathlessness	Yes	Yes
Pinheiro	28	Valsartan	40 mg	Q1538	F	71	-	Malaise	Yes	No
Pinheiro	28	Valsartan	40 mg	Q1538	F	71	-	Arm heaviness	Yes	No
Pinheiro	28	Valsartan	40 mg	Q1538	F	71	-	Lightheadedness	Yes	No
Rees-Jones	28	Valsartan	80 mg	Q1556	F	83	-	Knee pain	Yes	No
Rees-Jones	28	Valsartan	40 mg	Q1556	F	83	-	Excessive sweating	Yes	No
Aitchison	28	Valsartan	80 mg	1006	M	70	-	Myocardial infarction	Yes	Yes
Allin	28	Valsartan	80 mg	1011	F	79	-	Ankle edema	Yes	No
Allin	28	Valsartan	80 mg	1014	F	70	-	Ankle swelling	Yes	No
Baldwin	28	Valsartan	80 mg	1055	F	76	-	Elevated alkaline phosphatase	Yes	No
Bayman	28	Valsartan	80 mg	1058	M	66	-	Abnormal liver function tests (SGOT/SGPT)	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Berridge	28	Valsartan	40 mg	1070	F	65	-	Pan uveitis	Yes	Yes
Blagden	28	Valsartan	80 mg	1079	F	86	-	Angina	Yes	No
Collins	28	Valsartan	80 mg	1184	F	82	-	Myocardial infarction	Yes	Yes
								Death	Yes	Yes
Deering	28	Valsartan	80 mg	1214	M	70	-	Carcinoma of Bladder	Yes	Yes
								Death	Yes	Yes
Faut	28	Valsartan	40 mg	1235	F	73	-	Frequent micturition	Yes	No
Grillage	28	Valsartan	80 mg	1282	M	88	-	Bronchopneumonia	Yes	Yes
								Death	Yes	Yes
Jaiswal	28	Valsartan	40 mg	1348	F	66	-	Depression	Yes	No
Miller	28	Valsartan	40 mg	1473	F	71	-	Dry cough	Yes	No
Miller	28	Valsartan	80 mg	1481	M	73	-	Abdominal aortic aneurysm	Yes	Yes
								Toe ischemia	No	Yes
Parashchak	28	Valsartan	80 mg	1522	M	74	-	Atrial fibrillation	Yes	No
Rees-Jones	28	Valsartan	80 mg	1559	F	80	-	Angina	Yes	No
Sweeney	28	Valsartan	40 mg	1636	F	85	-	Diarrhea	Yes	Yes
								Vomiting	Yes	Yes
Cranfield	28	Valsartan	40 mg	1753	F	69	-	Vertigo	Yes	No
Cranfield	28	Valsartan	40 mg	1758	M	73	-	Dry cough	Yes	No
Silvert	28	Valsartan	40 mg	1804	F	75	-	Severe diarrhea	Yes	No
Parashchak	28	Valsartan	40 mg	1811	F	71	-	Cerebrovascular accident	Yes	Yes
Anand	28	Valsartan	40 mg	1856	M	69	-	Jejunum Tumor	Yes	Yes
Rees-Jones	28	Valsartan	40 mg	1928	F	74	-	Pain right thigh	Yes	No
Marbury	31	Valsartan	20 mg	Q085/5057	M	57	3	Flank pain	Yes	No
Marbury	31	Valsartan	20 mg	Q085/5057	M	57	3	Polycystic Kidney Disease	Yes	Yes
								Ruptured cyst left kidney	Yes	No
Marbury	31	Valsartan	20 mg	Q085/5057	M	57	3	Abdominal pain	Yes	No
								Nausea	Yes	No
								Vomiting	Yes	No
Anger	31	Valsartan	320 mg	Q141/5095	M	63	3	Diarrhea	Yes	No
Anger	31	Valsartan	320 mg	Q141/5095	M	63	3	Anxiousness	Yes	No
Anger	31	Valsartan	320 mg	Q141/5095	M	63	3	Cataracts	Yes	No
								Ringing in Ears	Yes	No
Weiss	31	Valsartan	160 mg	Q159/5104	F	43	3	Nausea	Yes	No
Weiss	31	Valsartan	160 mg	Q159/5104	F	43	3	Headache	Yes	No
Papademetrious	31	Valsartan	320 mg	Q580/5419	M	76	4	Tinnitus	Yes	No
Papademetrious	31	Valsartan	320 mg	Q580/5419	M	76	4	Anxiousness	Yes	No
								Ataxia	Yes	No
								Confusion	Yes	No
								Lightheadedness	Yes	No
Sugimoto	31	Valsartan	80 mg	Q803/5828	M	68	4	Weakness	Yes	No
Sugimoto	31	Valsartan	80 mg	Q803/5828	M	68	4	Dizziness	Yes	No
								Feeling faint	Yes	No
Anger	31	Valsartan	80 mg	145/5695	M	70	3	Difficulty voiding	Yes	No
Oparil	31	Valsartan	320 mg	279/5188	M	43	4	Impotence	Yes	No
Lewis	31	Valsartan	160 mg	295/5196	M	56	3	Depression	Yes	No
								Trouble sleeping	Yes	No
Serfer	31	Valsartan	20 mg	489/5506	M	46	3	Cardiac arrest	Yes	Yes
								Death	Yes	Yes
Harris	31	Valsartan	20 mg	553/5397	M	65	4	Angina	Yes	Yes

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DG	SAE
Velasquez	31	Valsartan	160 mg	659/5493	F	47	4	Abdominal pain	Yes	No
								Constipation	Yes	No
								Nausea	Yes	No
Drehobl	31	Valsartan	20 mg	677/5505	F	70	3	Abdominal pain	Yes	No
								Diverticulitis	Yes	No
Kief	31	Valsartan	320 mg	857/5782	M	51	3	Dizziness	Yes	No
Drehobl	31E	Valsartan	160 mg	168/5111	M	40	6	Chest pain	Yes	No
Drehobl	31E	Valsartan	160 mg	168/5111	M	40	6	Nausea	Yes	No
Drehobl	31E	Valsartan	160 mg	168/5111	M	40	6	Nervousness	Yes	No
Drehobl	31E	Valsartan	160 mg	173/5113	M	56	10	Decreased libido	Yes	No
Drehobl	31E	Valsartan	160 mg	173/5113	M	56	10	Decreased erections	Yes	No
								Penile flacidity	Yes	No
Lunde	31E	Valsartan	160 mg	214/5150	M	67	7	Probable Gilbert's syndrome	Yes	No
Lunde	31E	Valsartan	160 mg	214/5150	M	67	7	Increased urinary frequency	Yes	No
Strader	31E	Valsartan	160 mg	133/5562	M	43	6	Fatigue	Yes	No
Drehobl	31E	Valsartan	160 mg	179/5496	F	63	7	Lightheadedness	Yes	No
Dyke	31E	Valsartan	160 mg	192/5271	M	55	9	Wheezing	Yes	No
Hilty	31E	Valsartan	160 mg	198/5131	F	47	6	Vertigo	Yes	No
Hilty	31E	Valsartan	160 mg	209/5567	F	45	8	Vertigo	Yes	No
Lewis	31E	Valsartan	160 mg	287/5200	F	72	7	Cough	Yes	No
								Hoarseness	Yes	No
Harris	31E	Valsartan	160 mg	306/5205	F	43	6	Dysfunctional uterine bleeding	Yes	No
Hall	31E	Valsartan	160 mg	44/5432	F	49	6	Uterine mass	Yes	Yes
Lewis	31E	Valsartan	160 mg	468/5319	F	50	6	Hives	Yes	No
Kief	31E	Valsartan	160 mg	615/5538	M	47	6	Abnormal heart rhythm	Yes	No
Elinoff	31E	Valsartan	160 mg	701/5618	M	41	6	Prostatism	Yes	No
Oshrain	33	Valsartan	80 mg	165/1084	M	44	6	Dry cough	Yes	No
Ryan	33	Valsartan	80 mg	210/1098	F	70	5	Headache	Yes	No
Benz	33	Valsartan	80 mg	410/1201	F	60	5	Hives	Yes	No
Piraino	37	Valsartan	160 mg	009/RDB	M	29	3	Hypotension	Yes	No
Oliver	40	Valsartan	160 mg	04/CJ	M	20	3	Discomfort coughing	Yes	No
Oliver	40	Valsartan	160 mg	04/CJ	M	20	3	Productive cough	Yes	No
								Sore throat	Yes	No
								Wheezing	Yes	No
Litka	48	Valsartan	80 mg	005/MAY	M	25	3	Elevated SGPT	Yes	No
Lahvis	50	Valsartan	80 mg	296/5209	M	42	4	Lightheadedness	Yes	No
Lahvis	50	Valsartan	80 mg	296/5209	M	42	4	Congestion	Yes	No
								Drainage	Yes	No
Stoltz	50	Valsartan	160 mg	068/5050	M	51	4	Back pain	Yes	No
Surath	50	Valsartan	80 mg	1129/5829	M	43	5	Elevated SGOT/SGPT	Yes	No
Surath	50	Valsartan	80 mg	1140/5839	M	56	3	Exertional chest pain	Yes	Yes
Bloom	50	Valsartan	80 mg	126/5094	F	52	3	Bone metastases	Yes	Yes
Burch	50	Valsartan	80 mg	148/5108	F	48	5	Headache	Yes	No
Burch	50	Valsartan	80 mg	153/5114	F	48	3	Shortness of breath	Yes	No
Lahvis	50	Valsartan	160 mg	294/5210	M	52	4	Headache	Yes	No
Foley	50	Valsartan	80 mg	463/5330	M	47	5	Rash	Yes	No
Hilliard	50	Valsartan	80 mg	704/5519	M	65	3	Tiredness	Yes	No
Ryan	50	Valsartan	80 mg	804/5575	F	70	3	Headache	Yes	No
Spangenthal	50	Valsartan	80 mg	957/5693	M	47	3	Headache	Yes	No
								Tingling in arms	Yes	No

Discontinuations due to Adverse Events in Valsartan Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Innocenti	51	Valsartan	80 mg	1405	F	30	-	Renal colic with lithuresis	Yes	Yes
0222594	ANG 005	Valsartan	20 mg	Q1391	F	52		Chest pressure	Yes	No
0222594	ANG 005	Valsartan	20 mg	Q1391	F	52	-	Lightheaded	Yes	No
0001265	ANG 005	Valsartan	80 mg	01508530	F	56	-	Eyelid strange sensation Visual disturbance	Yes Yes	No No
0267373	ANG 005	Valsartan	20 mg	01896006	M	53	-	Headache Lightheaded feeling	Yes Yes	No No
0021294	ANG 005	Valsartan	20 mg	1-269384-7	M	44	-	Rash	Yes	No

Discontinuations due to Adverse Events in Valsartan/HCTZ Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Oparil	11E1	Valsartan/ HCTZ	80/25	Q004/502	M	50	15	Impotency	Yes	No
Garrett	11E1	Valsartan/ HCTZ	80/12.5	Q007/506	M	54	13	Pulmonary embolism	Yes	Yes
Wombolt	11E1	Valsartan	80 mg	Q016/515	M	72	14	Atrial fibrillation Cerebrovascular disease Complete heart block Right ventricular myocardial infarction	No No Yes Yes	Yes Yes Yes Yes
Serfer	11E1	Valsartan/ HCTZ	80/12.5	001/501	M	40	17	Fracture left elbow	Yes	No
Vaziri	11E1	Valsartan/ HCTZ	80/25	007/504	M	56	18	Cervical spondylosis Neck pain Right arm weakness Right leg weakness	Yes Yes No No	Yes Yes Yes Yes
Miller	11E1	Valsartan/ HCTZ	80/2[illegible]	007/505	F	68	14	Muscular chest pain	Yes	Yes
Ellison	11E1	Valsartan/ HCTZ	[illegible]25	006/507	F	67	18	Adenocarcinoma in situ Colon polyp Tubulovillous adenoma	Yes Yes Yes	Yes No Yes
Ansari	11E1	Valsartan/ HCTZ	80/[illegible]	[illegible]/509	M	72	14	Black stool	Yes	Yes
Grimm	11E1	Valsartan/ HCTZ	80/12.5	01[illegible]509	M	62	17	Arteriosclerotic heart disease Death	Yes Yes	Yes Yes
Chaudhery	11E1	Valsartan/ HCTZ	80/25	017/517	M	49	16	Cough Wheeze	Yes Yes	No No
Oparil	11E1	Valsartan HCTZ	80/25	021/517	F	57	15	Itching, chest, arms and neck	Yes	No
Grimm	11E1	Valsartan/ HCTZ	80/12.5	022/516	M	59	12	Decreased libido	Yes	No
Oparil	11E2	Valsartan/ HCTZ	80/25	Q003/501	M	65	19	Chest pain	Yes	Yes
Oparil	11E2	Valsartan/ HCTZ	80/25	Q003/501	M	65	19	Coronary artery disease	Yes	Yes
Chrysant	11E2	Valsartan/ HCTZ	80/12.5	002/502	M	66	21	Squamous cell carcinoma, larynx	Yes	Yes
Vaziri	11E2	Valsartan/ HCTZ	80/25	017/512	M	63	19	Bilateral flank pain	Yes	No

Discontinuations due to Adverse Events in Valsartan/HCTZ Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Cobler	11E2	Valsartan/ HCTZ	80/25	018/514	M	39	20	Decreased libido	Yes	No
Davis	19	Valsartan/ HCTZ	80/12.5	043/5031	F	66	5	Headache	Yes	No
Davis	19	Valsartan/ HCTZ	80/12.5	043/5031	F	66	5	Cough	Yes	No
Woehler	19	Valsartan/ HCTZ	80/12.5	722/5173	M	51	5	Cerebral aneurysm	Yes	Yes
Woehler	19	Valsartan/ HCTZ	80/12.5	722/5173	M	51	5	Intracranial bleed	Yes	Yes
Jain	19	Valsartan/ HCTZ	80/12.5	748/5416	M	53	4	Chest tightness	Yes	No
Jain	19	Valsartan/ HCTZ	80/12.5	748/5416	M	53	4	Shortness of breath	Yes	No
Corder	19	Valsartan/ HCTZ	80/25	1072/5739	F	46	5	Dizziness	Yes	No
Littlejohn	19	Valsartan/ HCTZ	80/25	180/5457	M	75	6	Rash	Yes	No
Rosen	19	Valsartan/ HCTZ	80/12.5	297/5196	F	74	4	Fatigue	Yes	No
Miller, C.	19	Valsartan/ HCTZ	80/25	406/5634	M	52	5	Acute lateral infarction	Yes	Yes
Williams, O.	19	Valsartan/ HCTZ	80/25	683/5488	M	66	4	Fatigue	Yes	No
Gricourt	20	Valsartan/ HCTZ	80/12.5	1091	M	38	-	Increased creatine kinase	Yes	Yes
Hutchinson	28	Valsartan/ HCTZ	80/12.5	1321	F	79	-	Left facial swelling	Yes	No
Hutchinson	28	Valsartan/ HCTZ	80/12.5	1321	F	79	-	Respiratory tract infection	Yes	No
Rees-Jones	28	Valsartan/ HCTZ	80/12.5	1556	F	83	-	Blurred vision	Yes	No
Rees-Jones	28	Valsartan Valsartan/ HCTZ	40 mg 80/12.5	1556	F	83	-	Chest pain Fatigue	Yes Yes	No No
Rees-Jones	28	Valsartan Valsartan/ HCTZ	40 mg 80/12.5	1556	F	83	-	Faint feeling Staggering gait	Yes Yes	No No
Arora	28	Valsartan/ HCTZ	80/12.5	1025	F	79	-	Dizziness Headache	Yes Yes	No No
Carr	28	Valsartan/ HCTZ	80/12.5	1113	F	73	-	Nausea	Yes	No
Hutchinson	28	Valsartan/ HCTZ	80/12.5	1324	F	86	-	Anxiety	Yes	No
Pinheiro	28	Valsartan/ HCTZ	80/12.5	1537	F	66	-	Dizziness	Yes	No
Sagar	28	Valsartan/ HCTZ	80/25	1573	F	73	-	Dizziness	Yes	No
Saul	28	Valsartan/ HCTZ	80/12.5	1586	M	82	-	Diarrhea	Yes	No
Whitby	28	Valsartan/ HCTZ	80/12.5	1673	M	68	-	Cerebrovascular accident	Yes	Yes
Carr	28	Valsartan/ HCTZ	80/12.5	1705	M	68	-	Inferior myocardial infarction	Yes	Yes

Discontinuations due to Adverse Events in Valsartan/HCTZ Patients

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Shane	31E	Valsartan/ HCTZ	160/12.5	115/5078	M	58	7	Hyponatremia	Yes	Yes
Shane	31E	Valsartan/ HCTZ	160/12.5	115/5078	M	58	7	Disorientation	Yes	Yes
Lewis	31E	Valsartan/ HCTZ	160/12.5	286/5191	F	49	9	Fatigue	Yes	No
Lewis	31E	Valsartan/ HCTZ	160/12.5	286/5191	F	49	9	Joint pain	Yes	No
Lewis	31E	Valsartan/ HCTZ	160/12.5	297/5197	M	34	7	Fatigue	Yes	No
Lewis	31E	Valsartan/ HCTZ	160/12.5	297/5197	M	34	7	Diarrhea	Yes	No
Neutel	31E	Valsartan/ HCTZ	160/25	696/5511	F	56	8	Weight gain	Yes	No
Neutel	31E	Valsartan/ HCTZ	160/25	696/5511	F	56	8	Stomach upset	Yes	No
Lewis	31E	Valsartan/ HCTZ	160/25	300/5328	M	67	8	Chest pain	Yes	No
Harris	31E	Valsartan/ HCTZ	160/12.5	314/5396	M	53	7	Dizziness Left arm paresthesia	Yes Yes	No No
Archer	31E	Valsartan/ HCTZ	160/25	429/5286	F	72	8	Paroxysmal atrial tachycardia	Yes	No
Hall	31E	Valsartan/ HCTZ	160/12.5	605/5794	F	48	8	Carcinoma of the breast	Yes	Yes

Serious Adverse Events Not Prematurely Discontinued

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Kraus	11	Valsartan	40 mg	Q009/504	F	38	8	Hepatomegaly	No	Yes
Miller	11E1	Valsartan	20 mg	Q013/511	M	46	9	Shortness of breath	No	Yes
Wombolt	11E1	Valsartan	80 mg	Q016/515	M	72	14	Worsening diabetes mellitus	No	Yes
Wombolt	11E1	Valsartan	80 mg	Q016/515	M	72	14	Osteoarthritis right knee	No	Yes
Gray	11E1	Valsartan	40 mg	Q021/518	F	57	11	Acute cholecytitis	No	Yes
Gray	11E1	Valsartan	40 mg	Q021/518	F	57	14	Retinal arteriolar occlusion	No	Yes
Vaziri	11E1	Valsartan	80 mg	Q028/520	F	48	16	Chest pain (gastric)	No	Yes
Vaziri	11E1	Valsartan	80 mg	Q028/520	F	48	16	Heartburn	No	Yes
Vaziri	11E1	Valsartan	80 mg	Q028/520	F	48	16	Anxiety attack	No	Yes
Archer	31E	Valsartan	160 mg	Q739/5805	M	70	8	Degenerative joint disease	No	Yes
Archer	31E	Valsartan	160 mg	Q739/5805	M	70	8	Benign prostatic hypertrophy	No	Yes
Kaihlanen	10	Valsartan	10 mg	002/501	F	51	6	Fractured right knee	No	Yes
Pool	11E1	Valsartan	80 mg	003/503	M	60	16	Flank pain	No	Yes
Ellison	11E1	Valsartan	40 mg	003/504	F	70	18	Basal cell carcinoma nose	No	Yes
Cobler	11E1	Valsartan	80 mg	004/504	M	58	11	Bile duct stone	No	Yes
Grimm	11E1	Valsartan	40 mg	007/507	M	62	14	Exertional chest pain	No	Yes
Wombolt	11E1	Valsartan	80 mg	007/509	M	62	14	Osteoarthritis left knee	No	Yes
Serfer	11E1	Valsartan	80 mg	008/507	M	74	14	Basal cell carcinoma	No	Yes
McNeer	11E1	Valsartan	20 mg	009/508	F	74	18	Peripheral vascular disease	No	Yes
Vaziri	11E1	Valsartan	80 mg	010/506	F	53	15	Intermittent chest pain, cardiac	No	Yes
Levine	102	Valsartan	160 mg	010/509	M	65	4	Worsening CHF	No	Yes
Yarbrough	11E1	Valsartan	80	012/512	F	55	18	Adenomatous hyperplasia with atypia, uterus	No	Yes
Gray	11	Valsartan	80 mg	014/513	M	52	8	Squamous cell carcinoma, vocal cord	No	Yes
Vaziri	11E1	Valsartan	20 mg	020/514	F	79	14	Basal skin carcinoma	No	Yes
Davis	11E1	Valsartan	20 mg	023/519	M	62	11	Amputation 3rd and 5th. fingers left hand	No	Yes
Lewin	09	Valsartan	20 mg	043/539	M	68	6	Hemorrhoids	No	Yes
Vigano	27	Valsartan	80 mg	1016/512	M	61	-	Inguinal hernia	No	Yes
Arora	28	Valsartan	80 mg	1027	M	83	-	Left cataract extraction	No	Yes
Scotto	51	Valsartan	80 mg	1076	F	54	-	Menometrorrhagia	No	Yes
Carr	28	Valsartan	40 mg	1114	F	68	-	Appendicitis	No	Yes
Charlton	28	Valsartan	40 mg	1137	M	76	-	Gallbladder disease	No	Yes
Iwaida	ANG 005	Valsartan	20 mg	11374	F	71	-	Cancer of the tongue	No	Yes
Charlton	28	Valsartan	40 mg	1139	F	66	-	Paget's disease	No	Yes
Berger	20	Valsartan	80 mg	1164	M	50	-	Vocal cord polyp	No	Yes
Waks	50	Valsartan	160 mg	1197/5896	F	74	Post-trial	Overdose (carbamazepine)	No	Yes
Stringer	19	Valsartan	80 mg	1202/5816	M	66	6	Squamous cell carcinoma arm	No	Yes
Parashchak	28	Valsartan	80 mg	1523	F	68	-	Fractured left ankle	No	Yes
Spira	28	Valsartan	80 mg	1618	M	65	-	Depression	No	Yes
Silvert	28	Valsartan	80 mg	1764	M	65	-	Gastroscopy/ duodenal ulcer	No	Yes
Rees-Jones	28	Valsartan	80 mg	1780	M	68	-	Inguinal hernia repair	No	Yes
Rees-Jones	28	Valsartan	40 mg	1843	F	71	-	Left knee arthroplasty	No	Yes

Serious Adverse Events Not Prematurely Discontinued

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Anand	28	Valsartan	40 mg	1855	F	81	-	Ophthalmic herpes zoster	No	Yes
Dyke	31E	Valsartan	160 mg	188/5127	F	47	8	Kidney stones	No	Yes
Rees-Jones	28	Valsartan	40 mg	1923	M	73	-	Hematuria	No	Yes
Gaman	17	Valsartan	80 mg	197/694	M	40	5	Diverticulitis	No	Yes
Coalson	17	Valsartan	80 mg	210/705	M	54	7	Melanoma right hip	No	Yes
Gann	19	Valsartan	80 mg	222/5148	M	58	3	Food poisoning	No	Yes
Weiss	19	Valsartan	160 mg	302/5202	M	50	5	Non-cardiac chest pain	No	Yes
Quadracci	19	Valsartan	80 mg	369/5245	M	65	3	Fractured left elbow	No	Yes
Archer	31	Valsartan	160 mg	434/5582	M	75	3	Inguinal hernia	No	Yes
Michel	23	Valsartan	40 mg	5119	M	71	-	Retinal vein thrombosis	No	Yes
Kief	31E	Valsartan	160 mg	614/5537	F	40	6	Appendicitis	No	Yes
De Sainte Lorette	23	Valsartan	80 mg	6388	F	69	-	Thrombophlebitis	No	Yes
Ansari	11E1	Valsartan/ HCTZ	80/12.5	001/501	F	78	18	Hypokalemia	No	Yes
Ansari	11E1	Valsartan/ HCTZ	80/12.5	001/501	F	78	18	Pneumonia	No	Yes
Oparil	11E1	Valsartan/ HCTZ	80/25	004/502	M	50	14	Worsening neck pain	No	Yes
Garrett	11E1	Valsartan/ HCTZ	80/12.5	007/506	M	54	13	Brain tumor	No	Yes
Sugimoto	31E	Valsartan/ HCTZ	160/12.5	460/5315	F	72	8	Herniated disc	No	Yes
Sugimoto	31E	Valsartan/ HCTZ	160/12.5	460/5315	F	72	8	Pinched nerve	No	Yes
Mieras	31E	Valsartan/ HCTZ	160/25	95/5065	M	42	10	Left flank pain	No	Yes
Mieras	31E	Valsartan/ HCTZ	160/25	95/5065	M	42	10	Nephrolithiasis	No	Yes
Chrysant	11E2	Valsartan/ HCTZ	80/25	001/501	M	41	20	Fractured scaphoid bone right wrist	No	Yes
Chaudhery	11E1	Valsartan/ HCTZ	80/12.5	003/503	F	53	16	Abdominal pain	No	Yes
Chrysant	11E1	Valsartan/ HCTZ	80/25	004/504	M	58	18	Basal cell carcinoma ear	No	Yes
McNeer	11E1	Valsartan/ HCTZ	80/12.5	007/505	M	62	16	Prostate cancer	No	Yes
Pool	11E1	Valsartan/ HCTZ	80/12.5	011/507	M	73	12	Basal cell carcinoma back	No	Yes
Chrysant	11E2	Valsartan/ HCTZ	80/25	016/516	M	59	20	Transient ischemic attack	No	Yes
Pool	11E1	Valsartan/ HCTZ	80/25	017/511	M	43	Post-trial	Stenosis of left common iliac vessel	No	Yes
Chrysant	11E1	Valsartan/ HCTZ	80/25	021/519	F	45	16	Fracture right ankle	No	Yes
Vaziri	11E1	Valsartan/ HCTZ	80/25	025/518	M	69	17	Cerebrovascular accident	No	Yes
Grimm	11E1	Valsartan/ HCTZ	80/25	027/520	M	48	15	Hydrocele recurred	No	Yes
Oparil	11E1	Valsartan/ HCTZ	80/12.5	027/525	M	54	12	Cyst neck	No	Yes
Marbury	11E2	Valsartan/ HCTZ	80/25	036/527	M	58	19	Benign prostatic hypertrophy	No	Yes

Serious Adverse Events Not Prematurely Discontinued

Investigator	Trial	Treatment	Dose	Patient #	Sex	Age	Visit	Adverse Experience	DC	SAE
Allin	28	Valsartan/ HCTZ	80/12.5	1009	F	77	-	Bladder carcinoma	No	Yes
Aitchison	28	Valsartan/ HCTZ	80/12.5	1789	M	76	-	Right hemiparesis	No	Yes
Rees-Jones	28	Valsartan/ HCTZ	80/12.5	1841	F	73	-	Right cataract surgery	No	Yes
Caldwell	19	Valsartan/ HCTZ	80/12.5	195/5129	F	47	3	Right ovarian cyst	No	Yes
Oparil	31E	Valsartan/ HCTZ	160/25	273/5182	M	62	9	Inguinal hernia	No	Yes
Archer	31E	Valsartan/ HCTZ	160/25	434/5582	M	75	8	Syncope	No	Yes
Harris	31E	Valsartan/ HCTZ	160/25	55[illegible]05	M	62	8	Right eye retinal tear	No	Yes
Glatte	19	Valsartan/ HCTZ	80/25	883/5595	M	45	6	Basal cell cancer chest	No	Yes
Oliver	40	Warfarin	10 mg	01/MH	M	36	3	Tiredness	No	Yes
Anand	28	Lisinopril	2.5 mg	1853	F	68	-	Endometrial adenocarcinoma Vaginal bleeding	No No	Yes Yes
Stein	26	Unknown	?	1033/32	F	62	-	Pulmonary edema cardiac cause Venrtricular failure	No No	Yes Yes
Oparil	11E1	Valsartan	20 mg	020/518	M	65	18	Adenomatous polyps sigmoid colon Adenovillous polyps ascending colon	No No	Yes Yes
Miller, C.	19	Valsartan/ HCTZ	80/12.5	953/5641	M	69	4	Benign prostatic hypertrophy Hydronephrosis	No No	Yes Yes
Corea	21	Amlodipine	5 mg	1012	M	60	-	Uretheral obstruction Uretheral disorder	No No	Yes Yes
Meridjen	23	Lisinopril	10 mg	6115	F	67	Post-trial	Auricular fibrillation Consciousness loss	No No	Yes Yes
Ginsberg	50	Placebo	[illegible]	274/5197	M	77	Post-trial	Cerebrovascular accident Death	No No	Yes Yes
Kliger	11E1	Valsartan	40 mg	009/506	M	48	12	Malignant lymphoma Splenomegaly	No No	Yes Yes
Yarbrough	11E1	Valsartan	80 mg	014/510	M	31	16	Right arm weakness Right sided facial weakness	No No	Yes Yes
Lewin	31	Valsartan	80 mg	265/5177	F	49	[illegible]	Chest pain Weakness	No No	Yes Yes
Lewin	31	Valsartan	80 mg	265/5177	F	49	4	Diarrhea Vomiting	No No	Yes Yes
McNeer	11E1	Valsartan	40 mg	006/506	M	50	13	Angina - chest pain Coronary artery disease	No No	Yes Yes
Garrett	11E1	Valsartan	20 mg	016/515	F	74	15	Cardiovascular collapse Death	No No	Yes Yes
Ruff	50	Valsartan	160 mg	347/5247	M	62	5	Blood in stool Sessile adenomatous polyp	No No	Yes Yes

Serious Adverse Events Not Prematurely Discon ed

Investigator	Trial	Treatment	Dose	Pt	Sex	Age	Visit	Adverse Experience	DC	SAE
Rees-Jones	28	Valsartan	40 mg	192/	M	74	-	Abdominal pain	No	Yes
								Esophageal ulcer	No	Yes
								Hematemesis	No	Yes
McInroy	19	Valsartan	160 mg	453/5313	F	61	-	Osteoarthritis left knee	No	Yes
								Knee pain	No	Yes
								Knee swelling	No	Yes
Oparil	11E1	Valsartan	20 mg	014/512	M	68	15	Heme positive stool	No	Yes
								Hiccups	No	Yes
								Nausea	No	Yes
								Vomiting	No	Yes
Lewis	31	Valsartan	20 mg	293/5194	M	64	4	Internal hemorrhoids	No	Yes
								Pancolonic diverticulitis	No	Yes
								Rectal bleeding	No	Yes
								Sigmoid polyp	No	Yes
Oparil	11E1	Valsartan/ HCTZ	80/25	010/510	M	60	14	Abdominal pain	No	Yes
								Cholelithiasis	No	Yes
							17	Abdominal pain	No	Yes
								Cholelithiasis	No	Yes
								Acute Cholelithiasis	No	Yes
								Nausea	No	Yes

Adverse Events in Protocol 11 1st Year Extension with Incidence ≥ 1%. [vol. 1.219, p. 169]

	N	%			N	%
Total Patients	399					
Patient with AE	281	70.4%				
Body as a Whole	82	20.6%		fracture	6	1.5%
Allergy	9	2.3%		myalgia	9	2.3%
Asthenia	6	1.5%		arm pain	16	4.0%
Peripheral Edema	10	2.5%		back pain	25	6.3%
Fatigue	12	3.0%		leg pain	13	3.3%
fever	6	1.5%		sprain/strain	7	1.8%
influenza symptoms	4	1.0%		**Nervous System**	121	30.3%
injury	13	3.3%		dizziness	30	7.5%
pain	6	1.5%		headache	18.8	4.7%
chest pain	8	2.0%		hypoesthesia	5	1.3%
weight increase	4	1.0%		insomnia	6	1.5%
Cardiovascular System	23	5.8%		decreased libido	6	1.5%
palpitations	4	1.0%		**Respiratory System**	97	24.3%
Digestive System	73	18.3%		coughing	25	6.3%
diarrhea	21	5.3%		dyspnea	5	1.3%
dyspepsia	18	4.5%		pharyngitis	16	4.0%
nausea	14	3.5%		respiratory disorder	8	2.0%
abdominal pain	9	2.3%		rhinitis	11	2.8%
periodontitis	5	1.3%		sinusitis	44	11.0%
vomiting	11	2.8%		upper respiratory infection	34	8.5%
Endocrine System	0	0.0%		**Skin and Appendages**	42	10.5%
Hematopoetic System	3	0.8%		purpura	5	1.3%
Infections and Infestations	55	13.8%		**Special Senses**	31	7.8%
infection	5	1.3%		conjunctivitis	5	1.3%
viral infection	43	10.8%		eye edema	1	0.3%
lab abnormality	8	2.0%		**Procedures**	2	0.5%
Metabolic and Nutritional Disorders	5	1.3%		**Urogenital System**	35	8.8%
Musculoskeletal System	101	25.3%		impotence	5	1.3%
arthralgia	28	7.0%		urinary frequency	6	1.5%
arthritis	5	1.3%		prostate disorder	5	1.3%
arthrosis	10	2.5%		urinary tract infection	8	2.0%
leg cramps	7	1.8%				

Patients Discontinued from Placebo Controlled Clinical Trials for Reasons Other Than Adverse Events.

Protocol	Patient #	Randomization #	Treatment	Reason Discontinued
5	1073	9	valsartan 20 mg	Withdrew Consent
9	2	502	placebo	Administrative Problems
9	19	516	valsartan 20 mg	Administrative Problems
9	7	507	placebo	Does not meet protocol criteria
9	10	511	placebo	Lost to follow-up
9	22	520	placebo	Non-compliant
9	24	519	placebo	Unsatisfactory Response
9	9	508	placebo	Withdrew Consent
9	6	506	valsartan 20 mg	Withdrew Consent
10	8	505	valsartan 160 mg	Does not meet protocol criteria
10	3	502	valsartan 40 mg	Non-compliant
10	16	510	valsartan 10 mg	Unsatisfactory Response
10	16	514	valsartan 10 mg	Unsatisfactory Response
10	19	517	valsartan 40 mg	Unsatisfactory Response
11	15	512	placebo	Abnormal Lab Result
11	4	505	placebo	Does not meet protocol criteria
11	29	523	placebo	Does not meet protocol criteria
11	28	520	valsartan 40 mg	Does not meet protocol criteria
11	13	509	valsartan 80 mg	Does not meet protocol criteria
11	2	503	valsartan 20 mg	Non-compliant
11	17	515	placebo	Unsatisfactory Response
11	16	513	valsartan 40 mg	Unsatisfactory Response
11	3	503	placebo	Withdrew Consent
17	260	758	fed valsartan 80 mg	Abnormal Lab Result
17	412	864	placebo	Abnormal Lab Result
17	83	582	fasted valsartan 80 mg	Administrative Problems
17	160	657	fasted valsartan 80 mg	Administrative Problems
17	81	581	fed valsartan 80 mg	Administrative Problems
17	131	631	fed valsartan 80 mg	Administrative Problems
17	133	632	fasted valsartan 80 mg	Does not meet protocol criteria
17	302	706	fasted valsartan 80 mg	Does not meet protocol criteria
17	78	670	fed valsartan 80 mg	Does not meet protocol criteria
17	275	773	fed valsartan 80 mg	Does not meet protocol criteria
17	27	527	placebo	Does not meet protocol criteria
17	351	560	placebo	Non-compliant
17	230	730	fasted valsartan 80 mg	Unsatisfactory Response
17	168	579	fed valsartan 80 mg	Unsatisfactory Response
17	259	757	fed valsartan 80 mg	Unsatisfactory Response
17	55	554	placebo	Unsatisfactory Response
17	151	651	placebo	Unsatisfactory Response
17	61	561	fasted valsartan 80 mg	Withdrew Consent
17	370	863	fasted valsartan 80 mg	Withdrew Consent
17	123	623	placebo	Withdrew Consent
17	214	713	placebo	Withdrew Consent
23	6285	935	placebo	Abnormal Lab Result
23	5122	122	valsartan 160 mg	Abnormal Lab Result
23	7021	1219	valsartan 80 mg	Administrative Proolems
23	5025	25	Lisinopril 10 mg	Does not meet protocol criteria
23	6068	619	Lisinopril 10 mg	Does not meet protocol criteria
23	6249	679	Lisinopril 10 mg	Does not meet protocol criteria
23	6129	639	placebo	Does not meet protocol criteria

Patients Discontinued from Placebo Controlled Clinical Trials for Reasons Other Than Adverse Events.

Protocol	Patient #	Randomization #	Treatment	Reason Discontinued
23	6189	848	placebo	Does not meet protocol criteria
23	6084	725	valsartan 160 mg	Does not meet protocol criteria
23	6268	803	valsartan 160 mg	Does not meet protocol criteria
23	5027	27	valsartan 40 mg	Does not meet protocol criteria
23	5223	223	valsartan 40 mg	Does not meet protocol criteria
23	6272	688	valsartan 40 mg	Does not meet protocol criteria
23	7280	1309	valsartan 40 mg	Does not meet protocol criteria
23	7426	1570	valsartan 40 mg	Does not meet protocol criteria
23	5024	24	valsartan 80 mg	Does not meet protocol criteria
23	5120	120	valsartan 80 mg	Does not meet protocol criteria
23	7076	1267	Lisinopril 10 mg	Lost to follow-up
23	5170	170	placebo	Lost to follow-up
23	7224	1395	valsartan 160 mg	Lost to follow-up
23	6508	925	valsartan 80 mg	Lost to follow-up
23	7300	1455	valsartan 40 mg	Non-compliant
23	7459	1578	valsartan 160 mg	Unsatisfactory Response
23	5210	210	valsartan 40 mg	Unsatisfactory Response
23	6078	723	valsartan 40 mg	Unsatisfactory Response
23	7229	1401	valsartan 40 mg	Unsatisfactory Response
23	7129	1321	valsartan 80 mg	Unsatisfactory Response
23	5209	209	Lisinopril 10 mg	Withdrew Consent
23	5121	121	placebo	Withdrew Consent
23	6054	617	valsartan 160 mg	Withdrew Consent
23	6123	641	valsartan 160 mg	Withdrew Consent
23	7311	1466	valsartan 160 mg	Withdrew Consent
31	202	5190	placebo	Abnormal Lab Result
31	493	5507	placebo	Abnormal Lab Result
31	217	5145	valsartan 80 mg	Abnormal Test
31	928	5789	placebo	Does not meet protocol criteria
31	636	5470	valsartan 160 mg	Does not meet protocol criteria
31	440	5304	valsartan 20 mg	Does not meet protocol criteria
31	487	5338	valsartan 320 mg	Does not meet protocol criteria
31	451	5306	valsartan 80 mg	Does not meet protocol criteria
31	526	5372	placebo	Lost to follow-up
31	101	5070	valsartan 160 mg	Lost to follow-up
31	367	5245	valsartan 160 mg	Lost to follow-up
31	608	5446	valsartan 160 mg	Lost to follow-up
31	817	5760	valsartan 320 mg	Lost to follow-up
31	228	5153	placebo	Non-compliant
31	280	5189	valsartan 160 mg	Non-compliant
31	313	5394	valsartan 20 mg	Non-compliant
31	727	5631	valsartan 20 mg	Non-compliant
31	798	5699	valsartan 20 mg	Non-compliant
31	810	5658	valsartan 20 mg	Non-compliant
31	226	5151	valsartan 320 mg	Non-compliant
31	230	5155	valsartan 80 mg	Non-compliant
31	15	5535	placebo	Unsatisfactory Response
31	142	5098	placebo	Unsatisfactory Response
31	334	5228	placebo	Unsatisfactory Response
31	377	5251	placebo	Unsatisfactory Response
31	109	5074	valsartan 160 mg	Unsatisfactory Response
31	332	5226	valsartan 160 mg	Unsatisfactory Response

Patients Discontinued from Placebo Controlled Clinical Trials for Reasons Other Than Adverse Events.

Protocol	Patient #	Randomization #	Treatment	Reason Discontinued
31	6	5006	valsartan 20 mg	Unsatisfactory Response
31	69	5047	valsartan 20 mg	Unsatisfactory Response
31	99	5068	valsartan 20 mg	Unsatisfactory Response
31	547	5591	valsartan 20 mg	Unsatisfactory Response
31	707	5543	valsartan 20 mg	Unsatisfactory Response
31	858	5726	valsartan 20 mg	Unsatisfactory Response
31	114	5079	valsartan 320 mg	Unsatisfactory Response
31	215	5144	valsartan 320 mg	Unsatisfactory Response
31	270	5225	valsartan 320 mg	Unsatisfactory Response
31	379	5254	valsartan 320 mg	Unsatisfactory Response
31	378	5252	valsartan 80 mg	Unsatisfactory Response
31	431	5585	valsartan 80 mg	Unsatisfactory Response
31	681	5500	valsartan 80 mg	Unsatisfactory Response
31	350	5389	placebo	Withdrew Consent
31	833	5678	placebo	Withdrew Consent
31	942	5608	valsartan 160 mg	Withdrew Consent
33	86	1044	valsartan 80 mg	Lost to follow-up
33	42	1224	HCTZ 25 mg	Unsatisfactory Response
33	53	1027	HCTZ 25 mg	Unsatisfactory Response
33	415	1202	HCTZ 25 mg	Unsatisfactory Response
33	121	1053	valsartan 80 mg	Unsatisfactory Response
33	352	1171	valsartan 80 mg	Unsatisfactory Response
33	232	1109	HCTZ 25 mg	Withdrew Consent
50	1129	5829	valsartan 80 mg	Abnormal Lab Result
50	648	5463	Lisinopril 10 mg	Administrative Problems
50	923	5663	valsartan 80 mg	Administrative Problems
50	317	5227	Lisinopril 10 mg	Does not meet protocol criteria
50	1051	5766	Lisinopril 10 mg	Does not meet protocol criteria
50	351	5254	placebo	Does not meet protocol criteria
50	363	5653	placebo	Does not meet protocol criteria
50	886	5634	Lisinopril 10 mg	Lost to follow-up
50	1138	5837	Lisinopril 10 mg	Lost to follow-up
50	731	5524	placebo	Lost to follow-up
50	821	5589	placebo	Lost to follow-up
50	922	5662	placebo	Lost to follow-up
50	248	5722	valsartan 80 mg	Lost to follow-up
50	249	5723	valsartan 80 mg	Lost to follow-up
50	777	5556	valsartan 80 mg	Lost to follow-up
50	1166	5858	valsartan 80 mg	Lost to follow-up
50	144	5104	Lisinopril 10 mg	Non-compliant
50	385	5275	Lisinopril 10 mg	Non-compliant
50	697	5742	placebo	Non-compliant
50	947	5720	placebo	Non-compliant
50	1126	5809	placebo	Non-compliant
50	621	5452	valsartan 80 mg	Non-compliant
50	632	5449	valsartan 80 mg	Non-compliant
50	757	5541	valsartan 80 mg	Non-compliant
50	108	5942	Lisinopril 10 mg	Unsatisfactory Response
50	498	5989	Lisinopril 10 mg	Unsatisfactory Response
50	542	5392	Lisinopril 10 mg	Unsatisfactory Response
50	36	5040	placebo	Unsatisfactory Response
50	54	5797	placebo	Unsatisfactory Response

Patients Discontinued from Placebo Controlled Clinical Trials for Reasons Other Than Adverse Events.

Protocol	Patient #	Randomization #	Treatment	Reason Discontinued
50	118	5086	placebo	Unsatisfactory Response
50	152	5112	placebo	Unsatisfactory Response
50	378	5271	placebo	Unsatisfactory Response
50	381	5273	placebo	Unsatisfactory Response
50	464	5328	placebo	Unsatisfactory Response
50	506	5362	placebo	Unsatisfactory Response
50	533	5381	placebo	Unsatisfactory Response
50	688	5495	placebo	Unsatisfactory Response
50	803	5576	placebo	Unsatisfactory Response
50	1077	5791	placebo	Unsatisfactory Response
50	117	5085	valsartan 80 mg	Unsatisfactory Response
50	127	5096	valsartan 80 mg	Unsatisfactory Response
50	149	5110	valsartan 80 mg	Unsatisfactory Response
50	243	5175	valsartan 80 mg	Unsatisfactory Response
50	377	5268	valsartan 80 mg	Unsatisfactory Response
50	382	5274	valsartan 80 mg	Unsatisfactory Response
50	423	5303	valsartan 80 mg	Unsatisfactory Response
50	425	5305	valsartan 80 mg	Unsatisfactory Response
50	427	5307	valsartan 80 mg	Unsatisfactory Response
50	556	5787	valsartan 80 mg	Unsatisfactory Response
50	709	5506	valsartan 80 mg	Unsatisfactory Response
50	714	5515	valsartan 80 mg	Unsatisfactory Response
50	1079	5793	valsartan 80 mg	Unsatisfactory Response
50	1081	5795	valsartan 80 mg	Unsatisfactory Response
50	258	5183	Lisinopril 10 mg	Withdrew Consent
50	635	5451	placebo	Withdrew Consent
50	698	5744	valsartan 80 mg	Withdrew Consent
50	854	5620	valsartan 80 mg	Withdrew Consent
50	1042	5760	valsartan 80 mg	Withdrew Consent
51	1029	28	enalapril 20 mg	Abnormal Lab Result
51	1331	327	enalapril 20 mg	Does not meet protocol criteria
51	1102	102	placebo	Does not meet protocol criteria
51	1315	315	valsartan 80 mg	Does not meet protocol criteria
51	1141	141	enalapril 20 mg	Lost to follow-up
51	1144	143	valsartan 80 mg	Lost to follow-up
51	1172	172	enalapril 20 mg	Unsatisfactory Response
51	1472	433	placebo	Unsatisfactory Response
51	1471	432	valsartan 80 mg	Unsatisfactory Response

OCT 7 1996

ADDENDUM TO MEDICAL OFFICER NDA REVIEW

NDA #: 20-665/BM
NDA Volume:
DRUG NAME: Valsartan
SPONSOR: Ciba Geigy
TYPE OF DOCUMENT: Response to Information Request
CORRESPONDENCE DATE: 9/24/96
DATE REVIEW COMPLETED: 10/7/96
MEDICAL OFFICER: Charles J. Ganley, M.D.

The sponsor provides information regarding the number of patients in the NDA who experienced a decrease in absolute neutrophil count (ANC) to less than 1.0 x 10^9/L. Table 1 lists the number of patients in each treatment group that experienced a decrease.

Table 1. Number of Patients with ANC < 1.0 x 10^9/L

		Treatments									
		Valsartan		*Valsartan/ Diuretic*		*ACEI*		*Placebo*		*Other*	
		N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Total Patients	*Baseline*	*3951*	*100*	*683*	*100*	*780*	*100*	*892*	*100*	*78*	*100*
	Treatment	*3282*	*100*	*643*	*100*	*639*	*100*	*841*	*100*	*80*	*100*
< 1.0 x 10^9/L	*Baseline*	*7*	*.18*	*0*	*0*	*2*	*.26*	*0*	*0*	*1*	*1.28*
	Treatment	*17*	*.52*	*2*	*.31*	*3*	*.47*	*0*	*0*	*1*	*1.25*

ACEI = angiotensin converting enzyme inhibitor.

The table does not include patients on ACEI Diuretics (N = 84), HCTZ (N = 127), HCTZ/other (N = 16) and valsartan/other (N = 37). None of these had low counts. Although 892 patients were randomized to placebo, none had counts less than 1000 x 10^6/L. The incidence rates were similar between valsartan and ACEI treated patients. It should, however, be noted that the total exposure in the valsartan group is probably much greater than in the ACEI group.

A complete listing of the patients and their ANC are attached. In general, most patients with baseline low ANC returned to normal despite therapy with valsartan or ACEI. Five of the 14 valsartan patients with post-randomization decreases in ANC had normal values at a later visit despite continued therapy.

Conclusion

The comparable incidence rates in the valsartan subjects compared to the ACEI subjects is of concern in view of the number of occurrences in the placebo group and the association of ACEI with agranulocytosis.

There is information suggesting that low ANC counts are unrelated to valsartan therapy:

- Five of the 14 valsartan patients had ANCs > 1000 x 10^6/L after the ANC nadir despite continued therapy. At least in these patients, the low ANC count is related to some other factor (e.g. lab error).
- It is likely that the patient exposure in the valsartan group is greater than the ACEI. If the incidence rates are calculated based on patient exposure, they would not be similar.
- The low ANC counts at baseline suggest that low ANCs are observed off of therapy. Consequently, sporadic low ANC counts, unrelated to therapy, should be expected in a clinical trial. In patients with low baseline ANC, the ANC was > 1000 x 10^6/L at subsequent measurements despite valsartan therapy.

• It does not appear that any of these patients experienced infections related to the low ANC[1]. This needs confirmation from the sponsor.

Before this issue can be dismissed, additional information is required from the sponsor.

Additional Information Requested from Nancy Price on 10/7/96

• Provide information regarding infections in the valsartan patients included in this list
• Information was provided on only 14 of the 17 valsartan patients with post-randomization decreases in ANC - provide information on the three missing subjects
• Calculate Rates as a function of exposure to therapy
• Recalculate incidence rate excluding patients who only had a single dose of therapy
• Do not double count patients (i.e. patients in open label studies are counted once in the controlled trial and once in the open label study - this inflates the denominator).

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / CSO / C. GANLEY/ R. LIPICKY

[1] The captopril label states that 'about half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis'.

ALL ABSOLUTE NEUTROPHIL VALUES FOR
PATIENTS WITH AT LEAS[illegible] ABSOLUTE NEUTROPHIL VALUE < 1000

OBS	TDRC	CENTNO	PATNO	PROTOCOL	VISI	NAME	LBUNTC	LANDC	LBNO	LBDT	LBUSEDQ	LBVALUE	LB
1	01Valsartan	1	1018	05	1.00	ABSTNEU	10E9/L	D	1	19920902	1	3.73	10E9/L
2	01Valsartan	1	1018	05	2.00	ABSTNEU	10E9/L	D	1	19920915	1	2.46	10E9/L R
3	01Valsartan	1	1018	05	3.00	ABSTNEU	10E9/L	D	1	19920922	1	2.96	10E9/L
4	01Valsartan	1	1018	05	4.00	ABSTNEU	10E9/L	D	1	19920929	1	0.83	10E9/L
5	01Valsartan	1	1018	05	5.00	ABSTNEU	10E9/L	D	1	19921006	1	3.55	10E9/L
6	01Valsartan	1	1018	05	6.00	ABSTNEU	10E9/L	D	1	19921013	1	5.93	10E9/L
7	01Valsartan	M7798H	18	09	1.00	ABSTNEU	10E9/L	USA	M7798H	19930402	1	4.73	T/MM3
8	01Valsartan	M7798H	18	09	5.00	ABSTNEU	10E9/L	USA	M7798H	19930503	1	5.15	T/MM3
9	01Valsartan	M7798H	18	09	7.00	ABSTNEU	10E9/L	USA	M7798H	19930601	1	3.90	T/MM3
10	01Valsartan	M7798H	18	09	10.00	ABSTNEU	10E9/L	USA	M7798H	19930712	1	0.44	T/MM3
11	01Valsartan	M7791Y	18	10	1.00	ABSTNEU	10E9/L	USA	M7791Y	19930129	1	1.62	T/MM3
12	01Valsartan	M7791Y	18	10	5.00	ABSTNEU	10E9/L	USA	M7791Y	19930224	1	1.16	T/MM3 R
13	01Valsartan	M7791Y	18	10	7.00	ABSTNEU	10E9/L	USA	M7791Y	19930324	1	0.96	T/MM3
14	01Valsartan	M7846G	5	11	1.00	ABSTNEU	10E9/L	USA	M7846G	19930410	1	1.63	T/MM3
15	01Valsartan	M7846G	5	11	5.00	ABSTNEU	10E9/L	USA	M7846G	19930508	1	0.64	T/MM3 R
16	01Valsartan	M7846G	5	11	6.00	ABSTNEU	10E9/L	USA	M7846G	19930513	1	3.87	T/MM3
17	01Valsartan	M7846G	5	11	8.00	ABSTNEU	10E9/L	USA	M7846G	19930619	1	1.00	T/MM3
18	01Valsartan	M7846G	5	11	111.00	ABSTNEU	10E9/L	USA	M7846G	19930814	1	4.15	T/MM3
19	01Valsartan	M7846G	5	11	113.00	ABSTNEU	10E9/L	USA	M7846G	19931008	1	3.89	T/MM3
20	01Valsartan	M7846G	5	11	114.00	ABSTNEU	10E9/L	USA	M7846G	19931208	1	4.32	T/MM3
21	01Valsartan	M7846G	5	11	116.00	ABSTNEU	10E9/L	USA	M7846G	19940413	1	3.55	T/MM3
22	01Valsartan	M7846G	5	11	118.00	ABSTNEU	10E9/L	USA	M7846G	19940903	1	4.42	T/MM3
23	01Valsartan	M7850G	16	11	1.00	ABSTNEU	10E9/L	USA	M7850G	19930503	1	6.25	T/MM3
24	01Valsartan	M7850G	16	11	5.00	ABSTNEU	10E9/L	USA	M7850G	19930604	1	5.89	T/MM3 R
25	01Valsartan	M7850G	16	11	8.00	APSTNEU	10E9/L	USA	M7850G	19930720	1	8.59	T/MM3
26	01Valsartan	M7850G	16	11	111.00	ABSTNEU	10E9/L	USA	M7850G	19930826	1	4.75	T/MM3
27	01Valsartan	M7850G	16	11	113.00	ABSTNEU	10E9/L	USA	M7850G	19931104	1	5.10	T/MM3
28	01Valsartan	M7850G	16	11	114.00	ABSTNEU	10E9/L	USA	M7850G	19940110	1	4.79	T/MM3
29	01Valsartan	M7850G	16	11	116.00	ABSTNEU	10E9/L	USA	M7850G	19940513	1	4.16	T/MM3
30	01Valsartan	M7850G	16	11	118.00	ABSTNEU	10E9/L	USA	M7850G	19941021	1	5.09	T/MM3
31	01Valsartan	M7875N	10	11	1.00	ABSTNEU	10E9/L	USA	M7875N	19930519	1	4.21	T/MM3
32	01Valsartan	M7875N	10	11	5.00	ABSTNEU	10E9/L	USA	M7875N	19930617	1	4.03	T/MM3 R
33	01Valsartan	M7875N	10	11	8.00	ABSTNEU	10E9/L	USA	M7875N	19930728	1	3.60	T/MM3
34	01Valsartan	M7875N	10	11	111.00	ABSTNEU	10E9/L	USA	M7875N	19930909	1	5.50	T/MM3
35	01Valsartan	M7875N	10	11	113.00	ABSTNEU	10E9/L	USA	M7875N	19931104	1	3.65	T/MM3
36	01Valsartan	M7875N	10	11	114.00	ABSTNEU	10E9/L	USA	M7875N	19940107	1	0.94	T/MM3
37	01Valsartan	M7875N	10	11	116.00	ABSTNEU	10E9/L	USA	M7875N	19940509	1	3.50	T/MM3
38	01Valsartan	M7875N	10	11	118.00	ABSTNEU	10E9/L	USA	M7875N	19941024	1	10.04	T/MM3
39	01Valsartan	M8209P	882	19	1.00	ABSTNEU	10E9/L	USA	M8209P	19940908	1	2.60	T/MM3
40	01Valsartan	M8209P	882	19	3.00	ABSTNEU	10E9/L	USA	M8209P	19941021	1	4.01	T/MM3 R
41	01Valsartan	M8209P	882	19	6.00	ABSTNEU	10E9/L	USA	M8209P	19941219	1	0.94	T/MM3

ALL ABS NEUTROPHIL VALUES FOR
PATIENTS WITH AT LEAS. E ABSOLUTE NEUTROPHIL VALUE < 1000

OBS	TDRC	CENTNO	PATNO	PROTOCOL	VISIT	LBNAME	LBUNTC	LANDC	LBNO	LBDT	LBUSEDQ	LBVALUE	LBUNT	
42	01Valsartan	M8213P	1033	19	1.00	ABSTNEU	10E9/L	USA	M8213P	19941006	1	0.74	T/MM3	R
43	01Valsartan	M8213P	1033	19	3.00	ABSTNEU	10E9/L	USA	M8213P	19941117	1	0.74	T/MM3	
44	01Valsartan	M8213P	1033	19	6.00	ABSTNEU	10E9/L	USA	M8213P	19950112	1	1.30	T/MM3	
45	01Valsartan	M8214U	414	19	1.00	ABSTNEU	10E9/L	USA	M8214U	19940831	1	0.90	T/MM3	R
46	01Valsartan	M8228S	975	19	1.00	ABSTNEU	10E9/L	USA	M8228S	19941007	1	2.11	T/MM3	R
47	01Valsartan	M8228S	975	19	3.00	ABSTNEU	10E9/L	USA	M8228S	19941117	1	1.97	T/MM3	
48	01Valsartan	M8228S	975	19	6.00	ABSTNEU	10E9/L	USA	M8228S	19950112	1	0.95	T/MM3	
49	01Valsartan	1	1016	21	1.00	ABSTNEU	10E9/L	I	1	19940525	1	0.43	10E9/L	R
50	01Valsartan	1	1016	21	4.00	ABSTNEU	10E9/L	I	1	19940729	1	0.38	10E9/L	
51	01Valsartan	1	1016	21	5.00	ABSTNEU	10E9/L	I	1	19940830	1	3.70	10E9/L	
52	01Valsartan	7	1227	21	1.00	ABSTNEU	10E9/L	I	1	19940315	1	1.93	10E9/L	R
53	01Valsartan	7	1227	21	5.00	ABSTNEU	10E9/L	I	1	19940621	1	0.37	10E9/L	
54	01Valsartan	7	1230	21	1.00	ABSTNEU	10E9/L	I	1	19940330	1	3.29	10E9/L	R
55	01Valsartan	7	1230	21	4.00	ABSTNEU	10E9/L	I	1	19940608	1	2.09	10E9/L	
56	01Valsartan	7	1230	21	5.00	ABSTNEU	10E9/L	I	1	19940708	1	0.75	10E9/L	
57	01Valsartan	7	1233	21	1.00	ABSTNEU	10E9/L	I	1	19940427	1	4.11	10E9/L	R
58	01Valsartan	7	1233	21	4.00	ABSTNEU	10E9/L	I	1	19940711	1	3.36	10E9/L	
59	01Valsartan	7	1233	21	5.00	ABSTNEU	10E9/L	I	1	19940810	1	0.63	10E9/L	
60	01Valsartan	2	5164	23	3.00	ABSTNEU	10E9/L	D	11	19941121	1	0.75	10E9/L	R
61	01Valsartan	2	5164	23	5.00	ABSTNEU	10E9/L	D	11	19950113	1	0.15	10E9/L	
62	01Valsartan	9	5602	23	3.00	ABSTNEU	10E9/L	D	11	19940831	1	0.93	10E9/L	R
63	01Valsartan	9	5602	23	5.00	ABSTNEU	10E9/L	D	11	19941103	1	2.75	10E9/L	
64	01Valsartan	1	1049	27	2.00	ABSTNEU	10E9/L	I	1	19941005	1	2.72	10E9/L	R
65	01Valsartan	1	1049	27	6.00	ABSTNEU	10E9/L	I	1	19941213	1	0.83	10E9/L	
66	01Valsartan	1	1049	27	7.00	ABSTNEU	10E9/L	I	1	19950110	1	0.59	10E9/L	
67	01Valsartan	1	1062	27	2.00	ABSTNEU	10E9/L	I	1	19941018	1	2.45	10E9/L	R
68	01Valsartan	1	1062	27	6.00	ABSTNEU	10E9/L	I	1	19950110	1	0.93	10E9/L	
69	01Valsartan	1	1062	27	7.00	ABSTNEU	10E9/L	I	1	19950207	1	2.36	10E9/L	
70	01Valsartan	M8186D	668	31	1.00	ABSTNEU	10E9/L	USA	M8186D	19941010	1	4.15	T/MM3	
71	01Valsartan	M8186D	668	31	2.00	ABSTNEU	10E9/L	USA	M8186D	19941108	1	5.51	T/MM3	R
72	01Valsartan	M8186D	668	31	4.00	ABSTNEU	10E9/L	USA	M8186D	19950104	1	0.53	T/MM3	
73	01Valsartan	M8313S	632	50	1.00	ABSTNEU	10E9/L	USA	M8313S	19940802	1	1.80	T/MM3	
74	01Valsartan	M8313S	632	50	2.00	ABSTNEU	10E9/L	USA	M8313S	19940826	1	0.62	T/MM3	R
75	01Valsartan	M8313S	632	50	3.00	ABSTNEU	10E9/L	USA	M8313S	19940926	1	1.76	T/MM3	
76	01Valsartan	10	1048	51	2.00	ABSTNEU	10E9/L	F	11	19941122	1	1.60	10E9/L	R
77	01Valsartan	10	1048	51	5.00	ABSTNEU	10E9/L	F	11	19950120	1	0.55	10E9/L	

ALL ABSOLUTE NEUTROPHIL VALUES FOR
PATIENTS WITH AT LEAST ONE ABSOLUTE NEUTROPHIL VALUE < 1000

OBS	TDRC	CENTNO	PATNO	PROTOCOL	VISIT	LBNAME	LBUNTC	LANDC	LBNO	LBDT	LBUSEDQ	LBVALUE	LBUNT	
78	07Valsartan/ Diuretics	M8499F	929	19	1.00	ABSTNEU	10E9/L	USA	M8499F	19941005	1	1.52	T/MM3	
79	07Valsartan/ Diuretics	M8499F	929	19	3.00	ABSTNEU	10E9/L	USA	M8499F	19941121	1	2.40	T/MM3	R
80	07Valsartan/ Diuretics	M8499F	929	19	6.00	ABSTNEU	10E9/L	USA	M8499F	19950113	1	0.88	T/MM3	
81	07Valsartan/ Diuretics	1	1051	27	2.00	ABSTNEU	10E9/L	I	1	19941005	1	4.59	10E9/L	R
82	07Valsartan/ Diuretics	1	1051	27	6.00	ABSTNEU	10E9/L	I	1	19941213	1	0.81	10E9/L	
83	07Valsartan/ Diuretics	1	1051	27	7.00	ABSTNEU	10E9/L	I	1	19950110	1	0.83	10E9/L	
84	20ACEI	8	7161	23	3.00	ABSTNEU	10E9/L	E	12	19941102	1	0.89	10E9/L	R
85	20ACEI	8	7161	23	5.00	ABSTNEU	10E9/L	E	12	19950113	1	1.64	10E9/L	
86	20ACEI	1	1056	27	2.00	ABSTNEU	10E9/L	I	1	19941007	1	2.93	10E9/L	R
87	20ACEI	1	1056	27	6.00	ABSTNEU	10E9/L	I	1	19941213	1	1.07	10E9/L	
88	20ACEI	1	1056	27	7.00	ABSTNEU	10E9/L	I	1	19950110	1	0.98	10E9/L	
89	20ACEI	202	1853	28	1.00	ABSTNEU	10E9/L	GB	1	19940423	1	0.79	10E9/L	R
90	20ACEI	202	1853	28	4.00	ABSTNEU	10E9/L	GB	2	19940528	1	4.41	10E9/L	
91	20ACEI	202	1853	28	4.00	ABSTNEU	10E9/L	GB	2	19940622	1	3.86	10E9/L	
92	20ACEI	202	1853	28	6.00	ABSTNEU	10E9/L	GB	2	19940720	1	3.46	10E9/L	
93	20ACEI	202	1853	28	8.00	ABSTNEU	10E9/L	GB	2	19941029	1	3.19	10E9/L	
94	20ACEI	202	1853	28	9.00	ABSTNEU	10E9/L	GB	2	19941126	1	2.60	10E9/L	
95	20ACEI	245	1347	28	1.00	ABSTNEU	10E9/L	GB	2	19940513	1	2.49	10E9/L	R
96	20ACEI	245	1347	28	4.00	ABSTNEU	10E9/L	GB	2	19940624	1	0.69	10E9/L	
97	20ACEI	245	1347	28	6.00	ABSTNEU	10E9/L	GB	2	19940822	1	3.58	10E9/L	
98	20ACEI	245	1347	28	8.00	ABSTNEU	10E9/L	GB	2	19941212	1	5.54	10E9/L	
99	20ACEI	M8308N	710	50	1.00	ABSTNEU	10E9/L	USA	M8308N	19940921	1	2.64	T/MM3	
100	20ACEI	M8308N	710	50	2.00	ABSTNEU	10E9/L	USA	M8308N	19941005	1	2.82	T/MM3	R
101	20ACEI	M8308N	710	50	5.00	ABSTNEU	10E9/L	USA	M8308N	19950104	1	0.38	T/MM3	
102	290ther	7	1234	21	1.00	ABSTNEU	10E9/L	I	1	19940427	1	4.63	10E9/L	R
103	290ther	7	1234	21	4.00	ABSTNEU	10E9/L	I	1	19940708	1	0.29	10E9/L	
104	290ther	7	1234	21	5.00	ABSTNEU	10E9/L	I	1	19940805	1	5.93	10E9/L	
105	290ther	7	1244	21	1.00	ABSTNEU	10E9/L	I	1	19940729	1	8.97	10E9/L	R
106	290ther	7	1244	21	4.00	ABSTNEU	10E9/L	I	1	19941007	1	6.67	10E9/L	
107	290ther	7	1244	21	5.00	ABSTNEU	10E9/L	I	1	19941104	1	6.34	10E9/L	

R = randomization

CONFIDENTIAL

STATISTICAL REVIEW AND EVALUATION

NDA: 20-665
Applicant: Ciba-Geigy Corporation
Name of Drug: Valsartan (CGP 48933)
Document Reviewed: Studies Reports on the submitted CANDA, volumes 1.69, 1.75, 1.80, 1.81, 1.85, 1.86, and 1.88. Received 01/04/96.

AUG 23 1996

1. INTRODUCTION

This application includes 10 placebo-controlled randomized multi-center studies, 05, 09, 10, 11, 17, 23, 25, 31, 50, and 51 to compare the efficacy and safety of valsartan 10, 20, 40 , 80, 160, and 320 mg with placebo in patients with essential hypertension. This submission also includes 7 active-controlled studies 19, 20, 21, 22, 27, 28, and 33. Studies 05, and 09 were forced titration studies. Study 19 was to investigate the combination therapy of valsartan with HCTZ and studies 20, 21, 22, 27, 28, and 33 were to compare valsartan to other antihypertensive drugs. However, the goal of study 33 was to assess the occurrence of cough in using valsartan compared to lisinopril and HCTZ.

Since the main objective of this submission is to evaluate the efficacy and safety of vlasratan doses versus placebo, this review will only include studies 10, 11, 17, 23, 31, 33, 50, and 51.

The primary efficay variable was the change from baseline in sitting diastolic blood pressure (SiDBP), except for study 10 in which supine diastolic blood pressure (SuDBP) was used for the primary efficacy variable. However, in this review the corresponding sponsor's analysis for the change from baseline in sitting systolic blood pressure (SiSBP), or supine systolic blood pressure (SuSBP) for study 10, is also presented. In these studies the primary (endpoint) data consisted of all patients who had a baseline measurement and at least one post-baseline measurement.

The sponsor stated that to avoid potential analysis problems due to small number of patients in some centers, investigators who had less than two patients in any treatment group were combined.

The sponsor's analyses of [redacted] placebo-controlled studies show that treatment by center interaction was not significant.

2. STUDY 10

This is a multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of once daily valsartan (10, 40, 80, and 160 mg) in patients with essential hypertension (SuDBP between 95 to 115 mmHg).

Following a 4-week washout period, 122 patients were randomized to receive placebo, or valsartan 10, 40, 80, or 160 mg once daily for 4 weeks.

The primary endpoint was the change from baseline in SuDBP. The change from baseline in SuSBP was also evaluated. Patients who had a baseline BP measurement and at least one double-blind measurement were included in the analysis. The analysis was conducted at the end of study to contain last available double-blind BP measurement for patients.

3. STUDY 11

This is a multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of once daily valsartan (20, 40, and 80 mg) in white patients with essential hypertension (SiDBP between 95 to 115 mmHg).

Following a 4-week washout period, 442 patients were randomized to receive either placebo or valsartan 20, 40, or 80 mg once daily for 6 weeks.

The primary endpoint was the change from baseline in SiDBP at the end of study. The change from baseline in SiSBP was also evaluated.

4. STUDY 17

This is a multicenter, randomized, double-blind, placebo-controlled, parallel study to assess the effect of food on the antihypertensive response of valsartan 80 mg in patients with essential hypertension (SiDBP between 100 to 114 mmHg).

Following 2-4 weeks of placebo washout period, 297 patients were randomized to receive once daily either valsartan 80 mg after a 10 hour fast and at least 2 hours prior to breakfast, or valsartan 80 mg with breakfast, or placebo (2:2:1 ratio) for 8 weeks.

The primary endpoint was the change from baseline in SiDBP at the end of study. The change from baseline in SiSBP was also evaluated.

5. STUDY 23

This is a multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of once daily valsartan (40, 80, and 160 mg) in elderly patients (≥65 years old) with essential hypertension (SiDBP between 96 to 114 mmHg).

Following a 2-week washout period, 652 patients were randomized to receive either placebo or valsartan 40, 80, 160 mg, or lisinopril 10 mg once daily in a 2:2:2:2:1 ratio for 8 weeks.

The primary endpoints were the changes from baseline in SiDBP and in SiSBP at the end of

study. The sponsor had not made any plan for the adjustment of the p-values for having two primary endpoints. However, the conclusions would be the same with or without adjustment, using any method known in practice for such an adjustment.

6. STUDY 31

This is a multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of once daily valsartan (20, 80, 160, and 320 mg) in patients with essential hypertension (SiDBP between 95 to 115 mmHg).

Following 2 to 4 weeks of a single-blind placebo washout period, 736 patients were randomized to receive either placebo, or valsartan 20, 80, 160, or 320 mg once daily for 8 weeks.

The primary endpoint was the change from baseline in SiDBP. The change from baseline in SiSBP was also evaluated.

In addition to measuring the cuff blood pressure, patients (from 10 selected centers) participated in ambulatory blood pressure monitoring (ABPM) sessions.

7. STUDY 50

This is a multicenter, randomized, double-blind, placebo-controlled, optional titration, parallel study to evaluate the efficacy and safety of valsartan and lisinopril for 12 weeks in patients with essential hypertension (SiDBP between 95 to 115 mmHg).

Following 2-4 weeks of a single-blind placebo washout period, 734 patients were randomized to one of four double-blind treatment groups. One group received placebo, one group received lisinopril 10 mg once daily (OD), and two groups received valsartan 80 mg once daily. After 4 weeks, patients were titrated to a higher dose if their SiDBP≥90 mmHg and there were no symptoms of orthostatic hypotension in the following manner. For the group receiving lisinopril 10 mg patients were titrated to lisinopril 20 mg, in one group receiving valsartan 80 mg patients were titrated to receive valsartan 80 mg BID, and the other group receiving valsartan 80 mg OD patients were titrated to receive valsartan 160 mg OD. The double-blind treatment continued for an additional 8 weeks.

The primary endpoint was the change from baseline in SiDBP at the end of 12 weeks study.

8. STUDY 51

This is a multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of once daily valsartan 80 mg and enalapril 20 mg for 8 weeks in patients with essential hypertension (SiDBP between 95 to 115 mmHg).

Following a 2-week washout period , 348 patients were randomized to receive either placebo or valsartan 80 mg, or enalapril 20 mg once daily in a 2:2:1 ratio for 8 weeks.

The primary endpoint was the change from baseline in SiDBP at the end of study. The change from baseline in SiSBP was also evaluated.

9. STUDY 33

This is a multicenter, randomized, double-blind, active-controlled, parallel study to assess the occurrence of cough following once daily administration of valsartan 80 mg, lisinopril 10 mg, or HCTZ 25 mg) in patients with essential hypertension (SiDBP between 95 to 115 mmHg) who had a proven history of ACE inhibitor induced cough.

Following 2 to 4 weeks of a single-blind placebo washout period, patient entered a 2-4 week lisinopril challenge phase to demonstrate the presence of ACE inhibitor induced cough. Once the occurrence of ACE inhibitor induced cough, patients entered a 2-week placebo washout period, followed by 6 weeks of double-blind treatment of either valsartan 80 mg, lisinopril 10 mg, or HCTZ 25 mg once daily.

A total of 129 patients were randomized to receive double-blind treatments.

10. REVIEWER'S COMMENTS

This reviewer has used the data submitted by the sponsor to check the sponsor's results of statistical analyses and to provide the following analyses that were not provided by the sponsor: the analyses for all the randomized patients and the acceptable patients (as will later on be described) at the end of studies 23 and 51, the analysis of acceptable patients at week 4 of study 50, summary statistics for the change from baseline in diastolic BP by gender and by race for studies 10, 11, 17, 23, and 51. Tables 1 to 6 were constructed by this reviewer to summarize the statistical results of analyses. Because of the conditional titration in patients doses after 4 weeks of double-blind treatment in study 50, the results of this study will be discussed separately and were not included in these tables. Tables 1 and 2 summarize the results for the diastolic BP for the endpoint and for the end of study analyses, respectively. The corresponding results for the systolic BP are summarized in Table 3 and 4. Table 5 was constructed to show some summary statistics at the endpoint by gender for studies 10, 11, 17, 23, 31, and 51. Table 6 gives a summary statistics for the effect of valsartan doses at the endpoint by race (blacks and non-blacks) for studies 10, 17, and 31.

The sponsor had made adjustments for the level of significance α according to the multiple comparison procedures that were specified in the protocols of studies 10, 11, 23, and 50 (Dunnett's procedure for studies 10 and 11, see reference 1, and Bonferroni's procedure for studies 23 and 50). No such adjustments were specified in the protocols of studies 17 and 51. Thus, to be consistent, this reviewer has chosen Bonferroni procedure to adjust the α level, which

means that the p-values for these two studies would be compared with α=0.025 instead of 0.05. The conclusions drawn from the results of the two studies will be based on this adjustment.

Table 1 shows that for study 10, in which the change from baseline in SuDBP was the primary endpoint, only valsartan 160 mg shows a significant (p=0.007) reduction in SuDBP versus that of placebo. For studies 11, 17, 23, 31, and 51 the change from baseline in SiDBP was the primary endpoint and their results shown in Table 1 are discussed by dose level as follows.

Valsartan 20 mg

In studies 11 and 31, valsartan 20 mg has resulted in a significantly ($p \leq 0.0021$) greater reduction in BP over that for placebo.

Valsartan 40 mg

Valsartan 40 mg was investigated in studies 10, 11, and 23. Only in study 11 valsartan 40 mg had resulted in a significant (p=0.001) reduction in BP over placebo. Perhaps the reason that this dose had not shown a significant result in study 10 is because of the small number of patients (24 patiens) in this group. On the other hand, study 23 considered only elderly patients (age $\geq$65 years old) and thus a non-significant result (p=0.695) could mean that this dose is not effective among elderly patients.

Valsartan 80 mg

Valsartan 80 mg was investigated in studies 10, 11, 17, 23, 31, and 51. The results of studies 11, 17 (the fasted group), 31, and 51 valsartan 80 mg has shown a significantly ($p \leq 0.001$) greater reduction in BP over that for placebo. The same reasons for the non-significant results which were described above for valsartan 40 could be applied for the non-significant results for valsartan 80 mg in studies 10 and 23.

Valsartan 160 mg

Valsartan 160 mg was investigated in studies 10, 23, and 31. Tables 1 shows that in study 31 valsartan 160 mg has resulted in a significantly ($p < 0.001$) greater reduction in BP over that for placebo. Again the non-significant result (p=0.072) for this dose in study 23 may suggest that valsartan 160 mg is not effective among the elderly.

Valsartan 320 mg

The effect of valsartan 320 mg in reducing BP was only investigated by study 31, which shows a significant ($p<0.001$) reduction in BP over that of placebo.

By examining the results presented in Table 2, one can see that the above findings are supported

by the results of analysing the end of study data. Also, the results of analyses for the systolic BP for the above studies, which are summarized in Tables 3 and 4, show that, except for valsartan 80 mg at the end of study 10, the above findings are duplicated for the reduction in the systolic BP over that of placebo.

Table A below summarizes the above finding in a symbolical form using Tables 1 and 2, in which the significant p-values were based on the specified multiple comparison procedures.

Table A. The results of tests for the change from baseline in diastolic BP versus that of placebo. These results are denoted by S=Significant, N=Non-significant, where the first letter is for the results for endpoint and the second for the end of study

	Valsartan Dose (in mg)					
Study	10	20	40	80	160	320
10	N,N		N , N	N , S	S , S	
11		S,S	S , S	S , S		
17				S+ , S		
23			N , N	N , N	N , N	
31		S,S		S , S	S , S	S , S
51				S , S		

+ A significant result was only found for the fasted group.

Protocol Violations and Acceptable patients

The number of patients who violated protocol and were considered as significant to affect the efficacy results ranges between 1 and 4 patiens in studies 10, 11, 17, and 31; but, in studies 23, 50, and 51 the numbers of patients who had violated protocol were 73, 69, and 23 patients, respectively. The two main causes of violation of the protocol were: first, the deviations from the planned time interval between the intake of trial medication and the measurement of blood pressure and second, the violation of inclusions criteria in the randomization for the double-blind treatment. Randomized patients who had no protocol violations were called by the sponsor "the acceptable patients".

The sponsor presented the analyses for the acceptable patients for studies 23, 50, and 51 for the endpoint data. However, it is important that the efficacy of valsartan is investigated through the analyses of the data for the acceptable patients at the end of studies. Thus, this reviewer had done that and the results are shown below in Table B.

Table B shows that valsartan 80 mg in both studies 50 and 51 had resulted in a significant (p-value=0.0001) reduction in SiDBP over that for placebo. But, in study 23 only valsartan 320 mg show such a significant result (p-value=0.0021), using α=0.019 for Dunnett multiple comparison procedure. These results are similar to those found for the endpoint data (Table 1) when all randomized patients were included in the analysis.

Table B. Results of analysis of SiDBP for the acceptable patients at the end of studies 23 and 51 and at week 4 for study 50.

Study	Treatment	N	Baseline SiDBP	Change from baseline*	p-value+
23	Placebo	130	101.20	-8.29	
	Vals 40 mg	128	100.93	-9.19	0.4905
	Vals 80 mg	124	101.42	-10.37	0.0993
	Vals 160 mg	125	101.99	-11.10	0.0314
	Lisin 10 mg	66	101.53	-13.09	0.0021
50	Placebo	163	100.88	-3.52	
	Vals 80 mg	331	101.18	-7.12	0.0001
	Lisin 10 mg	171	101.29	-7.13	0.0001
51	Placebo	130	101.86	-5.53	
	Vals 80 mg	133	101.44	-9.72	0.0001
	Enal 20 mg	66	102.33	-8.53	0.0084

* Using least square mean SiDBP for the specified week.
+ p-value for comparison versus placebo.

Valsartan BID regimen (study 50)

Study 50 is the only study that the effect of valsartan BID regimen on the reduction of BP has been investigated. But, this study was not properly designed to investigate the effects of the OD and the BID regimens of valsartan because of a conditional titration of patients doses which is described as follows. At the end of 4 weeks of double-blind treatments, if a patient's SiDBP was ≥90 mmHg (non-responder), the dose was doubled if that patient was in one of the two groups of patients who were receiving valsartan 80 mg OD or in the group of patients who was receiving lisinopril 10 mg OD; a non-responder patient from the second group of patients who was

receiving valsartan 80 mg OD went on valsartan 80 mg BID. Patients continue for 8 more weeks. With this conditional titration, the non-responders in the placebo group were not accounted for in the two new treatments: valsartan 160 mg OD and valsartan 80 mg BID. Consequently, a statistical analysis applied in this case may result in a bias in assessing the true effectivenesses of these two regimens relative to placebo. However, one may be justified in comparing the effectiveness of the BID regimen versus that of the OD regimen of valsartan for the non-reponders (titrated patients). Also, it is possible to use the information for the change from baseline at week 4 to statistically assess the effectiveness of valsartan 80 mg (OD) in the reduction of BP. The sponsor's analyses for week 4 and for comparing the OD and the BID regimens for the titrated patients at endpoint are shown below in Table C and D, respectively.

Table C shows that, after four weeks of double-blind treatment, valsartan 80 mg has resulted in a significantly ($p < 0.001$) greater reduction in BP over that for placebo.

Table C. Change from baseline in SiDBP for week 4 in study 50.

Treatment	N	Baseline	Week 4*	Change from baseline	p-value+
Placebo	183	100.93	97.70	-3.23	
Vals 80 mg	364	101.25	94.13	-7.12	<0.001
Lisin 10 mg	187	100.99	93.52	-7.47	<0.001

* Least square mean

+ p-value for comparison versus placebo.

Table D. Sponsor' Results of analysis for the change from baseline in SiDBP for the titrated patients at endpoint.

	BP at Baseline		LS Mean Change	
Treatment	N	SiDBP	In SiDBP	p-value*
Vals 80 OD/BID	114	102.9	-7.9	
Vals 80 /160 OD	121	101.8	-7.8	0.896

* p-value for comparison between the OD and the BID valsartan regimens.

Table D shows that the valsartan 160 mg OD group and the valsartan 80 mg BID group of patients, who were titrated to these regimens after not having responded to valsartan 80 mg OD treatment, did not show a significant ($p=0.896$) difference in their reductions of BP.

In addition to the above analysis, one may have an insight into the results of the reduction in BP at the end of study by giving some descriptive statistics about the averges of SiDBP and the changes from week 4 values for the different treatment groups. For this purpose, Table E was constructed as shown below.

Table E. Pateints SiDBP for the non-responders and the responders at week 4 and after the additional 8 weeks of double-blind treatment in study 50.

Treatment	BP at week 4		Change in SiDBP	
	N	SiDBP	Week 12 - 4	Drug effect*
Non-Respondent patients (SiDBP was ≥90 mmHg at week 4)				
Placebo	154	100.1	-0.9	
Vals 80 OD/BID	128	98.8	-3.7	-2.8
Vals 80 /160 OD	121	98.4	-3.8	-2.9
Lisin 10 /20 OD	129	97.2	-3.6	-2.7
Respondent patients (SiDBP was <90 mmHg at week 4)				
Placebo	29	85.6	3.2	
Vals 80 OD/BID	59	84.2	4.3	1.1
Vals 80 /160 OD	56	84.9	3.5	0.3
Lisin 10 /20 OD	58	84.3	0.2	-3.0

* Drug effect=Change from week 4 for drug - Change from week 4 for placebo.

Table E shows that, for patients whose SiDBP was ≥90 mmHg at week 4 and were randomized into two valsartan regimens, after 8 weeks of treatment the average drug effect (which is measured as the difference in the EP change from baseline for the valsartan groups over that of placebo group) was about 3 mmHg. On the other hand, Table E shows that, for those patients who had their SiDBP <90 mmHg at week 4 and continued in their respective regimens, after 8 weeks of treatment their SiDBP was higher than when they started by as much as 1 mmHg.

Dose Response

Study 31 is a large study in which valsartan doses 0, 20, 40, 80, 160, and 320 mg were studied. This reviewer has chosen this study to investigate the dose response of valsartan. Three different models (quadratic, logistic, and an E_{MAX} model adjusted for a baseline value) were fitted to the change from baseline in SiDBP at the end of study. The root mean square error (RMSE) criterion

was empolyed to select the best fitting model to the data. The results of analyses show the following RMSE values: 1.3390, 0.8295, and 0.1431 for the quadratic, logistic, and the E_{MAX} model, respectively. Graphs of the observed values and the fitted curve for each model are shown in Figures 1 to 3.

It is clear that the E_{MAX} model (adjusted for a baseline value) is the best fitted model for a dose response model.

From the above fitted models and by examining the results of the presented studies, and in particular studies 10 and 31 (see Tables 1 and 2), one can see that the minimum effective dose for valsartan could be 20 mg. But, these studies did not give evidence as to what might be the maximum tolarable dose for valsartan; in fact the dose response shown for study 31 did not reach a plateau at the maximum dose 320 mg of valsartan.

ABPM Measurements

At selected centers in study 31, patients had participated in an ABPM sessions. The total number of patients who participated in these sessions were 42, 44, 44, 41, and 45 for placebo, valsartan 20, 80, 160, and 320 mg, respectively. The sponsor had presented a number of analyses for the ABPM data including the ANCOVA and repeated measures analysis; the results are summarized in Tables 7 and 8, respectively. Table 7 shows that, based on a Bonferroni adjusted α level equals to 0.0125, all the above doses of valsartan had resulted in significantly greater changes (p-values $\leq$ 0.010) from baseline in the diastolic 24-hour ABPM average over that for placebo. Similar significant results are found for the systolic ABPM data.

The repeated measures analysis was carried out by assuming a model for a split-plot design which include treatment (as a main plot), center, time period, daytime or nighttime (as a sub-plot), treatemnt x center tratment x baseline and treatment x timeperiod interactions. This type of analysis does not account for the circadian variation of BP and ignores the fact that patients may differ in their BP pattern during a 24-hour period. Therefore, an analysis based on repeated measures for the two specified period may not give any meaningful interpretation for the BP behavior for all patients during the two specified periods. Consequently, a more realistic model, which would take into consideration the circadian variation of BP and other factors that affect the behavior of BP during a 24-hour period, need to be investigated. However, to view the results of such an analysis, this reviewer has presented the sponsor's analysis for repeated measures in Table 8.

Table 8 shows that for both the main-plot and the sub-plot analyses the valsartan doses had resulted in significantly (p-values $\leq$ 0.007) greater changes from baseline in the diastolic 24-hour ABPM average over that for placebo. Also, Table 8 shows that there were no significant differences (p-values $\geq$ 0.223) in the ABPM mean changes from baseline beween the daytime and nighttime periods for all tretment groups.

The sponsor had ploted the hourly averages for the ABPM data at visit 2 (baseline) and at visit 4 (after treatment). Figure 4 and 5 show the graphs for the two visits.

The Effect of Valsartan by Gender

Table 5 shows that in all the listed studies and for all dose levels of valsartan (except valsartan 40 mg in studies 10, 11, and 23 and valsartan 160 mg in study 23) females had benifited more than male patients in reducing their blood presssure. However, in almost all of these studies the female placebo effect is higher than the cooresponding ones for male patients. This situation had resulted in reversing the order of drug effect among female and male patients for a number of valsartan dose levels in some studies.

The Effect of Valsartan by Race

Not counting the results of study 10 because of the small number of black patients, Table 6 shows that for studies 17 and 31 and for all valsartan dose levels non-black patients have benifited more than black patients in getting the reduction of their BP. However, in studies 17 and 31 the placebo effect for non-black patients is higher than that for the black patients. This situation has brought the opposite of these results in all cases, except for the fasted group in study 17, in showing more drug effect among black than non-black patients.

Because of the conditional titration in the design of study 50 it would be of interest to examine patients responses by race at the end of the first 4 weeks of double-blind treatment and at the end of the addtional 8 weeks of treatment.

If one examines the results of study 50 for the first four weeks of double-blind treatment, which are presented in Table F below, one sees that valsartan 80 mg has resulted in a greater reduction

Table F. Blood pressure of patients (by race) at baseline and at week 4 for study 50.

Blacks				
	BP at baseline (week 0)		Change in SiDBP	
Treatment	N	SiDBP	Week 4 - 0	Drug effect*
Placebo	28	104.3	-1.0	
Vals 80 mg OD	48	103.5	-5.7	-4.7
Lisin 10 mg OD	27	100.9	-7.3	- 6.3

Table F (Continued)

Non-Blacks				
	BP at baseline (week 0)		Change in SiDBP	
Treatment	N	SiDBP	Week 4 - 0	Drug effect*
Placebo	155	100.3	- 3.5	
Vals 80 mg OD	316	100.9	-7.3	-3.8
Lisin 10 mg OD	160	101.0	-7.9	-4.4

* Drug effect=Change from week 4 for drug - Change from week 4 for placebo.

in BP among non-blacks than blacks patients. But, because of a greater placebo effect among the non-black patients compared to the black patients, the valsartan drug effect among blacks shows more than non-blacks. Thus, Table F above indicates that the results of study 50 show a treatment by race interaction that is not qualitative.

To examine the effect of valsartan in the reduction of BP by race after the first 4 weeks of double-blind treatment, two tables were constructed: Tables G and H. Table G is for patients who remained on their respective dose levels and Table H is for patients whose dose levels were titrated because their SiDBP was ≥90 mmHg at week 4.

Table G. Blood pressure of patients (by race) in study 50 whose SiDBP was <90 mmHg at week 4 and remained on their respecive dose levels during the additional 8 weeks of double-blind treatment.

Blacks				
	BP at week 4		Change in SiDBP	
Treatment	N	SiDBP	Week 12 - 4	Drug effect*
Placebo	1	89.3	.*	
Vals 80 mg OD	12	83.9	3.9	
Lisin 10 mg OD	9	85.0	-3.9	

Table G (Continued)

Non-Blacks				
	BP at week 4		Change in SiDBP	
Treatment	N	SiDBP	Week 12 - 4	Drug effect*
Placebo	28	85.4	3.2	
Vals 80 mg OD	103	84.6	3.9	0.7
Lisin 10 mg OD	58	84.2	0.8	-2.4

* Drug effect=Change from week 4 for drug - Change from week 4 for placebo.
+ No patient was counted at week 12

Table H. Blood pressure of patients (by race) in study 50 whose SiDBP was ≥90 mmHg at week 4 and had their dose levels titrated during the additional 8 weeks of double-blind treatment.

Blacks				
	BP at week 4		Change in SiDBP	
Treatment	N	SiDBP	Week 12 - 4	Drug effect*
Placebo	27	103.8	0.9	
Vals 80 OD/BID	19	101.7	-2.9	-3.8
Vals 80 /160 OD	17	103.0	-4.5	-5.4
Lisin 10 mg OD	18	97.8	-1.7	-2.6
Non-Blacks				
	BP at week 4		Change in SiDBP	
Treatment	N	SiDBP	Week 12 - 4	Drug effect*
Placebo	127	99.3	-1.3	
Vals 80 OD/BID	109	98.3	-3.8	-2.5
Vals 80 /160 OD	104	97.6	-3.7	-2.4
Lisin 10 /20 OD	111	97.1	-3.7	-2.4

* Drug effect=Change from week 4 for drug - Change from week 4 for placebo.

Table G shows that after 8 additional weeks of double-blind treatment, the SiDBP for patients who remained on their original regimen has increased over what it was at week 4 for the valsartan group and for both black and non-black patients.

Table H shows that, for the OD regimen, black patients showed a greater reduction in BP over non-black patients but, the opposite of this result was found for the BID regimen. Again, because of a high placebo effect among non-black patients the drug effect for both the OD and the BID regimens is more among black patients than non-blacks.

Table H also shows that black patients who were receiving valsartan 160 OD during the additional 8 weeks of double-blind treatment had their SiDBP decreased more than those in the valsartan 80 mg BID regimen. On the other hand for the non-black patients the reduction in SiDBP was the same for both the OD and the BID regimens.

The Effect of Valsartan on the Occurrence of Cough

The main purpose of study 33 was to evaluate the effect of valsartan on the occurrence of dry, persistent cough compared to other antihypertensive drugs: lisinopril 10 mg and HCTZ 25 mg. The sponsor had presented a statistical analysis, using the Cochran-Mantel-Haenszel Chi-square test, adjusted for center for week 3 and 6 combined. The results are summarized in Table I below.

Table I. The sponsor's results of analysing the number of Patients who had dry persistent dry cough during the double-blind period (measured at week 3 and 6).

Treatment	N*	n+	p-value#
Lisin 10 mg	45	31	
HCTZ 25 mg	42	8	<0.001
Vals. 80 mg	41	8	<0.001

* N=Total number of patients
+ n=Number of patients who had persistent dry cough
# comparison versus lisinopril 10 mg.

Table I shows that both valsartan 80 mg and HCTZ has resulted in a significantly lower cough rate compared to lisinopril 10 mg.

11. SUMMARY AND CONCLUSIC ' (HICH MAY BE CONVEYED TO THE SPONSOR)

The sponsor has presented the results of analyses of 10 placebo-controlled studies, 05, 09, 10, 11, 17, 23, 25, 31, 50, and 51 and 7 active-controlled studies 19, 20, 21, 22, 27, 28, and 33. Since the main objective of this submission is to evaluate the efficacy and safety of vlasratan doses versus placebo, this review has only included studies 10, 11, 17, 23, 31, 33, 50, and 51.

This reviewer has constructed Tables 1 to 6 to summarize the sponsor's results. Table 1 shows that in studies 11 and 31 valsartan 20 mg has resulted in a signifcantly ($p \leq 0.0021$) greater reduction in SiDBP over that for placebo but, only in study 11 valsartan 40 mg resulted in such a significant ($p=0.001$) reduction in BP over placebo. Studies 11, 17 (the fasted group), 31, and 51 had shown that valsartan 80 mg has resulted in a significantly ($p \leq 0.001$) greater reduction in SiDBP over that for placebo. Tables 1 also shows that in studies 10 and 31, valsartan 160 mg has resulted in a signifcantly ($p \leq 0.007$) greater reduction in BP (SuDBP for study 10 and SiDBP for study 31) over that for placebo. The effect of valsartan 320 mg in reducing BP mg was only investigated by study 31, which shows a significant ($p<0.001$) reduction in SiDBP over that of placebo.

Study 23 had investigated the effect of valsartan on the reduction of BP for the elderly patients (age ≥ 65 years old), its results show that none of the valsartan doses had resulted in a significant SiDBP reduction over that of placebo (see Tables 1 and 2).

In reviewing the results of these studies, it is observed that the above significant findings were true for the randomized patients and for the acceptable patients (when patients who violated protocol were excluded from analysis) at the end of studies and are also supported by the results of the ABPM data which was provided by study 31.

The results of analyses for the systolic BP (presented in Tables 3 and 4) show similar findings as those described above for the diastolic BP .

Study 50 is the only study that the effect of valsartan BID regimen on the reduction of BP has been investigated. But, since the non-responders in the placebo group were not accounted for in the design of this study, statistical analyses would not truly assess the effectiveness of these two regimens relative to placebo. However, the analysis for the non-responders shows that there is no significant ($p=0.896$) difference in the reduction of SiDBP between the 160 mg OD and the 80 mg BID regimens of valsartan.

Three different models (quadratic, logistic, and an E_{MAX} model that is adjusted for a baseline value) were fitted to the change from baseline in SiDBP at the end of study 31. The results show a dose response relationship for valsartan for which the E_{MAX} model (adjusted for a baseline value) is the best fitted model.

The submitted studies indicated that the minimum effective dose of valsartan could be 20 mg but, there is no evidence as to what might be the maximum tolerable dose for valsartan; in fact the dose respose shown for study 31 did not reach a plateau at the maximum dose 320 mg of valsartan.

Table 5 shows that in all listed studies and for most of the studied dose levels of valsartan females had benefited more than male patients in reducing their blood presssure. However, in almost all of these studies the female placebo effect is higher than the cooresponding ones for male patients. This situation had resulted in reversing the order of drug effect among female and male patients for a number of valsartan dose levels in some studies.

Table 6 shows that for studies 17 and 31 and for all valsartan dose levels non-black patients have benefited more than black patients in reducing their BP. However, in studies 17 and 31 the placebo effect for non-black patients is higher than that for the black patients and this has resulted in all cases, except for the fasted group in study 17, in having a higher drug effect among black patients than non-blacks.

Study 33 shows that, for week 3 and 6 combined, both valsartan 80 mg and HCTZ has resulted in a significantly lower cough rate (p-values <0.001) compared to lisinopril 10 mg (see Table I in section 10).

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This review consists of 17 pages, 8 tables, and 5 figures.

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Refernces

1. Hochberg, Y. and Tamhane, A.C. (1987). Multiple Comparison Procedures, Wiley, New York. Table 5, pages 391-398.

Table 1. Mean change from baseline in SuDBP (study 10) and in SiDBP(studies 11, 17, 23, 31, and 51) at endpoint

Study#	No. of Weeks	Treatment	N	Adj Mean BLine	Drug Change	Effect*	p-value+
10	4	Placebo	25	100.7	-3.80		
		Vals 10 mg	25	102.6	-5.39	1.59	0.418
		Vals 40 mg	24	101.6	-6.30	2.50	0.200
		Vals 80 mg	22	100.7	-9.09	5.29	0.016
		Vals 160 mg	24	101.0	-9.18	5.38	0.007@
11	6	Placebo	111	100.4	-4.76		
		Vals 20 mg	105	100.2	-7.77	3.01	0.0021&
		Vals 40 mg	113	100.4	-8.42	3.66	0.0001&
		Vals 80 mg	112	100.7	-8.03	3.27	0.0006&
17	8	Placebo	57	103.2	-4.24		
		Vals 80 mg,fasted	119	103.7	-8.65	4.41	0.001$
		Vals 80 mg,fed	109	104.0	-6.85	2.61	0.046$
23	8	Placebo	141	100.8	-8.6		
		Vals 40 mg	145	100.6	-9.1	0.5	0.695
		Vals 80 mg	139	101.2	-10.3	1.7	0.145
		Vals 160 mg	139	101.7	-10.7	2.1	0.072
		Lisin 10 mg	73	101.6	-12.3	3.7	0.008&
31	8	Placebo	145	100.7	-2.02		
		Vals 20 mg	139	100.8	-5.39	3.37	<0.001#
		Vals 80 mg	148	100.8	-7.22	5.20	<0.001#
		Vals 160 mg	147	101.4	-7.34	5.32	<0.001#
		Vals 320 mg	150	101.3	-8.50	6.48	<0.001#
51	8	Placebo	142	101.8	-5.3		
		Vals 80 mg	136	101.2	-9.4	4.1	0.0001$
		Enal 20 mg	69	102.2	-8.5	3.2	0.0029$

*Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.
+ p-value for comparison versus placebo.
@ Significant at α=0.015, using Dunnett's MC procedure.
& Significant at α=0.019, using Dunnett's MC procedure.
$ Significant at α=0.05.
# Significant at α=0.0125, using Bonferroni's MC procedure.

Table 2. Mean change from baseline at the end of studies in SuDBP (study 10) and in SiDBP (studies 11, 17, 23, 31, and 51)

Study#	Week	Treatment	N	BLine	Adj Mean Change	Drug Effect*	p-value+
10	4	Placebo	24	101.6	-3.84		
		Vals 10 mg	23	101.8	-6.61	2.77	0.138
		Vals 40 mg	22	101.2	-7.28	3.44	0.065
		Vals 80 mg	22	100.7	-8.99	5.15	0.012@
		Vals 160 mg	23	101.0	-9.15	5.31	0.004@
11	6	Placebo	105	100.3	-4.82		
		Vals 20 mg	102	100.2	-7.88	3.06	0.0014&
		Vals 40 mg	107	100.1	-9.31	4.49	0.0001&
		Vals 80 mg	110	100.3	-7.77	2.95	0.0019&
17	8	Placebo	48	103.5	-3.91		
		Vals 80 mg,fasted	108	104.2	-8.96	5.05	0.000$
		Vals 80 mg,Fed	102	104.7	-7.14	3 23	0.019$
23	8	Placebo	138	101.0	-8.1		
		Vals 40 mg	141	100.4	-9.1	1.0	0.404
		Vals 80 mg	135	101.1	-10.5	2.4	0.048
		Vals 160 mg	135	101.7	-10.8	2.7	0.028
		Lisin 10 mg	69	101.3	-12.3	4.2	0.005&
31	8	Placebo	135	100.6	-1.68		
		Vals 20 mg	132	100.8	-5.54	3.86	<0.001$
		Vals 80 mg	146	100.8	-7.32	5.64	<0.001$
		Vals 160 mg	139	101.4	-8.01	6.33	<0.001$
		Vals 320 mg	145	101.3	-8.83	7.15	<0.001$
51	8	Placebo	138	101.8	-5.5		
		Vals 80 mg	134	101.2	-9.7	4.2	0.0001$
		Enal 20 mg	66	102.0	-8.7	3.2	0.0029$

*Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.
+ p-value for comparison versus placebo.
@ Significant at α=0.015, using Dunnett's MC procedure.
& Significant at α=0.019, using Dunnett's MC procedure.
$ Significant at α=0.05.
# Significant at α=0.0125, using Bonferroni's MC procedure.

Table 3. Mean change from baseline in SuSBP (study 10) and in SiSBP (studies 11, 17, 23, 31, and 51) at endpoint

Study#	No. of Weeks	Treatment	N	Adj Mean BLine	Adj Mean Change	Drug Effect*	p-value+
10	4	Placebo	25	156.4	-1.32		
		Vals 10 mg	25	157.3	-3.64	2.32	0.581
		Vals 40 mg	24	149.8	-6.97	5.65	0.194
		Vals 80 mg	22	153.0	-11.07	9.75	0.039
		Vals 160 mg	24	155.1	-11.85	10.53	0.014@
11	6	Placebo	111	152.3	-0.64		
		Vals 20 mg	105	151.3	-8.36	7.72	0.0001&
		Vals 40 mg	113	150.5	-8.61	7.97	0.0001&
		Vals 80 mg	112	154.2	-10.03	9.39	0.0001&
17	8	Placebo	57	153.4	-1.93		
		Vals 80 mg,fasted	119	152.9	-7.81	5.88	0.009$
		Vals 80 mg,fed	109	155.3	-5.15	3.22	0.156$
23	8	Placebo	141	171.6	-9.5		
		Vals 40 mg	145	174.9	-12.2	2.7	0.168
		Vals 80 mg	139	173.5	-12.8	3.3	0.105
		Vals 160 mg	139	172.7	-12.6	3.1	0.094
		Lisin 10 mg	73	172.1	-16.5	7.0	0.003&
31	8	Placebo	145	152.5	-1.33		
		Vals 20 mg	139	151.6	-6.33	5.00	0.002#
		Vals 80 mg	148	151.9	-8.60	7.27	<0.001#
		Vals 160 mg	147	150.0	-8.96	7.63	<0.001#
		Vals 320 mg	150	150.9	-10.59	9.26	<0.001#
51	8	Placebo	142	161.0	-7.7		
		Vals 80 mg	136	161.8	-11.8	4.1	0.004$
		Enal 20 mg	69	161.5	-11.9	4.2	0.013$

*Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.
+ p-value for comparison versus placebo.
@ Significant at α=0.015, using Dunnett's MC procedure.
& Significant at α=0.019, using Dunnett's MC procedure.
$ Significant at α=0.05.
# Significant at α=0.0125, using Bonferroni's MC procedure.

Table 4. Mean change from baseline at the end of studies in SuSBP (study 10) and in SiSBP (studies 11, 17, 23, 31, and 51)

Study#	Week	Treatment	N	BLine	Adj Mean Change	Drug Effect*	p-value+
10	4	Placebo	24	155.8	-1.88		
		Vals 10 mg	23	156.5	-5.94	4.06	).333
		Vals 40 mg	22	148.8	-7.78	5.90	).176
		Vals 80 mg	22	153.0	-10.83	8.95	).051
		Vals 160 mg	23	154.1	-12.30	10.42	).013@
11	6	Placebo	105	151.9	-0.98		
		Vals 20 mg	102	151.2	-8.41	7.43	).0001&
		Vals 40 mg	107	150.1	-10.07	9.09	).0001&
		Vals 80 mg	110	154.1	-9.67	8.69	0.0001&
17	8	Placebo	48	152.3	-0.56		
		Vals 80 mg,fasted	108	151.9	-8.65	8.09	0.001$
		Vals 80 mg,Fed	102	153.8	-4.92	4.36	0.078
23	8	Placebo	138	171.8	-9.4		
		Vals 40 mg	141	174.6	-13.0	3.6	0.083
		Vals 80 mg	135	173.3	-13.0	3.6	0.080
		Vals 160 mg	135	172.2	-12.8	3.4	0.110
		Lisin 10 mg	69	171.8	-16.2	6.8	0.008&
31	8	Placebo	135	152.2	-1.65		
		Vals 20 mg	132	151.6	-6.36	4.71	0.004$
		Vals 80 mg	146	151.7	-8.57	6.88	<0.001$
		Vals 160 mg	139	149.9	-9.66	8.01	<0.001$
		Vals 320 mg	145	150.7	-10.94	9.29	<0.001$
51	8	Placebo	138	161.0	-7.7		
		Vals 80 mg	134	161.7	-12.3	4.6	0.001$
		Enal 20 mg	66	161.0	-12.1	4.4	0.014$

*Drug effect=(Adj. mean change for drug - Adj. mean change for placebo), reported as a positive value.
+ p-value for comparison versus placebo.
@ Significant at α=0.015, using Dunnett's MC procedure.
& Significant at α=0.019, using Dunnett's MC procedure.
$ Significant at α=0.05.
# Significant at α=0.0125, using Bonferroni's MC procedure.

Table 5. Changes by gender in SuDBP (study 10) and in SiDBP (studies 11, 17, 23, 31, and 51) at endpoint

PROTOCOL	Treatment	N	Baseline	Change from Baseline	Drug Effect*
	----Males----				
10	Placebo	12	101.92	-3.53	
10	Vals 10 mg	19	102.56	-4.84	1.31
10	Vals 40 mg	16	101.73	-7.42	3.89
10	Vals 80 mg	18	100.44	-7.24	3.71
10	Vals 160 mg	12	102.39	-8.06	4.53
	----Females----				
10	Placebo	13	101.49	-5.54	
10	Vals 10 mg	6	102.78	-7.22	1.68
10	Vals 40 mg	8	102.08	-5.25	-0.29
10	Vals 80 mg	4	102.00	-9.00	3.46
10	Vals 160 mg	12	99.67	-10.67	5.13
	----Males----				
11	Placebo	74	100.13	-3.67	
11	Vals 20 mg	75	100.43	-7.21	3.54
11	Vals 40 mg	76	100.57	-8.90	5.23
11	Vals 80 mg	86	100.33	-7.88	4.21
	----Females----				
11	Placebo	37	100.98	-6.51	
11	Vals 20 mg	30	99.50	-8.21	1.70
11	Vals 40 mg	37	100.08	-7.59	1.08
11	Vals 80 mg	26	100.22	-8.47	1.96
	----Males----				
17	Placebo	32	103.98	-2.81	
17	Vals 80 mg,fasted	73	103.78	-7.62	4.81
17	Vals 80 mg,fed	70	103.50	-6.04	3.23

Table 5 (continued)

PROTOCOL	Treatment	N	Baseline	Change from Baseline	Drug Effect*
	----Females----				
17	Placebo	25	102.45	-4.62	
17	Vals 80 mg,fasted	46	103.74	-10.03	5.41
17	Vals 80 mg,fed	39	105.08	-8.34	3.72
	----Males----				
23	Placebo	49	101.01	-7.47	
23	Vals 40 mg	46	100.96	-10.17	2.70
23	Vals 80 mg	48	100.11	-9.79	2.32
23	Vals 160 mg	54	101.48	-12.73	5.26
23	lisin 10 mg	24	102.96	-12.81	5.34
	----Females----				
23	Placebo	95	101.01	-9.48	
23	Vals 40 mg	101	100.57	-10.16	0.68
23	Vals 80 mg	94	101.80	-11.86	2.38
23	Vals 160 mg	87	101.92	-12.30	2.82
23	lisin 10 mg	50	100.95	-12.01	2.53
	----Males----				
31	Placebo	96	100.95	-2.22	
31	Vals 20 mg	92	100.58	-4.49	2.27
31	Vals 80 mg	87	100.86	-6.20	3.98
31	Vals 160 mg	93	101.69	-6.87	4.65
31	Vals 320 mg	95	101.38	-8.40	6.18
	----Females----				
31	Placebo	49	100.38	-2.40	
31	Vals 20 mg	47	101.11	-5.95	3.55
31	Vals 80 mg	61	100.94	-9.04	6.64
31	Vals 160 mg	54	100.90	-9.17	6.77
31	Vals 320 mg	55	101.21	-9.08	6.68

Table 5 (continued)

PROTOCOL	Treatment	N	Baseline	Change from Baseline	Drug Effect*
	----Males----				
51	Placebo	76	101.94	-4.89	
51	Vals 80 mg	64	101.76	-8.73	3.84
51	Enal 20 mg	40	102.30	-7.46	2.57
	----Females----				
51	Placebo	66	101.66	-4.10	
51	Vals 80 mg	72	100.74	-10.23	6.13
51	Enal 20 mg	29	101.98	-12.12	8.02

*Drug effect=(-1)x(Mean change for drug - Mean change for placebo).

Table 6. Changes by race in SuDBP (study 10) and in SiDBP (studies 17 and 31) at endpoint

PROT	Race	Treatment	N	BasLn	Change From BasLn	Drug Effect*
10	Black	Placebo	2	98.33	-4.67	
10	Black	Vals 10 mg	1	103.33	-8.00	3.33
10	Black	Vals 40 mg	2	98.67	-4.00	-0.67
10	Black	Vals 80 mg	3	106.89	-13.11	8.44
10	Black	Vals 160 mg	2	103.00	-3.00	-1.67
10	Non-Black	Placebo	23	101.99	-4.57	
10	Non-Black	Vals 10 mg	24	102.58	-5.31	0.74
10	Non-Black	Vals 40 mg	22	102.12	-6.94	2.37
10	Non-Black	Vals 80 mg	19	99.78	-6.68	2.11
10	Non-Black	Vals 160 mg	22	100.85	-9.94	5.37
17	Black	Placebo	11	104.89	-2.03	
17	Black	Vals 80 mg,fasted	20	104.17	-6.13	4.10
17	Black	Vals 80 mg,fed	24	103.84	-6.53	4.50
17	Non-Black	Placebo	46	102.94	-3.98	
17	Non-Black	Vals 80 mg,fasted	99	103.69	-9.04	5.06
17	Non-Black	Vals 80 mg,fed	85	104.19	-6.96	2.98
31	Black	Placebo	19	102.70	1.30	
31	Black	Vals 20 mg	12	103.67	-1.11	2.41
31	Black	Vals 80 mg	18	102.56	-5.81	7.11
31	Black	Vals 160 mg	25	101.41	-6.61	7.91
31	Black	Vals 320 mg	17	100.27	-5.53	6.83
31	Non-Black	Placebo	126	100.47	-2.82	
31	Non-Black	Vals 20 mg	127	100.48	-5.35	2.53
31	Non-Black	Vals 80 mg	130	100.65	-7.59	4.77
31	Non-Black	Vals 160 mg	122	101.40	-7.94	5.12
31	Non-Black	Vals 320 mg	133	101.45	-9.05	6.11

*Drug effect=(-1)x(Mean change for drug - Mean change for placebo).

Table 7. The sponsor's analysis for the ABPM averages over a 24-hour period in study 31.

Least Squares Mean Change from Baseline Over 24 Hours In Ambulatory Blood Pressure (Placebo-Subtracted)					
		Diastolic		Systolic	
Treatment	N	Mean Change From Baseline (mmHg)	p-value	Mean Change From Baseline (mmHg)	p-value
Placebo	42	-	-	-	-
Valsartan 20 mg	44	-3.5	0.010*	-5.9	0.008*
Valsartan 30 mg	44	-6.6	<0.001*	-11.0	<0.001*
Valsartan 160 mg	41	-5.5	<0.001*	-10.6	<0.001*
Valsartan 320 mg	45	-8.4	<0.001*	-14.3	<0.001*

*Statistically significant ($p<0.0125$) compared to placebo based on Bonferroni's procedure for multiple comparisons.
+The placebo effect was +0.7 mmHg for diastolic blood pressure and +1.0 mmHg for systolic blood pressure.

Table 8. The sponsor's repeated measures analysis of the ABPM data over a 24-hour period in study 31.

Repeated Measures Analysis Of Variance Results
For Mean Change From Baseline In Ambulatory Diastolic Blood Pressure At Visit 4
(All Randomized Patients At Centers Selected For ABP Monitoring)

Repeated Measures Analysis of Covariance

Source	d.f.	SS	MS	F	P-Value
Baseline	1	1583.16	1583.16	24.60	<0.001*
Center	8	547.78	68.47	1.06	0.391
Treatment	4	2707.74	676.94	10.52	<0.001*
Treatment-by-Baseline	4	381.52	95.38	1.48	0.210
Treatment-by-Center	32	1894.77	59.21	0.92	0.595
Main Plot Error	166	10684.05	64.36		
Daily Period	1	3.63	3.63	0.13	0.722
Treatment-by-Daily Period	4	101.09	25.27	0.89	0.472
Sub-Plot Error	211	6005.41	28.46		
Total (Corrected)	431	25137.04			

Main Plot

Treatment	LS Mean	S.E.
Placebo	0.59	1.01
Valsartan 20mg	-2.95	0.94
Valsartan 80mg	-5.79	0.97
Valsartan 160mg	-4.68	1.00
Valsartan 320mg	-7.87	0.96

Comparison	Estimate	S.E.	P-Value
20mg vs. P	-3.54	1.38	0.011**
80mg vs. P	-6.38	1.39	<0.001**
160mg vs. P	-5.27	1.42	<0.001**
320mg vs. P	-8.46	1.39	<0.001**

Sub Plot

Period/Treatment	LS Mean	S.E.
Daytime		
Placebo	0.88	0.88
Valsartan 20mg	-2.42	0.84
Valsartan 80mg	-5.86	0.85
Valsartan 160mg	-5.44	0.88
Valsartan 320mg	-7.03	0.84
Nighttime		
Placebo	-0.01	0.88
Valsartan 20mg	-3.81	0.84
Valsartan 80mg	-4.89	0.85
Valsartan 160mg	-4.50	0.88
Valsartan 320mg	-7.59	0.84

Comparison	Estimate	S.E.	P-Value
Day: 20mg vs. P	-3.30	1.21	0.007**
Day: 80mg vs. P	-6.74	1.23	<0.001**
Day: 160mg vs. P	-6.32	1.25	<0.001**
Day: 320mg vs. P	-7.91	1.22	<0.001**
Ngt: 20mg vs. P	-3.80	1.21	0.002**
Ngt: 80mg vs. P	-4.88	1.23	<0.001**
Ngt: 160mg vs. P	-4.49	1.25	<0.001**
Ngt: 320mg vs. P	-7.58	1.22	<0.001**
Placebo: Day vs. Ngt	0.88	1.16	0.448
20mg: Day vs. Ngt	1.39	1.14	0.223
80mg: Day vs. Ngt	-0.98	1.14	0.392
160mg: Day vs. Ngt	-0.94	1.18	0.426
320mg: Day vs. Ngt	0.56	1.12	0.621
Day vs. Night	0.18	0.51	0.722

Note: LS means are SAS Least Squares Means. To achieve identifiability, all effects involving baseline were deleted from the sub-plot analysis model. (The resulting sub-plot model included center, treatment, daily period, treatment-by-center interaction, treatment-by-daily period interaction, and main-plot error.)

All sums of squares (SS) are SAS Type III SS; however, main plot SS are not adjusted for sub-plot effects. Main plot LS mean standard errors (S.E.) are from the ANCOVA of daily means (using equal weights of 1/2 for night and day means). Main plot SS are from the ANCOVA of daily means x $\sqrt{2}$; the total main plot Type I SS in this ANCOVA are the same as the total main plot Type I SS in the sub-plot analysis.

Mean change from baseline was calculated by subtracting Visit 2 means for day and night, respectively, from the Visit 4 means for day and night.

Statistical significance levels: ** indicates p<0.0125, * indicates p< 0.050.

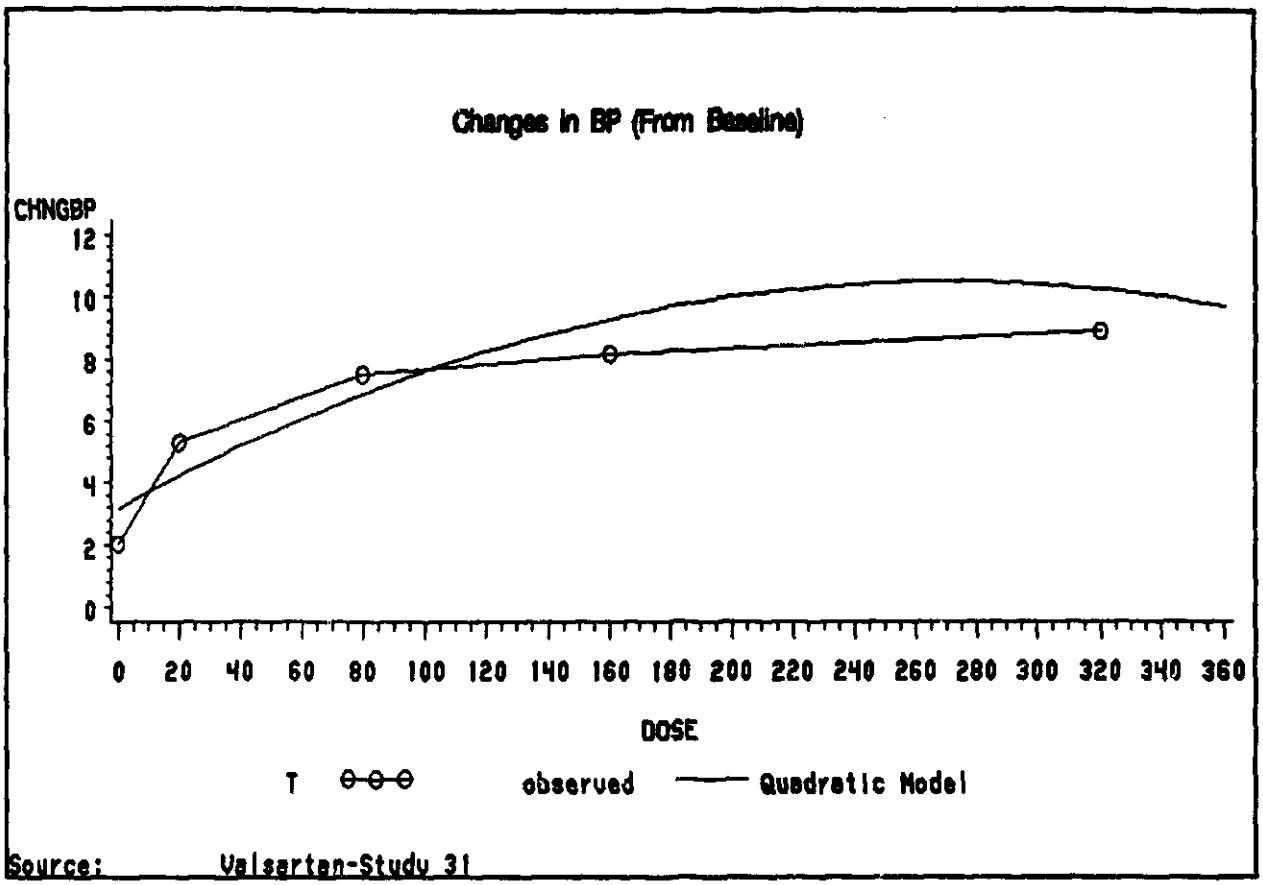


Figure 1. The observed changes from baseline in SiDBP and the estimated quadratic model for dose reponse model.

Model: Change=3.186 + 0.054*dose - 0.0001*(dose)^2

RMSE=1.3390 .

The dose levels studied were 0, 20, 80, 160, and 320 mg.

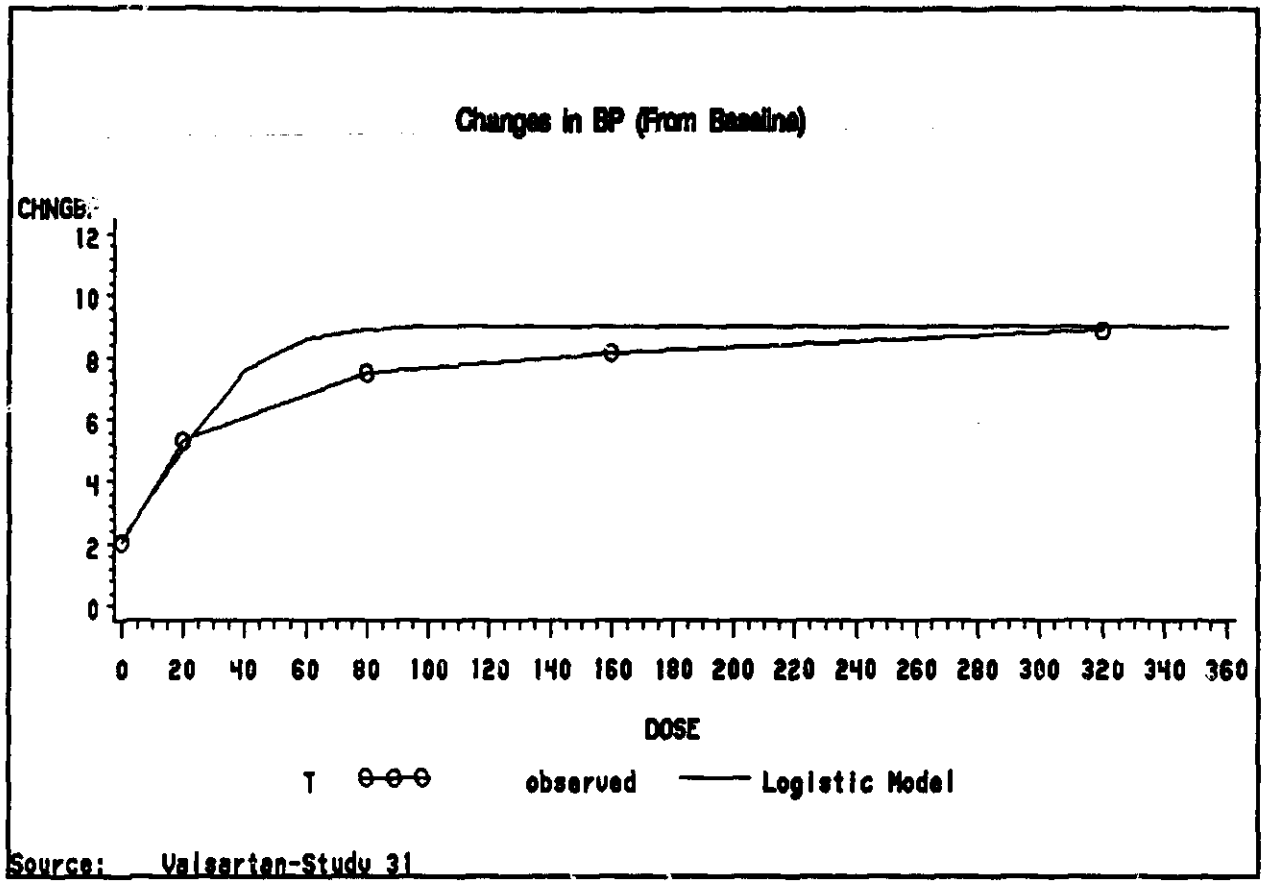


Figure 2. The observed changes from baseline in SiDBP and the estimated logistic model for dose reponse.

Model : Change= 9/[1 + 3.2.Exp(-(0.07)dose)].

RMSE=0.8295.

The dose levels studied were 0, 20, 80, 160, and 320 mg.

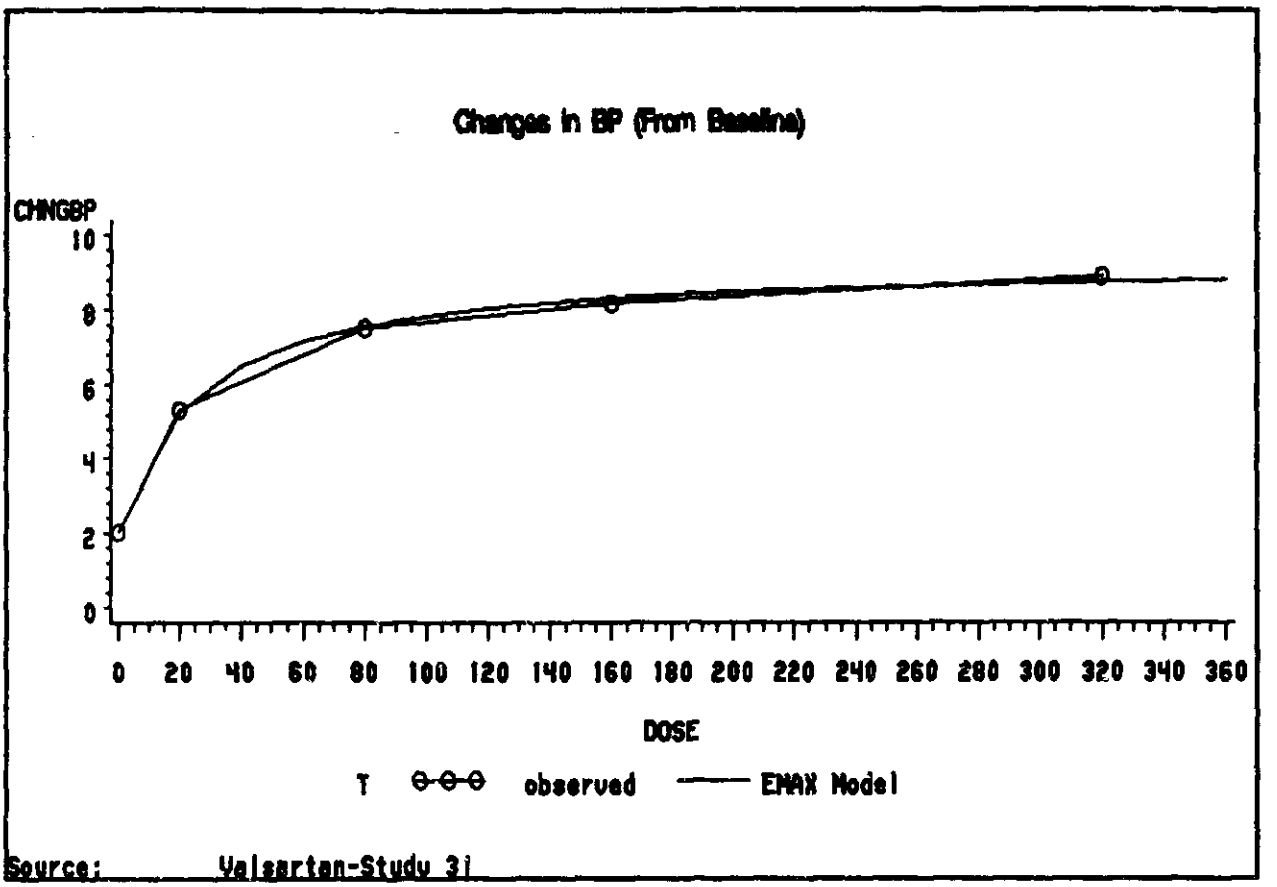


Figure 3. The observed changes from baseline in SiDBP and the estimated E_{MAX} model (adjusted for baseline value) for dose reponse.

Model : Change= 2.05 + (7.22).dose/(25.2 +dose).

RMSE=0.1431.

The dose levels studied were 0, 20, 80, 160, and 320 mg.

Visit 2 and Visit 4 24-hour mean ambulatory diastolic blood pressure (ABP) versus Visit 4 post-dosing hour endpoint - by visit and treatment group (all randomized patients at centers selected for ABP monitoring)
Visit = 2

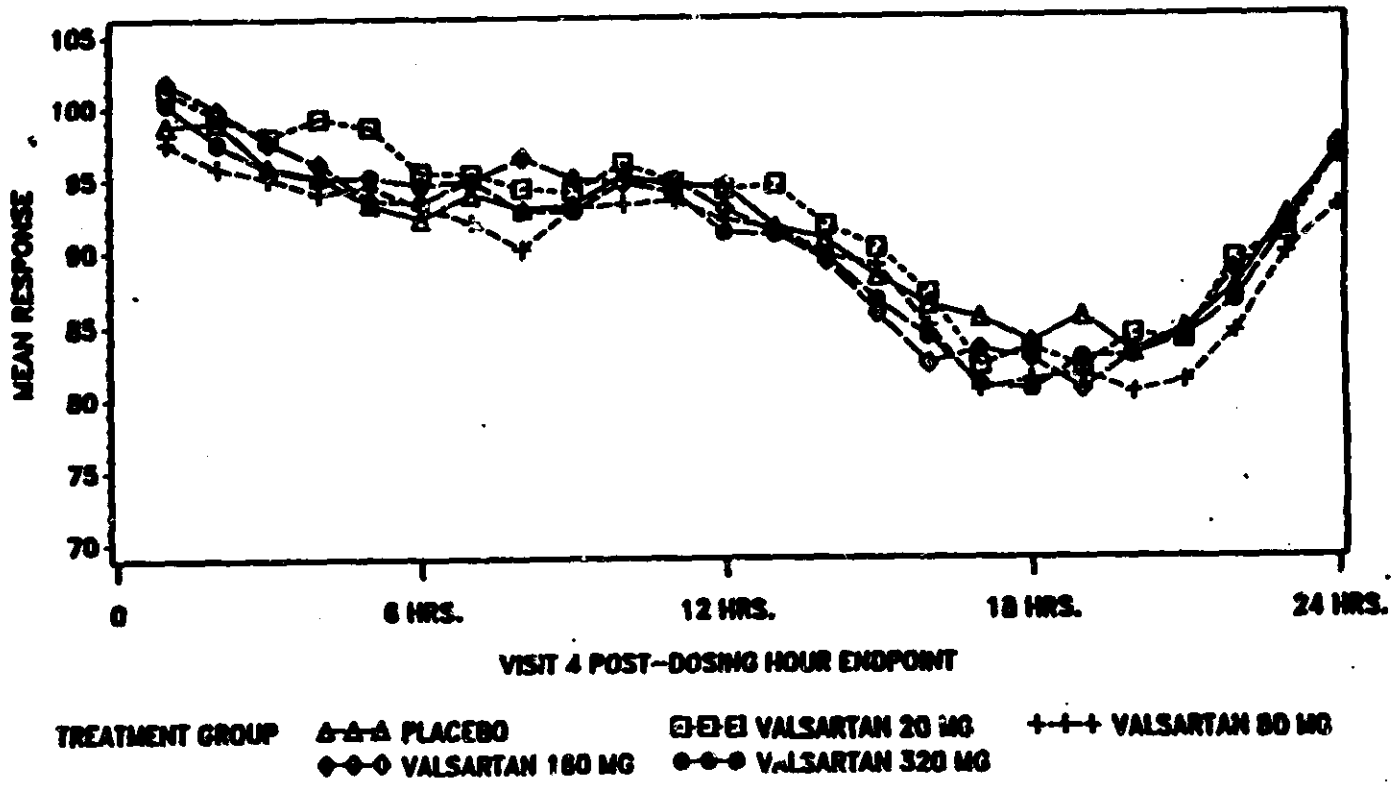


Figure 4. The sponsor's plot of the ABPM averages over a 24-hour period at baseline visit in study 31.

Visit 2 and Visit 4 24-hour mean ambulatory diastolic blood pressure (ABP) versus Visit 4 post-dosing hour endpoint - by visit and treatment group (all randomized patients at conters selected for ABP monitoring)
Visit = 4

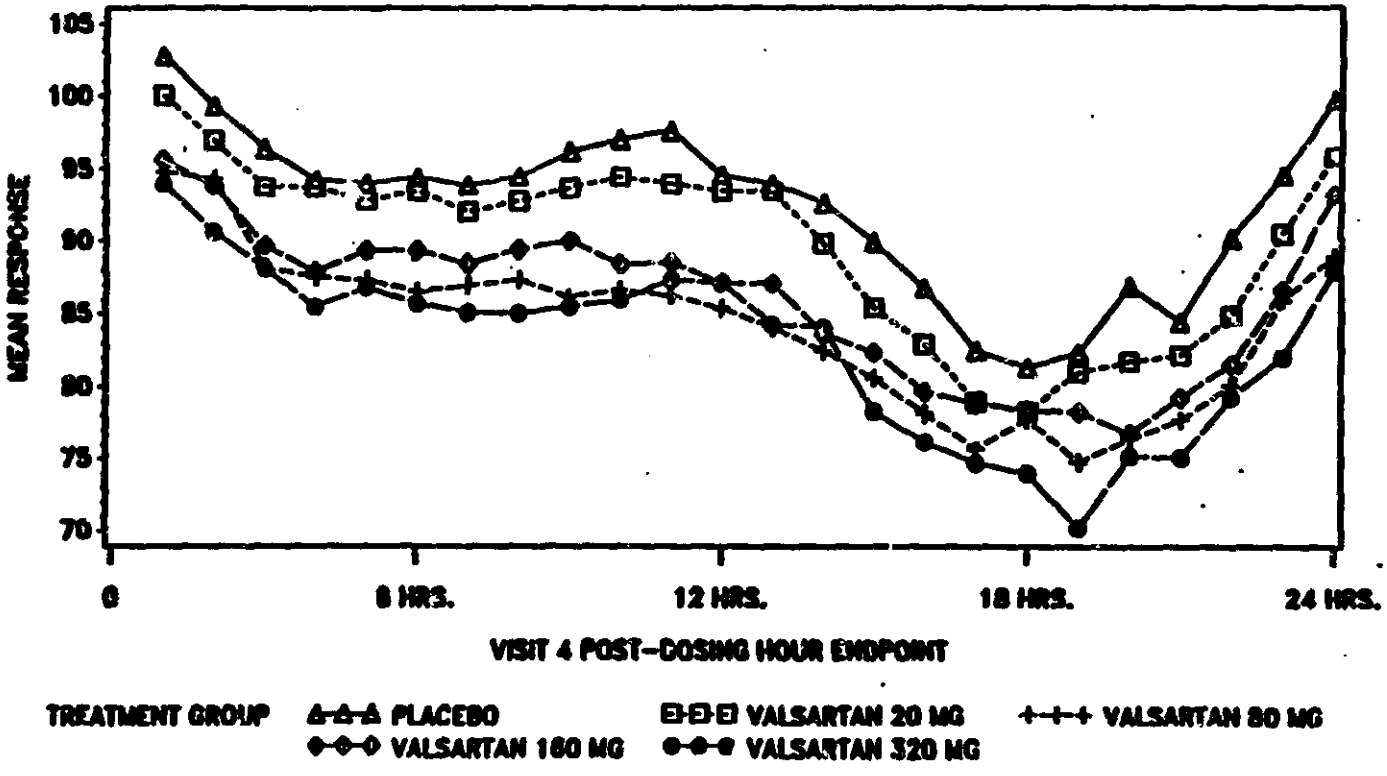


Figure 5. The sponsor's plot of the ABPM averages over a 24-hour period after treatment visit in study 31.

NOV 13 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 20-665 (Amendment-BC)
DRUG: valsartan (Diovan®) Capsules, 80 & 160mg
SPONSOR: Ciba Geigy
TYPE OF SUBMISSION: In-Vitro Dissolution: Response to FDA Comments
DATE OF SUBMISSION: 10/30/96
REVIEWER: Ameeta Parekh, Ph.D.

BACKGROUND: The original review of the clinical pharmacology and biopharmaceutics section of this NDA has been undertaken by OCPB (reviewer Dr. Zia-Amirhosseini). Based on the in-vitro dissolution data available, it was concluded that more than of the label dissolved at 30 minutes using USP basket at 100 rpm in 1000 ml pH 6.8 phosphate buffer. The dissolution specification however, was recommended to be not less than (Q) ... at 45 minutes (rather than 30 minutes) because all the stability data was collected at 45 minutes. The sponsor is requesting reconsideration of this issue and has proposed Q= in 30 minutes with the contention that

a) In negotiations with the Irish health authority, the firm has reached an agreement to tighten the dissolution specification to Q= at 30 minutes. The firm also contends that this is more stringent than Q= at 45 minutes. In the interest of international harmonization, the FDA is requested to consider Q= at 30 minutes.

b) The firm has provided a publication from PharmEuropa Vol 8, #3,, September 1996, which indicates specification of at least (Q=) of the active ingredient to dissolve within 45 minutes.

COMMENTS:

1. The data provided in the NDA for clinical and to-be-marketed capsules, 80 and 160 mg, reveal more than dissolution at 45 minutes for all capsules. The mean % dissolved exceeded (SD<5) at 45 minutes. The individual capsule in-vitro dissolution at 30 minutes for clinical and to-be-marketed lots showed that : dissolved (averages >), see attachment. In fact, the average dissolution at 15 minutes also exceeded

2. Although the data for valsartan capsules support a specification o. ... in 30 minutes, the original review widened it to 45 minutes as the stability data was obtained at this time point. Although the current data supports ... dissolution, in the interim, the firm's proposed specification of at 30 minutes may be accepted (instead of the originally recommended in 45 minutes).

3. The interim (draft) guidance for industry on Dissolution Testing of Immediate Release Solid Oral Dosage Forms (released to Trade Association on July 10, 1996), suggests a single point dissolution specification of Q=80% in 60 minutes or less as a quality control test. Based on the available data and discussions with Drs. Wolters and Malinowski, a tentative specification of Q= n 30 minutes may be recommended. However, since all clinical and to-be-marketed data supports Q n 30 minutes, a tighter final specification may be set based on review of stability data on three production batches.

RECOMMENDATION:
The proposed revised specification recommended by the firm (Q of in 30 minutes) should be accepted as an interim specification. Final specification will be set upon review of additional data on stability of three commercial lots.

Ameeta Parekh 11/13/96

Ameeta Parekh, Ph.D.
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. : 11/13/1996.

cc: NDA 20-665, HFD-110, HFD-860 (Malinowski, Parekh), HFD-870 (Drug, Chron, Reviewer files, Clarence Bott PKLN Rm. 13B-31), HFD-340 (Vish)

K. Bongiovanni

OCT 22 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 20-665 (Amendment-BB)
DRUG: valsartan (Diovan®)
SPONSOR: Ciba Geigy
TYPE OF SUBMISSION: In-Vitro Metabolism: Response to Comments
DATE OF SUBMISSION: 8/19/96
REVIEWER: Ameeta Parekh, Ph.D.

BACKGROUND: The original review of the clinical pharmacology and biopharmaceutics section of this NDA has been undertaken by OCPB (reviewer Dr. Zia-Amirhosseini). It was determined that approx. 13% and 86% of the orally administered drug (as solution) was recovered in urine and feces respectively (over 7 days). Biliary excretion was the major drug elimination route. Of the recovered amount, 80% was accounted for by unchanged drug. Thus 20% of administered dose (absolute bioavailability of solution:39%) or 50% of bioavailable dose is metabolized. A metabolite derived from hydroxylation of valsartan (valeryl 4-hydroxy valsartan) constituted about 23% of the bioavailable dose (9% of administered dose). This metabolite was determined to be pharmacologically inactive. The enzymes responsible for metabolism of valsartan were not determined at the time of this review and this was conveyed to the firm. OCPB had also recommended that the firm determine valsartan's CYP450 inhibition potential as a phase IV study.

In response to this request, the firm justified that valsartan apparently has a low affinity for cytochrome P450 and is metabolized only to a small percentage, therefore, identification of metabolizing enzyme pathways may not be clinically critical as far as changes in valsartan plasma levels (due to coadministered drugs) are concerned. In reference to valsartan's effect on CYP450 is concerned, the firm referred to the non-clinically significant interactions observed with warfarin (substrate for 2C9, 2C10 and 3A4; however pharmacokinetics of warfarin were not determined), cimetidine (substrate for 3A and 2C systems; cimetidine however, was administered 1 hour before valsartan administration) and indomethacin (substrate for 2C9). Firm stated that in 5 extensive debrisoquin (CYP 2D6) metabolizers, the ratio of hydroxy metabolite/parent drug was similar to 1 subject with less extensive debrisoquin metabolism. Based on these findings, the firm contends that the major isozyme families (CYP 2A, 2C and 2D) show no signficant interaction potential.

Sponsor's report on in-vitro metabolism was obtained from the reviewing pharmacologist and discussed with Drs. Collins (OTR) and Rahman (OCPB).

COMMENTS:

1. Minor phase I metabolism was detected in liver S12 fractions of mouse, rat, rabbit, dog, marmoset and man. The metabolism studies used a single human liver (a panel of livers is generally recommended); metabolism information is not available in c-DNA expressed system.

2. Dr. Jerry Collins' comments are attached. In summary, there do not seem to be any major concerns related to blood levels of valsartan when co-administered with other drugs specially since a major fraction of absorbed drug is excreted unchanged. The issue related to valsartan's metabolic enzyme inhibitory potential is still not fully characterized. Interaction studies in-vivo were conducted with HCTZ, furosemide, amlodipine, atenolol, digoxin, warfarin, cimetidine, indomethacin and glibenclamide. The following observations can be made from these studies:

- HCTZ: 28% and 26% decrease in AUC and Cmax resp. of HCTZ; no effect on valsartan; pharmacodynamics not examined; (decrease in HCTZ levels not related to metabolism as HCTZ minimally metabolized),
- Furosemide: 37% and 28% decrease in Cmax and AUC of furosemide; no effect on valsartan; larger decrease in SBP; (Furosemide glucuronide is the major metabolite. Acyl glucuronide appears to be the major conjugation pathway for valsartan but this is based on animal data),
- Amlodipine: No effect; pharmacodynamics not examined, (Although amlodipine is extensively metabolized, there was no change in pk when it was coadministered with valsartan, amlodipine extensively metabolized),
- Atenolol: No effect on pk; larger decrease in SBPand DBP, (Coadministration with atenolol has no impact on pharmacokinetics of both drugs however, atenolol is not metabolized),
- Digoxin: Effect on digoxin appeared negligible (dig. Drug levels were close to LOQ); no effect on valsartan; pharmacodynamics not examined,
- Warfarin: Pk of warfarin not determined; no effect on valsartan; no change on coagulation parameters,
- Cimetidine: Administration of valsartan 1 hour after cimetidine: no effect on pk of cimetidine (possibly because cimetidine was administered 1 hour before valsartan administration); 17% and 49% increase in AUC and Cmax resp. of valsartan; pharmacodynamics not examined
- Indomethacin: No effect on pk; pharmacodynamics as safety precaution,
- Glibenclamide: No effect on pk of glibenclamide; about 26% decrease in AUC and Cmax of valsartan; no change in pharmacodynamics; (major hydroxy metabolites) .

3. Note that the potential for a drug to inhibit metabolism of other drugs may be present not only for drugs metabolized by same pathway(s) but also for entirely different pathways. Impact of valsartan on metabolism of other drugs is still not fully characterized, however, losartan (another angiotensin II receptor antagonist which has

an active metabolite that has structural similarity to valsartan) did not interact with pharmacokinetics or dynamics of warfarin.

RECOMMENDATION:

Although a major fraction of administered valsartan dose is recovered as unchanged drug and is therefore minimally affected (in-vivo) by co-administration of other drugs, it's effect on metabolism of other drugs has not been fully characterized. Further in-vitro metabolism data to characterize its potential for affecting concentrations of other co-administered drugs is suggested. If such studies are undertaken, it is recommended that a panel of livers be used and metabolism information be derived from c-DNA expressed systems.

Ameeta Parekh

Ameeta Parekh, Ph.D. 10/22/96
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. : 10/22/96.

cc: NDA 20-665, HFD-110, HFD-860 (Malinowski, Parekh), HFD-870 (Drug, Chron, Reviewer files, Clarence Bott PKLN Rm. 13B-31), HFD-340 (Vish)

JUL 3 1996

BIOPHARMACEUTICS/PHARMACOKINETICS REVIEW

NDA: 20-665
SPONSOR: Ciba Pharmaceuticals Division
DRUG: Valsartan (CGP 48933: S-enantiomer of valsartan)
DOSAGE STRENGTHS AND FORM: 80 and 160 mg Capsule
DOSING REGIMEN: 80 or 160 mg per day
CLASSIFICATION: Antihypertensive (1S)
TYPE OF SUBMISSION: New Molecular Entity
DATES OF SUBMISSION: 12/28/95, 3/8/96, 3/22/96, 4/3/96, 4/22/96, 5/7/96, 5/29/96, 6/24/96
REVIEWER: Parnian Zia-Amirhosseini, Ph. D. (Consulted Raymond Miller,Ph.D., for review of the population PK and PD)

Terms and Abbreviations:

ACE = angiotensin converting enzyme
AUC = area under the curve
CI = confidence interval
PD = pharmacodynamic
PK = pharmacokinetic
PRA = plasma renin activity
RAS = renin-angiotensin system

SYNOPSIS:

Valsartan is an angiotensin II receptor (AT1) antagonist intended for treatment of hypertension. In this sense it is similar to losartan, Merck's approved angiotensin II receptor antagonist. Valsartan is a chiral molecule, but only the S-enantiomer will be marketed. The sponsor intends to market 80 and 160 mg capsules. The recommended dosing is once daily administration of 80 mg or 160 mg capsules.

Valsartan reaches its maximal plasma concentration in approximately two hours post-dosing. The average absolute bioavailability of an 80 mg valsartan capsule is and that of an 80 mg buffered solution is . The low absolute bioavailability of valsartan is most likely due to its limited solubility in solutions with low pH (e.g., gastric fluid). Valsartan has a low hepatic extraction ratio (ER=0.02). Seventy percent of an administered dose of valsartan is recovered in stool and 10% of the dose in urine as unchanged drug. Presence of food decreases both the rate and extent of absorption of valsartan (53% decrease in C_{max} and 41% decrease in $AUC_{0-\infty}$). The mean decrease in diastolic blood pressure caused by administration of valsartan under fed and fasted conditions differed by 1.8 mm Hg. The clinical significance of this difference is not clear at this time. Dr. Ganley will be examining this issue further.

The steady state volume of distribution of valsartan after intravenous administration is small (16.9 $\pm$ 6.9 L), suggesting that valsartan does not distribute into tissues extensively. Valsartan does not distribute significantly into red blood cells ($C_b \approx 0.6 C_p$). Approximately 95% of valsartan binds to plasma proteins; most of this binding is to albumin.

Following administration of an 80 mg oral solution of ^{14}C labeled drug, 90% of the radioactivity measured in plasma was identified as unchanged drug. During the four days following valsartan administration, approximately 93% of the radioactivity was recovered in urine and fecal samples. After seven days, approximately complete recovery (99%) of the

administered dose was obtained. Approximately 13% of the administered radioactivity was recovered in urine and 86% was recovered in the feces. Eighty percent of the administered dose was recovered in urine and fecal samples as unchanged drug. Thus, at most 20% of an administered (or 50% of the bioavailable) dose of valsartan is metabolized following administration of a buffered solution of valsartan. An identified metabolite (M1) which results from hydroxylation of valsartan, is the major metabolite and constitutes 23.3% of the bioavailable dose. M1 is pharmacologically inactive. The major route of elimination for valsartan and its metabolites appears to be biliary excretion (approximately 66% of the bioavailable dose). The enzyme system(s) responsible for metabolism of valsartan has(ve) not been identified. The effect of valsartan on CYP 450 enzyme system has not been investigated. However, the lack of any effect of co-administration of valsartan and warfarin (discussed on p. 3) on the anticoagulant properties of warfarin suggests that valsartan (at therapeutic levels) is not a CYP 2C9 inhibitor.

Valsartan exhibits approximately linear pharmacokinetics over the dosing range of 80-320 mg per day. Valsartan does not accumulate appreciably in plasma upon multiple dosing. Valsartan has a mean total clearance of 2.2 L/h, renal clearance of 0.6 L/h, and half-life of 6.2 h. Valsartan pharmacokinetics does not differ between males and females. Exposure (as measured by AUC_{0-inf}) to drug is higher (by 70%) in the elderly than the younger population. Valsartan also exhibits a longer average half-life (by 35%) in the elderly than in the young. The C_{max} and AUC_{inf} values for valsartan were not statistically significantly different among four groups of volunteers with varying renal function (as measured by creatinine clearance). No correlation was observed between exposure to valsartan (as measured by AUC_{0-48}) and creatinine clearance values. On average, patients with mild or moderate liver disease had two times higher exposure (as measured by AUC values) to valsartan compared to healthy volunteers (matched by age, sex, and weight). Intra-subject variability is about 20-34% for valsartan C_{max} and AUC. The average (from several studies) overall variability is 42% (range) for C_{max} and 50% (range of) for AUC. The inter-subject variability computed from the population PK analyses of sparse data collected from patients is 47% for CL and 69% for volume of distribution of valsartan.

In healthy volunteers, valsartan significantly decreased systolic blood pressure relative to baseline values, caused a small decrease in diastolic blood pressure, and had no effect on heart rate even under physical stress conditions. Sparse concentration-effect data (at steady state) from five different trials performed in hypertensive patients with a dose range of 10-320 mg per day were pooled and fitted to an Emax model. **These data suggest that the concentration-effect relationship for valsartan is flat over a wide concentration range (400-3600 ng/ml).** The mean Emax value is 4.58 $\pm$ 0.73 mm Hg and the EC50 value is 36.10 $\pm$ 29.40 ng/ml. It is noteworthy that 82% of the concentration values utilized in this data set were greater than 40 ng/ml and the majority of the other 18% were below the quantitation limit and given a set value of 25 ng/ml. Thus, the EC50 value cannot be accurately estimated based on this data set, but it is likely that it will be a small number. During the first six hours post-dosing, the majority of the examined patients had plasma valsartan concentrations greater than or equal to two times the reported mean EC50 values. Therefore, the majority of patients taking 80 mg of valsartan per day will have concentrations greater than the EC50 during the main portion of the dosing period (24 hours). **Thus, it is likely that the majority of patients will experience an effect on diastolic blood pressure**

close to the Emax, and that PK differences would not have a significant effect on the efficacy of valsartan at the proposed doses (80 or 160 mg per day). Even at a dose of 40 mg per day, valsartan would most likely be an effective antihypertensive agent.

Pharmacokinetic interaction studies were performed with amlodipine, digoxin, hydrochlorthiazide (HCTZ), furosemide, atenolol, warfarin, cimetidine, indomethacin, and glibenclamide. Cimetidine pre-administration causes a 49% increase in C_{max} and a 17% increase in AUC of valsartan. Co-administration of glibenclamide decreases the mean exposure to valsartan (as measured by AUC) by 26% and the mean C_{max} value by 27%. Co-administration of the other examined drugs does not influence the pharmacokinetic parameters of valsartan. Valsartan causes a decrease in the rate of absorption of (26% decrease in C_{max} and 13% decrease in T_{max}) and extent of exposure (by 28%) to HCTZ. Valsartan also decreases the rate of absorption (37% decrease in C_{max} and 33% decrease in T_{max}) of and extent of exposure (by 28%) to furosemide.

Pharmacodynamic interactions were examined with furosemide, atenolol, warfarin, and glibenclamide. The response (decrease in systolic blood pressure) following co-administration of valsartan and furosemide was greater than the response following administration of either drug alone. This effect appeared to be additive. The response (decrease in supine resting systolic and diastolic blood pressure) to the combined therapy of valsartan and atenolol was larger than the response to each drug alone during the first 8 hours post-dosing. Valsartan in combination with atenolol did not lower heart rate more than atenolol alone, which is consistent with valsartan having a negligible effect on heart rate. Valsartan did not affect the anti-coagulant properties of warfarin. Glibenclamide did not alter the pharmacodynamic properties of valsartan.

Two 80 mg clinical capsule formulations are bioequivalent to one 160 mg clinical and also one 160 mg final capsule formulations. The 160 mg clinical formulation and final formulations meet the FDA bioequivalence criteria for AUC but not for C_{max}. The 80 mg clinical capsule formulation has not been compared to the 80 mg final capsule formulation in vivo; however, these two products have similar dissolution profiles and a waiver for a bio-study can be granted. The dissolution specifications submitted by the sponsor are acceptable except that the dissolution specification should be set at Q= .. instead of the proposed value of

RECOMMENDATION:

This submission is acceptable provided the requested changes to the proposed labeling are made. Please forward the appropriate comments to the medical officer, the pharmacologist and the sponsor.

TABLE OF CONTENTS:

KINETIC STUDY	DOSE & OTHER INFO.	FORMULATION #, BATCH #. (European Nomenclature)	LOCATION OF STUDY (NDA Volume)
1) Protocol 16; PK after ^{14}C-labeled single dose in healthy volunteers	80 mg oral buffered solution (50 ml); N=6 M; age= 33-53	80 mg solution: Mo-20.8B-7, Mo-20.8B-10, Mo-20.8B-15	Switzerland (Vol. 1.42)
2) Protocol 47; Bioequivalence of clinical vs. final form. for 160 mg and 2x80 vs 160 mg clinical form. in healthy subjects	160 mg and 2x80 mg; single oral doses, N= 33 M; age=18-45	Clinical 80 mg: H-3576/E-15316 (Q897, 1052/5) Clinical 160 mg: H-3577/E-15177 (Q905, 1059/4) Final 160 mg: H-3785/E-15511 (Q960, T8/94/2)	U.S.A. (Vol. 1.44)
3) Protocol 15; Absolute Bioavailability of an oral capsule and an oral solution in healthy volunteers	80 mg capsule, 80 mg solution; 20 mg IV; single dose; N=12 M; age= 22-44	Clinical 80 mg capsule: H-3576 (Q897, 1052/1) Clinical 10 mg ampule: 16/309/1	Switzerland (Vol. 1.45)
4) Protocol 04; Angiot. II receptor blockade after single doses of valsartan in healthy volunteers	40 mg and 80 (2x40) mg single doses; N=6M; age=25-43	40 mg capsule: H3575 (Q891, 1051/1)	Switzerland/France (Vol. 1.680
5) Protocol 02; PK and PD after single dose in healthy volunteers	10, 30, 100, 300 mg oral doses of either 10mg or 100 mg capsule; N=10 M; age=22-51	10 mg capsule: Batch 1018/1 100 mg capsule; Batch 1019/1	Switzerland (Vol. 1.66)
6) Protocol 03; Pk & PD after single & multiple doses in healthy subjects	200 mg once daily oral admin. for 8 days; N=16 M;age=23-53	Clinical 40 mg capsule: H3575 (Q891, 1051/1) Clinical 80 mg capsule: H-3576 (Q897, 1052/1)	Switzerland (Vol. 1.67)
7) Protocol 30; valsartan PK/PD following angiot. II challenge in healthy volunteers (single & multiple doses) [BPK(US)1995/011]	80 mg once daily for 7 days; oral dose; N= 6M; age=21-28; 11 min long angiotensin II infusions given at different time points.	Clinical 80 mg capsule: H-3576, batch E-14940 angiot. II: H-2117k, E-14342	U.S.A (Vol. 1.64)
8) Protocol 48; Dose proportionality in healthy subjects (PK evaluation after single dose)	80, 2x80, 4x80 mg oral single doses ; N=13M; age=19-41	Clinical 80 mg: Form. H-3576, E-15411	U.S.A. (Vol. 1.46)
9) Protocol 06; Food Effect Study in healthy volunteers	2x80 mg singel oral dose; N=12M ; age=22-44	Clinical 80 mg capsule: H-3576 (Q897, 1052/1)	Britain (Vol. 1.50)
10)Protocol 17; Effect of Food on Efficacy in Mild to Moderately Hypertensive Patients	placebo fasted and fed; 80 mg valsartan per day fasted and fed	Clinical 80 mg capsule: H-3576, E-15059 (Q897)	U.S.A. (Vol. 1.92)
11) Protocol 13; Age effect after single oral dose admin. in healthy volunteers	80 mg single oral dose; N=24 (12 M, 12 F); age=young (18-27), old (65-89)	Clinical 80 mg capsule: H-3576 (Q897, 1052/1)	France (Vol. 1.49)
12) Protocol 12; Effect of Renal Function on PK	80 mg single oral dose; N=8F,11M ; age=26-75	Clinical 80 mg capsule: H-3576, E-15316	U.S.A. (Vol. 1.51)

) Protocol 46; PK in patients with impaired liver function and healthy volunteers	160 (2x80) mg oral single dose; N=12 patients, age=50-66 ;12 healthy subjects, age=50-67	Clinical 80 mg capsule: H-3576 (Q897, 1052/7)	Scotland (Vol. 1.52)
14) Population PK analysis of data from healthy volunteers and patients			foreign and domestic studies; analysis done in Switzerland (Vol. 1.47)
15) Population PD analysis in patients with mild to moderate hypertension	protocols 09, 10, 17, 27, 31		foreign and domestic studies; analysis done in U.S.A. (Vol. 1.47)
INTERACTION STUDIES	**DOSE & OTHER INFO.**	**FORMULATION #, BATCH #. (European Nomenclature)**	**LOCATION OF STUDY (NDA Volume)**
16) Protocol 37; PK interaction with amlodipine in healthy subjects	160 mg valsartan, 5 mg amlodipine tablet; single oral doses; N=12 M; age=20-46	Clinical 160 mg: H3577, E-15177 & E-15333	U.S.A. (Vol. 1.53)
17) Protocol 39; PK interaction with digoxin in healthy subjects	160 mg valsartan; 0.25 mg digoxin tablet, single oral doses; N=17M; age=20-41	Clinical 160 mg: H3577, E15177 (Q905; 1059/4)	U.S.A. (Vol. 1.54)
18) Protocol 07; PK interaction with hydrochlorthiazide in healthy subjects	160 mg valsartan; 25 mg HCTZ tablet; single oral doses; N=12 M; age=18-37	Clinical 80 mg: H3576 (Q897; 1052/2)	UK (Vol. 1.55)
19) Protocol 36; PK & PD interaction with furosemide	160 mg valsartan; 40 mg furosemide; single oral dose; N=12, age=23-52	Clinical 80 mg: H3576 (Q897, 1052/6)	Switzerland (Vol. 1.56)
20) Protocol 3[illegible]; PK & PD interaction with atenolol	160 mg valsartan, 100 mg atenolol, single oral doses, N-12 M, age-23-46	Clinical 80 mg: H3576 (Q897, 1052/6)	Switzerland (Vol. 1.57)
21) Protocol 40; Interaction with warfarin in healthy males	160 mg/day valsartan for 3 days, 160 mg/day valsartan for 7 days with 10 mg/day warfarin for first 3 days, 10 mg/day warfarin for 3 days, N=12 M; age=21-37	Clinical 80 mg: H3576 (Q897, 1052/2)	UK (Vol. 1.58)
22) Protocol 42; interaction with cimetidine in healthy volunteers	160 mg valsartan; 800 mg (4x200 mg) cimetidine one hour before valsartan; single oral doses; N=12M; age=18-50	Clinical 80 mg: H3576 (Q897, 1052/6)	Germany (Vol. 1.59)
23) Protocol 43; interaction with indomethacin in healthy volunteers	160 mg valsartan, 100 mg indomethacin, single oral doses, N=11 M, age=24-52	Clinical 80 mg: H3576 (Q897, 1052/6)	Germany (Vol. 1.60)
24) Protocol 52; interaction with glibenclamide in healthy volunteers	160 mg valsartan; 1.75 mg glibenclamide, single oral doses; N=12 M; age=24-52	Clinical 160 mg: H3577, E15177 (Q905; 1059/4)	Switzerland (Vol. 1.61)

IN VITRO STUDIES	LOCATION OF STUDY (NDA Volume)
1) BPK (US) 1994/023; Binding to serum and plasma proteins	U.S.A (Vol. 1.62)
2) BPK (F) 1995/010; binding to human serum proteins and effect of diclofenac, furosemide, & warfarin	France (Vol. 1.62)
3) DPD 1994/20; transprot of valsartan in the Caco-2 cell model	U.K. (Vol. 1.45)
4) Five assay development reports	domestic & foreign (Vol. 1.40)

LIST OF STUDIES THAT WERE NOT REVIEWED:

Four pharmacokinetic studies (protocols ANG-001, -002, -003, -007) that were performed with a tablet formulation intended for use in Japan .
Two pilot studies (protocols 14 and 53) in which IV doses of valsartan were administered to healthy volunteers.
A pharmacokinetic & pharmacodynamic (protocol 01) study in which a preliminary formulation of valsartan was administered.

SUMMARY OF PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERISTICS

I. Physicochemical Properties:

Valsartan has a chiral center (Fig. 1); however, only the S-enantiomer will be marketed. Inversion of the S-enantiomer to the R-enantiomer has not been observed (Report BPK(CH) 1995/072) in a plasma sample obtained from one healthy male volunteer who participated in an interaction study between valsartan and warfarin (Protocol 40). Valsartan is a white powder which is soluble in ethanol and methanol and slightly soluble in water (0.19 g/L @ 25°C). The drug has good solubility in solutions with a neutral to alkaline pH, but is poorly soluble in acidic media. The pKa values of valsartan in water @ 25°C are 4.73 for the tetrazole group (behaving as a weak acid) and 3.9 for the carboxylic acid group .

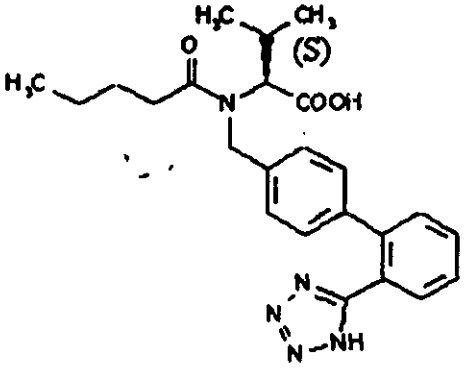


Fig. 1. Valsartan (S-enantiomer), molecular weight = 435.5 g/mole.

II. Metabolism and Distribution

1. Metabolic and Elimination Pathways

An ADME study (Protocol 16) was performed following oral administration of an 80 mg solution of radio-labeled valsartan. Valsartan was absorbed rapidly (median t_{max} = 1 h). Unchanged drug accounted for most of the radioactivity (mean AUC_{0-24} ratio = 90%) measured in plasma. During the four days following valsartan administration, approximately 93% of the radioactivity was recovered in urine and fecal samples. After 7 days, approximately complete recovery (99%) of the administered dose was obtained. Approximately 13% of the administered radioactivity was recovered in urine and 86% was recovered in the feces. 80.6% of the administered dose was recovered in urine and fecal samples as unchanged drug. At most 20% of an administered dose of valsartan is metabolized. This is equal to 50% of the bioavailable dose following administration of a buffered solution of valsartan.

39% of an orally administered dose of valsartan (in solution) is bioavailable (Protocol 15). This is equal to 31.2 mg for an 80 mg dose. The percent recoveries of the bioavailable dose of valsartan are presented in Table 1.

Table 1. The percent recoveries (mean values) of the bioavailable dose of valsartan after oral administration of an 80 mg radiolabeled dose (in solution).

Compound(s)	Excretion (% of the bioavailable dose)		
	Urine (0-48 h)	Feces (12-72 h)	Total
Unchanged Drug	25.0	35.5	59.6
Identified Metabolite (M1)	2.8	20.5	23.3
M1 plus Unidentified Metabolites	7.9	31.5	39.4*

*As indicated by the sponsor (see appendix), the metabolite balance is incomplete. This may be due to loss of radioactivity during sample processing and analysis. and/or not analyzing the later excreta portions with low levels of radioactivity.

As can be observed by the computed percent recoveries in stool samples (Table 1), the major route of elimination (66.1% of total) of valsartan and its metabolites is biliary excretion. Approximately 40% of the bioavailable dose of valsartan appears to be metabolized. Metabolite M1 which results from hydroxylation of valsartan, is the major metabolite and constitutes 23.3% of the bioavailable dose. M1 is pharmacologically inactive. *The sponsor has not identified the enzyme(s) responsible for this oxidative route of metabolism.* Approximately 1/3 (32.9%) of the bioavailable dose of valsartan is eliminated via urinary excretion.

Two unidentified possible metabolites and other unidentified trace compounds were found in urine and stool samples. In vitro metabolism studies have not been performed in order to identify the enzymes that metabolize valsartan or study the effect of valsartan on major metabolizing enzymes.

2. Volume of Distribution

The steady state volume of distribution after intravenous administration is small (16.9 ± 6.9 L), indicating that valsartan does not distribute into tissues extensively (Protocol 15).

3. Protein Binding (reports: BPK(US)1994/023 & BPK(F)1995/010)

Approximately 95% of valsartan binds to plasma proteins. The majority of this binding is to albumin. Percent bound values measured in vivo range between with an average value of 91.7%. Binding of valsartan to human plasma and serum proteins in vitro is independent of drug concentration over the range of 0.05-5.0 ug/ml (0.12-11.48 uM). Similarly, in vivo percent bound values are also independent of drug concentration over the concentration range of 104-2931 ng/ml (0.24-6.73 uM) (Report BPK(US)1994/023; samples from Protocol 10). The observed peak concentrations following once daily administration of a 160 mg capsule generally fall within the examined concentration ranges in the protein binding studies.

Presence of hydrochlorthiazide, a commonly co-administered agent, at usually observed concentrations (up to 0.15 ug/ml) did not alter the protein binding of valsartan to plasma proteins in vitro (BPK(US)1994/023). Diclofenac sodium (0.5 & 2.0 ug/ml), warfarin (0.2 &

2.0 ug/ml, and furosemide (0.5 & 4.0 ug/ml) did not affect the protein binding of valsartan (0.5 & 5.0 ug/ml) in vitro (BPK(F)1995/010). The concentrations of the agents used here are within the expected in vivo concentration ranges.

It is likely that valsartan does not distribute into red blood cells (protocol 16; $C_b \approx 0.6C_p$).

III. General Pharmacokinetics:

Absolute Bioavailability, Clearance, & Half-Life (Protocol 15, vol. 1.45)

Mean absolute bioavailability of the 80 mg clinical capsule formulation of Valsartan was found to be 0.23 ± 0.07 and that of an 80 mg solution of Valsartan 0.39 ± 0.07 in healthy male volunteers (Table 2). Total body clearance for Valsartan is 2.19 ± 0.39 (L/h) and the renal clearance is 0.62 ± 0.12 (L/h). Valsartan does not appear to distribute extensively into tissues (low volume). The buffered solution exhibited a higher bioavailability than the capsule formulation. This indicates that the low bioavailability of the capsule is partially due to dissolution problems.

Table 2. Average pharmacokinetic parameters following administration of single oral doses of an 80 mg capsule and an 80 mg buffered solution, and a 20 mg IV dose.

Parameter	20 mg (45.92 umol) IV formulation	80 mg (183.70 umol) clinical capsule formulation	80 mg (183.70 umol) buffered solution
Cmax (uM)		3.77 (1.45)	7.47 (1.96)
Tmax (h)		2	1
$AUC_{(0-24)}$ (umol.h/L)	21.55 (3.91)	19.62 (5.99)	32.88 (8.10)
Bioavailability	1.0	0.23 (0.07)	0.39 (0.07)
CL (L/h)	2.19 (0.39)		
Vss (L)	16.91 (6.90)		
MRT (h)	7.82 (3.32)		
$T_{1/2a}$ (h)	1.01 (0.13)		
$T_{1/2b}$ (h)	9.45 (3.83)	7.05 (1.58)	7.50 (1.73)
Urinary Excretion (% of dose over 24 hours)	28.95 (5.82)	7.34 (3.02)	12.55 (3.10)
CL_R (L/h)	0.62 (0.12)		

Using the clearance value computed following IV administration of valsartan and assuming hepatic metabolism only, the maximum bioavailability for valsartan can be computed as follows:

$F_{max} = 1 - ER = 1 - CL/Q_h = 1 - 2.19/90 = 1 - 0.024 = 0.975$

Thus, valsartan has a low hepatic extraction ratio (0.024 = ER).

Absorption characteristics of valsartan were also studied using Caco2 cells. These are human adenocarcinoma cells that when grown on permeable filters, differentiate to form polarized monolayers with properties which reflect the ileal epithelium. Using this system, the rate of transport of valsartan was shown to reflect the change in octanol/water partition coefficient with pH, such that transport was rapid at pH 6.0, and slow at pH 7.0. The transport of valsartan through the membrane was found to be a passive diffusion process as opposed to a proton-dependent active transport.

Dose Proportionality

Approximately linear increases in C_{max} and $AUC_{0-inf.}$ with increasing doses were observed after single administration of 80, 2x80 (160), and 3x80 (320) mg Valsartan to 13 male volunteers (i.e. dose normalized C_{max} and AUC values for the different doses are similar, respectively) (protocol 48). It should be noted that the highest recommended dose in the proposed labeling is 160 mg per day.

Table 3. Dose normalized mean PK parameters (times 10^6) for Valsartan after oral administration of single doses.

Dose (mg)	C_{max} (ng/ml)/Dose (ng)	$AUC_{0-inf.}$ (ng.h/ml)/Dose (ng)	Half-Life (h)
80	13.6	119.1	15.5 ± 25.6
160	13.3	94.9	6.4 ± 4.9
320	10.4	93.6	9.2 ± 6.2

Single versus Multiple Dose Administration

There is no significant accumulation of valsartan following repeated daily administration relative to single dose administration (protocol 30, 80 mg per day; protocol 03, 200 mg per day; see the pharmacodynamic section of the appendix). This is consistent with what would be predicted based on the average half-life (6.2 h) of valsartan relative to the dosing interval (24 hrs).

IV. Influence of Age and Gender:

Pharmacokinetics of Valsartan was studied in 24 young or old volunteers (12 young or elderly males & 12 young or elderly females) after single oral administration of an 80 mg dose (Protocol 13, Vol. 1.49). The elderly volunteers had a statistically significantly higher exposure (approximately 70% higher mean AUC_{0-inf}) to drug than the younger ones (Table 4 & Appendix). Valsartan exhibited a longer average half-life (by 35%) in the elderly group than in the young (Table 4).

Table 4. Mean pharmacokinetic parameters of valsartan after oral administration of an 80 mg single dose to young and old volunteers.

	YOUNG			OLD		
Parameter	**MEN**	**WOMEN**	**ALL**	**MEN**	**WOMEN**	**ALL**
AUC_{0-inf} (umol.h/L)	34.82 (9.41)	39.08 (14.34)	36.95 (11.78)	54.52 (29.51)	69.52 (31.59)	62.7* (30.15)
C_{max} (umol/L)	6.09 (1.31)	7.68 (4.40)	6.88 (3.20)	5.98 (2.62)	11.13 (3.78)	8.55 (4.11)
T1/2 (h)	6.27 (1.87)	5.22 (0.89)	5.23 (0.70)	5.25 (0.53)	7.74 (2.01)	7.07* (2.00)

*N=11

( ) The numbers in parentheses are standard deviation values.

Only a weak correlation (r^2=0.4) was observed between exposure (AUC_{inf}) and age when all the data points were examined (Fig. 2a). A stronger correlation (r^2=0.8) between exposure and age was observed in the elderly group (age range 65-89) (Fig. 2b). The r^2 value for the elderly group decreased to 0.2 when the three elderly subjects with the highest AUC values were excluded.

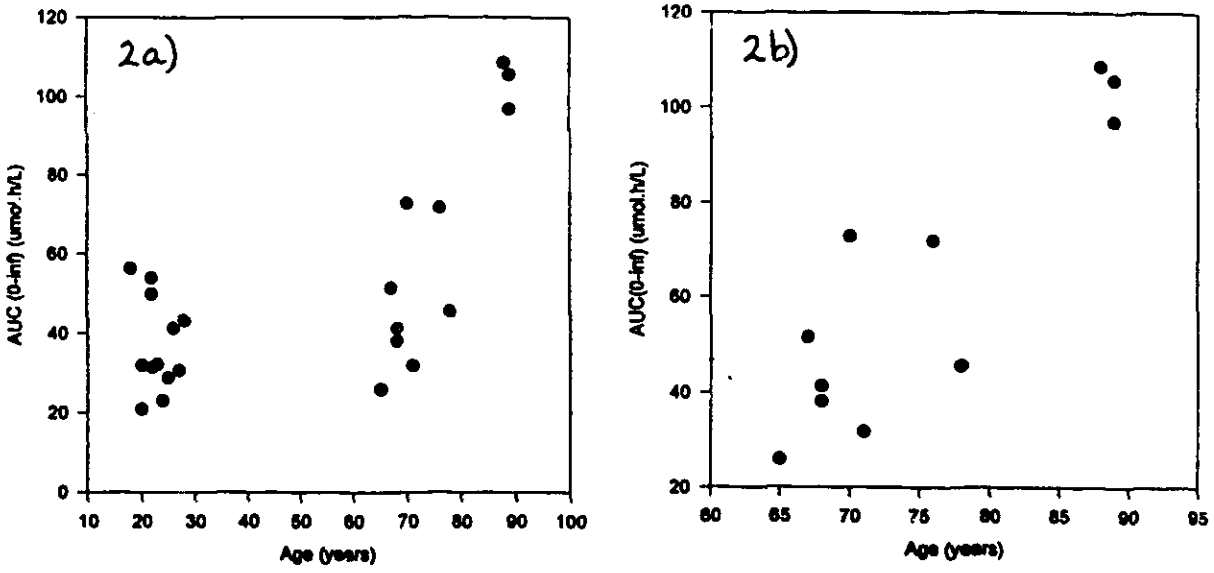


Figure 2. Exposure to valsartan as measured by AUC_{0-inf} plotted against age: a) includes data from both the young and elderly groups, b) data from the elderly group only.

The sponsor states that the higher mean AUC values in the elderly can not be unambiguously attributed to age differences. The difference between the young and the old groups was due to the fact that 5 out of eleven elderly subjects had much higher exposure levels (AUC_{0-inf}) than all the other ones. Three of these subjects were on other medications

prior to the start of this study. Two were taking a drug that is known to inhibit carbamazapine, a CYP2C9 substrate, metabolism. Thus, the firm mentions that increased AUC due to inhibition of metabolism can not be ruled out. We would have been able to gain more insight into this issue if the firm had performed in vitro metabolism studies (i.e. shown that CYP2C9 can metabolize valsartan and valsartan metabolism is inhibited in vitro in the presence of CYP2C9 inhibitors or substrates). It is true that one of the identified metabolic pathways for valsartan is an oxidative one, but this oxidation may be performed by a variety of enzymes.

No statistically significant gender differences in exposure (as measured by AUC) to valsartan (80 mg dose) were observed in the populations who participated in studies that examined the effects of renal impairment (protocol 12) and age (protocol 13) on PK of valsartan (analysis performed by reviewer). However, the power to detect a difference in each study was low.

V. Effect of Food on PK and PD Parameters:

Presence of food (standard FDA recommended breakfast; appendix) appeared to slow down the rate of absorption of Valsartan (mean T_{max} fed/fasted: 6.1/2.5 h) in healthy male volunteers following administration of a 160 mg dose (protocol 06). The mean C_{max} value (fed/fasted: 3.89/8.26 umol/L) decreased by 53% when Valsartan was taken with food (Fig. 3a, mean of twelve values). Exposure (mean AUC_{0-inf} fed/fasted: 30.5/51.9 umol.h/L) to Valsartan decreased by approximately 41% in the presence of food. Eleven of the twelve studied subjects followed the above mentioned changes observed in the mean pharmacokinetic parameters. Subject 8 had higher AUC_{0-inf} and C_{max} values when he took the drug with food (Fig. 3b); however, he did have a decrease in the rate of absorption (increased T_{max}).

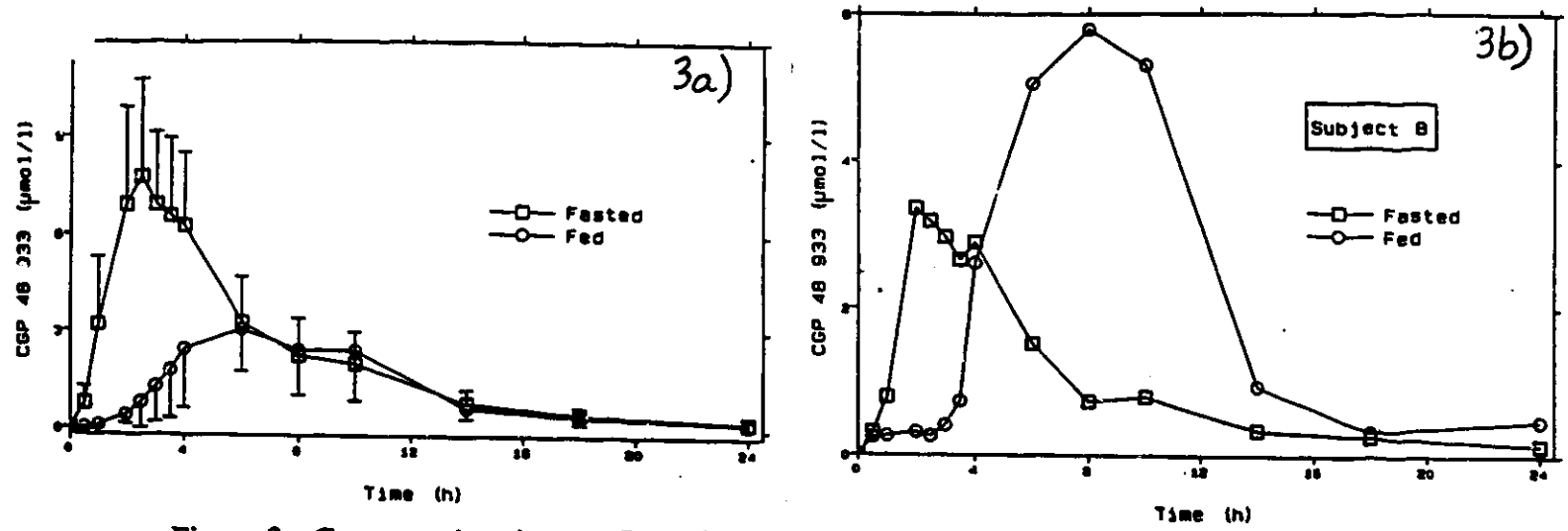


Figure 3. Concentration-time profiles of valsartan (CGP48933) under fasted (open squares) and fed (open circles) conditions: a) mean data from all 12 subjects, b) data from subject 8 only. *(To convert umol/L to ng/ml multiply the concentration value by 435.5)*

An unexplained period effect in the magnitude of the observed differences in mean AUC and C_{max} values between the fed and fasted states was present.

The mean value of decrease in blood pressure relative to baseline was larger following administration of 80 mg valsartan under fasted condition than that following fed state, and both

of these changes were larger than that following placebo treatment (protocol 17, a parallel design study). The mean values of change in trough sitting diastolic blood pressure, the primary variable, following fasted and fed administration of valsartan were not statistically significantly different from each other (criteria: a 3 mm Hg difference with a power of 80%) but did differ statistically significantly from that following placebo treatment (Table 5). The mean value of change in trough sitting systolic blood pressure, the secondary variable, following fasted administration of valsartan was statistically significantly different from that following placebo treatment (appendix). However, no statistical significance was observed for the difference in mean change in sitting systolic blood pressure between fed valsartan administration and placebo treatment.

Table 5. Summary of the Least Squares Mean and Between-Treatment Comparisons of Change from Baseline (Visit 3) in Trough Mean Sitting Diastolic Blood Pressure (mmHg) for All Randomized Patients

	Endpoint	Visit 7
Mean Change from Baseline		
Placebo	-4.24	-3.91
Valsartan 80 mg, fasted	-8.65	-8.96
Valsartan 80 mg, fed	-6.85	-7.14
P-Value		
Valsartan fasted vs. fed†	0.082	0.078
Valsartan fasted vs. placebo	0.001‡	<0.001‡
Valsartan fed vs. placebo	0.046‡	0.019‡

† The a posteriori power to detect a 3 mmHg difference between the valsartan 80 mg fasted versus fed treatment groups was 0.83 at both Endpoint and Visit 7.

‡ Indicates a statistically significantly greater reduction in trough mean sitting diastolic blood pressure as compared to placebo.

The mean trough valsartan concentrations were similar under fed and fasted conditions and less than 400 ng/ml (see appendix).

VI. Influence of Disease States:

Renal Impairment

Pharmacokinetics of Valsartan has been examined following administration of a single 80 mg oral dose of the drug to four different groups of volunteers with varying degrees of renal impairment as defined by creatinine clearance values (see appendix). No correlation was observed between exposure to drug (AUC_{0-48}) and creatinine clearance values (range of 11-195 ml/min). The group identified to have severe renal impairment had creatinine clearances within the range of 11-28.8. The C_{max} and AUC_{inf} values were not statistically significantly different among the examined groups. Although two of the five subjects in the group with severe renal impairment had much higher (by a factor of 2-3x) exposure (AUC) and half-life values compared to the other subjects in all the studied groups. These two subjects were not taking any other medications at the time of dosing. A statistically significant difference in $T_{1/2}$ values was observed between the control group (5.5 ± 2.2 h) and patients with mild renal impairment (10.6 ± 4.4 h) and between the control group and patients with severe renal impairment (11.2 ± 5.1 h). A statistically significant difference in half-life values (5.5 ± 2.2

vs. 4.5 ± 0.6) was not observed between the control group and patients with moderate renal impairment (reviewer's analysis). Half-life values do not correlate significantly with creatinine clearance values (Corr. Coeff. -0.4).

The difference in half-life may have been explained by an increase in volume due to changes in protein binding (i.e. fu) if valsartan was not a low extraction ratio drug. However, any change in volume of distribution caused by changes in binding would have a similar effect on clearance and therefore no effect on the elimination half-life. Thus, the difference in half-life between the control group and the groups with mild or severe renal impairment is most likely due to the variability in pharmacokinetics of valsartan. Furthermore, even with a half-life of 11 hours, drug levels would reach steady state within 2 days and no appreciable accumulation should occur with a once a day dosing regimen. Therefore, these differences are most likely not clinically significant.

Liver Disease

On average, patients with mild or moderate liver disease have two times higher exposure (as measured by AUC values) to valsartan compared to healthy volunteers (matched by age, sex, and weight) (Table 6). There exists a tendency for AUC to increase as bilirubin concentrations increase (see appendix). This finding is not surprising considering the fact that about 66% of the bioavailable dose of valsartan is eliminated via biliary excretion. Such a tendency does not apply however to half-life values. The similarity in half-life between the liver impaired patients and the control group implies that the observed difference in AUC is a function of protein binding changes (i.e. volume of distribution is changing also) as opposed to impaired biliary excretion. In the absence of fraction unbound measurements in these subjects it is not possible to distinguish between these two cases. Although, in one subject with moderate liver impairment (subject 10), half-life of valsartan appeared to have lengthened to the extent that its determination during the 36 hour sampling time window was not possible. Nevertheless, even with the higher exposure levels, the patients with impaired liver disease appeared to tolerate a 160 mg dose of valsartan well.

Table 6. Mean pharmacokinetic parameters for valsartan in patients with mild or moderate liver impairment and healthy volunteers.

Group	AUC $_{(0\text{-}36)}$ (umol.h/L)	AUC $_{(0\text{-}inf)}$ (umol.h/L)	C_{max} (umol/L)	T1/2 (h)
Patients (Mild)	107.4 (17.4)	111.6 (21.7)	13.6 (2.8)	7.5 (1.9)
Matching Volunteers (Mild)	49.2 (10.6)	50.9 (12.0)*	8.1 (1.6)	7.7 (3.5)
Patients (Moderate)	133.3 (87.6)	113.0 (74.5)**	10.5 (5.2)	9.9 (2.4)**
Matching Volunteers (Moderate)	48.0 (19.4)	49.0 (21.7)	7.1 (3.0)	8.3 (1.9)

*Excluding subject 13.

**Excluding subjects 8 and 10.

VII. Population Pharmacokinetics in Patients:

Sparse steady state concentration data from 92 patients in one of the clinical trials (protocol 10) was utilized for population pharmacokinetic analysis. Due to the small number of sampling points (only 4 per patient per visit), a one compartment model with zero-order absorption was applied. Estimates of the PK parameters are shown in Table 7.

Table 7. Estimate of clearance and volume of distribution of valsartan obtained using population PK analysis.

Parameter	CL (L.year/h)	V (L.year)	Duration of Zero Order Input (h)
Estimate (SE)	76 (4.5)	515 (61)	2.2 (0.14)

For a 40 year old patient, the clearance and volume of distribution would be 1.9 L/h and 13 L. As indicated by the reported parameter values, age was found to be a significant covariate. Clearance and volume of distribution decrease with increasing age, these observations are consistent with the results obtained in protocol 13 (increasing AUC with increasing age). No gender effect was observed and the effect of race was not investigated due to the small number of non-whites in the protocol.

VIII. Pharmacodynamics:

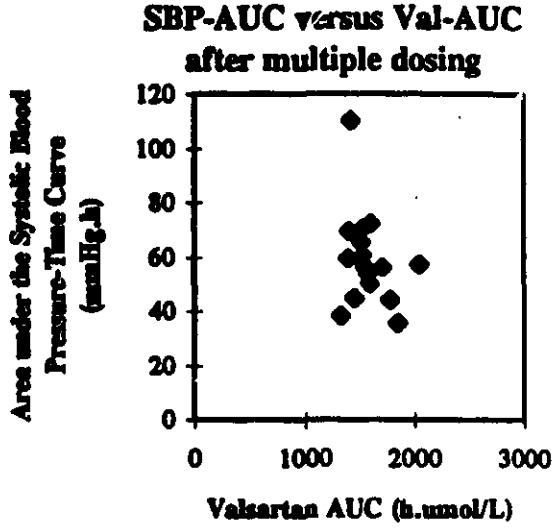
Valsartan has been shown to block the angiotensin II receptor (i.e. increase angiotensin II concentration) in healthy volunteers (protocols 01, 02, 03, 04). Following single dose (200 mg) administration of valsartan to healthy volunteers (16 males), an increase in the plasma concentration of angiotensin II was observed relative to placebo treatment. Following multiple (200 mg per day) administration of valsartan to the same group of volunteers, the angiotensin levels were significantly higher than those observed after administration of a single dose (protocol 03, appendix). The mean AUC(0-24) for angiotensin II on day 1 was 409 ± 316 and on day 8 was 1174 ± 760 (fmol.h/ml). The corresponding AUC values following placebo treatment were: 103 ± 39 and 136 ± 68 (fmol.h/ml) (reviewer's analysis, appendix). Thus, the effect of valsartan on angiotensin levels appears to be enhanced after repeated exposure to the drug.

However, no correlation was observed between area under the angiotensin concentration-time curve and area under the valsartan concentration-time curve. This is probably due to the complex feed-back mechanisms involved with the regulation of the renin-angiotensin system (RAS) (protocols 3,4,36, 38). Maximum angiotensin II concentration was observed in the majority of subjects 6 hours following administration of valsartan; however, maximum valsartan concentrations were observed at approximately 2 hours following drug intake (protocol 03).

Administration of valsartan (200 mg per day) to healthy volunteers seemed to have different effects on systolic and diastolic blood pressures and to be dependent on the length of exposure to drug. In one study (protocol 03), the value of the area under the supine systolic blood pressure-time curve (AUC_{0-24}) following multiple dose administration of valsartan was statistically significantly different from that following multiple dose administration of placebo (appendix, reviewer analysis). However, the corresponding AUC values were not statistically significantly different following single dose administration of valsartan and placebo.

Furthermore, there was no statistically significant difference in AUC of the supine diastolic blood pressure-time curve between valsartan treatment and placebo treatment following single or multiple dose administration of either (protocol 03, reviewer's analysis). No correlation was observed between the AUC of systolic blood pressure-time curve and the AUC of valsartan concentration-time curve in healthy volunteers (Fig. 4) (protocols 03).

Figure 4. Area under the systolic blood pressure-time curve versus area under the valsartan concentration-time curve on day 8 of a multiple dosing regimen consisting of 200 mg drug per day in healthy volunteers.



Following challenge doses of angiotensin II, concomitant valsartan administration to healthy volunteers resulted in a decrease in blood pressure. Relative to placebo treatment, valsartan administration caused a statistically significant decrease in systolic blood pressure (after baseline correction) when iv infusions of angiotensin II were administered (significant differences were observed between AUC of the blood pressure-time curve following administration of placebo and that following valsartan treatment; protocol 30, 80 mg single and multiple doses, appendix).

Valsartan administration in healthy volunteers did not have any effect on heart rate, urinary output (volume) and urinary uric acid secretion (protocol 03).

Sparse concentration-effect data (steady state) from five different trials performed in hypertensive patients with a dose range of 10-320 mg per day were pooled and fitted to an Emax model. These data suggest that the concentration-effect relationship for valsartan is flat over a wide concentration range (400-3600 ng/ml) (see population PD in appendix). The mean Emax value is 4.58 $\pm$ 0.73 mm Hg and the EC50 value is 36.10 $\pm$ 29.40 ng/ml. It is noteworthy that 82% of the concentration values utilized in this data set were greater than 40 ng/ml and the majority of the other 18% were below the quantitation limit and given a set value of 25 ng/ml. Thus, the EC50 value cannot be accurately estimated based on this data set. Nevertheless during the first six hours post-dosing, the majority of the examined patients had plasma valsartan concentrations greater than or equal to two times the reported mean EC50 values. Therefore, the majority of patients taking 80 mg of valsartan per day will have concentrations greater than the EC50 during the main portion of the dosing period (24 hours). Thus, it is likely that the majority of patients will experience an effect on diastolic blood pressure close to the Emax, and that PK differences would not have a significant impact on the efficacy of valsartan at the proposed doses (80-160 mg). During the Biopharm Day meeting, Dr. Ganley noted that the physiologic changes brought about by valsartan administration may cause toxicity to the kidneys (e.g. renal failure). Such toxicity has been reported with

losartan. At the this time, the presence or absence of a relationship between the extent of exposure to losartan and extent of renal toxicity can not be established. Thus, due to this possible toxic effect of valsartan on the kidneys, PK differences may become important in terms of safety.

IX. Drug-Drug Interactions:

Pharmacokinetic Interactions

Co-administration of valsartan caused a 28% decrease in body exposure (as measured by AUC_{0-inf}) to hydrochlorthiazide (HCTZ) and a 26% decrease in C_{max} of HCTZ (statistically significant changes). HCTZ did not affect the pharmacokinetic parameters of valsartan (changes of less than 20% were observed in its PK parameters). (protocol 07)

Co-administration of valsartan and furosemide caused a decrease in mean C_{max} of furosemide (by 37%), mean exposure to furosemide(AUC_{0-24}, by 28%), and the mean percentage of dose excreted as unchanged furosemide (Ae_{0-24}, by 20%) relative to when furosemide was given alone. Co-administration of valsartan and furosemide did not affect the pharmacokinetic parameters of valsartan (changes of less than 20% relative to drug administration by itself). The values of the within subject variability for valsartan's C_{max} and AUC were 21% and 20%, respectively. (protocol 36)

Co-administration of valsartan did not affect the pharmacokinetics of amlodipine and neither did amlodipine have any effect on PK parameters of valsartan. (protocol 37)

No pharmacokinetic interaction was observed when valsartan and atenolol were co-administered. However, coefficients of variation for C_{max} and AUC_{inf} for valsartan after the combined therapy (45% and 47%) were lower than those (57% and 56%) after valsartan therapy alone. (protocol 38)

Co-administration of digoxin and valsartan did not affect the pharmacokinetic parameters (changes of less than 20% were observed in the parameters) of valsartan. Valsartan and digoxin co-administration did not affect the mean C_{max} and T_{max} values for digoxin relative to when digoxin was administered alone. The effect of co-administration of these drugs on AUC_{0-inf} of digoxin could not be determined with high certainty, because detectable concentrations were not measured long enough post-dosing (p.d.) to allow an accurate estimate of the elimination rate constant (i.e. couldn't compute C_{last}/k_{elim}). Moreover, digoxin concentrations were below the detection limit in the majority of samples collected beyond the 24 hour time point following dosing. (protocol 39)

Co-administration of valsartan and warfarin had no effect on the pharmacokinetic parameters of valsartan. Pharmacokinetic parameters of warfarin were not determined in this study. (protocol 40)

Administration of valsartan an hour after ingestion of cimetidine did not affect the PK parameters of cimetidine. This is consistent with the facts that cimetidine is rapidly absorbed (T_{max}=45-90 min) and has a relatively short half-life (2 hours). Cimetidine pre-administration caused only a 17% increase in AUC of valsartan and a 49% increase in C_{max} relative to when valsartan was given alone. Thus, cimetidine appears to affect the rate of absorption of valsartan. A within subject variability of 33.7% for C_{max} and 22.5% for AUC_{0-48} was reported by the firm for valsartan. The reported intra-subject variability was lower for cimetidine: 19.2% for C_{max} and 11.7% for AUC_{0-48}. (protocol 42)

Co-administration of valsartan and indomethacin did not affect the mean values of either drug's pharmacokinetic parameters. The within subject variability for C_{max} and AUC_{0-t} of valsartan were 30.1 and 20.6%, respectively. (protocol 43)

Co-administration of valsartan did not affect the pharmacokinetic parameters of glibenclamide. However, co-administration of glibenclamide decreased the mean AUC_{0-inf} of valsartan by 26% and the mean C_{max} by 27%. (protocol 52)

Pharmacodynamic Interactions

When valsartan and furosemide were co-administered, a larger decrease (relative to baseline) in systolic blood pressure was observed compared to when each drug was administered alone (Fig. 5). Overall, systolic blood pressure was statistically significantly lower after the combined treatment in comparison with either treatment alone. This effect appears to be additive. There were no significant differences in the effect on diastolic blood pressure and heart rate between the different treatments. (protocol 36)

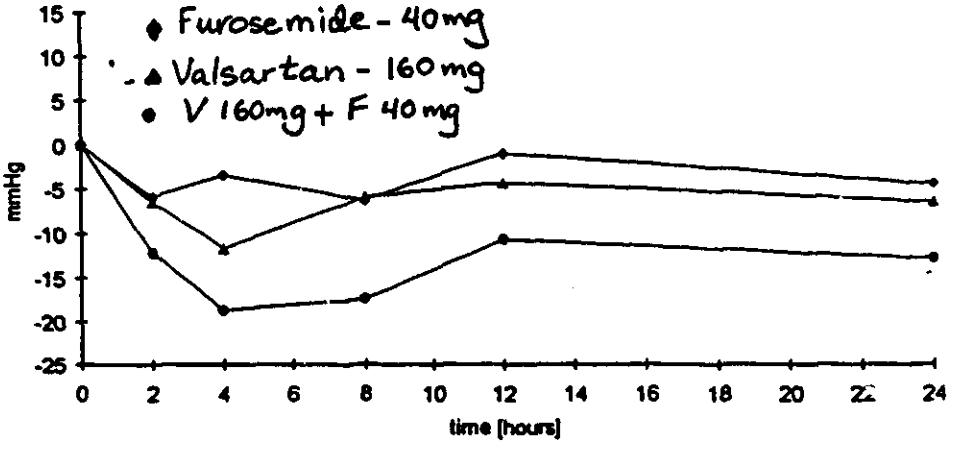


Figure 5. Changes in systolic blood pressure from baseline, mean of data obtained from 12 volunteers.

There were no significant differences in urinary volume, creatinine clearance, and excretion of sodium and potassium after the combined treatment of valsartan and furosemide in comparison with either treatment alone. (protocol 36)

In a study where possible interactions between valsartan and atenolol were examined, three hemodynamic parameters (heart rate, systolic and diastolic blood pressures) were measured both in supine resting position and during exercise at two different workload levels. In supine resting position, mean values of systolic and diastolic blood pressure up to 12 hours post dosing were lower after the combined therapy compared to administration of each drug alone. Mean heart rate values in supine resting position were also lower after the combination treatment compared to valsartan alone; however, similar to that observed after atenolol alone. During exercise, mean heart rate and systolic blood pressure values were both lower after the combined therapy compared to valsartan therapy alone, but both of these parameters were similar to those obtained after atenolol administration. Mean values of diastolic blood pressure were similar among the three treatments. (protocol 38)

Co-administration of valsartan and warfarin did not have a significant effect (< 15% change) on the examined coagulation parameters. (protocol 40)

Co-administration of glibenclamide did not seem to alter the pharmacodynamic

properties of valsartan. (protocol 52)

X. Formulations:

The clinical and final formulations for the 80 and 160 mg clinical capsule formulations have different compositions (Appendix). The manufacturing site for the clinical lots of both dose strengths is in Horsham, UK. The manufacturing site for the to-be-marketed (final) formulation for both strengths is in Stein, Switzerland. The designation of formulation for these dose strengths are as follow:

Clinical 80 mg - Q897 or H3576	Final 80 mg - Q961
Clinical 160 mg - Q905 or H3577	Final 160 mg - Q960 or H3785

In addition to the 80 and 160 mg capsule dosage strengths, other dose strength capsule formulations (e.g. 20 mg and 40 mg) were utilized in the performed studies (see Appendix for composition). However, only the 80 and 160 mg capsule dose strengths will be marketed.

XI. Bioequivalence (Protocol 47):

In many of the PK studies a 160 mg dose was administered as two 80 mg clinical capsule formulations. Thus, a bioequivalence study has been performed whereby single doses of 160 mg final, 160 mg clinical, and 2x80 mg clinical dosage forms of valsartan were administered to healthy male volunteers. Two 80 mg clinical capsules are bioequivalent to one 160 mg final and clinical capsule formulations. When comparing the 160 mg final formulation to the 160 mg clinical formulation, the upper limit of the 90% confidence interval for C_{max} is greater than the allowed value of 1.25 by 0.07. However, the confidence interval for AUC falls within the acceptable range of 0.80-1.25. (see appendix) The lack of bioequivalence on C_{max} is likely not a major safety concern, because doses of up to 320 mg have been administered and tolerated in clinical trials and the response to valsartan appears to be independent of concentration of valsartan over a wide concentration range (400-3600 ng/ml).

The coefficients of variations for C_{max}, AUC_{0-36}, AUC_{0-inf}, and $T_{1/2}$ measured in this study were high (a range of). On average, the smallest coefficients of variations (range) for the above mentioned parameters were observed following administration of 2x80 mg clinical dosage form and the largest values following administration of the 160 mg clinical dosage form (range). In general, valsartan pharmacokinetics exhibits high overall variability.

The 80 mg clinical formulation has not been compared to the 80 mg final formulation in this study; however, these products have been shown to have similar dissolution profiles (see dissolution section in the Appendix).

XII. DISSOLUTION:

Valsartan is highly soluble in buffered solutions with a pH value greater than 5.0. It is slightly soluble in water. The sponsor examined the dissolution characteristics of the highest strength (160 mg) valsartan capsules in three different media: deionized water, 0.1 N hydrochloric acid, and USP phosphate buffer at pH 6.8. The best dissolution (highest percent dissolved) profile was observed in phosphate buffer (see Appendix for dissolution profiles). Thus, the sponsor chose this as the dissolution medium. The following dissolution specifications were proposed by the sponsor for both capsule strengths:

Apparatus:	USP Dissolution Apparatus #1 (basket)
Speed:	100 rpm
Medium:	USP Phosphate buffer, pH 6.8
Volume:	1000 ml
Sampling time:	*45 min*
Specification:	not less than ( )

The submitted dissolution profiles show that more than is dissolved at the 30 minute time point. Thus, theoretically the spec. should be dissolved in 30 min. However, since all the stability data has been done using a 45 min time point, OCPB recommends a specification of not less than (Q) at 45 min. Interpretation of these dissolution specifications using the acceptance table on page 1793 of USP 1995 is as follow:

individual 6 of 6 values ≥85%
average of 12 values ≥80% and individual 12 of 12 values ≥65%
average of 24 values ≥80% and individual 24 of 24 values ≥55%
and individual 22 of 24 ≥65%

The 80 mg clinical capsules and the 80 mg final capsules have similar dissolution profiles. Also, the dissolution profile of 2x40 mg clinical capsules is similar to that of an 80 mg clinical capsule.

XIII. Assay Methodology:

been
in
of

COMMENTS TO THE MEDICAL OFFICER:

1. If appropriate, please revise the statement regarding the "intake of valsartan with or without food" in the "Dosage and Administration " section of labeling based on your analysis of data from protocol 17 and other clinical trials.

2. Please examine the statement regarding "potassium sparing diuretics" given in the "drug-drug interaction" section of the labeling.

3. Dosage and Administration and Clinical Pharmacology Sections of the Labeling: Please add the appropriate recommendation regarding the use or non-use of valsartan in patients with severe renal impairment.

COMMENTS TO THE PHARMACOLOGIST:

1. Please confirm the following claim made by the sponsor in the clinical pharmacology section: "Studies in rats indicate that valsartan crosses the blood-brain barrier poorly, if at all."

GENERAL COMMENTS TO THE SPONSOR:

1. As a phase four commitment, the Office of Clinical Pharmacology and Biopharmaceutics requests that you utilize in vitro methodologies to determine if valsartan inhibits CYP 450 enzymes.

LABELING (Please rearrange and rewrite parts of the Clinical Pharmacology Section as follows):

Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours post dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration. Mean absolute bioavailability for the capsule formulation is 23% (range 10-35%). Food decreases the extent of exposure (as measured by AUC) to valsartan by 41% and peak plasma concentration (C_{max}) by 53%.

AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Following oral administration, the average plasma elimination half-life is about 6 hours. Valsartan does not accumulate in plasma appreciably following repeated administration.

Metabolism and Elimination:

Following oral administration of a buffered solution of ^{14}C-labeled valsartan, approximately 13% of radioactivity is recovered in the urine and 83% in the feces. The majority of unchanged valsartan is excreted in the feces (70% of an administered dose) and a smaller fraction in the urine (10% of the dose). Thus, at most 20% of an administered dose (or 50% of the bioavailable dose) of valsartan may be metabolized. Approximately 9% of an administered dose (or 23% of the bioavailable dose) of valsartan is recovered in the feces and urine as a hydroxylated metabolite, valeryl 4-hydroxy valsartan. Three unidentified compounds accounted for a total of approximately 6% of the dose in feces and urine. The enzyme(s) responsible for the metabolism of valsartan has(ve) not been identified.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (or 28% of total clearance).

Distribution

The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan does not distribute into red blood cells. Studies in rats indicate that valsartan crosses the blood-brain

barrier poorly, if at all. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations

Pediatric: The pharmacokinetics of valsartan have not been investigated in patients < 18 years of age.

Geriatric: **Exposure (as measured by AUC) to valsartan is higher by 70% in the elderly than in the young. The half-life is longer by 35% in the elderly compared to the young.**

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Race: **The effect of race on the pharmacokinetics of valsartan has not been studied.**

Renal Insufficiency: There is no apparent correlation between renal function (as measured by creatinine clearance) and exposure (as measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild to moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance < 10 mL/min) or patients undergoing dialysis. It is unknown if valsartan may be removed by hemodialysis. In the case of severe renal disease, exercise caution with dosing of valsartan (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: **On average, patients with mild or moderate liver disease have two times higher exposure (as measured by AUC values) to valsartan compared to healthy volunteers (matched by age, sex, and wight).** Caution should be exercised with dosing of valsartan to patients with severe liver disease (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Hydrochlorthiazide (HCTZ): Co-administration of valsartan caused a 28% decrease in body exposure (as measured by AUC_{0-t}) to hydrochlorthiazide and a 26% decrease in C_{max} of HCTZ. HCTZ did not affect the pharmacokinetic parameters of valsartan.

Furosemide: Co-administration of valsartan and furosemide caused a decrease in mean C_{max} of furosemide (by 37%), mean exposure to furosemide(AUC_{0-24}, by 28%), and the mean percentage of dose excreted as unchanged furosemide (Ae_{0-24}, by 20%) relative to when furosemide was given alone. Co-administration of valsartan and furosemide did not affect the pharmacokinetic parameters of valsartan. The pharmacodynamic response (decrease in systolic blood pressure) following co-administration of valsartan and furosemide was greater than the response following administration of either drug alone. This effect was approximately additive.

Amlodipine: Co-administration of valsartan did not affect the pharmacokinetics of amlodipine and neither did amlodipine have any effect on PK parameters of valsartan.

Atenolol: No pharmacokinetic interaction was observed when valsartan and atenolol were co-administered. The response (decrease in supine resting systolic and diastolic blood pressure) to the combined therapy of valsartan and atenolol was larger than the response to each drug alone during the first 8 hours post-dosing. Valsartan in combination with atenolol did not lower heart rate more than atenolol alone.

Digoxin: Co-administration of digoxin and valsartan did not affect the pharmacokinetic parameters of valsartan. Valsartan and digoxin co-administration did not affect the mean C_{max} and T_{max} values for digoxin relative to when digoxin was administered alone. **The effect of co-administration of these drugs on the extent of body exposure to digoxin could not be determined with high certainty.**

Warfarin: Co-administration of valsartan and warfarin had no effect on the pharmacokinetic parameters of valsartan. Pharmacokinetic parameters of warfarin were not determined in this study. Valsartan did not affect the anti-coagulant properties of warfarin.

Cimetidine: Administration of valsartan an hour after ingestion of cimetidine did not affect the PK parameters of cimetidine. Cimetidine pre-administration caused a 17% increase in AUC of valsartan and a 49% increase in C_{max} relative to when valsartan was given alone. Thus, cimetidine appears to increase the rate of absorption of valsartan.

Indomethacin: Co-administration of valsartan and indomethacin did not affect either drug's pharmacokinetic parameters.

Potassium Sparing Diuretics: Concomitant use of potassium-sparing diuretics, potassium supplements, or salt substitutes that contain potassium may lead to hyperkalemia.

CYP 450 Interactions: The effect of inhibitors and inducers of CYP 450 or other drug systems on the elimination of valsartan is unknown. Therefore, blood pressure should be monitored when patients initiate concomitant drug therapy. The effect of valsartan on CYP 450 enzymes has not been examined.

Parnian Zia-Amirhosseini, Ph.D. P.Z. Amirhosseini Date 7/2/96
Division of Pharmaceutical Evaluation I

Ameeta Parekh, Ph.D. Ameeta Parekh Date 7/3/96

Biopharm. Day 6/17/96 ; Attendees: D. Bashaw, C. Ganley, J. Hunt, H. Malinowski, A. Parekh, A. Tamura, T. Tozer.
cc: NDA20-665, HFD-110, HFD-860 (H. Malinowski, M. Mehta), HFD 870 (Clarence Bott: Chron, Drug, Review), FOI (HFD-19)

K. Bangivanni
SEP 30 1996

NDA #20,665

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

G. Jagadeesh, Ph.D.
09-30-1996

ORIGINAL SUBMISSION DATE December 28, 1995

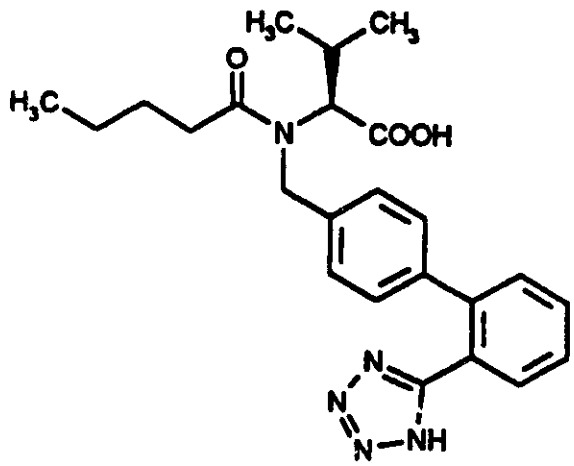
CENTER RECEIPT DATE December 28, 1995

SPONSOR CIBA-GEIGY Corporation
556 Morris Avenue
Summit, NJ 07901

DRUG Diovan® (Valsartan)

CHEMISTRY Valsartan (CGP 48933) is (S)-N-valeryl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-valine. It contains two acidic functions and includes one asymmetric center. CGP 48933 is free diacid, hydrophilic and the pure S-enantiomer. The corresponding (R)-enantiomer, which is less active in biological tests, is known as CGP 49309.

Structural Formula



M.W. 435.5

FORMULATION Capsules for oral administration containing 80 or 160 mg of valsartan (inactive ingredients: cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate and titanium dioxide).

PHARMACOLOGICAL CLASS Angiotensin II receptor antagonist

PROPOSED INDICATION Hypertension

PROPOSED DOSAGE REGIMEN 80 mg once daily in most patients. The maximum recommended dose is 160 mg once daily

IND UNDER WHICH CLINICAL TRIALS WERE CONDUCTED

TABLE OF CONTENTS

INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is an important regulatory element in the maintenance of cardiovascular homeostasis, sodium and water balance in normal and hypertensive subjects. The peripheral manifestations of hypertension and chronic congestive heart failure can be attributed to the compensatory activity of this hormonal system. The active hormone of this system is angiotensin II (AII), an octapeptide. It is one of the most potent vasoconstrictor agents known. Angiotensin II is formed by the action of angiotensin converting enzyme (ACE) on Angiotensin I. Angiotensin II binds to AT_1 receptors in vascular smooth muscle, sympathetic prejunctional nerve endings, adrenal gland, and the distal renal tubule. This results in vascular smooth muscle constriction, catecholamine release, aldosterone formation and renal sodium absorption. These actions, mediated at the level of the AT_1 receptor, result in increased vascular resistance and intravascular volume, thereby precipitating high blood pressure.

The pressor activity of angiotensin II can be inhibited by preventing its formation (by inhibiting renin or ACE) or by blocking the receptors to which it binds. Recently, an array of subtype-specific receptor antagonists, primarily nonpeptides, has been used to unravel the pharmacological mechanisms of the angiotensin II receptors. Two major subtypes (AT_1 and AT_2) of angiotensin II receptors have been recognized using subtype-specific antagonists.

The subject of this review, CGP 48933 (Valsartan), is an orally active, competitive, non-peptidic, potent specific antagonist of angiotensin II at the AT_1 receptor subtype. The sponsor's NDA contains extensive preclinical data supporting this classification.

1. PHARMACODYNAMICS

1.1. Studies Related to Proposed Therapeutic Indication

1.1.1. *In Vitro:*

1.1.1.1. Receptor Specific Studies

CGP 48933 was shown to bind with high affinity to the AT_1 angiotensin II receptor in human adrenal cortex (K_i, 1.87nM), rat aortic smooth muscle cells (IC_{50}, 8.94 nM; K_i, 7.33 nM) and rat adrenal glomerulosa (IC_{50}, 5.5 nM) and with slightly lower affinity to dog aorta (IC_{50}, 56 nM) and to dog adrenal glomerulosa (IC_{50}, 126 nM). This indicates that a species difference may exist in the binding affinity of CGP 48933 to AT_1 receptors. The affinity of CGP 48933 for the AT_2 receptor (human uterus) was more than 10,000 times lower than for the AT_1 receptor. CGP 48933 was also evaluated for binding affinity at various neurotransmitter receptor sites and for calcium channel binding site affinity. Test compound at a concentration of 10 μM, exhibited marginal effects on α_1-adrenergic (15% inhibition) and histamine$_1$ (18% inhibition) receptors. No or negligible interactions were observed at other receptor sites studied.

1.1.1.2. Studies in Isolated Tissues

Angiotensin II-induced contractions in isolated rabbit aortic rings were inhibited in a concentration-dependent manner by CGP 48933 (0.3, 1, 3 and 10 nM, Fig. 1). The threshold dose was 0.3 nM and a maximum inhibition of angiotensin II-induced contractions was obtained with 3 nM CGP 48933. The concentration of 10 nM abolished completely the effects of angiotensin II and the calculated IC_{50} was 1.4 nM. However, it is not clear from the report whether the antagonism was competitive in nature. At a concentration 1500-fold higher than the IC_{50} value, CGP 48933 did not affect contractions induced by norepinephrine, serotonin or KCl, demonstrating that CGP 48933 is a selective antagonist of angiotensin II for the vascular AII receptor. No agonistic effects were observed up to a tested concentration of 2 μM.

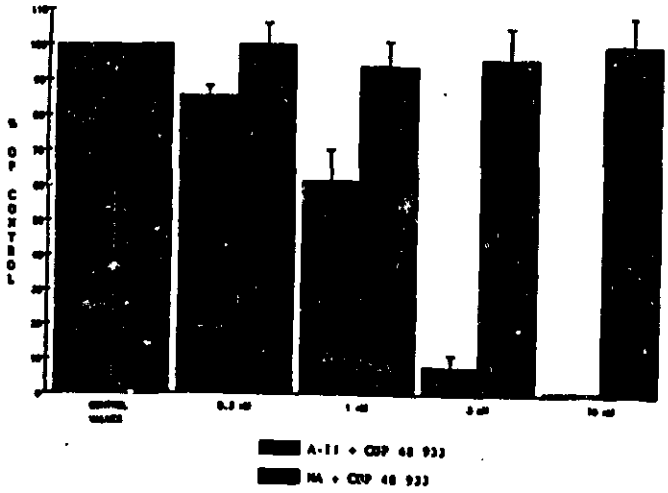


Fig. 1: Effects of CGP 48933 on contractions induced by angiotensin-II and noradrenaline (NA) in rabbit aortic rings.

In another study, the effects of antihypertensive therapy on the endothelial dysfunction in hypertension were investigated in SHR vascular beds. Animals were treated for 8 weeks with CGP 48933, the calcium channel blocker nifedipine, or the ACE inhibitor benazepril (each 10

mg/kg/day, p.o.). All forms of therapy inhibited the systolic b.p. to a comparable degree (18-33 mm Hg) and reduced, but did not normalise, medial hypertrophy in SHR. At the end of 8 weeks, mesenteric resistance arteries were perfused. The inhibition of norepinephrine-induced contraction by endothelin-1 that was lost in SHR was restored by CGP 48933 or nifedipine, but not by benazepril, to levels comparable to WKY rats. In addition, left anterior descending coronary artery ring segments removed from the same animals showed increased endothelial-dependent relaxations in response to acetylcholine but no changes in the contractile response to serotonin or in degree of relaxation induced by the nitric oxide donor, 3-morpholino-sydnonimine. Thus, these two studies suggest that antihypertensive therapy with CGP 48933 appears to improve vascular endothelial responsiveness so as to facilitate local blood flow to vital organs.

The effect of CGP 48933 on angiotensin II-stimulated aldosterone production was investigated in dispersed bovine adrenal glomerulosa cells. CGP 48933 (300 nM) shifted the angiotensin II concentration (0.01 nM to 1 μM) response curve to the right. The calculated EC_{50} and pA_2 values were 49 nM and 8.41, respectively. CGP 48933 reduced angiotensin II-stimulated aldosterone production to near control values (Fig. 2). In contrast, CGP 48933 did not reduce potassium-mediated aldosterone production.

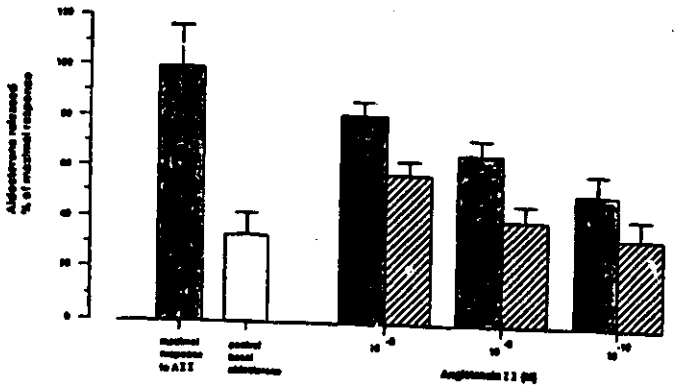


Fig. 2: Effect of CGP 48933 (300 nM) on angiotensin II-induced aldosterone production within a relevant and narrow antagonist sensitive A-II concentration range. *Shaded* bars represent A-II alone. *Hatched* bars A-II with added CGP 48933. Data represent the mean ± SEM in % of maximal A-II response of four different bovine adrenal glomerulosa cell preparations.

CGP 48933 was evaluated for its agonist activities, if any, on guinea pig ileum and atria. In both experiments CGP 48933 was tested in concentrations ranging from 0.023 to 230 μM. At concentrations of 23 and 230 μM, CGP 48933 exerted marginal reductions in both the rate of contraction in the spontaneously beating right atria and the force of contraction in the electrically stimulated left atria. In the guinea pig ileum, the compound did not induce contractions at any of the tested concentrations.

The potency of CGP 49309, the R-enantiomer of CGP 48933 was investigated. CGP 49309 binds to AT_1 receptors in cultured smooth muscle cells (species and type not given in the report) with an IC_{50} of 0.45 μM, which is approximately 1000-fold less than for CGP 48933, which has an IC_{50} of 9 nM. Similarly, in rabbit aortic ring, CGP 49309 inhibited angiotensin II-induced contractions with an IC_{50} of 0.1 μM, which is approximately 100-fold greater than the IC_{50} value of 1.4 nM documented for CGP 48933. Thus, CGP 49309 is considerably weaker than CGP 48933.

1.1.2. ***In Vivo:***

1.1.2.1. Studies in Rats

Normotensive Rats: The ability of CGP 48933 to selectively antagonise AII-induced (0.4 µg/kg, i.v. bolus) pressor response was measured in pithed animals following oral (3 and 10 mg/kg) administration.

CGP 48933 at a dose of 3 mg/kg (Table 1) did not affect basal b.p. or pressor responses induced by electrical stimulation of the sympathetic outflow (40 mA, 1 msec, 1 Hz for 10 sec) and by norepinephrine (0.4 µg/kg, i.v.). However, pressor responses to angiotensin II were significantly inhibited after CGP 48933 (by 53%) as compared to control rats. At a dose of 10 mg/kg (Table 2), CGP 48933 reduced basal b.p. values (by 29%), the response to angiotensin II (by 87%), and the pressor response to electrical stimulation (by 43%), but not the response to norepinephrine . In the same preparation, its enantiomer CGP 49309, inhibited angiotensin II-induced pressor response by 5%. This indicates that CGP 48933 is a potent, selective and orally active antagonist of angiotensin II at the vascular receptor.

TABLE 1

EFFECTS OF ORAL ADMINISTRATION OF 3 MG CGP 48933/KG ON INITIAL BLOOD PRESSURE AND ON PRESSOR RESPONSES INDUCED BY ANGIOTENSIN-II (A-II), ELECTRICAL STIMULATION OF THE SYMPATHETIC OUTFLOW (E.S.) AND NORADRENALINE (NA) IN THE PITHED RAT. *= P < 0.01

	Initial values b.p. mm Hg	Pressor responses (mmHg,, delta values)		
		A-II	E.S.	NA
Controls, n=11	56.6 ± 2.2	77.1 ± 4.8	44.1 ± 4.7	69.3 ± 2.4
CGP 48 933 3 mg/kg p.o., n=7	56.3 ± 2.0	36.1 ± 3.2*	4 7.3 ± 5.4	71.1 ± 3.0

TABLE 2

EFFECTS OF ORAL ADMINISTRATION OF 10 MG CGP 48933/KG ON INITIAL BLOOD PRESSURE AND ON PRESSOR RESPONSES INDUCED BY ANGIOTENSIN-II (A-11), ELECTRICAL STIMULATION OF THE SYMPATHETIC OUTFLOW (E.S.) AND NORADRENALINE (NA) IN THE PITHED RAT. *= P < 0.01

	Initial values BP, mmHg	Pressor responses (mmHg, delta values)		
		A-II	E.S.	NA
Controls, n=8	64.1 ± 5.3	76.4 ± 5.7	51.6 ± 5.0	67.5 ± 5.9
CGP 48 933 10 mg/kg p.o., n=6	45.5 ± 4.0*	10.2 ± 3.2*	29.5 ± 6.2	54.8 ± 8.3

In other studies, angiotensin II-induced (1 μg/kg/min, i.p.) fibroblast proliferation and myocyte necrosis in the rat was prevented by CGP 48933 (1 μg/kg/min, i.p.) but not by the AT_2 receptor antagonist PD 123319. Thus, it is concluded that these cardiotoxic effects of angiotensin II are directly or indirectly mediated by the AT_1 receptor subtype.

Renal hypertensive Rats: The dose-response effects of CGP 48933, administered intravenously (Fig 3) or orally (Fig. 4), on b.p. and heart rate were studied in the 2 kidney, 1 clip renal hypertensive rat. Renin-dependent hypertension was established in male rats by constriction of one renal artery. In those animals administered CGP 48933 orally, systolic b.p. and heart rate were measured before and 2, 4, 24, 48 and 72 hr after administration indirectly in the tail arteries with an inflatable cuff and a piezoelectric detector attached to a pen recorder. A second set of animals were catheterized for blood pressure and heart rate recording, and for intravenous administration of drug. Rats remained conscious throughout the study period, were restrained for oral and unrestrained for i.v. experiments. Only rats with systolic b.p. higher than 220 mm Hg were used. The decrease in b.p. after either oral or i.v. administration of CGP 48933 was dose-dependent. The threshold dose for lowering b.p. was approximately 0.03 mg/kg, i.v. and between 1 and 3 mg/kg, orally. With the i.v. administration (0.01-10 mg/kg, single bolus), the peak hypotensive effect was observed at 10 min and was followed by a recovery towards initial values. This was slowly followed by a secondary prolonged fall in b.p., taking an hour to develop into a maximum effect and then persisting for up to 24 hours (Fig.3). Meanwhile, there was a transient increase in heart rate in the first 30 min after injection that was not dose-dependent. The transient recovery of b.p. and increase in heart rate observed after i.v. administration of CGP 48933 was blocked by pretreatment with propranolol (1 mg/kg, i.v., administered 30 min before an i.v. bolus injection of CGP 48933). The maximum effect induced by test compound was similar to that induced by the ACE inhibitor, enalaprilat (3 mg/kg, i.v.). CGP 48933 at an i.v. dose of 1 mg/kg and an oral dose of 10 mg/kg induced maximum hypotensive responses.

With single oral administration, peak effect developed after about 4 h and persisted for more than 24 hr (Fig. 4). No significant changes in heart rate were observed. Repeated administration did not reveal any signs of tolerance or accumulation. The ratio between the blood pressure decreases after i.v. andoral administration indicates a functional oral bioavailability of approximately 10%.

In a rat model of renal hypertension (induced in Wistar rats by clipping the left renal artery) and pressure overload, CGP 48933 (3 and 10 mg/kg/day for 12 weeks, i.p.) induced regression of left ventricular hypertrophy, prevented progressive LV chamber dilation and normalized the LV systolic wall stress as monitored using magnetic resonance imaging *in vivo*. The results suggest that AT_1 blockade was equally effective in terms of regression of LV hypertrophy as well as improvement in LV function.

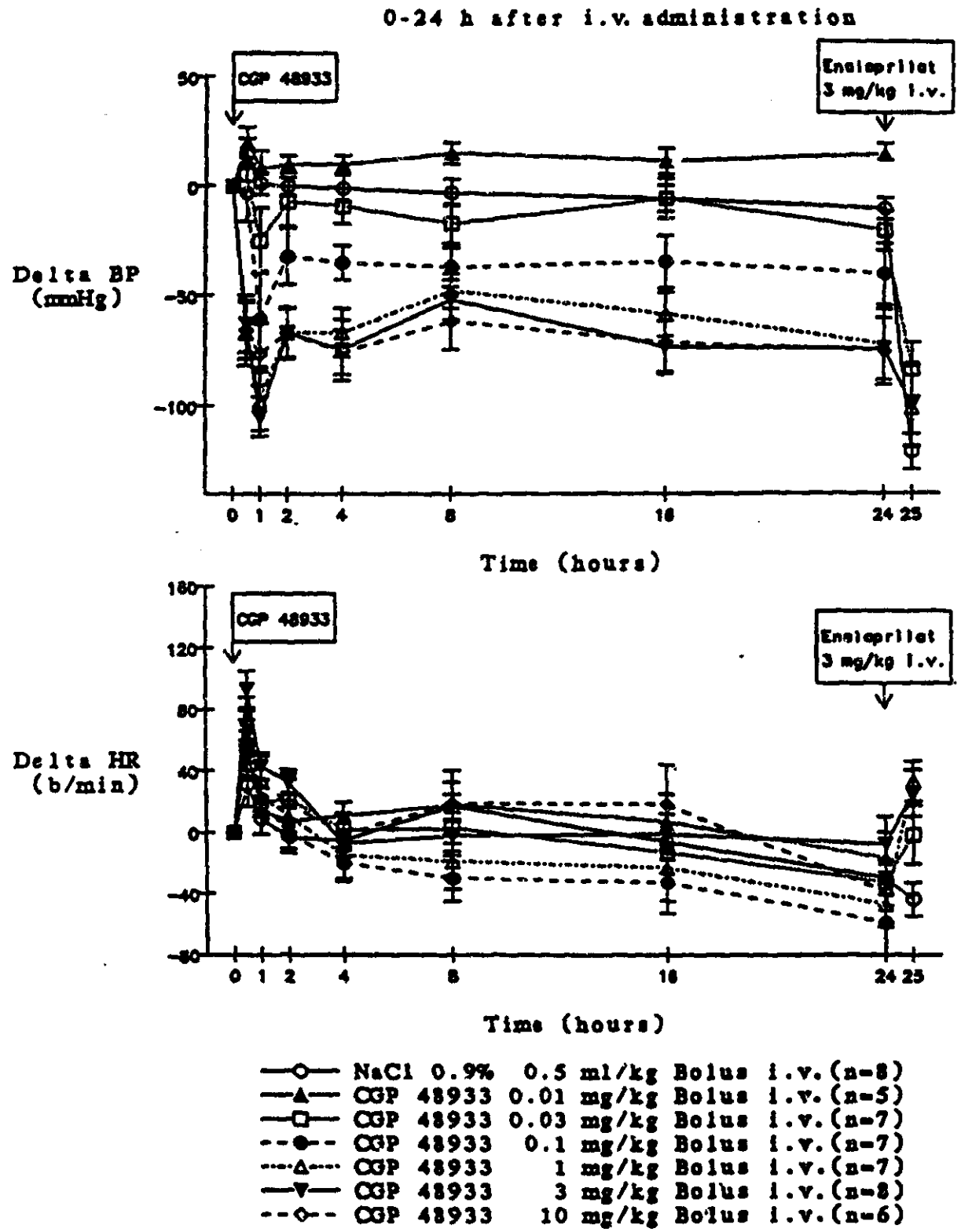


Fig. 3: Effects of CGP 48933 (i.v. administration) on blood pressure and heart rate in conscious renal hypertensive rats.

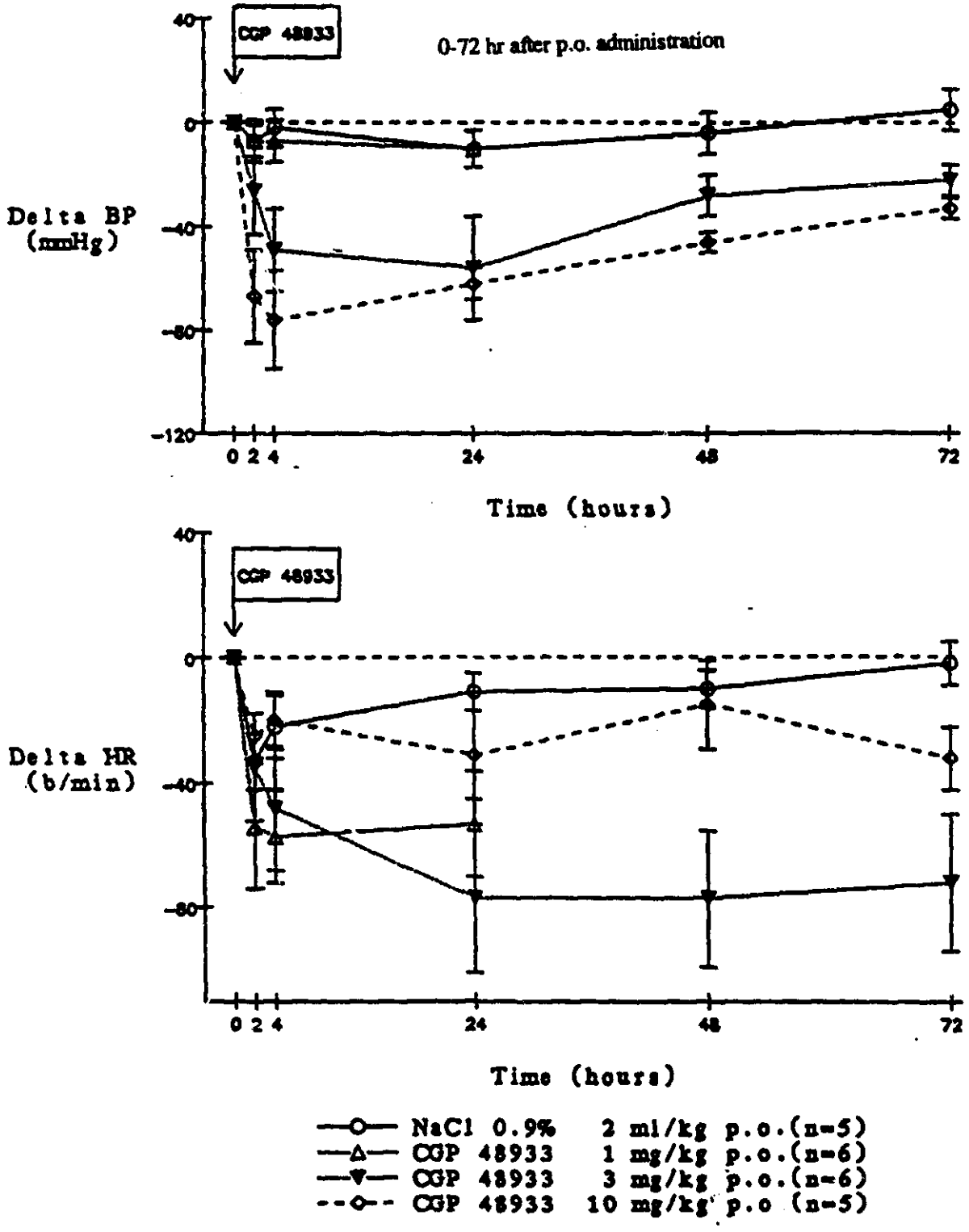


Fig. 4: Effects of CGP 48933 (oral administration) on blood pressure and heart rate in conscious renal hypertensive rats.

Spontaneously Hypertensive Rats: Administration of either CGP 48933 (2 mg/kg, p.o.) or the diuretic hydrochlorothiazide (10 mg/kg, p.o.) alone to SHR resulted in a similar, moderate decrease in b.p. The combination of the two drugs was clearly more effective. The effect on b.p. was additive.

In other studies, prolonged administration of CGP 48933 at 10 mg/kg/day for 27 days in SHR or for 13 weeks in normotensive rats and marmosets up to a dose of 600 mg/kg/day did not affect either the K_D or the Bmax in several tissues examined. This suggests that desensitization of the angiotensin II receptor during chronic treatment is unlikely to occur. However, slight elevations in both plasma creatinine and urea were observed in marmosets and rats after four weeks of dosing which was likely a consequence of the degree of blood pressure reduction in these normotensive animals.

Normal and Sodium-depleted Rats: This study investigated the effects of acute blockade of the RAAS with CGP 48933 on plasma renin, angiotensin, and aldosterone levels in rats in normal sodium balance as well as in sodium-depleted conditions.

Two sets of experiments were conducted. In the first, male rats were depleted of sodium by dietary salt restriction over a period of two weeks and then treated orally with vehicle, or with CGP 48933 in a single dose of 10 mg/kg, a dose producing a maximal lowering of b.p. (see above). Blood was collected from separate groups of anesthetized animals before and 4, 6, 24, and 72 hours after treatment. In the second study, both sodium-unrestricted (sodium normal balance) and sodium-depleted rats (two groups) were used. Both sets of animals were surgically instrumented for recording b.p. and to infuse angiotensin II (0.1 µg/min, i.v. for 30 min). At time 0, angiotensin II was infused and blood was withdrawn at the end of infusion for aldosterone determination. The rats were treated orally with CGP 48933 (10 mg/kg), or vehicle. Angiotensin II infusion was repeated 3.5, 5.5 and 23.5 hr after treatment, and blood was withdrawn at the end of the infusion (4, 6 and 24 hr).

CGP 48933 *per se* in sodium restricted rats significantly increased both angiotensin II and renin levels 4, 6 and 24 hr after treatment. The 4- and 6-hr levels were significantly greater than the 24- and 72-hr levels (Fig. 5). CGP 48933 *per se* further elevated plasma concentrations of aldosterone in salt depleted rats, which had been elevated more than 10-fold compared to animals on a normal-sodium diet (Fig. 6). In normal rats, CGP 48933 blocked the rise in plasma aldosterone concentrations induced by the challenge dose of angiotensin II at 4 and 6 hr after treatment. At 24 hr after treatment, the plasma level of aldosterone was reduced by 27% and was no longer significantly different from vehicle control (Fig.6). However, the angiotensin II-stimulated aldosterone release in sodium-restricted rats was totally blocked 4 hr after treatment with CGP 48933. At 24 hr, aldosterone release was still inhibited by 70% in comparison with the control group (Fig.7). The data from these two studies suggest that low-sodium-induced aldosterone release is not mediated via the angiotensin II adrenal receptor and that factors other than angiotensin II are important in controlling aldosterone secretion.

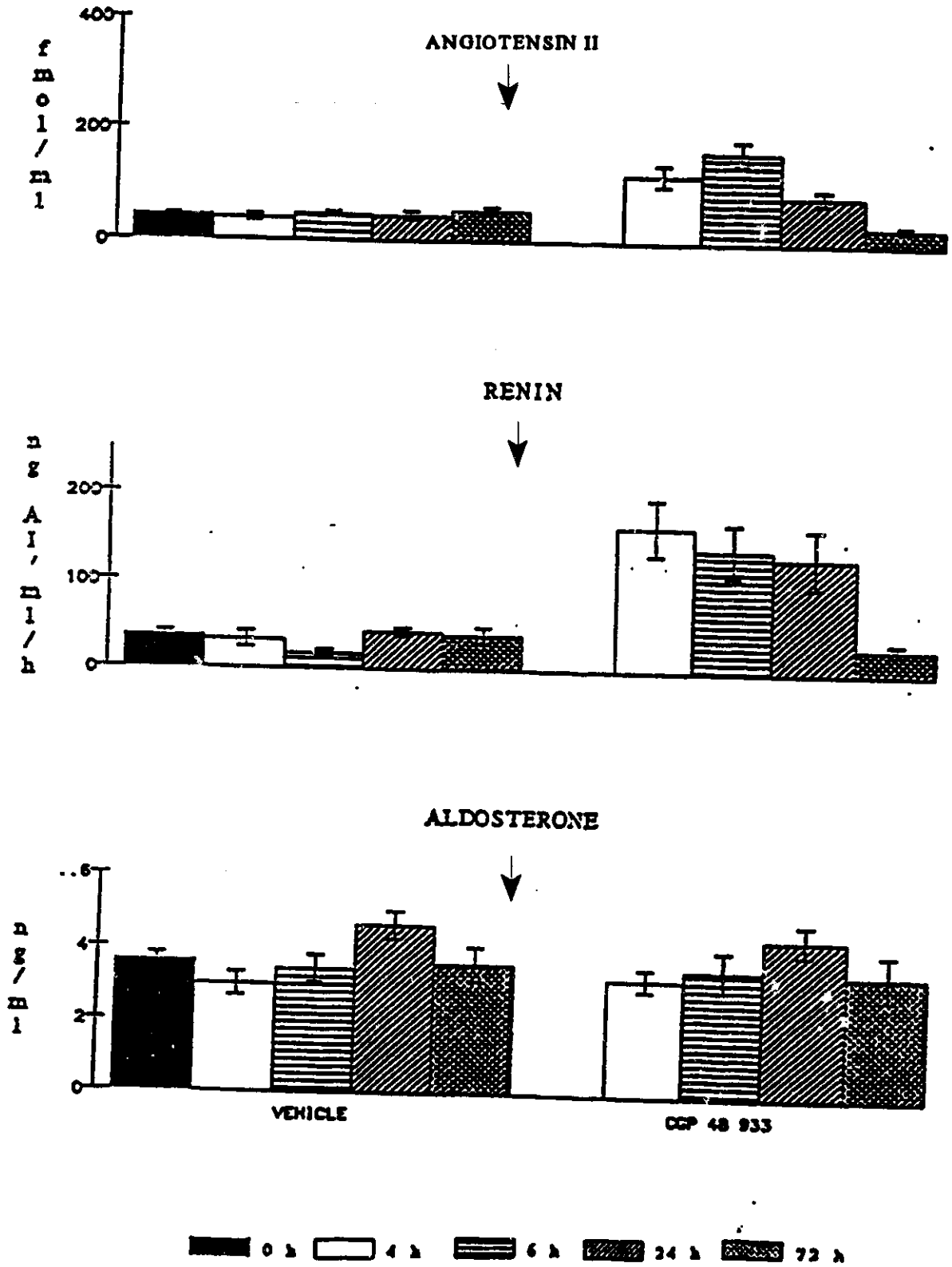


Fig. 5: Effect of CGP 48933 (10 mg/kg, p.o.) on basal plasma concentration of angiotensin-II, renin and aldosterone in sodium depleted RA25 rats.

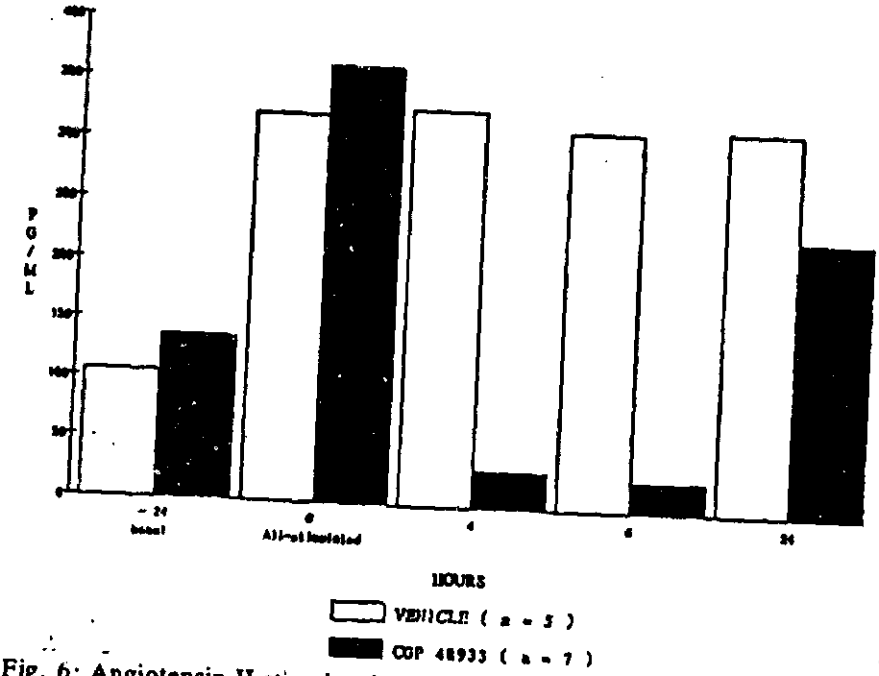


Fig. 6: Angiotensin-II-stimulated plasma aldosterone in normal RA25 rats before and after CGP 48933 (10 mg/kg, p.o.).

In both sodium-restricted and unrestricted rats, CGP 48933 (10 mg/kg, p.o.) *per se* produced a decrease in b.p. of approximately 15 mm Hg. This effect was maintained over 24 hr. This dose also blocked the pressor response to angiotensin II up to 6 hr and showed a partial recovery after 24 hr (Fig. 8). In résume, CGP 48933 effectively blocks the angiotensin II receptor on the renin-producing cells, thereby inhibiting the negative feedback regulation of angiotensin II. Consequently, the levels of renin and angiotensin circulating in the blood are increased. Further, angiotensin II- but not low-sodium diet-induced stimulation of aldosterone release was blocked by CGP 48933.

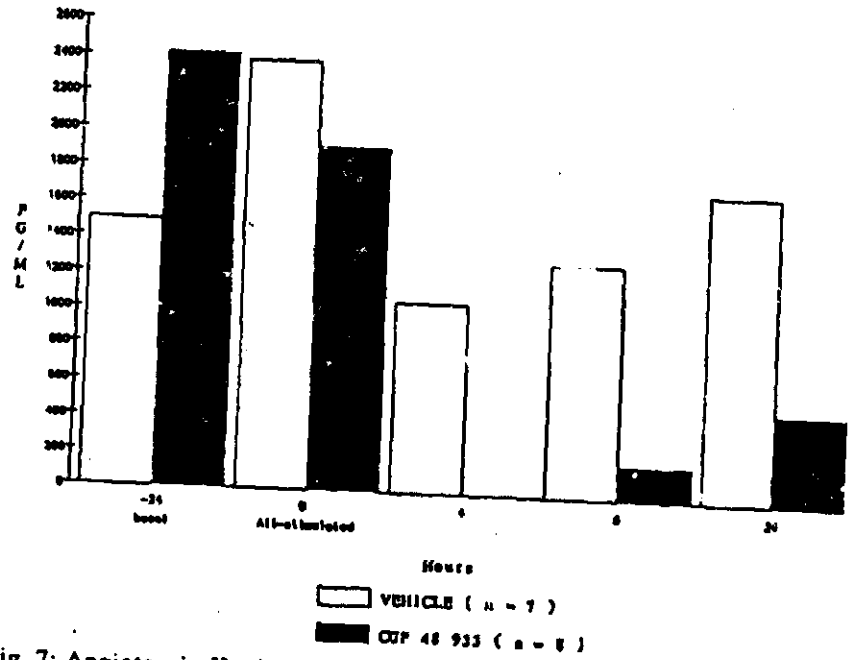


Fig. 7: Angiotensin-II-stimulated plasma aldosterone in salt depleted RA25 rats before and after CGP 48933 (10 mg/kg, p.o.).

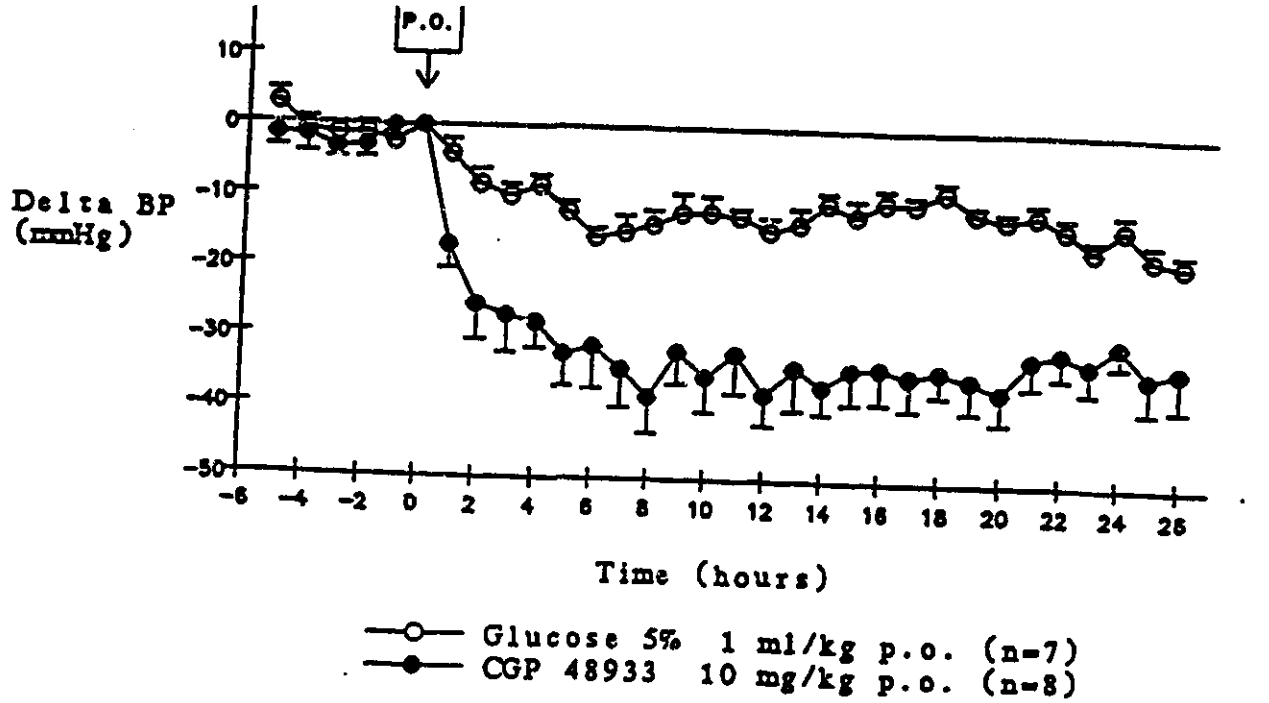


Fig. 8: Angiotensin II was infused for 30 min before blood collection at 4, 6 and 24 hr in low salt conscious rats.

1.1.2.2. Studies in Dogs

Sodium-depleted Dogs: The objective of this study was to determine if CGP 48933, by blocking angiotensin II receptors, could lower b.p. in the sodium depleted conscious dog.

Male mongrel and beagle dogs were maintained on a low sodium diet with free access to tap water for at least 7 days and, 24 hr prior to experiment, received an intramuscular injection of 1 mg/kg furosemide to enhance the level of sodium depletion. Each animal was trained over a period of several weeks to remain quietly for a 90 min period in the recumbent position with each limb loosely secured with leather straps to a corner of the table. On the day of experiment, the right upper limb was used to insert a 10 gauge needle into the lumen of the femoral artery for the purpose of recording b.p. and heart rate, and to collect blood samples. CGP 48933 or vehicle was administered intravenously through a 23 gauge needle inserted into the lumen of the cephalic vein of the right upper forelimb. All needles with syringes were secured to the forelimbs with adhesive tape.

Blood pressure and heart rate were allowed to stabilize for a 10 min period. CGP 48933 (3 mg/kg) or vehicle was injected and the parameters were monitored continuously. Enalaprilat (0.4 mg/kg) or saline (1 ml/kg) was injected 60 min after injection of the CGP 48933 and b.p. and heart rate were determined for the following 15 min period. Blood (5 ml) for the measurement of plasma concentrations of angiotensin II was collected from the arterial catheter immediately before and again 15 and 60 min after injection of the CGP 48933 or vehicle.

Intravenous injection of CGP 48933 (3 mg/kg) produced an immediate reduction in b.p., reaching a maximum fall of 25 mm Hg after 10-15 min. During the next hour, b.p. progressively returned, though not completely, to control levels (Fig. 9). CGP 48933 also decreased heart rate. Plasma angiotensin II levels, that remained constant in vehicle treated animals, showed an immediate and approximately 4-fold increase within 15 min after CGP 48933 administration. Its rise and fall during the one hour observation period followed b.p. pattern (Table 3). Decreased b.p. directly stimulates renin release. Increase in angiotensin II levels is due to both the removal of the negative feedback of angiotensin II on renin release and the decrese in b.p. The large fall in b.p. initially induced by CGP 48933 suggests a maximum or near maximum blockade of the vascoconstrictor actions of angiotensin II. However, the response was short lived. The low potency of CGP 48933 in the dog may also be a consequence of the low affinity of CGP 48933 for AT_1 receptors in this animal species compared to rat (see section #1.1.1.1).

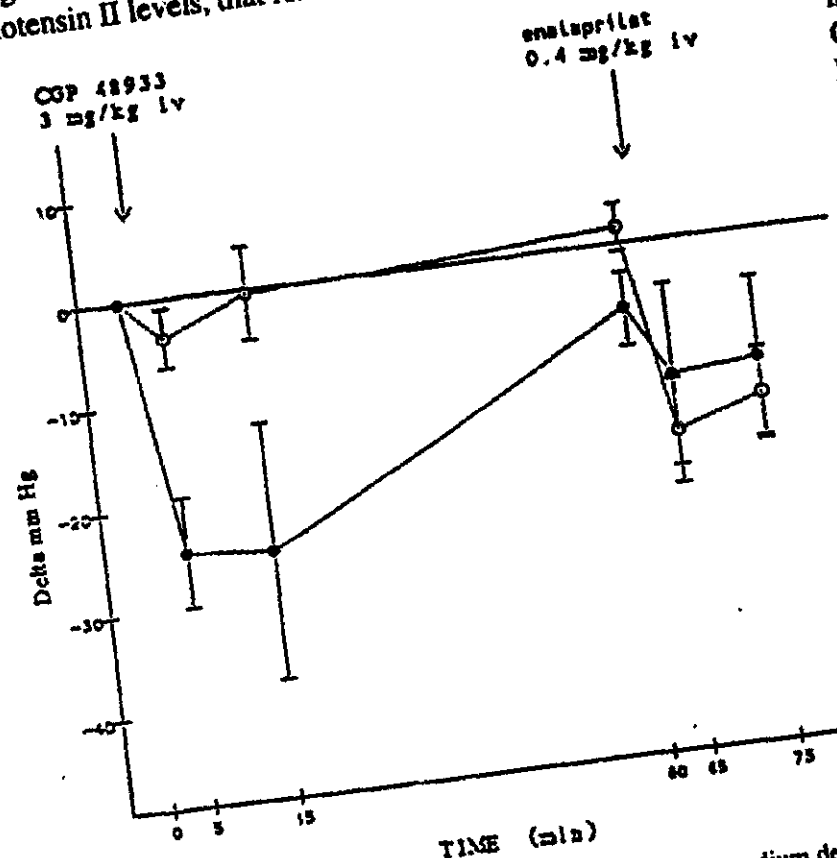


Fig. 9: Effect of CGP 48933 (3 mg/kg, i.v.) on blood pressure in sodium depleted dogs. Results are shown as change in b.p. from preinjection values. Each point represents the mean ± S.E. The initial control values in the 2 groups of experiments are as follows: control 140 ± 8 mm Hg; CGP 48933: 146 ± 9 mm Hg.

TABLE 4

EFFECT OF INTRAVENOUS INJECTION OF 3 MG/KG CGP 48933 ON PLASMA ANGIOTENSIN II (FMOL/ML). RESULTS ARE EXPRESSED AS MEAN ± SE. NUMBERS IN PARENTHESES ARE THE NUMBER OF EXPERIMENTS.

	Control (0 min)	15 min	60 min
Vehicle, 1 ml/kg (8)	99 ± 22	121 ± 21	104 ± 22
CGP 48933 (3 ml/kg) (4)	84 ± 36	283 ± 90	185 ± 21

Renal Hypertensive Dogs: The left renal artery of male beagle dogs was constricted by a silver clip so that the blood flow was reduced to approximately 30-40% of the original flow (2-kidneys 1-clip). The blood pressure was measured from the chronically cannulated right femoral artery. The dogs were used 2 weeks after the surgery in the conscious state. Drugs were given orally either once (10 and 30 mg/kg) or once a day for 10 days (30 mg/kg). Blood pressure and heart rate were monitored just before the first drug treatment and on the 1st (5 hr), 2nd (0, 5 hr), 3rd (0, 5 hr), 7th (0, 5 hr), and 10th (0, 5 hr) days of administration and 1 and 2 days after the final administration.

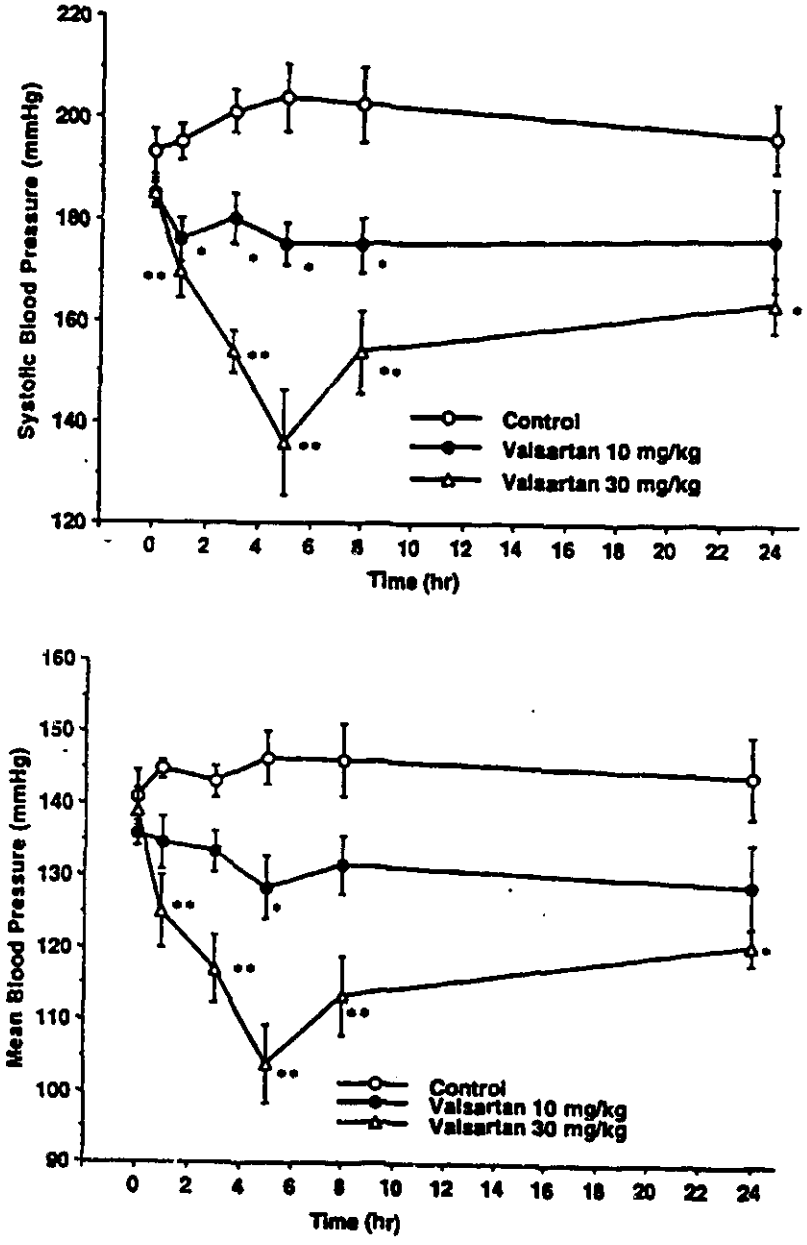


Fig. 10: Effect of CGP 48933 given orally on systolic (top panel) and mean b.p. (Bottom panel) in renal hypertensive dogs. Values represent mean ± SE (n=4). *: p <0.05, **:p <0.01 significantly different from control (Dunnett's test).

CGP 48933 at a single dose of 30 mg/kg, p.o. reduced mean blood pressure from 139 ± 3 mmHg before treatment to 125 ± 5 mmHg at 1hr, 117 ± 5 mmHg at 3hr, and 104 ± 5 mmHg at 5hr after drug administration (Fig. 10 lower panel). The maximum reduction of systolic blood pressure from control value by 29 and 68 mmHg was observed 5 hr (peak effect) after administration at 10 and 30 mg/kg, respectively (Fig. 10 upper panel). The drug had no effect on heart rate. Under repeated oral administration of CGP 48933 (30 mg/kg/day for 10 days), the antihypertensive effect on the first day was similar to that of the single administration (as above). The antihypertensive effect lasted throughout the drug administration period. There was no rebound phenomenon after withdrawl of the drug (measured 1 and 2 days after the final administration).

1.1.2.3. Study in the Sodium-depleted Marmoset

The aim of the study was to determine the effects of CGP 48933 on mean arterial b.p. and heart rate in conscious, normotensive, sodium-depleted marmosets.

Marmosets of both sexes were fed a low sodium diet supplemented with fruit for 14 days. They were pretreated with furosemide (5 mg/kg, i.m.) 18 hr before begining the experiment. Under anesthesia, catheters were implanted in either a tail or femoral vein for injection of drug or vehicle and in a femoral artery for b.p. measurement and were exteriorized at the tail. Animals were allowed to recover for at least 20 hr before begining an experiment. On the day of the experiment, animals were placed in restraining tubes for continuous measurement of b.p. and heart rate. They had been previously trained to adapt to this procedure. After initial stabilization period of 1 hr, CGP 48933 (0.03, 0.1, 0.3 or 1 mg/kg) was administered as a single bolus i.v. injection. Blood pressure and heart rate were recorded up to 120 min, and after 24 hr, enalaprilat (ACE inhibitor, 3 mg/kg, i.v.) was given to measure the extent of recovery of b.p. from a dose of the test drug. In another set of experiments, marmosets were adminstered test drug orally (0.03, 0.1, 0.3. 1 or 3 mg/kg) and b.p. was recorded up to 5 hr.

CGP 48933 in i.v. and p.o. doses of 0.1 mg/kg and above induced falls in b.p. The maximum effect occurred within 10 min after i.v. and 2 hr after oral administration and the antihypertensive effect persisted for up to 2 hr with i.v. (Fig. 11) and up to 5 hr with oral administration (Fig. 12). A full response to the ACE inhibitor, enalaprilat, was observed 24 hr after administration of CGP 48933 in both dose regimens, indicating complete recovery of b.p. No consistent reflex tachycardia was observed after i.v. or oral administration of CGP 48933. The results suggest that CGP 48933 is hypotensive in sodium-depleted marmosets, is not as long acting as in the renal hypertensive rat, but is longer acting than in sodium-depleted dogs.

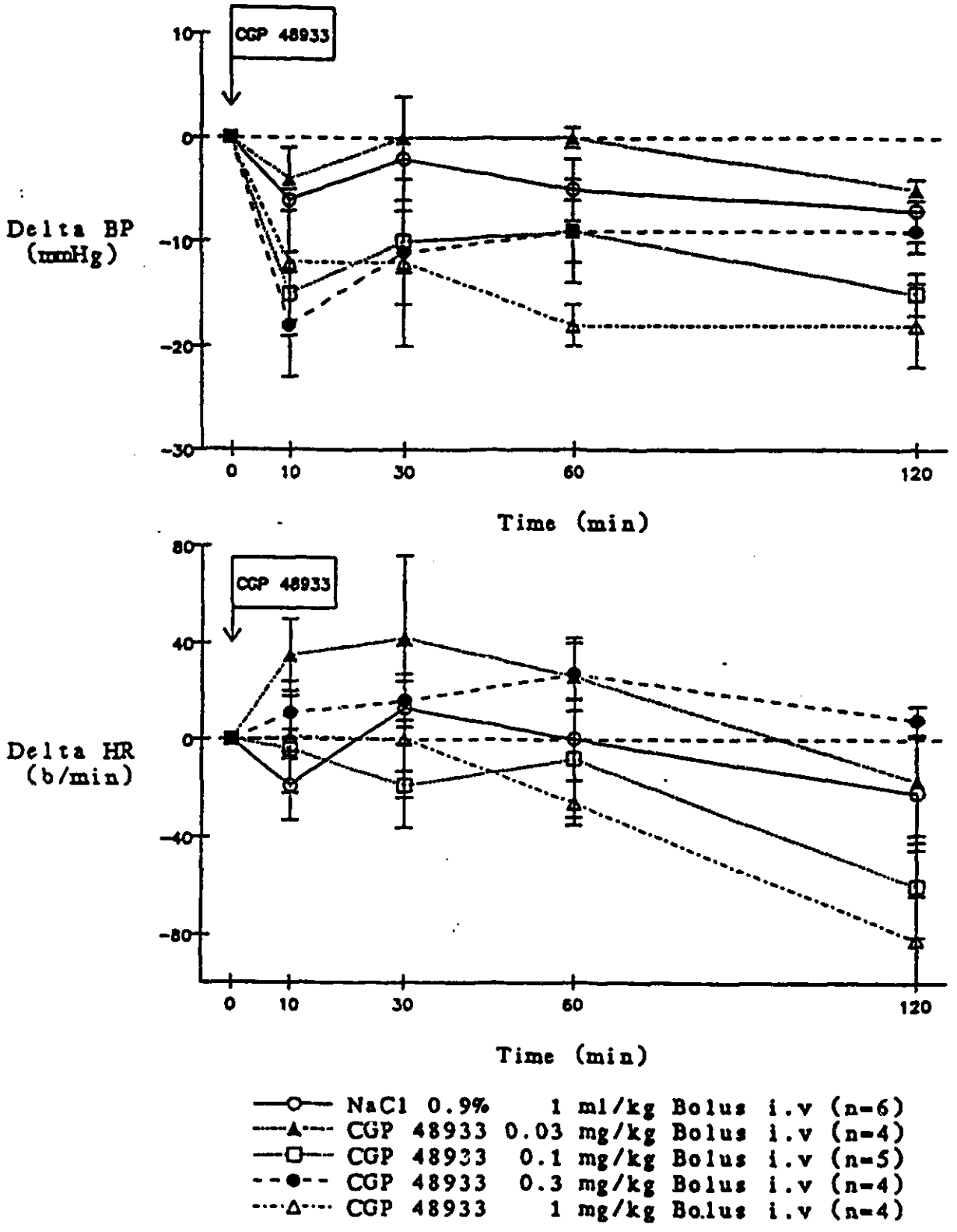


Fig. 11: Effect of CGP 48933 (i.v. administration) on blood pressure and heart rate in conscious sodium-depleted marmosets.

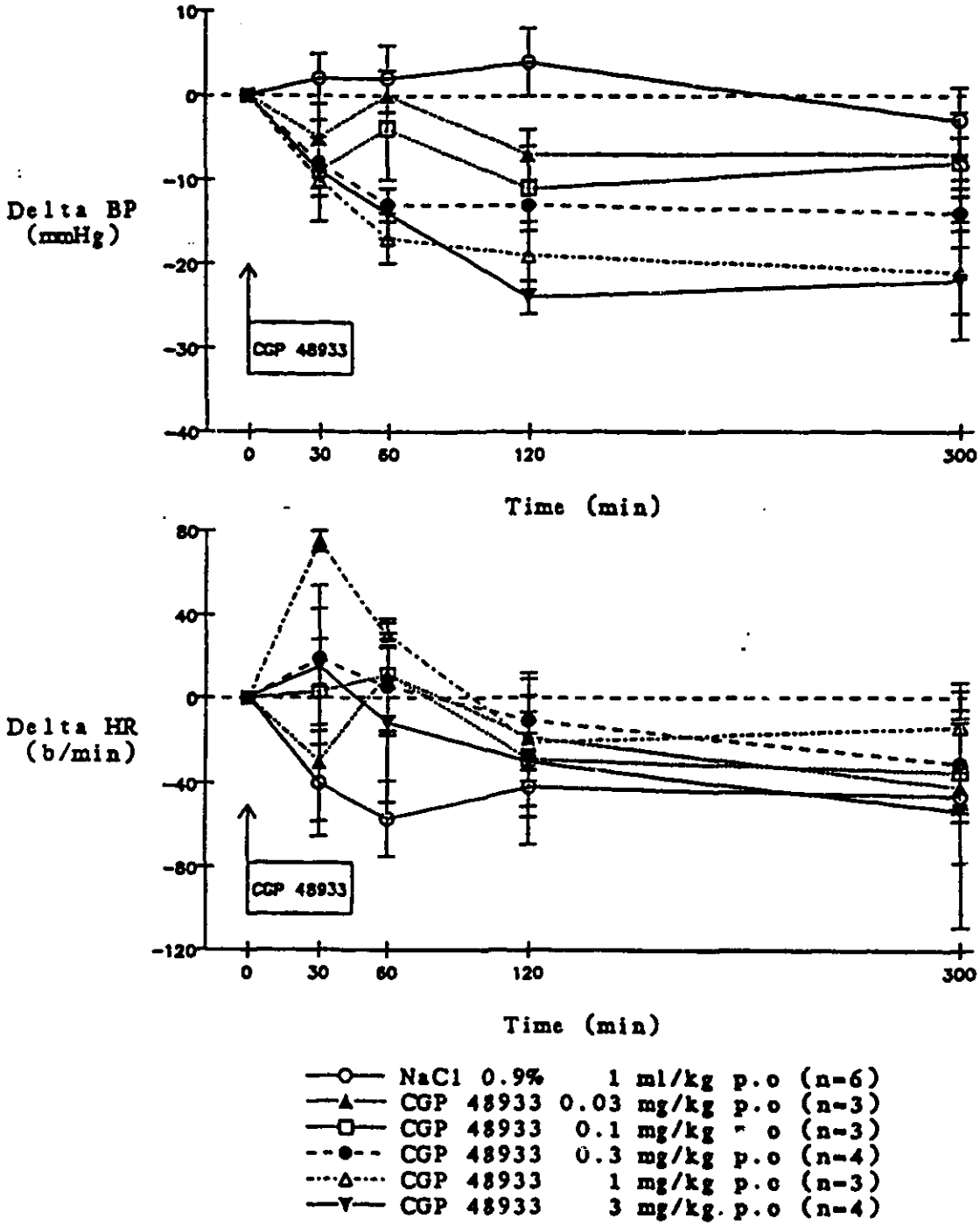


Fig. 12: Effects of CGP 48933 (oral administration) on blood pressure and heart rate in conscious sodium-depleted marmosets.

1.2. Other Studies

1.2.1. Cardiovascular Pharmacology

Effects of CGP 48933 on arterial pressure, aortic dP/dt_{max}, ECG and respiratory function were studied in anesthetized cats. All four animals survived cumulative intravenous injections (0.01-10 mg/kg) of CGP 48933. Doses 0.1 and 0.3 mg/kg caused marginal decreases in b.p., while 1 to 10 mg/kg resulted in slight step-wise decreases of about 10 mm Hg. Aortic dP/dt_{max} showed marginal and transient increases after 0.3 and 1 mg/kg, and slight increases after 3 and 10 mg/kg. Test compound did not affect respiratory function, heart rate or the ECG pattern up to the highest tested dose of 10 mg/kg.

1.2.2. Renal Pharmacology

Effects of CGP 48933 on urine and electrolyte excretion were determined in conscious female rats. Animals were given 3, 10, 30 or 100 mg/kg CGP 48933 (n=7 to 8 per dose) in 2 ml/kg of a 0.5% aqueous solution of methylcellulose by gavage. Urinary volume, and the concentrations of sodium, potassium and chloride were determined in urine collected over 2 three-hour periods. No effect of CGP 48933 was observed on any of the parameters in the first three hour collection, while in the subsequent three hours, a significant decrease in urine volume was observed (Table 4). In addition, distinct dose-related reductions (30 and 50%) in sodium and chloride excretion, and slight decreases in potassium excretion, were noted after 30 and 100 mg/kg (Table 4).

TABLE 4
EFFECTS OF CGP 48933 ON URINE AND ELECTROLYTE EXCRETION (3-6 HR) IN THE RAT

Treatment	Dose mg/kg	μeq/kg/hr Na^+	μeq/kg/hr K^+	μeq/kg/hr Cl^-	ml/kg/hr Urine
Control	-	143 ± 23	131 ± 16	136 ± 16	1.63 ± 0.14
CGP 48933	3	131 ± 21	124 ± 9	108 ± 22	1.17 ± 0.18
CGP 48933	10	143 ± 28	148 ± 22	142 ± 14	1.40 ± 0.15
CGP 48933	30	100 ± 18	99 ± 17	92 ± 11*	1.50 ± 0.11
CGP 48933	100	71 ± 11	102 ± 13	69 ± 8*	0.89 ± 0.12**

Values given are means ± SEM. *: $P < 0.05$ *versus* controls; **: $P < 0.01$ *versus* controls

1.2.3. CNS Pharmacology

Global behavioral assessment: Groups of male mice were given CGP 48933 (in 0.5% methocel) orally in doses of 1, 3, 10, 30, 100 or 300 mg/kg (n=4 per dose). All mice were continuously observed for the occurrence of symptoms for first 30 min and again 1, 2, 4, 6 and 24 hr after drug administration.

CGP 48933 did not induce any effect on the animal's spontaneous behavioral patterns. Further,

none of the tested doses induced either convulsions or death during the observation period.

Potentiation of ethanol-induced narcosis: Narcosis is induced by high concentrations of alcohol and by hypnotics such as barbiturates. Any drug that prolongs or shortens the process (e.g. sleep) can be interpreted as a potential hypnotic/sedative or antihypnotic.

CGP 48933 dissolved in 0.5% methocel was administered to rats at oral doses of 1, 3, 10, 30 or 100 mg/kg (10 mice/dose) 2 hr prior to an i.p. injection of 45% ethyl alcohol (10 ml/kg). Sleeping-time was defined as the interval (in minutes) between the loss and recovery of the righting reflex. Recovery was considered to be complete if the rat was able to right itself three times in succession after the initial righting reaction. CGP 48933 at any of the five doses tested lacked significant effect on ethanol-induced narcosis. Thus CGP 48933 is devoid of sedative or hypnotic potential.

Passive avoidance: Disturbance of cognitive processes, e.g. memory, tests the functional integrity of the brain. Drugs that influence the central neural functions are likely to interfere with memory processing. Drugs such as benzodiazepines, barbiturates and antiepileptics have memory disturbing effects. In the present study the effect of CGP 48933 was studied on the memory or 'learned experience' gained by rats in short-term training.

The test, 'one-trial dark avoidance', teaches mice to avoid entry into a dark box, which they normally enter because of their innate motivation or preference for dark. By doing so, they are punished by means of a brief electric footshock. When test is repeated 24 hr later, animals tend to remain for a longer time outside the dark box rather than entering the dark box. Thus an increase in latency during retest reflects a conflict between the innate motivation and the learned experience. Prolongation of the time spent outside the dark box was taken as a measure of learning performance and comparisons of retention between controls and treated groups indicated drug effects on retention performance. Retention was tested 3 days later under the identical conditions.

Mice (sex not given, n=20 per dose and vehicle, respectively) were given CGP 48933 orally in doses of 1, 3, 10, 30 or 100 mg/kg 2 hr before the training-trial. CGP 48933 did not negatively interfere with learning. There were no significant differences between the treated and the control groups.

Rota-rod test: In this test, animals are forced to keep their balance for a given period of time on a rotating cylinder. This requires functional integrity of diverse CNS centers and thus any signs of deteriorating performance may be indicative of interference with motor coordination, muscle relaxation and/or perception.

Male rats were trained before the study to stay on the rotating (at a speed of 11 rpm) cylinder for 300 sec. CGP 48933 dissolved in 0.5% methocel was administered orally at dosages of 1, 3, 10, 30, 100 or 300 mg/kg (n=8 per dose). Controls received vehicle. Performances were assessed

repeatedly 0, 1, 2, 4, 8 and 24 hr after administration of the drug or vehicle. All animals remained on the cylinder for the entire 300 sec and thus CGP 48933 had no significant influence on endurance time at any of the measurements.

Water consumption: Angiotensin II receptors (mainly AT_1) in the brain control water balance by increasing fluid-intake. Experimentally it has been demonstrated that water-intake increases in animals after intracerebroventricular or systemic administration of angiotensin II and this is blocked by angiotensin II antagonists. The present study was designed to study whether CGP 48933 affects spontaneous water-intake in rats.

CGP 48933 was administered in dosages of 1, 10, 30, 100 or 300 mg/kg to groups of 6 male rats per dose. Each rat's water consumption was recorded 1, 2, 3, 4, 12 and 24 hr after administration. Results indicated that CGP 48933 did not significantly affect water consumption at any of the doses tested.

Motility test: Stimulants increase and sedatives decrease motility. Two parameters that contribute to overall motility in rodents are locomotor activity (horizontal dislocations) and rearing (vertical movements). CGP 48933 was administered orally to male rats at dosages of 1, 3, 10, 30 or 100 mg/kg (n=8 per dose) one hour before the animals were placed into a transparent box. The frequencies of horizontal and vertical movements were recorded for the next 60 min. Comparison between drug-treated groups and controls indicated that CGP 48933 was devoid of any notable effects in this test.

1.2.4. Effect on Intraocular Pressure in a Rabbit Glaucoma Model

The study was designed to investigate the intraocular pressure-lowering effect of topically applied CGP 48933 in the glucose-induced transient hypertensive rabbit.

New Zealand white rabbits of both sexes were screened for any abnormal eye defects and grouped as follows:

Group 1: CGP 48933 at a 2% concentration in right eye/saline in left eye, n=6
Group 2: CGP 48933 at a 0.5% concentration in right eye/saline in left eye, n=6
Group 3: Physiological saline bilaterally (control), n=6

The right eye was treated with CGP 48933, the left with vehicle (saline) solution. Animals were dosed twice, two hours and one hour prior to start (0 min) of an i.v. glucose infusion (20 mg/kg, for 10 min).

During the transient induced ocular hypertension, there were significant differences after 10, 20 and 40 minutes between treated *versus* contralateral and treated *versus* control eyes reflecting an antihypertensive action of CGP 48933. The reduction in percent and the statistical significance of the respective differences are shown in table 5. The 2% solution was slightly more effective than

the 0.5% solution. The results show a marked efficacy in lowering intraocular pressure in the glucose-loaded rabbit glaucoma model during the transient ocular hypertension, but not in the normotensive rabbit eye (before glucose infusion). No eye irritation was observed after instillation of the solutions but CGP 48933 resulted in a dose-related miosis; pupillary diameter decreased from 6 to 3.5 mm with 2% and 6 to 4 mm with 0.5% solutions.

TABLE 5

INTRAOCULAR PRESSURE LOWERING EFFECT OF CGP 48933 IN THE GLUCOSE-LOADED RABBIT OCULAR HYPERTENSIVE GLAUCOMA MODEL.

	Decrease in IOP (%)					
	Vs Contralateral eye			*Vs* Saline control		
	Time Point (min)			Time point (min)		
	10	20	40	10	20	40
CGP 48933 2%	17.6	13.7	9.6	16.6	13.8	-1.9
CGP 48933 0.5%	14.9	7.8	5.1	12.8	0.7	-8.8
Saline control	0.0	-0.7	-3.3			

2. PHARMACOKINETICS

2.1. Single Oral and Intravenous Administration of CGP 48933 in Rats (Report #B15/1992)

This non GLP study was conducted by the division of Pharmacological Chemistry, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland between September 25 and November 15, 1990. The aim of the study was to obtain information on the pharmacokinetics of CGP 48933 after single oral and intravenous administration to random bred pedigree albino rats (Tif:RAIf, SPF) and to compare different formulations.

Four different formulations of CGP 48933 (batch #6) were prepared and administered either intravenously (1 mg/kg) or orally (10, 100 or 600 mg/kg) to groups of fasted rats as given in Table 2.1.1. The animals weighed between 130 and 253 g. Plasma levels of CGP 48933 were analysed from blood samples collected by retro-orbital puncture under anesthesia at 5 and 15 min (i.v. study only), 0.5, 1, 2, 4, 8 and 24 hr (both i.v. and oral studies) postdose. It should be noted that 2 to 4 animals (male and female combined) were used per dose and the same animal served as a blood donor at 6-8 different time points.

TABLE 2.1.1.
FORMULATION DOSE AND MODE OF ADMINISTRATION OF CGP 48933 IN RATS

Experiment No.	Species	Sex	Formulation	Dose [mg/kg]	Mode of administration
1	Rat	M	Solution in phosphate buffer pH 7	1	i.v
		M	Solution in phosphate buffer pH 7	10	p.o.
2	Rat	M/F	1% Suspension phosphate buffered pH 7 Klucel	100	p.o.
2	Rat	M/F	6% Suspension in 0.5% aqueous Klucel	600	p.o.
2	Rat	M/F	6% Solution in NaOH (0.25M)	600	p.o.

CGP 48933 was rapidly absorbed (t_{max} 0.5-1 hr) following oral administration at doses of 10 and 100 mg/kg, and plasma concentrations had returned to baseline values within 24 hr post-dosing. At the highest dose (600 mg/kg), CGP 48933 was absorbed rather slowly (t_{max} 1-8 hr) and plasma concentrations had not returned to baseline values at the end of sampling period. An extremely high variability was observed in the plasma concentrations of CGP 48933 due to a small number of observations. The estimated absolute bioavailability of CGP 48933 given as a solution at pH 7 in phosphate buffer was 73%. No difference in systemic bioavailability of CGP 48933 was observed between a dose of 600 mg/kg CGP 48933 given as a suspension in 0.5% Klucel and the same dose given as a solution in 0.25M NaOH (Table 2.1.2).

TABLE 2.1.2.
PHARMACOKINETIC PARAMETERS OF CGP 48933 DETERMINED IN THE RAT

Exp. No.	Animal No.	Sex	Formulation	Dose [mg/kg]	Route	AUC[a]	Cmax[b]	tmax [h]
1	mean n=2 to 4	M	Solution in phosphate buffer pH 7	1	i.v	2.1	9.2	-
1	mean n=2 to 4	M	Solution in phosphate buffer pH 7	10	p.o.	15.3	5.5	0.5
2	154	M	1% suspension phosp bufr pH 7 Klucel	100	p.o.	714.7	591.4	0.5
	155	M	1% suspension phosp bufr pH 7 Klucel	100	p.o.	152.6	35.9	0.5
	159	F	1% suspension phosp bufr pH 7 Klucel	100	p.o.	231.6	33.0	2.0
	160	F	1% suspension phosp bufr pH 7 Klucel	100	p.o.	162.3	18.0	0.5
	161	M	6% suspension in 0.5% aqueous Klucel	600	p.o.	618.1	38.0	8.0
	166	F	6% suspension in 0.5% aqueous Klucel	600	p.o.	513.4	32.6	1.0
	162	M	6% Solution in NaOH (0.25M)	600	p.o.	639.6	82.8	0.5
	167	F	6% Solution in NaOH (0.25M)	600	p.o.	770.6	352.6	0.5

a: h.µmol/l, b: µmol/l

2.2. Single Oral and Intravenous Administration of CGP 48933 in Marmosets (*Callithrix jacchus*) (Report # B15/1992)

This non GLP study was conducted by the division of Pharmacological Chemistry, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland from December 6 to 12, 1990. The aim of the study was to obtain information on the pharmacokinetics of CGP 48933 after single oral and intravenous administration to marmosets and to compare different formulations.

Three different formulations of CGP 48933 (batch #6) were prepared and administered either intravenously (1 mg/kg, bolus) or orally (100 or 600 mg/kg) to groups of non-fasted marmosets. The animals weighed between 295 and 482 g. Plasma levels of CGP 48933 were analysed from blood samples collected from the femoral vein in conscious state at 5 and 15 min (i.v. study only), 0.5, 1, 2, 4 (both oral and i.v.), 8 and 24 hr (oral only) postdose.

CGP 48933 was rapidly absorbed following oral administration in both male and female marmosets at doses of 100 mg/kg and in males at 600 mg/kg with t_{max} about 2 hr. Female marmosets dosed with 600 mg/kg displayed a later t_{max} (8 hr)(Table 2.2.1). Plasma concentrations of CGP 48933 had returned to baseline values within 24 hr postdosing in all groups. The increase in AUC between the doses of 100 mg/kg and 600 mg/kg was dose dependent but less than dose proportional; lack of adequate number of animals (n=2/sex/dose) or individual animal data in the report precludes further interpretation of the results. The estimated absolute bioavailability of CGP 48933 (based on the AUC after oral and i.v. administration) was similar at 100 and 600 mg/kg, about 3% in males and 9.5% in females.

TABLE 2.2.1.
PHARMACOKINETIC PARAMETERS OF CGP 48933 DETERMINED IN MARMOSETS

Animal No.	Sex	Formulation	Dose [mg/kg]	Route	AUC[a]	Cmax[b]	tmax [h]
mean n=2 to 4	M	0.04% Solution phosphate buffer pH 7	1	i.v	13.4	18.2	-
mean n=2 to 4	F	0.04% Solution phosphate buffer pH 7	1	i.v	8.5	19.1	-
mean n=2 to 4	M	2% Suspension in 0.5% aqueous Klucel	100	p.o.	44.6	11.0	2
mean n=2 to 4	F	2% Suspension in 0.5% aqueous Klucel	100	p.o.	78.9	10.4	2
mean n=2 to 4	M	12% Suspension in 0.5% aqueous Klucel	600	p.o.	205.8	46.5	2
mean n=2 to 4	F	12% Suspension in 0.5% aqueous Klucel	600	p.o.	493.1	38.4	8

a: h.µmol/l, b: µmol/l

2.3. Absorption and Disposition of ^{14}C-labelled CGP 48933 in Rats and Marmosets (Report #DM 3/1992, Study Protocol T91-7032)

This non GLP study was conducted by the division of Preclinical Safety/Drug Metabolism, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland from October 1991 to February 1992. The aim of the study was to investigate the absorption and disposition of ^{14}C-labelled CGP 48933 in male rats and male marmosets.

Solutions of [^{14}C]CGP 48933 (batch #MO-20.8B and MO-20.8B-2) were prepared in phosphate buffer pH 7 (0.07 mol/l). The drug was administered at a dose of 1 mg/kg intravenously as a bolus injection into tail vein of rat and femoral vein of marmoset. It was also administered orally (by gavage) at a dose of 3 mg/kg for male rat (random bred pedigree albino rats Tif:RAIf, SPF) and 1 mg/kg for male marmoset (*Callithrix jacchus*) The rats were 6-9 weeks old and weighed 195-280 g, while marmosets weighed 200-400 g. It is not clear from the report whether the animals were fasted before and during drug administration.

For the kinetic experiments, blood samples were collected from the retroorbital plexus of rat at 0 (orally dosed animals only), 0.08 (i.v. only), 0.25, 0.5, 1, 2, 4, 8, 24 (both i.v. and oral), 48 and 72 hr (oral only) after dosing. All dosed rats served as donors of blood at all time points (n=3/route/time point). In case of marmosets, blood was collected from the femoral vein at 0 (orally dosed animals only), 0.17 (i.v. only), 0.5, 1, 2, 4, 8, 24 and 48 hr (both i.v. and oral) after dosing and each marmoset served as donor at only four time points (n=4/route but 2/time point).

For the excretion experiments, urine was quantitatively collected on ice up to 96 and 168 hr postdose for marmosets (n=3) and rats (n=3), respectively; fractions were changed after 8 and 24 hr and thereafter daily. Feces were quantitatively collected daily for the same duration. In bile duct cannulated rats (n=5/route), bile was quantitatively collected on ice from conscious animals for time intervals of 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 and 24-48 hr after i.v. or oral administration of CGP 48933. Urine and feces were collected from the same animals up to 24 hr; fractions were changed after 8, 24 and 48 hr. For distribution studies, the rats (n=3/route) were killed under anesthesia and selected organs and tissues obtained by dissection were subjected to radiometry (n=3).

Results

Kinetics: The concentrations of radioactivity in both blood and plasma started to decline rapidly in a multiexponential manner after intravenous administration of 1 mg/kg ^{14}C-CGP 48933 to rats. The drop reached to a low level by 8 hr and radioactivity was no longer detectable in any of the animals at 24 hr postdose (Table 2.3.1). With oral administration, the concentrations of radioactivity reached peak in about 15 minutes and started to decline thereafter in a multiexponential manner (Table 2.3.2). The concentration-time profile suggested that the absorption was prolonged. The concentrations of radioactivity were below the level of detection at 24, 48 and 72 hr. In marmosets, the rate of decline of the radioactivity in blood and plasma

TABLE 2.3.1.: Concentrations of radioactive substances in blood and plasma of male rats after intravenous administration of 1 mg/kg ^{14}C-labeled CGP 48 933.

14C-Concentration expressed in pmol/g								
Time	in blood				in plasma			
[h]	RA4	RA5	RA6	Mean	RA4	RA5	RA6	Mean
.08	2893	3589	6158	4210	5592	7610	12850	8684
.25	849	1458	1701	1336	1597	1458[b]	3324	2126
.50	442	778	858	693	781	3019[b]	1606	1802
1.00	237	375	478	363	424	694	835	651
2.00	251	137	290	226	407	227	497	377
4.00	70	58	152	94	108	88	254	150
8.00	12	50	33	32	16	85	55	52
24.00	NS	NS	NS	0	NS	NS	NS	0
AUC[a]	1473	2064	2782	2106	2516	4060	5076	3884

a : [(pmol/g).h]; 0.08 - 24 hours
b : the samples were most likely exchanged
NS: not significant

TABLE 2.3.2.: Concentrations of radioactive substances in blood and plasma of male rats after peroral administration of 3 mg/kg ^{14}C-labeled CGP 48 933.

14C-Concentration expressed in pmol/g								
Time	in blood				in plasma			
[h]	RA10	RA11	RA12	Mean	RA10	RA11	RA12	Mean
0.00	NS	NS	NS	0.0	NS	NS	NS	0.0
.25	1766	2489	1620	1942	3368	4229	2684	3427
.50	1732	2024	1106	1621	3317	3408	1980	2902
1.00	1043	1412	644	1033	1798	2345	1109	1751
2.00	1270	636	524	810	1898	1031	790	1240
4.00	605	395	542	514	941	621	842	801
6.00	234	163	538	312	329	245	812	462
8.00	98	157	151	135	138	213	228	193
24.00	NS	67	57	41	NS	60	64	41
48.00	NS	6	NS	2	NS	NS	NS	0
72.00	NS	NS	NS	0	NS	NS	NS	0
AUC[a]	6330	7370	6740	6813	10100	10400	10100	10200

a : [(pmol/g).h]; 0 - 72 hours
NS: not significant

TABLE 2.3.3.: Concentrations of radioactive substances in blood and plasma of male marmosets after intravenous administration of 1 mg/kg ^{14}C-labeled CGP 48 933.

14C-Concentration expressed in pmol/g										
Time	in blood					in plasma				
[h]	MA 82	MA 83	MA 84	MA 85	Mean	MA 82	MA 83	MA 84	MA 85	Mean
.17	1588	3176	-	-	2382	3621	6282	-	-	4951
.50	-	-	560	779	669	-	-	1274	1666	1470
1.00	318	715	-	-	516	726	1166	-	-	946
2.00	-	-	183	512	349	-	-	392	760	576
4.00	112	339	-	-	225	217	507	-	-	362
8.00	-	-	79	54	67	-	-	137	100	119
24.00	21	29	-	-	25	37	42	-	-	39
48.00	-	-	4	11	8	-	-	7	16	12
AUC[a]					3522					6200

a: [(pmol/g).h] ; 0.17-48 hours
-: no sample taken

TABLE 2.3.4.: Concentrations of radioactive substances in blood and plasma of male marmosets after peroral administration of 1 mg/kg ^{14}C-labeled CGP 48 933.

14C-Concentration expressed in pmol/g										
Time	in blood					in plasma				
[h]	MA 80	MA 81	MA 86	MA 87	Mean	MA 80	MA 81	MA 86	MA 87	Mean
.00	NS	NS	-	-	0	NS	NS	-	-	0
.50	-	-	401	573	487	-	-	807	1264	1035
1.00	144	1542	-	-	843	340	2414	-	-	1377
2.00	-	-	388	510	449	-	-	831	1058	945
4.00	38	786	-	-	412	88	1089	-	-	588
8.00	-	-	36	44	40	-	-	88	89	88
24.00	2	27	-	-	14	5	33	-	-	19
48.00	-	-	NS	NS	0	-	-	1	1	1
AUC[a]					3465					5874

a : [(pmol/g).h] ; 0-48 hours
- : no sample taken
NS: not significant

after intravenous administration of 1 mg/kg ^{14}C-CGP 48933 was slightly slower than that observed in the rats. In contrast to the rat data, the concentrations of radioactivity in the marmoset were still above the detectable level 48 hr after dosing (Table 2.3.3). Similar declines in ^{14}C concentrations were observed after oral administration (Table 2.3.4). Because of limited number of animals/route of administration (2-3 animals per time point), half-life of radioactivity in blood and plasma was not calculated. Further, the sponsor states that in both rats and marmosets the specific AUC's (AUC/dose) for radioactivity in blood and plasma after oral administration were comparable to those found after i.v. dosing. However, there is no data in the report to verify this claim.

Distribution: Highest concentrations of radioactivity in the rat (only species studied) were observed in the liver, plasma, kidney and blood within 5 minutes after i.v. dosing. The uptake of the radioactivity was highest in liver . With oral administration, the uptake of the radioactive substance 15 min postdose was highest for the stomach followed by the liver, small intestine and plasma.

Excretion: The elimination of the radioactive substance from the system was rapid and complete in rats but sluggish and incomplete after 4 days in marmosets with both oral and i.v. dosing. Renal excretion constituted less than 2.0% of the dose in rats (n=3/route), while it was up to 16% of the dose in marmosets.

The first-pass biotransformation of CGP 48933 was investigated in bile duct cannulated rats. In these animals more than 95% of the absorbed dose was excreted in the bile after an i.v. dose of 1 mg/kg ^{14}C-CGP 48933 (Table 2.3.5). However, after oral administration of 3 mg/kg ^{14}C-CGP 48933, the recovery of radioactivity in the bile was between 22% and 45% (mean 32%) of the absorbed dose. Excretion in the feces as unabsorbed compound in orally dosed rats accounted 1 to 51% of the administered dose (see Table 2.3.6). Further, the total recovery of radioactivity in the excreta of these animals ranged from 25 to 97% (mean of 52%). Incomplete and highly variable recovery in individual animals (n=5), according to the sponsor, was due to the stress put on the animals by the surgical procedure.

Absorption: In rats, experiments with bile duct cannulated animals indicated that an orally administered dose of 3 mg/kg ^{14}C-CGP 48933 was absorbed to an extent of 22-46%. In marmosets, the sluggish and incomplete excretion of radioactivity after either route of administration suggests that after oral dosing most of the radioactivity excreted with the feces (75-80% of the dose) was due to the biliary excretion of absorbed material rather than to the fecal excretion of unabsorbed compound. Thus, in both rats and marmosets, after administration of ^{14}C-CGP 48933, most of the dose was excreted with the feces, irrespective of the route of administration.

TABLE 2.3.5.:

Cumulative excretion of radioactive substances in bile, urine and faeces of male rats after intravenous administration of 1 mg/kg ^{14}C-labeled substance.

Time interval (h)	Elimination in % of administered radioactivity																		Mean in bile, urine and faeces
	Bile						Urine						Faeces						
	RA64	RA65	RA66	RA67	RA68	Mean	RA64	RA65	RA66	RA67	RA68	Mean	RA64	RA65	RA66	RA67	RA68	Mean	
0- 2	85.9	72.5	88.0	66.5	81.5	82.9													82.9
2- 4	8.6	14.3	6.8	8.4	16.0	10.8													10.8
4- 6	2.3	4.6	1.8	2.8	4.6	3.1													3.1
6- 8	1.1	2.1	0.8	1.0	2.1	1.4	0.7	M	1.2	M	1.0	0.7	M	M	M	M	M	0.00	2.2
8- 12	0.8	1.6	0.7	0.8	1.5	1.1													1.1
12- 24	0.4	0.8	0.4	0.5	0.7	0.6	0.3	M	0.2	M	0.2	0.1	0.2	<0.1	0.1	<0.1	0.1	0.1	0.8
24- 48	0.1	M	0.1	0.1	0.1	0.1	<0.1	M	<0.1	M	<0.1	<0.1	M	M	<0.1	M	M	<0.1	0.1
0- 48	99.3	95.9	98.4	99.3	106	99.9	1.0	0.0	1.4	0.0	2.1	0.9	0.2	<0.1	0.1	<0.1	0.1	0.1	100.9

M : no sample

TABLE 2.3.6.:

Cumulative excretion of radioactive substances in bile, urine and faeces of male rats after peroral administration of 3 mg/kg ^{14}C-labeled substance.

Time interval (h)	Elimination in % of administered radioactivity																		Mean in bile, urine and faeces
	Bile						Urine						Faeces						
	RA56	RA57	RA58	RA59	RA60	Mean	RA56	RA57	RA58	RA59	RA60	Mean	RA56	RA57	RA58	RA59	RA60	Mean	
0- 2	4.17	7.31	8.92	8.18	4.90	6.71													6.71
2- 4	5.77	11.2	5.63	6.84	8.76	7.64													7.64
4- 6	4.55	7.54	2.75	2.65	11.1	5.72													5.72
6- 8	4.04	5.06	1.40	3.52	7.32	4.26	.25	.57	M	.46	.36	.33	M	M	M	M	M	0.00	4.59
8- 12	4.20	6.31	1.40	3.55	4.34	3.78													3.78
12- 24	5.69	6.19	1.88	2.47	1.75	3.60	.43	.72	.04	.16	.04	.28	27.9	40.0	3.44	13.6	1.01	17.0	20.88
24- 48	2.04	.87	.19	M	M	.03	.05	.16	.00	M	M	.04	M	11.3	M	M	M	2.25	3.12
0- 48	30.5	44.5	22.3	26.2	38.2	32.5	0.73	1.46	0.04	0.62	0.40	0.65	27.9	51.3	2.44	13.6	1.01	19.3	52.5

M : no sample

2.4. Absorption and Disposition of ^{14}C-labelled CGP 48933 in Mice (Report #DM(EU) 12/1994, Study Protocol 92-7033)

This non GLP study was conducted by the division of Preclinical Safety/Drug Metabolism, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland from October 1992 to November 1993. The aim of the study was to investigate the absorption and disposition of ^{14}C-labelled CGP 48933 in male mice.

Solutions of [^{14}C]CGP 48933 (batch #MO-20.8B, MO-20.8B-1, MO-20.8B-4 and MO-20.8B-3) were prepared in phosphate buffer pH 7 (0.07 mol/l). The drug was administered at a single dose of 3 mg/kg intravenously as a bolus injection into the tail vein of the mouse (Tif:MAGf(SPF)). The same formulation was administered at a dose of 3 mg/kg orally (by gavage). The next two higher oral doses, 200 and 600 mg/kg (also given by gavage), were suspended in 0.5% aqueous Klucel. The mice dosed with 3 mg/kg were fasted from 15 hr before to 6 hr after the adminstration, whereas the animals dosed with 200 or 600 mg/kg were not. The mice weighed 18-31 gm.

Blood was collected from the heart after anesthesia and exsanguination at 0.08, 0.5, 2, 4 and 8 hr from i.v. dosed animals; 0.25, 1, 2 (only in mice receiving 3 mg/kg p.o), 4, 8 and 24 (the latter hour only from mice receiving 200 and 600 mg/kg) hr after dosing (n=3/dose and time point). For the excretion experiments, mice were housed individually. Urine was collected separately on ice, on day 1 in two fractions: 0-8 hr and 8-24 hr, and thereafter daily up to 96 hr. Feces were quantitatively collected daily up to 96 hr. Bile was not collected in this study. For distribution studies, mice (n=3/route/dose) were killed under anesthesia and selected organs and tissues obtained by dissection were subjected to radiometry.

Results

Kinetics: The concentrations of radioactivity in plasma started to decline rapidly in a multiexponential manner after intravenous administration of 3 mg/kg ^{14}C-CGP 48933 to mice. The mean ^{14}C concentrations in plasma declined rapidly from 25 to about 0.9 µmol/l between 5 and 30 minutes, thereafter the concentrations decreased markedly slower and were 0.12 µmol/l at 2 hr and 0.05 µmol/l at 8hr, the last time point studied. With oral administration of 3 mg/kg the maximum mean ^{14}C concentration (1.9 µmol/l) was measured at 15 min, the first time point investigated, and started to decline distinctly thereafter up to 4 hr and remained approximately constant up to 8 hr, the last investigated time point (Table 2.4.1). On the other hand, in mice receiving 200 and 600 mg/kg doses, ^{14}C concentrations declined slowly up to 8 hr and were below the limit of detection after 24 hr (Table 2.4.1). This suggests a prolonged absorption phase at high doses. The absolute amount of CGP 48933 absorbed orally increased with increasing doses, but less than dose proportionally: the proportion of the dose absorbed orally decreased with increasing dose from 25% at 3 mg/kg to 13% at 200 mg/kg to 8% at 600 mg/kg. These numbers are in good agreement with AUC values (Table 2.4.2).

TABLE 2.4.1.

MEAN (N=3) CONCENTRATIONS OF TOTAL RADIOACTIVE SUBSTANCES (^{14}C) AND OF UNCHANGED CGP 48933 (BOTH EXPRESSED AS µMOL/L) IN PLASMA OF MALE MICE AFTER I.V. OR ORAL ADMINISTRATION OF [^{14}C]CGP 48933.

Time [HR]	3 mg/kg, i.v.		3 mg/kg, p.o.		200 mg/kg, p.o.		600 mg/kg, p.o.	
	^{14}C	CGP 48933	^{14}C	CGP 48933	^{14}C	CGP 48933	^{14}C	CGP 48933
0.08	24.95	14.60	ND	ND	ND	ND	ND	ND
0.25	ND	ND	1.86	0.61	6.56	3.34	41.42	21.94
0.5	0.89	0.58	ND	ND	ND	ND	ND	ND
1.0	ND	ND	0.85	0.39	8.31	3.68	12.45	2.91
2.0	0.12	0.00	0.13	0.07	ND	ND	ND	ND
4.0	0.10	0.00	0.04	0.00	4.81	1.88	10.87	4.89
8.0	0.05	0.00	0.10	0.08	3.16	1.68	3.68	2.38
24.0	ND	ND	ND	ND	0.00	0.00	<0.01	0.00
AUC[a]	6.70	3.60	2.19	0.91	67.30	31.95	118.9	57.3

a: $AUC_{(0\text{-}24h)}$ expressed as µmol/l.hr, ND: not determined. Not significant or not detected or below detection level is given as 0.00.

TABLE 2.4.2.
SPECIFIC AUC'S (AUC/DOSE), OF TOTAL ^{14}C SUBSTANCE(S) AND OF UNCHANGED CGP 48933 IN PLASMA OF MICE

	Dose and route of administration			
	3 mg/kg i.v.[a]	3 mg/kg p.o.[b]	200 mg/kg p.o.[c]	600 mg/kg p.o.[c]
Total ^{14}C	2.23	0.73	0.34	0.20
CGP 48933	1.20	0.30	0.16	0.10
Bioavailability (%)	-	25	13	8

a: AUC [(μmol/l).hr/(mg/kg)] calculated from 5 min to 8 hr
b: AUC calculated from 0 to 8 hr;
c:AUC calculated from 0 to 24 hr.

Excretion: The elimination of the radioactive substance from the system was rapid and between 74 and 90% within 24 hr. Like in rats and marmosets, the bulk of the dose (60-90%), was excreted in the feces within 24 hr (Table 2.4.3, 2.4.4). Thus, in all three species, irrespective of the route of administration the bulk of the administered dose was recovered in the feces suggesting that systemically absorbed compound is excreted predominantly with bile. The i.v. data indicate that the proportion of the systemically available dose excreted renally in mice (8%) was higher than that in rats (2% of the dose) but lower than that in marmosets (13%). At the end of the excretion experiments (96 hr post dose), the residual ^{14}C concentrations were below the limit of detection in almost all organs and tissues investigated, irrespective of the dose and route of administration.

TABLE 2.4.3.: Excretion in urine and faeces (3 mg/kg i.v. and p.o.)

Excretion of total radioactive substances with urine and faeces of male mice after intravenous and peroral administration of 3 mg/kg [^{14}C]CGP 48 933.

intravenous

Elimination in % of administered radioactivity

Time interval [h]	Urine				Faeces				Urine/ faeces
	MA94	MA95	MA96	Mean	MA94	MA95	MA96	Mean	Mean
0- 8	5.31	7.21	8.65	7.06	-	-	-	0.00	7.06
8-24	0.33	0.88	0.37	0.53	86.69	85.55	85.52	85.92	86.45
24-48	0.41	0.12	0.23	0.25	0.53	0.31	0.49	0.44	0.70
48-72	0.14	0.12	0.12	0.13	0.11	0.14	0.10	0.12	0.25
72-96	0.17	0.09	0.09	0.12	0.06	0.10	0.10	0.09	0.20
0-96	6.36	8.43	9.46	8.08	87.39	86.11	86.21	86.57	94.65

- Faeces of 0-24 hours were collected in one fraction.

The radioactivity in the final cage washings accounted for:
mice 94 = 1.55% of the dose
mice 95 = 1.42% of the dose
mice 96 = 1.55% of the dose

peroral

Elimination in % of administered radioactivity

Time interval [h]	Urine				Faeces				Urine/ faeces
	MA4	MA5	MA6	Mean	MA4	MA5	MA6	Mean	Mean
0- 8	2.81	2.42	2.62	2.62	-	-	-	0.00	2.62
8-24	3.43	1.95	0.71	2.03	86.06	86.31	90.41	87.59	89.62
24-48	0.67	0.54	0.07	0.43	2.16	0.85	0.50	1.17	1.60
48-72	0.09	0.13	0.05	0.09	0.12	0.09	0.11	0.11	0.20
72-96	0.03	0.11	0.05	0.06	0.05	NS	0.02	0.02	0.09
0-96	7.04	5.15	3.50	5.23	88.40	87.26	91.04	88.90	94.13

- Faeces of 0-24 hours were collected in one fraction.

The cage washings were used to homogenise the 0-24 hour faeces fraction.

TABLE 2.4.4.: Excretion in urine and faeces (200 and 600 mg/kg p.o.)

Excretion of total radioactive substances with urine and faeces of male mice after peroral administration of 200 or 600 mg/kg [^{14}C]CGP 48 933.

200 mg/kg

Excretion in % of administered radioactivity

Time interval [h]	Urine				Faeces				Urine/ faeces
	MA37	MA38	MA39	Mean	MA37	MA38	MA39	Mean	Mean
0- 8	1.57	0.94	1.51	1.34	-	-	-	0.00	1.34
8-24	9.51	5.50	2.97	6.00	70.05	59.80	74.49	68.12	74.11
24-48	0.71	0.61	1.17	0.83	0.30	9.96	5.87	5.38	6.21
48-72	0.05	0.08	0.18	0.10	0.04	0.10	0.18	0.11	0.21
72-96	0.02	0.09	0.03	0.05	NS	0.18	0.03	0.07	0.12
0-96	11.90	7.23	5.86	8.32	70.40	70.05	80.58	73.68	81.99

- Faeces of 0-24 hours were collected in one fraction.

The radioactivity in the final cage washings accounted for:
mice 37 = 0.02% of the dose
mice 38 = 5.27% of the dose
mice 39 = 0.10% of the dose

600 mg/kg

Excretion in % of administered radioactivity

Time interval [h]	Urine				Faeces				Urine/ faeces
	MA73.	MA74	MA75	Mean	MA73	MA74	MA75	Mean	Mean
0- 8	0.84	0.49	0.77	0.70	-	-	-	0.00	0.70
8-24	0.81	0.89	2.36	1.35	81.28	85.33	88.62	85.08	86.43
24-48	0.16	0.15	0.14	0.15	0.54	0.37	0.23	0.38	0.53
48-72	0.13	0.05	0.02	0.07	0.22	0.11	0.14	0.16	0.22
72-96	0.02	0.00	0.01	0.01	0.20	0.12	0.04	0.12	0.13
0-96	1.95	1.59	3.30	2.28	82.24	85.93	89.03	85.74	88.02

- Faeces of 0-24 hours were collected in one fraction.

The radioactivity in the final cage washings accounted for:
mice 73 = 2.61% of the dose
mice 74 = 2.21% of the dose
mice 75 = 2.73% of the dose

2.5. Disposition of High Oral doses of ^{14}C-labelled CGP 48933 in Rats and Marmosets (Report #DM(EU) 20/1994, Study Protocol T91-7032)

This non GLP study was conducted by the division of Preclinical Safety/Drug Metabolism, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland from March 1992 to July 1994. The aim of the study was to investigate the absorption and disposition of ^{14}C-labelled CGP 48933 following high oral doses in male rats and male marmosets.

Suspensions of [^{14}C]CGP 48933 (batch #MO-20.8B-1, B-3, B-12, B-13, B-18) were prepared in 0.5% aqueous Klucel HF. The drug was administered orally by gavage at a single dose of 60 or 600 mg/kg for male rats and 60 or 400 mg/kg for male marmosets. The animals were dosed in a non-fasted status. The rats (Tif:RAlf, SPF) were 6-8 weeks old and weighed 190-270 g, while marmosets (*Callithrix jacchus*) were 16-60 months old and weighed 309-441 g.

For the kinetic experiments, blood samples of about 0.5 ml/time point were collected from the retroorbital plexus of rat at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 96, 120, 144 and 168 hr after dosing. All dosed rats served as donors of blood at all time points (n=3/route/time point, see Tables 2.5.1 and 2.5.2) In case of marmosets, blood (1 ml) was collected from the femoral vein at 0, 0.5, 1, 2, 4, 8, 24 and 48 hr after dosing and each marmoset served as donor at all time points (n=4/route but samples could not taken at all time points, see Tables 2.5.3 and 2.5.4).

For the excretion experiments, rats were housed individually and urine was quantitatively collected on ice 8 hr after dosing and thereafter daily on ice up to 168 and 96 hr postdose for rats (n=3) and marmosets (n=3), respectively. Feces were quantitatively collected daily for the same duration. For distribution studies, rats (n=3/route) were killed under anesthesia and selected organs and tissues obtained by dissection were subjected to radiometry (n=3). Bile was not collected in the study.

Results

Kinetics: The concentration of radioactivity in plasma was higher than in blood in both species at all investigated time points suggesting an only marginal affinity of radioactive compounds to the blood cell. The ^{14}C concentration-time profiles in blood and plasma for both species were quite complex, displaying multiple peaks and shoulders, suggesting irregular absorption. At either dose level, the inter-individual variation in the blood and plasma ^{14}C concentrations was large, possibly due to inter-individual differences in the extent and/or the rate of oral absorption. Hence the mean value computed from the study cannot be regarded as representative for the kinetics in individual animals (Table 2.5.1). In both species, the ^{14}C concentrations in plasma were below the limit of detection after 72 hr at the latest, irrespective of the dose.

The mean specific blood-^{14}C AUC's after 60 or 600 mg/kg doses in rats (1.8 (µmol/l).h/(mg/kg)) were similar to those found after oral administration of 3 mg/kg (2.3 (µmol/l).h/(mg/kg))(see Table 2.3.2), indicating a dose proportional increase in the absolute quantity of test substance

orally absorbed and a dose proportional increase in systemic exposure of the rats to ^{14}C substances up to doses of 600 mg/kg [^{14}C]CGP 48933 (Table 2.5.1).

The specific AUC's of radioactive substances in the blood and plasma of marmosets were lower than those found earlier after oral administration of 1 mg/kg (see section 2.3 and Table 2.3.4). After the 60 mg/kg dose, the specific blood-^{14}C AUC (1.8 (µmol/l).h/(mg/kg)) was about 50% and after the 400 mg/kg dose (0.65 (µmol/l).h/(mg/kg)) about 20% of that obtained after i.v. or oral adminstration of 1 mg/kg (3.5 (µmol/l).h/(mg/kg)) (refer Tables 2.3.3 and 2.3.4), indicating that the orally absorbed quantity of CGP 48933 and the systemic exposure to marmosets ^{14}C increased dose dependently but in a less than dose proportional fashion (Table 2.5.1).

TABLE 2.5.1.
MEAN (N=3) CONCENTRATIONS (µMOL/L) OF RADIOACTIVE SUBSTANCES IN BLOOD AND PLASMA OF MALE RATS AND MALE MARMOSETS AFTER ORAL ADMINISTRATION OF [^{14}C]CGP 48933.

Time [HR]	Rat				Marmoset			
	60 mg/kg		600 mg/kg		60 mg/kg		400 mg/kg	
	Blood	Plasma	Blood	Plasma	Blood	Plasma	Blood	Plasma
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	5.10	10.79	17.38	33.73				
0.5	6.49	13.31	13.38	25.65	41.09	80.14	8.84	19.65
1.0	9.13	17.82	9.27	18.12	9.99	21.47	5.73	13.95
2.0	13.29	24.69	12.25	20.60	42.01	84.16	22.00	52.24
4.0	8.13	14.51	47.54	82.57	1.58	3.48	17.86	36.98
6.0	9.97	16.72	44.93	75.04				
8.0	3.57	5.57	29.38	46.11	1.38	2.25	15.44	27.51
24	0.47	0.74	24.38	38.05	0.00	0.20	0.50	0.76
48	0.11	0.17	4.10	6.69	0.00	0.16	0.00	0.41
72	0.00	0.04	0.00	0.00				
96	0.00	0.00	0.00	0.00				
120	0.00	0.00	0.00	0.00				
144	0.00	0.00	[illegible]	0.00				
168	0.00	0.00	0.00	0.00				
AUC[a]	111	190	1062	1697	110	221	260	505

a: $AUC_{(0\text{-}96h)}$ expressed as µmol/l.hr; blank space indicates the interval was not included in the study

Excretion: The elimination of the radioactive substance from the system in both species was virtually complete within 4-7 days, irrespective of the dose (Tables 2.5.5 to 2.5.6). The residual ^{14}C concentrations in organs and tissues at day 7 post dosing in rats were very close to or below the limit of detection, indicating an almost complete excretion of radioactive substances. In rats, 0.3 to 1.5% of the dose was excreted with the urine within 7 days. In marmosets, 1.9 to 6.8% of the dose was excreted with the urine within 4 days. In both species, the bulk of radioactivity (84 to 100% of the dose) was excreted with the feces.

TABLE 2.5.2.: Excretion after p.o. administration of 60 mg/kg to rats

Excretion of radioactive substance(s) in urine and faeces of male rats after peroral administration of 60 mg/kg [^{14}C]CGP 48 933.

Excretion in % of administered radioactivity

Time interval [h]	Urine				Faeces				Urine and faeces Mean
	RA84	RA85	RA86	Mean	RA84	RA85	RA86	Mean	
0- 8	0.36	0.35	0.33	0.35	-	-	-	-	0.35
8- 24	0.32	0.25	0.59	0.39	79.76	84.67	69.21	77.88	78.26
24- 48	0.03	0.03	0.10	0.05	8.84	10.92	27.19	15.65	15.70
48- 72	0.00	0.01	0.01	0.01	0.27	0.57	0.79	0.54	0.55
72- 96	0.00	0.01	0.00	0.00	0.03	0.08	0.06	0.06	0.06
96-120	0.00	0.00	0.00	0.00	0.02	0.02	0.02	0.02	0.02
120-144	0.00	0.00	0.00	0.00	0.01	0.02	0.00	0.01	0.01
144-168	0.00	0.00	0.00	0.00	0.02	0.00	0.02	0.01	0.01
0-168	0.71	0.85	1.05	0.80	88.95	96.28	97.30	94.17	94.98

-: Faeces were collected in one fraction between 0 and 24 hours

In the cage wash was found Rat 84: 1.58% of the dose
Rat 85: 2.20% of the dose
Rat 86: 1.48% of the dose

TABLE 2.5.3. Excretion after p.o. administration of 600 mg/kg to rats

Excretion of radioactive substance(s) in urine and faeces of male rats after peroral administration of 600 mg/kg [^{14}C]CGP 48 933.

Excretion in % of administered radioactivity

Time interval [h]	Urine				Faeces				Urine and faeces
	RA90	RA91	RA92	Mean	RA90	RA91	RA92	Mean	Mean
0- 8	0.03	0.04	0.08	0.05	-	-	-	-	0.05
8- 24	0.13	0.18	0.99	0.43	31.78	61.37	63.22	52.12	52.55
24- 48	0.34	0.04	0.40	0.26	24.56	29.88	35.37	29.94	30.20
48- 72	0.01	0.01	0.05	0.02	4.72	4.00	4.30	4.34	4.36
72- 96	0.00	0.00	0.01	0.00	0.43	0.15	0.21	0.27	0.27
96-120	0.00	0.00	0.00	0.00	0.03	0.02	0.03	0.03	0.03
120-144	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.01
144-168	0.00	0.00	0.00	0.00	0.02	0.01	0.02	0.02	0.02
0-168	0.51	0.26	1.53	0.77	61.55	95.44	103.2	86.72	87.48

- : Faeces were collected in one fraction between 0 and 24 hours

In the cage wash was found Rat 90: 0.56% of the dose
Rat 91: 1.30% of the dose
Rat 92: 1.34% of the dose

2.6. Distribution and Accumulation of Radioactivity After Single and Repeated Administration of ^{14}C-labelled CGP 48933 in Rats (Report #DM 12/1992, Study Protocol T91-7032)

This non GLP study was conducted by the division of Preclinical Safety/Drug Metabolism, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland in December 1991. The aim of the study was to investigate the extent of accumulation of ^{14}C-labelled CGP 48933 in the body after subchronic treatment in male rats.

Solutions of [^{14}C]CGP 48933 (batch #MO-20.8B-2) were prepared in phosphate buffer pH 7 at a concentration of 0.3 mg/g. The drug was administered to non-fasted male rats orally (by gavage) at a single dose of 3 mg/kg or once daily for 10 days at a dose of 3 mg/kg. The rats (Tif:RAIf, SPF) were 6-9 weeks old and weighed 250-280 g.

Twenty- four hours after the single or the last of 10 daily doses, the rats were exsanguinated under anesthesia and selected organs and tissues obtained by dissection were subjected to radiometry.

Results

The ^{14}C concentrations in the organs and tissues of rats receiving single oral dose were at or below the limit of detection, except for the liver (0.19-0.29 nmol/g), the stomach (0.01-0.41 nmol/g), the small intestine (0.02-0.16 nmol/g) and the kidney (0.02-0.03 nmol/g). Twenty-four hours after the last of 10 once daily doses of 3 mg/kg, ^{14}C concentrations in most of the organs and tissues were below the limit of detection (<0.2 nmol/g). In the liver, the ^{14}C concentrations were approximately 9-fold higher than after a single dose (Table 2.6.1).

TABLE 2.6.1.

MEAN ^{14}C CONCENTRATIONS (NMOL/G) IN ORGANS AND TISSUES OF MALE RATS 24 HOURS AFTER A SINGLE OR TEN ONCE DAILY ORAL DOSES OF 3 MG/KG [^{14}C]CGP 48933

SAMPLE	SINGLE DOSE	10 DOSES
Blood	0.00	0.05
Plasma	0.00	0.18
Salivary	0.00	0.01
Thyroid	0.00	0.00
Thymus	0.00	0.00
Lung	0.00	0.06
Heart	0.00	0.02
Aorta	0.00	0.02
Liver	0.24	2.12
Pancreas	0.00	0.01
Spleen	0.00	0.00
Adrenal	0.00	0.02
Kidney	0.02	0.29
White Fat	0.00	0.01
Testis	0.00	0.01
Muscle	0.00	0.01
Sciatic nerve	0.00	0.05
Bone marrow	0.00	0.03
Stomach	0.16	0.69
Small intestine	0.07	0.66
Skin	0.00	0.02
Brown fat	0.00	0.09
Eye	0.00	0.02
Brain	0.00	0.00

2.7. Biotransformation of CGP 48933 *in vitro* in Liver From Mouse, Rat, Rabbit, Dog, Marmoset and Man, and *in vivo* in Mouse, Rat and Marmoset (Report #DMET(EU) 15/1995, Study Protocols T91-7032, 91-7038, 92-7033 and amendment dated 07/5/96)

These non GLP studies were conducted by the division of Preclinical Safety/Drug Metabolism, Pharma-Research and Development of Ciba-Geigy Ltd., CH-4002, Basle, Switzerland from November 1991 to July 1994. The report describes the biotransformation of CGP 48933 (a) *in vitro* with postmitochondrial liver fractions (S12) of the male mouse, rat, rabbit, dog, marmoset and man; (b) *in vitro* with male rat hepatocytes; (c) *in vitro* with male rat liver slices and (d) *in vivo* with metabolite profiles of urine, feces and bile from male rats, and urine and feces from male mice and marmosets.

In vitro postmitochondrial liver fractions: Liver pieces obtained from mouse, rat, rabbit, dog, marmoset and man (male kidney donor) were homogenized and centrifuged separately and the postmitochondrial fraction (S12) was isolated. S12 from each species was incubated with an NADPH-regenerating system and 5, 50 or 500 µmol/l [^{14}C]CGP 48933 (dissolved in methanol). The incubations were for 30, 60 120 or 180 min. Rat S12 was also incubated with uridine 5'-diphospho-glucuronic acid (UDPGA) as a cofactor for glucuronidation by UDGPT and 100 µmol/l [^{14}C]CGP 48933 (with or without addition of NADPH-regenerating system) for 180 min. The incubation mixtures were analyzed by HPLC with radiodetection.

In vitro rat hepatocytes: Rat hepatocytes (from one animal only) were incubated with 50 µmol/l [^{14}C]CGP 48933 (dissolved in methanol) for up to 6 hr. Aliquots were taken at selected time points for analysis of fractions by HPLC.

In vitro rat liver slices: Rat liver slices (n=1) were incubated with William's E medium containing 50 µmol/l [^{14}C]CGP 48933 (dissolved in acetone) for 1, 2, 3 and 6 hr. Incubation was terminated by freezing the samples. The residue was reconstituted before analysis by HPLC.

In vivo metabolite profiles in mice, rats and marmosets: [^{14}C]CGP 48933 (batch #MO-20.8A) was dissolved in aqueous phosphate buffer (70 mM, pH 7) and [^{14}C]CGP 48933 was administered intravenously at a single dose of 1 mg/kg to rats and marmosets, and 3 mg/kg to mice. It was also administered orally (by gavage) at a single dose of 1 mg/kg for marmosets, 3 and 200 mg/kg for mice, and 3, 60 and 600 mg/kg for rats (n=3/dose group for each species). Urine and feces from all three species were collected at time intervals specified in Tables 2.7.2 through 2.7.4. Bile samples were collected only from rats (n=5/dose group).

Results

No metabolite peaks were detected at the lowest drug concentration of 5 µmol/l with S12 liver fractions from any of the species tested. The limit of detection was 50 µmol/l. No metabolite peaks were observed at any concentrations of CGP 48933 with S12 fractions from the mouse, rat,

rabbit and dog. Two minor metabolite peaks, P2 and P3 which are more polar than the parent compound, were detected in the human and marmoset S12 fractions at drug concentrations of 50 µmol/l. Incubation of rat S12 fractions with UDPGA enabled *in vitro* glucuronidation of CGP 48933. This resulted in detection of a minor metabolite, peak P4, which accounted for less than 2% of the total radioactivity. This metabolite had the same chromatographic behavior in HPLC as the main rat biliary metabolite, peak P4, which was identified as the acyl glucuronide of CGP 48933.

Incubation of [^{14}C]CGP 48933 with rat hepatocytes yielded three metabolite peaks. The major metabolite, peak P4, accounted for about one third of the radioactivity in the incubation medium (Table 2.7.1) and had the same chromatographic behavior in HPLC as the main rat biliary metabolite, peak P4. Metabolite peaks P2 and P3 accounted for about 7 and 2%, respectively, of total radioactivity. The metabolite peak P2 had the same retention time as metabolite peak P2 observed in rat urine.

TABLE 2.7.1: ***In vitro* metabolism of [^{14}C]CGP 48 933 by rat hepatocytes.**

[^{14}C]CGP 48 933 (50 µmol/L) was incubated with rat hepatocytes. Analysis was performed by reversed phase HPLC with on-line radiodetection. The values are the mean of two parallel incubations. The recovery from the incubations was 92 to 95%.

Sample origin	Incubation time [h]	Radioactivity in peak [% of analysed sample]1)					
		P1	P2	P3	P4	P5	CGP 48 933
Hepatocytes	0		3.1	0.5	2.4		86.3
	1		5.9	1.7	14.2		74.3
	2		6.5	1.7	27.7		58.6
	3		6.6	1.6	33.8		50.9
	6		7.1	1.9	33.7		51.3
Blank2)	6		2.5	0.3	2.6		87.3

1) blank indicate that no peak was detected
2) Incubation without hepatocytes

Rat liver slices also metabolized CGP 48933 mainly to its acyl glucuronide (peak P4), which accounted for about 20% of total radioactivity.

In vivo oxidative biotransformation of CGP 48933 was measured in urine and feces from mice, rats and marmosets and in bile from rats. The drug was excreted predominantly in the feces of all species. In the mouse, the renal excretion contributed 5-11% of the total dose. The 0-8 hr urine (2-5% of the dose) consisted of 3 major metabolite peaks, P1, P2 and P5, and several minor metabolite peaks (not identified in the report). The 8-24 hr urine (3-10% of the dose) contained mainly unchanged CGP 48933 and the metabolite peak P5 (Table 2.7.2). The fecal extract, which accounted for 65-90% of the radioactive dose, contained mainly unchanged compound (>80%)

and the metabolite peak P5.

TABLE 2.7.2.: ***In vivo* metabolism of [^{14}C]CGP 48 933 in the mouse.**

Excretion of [^{14}C]CGP 48 933 and its metabolites in the urine and faeces. Analysis was performed by reversed phase HPLC with on-line radiodetection.

Sample origin	Route of administration	Dose [mg/kg]	Animal No.	Collection period [h]	Excretion [% of dose][1)]	Radioactivity in peak [% of collected sample] 2)					
						P1	P2	P3	P4	P5	CGP 48 933
URINE	i.v.	3.0	1	0-8	2.1	13	41			30	
	i.v.	3.0	2	0-8	3.1	14	40			24	
				8-24	2.4	8	8			9	69
	i.v.	3.0	3	0-8	4.9	11	36			34	
URINE	p.o.	3.0	4	0-8	2.8	13	51			10	
				8-24	3.4					28	60
	p.o.	3.0	5	0-8	2.4	14	47			8	7
	p.o.	3.0	6	0-8	2.6	17	50			6	
	p.o.	200	37	0-8	1.6	8	34			9	48
				8-24	9.5					4	95
	p.o.	200	38	8-24	5.5		3			6	91
	p.o.	200	39	8-24	3.0		3			24	71
FAECES	i.v.	3.0	1	0-24	79.4			2		4	88
	i.v.	3.0	2	0-24	65.0					7	93
	i.v.	3.0	3	0-24	78.9					6	95
FAECES	p.o.	3.0	4	0-24	86.0		2		1	12	82
	p.o.	3.0	5	0-24	86.3					8	93
	p.o.	3.0	6	0-24	90.4		2		1	1	94
	p.o.	200	37	0-24	70.0						100
	p.o.	200	38	0-24	53.8					5	95
				24-48	10.0						100
	p.o.	200	39	0-24	74.5					15	85

1) Data from ADE study [2]
2) blank indicate that no peak was detected

In the rat, less than 2% of the administered i.v. dose and less than 3% of the administered oral dose was excreted with the urine. P2 was the major metabolite (47-67%) detected in the urine following i.v. dosing but was only a minor metabolite (7%) following oral dosing. In the feces, the radioactivity was almost exclusively due to parent CGP 48933 (Table 2.7.3). The radioactivity excreted with the bile (91-100% after i.v., 18-65% after p.o.), irrespective of the route of administration and the dose, was predominantly unchanged CGP 48933 and one metabolite peak, P4. This metabolite accounted for 8-62% of the radioactivity, higher after oral than after i.v. administration of test substance (Table 2.7.3). The metabolite peak P4 was also found in rat hepatocytes and rat S12 liver fraction co-incubated with UDPGA. The latter observation suggests that glucuronidase does not hydrolyze the metabolite peak P4. The most intriguing aspect of the study is the conspicuous absence of P4 in the feces. The sponsor suggests that its absence in feces might be due, after its formation and excretion in the bile, to hydrolysis in the rat intestine and/or the feces. The sponsor has characterized only the metabolite peak P4. The molecular mass of this metabolite was 611 Da., i.e., 176 Da. higher than that of the parent compound. Further

characterization studies showed that the metabolite is the resultant product of conjugation of CGP 48933 with glucuronic acid. Thus, the biliary metabolite is the acyl glucuronide of CGP 48933.

TABLE 2.7.3.: ***In vivo* metabolism of [^{14}C]CGP 48 933 in rats.**

Excretion of [^{14}C]CGP 48 933 and its metabolites in the urine, faeces and the bile. Analysis was performed by reversed phase HPLC with on-line radiodetection.

Sample origin	Route of administration	Dose [mg/kg]	Animal No.	Collection period [h]	Excretion [% of dose][1]	Radioactivity in peak [% of collected sample] 2)					
						P1	P2	P3	P4	P5	CGP 48 933
URINE	i.v.	1.0	1	0-8	1.4	7	67	6			13
	i.v.	1.0	2	0-8	1.9		47				43
URINE	p.o.	600	77	8-24	2.3	5	7				88
FAECES	i.v.	1.0	1	8-24[3]	92.9						100
	i.v.	1.0	2	8-24[3]	89.4						100
	i.v.	1.0	3	8-24[3]	94.0						100
FAECES	p.o.	3.0	7	8-24[3]	71.6						100
				24-48	2.5						100
	p.o.	3.0	8	8-24[3]	72.2						100
	p.o.	3.0	9	8-24[3]	73.5						100
	p.o.	3.0	56	12-24[3]	27.9						100
	p.o.	3.0	57	12-24[3]	4.0						100
				24-48	11.3						100
	p.o.	3.0	59	12-24[3]	13.6						75[6]
FAECES	p.o.	60	81	0-24	66.2						100
				24-48	16.7						100
	p.o.	60	82	0-24	69.1						100
	p.o.	60	83	0-24	79.3						100
FAECES	p.o.	600	75	0-24	64.0						100
	p.o.	600	76	0-24	48.1						100
				24-48	28.9						100
				48-72	5.1						100
	p.o.	600	77	0-24	81.7						100
BILE	i.v.	1.0	64	0-6	96.8				15		85
	i.v.	1.0	65	0-6[5]	91.4				19		81
	i.v.	1.0	66	0-6[5]	96.5				16		84
	i.v.	1.0	67	0-6[5]	97.0				14		86
	i.v.	1.0	68	0-6[5]	102.0				8		92
BILE	p.o.	3.0	25	0-48	48.5				62		38
	p.o.	3.0	26	0-48[5]	69.0				32		68
	p.o.	3.0	56	0-48[5]	30.5				39		61
	p.o.	3.0	57[4]	0-2	7.3				19		81
		3.0		6-8	5.0				18		82
		3.0		12-24	6.2				22		78
	p.o.	3.0	58	0-48[5]	22.3				38		62
	p.o.	3.0	59	0-24[5]	38.3				43		57
	p.o.	3.0	60	0-24[5]	26.2				18		82

1) Data from ADE study [3]

2) Blank indicate that no peak was detected

3) No faeces sample collected between 0 and 8 or 12 hours (no defaecation)

4) Only selected bile samples from this animal were analysed

5) Pooled bile fractions

6) In the faeces of Rat No. 59 a metabolite less polar than CGP 48 933, different from P1 to P5, accounting for about 25% of the faecal radioactivity was observed

In the marmoset, a minor fraction of the dose (2-16%) was excreted with the urine within 96 hr. The first 8-hr urine consisted mainly (average 72%) of parent compound and the rest was made up of several metabolites. Of these, metabolite peak P3 was most prominent (Table 2.7.4) and was not cleavable by enzymatic or basic hydrolysis. This metabolite is similar to the main fecal metabolite in marmosets and to the metabolite peak P3 found in marmoset S12 liver fractions. Urine samples collected after 24 hr contained exclusively unchanged CGP 48933. The radioactivity in feces was mainly (≥71%) represented by parent compound. One fecal metabolite, peak P3, was observed at lower doses only (1 mg/kg, i.v. or p.o.). Strangely, none of the metabolites were identified in the feces at higher doses (60 and 400 mg/kg, p.o.).

TABLE 2.7.4.: ***In vivo* metabolism of [^{14}C]CGP 48 933 in the marmoset.**

Excretion of [^{14}C]CGP 48 933 and its metabolites in the urine and faeces. Analysis was performed by reversed phase HPLC with on-line radiodetection.

Sample origin	Route of administration	Dose [mg/kg]	Animal No.	Collection period [h]	Excretion [% of dose][1]	Radioactivity in peak [% of collected sample] 2)					
						P1	P2	P3	P4	P5	CGP 48 933
URINE	i.v.	1.0	28	0-96	12.1			24			76
	i.v.	1.0	29	0-96	15.6			21			79
	i.v.	1.0	30	0-8[3]	8.8		8	7	2		83
				24-48	1.8						100
				72-96	0.4						100
URINE	p.o.	1.0	35	0-48	6.9		4	9			87
	p.o.	1.0	36	0-48	9.0			10			90
	p.o.	1.0	37	0-8	1.1	6	5	11			84
				8-24	3.0		8	28			66
	p.o.	60	42	0-8	2.5	4	6	11			71
				8-24	1.1			13			87
	p.o.	60	43	0-8	2.7	6		11	4		72
	p.o.	60	44	0-8	0.5	14	12				75
	p.o.	400	49	0-8	0.4	20		8	7		60
				8-24	1.3	7		13			71
				24-96	3.0						100
	p.o.	400	50	0-8	1.9	12	4	8	6		67
	p.o.	400	51	0-8	1.1	12		14			73
FAECES	i.v.	1.0	28	24-48[3]	41.1			29			71
	i.v.	1.0	29	8-24[3]	23.3			5			90
	i.v.	1.0	30	8-24[3]	37.0			5			95
				24-48	29.4			5			91
				48-72	8.6			8			92
FAECES	p.o.	1.0	35	24-48[3]	58.5			9			91
	p.o.	1.0	36	48-72[3]	36.3			7			88
	p.o.	1.0	37	8-24[3]	58.8			13			87
				24-48	14.0			13			87
				48-72	2.7			18			82
	p.o.	60	42	0-24	72.4						96
	p.o.	60	43	0-24	48.5						100
				24-96	39.0						100
	p.o.	60	44	0-24	52.9						100
	p.o.	400	49	0-24	8.9						100
				24-96	75.8						100
	p.o.	400	50	24-48	36.6						100
	p.o.	400	51	0-24	42.8						100

1) Data from ADE study [3]
2) Blank indicate that no peak was detected
3) No sample between 0 and 8, 12 or 24 hour

2.8. *In vitro* Binding of CGP 48933 to Protein in Serum and/or Plasma of Human, Rat, Mouse, Dog, Marmoset and Rabbit , and *in vivo* binding to Human Plasma Proteins (Report #BPK(US) 1994/023)

The Bioanalytics and Pharmacokinetics division of Ciba-Geigy Corporation, Ardsley, New York conducted this non GLP study. The date of study is not given (date of report: April 4, 1994). The objectives of the study were to (a) determine *in vitro* binding of CGP 48933 to human and marmoset plasma proteins and to sera of rat, mouse, rabbit, and dog; (b) evaluate the effect of hydrocholorothiazide on the protein binding of test substance; and, (c) compare *in vitro* results with the *in vivo* protein binding observed in plasma samples from a clinical trial (protocol 10).

The binding of CGP 48933 at concentrations of 0.05, 0.5, 1 and 5 µg/ml was investigated in human plasma and human serum. CGP 48933 binding to dog, mouse, and rabbit sera was determined at concentrations of 1 to 100 µg/ml. The concentrations of test substance for experiments in rat serum and marmoset plasma were respectively, 0.5 to 100 µg/ml and 0.5 to 50 µg/ml. The binding of [^{14}C]CGP 48933 at concentrations of 0.05 and 5 µg/ml to human plasma was measured in the presence of unlabelled HCTZ at concentrations of 0.00015 to 0.15 µg/ml. A 4 hr equilibrium time was used for all experiments. Protein binding determinations were carried out by equilibrium dialysis at 37°C. The binding of CGP 48933 was also investigated in plasma samples from a clinical trial in which patients received single daily doses of 10 to 160 mg of the drug for 4 weeks.

Results:

The binding of CGP 48933 to human serum, plasma and serum proteins remained relatively constant (81 to 98.6%) over the concentration range tested. Albumin was the main protein involved in the binding of CGP 48933 to serum proteins (88 to 98%). The binding to human albumin was comparable among the three batches of albumin tested (mean values ranging from 89.3 to 95.8%). CGP 48933 did not significantly bind to either alpha-1-acid glycoprotein or gamma globulin. Thus, the binding of test substance to human plasma was determined to be essentially equal to that observed for human serum albumin. *In vivo* studies exhibited similar binding characteristics of CGP 48933 to those observed in the *in vitro* experiments.

No change in the bound fraction of CGP 48933 was observed when HCTZ was added at concentrations equivalent to those observed following a combined single 50 mg oral HCTZ and 160 mg oral CGP 48933 dose.

The mean fraction of CGP 48933 bound to proteins in sera and/or plasma of rat, dog, rabbit and marmoset ranged from 94 to 97%. In the mouse, the mean binding value was about 10% lower (82%) than that observed in human and the other animal species.

2.9. Pharmacokinetics in Man

Protocol 01, Report #B10/1992

The pharmacokinetics of CGP 48933 were evaluated in healthy male volunteers (not clear whether the subjects were fasted) after administration of single doses ranging from 10 to 400 mg. In this European protocol, a total of 32 healthy subjects entered the study. Of these, 24 subjects received test substance in dosages of 10, 20, 50, 100, 150, 200, 300 and 400 mg (n=3/dose), while 8 subjects (1 at each dose level) received placebo. Blood samples were taken before and at 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 hr after dosing. Urine was collected over the periods: 0-2, 2-4, 4-6, 6-8 and 8 to 24 hr postdosing to estimate CGP 48933 concentration. Besides drug levels, renin activity, aldosterone and angiotensin II levels were measured from the blood samples.

CGP 48933 was well tolerated in all subjects except for mild and unspecific adverse experiences. Plasma levels of CGP 48933 and renin activity increased at all dose levels, although there was considerable inter-individual variability. Maximal increases occurred at approximately 4 hr after dosing. The duration of effect tended to be prolonged after doses greater than 100 mg, lasting up to 24 hr after dosing. There was a weak dose-effect relationship with the parameters measured. However, plasma aldosterone levels remained unchanged.

Not all subjects at all dose levels demonstrated detectable CGP 48933 plasma levels. Thus, the inter-individual variation was considerable, especially after the lower doses (between 10 and 100 mg). Although there was a general tendency of the drug plasma levels to increase with increasing doses (Table 2.9.1), the individual data showed a wide scatter and overlap between the various doses. Median T_{max} values varied from 2 to 4 hr.

TABLE 2.9.1.
HUMAN PHARMACOKINETIC DATA* (PROTOCOL #01)

Dose, mg	Cmax, µmol/l	Tmax, h	AUC, h.µmol/l
10	0.06	2	0.26
20	0.40	2	3.85
50	0.24	3	1.19
100	0.50	3	2.90
150	1.04	4	8.80
200	1.01	4	5.14
300	1.11	4	10.09
400	1.80	2	8.70

*Parameter values are expressed as mean

The amount of CGP 48933 excreted in urine did not increase with dose. Between 1.4 and 5.7% of the dose was recovered as unchanged CGP 48933 over the 24-hr period after dosing. Mean cumulative urinary excretion was 3.01, 4.2, 3.84, 3.08, 3.56, 2.45, 2.28 and 2.38% of dose after the 10, 20, 50, 100, 150, 200, 300 and 400 mg doses, respectively. This suggests that metabolism and/or non-renal clearance is the main elimination pathway for CGP 48933.

Protocol 02. Report #HPH 91111

This was a double blind, placebo controlled, single dose, cross over study. The normal volunteers (not clear whether the subjects were fasted) received CGP 48933 in single doses of 10, 30, 100 or 300 mg, with a treatment free interval of at least 1 week between placebo and CGP 48933 administrations. Blood samples were collected predose, and at 1, 2, 3, 4, 6, 8, 10 and 24 hr after dosing. Urine was collected over the 24 hr interval after dosing, and analyzed for unchanged CGP 48933 by HPLC. Blood samples were analyzed for plasma concentrations of CGP 48933, renin activity and angiotensin II levels.

Administration of CGP 48933 to normotensive subjects proved to be well tolerated and the drug was a biologically active angiotensin II receptor antagonist at all doses tested. In spite of wide variation in biological response of the RAS, there was an overall relationship between dose and biochemical effects. CGP 48933 was detected in plasma at all dose levels in most of the subjects 1 hr postdosing. As in the previous study, high inter- and intra-subject variability were observed in the pharmacokinetic parameters evaluated. Time to reach maximum level varied from individual to individual (median value: 2 to 4 hr). Though AUC values increased with increasing doses, the increase was not dose proportional, and dose adjusted AUC (AUC specific) values decreased with increasing doses (Table 2.9.2). Urinary excretion of unchanged CGP 48933 did not increase with increasing doses and was maximum within 8 hr after dosing. Mean cumulative urinary excretion over 24 hr postdose was 5.43, 5.71, 2.54 and 2.5% of dose after the 10, 30, 100 and 300 mg CGP 48933, respectively. Since only a small proportion of the administered dose, 1 to 9%, was excreted unchanged in urine, the main elimination pathway for CGP 48933 is metabolism and/or non-renal clearance.

TABLE 2.9.2.
HUMAN PHARMACOKINETIC DATA* (PROTOCOL #02)

Dose, mg	Cmax, µmol/l	Cmax/dose µmol/l/µmol	tmax, h	AUC, µmol/l	AUC/dose h.µmol/l/µmol
10	0.23	0.023	2	1.62	0.17
30	0.39	0.013	2	2.94	0.10
100	0.68	0.007	3	5.82	0.06
300	1.47	0.005	4	14.96	0.05

*Parameter values are expressed as mean

Pooled data from protocols 03, 04, 06, 07, 13, 14, 15, 30, 36, 37, 38, 39, 42, 43, 47 and 48 (Amendment dated 13, 1996)

CGP 48933 reaches its maximal plasma concentration in approximately 2 hours postdosing. The average absolute bioavailability of an 80 mg dose is 23%. The low bioavailability is most likely due to its limited solubility in solutions with low pH (e.g., gastric acid).

TABLE 2.9.3.
OVERVIEW OF PHARMACOKINETIC DATA IN MAN
MEAN PLASMA CGP 48 933 AUC, CMAX AND TMAX IN HEALTHY MALE VOLUNTEERS FOLLOWING A SINGLE ORAL DOSE OF VALSARTAN UNDER FASTING CONDITIONS.

Dose, mg	Dose (mg/kg)*	N	Cmax, mg/L	Tmax, h	AUC, h.mg/L
40	0.57	6	1.28	2	7.9
80	1.14	49	1.96	2	11.2
160	2.29	245	2.46	2	15.3
200	2.86	16	3.46	2	21.3
320	4.57	13	3.33	3	28.3**

N = number of volunteers.
*Assuming a 70 kg weight for a healthy volunteer
** AUC(0-48h)

As in animals, CGP 48933 excretion is primarily fecal (approximately 70% of administered dose as unchanged drug), a reflection of extensive biliary excretion (88% of the dose). Only 10% of the dose is excreted in urine as unchanged drug. Thus, approximately 20% of an administered dose of CGP 48933 is metabolized. A metabolite (M1) which results from hydroxylation of CGP 48933, is the major metabolite and constitutes 23.3% of the bioavailable dose. According to the sponsor, M1 (valeryl-4-hydroxy metabolite or CGP 71580) is pharmacologically inactive. This metabolite was also found in marmosets (see Figure 4.1 under Overall Summary and Evaluation).

3. TOXICOLOGY

3.1. *Acute Toxicity Studies*

3.1.1. Acute Oral Toxicity Study in Rats

Location of Data: Vol. 13

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Report #010/93/SL, Test #92-6080, Exp #92R006

Study Dates: Dosing initiated: 2/2/93
Last necropsy: 3/4/93

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch #800391) were prepared in 0.5% CMC/0.5% Tween 80 in purified water. The drug was administered once, orally by gavage (20 ml/kg) at doses of 1000 or 2000 mg/kg (n=5/sex/dose). No control group in this study. Animals (Sprague Dawley, strain: Tif:RAlf (SPF)) receiving 1000 mg/kg were 46 - 53 days old and weighed between 165 gm and 195 gm (male) and 162 gm and 172 gm (female) when allocated to treatment. Animals receiving 2000 mg/kg were 64 - 71 days old and weighed between 320 gm and 325 gm (male), and 214 gm and 223 gm (female) when allocated to treatment. The rats were housed singly and kept at an average temperature of 21°C.

Observations/Measurements: All animals were frequently observed during the first 48 hours, after that daily, for any clinical signs and mortalities. Body weights and food consumption were measured daily. Necropsies were done at the end of the study on day 15; histopathological examinations were not done.

Results: No animals died. No treatment-related effects were observed either on body weights or food consumption. No clinical signs of toxicity were observed and no gross lesions were seen during the necropsy of the animals. The threshold for observed acute oral toxicity of CGP 48933 in this study was more than 2000 mg/kg body weight.

3.1.2. Acute Oral Toxicity Study in Marmosets

Location of Data: Vol. 13

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Report #012/93/SL, Test #92-6081, Exp #92J005

Study Dates: Dosing inititated: 3/2/93
Necropsied: 3/16/93

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch #800391) were prepared in 0.5% CMC/0.5% Tween 80 in purified water. Two male marmosets (*Callithrix jacchus*) of ages 2 years 9 months and 4 years 5 months and weighing 338 and 447 gm, respectively, at the start of the study, received single 1000 mg/kg oral gavage (20 ml/kg) doses of CGP 48933. Animals were singly housed.

Observations/Measurements: Both marmosets were frequently observed throughout the day for any clinical signs and mortalities for 14 days following treatment. Body weights and food consumption were measured daily. Necropsies were performed at termination of the study; histopathological examinations were not performed.

Results: No animals died. One animal showed moderate to severe vomiting of white material four times, viz. 5, 10, 11 and 11.5 min post dose. The other animal vomited once, 70 min after dosing. No treatment-related effects were observed either on body weights or food consumption. No clinical signs of toxicity were observed and no gross lesions were seen during the necropsy of the animals. Thus, the threshold for observed acute (non lethal) oral toxicity of CGP 48933 in marmosets was $\leq$1000 mg/kg.

3.1.3. Acute Oral Toxicity Study in Marmosets (Repeated)

Location of Data: Vol. 13

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals. Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Report #039/94/SL, Test #94-6129

Study Dates: Dosing initiated in males: 7/12/94, in females: 7/14/94
Last necropsy: 7/28/94

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch #800393) were prepared in 0.5% CMC/0.5% Tween 80 in purified water. One male (480 gm) and one female (495 gm) marmoset (*Callithrix jacchus*) of age 3 years and 1 month, at the start of the study, received single 600 mg/kg oral gavage (10 ml/kg) doses of CGP 48933. Selection of the dose was based on the previous study, in which a dose of 1000 mg/kg caused emesis. The animals were housed individually in one room.

Observations/Measurements: Both marmosets were frequently observed throughout the day for any clinical signs and mortalities for 14 days following treatment. Body weights and food consumption were measured daily. Necropsies were performed at termination of the study; histopathological examinations were not performed. Organs were not weighed. Tissue samples were collected from both animals for macroscopic examination.

Results: No animals died. No treatment-related effects were observed either on body weights or food consumption. No clinical signs of toxicity were observed and no gross lesions were seen during the necropsy of the animals. The threshold for observed acute oral toxicity of CGP 48933 in marmosets was more than 600 mg/kg body weight.

3.2. ***Subchronic and Chronic Studies***

Studies in rats

3.2.1. Fourteen-Day Oral Toxicity Study in Rats

Location of Data: Vol. 17

Testing Facility: Pharma-Toxicology, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Report #004/91/SL, Test #90-6289, Experiment #91R003

Study Dates: Dosing initiated: 1/29/91
Necropsied: 2/13/91

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch #charge 6) were prepared in 0.5% CMC/0.1% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily for fourteen consecutive days at doses of 60, 200 or 600 mg/kg. Control animals received the vehicle in a similar manner. The male and female rats (Sprague-Dawley, strain RAIf(SPF)) were 35 to 49 days old and had a body weight range of 125-140 g (male) and 120-135 g (female) at the start of the study. Each group consisted of 5 male and 5 female rats. The rats were housed in cages of 5 and kept at an average temperature of 21 °C. The doses were selected following consideration of a pilot acute oral toxicity study in which the highest dose of 600 mg CGP 48933/kg did not produce any clinical signs or untoward effects.

Observations/Measurements: All animals were frequently observed daily for any clinical signs. Body weights and food consumption were measured daily. Hematology and serum biochemistry were performed on blood samples collected from all rats on day 13. A urinalysis was performed on samples collected (16 hours period) on days 9 (males) and 10 (females). A full necropsy was performed at the end of the study. The following organs were weighed from all rats that were killed at the end of the study:

adrenals
brain
heart
kidneys
liver
lungs
ovaries
pituitary
prostate
salivary glands (submaxillary)
seminal vesicles
spleen
testes/Epididymides
thymus
thyroids/parathyroids
uterus

The following tissues/organs were taken at necropsy and preserved for histology.

Adrenals	Kidneys	Seminal vesicles
Aorta	Knee joint	Skeletal muscle (thigh)
Axillary lymph node	Liver	Skin
Bone marrow (sternum, femur)	Lungs	Spinal cord (cervical, thoracic, lumbar)
Brain	Mammary area	
Colon	Mesenteric lymph node	Spleen
Duodenum	Oesophagus	Stomach
Eyes/Optic Nerves	Ovaries	Testes/Epididymides
Gross lesions	Pancreas	Thymus
Harderian glands	Peripheral nerve (Sciatic)	Tongue
Thyroids/Parathyroids	Pituitary	Trachea
Heart	Prostate	Urinary bladder
Ileum	Rectum	Uterus
Jejunum	Salivary glands	Vagina

Eyes, Harderian glands and optic nerves were fixed in Davidsons' fluid. Brain and spinal cord were fixed in 10% neutral buffered formalin. All other tissues were fixed in Bouin's fluid. Where possible a reserve set of tissues was fixed in 10% neutral buffered formalin.

Results: There were no deaths and no clinical signs. An apparent slight reduction from concurrent control body weight gain in males ($p > 0.05$) and food consumption in both sexes ($p > 0.05$) was observed in all treated groups. However, the findings have no biological significance because of non dose-relationship and mean values that were within 10% of control. Slight increases ($p < 0.05$) above concurrent control blood urea nitrogen were found in males at 200 mg/kg (+28%) and in both sexes at 600 mg/kg (+35% ♂, +22% ♀). Urine volume in males was slightly increased above concurrent control volume at low (+45%), mid (+ 30%) and high (+85%) dose levels ($p > 0.05$). No differences due to treatment were seen in hematology parameters.

There were no organ weight changes attributable to treatment. At necropsy, one high dose male showed a dark depressed area in the glandular stomach, while the other two high dose males showed a small depression in the kidney and a dilated pelvis. The sponsor considered none of these findings to be toxicologically important. There were no histopathological findings related to treatment.

3.2.2. Three-Month Oral Toxicity Study in Rats

Location of Data: Vol. 18-19

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Report #007/92/SL, Test #90-6301, Experiment #91R015

Study Dates: Dosing initiated: 10/09/91
Last necropsy: 2/06/92

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch #800291) were prepared in 0.5% CMC/0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily for three consecutive months at doses of 60, 200 or 600 mg/kg. Control animals received the vehicle in a similar manner. The male and female rats (Sprague-Dawley, strain RAIf(SPF)) were 35 to 49 days old and had a body weight range of 78-95 g (male) and 75-95 g (female) at the start of the study. The rats were housed in cages of 5 and kept at an average temperature of 21 °C. Table 3.2.2.1 gives the experimental design of the study.

TABLE 2.2.1
CGP 48933: STUDY DESIGN. TEST #90-6301.

Group	Dose, mg/kg/day	No. of animals, sex	Duration
1	Control	10 ♂ + 10 ♀ 5 ♂ + 5 ♀	3 months 3 months + 1 month recovery
2	60	10 ♂ + 10 ♀	3 months
3	200	10 ♂ + 10 ♀ 5 ♂ + 5 ♀	3 months 3 months + 1 month recovery
4	600	10 ♂ + 10 ♀ 5 ♂ + 5 ♀	3 months 3 months + 1 month recovery

Observations/Measurements: All animals were observed daily for mortalities and clinical signs. Body weights were recorded daily during treatment period and weekly during recovery period, and food consumption was measured weekly. Water consumption was measured from week 6 of the treatment period and during the recovery period. An ECG recording was made from 3 males and 3 females from each group pretest and during weeks 4, 8 and 12. At week 16, a recording was made from 3 males and 3 females from the control, 200 mg/kg and 600 mg/kg groups. Hematology and serum biochemistry values were determined on blood samples collected from all rats pretest and during weeks 5, 9 and 13, and all recovery rats during week 17. Urinalysis

determinations were made on samples collected (16 hours period) from all rats during weeks 5, 9 and 13, and all recovery rats during week 17. A full necropsy was performed on all rats. Organ weights were determined for all rats killed at the end of the study. Microscopic examination was conducted on tissues from all control and high dose animals. See section 3.2.1. for the list of organs weighed and tissues/organs taken at necropsy and preserved for histology. If lesions were found in high dose animals, the affected tissues and organs were examined in rats from the other two dose groups and from the corresponding groups killed at the end of the recovery period.

Results: There were no treatment-related clinical signs or deaths. A female control rat died during blood sampling during week 5 (no abnormal findings at necropsy). Treatment did not affect body weight gain, food consumption or ECG. During the treatment period there was a slight but significant and dose-dependent increase in water consumption in males receiving 200 or 600 mg/kg. Although males at 60 mg/kg consumed (marginally) more water than the controls, the difference was not significant. A dose-dependent increase in mean blood urea was observed in males. The percent increases at the 200 and 600 mg/kg dose levels in weeks 5, 9 and 13 were, respectively, 16.65, 41; 36.2, 46.5; and 51.6, 89. During the recovery period mean urea levels of treated rats were similar to those of the controls. Red cell parameters (RBC, hemoglobin and packed cell volume) dropped in both sexes at the 600 mg/kg dose level (at all measurement times) to produce mild anemia. Values returned to normal during the recovery period. A slight nondose-related increase in urine volume in males at all dose levels throughout the treatment period may reflect a slight pharmacological effect and correspond to the slight increase in water consumption noted above.

There were no treatment-related findings at necropsy. Dose-dependent decreases (up to 19%) in absolute and relative heart and liver weights compared to concurrent control were noted for males at all dose levels including those in recovery groups. This reduction, according to the sponsor, reflects the pharmacological activity of the compound. At 600 mg/kg, absolute and relative thymus weights were moderately lower than control for both males and females, pituitary weights were moderately higher than control in females but lower than control in males, and spleen weights were minimally decreased compared with controls in males only. There were no drug-related histopathological findings for any of these organs and, except for heart and liver, no significant differences in organ weight values for animals killed at the end of the recovery period.

A minimal increase in incidence of renal tubular hyperplasia of proximal straight tubules in the outer medulla was observed in 6/10 males given 600 mg/kg and 2/10 males given 200 mg/kg. Two high dose male rats also showed a minimal increase in tubular basophilia within the cortex and medulla, generally accompanied by basement membrane thickening. Hypertrophy of renin-producing cells resulting in hypertrophy of the renal glomerular afferent arterioles occurred in 17 of 20 (9 ♂, 8 ♀) rats given 600 mg/kg and 12 of 20 (7 ♂, 5 ♀) animals given 200 mg/kg. Microscopic examination of kidneys of recovery group animals suggests that these effects of CGP 48933 are completely reversible.

In summary, oral administration of CGP 48933 at doses of 200 and 600 mg/kg for 3 months was

associated with dose-dependent increases in blood urea, increased water consumption, increased urine output, decreases in both absolute and relative heart weights, and morphologic changes in the kidneys. Even at 60 mg/kg, both absolute and relative heart weights were reduced, rats consumed marginally more water and voided more urine. Thus, the study failed to establish a no-effect dose level. The sponsor, however, considers all the changes observed, even at high doses, to be of no toxicological significance.

3.2.3. 6/12-Month Oral Toxicity Study in Rats

Location of Data: Vol. 20-21, 39(toxicokinetics)

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Report #032/93/SL, Test #91-6140, Experiment #91R011
Pharmacokinetics: Report #BPK(CH) 1994/054, Test #92-7009, Experiment #92R012

Study Date: Dosing inititated: 03/04/92
Last necropsy: 4/01/93

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch #800391) were prepared in 0.5% CMC/0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily for six (interim treatment period) or 12 (main treatment period) consecutive months at doses of 20, 60 or 200 mg/kg. Control animals received the vehicle in a similar manner. The male and female rats (Sprague-Dawley, strain RAIf(SPF)) were 35 to 49 days old and had a body weight range of 78-107 g (male) and 78-97 g (female) at the start of the study. The rats were housed in cages of 5 and kept at an average temperature of 21°C. Table 3.2.3.1 gives the experimental design of the study. The dosages were based on the results of a 3-month study (Test #90-6301, Section #3.2.2) where at 600 mg/kg increases in blood urea were observed in both sexes. Increased water consumption in that study was seen at all dose levels (60, 200 and 600 mg/kg) and morphological changes in kidney (incidence dose-related) were observed in male animals receiving 200 and 600 mg/kg/day.

Observations/Measurements: All animals were observed daily for mortalities and clinical signs. Body weights and food consumption were recorded weekly during the treatment and recovery periods. Water consumption was measured daily and presented weekly for each group. Ophthalmic and hearing examinations were made on all rats during the pretest period and on all rats from control and high dose groups during weeks 13, 26 and 52 and on recovery rats from control and high dose groups during week 56. ECG recording was made from 3 males and 3 females from each group pretest and during weeks 12, 25, 51 and during week 55 (recovery). Hematology and serum biochemistry measurements were performed on all rats from blood samples collected from the retro-orbital plexus under light anesthesia during the pretest period, weeks 13, 26 and 52 and during week 4 of recovery. Urinalysis determinations were made on samples collected (16 hour period overnight) from all rats during weeks 11, 24 and 50 and during week 4 of recovery. A full necropsy was performed on all rats. Organ weights were determined for all rats killed at the end of the study. Microscopic examination was conducted on tissues from all control and high dose animals. See section 3.2.1. for the list of organs weighed and tissues/organs taken at necropsy and preserved for histology. If lesions were found in high dose animals, the affected tissues and organs were examined in rats from the other two dose groups and from the corresponding groups killed at the end of the recovery period.

For pharmacokinetics study, blood samples (0.5 ml) were collected from 5 male and 5 female rats per group (exc ontrol) during weeks 13, 26, 39 and 52 at 0.5, 2, 4, 8 and 24 hr after administration o. P 48933. The same animals (2 to 5/sex) were reused at each time point.

TABLE 3.2.3.1
CGP 48933: STUDY DESIGN AND MORTALITY. TEST #91-6140

Group	Dose, mg/kg/day	No. of animals, sex	Duration of treatment	Mortality: No. of deaths and reasons
1	Control	10 ♂ + 10 ♀ 20 ♂ + 20 ♀ 5 ♂ + 5 ♀	6 months 12 months 12 months + 1 month recovery	1 ♂ killed on day 325, probably misintubation resulting in severe clinical signs
2	20	10 ♂ + 10 ♀ 20 ♂ + 20 ♀ 5 ♂ + 5 ♀	6 months 12 months 12 months + 1 month recovery	2 ♂ killed on days 75 & 325; 1 ♂ found dead on day 266: all dosing accidents. 1 ♀ killed on day 126: lethargy, moribund
3	60	10 ♂ + 10 ♀ 20 ♂ + 20 ♀ 5 ♂ + 5 ♀	6 months 12 months 12 months + 1 month recovery	2 ♂ killed on days 141 & 266, 1 ♀ killed on day 301, 1 ♂ found dead on day 266: dosing accidents. 1 ♀ killed on day 286: swelling of and discharge from the vagina.
4	200	10 ♂ + 10 ♀ 20 ♂ + 20 ♀ 5 ♂ + 5 ♀	6 months 12 months 12 months + 1 month recovery	1 ♂, 1 ♀ killed on days 267 &148: dosing accidents. 1 ♀ killed day 28: hunched, body wt. Loss. 1 ♀ killed on day 148: hunched, lethargy. 1 ♀ killed on day 294 due to the disabling effect of tissue mass

Results: A total of 15 unscheduled deaths or moribund sacrifices occurred during the treatment period. Most of these deaths/sacrifices were considered associated with dosing accidents (Table 3.2.3.1). Although three unscheduled sacrifices at the high dose, and 1 each at the mid and low doses were not related to misintubation, the report concludes that none of the losses were due to treatment with test substance. There were no mortalities during the recovery period. No clinical signs were observed that were considered due to treatment with CGP 48933.

Treatment had a significant effect on body weight gain (relative to control gain) in males receiving 200 or 60 mg/kg/day. Male rats in these groups showed a dose-related decrease (p values not provided) in body weight gain from week 8 through 26 of the study. During weeks 27 to 52, body weight gains were reduced only in high dose males. Males receiving 20 mg/kg/day and females in all dose groups showed no treatment-related effects on body weight. Further, body weight gains were similar in all groups during the recovery period. A small reduction in food consumption was observed only in males receiving 200 or 60 mg/kg/day for the entire treatment period. The

difference from control was 5.6% and 4.3% for high dose and mid dose males, respectively. During the first 26 weeks of treatment the maximum difference from controls for high dose males was 10% except for week 13 when the difference was 14%. However, the sponsor does not consider this to be of any toxicological significance. During the treatment period there was a significant increase in water consumption in males receiving 200 mg/kg/day. The difference from controls varied between approximately 15% and 30% throughout the treatment period. Males at 20 and 60 mg/kg/day also consumed (marginally) more water than the control during the first five weeks of treatment. Females showed no treatment-related effects on food or water consumption. No abnormalities were detected in male or female rats at ophthalmic, hearing or ECG examinations.

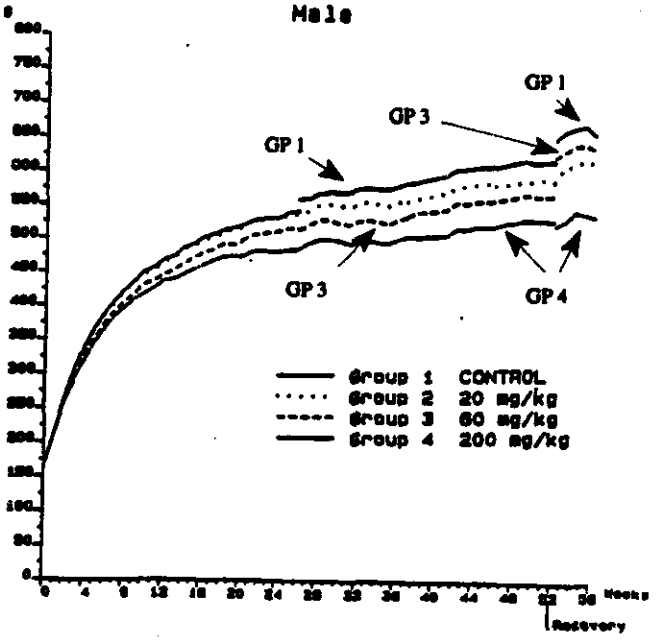


Fig. 3.2.3.1.: Mean body weight (gm) in male rats.

Minor differences from baseline in clinical chemistry, hematology and urinalysis values were observed in mid and high dose groups. Notable was a dose-related increase in mean blood urea at all sampling weeks in males. Dose-related decreases in absolute and relative heart weights were observed at all dose levels in both sexes. A slight decrease in liver weight for high dose males was observed at the terminal sacrifice (Table 3.2.3.2). Statistical significance of these differences was

TABLE 3.2.3.2
GROUP MEAN ORGAN WEIGHTS (GM). TEST #91-6140

Group		Terminal body weight		Heart				Liver			
				Absolute		% of body wt.		Absolute		% of body wt.	
		I	M	I	M	I	M	I	M	I	M
Control	Male	498	612	1.562	1.763	0.322	0.289	17.9	20.1	3.53	3.29
	Female	295	343	1.065	1.204	0.360	0.349	10.9	11.3	3.68	3.41
20 mg/kg/day	Male	540	588	1.440	1.598	0.267	0.272	20.1	18.7	3.73	3.18
	Female	298	354	1.054	1.163	0.355	0.329	10.0	11.4	3.34	3.24
60 mg/kg/day	Male	522	560	1.345	1.469	0.258	0.263	18.9	17.5	3.63	3.14
	Female	288	354	0.926	1.124	0.322	0.321	10.3	12.0	3.57	3.39
200 mg/kg/day	Male	488	534	1.222	1.427	0.251	0.268	16.6	16.9	3.40	3.15
	Female	308	355	0.929	1.081	0.304	0.306	10.4	11.7	3.37	3.30

I: Interim sacrifice; M: Main sacrifice

not addressed. A trace of arteriolar hypertrophy was noted in the kidneys of 15/19 high dose animals (10 males and 5 females) at the interim sacrifice and in 4 (males)/36 high dose animals at the terminal sacrifice. There were no similar findings in the kidneys of animals that had received 20 or 60 mg/kg/day or in animals examined after the recovery period.

In summary, daily treatment with CGP 48933 by oral gavage for 52 weeks at a dosage of 200 mg/kg/day was associated with a decrease in body weight gain and food consumption, and increases in urea and water consumption, relative to concurrent control. Food consumption and body weight gain, clinical chemistry, hematology and urinalysis were affected to a lesser degree at a dosage of 60 mg/kg/day. Additionally, a dose-related decrease in both absolute and relative heart weights was noted at all dose levels in both 6- and 12-month sacrificed animals. The low heart weight is thought to be related to the pharmacological action of drugs of this class and is normally observed in studies with ACE inhibitors. Microscopic examination revealed a trace of arteriolar hypertrophy in the kidneys of high dose animals killed after 6 or 12 months on study. It is suggested that drugs of this class induce morphological changes in the kidneys characterized by either hypertrophy or hyperplasia of the juxtaglomerular cells. Such a change is considered a pharmacologically stimulated response. None of the changes associated with CGP 48933 during the treatment period were observed during the recovery period, suggesting that the effects of CGP 48933 are reversible in rats.

CGP 48933 was absorbed rapidly (Tmax: 0.5 hr). The systemic exposure increased with the increase in dose but not in a proportional manner. (Table 3.2.3.3). The kinetics remained unchanged after repeated dosing. There was no difference in the systemic exposure between male and female animals .

TABLE 3.2.3.3

PHARMACOKINETIC PARAMETERS DURING REPEATED ORAL ADMINISTRATION OF CGP 48933 TO THE RATS. RESULTS ARE GIVEN AS MEAN. TEST #91-6140, #92-7009.

Week	Sex	Dose [mg/kg]	Cmax [µmol/L]	Tmax [h]	AUC(0.5-24h) [h(µmol/L)]	R*
13	M	20	9.2	0.5	48.1	
	M	60	22.8	0.5	94.6	
	M	200	44.0	0.5	216.3	
	F	20	4.6	0.5	28.0	
	F	60	22.9	0.5	56.2	
	F	200	24.5	0.5	127.4	
26	M	20	11.0	0.5	40.3	0.84
	M	60	18.1	0.5	80.7	0.85
	M	200	26.5	0.5	172.6	0.80
	F	20	4.0	0.5	15.1	0.54
	F	60	12.3	0.5	69.4	1.23
	F	200	16.4	0.5	155.9	1.22
39	M	20	16.7	0.5	75.7	1.57
	M	60	28.7	0.5	106.0	1.12
	M	200	44.8	0.5	218.4	1.01
	F	20	13.9	0.5	19.6	0.70
	F	60	22.2	0.5	126.5	2.25
	F	200	36.9	0.5	220.4	1.73
52	M	20	16.2	0.5	37.0	0.77
	M	60	24.4	0.5	119.9	1.27
	M	200	30.4	0.5	207.5	0.96
	F	20	5.1	0.5	20.3	0.73
	F	60	17.4	0.5	96.3	1.71
	F	200	21.3	0.5	184.3	1.45

(*R: Accumulation ratio = week n/week13)

3.2.4. 14-Day Intravenous Toxicity Study in Rats

Location of Data: Vol. 25

Testing Facility: Preclinical Safety, Section of Toxicology/Pathology, Ciba-Geigy Limited, Basel, Switzerland.

Identification No.: Test #92-6148

Study Dates: Dosing initiated: 10/05/92
Necropsied: 10/19/92

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Solutions of CGP 48933 (batch #16/047/1) in physiological saline were administered intravenously (10 ml/kg) into the tail vein, once daily for 14 consecutive days to groups of 5 male and 5 female rats at doses of 10, 30 or 100 mg/kg. Control animals received 0.9% NaCl in a similar manner. The male and female rats (Sprague-Dawley, strain: RAIf(SPF)) were 6 to 8 weeks old and had a body weight range of 175-286 gm at the time of dosing. Groups of 5 animals were housed in cages with diet and water *ad libitum*. The dose was selected based on the results of a pilot 14-day i.v. toxicity study in rats of the same strain. In that study, a dose of 100 mg/kg was tolerated without overt clinical signs or mortality but was associated with slight elevation in plasma creatinine and BUN values. Additionally, kidney pathology (subacute tubular lesions, hydronephrosis and pyelitis in females and pelvic dilatation in males) was observed.

Observations/Measurements: All animals were observed daily for mortalities and clinical signs. Body weight and food consumption were recorded daily during the treatment period. Water consumption was measured daily and presented weekly for each group. Hearing was tested for all rats terminally. Hematology and serum biochemistry values were determined on blood samples collected from all rats at the end of the study. Urinalysis determinations were made on samples collected from all rats on days 3 and 12. A full necropsy was performed on all rats on day 15. The weights of the following organs were recorded for all rats killed at the end of the study: adrenal glands, axillary lymph nodes, brain, epididymides, heart, kidneys, liver, lungs, mandibular glands, ovaries, pituitary gland, prostate, seminal vesicles, spleen, testes, thymus, thyroid with parathyroid glands and uterus. The following tissues from all control and high dose animals were sampled for microscopic examination: bone with bone marrow: sternum/femur, cecum, colon, duodenum, esophagus, eyes with optic nerves, harderian glands, ielum, tissues from the injection site, jejunum, knee joint, pancreas, rectum, sciatic nerve, skin with mammary area, spinal cord, stomach, thigh muscle, tongue, trachea, urinary bladder, vagina, tissues from all the weighed organs, and all other organs/tissues showing gross abnormalities during necropsy.

Results: There were no test substance-related physical signs, deaths or gross lesions observed during the treatment period. No treatment-related changes in body weight, food consumption or

water intake were evident. Sodium levels were slightly reduced below concurrent control levels in both sexes. Minimal and not significant elevations above concurrent control in serum magnesium, glucose, urea and creatinine were noted in males receiving the high dose. Also, males receiving 30 mg/kg/day showed slight elevations in serum magnesium, glucose and creatinine. Slight reductions in erythrocytic parameters (hemoglobin concentration, RBC, mean corpuscular volume) and WBC (in mid dose males also) were observed in high dose males. Partial thromboplastin time was prolonged in both males and females at 100 and 30 (10 in females only) mg/kg/day. Urinary pH urine was significantly elevated in high dose males on days 3 and 12, and in high dose females on day 3 only.

Slight and nonsignificant decreases in absolute and relative (to body and brain) heart weights (both sexes) and liver and spleen weights (males only) were observed in the high dose group. Prostate, thyroid and lungs in high dose males, and ovaries in high dose females showed significantly ($P < 0.05$) reduced weights. None of the organ weight findings were considered to be toxicologically significant since no pathology was evident in any of these organs at autopsy. No treatment-related macroscopic or microscopic findings were observed in any tissues or organs. Also, test substance injected intravenously caused no relevant irritative changes at the injection sites.

In summary, intravenous injection of doses up to 100 mg/kg/day of CGP 48933 for 14 consecutive days to rats caused no overt clinical signs or mortality. However, the high dose caused slight alterations in clinical biochemistry, hematology, urinalysis and organ weights but with no histopathological correlates.

Studies in marmosets

3.2.5. Fourteen-Day Oral Toxicity Study in Marmosets (*Callithrix jacchus*)

Location of Data: Vol. 25

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Test #91-6021, Experiment #91J003, Report #006/91/SL

Study Dates: Dosing initiated in males: 02/26/91, in females: 02/27/91
Last necropsy: 03/13/91

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 were prepared in 0.5% CMC. The drug was administered orally by gavage (10 ml/kg), once daily for fourteen consecutive days at doses of 60, 200 or 600 mg/kg (n= 2 ♂ + 2 ♀/dose). By mistake, on the first day of study low dose males received 90 mg/kg instead 60 mg/kg. Control animals (2 ♂ + 2 ♀) received the vehicle in a similar manner. The male and female marmosets were housed singly and were 18 to 48 months old with a body weight range of 306-461 g at the start of the study. The doses were selected following consideration of a range finding study (sponsor expt. #91J001) in which CGP 48933 was administered orally at increasing doses of 100→200→600 mg/kg to marmosets for 4 consecutive days at each dose level, followed by a 3-day recovery period prior to each dose increase. In that study, treatment-related effects were observed only at 600 mg/kg/day and consisted of slight to moderate increases in BUN, creatinine, magnesium and phosphate levels; microscopic observations of minimal renal tubular casts, cell debris and proteinaceous material; minimal renal cortical tubular dilatation; and marked lymphocytic infiltration of the gastric cardia.

Observations/Measurements: All animals on the 14-day study were frequently observed throughout the day for any clinical signs. Body weights were recorded three times a week and reported once weekly, and food consumption was measured daily. Hematology and blood chemistry values were determined on blood samples collected from all animals on days 0 and 13. A urinalysis was performed on samples collected over a 16-hour period on days 10 (males) and 9 (females). A full necropsy was performed at the end of the study. The following organs were weighed from all marmosets that were killed at the end of the study:

adrenals	lungs	seminal vesicles,
brain	ovaries	spleen
heart	pituitary	testes/Epididymides
kidneys	prostate	thymus
liver/gall bladder	salivary glands (submaxillary)	thyroids/parathyroids,
		uterus

The following tissues/organs were taken at necropsy and preserved for histology.

Adrenals	Knee joint	Skeletal muscle (thigh)
Aorta	Liver	Skin
Axillary lymph node	Lungs	Spinal cord (cervical, thoracic, lumbar)
Bone marrow (sternum, femur)	Mammary area	
Brain	Mesenteric lymph node	Spleen
cecum	Oesophagus	Stomach (cardia, fundus, pylorus)
Colon	Ovaries	Testes/Epididymides
Duodenum	Pancreas	Thymus
Eyes/Optic Nerves	Peripheral nerve (Sciatic)	Thyroids/Parathyroids
Gross lesions	Pituitary	Tongue
Heart	Prostate	Trachea
Ileum	Rectum	Urinary bladder
Jejunum	Salivary glands (submaxillary)	Uterus
Kidneys	Seminal vesicles	Vagina

Eyes and optic nerves were fixed in Davidsons' fluid. Brain and spinal cord were fixed in 10% neutral buffered formalin. All other tissues were fixed in Bouin's fluid. Where possible a reserve set of tissues was fixed in 10% neutral buffered formalin.

Results: There were no deaths. One high dose male vomited immediately after dosing on days 8, 9 and 11. Vomit on a food tray was noted for a high dose female on day 9. There were no differences in body weight gain, food consumption or hematological and urinalysis parameters between control and treated animals. Blood urea levels were above control in one mid dose male (+105%) and both high dose males (+90 and +152%), and both high dose females (+ 240 and 366%) at day 13.

Decreases in mean absolute and relative kidney (27%, 10%), liver (30%, 14%) and spleen (40%, 23%) weights were recorded in female marmosets given 600 mg/kg. However, these and other organs did not show any morphologic pathology related to treatment. Thus, the sponsor considers these findings to be of uncertain toxicological significance.

In summary, 600 mg CGP 48933/kg caused emesis and increased blood urea levels in both male and female marmosets and decreased absolute and relative kidney, liver and spleen weights in females. Increased blood urea levels were also observed in mid dose (200 mg/kg) males. There were no drug-related findings at necropsy or microscopy. The no-effect dose level (based on the increase in BUN) was 60 mg/kg.

3.2.6. Three-Month Oral Toxicity Study in Marmosets (*Callithrix jacchus*)

Location of Data: Vol. 26

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Test #90-6302, Expt. #91J010, Report #028/91/SL

Study Dates: Dosing initiated: 05/21/91
Last necropsy: 09/25/91

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch "#charge 6" and #800191) were prepared in 0.5% CMC/0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily for three consecutive months at doses of 30, 60, 200 or 600 mg/kg. Due to adverse effects at 600 mg/kg, animals of this dosage group were not dosed on days 19-22; dosing resumed on day 23 (except one male who was not dosed again until day 28) at a lower dosage of 400 mg/kg (Table 3.2.6.1). Control animals received the vehicle in a similar manner. The animals were 17 to 37 months old and had a body weight range of 308-511 gm at the start of the study. Animals were housed singly or in pairs of same sex.

TABLE 3.2.6.1
CGP 48933: EXPERIMENTAL DESIGN. TEST #90-6302

Group	Dose, mg/kg/day	No. of animals, sex	Duration
1	Control	3 ♂ + 3 ♀ 3 ♂ + 3 ♀	3 months 3 months + 1 month recovery
2	30	3 ♂ + 3 ♀	3 months
3	60	3 ♂ + 3 ♀	3 months
4	200	3 ♂ + 3 ♀ 3 ♂ + 3 ♀	3 months 3 months + 1 month recovery
5	600 → 400 mg*	4 ♂ + 4 ♀ 2 ♂ + 2 ♀	3 months 3 months + 1 month recovery

*: 600 mg/kg up to day 19, no dose on days 20-22, resumed dosing on day 23 at 400 mg/kg.

Observations/Measurements: All animals were observed daily for mortalities and clinical signs. Body weights were recorded once a week and food consumption was measured daily. Ophthalmic and hearing examinations were conducted on all marmosets during the pretest period and during weeks 4, 8, 12 and 16 (recovery period). ECG recordings were made from all marmosets pretest

and during weeks 4, 8, 12 and 16. Hematology and serum biochemistry measurements were made on blood samples collected from all animals during the pretest period, weeks 5, 9 and 13, and from marmosets of the recovery groups during week 17. Urinalysis determinations were made on 16 hr samples collected during weeks 5, 9 and 13, and from animals of the recovery g ups during week 17. A full necropsy, including organ weight determinations and microscopic examination of tissues, was performed on all marmosets. The following organs were weighed from all marmosets that were killed at the end of the study:

adrenals	lungs	seminal vesicles,
brain	ovaries	spleen
heart	pituitary	testes/epididymides
kidneys	prostate	thymus
liver/gall bladder	salivary glands (submaxillary)	thyroids/parathyroids,
		uterus

The following tissues/organs were taken at necropsy and preserved for histology.

Adrenals	Knee joint	Skeletal muscle (thigh)
Aorta	Liver	Skin
Axillary lymph node	Lungs	Spinal cord (cervical, thoracic,
Bone marrow (sternum, femur)	Mammary area	lumbar)
Brain	Mesenteric lymph node	Spleen
Cecum	Oesophagus	Stomach (cardia, fundus, pylorus)
Colon	Ovaries	Testes/Epididymides
Duodenum	Pancreas	Thymus
Eyes/Optic Nerves	Peripheral nerve (Sciatic)	Thyroids/Parathyroids
Gall bladder	Pituitary	Tongue
Gross lesions	Prostate	Trachea
Heart	Rectum	Urinary bladder
Ileum	Salivary glands (submaxillary)	Uterus
Jejunum	Seminal vesicles	Vagina
Kidneys		

Eyes and optic nerves were fixed in Davidsons' fluid. Brain and spinal cord were fixed in 10% neutral buffered formalin. All other tissues were fixed in Bouin's fluid. Where possible a reserve set of tissues was fixed in 10% neutral buffered formalin.

Results: Four high dose animals and one from the 200 mg/kg group were killed for humane reasons. Two high dose females killed on day 11 were found moribund and experienced emesis, ptosis, body tremors, marked lethargy and diarrhea on a number of days before sacrifice. One high dose male killed on day 23 had slight ataxia, moderately reduced activity, "ear tufts on end" and slight dehydration. A few days before sacrifice this animal showed signs of emesis, body tremors, underactivity and apparent dehydration. Another high dose male killed on day 25 of the recovery period showed severe lethargy, severe diarrhea with red staining, apparent dehydration and pale gums. One 200 mg/kg dosed female marmoset was found on day 20 collapsed in the cage, unable to move, hunched posture, white patches on tongue, piloerection, pupils constricted and was sacrificed. Histopathological examination of all five of these marmosets showed moderate to

severe nephropathy.

All high dose animals vomited throughout the treatment period, from immediately following dosing to 4 hours after dosing. Vomiting was severe during the first three weeks of the study when the dose was 600 mg/kg, the vomit being blood stained on occasions. The frequency of emesis decreased in this group when the dosage was reduced to 400 mg/kg. Emesis was also observed in 4/6 males and 3/6 females dosed at 200 mg/kg on occasions from weeks 4 to 13. Occasional post dose salivation was observed in a male and two females given 600→400 mg/kg, and in one female given 200 mg/kg. Piloerection, body tremors and hunched posture were observed on occasions during the treatment period in some animals from both high and mid dosage groups but were not dose dependent. A slight to moderate loss of skin elasticity was observed in both 600→400 mg/kg and 200 mg/kg dosed animals from week 7. Animals showing a moderate or marked loss of skin elasticity were given between 7 and 10 ml of 0.9% saline solution on a daily basis. All animals in both dosage groups showed recovery by the end of week 14. No treatment-related signs were observed in the lower two dosage groups.

Unlike the control and lower two dosage groups, animals receiving 600→400 and 200 mg/kg lost body weight every week of measurement. At the end of treatment (week 13) these animals weighed 6 to 8% below their initial weight, while control animals had gained 4 to 8%. The animals in the top two dosage groups did not fully regain their starting body weight even at the end of the recovery period (week 18). There was a higher incidence of days in which marmosets given 600→400 and 200 mg/kg consumed no food when compared to control marmosets. Another observation made by the sponsor was these animals were reluctant to eat (consequently loss of body weight) during or after some specific experimental procedures or just because of "discomfort" on intake of the drug.

Slight to very marked increases in blood urea (up to 1103%), creatinine (up to 989%) and alkaline phosphatase (up to 136%) were observed at weeks 5, 9 and 13 in almost all animals given 600→400 and 200 mg/kg (except creatinine in females at 200 mg/kg) and in one or two animals given 60 and 30 mg/kg. All these values were similar to those of the control animals or initial starting values by the end of the recovery period. Any meaningful statistical evaluation of the data is difficult because of the low number of animals per group and variation in individual readings, including control. Table 3.2.6.2 gives percent change in the values based on the group means.

All marmosets in the 600→400 and 200 mg/kg dosage groups exhibited a moderate anemia, without a high reticulocyte response, at week 5 with hemoglobin, RBC and PCV values remaining low through week 13 (Table 3.2.6.3). The severity was related to dosage. Anemia was still observed at the end of the recovery period although some improvement was seen in females receiving 400 mg/kg and in males and females at 200 mg/kg. No abnormalities were detected in the urinalysis.

TABLE 3.2.6.2
NOTABLE CHANGES IN THE CLINICAL CHEMISTRY PARAMETERS. GROUP MEAN VALUES ARE EXPRESSED AS PERCENTAGE CHANGE FROM THEIR OWN INITIAL READING AT WEEK 0. TREATMENT CONTINUED FOR 13 WEEKS (91 DAYS). TEST #90-6302

Dose		Urea			Alkaline Phosphatase			Creatinine		
		Wk 5	Wk 9	Wk 13	Wk 5	Wk 9	Wk 13	Wk 5	Wk 9	Wk 13
Control	♂	+58	-18	+41	+27	+18	+13	+4	-2	-4
	♀	-7	-2	+5	+17	+33	+11	-2	-6	-4
30	♂	-12	+14	+45	+45	+17	+11	0	+2	+6
	♀	+25	-18	+9	+28	+6	-10	+15	0	+7
60	♂	-0.3	+0.5	+45	+32	+25	+17	+9	+9	+4
	♀	-13	+4	+20	+31	+22	+10	-14	-22	-14
200	♂	+65	+170	+117	+32	+48	+28	+15	+235	+20
	♀	+20	+27	+77	+38	+19	+18	0	-4	+9
600-400	♂	+96	+98	+312	+54	+33	+59	-6	+156	+58
	♀	+5	+156	+148	+52	+82	+57	0	+395	+132

There were no significant differences in organ weights that could be attributed to drug treatment. All five animals sacrificed before term displayed pale kidneys. One high dose female also showed enlargement and mottling of both kidneys. A pale or tan colored friable liver and focal red discoloration of the stomach occurred in two high dose females. Dark red patches on the lungs were seen in one high dose male sacrificed during the recovery period. The 200 mg/kg female marmoset which died on day 20 exhibited pale adrenals, liver and kidneys with focal red discoloration of the stomach. Among high dose animals sacrificed at term two animals exhibited pale kidneys. There were no treatment-related findings in any other animals.

TABLE 3.2.6.3
NOTABLE CHANGES IN THE HEMATOLOGICAL PARAMETERS. GP MEAN VALUES ARE EXPRESSED AS PERCENT CHANGE FROM THEIR OWN INITIAL READING AT WEEK 0. TREATMENT CONTINUED FOR 13 WEEKS (91 DAYS) FOLLOWED BY 4 WEEKS OF RECOVERY (WEEK 17). TEST #90-6302

Dose		Hemoglobin				Red blood Cells				Packed Cell Volume			
		Wk 5	Wk 9	Wk 13	Wk 17	Wk 5	Wk 9	Wk 13	Wk 17	Wk 5	Wk 9	Wk 13	Wk 17
60	♂	-4	-6	-4	nd	-5	-7	-6	nd	-3	-8	-6	nd
	♀	nc	-4	+4	nd	-2	-4	+7	nd	nc	-4	+5	nd
200	♂	-9	-13	-14	-9	-9	-10	-11	-3	-9	-11	-13	-5
	♀	-6	-10	-9	-6	-8	-11	-8	-6	-7	-11	-10	-4
600-400	♂	-17	-18	-23	-21	-17	-15	-20	-7	-16	-18	-22	-17
	♀	-21	-20	-13	-11	-21	-23	-14	-9	-18	-20	-13	-6

nc: no change; nd: not determined; wk: week; -/+: decrease/increase

Microscopically, a range of changes in kidneys was observed in 4 of 5 animals (two females and one male at the high dose and one female at the 200 mg/kg level) that were terminated early in the study. A severe treatment-related nephropathy comprised varying incidences and severities of: tubulo-interstitial nephritis; tubular hyperplasia, indicative of tubular regeneration; tubular casts consisting of both proteinaceous and cellular debris; tubular dilatation; tubular degeneration comprised variously of necrosis, epithelial sloughing, vacuolation and eosinophilic cytoplasmic droplets; tubular lipid droplets; altered glomeruli characterized by nuclear pyknosis and increased mesangial substance. Besides this, both high dose females had ulceration of the stomach, and moderate and marked diffuse lipid vacuolation of the liver with multiple, small vacuoles in hepatocytes characterized by increased severity in periportal hepatocytes. One female marmoset showed moderate generalized adrenal cortical hypertrophy, which included minimal diffuse hypertrophy of the zona glomerulosa. The female marmoset receiving 200 mg/kg exhibited pyelonephritis and tubular cysts besides the incidences related to nephropathy described above. Moderate gastritis, in part erosive, with minimal focal necrosis, moderate diffuse esophagitis, moderate adrenal cortical hypertrophy and minimal hepatic periportal lipid vacuolation were also seen in this animal.

Among scheduled deaths, 4/5 high dose marmosets (2 males and 2 females) had treatment-related nephropathy, which was similar to that exhibited by those killed prematurely (as described above) but less severe. Tubular degeneration, tubular lipid droplets and glomerular changes were not seen but tubular basophilia was a significant component in all four animals. Minimal hypertrophy of renal afferent and efferent arterioles and interlobular arteries occurred in all 5 animals. The sponsor considers these effects to reflect the pharmacological activity of the compound since it is documented that all ACE inhibitors produce hypertrophy of renin producing cells at these sites. The severity of renal extra-medullary hemopoiesis was increased in all these animals. This correlated well with the occurrence of anemia in most of the animals. At 200 mg/kg, two male marmosets showed renal pathology. One animal showed marked degeneration of tubules and dilated Bowman's spaces, such that both contained considerable amounts of a globular, foamy material that did not stain for either lipid, mucopolysaccharide or amyloid. The other animal showed a minimal to moderate degree of tubulo-interstitial nephritis, tubular basophilia and tubular casts. There were no treatment-related findings in marmosets receiving 30 or 60 mg/kg doses of CGP 48933.

One high dose male marmoset that died during the recovery period (on 116th day) had nephropathy and the severity of it was similar to that seen in animals at this dose level killed at the end of the treatment period (see above). However, there was a greater evidence of regeneration as indicated by marked tubular hyperplasia. Minimal hypertrophy of afferent and efferent arterioles and interlobular arteries were present. Further, the sponsor observes that additional findings in the intestinal tract (minimal to marked lymphocytic enteritis), liver (minimal cholangitis, minimal multifocal chronic hepatitis, minimal focal necrosis) and gall bladder (moderate cholecystitis) are typically a feature of chronic debilitation in the marmoset and are likely to have contributed to early termination of this animal. Among scheduled deaths, a treatment-related nephropathy was

present in all three remaining high dose recovery group animals (2 females and 1 male). The characteristics of the nephropathy were similar to those seen at this dose level at the end of the treatment period, but severity was slightly reduced suggesting that recovery from these changes was partial. The level of renal extra-medullary hemopoiesis was also increased in these animals. At 200 mg/kg, one female killed at the end of the recovery period showed minimal tubulo-interstitial nephritis and trace tubular lipid droplets which were considered likely to be related to treatment but it was almost complete recovery in the rest of the animals.

In summary, marmosets of both sexes were administered CGP 48933 at dosages of 30, 60, 200 and 600 mg/kg for 3 months. Due to adverse effects at 600 mg/kg, animals were dosed at 400 mg/kg from day 23 and the severity of the clinical signs reduced. Four high dose animals and one receiving 200 mg/kg were killed for humane reasons. These and 4 other high dose and 2 other mid dose animals (i.e., 7/8 in all at the high dose and 3/6 in all at 200 mg/kg) exhibited moderate to severe toxic nephropathy. This was characterized by histological findings in the renal tubules, and marked increases in blood urea, creatinine and alkaline phosphatase. Also seen at the high dose was minimal hypertrophy of glomerular afferent and efferent arterioles and interlobular arteries, stomach ulcers, adrenal cortical hypertrophy and moderate to marked hepatic lipid vacuolation. The severity of increased levels of renal extra-medullary hemopoiesis observed in high dose animals correlated well with the occurrence of anemia. Recovery from these changes was partial in high dose animals and largely complete at 200 mg/kg.

3.2.7. 6/12-Month Oral Toxicity Study in Marmosets (*Callithrix jacchus*)

Location of Data: Vol. 27-28, and 39 (toxicokinetics)

Testing Facility: Preclinical Safety, Ciba-Geigy Pharmaceuticals, Stamford Lodge, Wilmslow, Chesire, U.K.

Identification No.: Test #91-6141, Experiment #91J007, Report #025/93/SL
Pharmacokinetics: Report #BPK (CH) 1994/053

Study Dates: Dosing initiated: 01/14/92
Last necropsy: 02/10/93

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Suspensions of CGP 48933 (batch 800391) were prepared in 0.5% CMC/0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily for 6 or 12 months at doses of 12, 40 or 120 mg/kg. Control animals (group 1) received the vehicle in a similar manner. Table 3.2.7.1. gives the experimental design of the study. Both male and female marmosets (*Callithrix jacchus*) weighed between 270 and 570 gm and were between 18 and 85 months of age at the start of the study. Animals were housed singly or in pairs of same sex.

TABLE 3.2.7.1
CGP 48933: STUDY DESIGN AND MORTALITY. TEST #91-6141

Group	Dose, mg/kg/day	No. of animals, sex	Duration of treatment	Mortality
1	Control	2 ♂ + 2 ♀ 4 ♂ + 4 ♀ 2 ♂ + 2 ♀	6 months 12 months 12 months + 1 month recovery	None
2	12	2 ♂ + 2 ♀ 4 ♂ + 4 ♀ 2 ♂ + 2 ♀	6 months 12 months 12 months + 1 month recovery	None
3	40	2 ♂ + 2 ♀ 4 ♂ + 4 ♀ 2 ♂ + 2 ♀	6 months 12 months 12 months + 1 month recovery	None
4	120	2 ♂ + 2 ♀ 4 ♂ + 4 ♀ 2 ♂ + 2 ♀	6 months 12 months 12 months + 1 month recovery	1 male killed on humane grounds on day 220. Pathology did not reveal any treatment-related effect

Observations/Measurements:

Mortalities		daily
Clinical signs		daily
Body weights		weekly
Food consumption		daily
Blood sampling for kinetics study		during weeks 23, 36 and 49
Ophthalmic, hearing and E.C.G. exams.		weeks 0, 12 24/25,38, 51 and 5[illegible] (recovery period)
Blood chemistry, hematology and urinalysis		weeks 0, 13, 26,39, 52 and 56 (recovery period)
Pathology:	-necropsy -organ weights -microscopy	on all animals.

The following organs were weighed from all marmosets that were killed at the end of the study:

adrenals	lungs	seminal vesicles,
brain	ovaries	spleen
heart	pituitary	testes/epididymides
kidneys	prostate	thymus
liver/gall bladder	salivary glands (submaxillary)	thyroids/parathyroids,
		uterus

The following tissues/organs were taken at necropsy and preserved for histology.

Adrenals	Knee joint	Skeletal muscle (thigh)
Aorta	Liver	Skin
Axillary lymph node	Lungs	Spinal cord (cervical, thoracic,
Bone marrow (sternum, femur)	Mammary area	lumbar)
Brain	Mesenteric lymph node	Spleen
Cecum	Oesophagus	Stomach (cardia, fundus, pylorus)
Colon	Ovaries	Testes/Epididymides
Duodenum	Pancreas	Thymus
Eyes/Optic Nerves	Peripheral nerve (Sciatic)	Thyroids/Parathyroids
Gall bladder	Pituitary	Tongue
Gross lesions	Prostate	Trachea
Heart	Rectum	Urinary bladder
Ileum	Salivary glands (submaxillary)	Uterus
Jejunum	Seminal vesicles	Vagina
Kidneys		

Eyes and optic nerves were fixed in Davidsons' fluid. Brain and spinal cord were fixed in 10% neutral buffered formalin. All other tissues were fixed in Bouin's fluid. Where possible a reserve set of tissues was fixed in 10% neutral buffered formalin.

For pharmacokinetics study, blood samples were collected from all animals except control during

weeks 23, 36 and 49, two hours after administration of CGP 48933.

Results: One high dose male was killed on humane grounds on day 220 of the study. Pathology did not reveal any treatment-related effect.Vomiting was observed on several occasions in almost all animals (8 males and 7 females) receiving 120 mg/kg/day and on a few occasions in 3 males and 5 females receiving 40 mg/kg/day, from immediately after dosing to up to 3 hr post dose. Among low dose animals, 3 males and 3 females vomited on up to 3 occasions, mainly during the first 26 weeks of the treatment period. The sponsor considered the vomiting to be the result of the taste of drug substance rather than a direct toxic effect on the GIT. Lack of any histopathological findings confirms the absence of gastrointestinal irritation caused by test substance. Fives males and 4 females in the high dose group, 3 males and 3 females in the mid dose group and one female in the low dose group showed slight to moderate loss of skin elasticity on a few occasions during the latter half the treatment period. This was probably due to mild dehydration resulting from vomiting. No clinical signs were observed during the recovery period.

No significant effects on body weight gain were observed in treated groups. A slight reduction in food consumption during the treatment period was observed in animals receiving 120 mg/kg/day and in females receiving 40 mg/kg/day. Further, the high dose animals continued to show a slight reduction in food consumption even during the recovery period. Treatment did not significantly affect hematological or urinalysis parameters, water consumption, hearing, ophthalmic or ECG parameters.

Four females and 1 male receiving 120 mg/kg/day showed a slight to a marked increase in blood urea and creatinine levels on several occasions. Two mid dose group males also showed a slight increase in urea and one of them showed an increase in creatinine. The increases are relative to concurrent control and pretest values. The sponsor considers these changes (which were not observed during the recovery period) as expected responses to the test article and of no toxicological significance.

There were no organ weight changes that could be attributed to treatment. Lesions were observed in several animals at scheduled necropsy. However, none of them was dose-related. A total of 4 high dose females (1 at interim sacrifice, 2 at terminal sacrifice and 1 at the end of recovery) exhibited renal arteriolar hypertrophy. No such changes were seen in other treated groups. This was considered a morphological change in response to the pharmacological activity of the compound. Diminution of bone marrow cellularity with a concomitant increase in marrow fat was seen in 4 high dose animals at the interim sacrifice and in one high dose female at the terminal sacrifice. This was not seen in recovery animals or in any other dose groups. The sponsor considers these changes to reflect the age range of the animals since they were not accompanied by significant alterations in peripheral blood. However, there is no data in the report that support their claim.

In summary, oral administration of CGP 48933 at doses of 12, 40 or 120 mg/kg/day for 6 or 12 months resulted in only minor non-specific clinical changes. Microscopic examination revealed

renal arteriolar hypertrophy in some high dose females. However, these changes were not considered to be of toxicological significance.

The plasma concentrations of CGP 48933 increased approximately in a dose proportional manner in both sexes (Table 3.2.7.2). There was no significant accumulation or diminution of CGP 48933 between weeks 23 and 36 or 49.

TABLE 3.2.7.2
PLASMA CONCENTRATIONS OF CGP 48933 AFTER REPEATED ORAL DOSING IN MARMOSETS.
TEST #91-6141, REPORT #BPK (CH) 1994/053

Dose (mg/kg/day)	Week #	Mean (SD) concentration, µmol/liter	
		Males	Females
12	23	1.32 ± 0.63	3.39 ± 1.71
	36	2.56 ± 1.42	1.76 ± 0.92
	49	2.24 ± 0.73	2.09 ± 0.96
40	23	4.61 ± 2.61	4.39 ± 2.30
	36	4.07 ± 1.78	4.32 ± 1.05
	49	3.40 ± 1.39	4.32 ± 2.68
120	23	12.29 ± 3.47	11.22 ± 5.86
	36	18.64 ± 10.40	16.86 ± 16.26
	49	10.33 ± 3.78	6.32 ± 3.23

3.2.8. 14-Day Intravenous Toxicity Study in Marmosets (*Callithrix jacchus*)

Location of Data: Vol. 29

Testing Facility: Preclinical Safety, Section of Toxicology/Pathology, Ciba-Geigy Ltd., Basel, Switzerland.

Identification No.: Test #92-6149

Study Dates: Dosing initiated: 11/02/92
Last necropsy: 11/17/92

GLP Compliance: Studies were done in accordance with GLP regulations.

Methods: Solutions of CGP 48933 (batch #16/047/1) in physiological saline were administered intravenously (1 ml/kg) into the vena femoralis of the right or left leg, once daily for 14 consecutive days to groups of 3 male and 3 female marmosets (*Callithrix jacchus*) at doses of 6, 20 or 60 mg/kg. Control animals received 0.9% NaCl in a similar manner. Marmosets weighed between 561 and 584 gm, were between 9 and 41 months of age at the start of dosing and were housed singly or single sex paired. The doses were selected based on the results of an i.v. rising-dose tolerance study in 1 male and 1 female marmoset. In that study, the highest dose (100 mg/kg for 4 consecutive days) was tolerated without overt clinical signs or mortality; however, a slight reduction in body weight and food consumption was observed at 30 and 100 mg/kg/day in both animals.

Observations/Measurements: All animals were observed daily for mortalities and clinical signs. Body weight, and food and water consumption were recorded twice a week and daily, respectively, during the treatment period. Hematology and serum biochemistry values were determined on blood samples collected from all animals before the test and at the end of study. Urinalysis determinations were made on samples collected from all animals over a 3-hr period on day 0 and week 2 before the administration of the test drug. A full necropsy was performed on all marmosets on study day 15. Organ weights were determined for all animals killed at the end of the study. Microscopic examination was conducted on tissues from all control and high dose animals. The following organs were weighed from all marmosets that were killed at the end of the study:

adrenals
axillary lymph nodes
brain
epididymides
heart
kidneys
liver
lungs
mandibular glands
ovaries
pituitary
prostate
salivary glands (submaxillary)
spleen
testes
thymus
thyroids/parathyroids
uterus

The following tissues/organs were taken at necropsy and preserved for histology.

Adrenals	Knee joint	Skin
Aorta	Lacrimal glands	Spinal cord
Bone marrow (sternum/ femur)	Liver	Spleen
Brain	Lungs	Stomach
Cecum	Lymph nodes: axillary,	Submaxillary glands
Colon	mesenteric/submandibular	Testes
Duodenum	Mammary area	Thigh muscle
Epididymides	Oesophagus	Thymus
Eyes/Optic Nerves	Ovaries	Thyroids/Parathyroids
Gall bladder	Pancreas	Tongue
Heart	Pituitary	Trachea
Ileum	Prostate	Urinary bladder
Injection sites	Rectum	Uterus
Jejunum	Sciatic nerve	Vagina
Kidneys	Seminal vesicles	

and all other organs /tissues showing gross abnormalities during necropsy.

Results: There were no test substance-related physical signs, deaths or gross lesions observed during the treatment period. No treatment-related changes in body weight were evident. At the end of treatment, food intake was reduced in all animals including control. Neither clinical biochemistry nor hematological parameters showed any meaningful changes at any dose level compared to pretest or control values. The urinalysis showed the presence of glucose (values not provided) in high dose marmosets (2 males and 2 females). The appearance of glucose in the urine in the absence of hyperglycemia is puzzling. Although tubular dilatation and pyelonephritis (both grade 2 of 5) were observed in one of these females and one of these males, respectively, there was no renal histopathology in the other animals with glycosuria, suggesting diseased kidney may not be the target organ to consider in the excretion of glucose in the urine. Another factor to consider is the stress of daily intravenous injections and prolonged retention in the metabolism cages during urine collection.

No relevant organ weight changes were noted at any dose levels. Further, there were no treatment-related macroscopic or microscopic findings in any tissues or organs except for the minor kidney pathology noted above in two marmosets. A slight trend to increased myonecrosis at injection sites was observed in high dose marmosets.

In summary, intravenous injection of doses up to 60 mg/kg/day of CGP 48933 for 14 consecutive days to marmosets caused no overt clinical signs or mortality, did not result in alterations in clinical biochemistry, hematology, or organ weights, but was associated with glucosuria and minor kidney pathology.

3.3. GENOTOXICITY

3.3.1. Ames (Bacterial Mutagenicity) Test (Report #AFP 63)

This non-GLP study was conducted by a contract laboratory,-
. Study completed June 24, 1991.

Ames test permits the detection of gene mutations induced by the test compound or its metabolites in histidine-requiring strains of Salmonella typhimurium and in a tryptophan-requiring strain of E. coli.

CGP 48933 was evaluated for induction of reverse mutations at selected histidine loci in *Salmonella typhimurium* strains, TA 1537, TA 98, TA 100 and at the tryptophan locus in one E. coli tester strain (WP2 uvrA) in the presence and absence of a rat liver metabolic activation system (S-9 mix from Aroclor 1254 treated rats).

CGP 48933 was dissolved in dimethylsulfoxide or water and tested at concentrations of 0, 5 (with S-9 mix only), 15.8, 50, 158, 500, 1580 and 5000 µg/plate. Each concentration of CGP 48933 was tested in all the strains, both in the presence and absence of S-9 mix. CGP 48933 formed a macroscopically visible precipitate at doses ≥ 1580 µg per plate in the presence and absence of S-9 mix. No significant toxicity occurred up to the highest dose tested. In order to increase the sensitivity of the test towards compounds which are activated to mutagenic epoxides, the epoxide hydrolase inhibitor and glutathione depletor, 1,1,1-trichloropropene 2,3-oxide was used with TA-98 in presence of S-9 mix. The reference positive controls (benzopyre, 2-aminoanthracene, 3-methylcholanthrene, benzopyrene 4,5-oxide, ENNG and MNNG) were run concurrently with each assay and produced significant increases in the number of spontaneous revertants for one or more strains.

The results indicated that CGP 48933 was not mutagenic under these experimental conditions up to a maximum tested dose of 5000 µg/plate.

Another (but GLP) study (Test #916046) was conducted at the sponsor's foreign laboratory (Genetic toxicology, Ciba-Geigy Ltd., Basle, Switzerland) between May 29, 1991 and June 7, 1991. That study, which included an additional tester strain, TA-1535, also indicated that CGP 48933 was not mutagenic.

3.3.2. Gene Mutation Test With Chinese Hamster V79 Cells (Test #916179)

This GLP study was conducted by the Laboratories of Genetic Toxicology, Pharmaceutical Division, Ciba-Geigy Limited, Basle, Switzerland between November 11 and March 11, 1992.

The assay system detects gene mutations (base pair substitutions, frameshift mutations and deletions induced by the test substance) from the parental type to the mutant form which gives

rise to a change in an enzymatic or functional protein. Mutagenic effects are manifested by the appearance of cells resistant to 6-thioguanine (6-TG) and can be quantified by comparison of the numbers of 6-TG resistant colonies in the treated and control cultures. The experiment was also conducted in the presence of rat-liver postmitochondrial fraction S9 (from Aroclor 1254 treated rats) and co-factors in order to ensure that any mutagenic effect of metabolites of the test compound would also be detected.

In both original and confirmatory experiments conducted in the presence of S-9, CGP 48933 was dissolved in DMSO at concentrations of 51.41, 154.22, 462.67 and 1388.00 µg/ml. In both original and confirmatory experiments conducted in the absence of S-9, CGP 48933 was dissolved in DMSO at concentrations of 205.56, 616.67, 1850 and 5550 µg/ml. In the preliminary cytotoxicity experiments, the viability of cells treated for 5 hrs with CGP 48933 in the presence of metabolic activation was reduced to a value lower than 10% of the negative control (DMSO) at concentrations above 1388 µg/ml. The test substance precipitated as a clot at concentrations of 1850 and 5550 µg/ml, with and without S-9 mix, respectively. Without activation, the viability of the cells treated for 21 hr with CGP 48933 was reduced to a value lower than 10% of the negative control at the concentration of 5550 µg/ml.

V-79 cell cultures were exposed to four concentrations of CGP 48933, a positive and a negative (DMSO) control. In the non-activated part of the experiment, the positive control was the ultimate mutagen ethylmethansulfonate (300 nl/ml). In the part with metabolic activation the positive control was the promutagen N-nitroso-dimethylamine (1 µg/ml). The treatment was terminated by washing cells with phosphate buffered saline. The cells were incubated at 37°C for 7-8 days during which the cells could recover and divide to express the mutant phenotype. The number of colonies which develop within 7-8 days in these cultures reflect the viability at the end of treatment. The high density cultures are subjected to the mutant selection procedure by supplementing the growth medium with 8 µg/ml 6-TG. Only cells mutated at the hgprt locus could survive the 6-TG treatment. The number of colonies formed in these flasks during 7-8 days of incubation at 37°C reflect the overall number of mutations induced by the treatment with the test substance or the mutagen (i.e. positive control). The mutant colonies are counted and results are expressed as 'mean mutant frequency'. Genotoxic agents significantly increase mutant frequencies.

In these experiments, the positive controls elicited the expected response, whereas cultures treated with CGP 48933 exhibited no increase in mutant frequency.

3.3.3. Cytogenetic Test on Chinese Hamster Ovary Cell Line (Test #916181)

This GLP study was conducted by the Laboratories of Genetic Toxicology, Pharmaceutical Division, Ciba-Geigy Limited, Basle, Switzerland between November 18, 1991 and January 21, 1992.

The cell line CHO CCL 61, derived from Chinese hamster ovary cells, was used for testing

cytotogenic activity (structural chromosome aberrations). One original and two confirmatory experiments were each performed with and without rat liver S-9 microsomal fraction (metabolic activation) and different concentrations of CGP 48933.

The cells were exposed to CGP 48933 concentrations of 0, 81.88, 163.75 and 327.5 µg/ml for 18 hrs and concentrations of 163.75, 327.5 and 655 µg/ml for 42 hr without S-9 microsomal fraction. To ensure that any clastogenic effects of metabolites of the test substance formed in mammals would also be detected, in three experiments (one original and two confirmatory studies) CGP 48933 concentrations of 0, 327.5, 655 and 1310 µg/ml were incubated for 3 hr (original study) followed by separate 15-hour and 39-hour recovery periods with rat liver S-9 fraction.

None of the studies involving test substance revealed any significant increase in the number of specific chromosomal aberrations (0 to 3.5%) for any culture. On the other hand, treatment of cultures with mitomycin-C and cyclophosphamide (positive controls) produced significant increases in the rate of specific chromosomal aberrations (17 to 38%) in both original and confirmatory studies. The threshold required for a positive response is 6%. Thus, the study report concludes that CGP 48933 has no clastogenic effect in Chinese hamster ovary cells.

3.3.4. Micronucleus Test in Rat (*in vivo*) (Test #916177)

This GLP study was conducted by the Laboratories and Animal Facilities of Genetic Toxicology, Pharmaceutical Division, Ciba-Geigy Limited, Basle, Switzerland between November 4, 1991 and February 24, 1992.

The purpose of the study was to investigate the potential of CGP 48933 to produce clastogenic or aneugenic effects in rats. Solutions of CGP 48933 prepared in arachis oil were administered orally (at a volume of 10 ml/kg) by gavage as single doses of 781.3, 1562.5 or 3125 mg/kg (15 rats/sex/dose). Two additional groups of male and female rats (5/sex/ group) were dosed once orally with vehicle (10 ml/kg, negative control) or once intraperitoneally with cyclophosphamide (20 mg/kg, positive control) . Approximately 16, 24 and 48 hr after CGP 48933, vehicle (24 hr only) or cyclophosphamide (24 hr only) administration, rats (5/sex/group) were sacrificed. Bone marrow was isolated from both femurs and smears onto slides were prepared for evaluation. Frequency of micronucleated polychromatic erythrocytes (MN-PCE) for each sample was determined. The mean number of MN-PCE accepted for the negative control was ≤0.2% and the test substance was considered to be active if MN-PCE exceeded 0.2%.

CGP 48933 was well tolerated except for the death of one female rat 24 hr after being given 1562.5 mg/kg. The mean percentage of MN-PCE for negative and postive controls, and drug treatment were, respectively, 0, 0.54 and 0.01 to 0.10. Thus, sponsor concludes that CGP 48933 does not have clastogenic activity in rat bone-marrow cells.

3.4. REPROTOXICITY

3.4.1. Oral Fertility and Reproductive Toxicity (Segment I) Study in Rats

Location of Data: Vol. 31

Testing Facility: Division of Preclinical Safety, Pharmaceutical Division, Ciba-Geigy Corporation, 556 Morris Avenue, Summit, NJ 07901.

Identification No.: Report #94004, Master Index Number 924222

Study Dates: Dosing Initiated 11/16/92 (males) and 2/1/93 (females)

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Sprague-Dawley (Crl:COB CD[SD]BR) rats from Charles River laboratories; Males were approximately 14 weeks of age and weighed 426-564 gm, while females were approximately 11 weeks of age and weighed 231-307 gm at initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (lot #800192) were prepared in 0.5% CMC with 0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily to three groups of 12 males and 24 females each at doses of 10, 50 or 200 mg/kg. Control animals (group 1) received the vehicle in a similar manner. Males were dosed for 90 days prior to mating, during the three-week mating period and three weeks thereafter. The females were treated for 14 days prior to mating, during mating and until day 19 of gestation (cesarean-sectioned animals) or through day 20 of lactation (natural delivery females).

Observations/Measurements: All animals were observed for physical signs once daily. Alopecia was recorded weekly. Body weights and food consumption were recorded weekly. Females killed on day 20 of gestation (~ 2/group) were examined for reproductive status, corpora lutea and implants were counted and the latter were classified as live fetus, dead fetus or resorption. Ovarian, oviduct and uterine weights were recorded at necropsy. All fetuses were examined externally and live fetuses were weighed and sexed and saved for visceral and gross examinations. One-third of the fetuses from each litter were fixed in Bouin's solution for kidney pathology and the rest were placed in 70% ethanol for skeletal examinations. The kidneys from all fetuses were examined grossly, while kidneys from control and high dose fetuses were subjected to histologic processing for potential effects of test substance on fetal kidney development.

Females in the second group were allowed to deliver their litters and were sacrificed on day 21 of lactation, and necropsied. The F_1 pups were counted, examined externally, and sexed on postnatal day 0. Clinical signs and body weights were recorded on postpartum days 0, 4, 7, 14, 21, 28 and 35. All litters were reduced to 4 males and 4 females on lactation day 4. The developmental parameters studied were righting reflex (day 0 to 2), pinna detachment (day 0 to 2), ear canal

opening (day 13 to 16), eye opening (day 14 to 17), Preyer's reflex (day 21 to 28), pupillary reflex (day 35 to 42), testes descent (day 22 to 28) and vaginal opening (day 32 to 40). Behavioral tests were performed on 1 male and 1 female animal from each litter and included passive avoidance acquisition (day 26), passive avoidance retention (day 33), open field motor activity (day 40) and fore- and hindlimb grip strength (day 33). At 10 weeks of age, one male and one female from each litter were mated with animals from other litters within the same dose group until a sperm-positive washing was recorded. The number of implantation sites, stillbirths and male and female F_2 newborn pups in each litter were recorded after birth; then the litter and F_1 animals were euthanized.

Results: There were no test substance-related deaths in the study. One high dose male died as a result of an intubation accident on day 20 and another high dose male died on day 69. The latter animal died as a result of low food consumption with an associated loss of body weight (104 gm) between days 56 and 63. This was attributed to missing teeth. A treatment-related clinical sign of salivation (after dosing) was observed in 4/12 mid dose and 12/12 high dose male animals. Other clinical signs such as alopecia, chromodacryorrhea, diarrhea, staining, stool changes were considered incidental based on a low incidence of occurrence and the absence of a dose-response relationship. No treatment-related changes in food consumption were observed in males at any dose level. Overall (treatment days 0-126), there was a dose-dependent reduction in body weight gain for males at 50 and 200 mg/kg/day, but these reductions (7 and 18% of control gain, respectively) were not statistically significant. On the other hand, body weight gain from day 49 to day 63 was significantly lower ($P < 0.05$) and body weight loss from day 91 to day 98 significantly higher ($P < 0.05$) than control for the high dose male group. There were no treatment-related necropsy findings in the males. Also, there was no effect of CGP 48933 on absolute or relative testes weights at any dose level. Reproductive performance of mated males, as evidenced by percent females inseminated, and percent pregnant indices, was not affected by drug treatment.

There were no parental F_0 female mortalities in the study. A treatment-related salivation was observed in 18/24 highdose and 1/24 middose females. Average food consumption was significantly ($P \leq 0.05$-0.01) lower in females at 200 mg/kg during premating days 0-14 and gestation days 0-6 . Non-statistically significant reductions (7 to 14%) relative to control females were noted during gestation days 6 to 20. A statistically significant treatment-related decrease in body weight (approximately 7 to 11% below the concurrent control value) in the high dose group was noted on premating days 7 and 14, gestation days 0, 6, 13 and 20 and lactation day 0. In the same group, treatment-related significant reductions in body weight gain (22 to 62% of the concurrent control value) were observed on premating days 0 to 7 and gestation days 0 to 20. There were no changes in body weight parameters in females dosed at 10 or 50 mg/kg/day. There were no test substance-related gross lesions found at necropsy in F_0 females sacrificed at the end of the study.

F_0 fertility parameters were not altered with the treatment. In the 10 and 200 mg/kg/day c-sectioned groups, there were slightly (not statistically significantly) fewer corpora lutea, implants and live fetuses than control. Since these responses were not dose-related, they were considered

incidental. Pre- and postimplantation losses were slightly higher than control in the 10 and 50 mg/kg/day groups, but the differences are not significant. Gross examination of fetuses did not reveal any compound-related findings. There were no compound-related gross or microscopic abnormalities in the fetal kidneys.

There were no effects of test drug on any of the reproductive parameters in the natural delivery groups. Higher percent stillbirths (3.86 ± 8.59 *versus* 0 in the control) observed at 50 mg/kg was considered incidental due to the lack of a dose-response relationship. There were no treatment-related changes in mean litter size, pup sex ratio or survival or clinical signs at any dose level during the study. In general, pup weight at all dose levels tended to be slightly lower than control. The differences, however, were not dose-related and not statistically significant. The sponsor attributes them to the large litter size and biological variation resulting in a higher control value. There was no effect of treatment on the development of F_1 pups except for statistically significant ($P \leq 0.05$) increases in time to ear canal opening in mid and highdose female groups. However, the sponsor considers these small increases (up to 1%) to be biologically insignificant. In behavioral testing, the open field motor activity parameter showed a significant increase in peripheral and total beam breaks in females at 200 mg/kg/day. Passive avoidance testing of males and females in all treated groups resulted in an increase in trials to success during the retention (memory) phase. This observation seemed to be unrelated to the treatment since the retention score (average latency per trial) and the difference between the learning and retention trials (which is an indication of memory relative to learning) were not statistically significantly different from control.

CGP 48933 had no adverse effects upon the reproductive capacity of the F_1 generation at any dose level tested.

In summary, treatment-related effects were noted in parental F_0 animals at doses of 50 or more mg/kg/day, and consisted of (a) salivation in males at 50 and 200 mg/kg/day and in females at 200 mg/kg/day; (b) decreased food consumption in females at 200 mg/kg/day; and (c) decreased body weight in both sexes at 200 mg/kg/day and reduced body weight gain in males at 50 and 200 mg/kg/day and in females at 200 mg/kg/day. Thus, the no observed effect dose level in this study for maternal toxicity was 10 mg/kg/day, and for developmental toxicity was >200 mg/kg/day.

3.4.2. Oral Developmental Toxicity (Segment II) Study in Rats

Location of Data: Vol. 32

Testing Facility: Division of Preclinical Safety, Ciba-Geigy Pharmaceutical, Stamford Lodge, Wilmslow, Cheshire, U.K.

Identification No.: Report #008/92/SL, Test #916067, Exp. #91R713

Study Dates: Dosing initiated 10/28/91

GLP Compliance: Studies were done in accordance with GLP regulations

Animals: Female Sprague-Dawley (Tif:RAIf(SPF)) rats were approximately 14-17 weeks of age and weighed 243-358 gm when allocated to the study.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (lot #800291) were prepared in 0.5% CMC with 0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily to three groups of 25 mated females each at doses of 60, 200 or 600 mg/kg on gestational days 6 through 15. Control animals (group 1) received the vehicle in a similar manner.

Observations/Measurements: All animals were observed for physical signs once daily. Body weights and food consumption were recorded on day 0 and on days 6 through 15 and 20 of gestation. All animals were killed on day 20 of gestation, and the number of copora lutea, implants, early and late resorptions (including dead fetuses) and live fetuses were counted. Collective placental weights for each litter were recorded. Additionally, abdominal viscera including kidneys were examined for all F_0 females. All fetuses were weighed, sexed, and examined externally before necropsy. Approximately half the fetuses were fixed in Bouin's solution for visceral examination and the rest were placed in 70% ethanol for skeletal examinations.

Results: There were no mortalities. There were no test substance-related physical signs, deaths, abortions or gross lesions observed at necropsies. A total of 10 females were found to be not pregnant. The distribution of non-pregnant females between the control and dose groups did not indicate any efffect of CGP 48933. Maternal body weight gain was reduced in a dose-related manner in both 200 and 600 mg/kg/day groups on days 15 and 20 of gestation. However, on both days of measurement, the data was statistically significant ($P \leq 0.05$) for the high dose group only. There was no effect of CGP 48933 on maternal food consumption. The reproductive performance as assessed by number of corpora lutea, implants, live fetuses/litter, and pre- and postimplantation losses were not influenced by test drug at any dose level. But the high dose group mean fetal weight was 4.6% below control ($P \leq 0.05$). This effect was considered by the sponsor to be a consequence of reduced maternal body weight. There were no other toxicologically significant findings at maternal necropsy.

A non statistically significant increase in the incidence of dilated brain ventricles in the high dose fetuses (17/159, 10.7%) in comparison to concurrent control (9/159, 5.7%) was attributed to the increased number of low weight fetuses in the high dose group. An association between dilation of the lateral brain ventricle and low birth weight has been reported in the literature. Further, the fetal incidence in the 600 mg/kg/day group (10.7%) is well within the historical control range (1.5 to 17.4%, data pooled from 4 different studies, amendment dated 9/23/96). An increased incidence of an extra cleft in the median lobe of the liver was observed at all three dose levels, statistically significant ($P \leq 0.05$) at 200 mg/kg/day. According to the sponsor, the cleft in the median lobe of the liver is a structural variant in this strain of rat and the incidence in all groups was below the upper limit of historical control incidence. Another notable visceral observation was the occurrence of "extreme dilation" of the ureters in 3 fetuses from 2 litters at 600, 1 fetus at 200, and 2 fetuses from 2 litters at 60 mg/kg/day. Extreme dilation was not seen in concurrent control fetuses (Table 3.4.2.1). The incidence observed in the high dose group was claimed to be just above the maximum historical control group incidence.

Two fetuses in two litters at 600 mg/kg/day had a curved and shortened femur ($P \leq 0.05$). The finding was absent in the other two dose groups as well as in the control group. "The appearance of the femur suggested mechanical damage, in that it resembled a transverse fracture in the middle of the bone." The sponsor contends that a similar finding was reported in a control fetus in a previous study. Increases over concurrent control in sites of incomplete ossification of the sternebrae of fetuses in low (+26%) and high dose (+43%) groups were not statistically significant (Table 3.4.2.1). The highest incidence was also below the maximum historical control incidence for this finding and thus was considered not to be of toxicological insignificance.

In summary, the no observed effect dose level for maternal toxicity as indicated by decreased body weight gain was 200 mg/kg/day. Though there was no evidence of teratogenicity or increased embryonic or fetal mortality in rats at doses up to 600 mg/kg/day, this dose reduced fetal birth weight significantly. There were no effects of CGP 48933 at 60 mg/kg/day.

TABLE 3.4.2.1
FETAL EXTERNAL, VISCERAL AND SKELETAL OBSERVATIONS. TEST #916067

Observations	M/V	Dose (mg/kg/day) Control	60	200	600
		dams/fetuses	dams/fetuses	dams/fetuses	dams/fetuses
1. External observations					
Number examined:		22/327	23/304	21/269	24/333
2. Visceral observations					
Number examined:	V	22/159	23/144	20/129	24/159
Nasal cavities dilated	V	1/1	3/3	5/6	2/2
Brain-lateral ventricle dilated	V	6/7	1/1	5/6	9/15
Brain-third ventricle dilated	V	1/1	1/1	0/0	3/3
Liver extra cleft in median lobe	V	3/3	6/7	10/12	7/9
Ureter dilated	V	9/20	6/6	4/6	13/24
Ureter dilated extreme	V	0/0	2/2	1/1	2/3
3. Skeletal observations					
Number examined:		22/168	23/160	21/140	24/174
Femur shortened and mis-shapened	V	0/0	0/0	0/0	2 /2
Sternebrae incompletely ossified	V	17/46	18/55	55/16	20/68

M: malformations, V: variant

3.4.3. Perinatal and Postnatal Reproductive Toxicity (Segment III) Study in Rats

Location of Data: Vol. 33

Testing Facility: Division of Preclinical Safety, Ciba-Geigy Corporation, Pharmaceuticals Division, Summit, New Jersey.

Identification No.: Report #94056, Test #936207, Study MIN 944019

Study Dates: Dosing initiated 2/16/94 (day 15 of gestation)

GLP Compliance: Studies were done in accordance with GLP regulations

Animals: Female Sprague-Dawley (Crl: COBS CD(SD)BR) rats were approximately 14 weeks of age and weighed 220-309 gm on day 0 of gestation.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (lot #800193) were prepared in 0.5% CMC with 0.5% Tween 80. The drug was administered orally by gavage (10 ml/kg), once daily to three groups of mated females at doses of 60 (n=21), 200 (n=21) or 600 (n=26) mg/kg/day from gestation day 15 to lactation day 20. Control animals (group 1, n=26) received the vehicle in a similar manner. Five pregnant rats each from the control and high dose groups were dosed only through gestation day 20 (total of 6 doses) in order to evaluate the fetal kidneys.

Observations/Measurements: All animals were observed for physical signs and mortality once daily from gestation day 0 through lactation day 21. Body weights and food consumption were recorded on gestation days 0, 6, 13, 15 and 20 and lactation days 0, 7, 14 and 21 (body weights only). The first five pregnant dams in the control and high dose groups (1 and 4, respectively) were sacrificed on gestation day 20. Each live fetus was counted and identified by its position in the uterine horn. Fetuses were not sexed and were discarded after removal of kidneys for gross and microscopic evaluation. No other organs or tissues were saved for examination. The remaining dams were killed on lactation day 21, the external body and major viscera were grossly examined and the number of implantation sites counted.

All F_1 pups were counted, examined externally for malformations, weighed and sexed on postnatal day 0. Futher, pups were examined for clinical signs and mortality, and weighed on postpartum days 4, 7, 14 and 21. Litters were culled to 4 males and 4 females on postpartum day 4. The pups were tested for righting reflex on postnatal days 0 to 2, pinna detachment on days 3 to 5, ear canal opening on days 13 to 16, and eye opening on days 14 to 17. All surviving pups were killed on day 21 and discarded without further examination.

Results: There were no treatment-related physical signs, deaths, abortions or gross lesions observed at necropsies. One control animal died on the first day of dosing (gestation day 15); that death was attributed to misintubation. A statistically significant, treatment-related reduction in

mean body weight gain was observed at 600 mg/kg/day on gestation days 15 to 20. There was no effect of treatment at doses ≤200 mg/kg/day. A body weight loss was observed for all (including control) groups on lactation days 14 to 21 (Table 3.4.3.1). Group mean food consumption was 13.3 % ($P \leq 0.01$) and 10 to 11% ($P \leq 0.05$) below control, respectively, at 600 mg/kg/day on gestation days 15 to 20, and at doses ≥200 mg/kg/day on lactation days 0 to 7 (Table 3.4.3.2). There were no treatment-related effects on reproductive performance of F_0 females.

Microscopic evaluation of fetal kidney showed minimal, spontaneous dilatation of the renal pelvis in both control and high dose groups with an incidence of 9% and 13%, respectively. However, these values are much lower than that seen in control fetal rat kidneys from a previous study with CGP 48933 (see section #3.4.1). Incidence of pelvic enlargement or distention varied considerably, ranging from 6-63% in the control litters and 11-71% in the high dose group litters. The sponsor considers many of these apparent distentions were to be artifactual, produced during manipulation of small organs under the dissecting microscope. Further, microscopic evaluation most often did not confirm these gross observations.

TABLE 3.4.3.1
MEAN ± S.D. MATERNAL BODY WEIGHT GAIN (GM) DURING GESTATION AND LACTATION

	DOSE LEVEL (MG/KG/DAY)			
DAYS	CONTROL (0)	60	200	600
Gestation				
0-6	40.81 ± 9.44 N26	39.90 ± 10.02 N21	46.48 ± 25.62 N21	40.73 ± 7.90 N26
6-13	44.69 ± 9.24 N26	47.48 ± 7.27 N21	39.76 ± 26.87 N21	44.54 ± 7.84 N26
13-15	12.58 ± 5.23 N26	10.76 ± 8.38 N21	11.62 ± 5.08 N21	12.15 ± 6.98 N26
15-20	77.04 ± 11.45 N26	75.43 ± 13.35 N21	71.81 ± 14.70 N21	66.58 ± 12.09* N26
Lactation				
0-7	29.38 ± 12.06 N21	27.15 ± 11.99 N20	22.48 ± 9.78 N21	26.67 ± 14.35 N21
7-14	21.14 ± 14.13 N21	18.55 ± 14.95 N20	20.75 ± 12.89 N20	28.10 ± 11.18 N20
14-21	-26.19 ± 18.57 N21	-19.60 ± 14.62 N20	-11.70 ± 16.27* N20	-26.70 ± 17.94 N20

In cases of statistical significance, *: for $.01 < p <= .05$

TABLE 3.4.3.2
MEAN ± S.D. MATERNAL FOOD CONSUMPTION (GM/DAY) DURING GESTATION AND LACTATION

DAYS	CONTROL (0)	DOSE LEVEL (MG/KG/DAY) 60	200	600
Gestation				
0-6	27.65 ± 3.21 N26	28.34 ± 2.96 N21	27.71 ± 2.44 N21	28.23 ± 2.32 N26
6-13	30.45 ± 3.51 N26	31.01 ± 3.20 N21	30.87 ± 3.98 N21	30.57 ± 2.63 N26
13-15	32.29 ± 4.41 N26	32.83 ± 3.57 N21	31.57 ± 3.90 N21	31.77 ± 3.60 N26
15-20	32.61 ± 13.54 N26	32.90 ± 3.45 N21	31.12 ± 2.913 N21	28.28 ± 3.27** N26
Lactation				
0-7	46.68 ± 5.58 N20	44.45 ± 3.65 N20	41.5 ± 4.70** N21	42.11 ± 6.33* N20
7-14	65.96 ± 5.00 N20	64.95 ± 7.15 N19	65.04 ± 4.89 N20	6i.77 ± 6.15 N20

In cases of statistical significance, *: for .01 < p < = .05, ** : for p <= .01

There were no treatment-related clinical signs in the F_1 pups during the postnatal days. Reductions in pup survival were observed in the high dose group on both precull and postcull days. The decreases were statistically significant ($P \leq 0.01$) on postnatal days 0 to 4 for both sexes pooled and on on days 4 to 21 for male pups (Table 3.4.3.3). Thirteen of the 21 high dose group litters lost at least one pup during postnatal days 0 to 4, as compared to the control group in which 7 of 21 litters lost at least a single pup. The sponsor asserts that the greater effect on male pup survival was attributable to random biological variation; both sexes were presumed to be equally affected. Significant ($P \leq 0.05$) treatment-related reductions in pup body weight were observed throughout the lactation period for both male and female pups except on day 4 for female pups at the 600 mg/kg/day dose level. There was no effect of treatment on mean pup body weight in other groups (Table 3.4.3.4).

Significant increases in the mean time to complete pinna detachment in both sexes and ear canal opening in males were noted in the high dose group. These delays reflect on low birth weight. Additionally, a slight but statistically significant increase in the mean time to complete pinna detachment in males was observed in the 200 mg/kg/day group. Since this effect was not associated with any effects on body weight or survival, the sponsor considers it to be incidental to treatment.

TABLE 3.4.3.3
SUMMARY OF F_1 GENERATION: SURVIVAL (MEAN ± S.E) BY SEX AND SEXES POOLED

PARAMETER	DOSE LEVEL (MG/KG/DAY) CONTROL (0)	60	200	600
Survival Indices by Sex:				
Mean % males surviving Days 0-4 (precull)	97.50 ± 1.18 (21)	92.53 ± 4.80 (21)	97.73 ± 1.70 (21)	92.87 ± .70 (21)
Mean % males surviving Days 4-21 (postcull)	100.00 ± 0.00 (21)	100.00 ± 0.00 (20)	95.24 ± 4.76 (21)	91.67 ±4.98** (21`
	CA3			
Mean % females surviving Days 0-4 (precull)	97.35 ± .70 (21)	93.78 ± 4.76 (21)	98.25 ± 1.21 (21)	91.88 ± 3.17 (21)
Mean % females surviving Days 4-21 (postcull)	98.81 ± 1.19 (21)	97.50 ± 1.72 (20)	94.05 ± 4.85 (21)	95.24 ± 4.76 (21)
Survival Indices Sexes Pooled:				
Mean % pups surviving Da s 0-4 (precull)	97.65 ± 0.84 (21)	93.26 ± 4.72 (21)	98.35 ± 1.11 (21)	91.96 ± 2.65** (21)
Mean % pups surviving Days 4-21 (postcull)	99.40 ± 0.60 (21)	98.75 ± 0.86 (20)	94.64 ± 4.77 (21)	93.45 ± 4.77 (21)

** Statistically different from the control group at $p \leq 0.01$.

In conclusion, oral administration of 600 mg/kg of CGP 48933 to pregnant rats caused a decrease in mean body weight gain during gestation and mean food consumption (also at 200 mg/kg/day) during gestation and lactation. Developmental toxicity was expressed in F_1 pups as reduced postnatal survival, decreased body weights and functional development in the 600 mg/kg/day group. There were no treatment-related effects on labor, delivery, reproductive parameters or fetal kidney development. The no effect dose (for decreased food consumption) is 60 mg/kg/day and not 200 mg/kg/day as claimed by the sponsor.

TABLE 3.4.3.4
SUMMARY OF F_1 GENERATION: BODY WEIGHT (MEAN ± S.E)(GRAMS)

Postpartum day	DOSE LEVEL (MG/KG/DAY) CONTROL (0)	60	200	600
		MALES		
0	6.59 ± 0.13 (21)	6.59 ± 0.13 (21)	6.49 ±0.13 (21)	5.99 ± 0.13** (21)
4 (Precull)	9.94 ± 0.30 (21)	10.05 ± 0.31 (20)	9.74 + 0.30 (21)	8.91 ± 0.30* (21)
4 (Postcull)	10.00 ± 0.30 (21)	10.02 ± 0.31 (20)	9.73 ± 0.30 (21)	8.94 ± 0.30* (21)
7	16.08 ± 0.56 (21)	16.04 ± 0.58 (20)	15.20 ± 0.57 (21)	13.65 ± 0.57** (21)
14	34.08 ± 0.86 (21)	33.67 ± 0.88 (20)	33.30 ± 0.89 (20)	30.12 ± 0.88** (20)
21	55.36 ± 1.25. (21)	55.38 ± 1.29 (20)	54.18 ± 1.28 (20)	47.34 ± 1.28** (20)
		FEMALES		
0	6.19 ± 0.11 (21)	6.21 ± 0.11 (21)	6.09 ± 0.11 (21)	5.73 ± 0.11** (21)
4 (Precull)	9.30 ± 0.27 (21)	9.54 ± 0.28 (20)	9.14 ± 0.28 (21)	8.60 ± 0.27 (21)
4 (Postcull)	9.23 ± 0.27 (21)	9.70 ± 0.28 (20)	9.17 ± 0.28 (21)	8.57 ± 0.27 (21)
7	14.68 ± 0.48 (21)	15.61 ± 0.50 (20)	14.23 ± 0.49 (21)	13.30 ± 0.49* (21)
14	31.98 ± 0.77 (21)	33.45 ± 0.79 (20)	32.03 ± 0.80 (20)	29.55 ± 0.79* (20)
21	51.62 ± 1.16 (21)	55.08 ± 1.19* (20)	52.28 ± 1.20 (20)	46.14 ± 1.18** (20)

Statistically different from the control group at $p \leq 0.05$.
Statistically different from the control group at $p \leq 0.01$.

3.4.4. Oral Developmental Toxicity (Segment II) Study in Dutch Belted Rabbits

Location of Data: Vol. 33

Testing Facility: Division of Preclinical Safety, Ciba-Geigy Pharmaceutical, Stamford Lodge, Wilmslow, Cheshire, U.K.

Identification No.: Report #009/92/SL, Test #916070, Exp #91L717

Study Dates: Dosing initiated 12/15/91

GLP Compliance: Studies were done in accordance with GLP regulations

Animals: Dutch Belted female rabbits were approximately 14-17 weeks of age and weighed 2006-3012 gm at the time of initiation of dosing.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (lot #800291) were prepared in 0.5% CMC with 0.5% Tween 80. The drug was administered orally by gavage (1 ml/kg), once daily to three groups of 20 pregnant females each at doses of 2, 5 or 10 mg/kg on gestation days 6 to 18. Control animals (group 1, n=20) received the vehicle in a similar manner. All animals including control received 60 ml of 0.9% w/v saline daily by gavage, approximately 2 hr post dose on the first day of dosing and thereafter at dosing. Saline treatment continued until day 28. The dosages were based on the results of a dose range finding study in saline supplemented (Dutch Belted) rabbits (report #002/92/SL), in which increased mortality was observed at doses as low as 30 mg/kg/day and frequency of total litter loss increased at doses as low as 15 mg/kg/day.

Observations/Measurements: All animals were observed once daily for physical signs of toxicity. Body weights were recorded on gestation days 0, 6, 10, 14, 18, 21, 25 and 28. Food consumption was measured on days 0, 6, 13, 19, 24 and 29 of gestation. All animals were killed on day 28 of gestation, uterine contents were examined (position and number of resorbed and viable fetuses noted), corpora lutea counted and fetal and placental weights recorded.

All fetuses were sexed and given external, visceral and skeletal examinations. The heads of half of the fetuses in each litter were fixed in Bouin's fluid for subsequent examination following coronal hand serial sectioning.

Results: There were a total of 15 unscheduled deaths during the study, which occurred in all dose groups including the control. Table 3.4.4.1 illustrates the fates and pregnancy outcomes of animals in the study. Since all deaths were the result of dosing errors, respiratory infection or accidental injury, the sponsor considers none of them to be treatment-related. There were no clinical signs observed that were considered to be treatment-related. At necropsy, an increase in the incidence of excess fluid in the thoracic and abdominal cavities was noted in maternal animals receiving 5 and 10 mg/kg/day.

TABLE 3.4.4.1
SUMMARY OF FATE OF MATERNAL ANIMALS. TEST #916070

	Dose level, mg/kg/day [no. of animals]			
	control [20]	2 [20]	5 [20]	10 [20]
Killed *in extremis*[a]	2	1	0	1
Humane kill[b]	1	3	1	3
Found dead	1	1	0	1
Aborted	2	1	2	3
Total litter loss	1	0	3	8
Pregnant to term with live young	13	14	14	4

a: means the animal was found in a state close to the death and was therefore killed
b: means that the animal, although not close to death, was displaying signs considered to be adverse enough to require killing for humane reasons.

There were no clear dose-related effects on body weight. None of the groups gained weight over the gestation day 6-18 treatment period and control and mid dose groups lost weight during this period. Similarly, there were no treatment-related effects on food consumption.

A markedly elevated incidence of dams with totally resorbed litters at the high dose, coupled with other losses (deaths, unscheduled sacrifices and abortions) in all groups, left only 4 pregnant animals in the high dose group at delivery (Table 3.4.4.1). For those animals pregnant at delivery, the number of implantations was lower and the preimplantation loss was higher in the high dose group than in the control group. A significant ($P \leq 0.05$) increase in the incidence of resorptions in the mid dose group contributed to a higher than control postimplantation loss for that group. The % postimplantation loss at the high dose, although greater than control, was less than at seen at the mid dose (Table 3.4.4.2), but in view of the increase in the incidence of pregnancy losses seen in both of these groups, the increases in postimplantation loss are considered to be treatment-related.

In the mid dose group there was a slight and not statistically significant reduction in mean fetal weight associated with an increase in the incidence of small fetuses (defined as 26 gm or less). The incidence of small fetuses across various groups was as follows:13.9% (6 litters), 5.5% (3 litters), 28.6% (8 litters) and 7.7% (1 litter) in control, low-, mid- and high dose groups, respectively. There was no effect of CGP 48933 on placental weights.

External examination of fetuses did not reveal any treatment-related abnormalities. There was an increase in the incidence of dilated ventricles of brain in the treated groups: 5.6 % (2 fetuses/2 litters), 12.5 % (4 fetuses/3 litters), 15.6 % (5 fetuses/4 litters) and 16.7 % (1 fetus) at 0, 2, 5 and 10 mg/kg/day, respectively. The highest incidence was only marginally above the historical control range (4.4% to 13.5%, data pooled from 4 different studies, amendment dated 9/23/96). Irrespective of the dose group, this finding was generally associated with low fetal weight.

TABLE 3.4.4.2
GROUP MEAN CESARIAN NECROPSY DATA (MEAN ± S.D.) TEST #916070

Parameters	Dose, mg/kg/day [litters][1]			
	control [13][1]	2 [14]	5 [14]	10 [4]
No. of corpora lutea	8.6 ± 1.4	8.1 ± 1.7	8.6 ± 1.9	8.5 ± 2.4
No. of implantations	6.7 ± 2.5	6.1 ± 1.8	6.9 ± 2.0	4.0 ± 2.2
No. of viable fetuses	6.1 ± 2.4	5.2 ± 2.2	5.0 ± 2.2	3.3 ± 2.2DR*
Preimplantation loss (%)	22.8 ± 22.4	25.3 ± 16.4	19.8 ± 16.7	47.1 ± 32.6
Postimplantation loss (%)	10.5 ± 19.0	14.8 ± 22.9	26.8 ± 25.1	15.0 ± 30.0
Fetal weight (gm)	31.3 ± 2.9	31.8 ± 2.8	29.7 ± 5.1	33.5 ± 3.9
Placental weight (gm)	4.5 ± 0.6	4.7 ± 0.6	4.5 ± 0.7	5.2 ± 1.5
Proportion of male fetuses (%)	50.6 ± 25.1	50.2 ± 28.9	59.0 ± 24.6	14.6 ± 17.2

1: Dams with totally resorbing litters at necropsy were excluded from calculations
DR*: significant (≤0.05) using the dose response test

Skeletal examination of fetuses revealed a number of observations in all groups. Though a majority of them showed no association with treatment, increases in the incidence of incomplete ossification of sternebrae, centra and of metacarpals, and bifid and mishapen sternebrae in the 5 mg/kg/day group were restricted to low birth weight fetuses. Further, dose-related increases in the incidence of thickened ribs were observed at both 5 and 10 mg/kg/day. Any meaningful conclusions on the effect of treatment on fetuses cannot be drawn from this study because of an insufficient number of fetuses (litters) in the high dose group [13(4) *versus* 79(13) in control group]. This led the sponsor to conduct another segment II study in the rabbit (see next section).

3.4.5. Oral Developmental Toxicity (Segment II) Study in New Zealand White Rabbits

Location of Data: Vol. 34

Testing Facility: Subdivision of Toxicology, Preclinical Safety, CIBA Pharmaceuticals, 556 Morris Avenue, Summit, NJ 07901.

Identification No.: Report #94045, MIN 934168

Study Dates: Dosing initiated 11/08/93 (day 7 of gestation)

GLP Compliance: Studies were done in accordance with GLP regulations

Animals: Female New Zealand white rabbits (Hra:(NZW)SPF) were approximately 23-26 weeks of age and weighed 2.9-4.4 kg on gestation day 0.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (lot #800393) were prepared in aqueous 3% corn starch. The drug was administered orally by gavage (5 ml/kg), once daily to three groups (#3, 4 and 5) of 20 pregnant females each at doses of 2, 5 or 10 mg/kg on gestation days 7 to 19. Control animals (groups 1 and 2, n=20 each) received the vehicle in a similar manner. The treated animals and control group 2 received saline as drinking water (60 ml of 0.9% NaCl/day) during the dosing period. Control group 1 received tap water to monitor potential changes in the saline control group. In a previously conducted segment II study (see section 3.4.4.), reproductive and fetal parameters could not be evaluated at 10 mg/kg/day due to low numbers of litters available for assessment. This was in part due to an increase in non-treatment-related mortalities and abortions. However, the number of dams producing litters with all dead fetuses was increased at 5 and especially at 10 mg/kg/day.

Observations/Measurements: All animals were observed once daily for physical signs of toxicity. Body weights were recorded on gestation days 0, 7, 10, 14, 20, 24 and 29. Food consumption was measured daily on gestational days 5-29. Rabbits surviving to scheduled necropsy on day 29 of gestation, and those that died or delivered prior to this date, were examined grossly for any abnormalities. Corpora lutea were counted and uterine contents were examined (live and dead fetuses and implantation sites counted).

All fetuses were sexed and given external, visceral and skeletal examinations. Following coronal serial sectioning of the head, brain and ventricles were examined. No tissues were examined histologically.

Results: There were a total of 5 unscheduled deaths, 2 treatment-related and 3 nontreatment-related, during the study. Two does, one in the 10 and the other in the 5 mg/kg/day group, were found dead on gestation days 28 and 20, respectively. The high dose animal showed no effects on food consumption or body weight and there were no remarkable findings upon necropsy. The mid dose animal exhibited soft, decreased and/or no stool, as well as body weight loss and severely

reduced food consumption prior to death. Necropsy revealed gas-filled stomach/intestines and no food in the stomach. There were no deaths considered to be treatment-related at 2 mg/kg/day. One of the non-treatment-related deaths occured at the mid dose (gestation day 17) and two occurred at the high dose (gestation days 18 and 20). All these deaths were ascribed to misgavage as indicated by the necropsy findings. Additionally, a non-saline control doe delivered on gestation day 29 and thus was sacrificed on the same day. Necropsy of this doe revealed gas-filled intestines.

Clinical signs and necropsy findings observed in this study were considered by the sponsor to be incidental to treatment with CGP 48933 due to their isolated occurrence or the lack of a dose-response relationship.

There was no effect of treatment on average maternal body weight gain during gestation. However, the saline control group showed a statistically significant reduction ($P \leq 0.05$) in mean corrected body weight gain on gestation day 29 compared to the non-saline control group. The saline control group consumed significantly less food than the non-saline control group ($P \leq 0.05$) only on gestation days 14 and 15. These reductions were considered indicative of a slight effect of saline on food consumption. Treatment with CGP 48933 resulted in statistically significant and transient reductions (19% in 2 and 5 mg/kg/days groups and 21% in 10 mg/kg/day group) in mean food consumption at all dose levels compared with the saline control group on gestation days 7 and 8. The data was highly variable and not significant for the rest of the study days.

Treatment with test substance at 10 mg/kg/day resulted in a slight and not statistically significant reduction in mean number of live fetuses, coupled with a slight and not statistically significant increase in mean number of late resorptions. Four of 13 high dose litters had 2 or more late resorptions *versus* no more than one late resorption in any saline control litter. An elevated postimplantation loss in the high dose group was also not statistically significant (Table 3.4.5.1). All other reproduction parameters, including fetal weights, were not influenced by test substance and there were no significant fetal differences between the saline supplemented and unsupplemented control groups.

There were no treatment-related malformations or variations in fetuses at any dose level. A single visceral malformation (hydrocephaly, dilated brain ventricles or agenesis of the gall bladder) was observed in 3 fetuses from 3 (different) litters in the 10 mg/kg/day group. Since the incidence of each of these 3 malformations (which were not observed in either concurrent control group) was within the historical control range, the increase in the total number of fetuses/litters with visceral malformations ($P<0.05$) was considered by the sponsor to be incidental to CGP 48933 administration. There were no skeletal malformations or variations attributed to treatment with CGP 48933.

TABLE 3.4.5.1
SUMMARY OF LAPAROTOMY DATA FROM F_0 FEMALES. (MEAN ± STANDARD DEVIATION). MIN 934168

Parameter	Dose Level (mg/kg/day)				
	Control (0)[1]	0[2]	2[2]	5[2]	10[2]
No. females inseminated	20	20	20	20	20
No. females pregnant	18	13	17	18	16
No. litters examined	17	13	17	16	13
No. of corpora lutea	11.24 ± 2.82	12.31 ± 2.43	12.12 ± 2.26	12.06 ± 2.14	11.46 ± 1.66
No. of implants	7.41 ± 3.24	9.15 ± 3.24	9.53 ± 3.00	9.38 ± 2.03	9.08 ± 2.40
No. of early resorptions	0.35 ± 1.00	0.46 ± 0.88	0.71 ± 1.31	0.44 ± 0.63	0.08 ± 0.28
No. of late resorptions	0.06 ± 0.24	0.15 ± 0.38	0.35 ± 0.79	0.63 ± 1.54	1.85 ± 3.21
No. of resorptions	0.41 ± 1.00	0.62 ± 0.87	1.06 ± 1.52	1.06 ± 1.69	1.92 ± 3.23
No. of live fetuses	7.00 ± 3.04	8.54 ± 3.07	8.47 ± 2.94	8.31 ± 2.06	7.15 ± 3.26
No. of dead fetuses	0	0	0	0	0
Postimplantation loss	0.41 ± 1.00	0.62 ± 0.87	1.06 ± 1.52	1.06 ± 1.69	1.92 ± 3.23
% postimplantation loss	6.09 ± 14.11	5.95 ± 8.65	10.31 ± 15.97	10.07 ± 16.46	20.98 ± 29.58
Sex ratio (% males)	50.42	53.15	54.17	50.38	51.61
Male fetal weight	47.40 ± 1.31	43.68 ± 1.43	44.69 ± 1.20	47.17 ± 1.25	43.27 ± 1.47
(n)	(16)	(12)	(17)	(16)	(12)
Female fetal weight	46.01 ± 1.45	43.67 ± 1.62	41.99 ± 1.42	45.15 ± 1.42	41.92 ± 1.68
(n)	(16)	(12)	(16)	(16)	(12)

1: tap water for drinking
2: saline for drinking

In summary, in the current study, there was a slightly increased total number of resorptions, and slightly increased (number and percent) postimplantation loss at 10 mg/kg/day. In contrast, in the previously conducted study, a marked increase in total litter loss was observed at this dose. The cause of this discrepancy may not be ascertained fully but these two studies differ in two aspects: in the current study, New Zealand white rabbits were utilized instead of Dutch Belted rabbits, and drug solution was prepared in aqueous 3% corn starch instead of CMC with Tween 80. A comparison of saline supplemented and unsupplemented control groups indicated that saline supplementation reduces maternal body weight gain and food consumption but has no apparent effect on litter parameters in the New Zealand white rabbit.

3.4.6. Oral Developmental Toxicity (Segment II) Study in Mice

Location of Data: Vol. 30

Testing Facility: Division of Preclinical Safety, Ciba-Geigy Pharmaceutical, Stamford Lodge, Wilmslow, Cheshire, U.K.

Identification No.: Report #042/93/SL, Test #936133, Exp. #93M032

Study Dates: Dosing initiated 08/04/93 (day 6 of gestation)

GLP Compliance: Studies were done accordance with GLP regulations

Animals: Female mice (CD-1) from Charles River Laboratories were approximately 13 weeks of age at the start of the study and weighed 26.1-36.0 gm on day 0 of gestation.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (batch 800492), prepared in 0.5% CMC with 0.5% Tween 80, were administered orally by gavage (10 ml/kg), once daily, to three groups of 28, 34, and 32 mated females each at doses of 60, 200 and 600 mg/kg, respectively, on gestation days 6 through 15. Control animals (group 1, n=42) received the vehicle in a similar manner. The difference in the number of animals in each group was the result of a high number and uneven distribution of nonpregnant animals across the groups. Additional animals were added in order to achieve approximately equal numbers of females surviving to termination with live young in each group. The doses were selected following consideration of a dose-range finding study in non-pregnant mice in which the highest dose of 600 mg/kg/day for 10 days did not produce any clinical signs or untoward effects. However, 50% of the animals showed slight reductions in body weight.

Observations/Measurements: All animals were observed for physical signs once daily. Body weights were recorded on gestation days 0, 6, 10, 16 and 18. Food consumption was measured on gestation days 0-6, 6-10, 10-16 and 16-18. All animals were killed on day 18 of gestation, and corpora lutea, implants, early and late resorptions (including dead fetuses) and live fetuses were counted. Collective placental weights for each litter were recorded. Additionally, abdominal viscera including kidneys were examined for all F_0 females. All fetuses were weighed, sexed, and examined externally before necropsy. Approximately half the fetuses were fixed in Bouin's solution for visceral examination and the rest were placed in 99% ethanol for skeletal examination.

Results:There were no treatment-related physical signs, abortions or gross lesions observed at necropsies. One low dose animal was found dead on gestation day 12 and one mid dose animal was killed on gestation day 9; both losses were attributed to misintubation. One control, one mid dose and two high dose animals littered early on the day of scheduled necropsy and were sacrificed. A total of thirty two animals were not pregnant at necropsy (Table 3.4.6.1).

TABLE 3.4.6.1
FATE OF F_0 ANIMALS. TEST #936133

Group: Dosage (mg/kg/day):	#1 Control	#2 60	#3 200	#4 600
Total number of females mated	42	28	34	32
Littered early	1	0	1	2
Found dead	0	1	0	0
Killed	0	0	1	0
Pregnant	28	24	25	26
Pregnant at terminal necropsy with viable young	27	23	24	23
Not pregnant at terminal necropsy	14	4	8	6
Appeared not pregnant at necropsy but with a positive Salewski's stain result	0	0	0	1

There was no effect of treatment on average maternal body weight gain during the dosing period. Effects on food consumption could not be interpreted precisely due to high variation within the groups. Yet, the average food consumption was lower in all treated groups than control on all days of measurement. However, there is no dose response relationship and the differences are not statistically significant. There were no treatment-related effects on reproductive parameters of F_0 females (Table 3.4.6.2).

Cleft palate was observed in one fetus at 600 mg/kg/day (litter incidence of 4.35%) and two fetuses from two different litters at 200 mg/kg/day (8.33%) (Table 3.4.6.3). Though absent in the concurrent control animals, the historical control data showed a litter incidence of 7.6%. Because of this and the absence of a dose response relationship, the sponsor argues that the cleft palates were not attributable to treatment with CGP 48933.

Globular heart was limited to two fetuses from two litters in the high dose group. Since there were no other heart-related anomalies at this dose, the sponsor does not consider this incidence to be of any toxicological significance. Historical control data is not available. Another fetus from the high dose group exhibited a displaced subclavian artery. The incidence of dilated nasal cavities at 600 mg/kg/day (3 fetuses from 3 dams, 13.6%) and 200 mg/kg/day (5 fetuses from 5 dams, 20.8%) was higher than concurrent control (1 fetus, 3.7%), but not historical control (21%). The dilation of third (one fetus) and lateral ventricles (2 fetuses from 2 litters) was observed only at 200 mg/kg/day and was thus not considered to be of any toxicological significance (Table 3.4.6.3).

Skeletal examinations showed a number of findings (mandibles incompletely ossified, occipital bone bifid, widened anterior fontanelle and sternebrae dumb-bell/asymmetrically dumb-bell), which reached statistical significance in fetuses from the mid dose group. Absence of an increase in the 600 mg/kg/day group resulted in the sponsor not considering these findings to be of any toxicological significance. Increases in the incidence of unossfied centra in high and mid dose group fetuses were not statistically significant (Table 3.4.6.3).

TABLE 3.4.6.2
GROUP MEAN CAESARIAN NECROPSY DATA. TEST #936133

PARAMETER		DOSE LEVEL (MG/KG/DAY) CONTROL (0)	60	200	600
Number of Implantations	Mean	13.9	12.8	12.8	12.3
	SD	1.8	3.6	2.3	3.3
	N	27.0	23.0	24.0	23.0
Early Resorptions	Mean	0.9	0.7	0.6	0.4
	SD	1.2	0.8	0.9	0.6
	N	27.0	23.0	24.0	23.0
Late Resorptions	Mean	0.3	0.3	0.5	0.5
	SD	0.5	0.9	0.7	0.6
	N	27.0	23.0	24.0	23.0
Total resorptions	Mean	1.2	1.0	1.1	0.9
	SD	1.4	1.0	1.0	0.9
	N	27.0	23.0	24.0	23.0
Number of Viable Fetuses	Mean	12.0	11.8	11.7	11.4
	SD	2.3	3.4	2.6	3.2
	N	27.0	23.0	24.0	23.0
Post-implantation Loss (%)	Mean	9.1	7.6	9.2	8.5
	SD	10.7	7.4	9.4	11.2
	N	27.0	23.0	24.0	23.0
Litter Mean Fetal Weight (g)	Mean	1.3	1.4	1.3	1.4
	SD	0.1	0.2	0.1	0.1
	N	27.0	23.0	24.0	23.0
Mean Fetal Weight of Male Fetuses (g)	Mean	1.3	1.4	1.3	1.4
	SD	0.1	0.2	0.1	0.1
	N	27.0	23.0	24.0	22.0
Mean Fetal Weight of Female Fetuses (g)	Mean	1.3	1.3	1.3	1.3
	SD	0.1	0.1	0.1	0.1
	N	27.0	22.0	24.0	23.0
Proportion of Male Fetuses (%)	Mean	44.9	52.5	46.3	45.3
	SD	13.7	17.6	13.7	17.5
	N	27.0	23.0	24.0	23.0

SD: standard deviation

TABLE 3.4.6.3
FETAL EXTERNAL, VISCERAL AND SKELETAL OBSERVATIONS. TEST #936133

Observations	M/V	Dose (mg/kg/day) Control dams/fetuses	60 dams/fetuses	200 dams/fetuses	600 dams/fetuses
1. External observations					
Number examined:		27/324	23/271	24/280	23/263
Cleft palate	M	0	0	2/2	1/1
Severe exencephaly	M	1/1	0	0/0	0/0
2. Visceral observations					
Number examined:		27/152	23/130	24/136	22/122
Right subclavian artery	M	0	0	0/0	1/1
Reduced thickness of ventricle walls	M	0	0	1/1	0/0
Nasal cavities dilated	V	1/1	1/1	5/5	3/3
Brain-lateral ventricle dilated	V	0	0	1/1	0
Brain-third ventricle dilated	V	0	0	2/2	0
Heart globular	V	0	0	0	2/2
3. Skeletal observations					
Number examined:		27/172	23/141	24/144	23/141
Lumbar vertebrae-only 5 present	M	1/1	0	2/5	1/2
Mandibles-incompletely ossified	V	3/3	2/3	5/10	2/2
Bifid occipital	V	0	0	3/3	0
Widened anterior fontanelle	V	3/3	1/2	6/10	2/3
Centra incompletely ossified	V	3/4	4/4	6/7	6/9
Centra not ossified	V	2/3	1/6	6/6	6/6
Sternebrae- dumb-bell/asymmetricaliy dumb bell	V	4/5	3/5	8/13	8/10

M: malformation, V: variant

3.4.7. Plasma Concentrations of CGP 48933 in Pregnant Rats During a 13-day Gestation Study

Location of Data: Vol. 38 of the original submission and amendment dated March 7, 1996.

Testing Facility: Division of Preclinical Safety, Ciba-Geigy Pharmaceutical, Stamford Lodge, Wilmslow, Cheshire, U.K.

Identification No.: Report #BPK (CH) 1995/023 and 040/94/SL, Test #947902

Study Dates: Animals dosed from 4/11/94 to 5/27/94

GLP Compliance: Studies were done in accordance with GLP regulations.

Animals: Female Sprague-Dawley (Tif:RAIf(SPF)) rats were 17 weeks of age and weighed 290-390 gm at allocation.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 (batch #800393) were prepared in 0.5% CMC with 0.5% Tween 80. The drug was administered orally (by gavage) to three groups of mated females on gestation day (GD) 6 or 13 or from day 6 to 13 of gestation, at a dose of 600 mg/kg/day. Since at necropsy a large number of animals were found to be nonpregnant, additional animals were added to supply the required number of blood samples (Table 3.4.7.1). Control animals (group 1) received the vehicle, in a similar manner, on days 6-13 of gestation.

TABLE 3.4.7.1.
STUDY DESIGN. STUDY #947902

Group	Dose (mg/kg/day)	N/group		Days dosed	# pregnant	Time of sampling (h postdose)	
		Initial	Suppl			Initial	Supplemental
1	Control	5	0	6-13	5	GD13 @ 3 h (n=5)	None
2	600	10	8	6-13	12	GD13 @ 1, 4, 12 h (n=5)* 2, 8, 24 h (n=5)*	GD13 @ 1, 4, 12 h (n=5)* 2, 8, 24 h (n=3)*
3	600	10	6	13 only	10	GD13 @ 1, 4, 12 h (n=5)* 2, 8, 24 h (n=5)*	GD13 @ 1, 4, 12 h (n=2)* 2, 8, 24 h (n=4)*
4	600	15	6	6 only	16	GD6 @ 1, 4, 12 h (n=5)* 2, 8, 24 h (n=5)*	GD6 @ 1, 8 h (n=1)* 2, 12 h (n=5)*

* Same animals were used for all time points.

Observations/Measurements: All animals were observed for physical signs and mortalities once daily. Body weights were recorded on day 0 and daily from day 6 to termination. However, the report contains data for days 0, 6, 9 and 13 only. All animals from groups 1, 2 and 3 were killed on the 14th day after mating and group 4 animals were killed on the 8th day after mating. Blood

samples (0.7 ml) were collected in heparinized tubes from all animals at time points indicated in Table no. 3.4.7.1.

Results: There were no clinical signs observed which were considered attributable to drug treatment. There were no changes in body weight in any of the drug-treated groups relative to control animals. The sponsor asserts that mean plasma concentrations determined on day 6 or 13 in rats dosed only on those days were similar to that measured after repeated oral administration of CGP 48933. However, the lack of a significant difference in AUC between animals receiving one or eight daily doses could be due to the small number of animals used in each group and to large standard deviations (Table 3.4.7.2). The systemic exposure in pregnant rats was comparable to the exposure estimated in a previous study in non-pregnant rats at the same dose level (see pharmacokinetics section #2.5).

TABLE 3.4.7.2.
MEAN ± S.D. PLASMA CONCENTRATIONS (µMOL/L) AND AUC OF CGP 48933 FOLLOWING SINGLE OR MULTIPLE ORAL DOSING WITH CGP 48933 AT 600 MG/KG*. TEST #947902

Time point (hr)	Group 2 (dosed days 6-13) [N=]	Group 3 (dosed day 13 only) [N=]	Group 4 (dosed day 6 only) [N=]
1	9.89 ± 4.99 [5]	15.18 ± 10.08 [5]	17.27 ± 9.32 [5]
2	13.49 ± 6.93 [7]	10.63 ± 9.41 [5]	7.12 ± 4.35 [6]
4	8.55 ± 7.68 [5]	6.81 ± 3.30 [5]	11.52 ± 5.38 [5]
8	12.71 ± 14.94 [7]	6.00 ± 4.76 [5]	10.01 ± 7.96 [5]
12	5.77 ± 2.49 [5]	5.15 ± 3.19 [5]	3.95 ± 2.41 [6]
24	2.6 ± 1.29 [3]	2.85 ± 3.62 [3]	1.24 ± 0.74 [5]
AUC (1-24hr) [h(µmol/l)]	163.4	126.3	133.0

* Test substance was not detected in the plasma samples from the control group.

3.4.8. Transfer of Radioactive Substances to the Embryo-Fetal Compartment of Rats After Oral Administration of 600 mg/kg [^{14}C]CGP 48933

Location of Data: Vol. 38

Testing Facility: Division of Preclinical Safety/Drug Metabolism, Ciba-Geigy Ltd., Basle, Switzerland.

Identification No.: Report #DM 22/1993, Test #937004

Study Dates: April to August 1993 (dosing dates not provided)

GLP Compliance: Studies were NOT done in accordance with GLP regulations

Animals: Female Sprague-Dawley (Tif:RAIf(SPF)) rats were approximately 12-15 weeks of age and weighed 280-350 gm on day 13 and averaged about 380 gm on day 18 of gestation.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 were prepared in 0.5% Klucel[1] HF (1 gm of suspension contains 60.1 mg of [^{14}C]CGP 48933). The suspending agents (CMC and Tween 80) used in teratogenicity studies were not used in this study since the labeled compound could not be suspended homogeneously in them. Rats were dosed with 600 mg/kg [^{14}C]CGP 48933 orally (by gavage) on day 13 or 18 of gestation.

Observations and Measurements: The distribution of radiolabelled substance(s) in selected organs and tissues including blood and plasma was determined 1, 8 and 24 hours (n=2-3 rats/time point) post dose on day 13 of gestation only. The residual concentrations of radioactive substance(s) in organs and tissues were also determined 96 hours post dose for rats dosed on day 13 of gestation For the whole-body autoradiography experiments, single animals were sacrificed at 1 or 24 hours post dose for rats dosed on day 13 or 18 of gestation. For the excretion experiments, the urine was quantitatively collected in fractions between 0 and 8 hr, 8 and 24 hr, and thereafter daily up to 96 hr after administration. Feces were collected quantitatively daily up to 96 hr post dose. The excretion studies were conducted on rats (n=3) dosed on day 13 of gestation only.

Results: The distribution of radioactivity throughout the body 1 and 24 hr post dose in rats dosed on day 18 of gestation was similar to that observed on day 13 of gestation. High amounts of unabsorbed radioactive substance(s) were present in the stomach at 1 and 8 hr after dosing (75-97% of the dose) and at twenty four hours after dosing (26-44% of the administered dose).

Liver, kidney and small intestine showed a higher distribution (5-22% of the dose) of labeled drug substance than did the remaining investigated organs and tissues. (Table 3.4.8.1). The ^{14}C concentrations in plasma (5.8% at 1 hr) were 1.5- to 1.9-fold higher than those in blood (3.3% at 1

[1] Klucel is hydroxypropyl cellulose

hr) at all time points. Between 1 and 24 hr after administration, the decline of radioactive substance(s) from blood and plasma of rats was distinctively slow, suggesting a prolonged absorption and is keeping with the high amounts of unabsorbed material found in the stomach up to 24 hr post dose. The radioactive concentrations in most of the other organs and tissues were markedly lower than those of blood and plasma. Distinct ^{14}C concentrations were found in the

TABLE 4.8.1
DISTRIBUTION OF [^{14}C]CGP 48933 (nmol/gm) IN RATS AND UPTAKE INTO THE FETUS 1, 8 AND 24 HOURS AFTER SINGLE ORAL DOSE OF 600 MG/KG [^{14}C]CCGP 48933 ON DAY 13 OF GESTATION.
TEST #937004

Sample	1 HR	8 HR	24 HR
Blood	19.7	6.5	5.3
Plasma	32.3	13.7	9.9
Salivary	4.7	0.9	0
Thyroid	0.0	13.1	0
Thymus	0.8	0	0
Lung	10.9	2.2	1.7
Heart	4.3	0	0
Aorta	0.0	0	0
Liver	117.4	48.3	61.4
Pancreas	2.3	0	0
Spleen	2.6	0	0
Adrenal	5.4	1.4	0
Kidney	24.1	13.0	12.2
White fat	1.9	0.5	0
Ovary	7.5	2.5	0
Muscle	1.3	0	1.4
Sciatic nerve	0.0	0	0
Bone marrow	0.0	0	0
Stomach	472.2	135.4	30.0
Small intestine	131.5	15.6	54.3
Skin	7.5	1.6	0
Brown fat	2.4	0	0
Eye	1.0	0	0
Brain	0.6	0	0
Mammary gland	4.4	2.4	1.1
Amniotic fluid	0.0	0	0
Placenta 5.7[a]	1.7[b]	0.8[c]	
Foetus	0.0[a]	0[b]	0[c]

a: Means of 5 or 6 placentas or fetuses for each individual animal. Radioactivity was detected in 3 of 5, 6 of 6 and 5 of 6 placentas (n=3).
b: Means of 6 placentas or fetuses for each individual animal. Radioactivity was detected in 2 of 6 and 3 of 6 placentas and not significant in third rat (n=3).
c: Means of 6 placentas or fetuses for each individual animal. Radioactivity was detected in 2 of 6 placentas and not significant in second rat (n=2).

mammary glands and the placentas, whereas the ^{14}C levels in the fetuses were below the limit of detection. No radioactivity was detected in the amniotic fluid between 1 and 24 hr of dosing. On

the contrary, in dams dosed on day 18 of gestation, a weak uptake of ^{14}C substance(s) was observed in the placentas at 1 and 24 hr post dose and in the fetuses at 24 hr post dose.

The radioactivity was completely excreted within 4 days: about 97% of the dose in the feces and about 2.3% in the urine in rats dosed on day 13 of gestation (Table 3.4.8.2). The residual concentrations of radioactive substance(s) in almost all investigated organs and tissues were at or below the limit of detection at 96 hr post dose. Residual concentrations substantially above the background were only found in the liver, kidneys and the mammary glands.

TABLE 3.4.8.2
EXCRETION OF RADIOACTIVE SUBSTANCES IN URINE AND FECES OF PREGNANT RATS AFTER ORAL ADMINISTRATION OF 600 MG/KG [^{14}C]CGP 48933 ON DAY 13 OF GESTATION. TEST #937004

	Excretion in % of administered adioactivity								
Time interval	Urine				Faeces				Urine and feces
Hr	RA10	RA11	RA12	Mean	RA10	RA11	RA12	Mean	Mean
0- 8	0.75	0.22	M	0.32	-*	-*	-*	-*	0.32
8-24	1.42	0.91	1.12	1.15	43.90	16.97	4.23	21.70	22.85
24-48	0.30	0.90	0.99	0.73	45.58	50.50	66.13	54.07	54.80
48-72	0.03	0.16	0.19	0.13	6.22	28.99	24.88	20.03	20.16
72-96	NS	0.01	0.02	0.01	1.20	2.17	1.69	1.68	1.69
0-96	2.50	2.19	2.32	2.34	96.91	98.63	96.93	97.49	99.83

NS: not significant
M: no sample
* : Feces samples were collected in one fraction between 0 and 24 hours after administration

In summary, the extent and/or rate of absorption of 600 mg/kg ^{14}C-CGP 48933 orally administered to pregnant rats on day 13 or 18 of gestation was low. The concentrations of radioactive substance(s) in blood, plasma, organs and tissues of the dam were low. The ^{14}C levels in the placentas were even lower than in the maternal blood. Radioactivity was detectable in mammary glands, suggesting the possible excretion with the milk in lactating animals. Though the label was not detectable in fetuses on day 13 of gestation it was quantifiable in fetuses on day 18 of gestation. Thus, the study indicates that CGP 48933 and/or its metabolites are not transferable to the embryo-fetal compartment of pregnant rats during the period of organogensis, but may do so when the dam is dosed toward the end of the gestation period (i.e., day 18 of gestation).

3.4.9. Transfer of Radioactive Substances to the Embryo-Fetal Compartment of Rats After Oral Administration of 60 mg/kg [^{14}C]CGP 48933

Location of Data: Vol. 38

Testing Facility: Division of Preclinical Safety/Drug Metabolism, Ciba-Geigy Ltd., Basle, Switzerland.

Identification No.: Report #DMET(EU) 9/1995, Test #947012

Study Dates: May/June 1994 to March/April 1995 (dosing dates not provided)

GLP Compliance: Studies were **NOT** done in accordance with GLP regulations

Animals: Female Sprague-Dawley (Tif:RAIf(SPF)) rats were approximately 10-16 weeks of age and weighed 211-333 gm on day 13 of gestation (May 1994). At the time of dissection it was discovered that half of the animals were not pregnant; the study was repeated in March 1995 with a few more animals. Body weights for the latter (replacement) study are not given.

Mode of Administration/Dosage Levels: Suspensions of CGP 48933 in 0.5% sodium CMC and 0.5% Tween 80 in water contained 6.54 mg (for rats dosed in May 1994, batch #Mo-20.8B-11) or 6.34 mg (for rats dosed in April 1995, batch #Mo-20.10A-1) of [^{14}C]CGP 48933/gm. Each animal received orally (by gavage) approximately 60 mg [^{14}C]CGP 48933/kg body weight on day 13 of gestation. This study differed from the previous study (Test #937004, section #3.4.8) in dose and formulation. In the previous study, 600 mg/kg [^{14}C]CGP 48933 was administered as a suspension in Klucel on day 13 of gestation. In that study, the extent of oral absorption was low and the uptake of radioactivity into the fetus was at or below the limit of detection. Therefore it was hard to conclude that CGP 48933 /or its metabolites are transferred to the embryo-fetal compartment of pregnant rats during the period of organogenesis. The present study employed a dose 10 times lower than in the previous dam-fetus ^{14}C transfer study and the same formulation as used in the teratology study (sections 3.4.1 to 3.4.3). Of 12 animals gavaged in May 1994, 5 were nonpregnant at the time of sacrifice. Of 8 animals dosed in March 1995, all were pregnant at the time of sacrifice. Thus the total number of animals evaluated was 15.

Observations and Measurements: The distribution of radiolabelled substance(s) in selected organs and tissues, including blood and plasma, was determined 1 (n=3), 8 (n=5) and 24 (n=4) hr post dose on day 13 of gestation. Unlike in the previous study, animals in this study were not subjected to whole body autoradiography. For the excretion experiments (n=3, same animals at all time-points), the urine was quantitatively collected in three fractions: 0 - 8 hr, 8 - 24 hr, and 24 - 48 hr after administration. Feces were collected quantitatively in two fractions: 0 - 24 hr and 24 - 48 hr post dose.

Results: The ^{14}C concentrations in plasma were highest at 1 hr and decreased with time. They were below the limit of detection in 1/3 rats 48 hr post dose. The plasma concentrations at all time points

were 1.6 to 1.9-fold higher than those in blood. Figure 3.4.9.1 shows the time course of the specific ^{14}C concentrations in blood and plasma in this and the previous study. The relative extent of absorption after 60 mg/kg (present study) was higher than after 600 mg/kg (see section #3.4.8). Following 60 mg/kg, the specific $AUC_{(0\text{-}24\ hr)}$ of ^{14}C (1.7 µmol/l.h/mg/kg) was about 3-fold higher than after 600 mg/kg.

This suggests that the previous study is not an accurate display of distribution of drug substance in pregnant rats during the period of organogenesis. The most probable reason was the choice of Klucel over CMC as a suspending agent. Based on the estimated specific AUC, the oral absorption in pregnant rats in this study was at least 50% of that obtained from a kinetic study in male rats at the same dose level (study #DMEU20/1994, section #2.5).

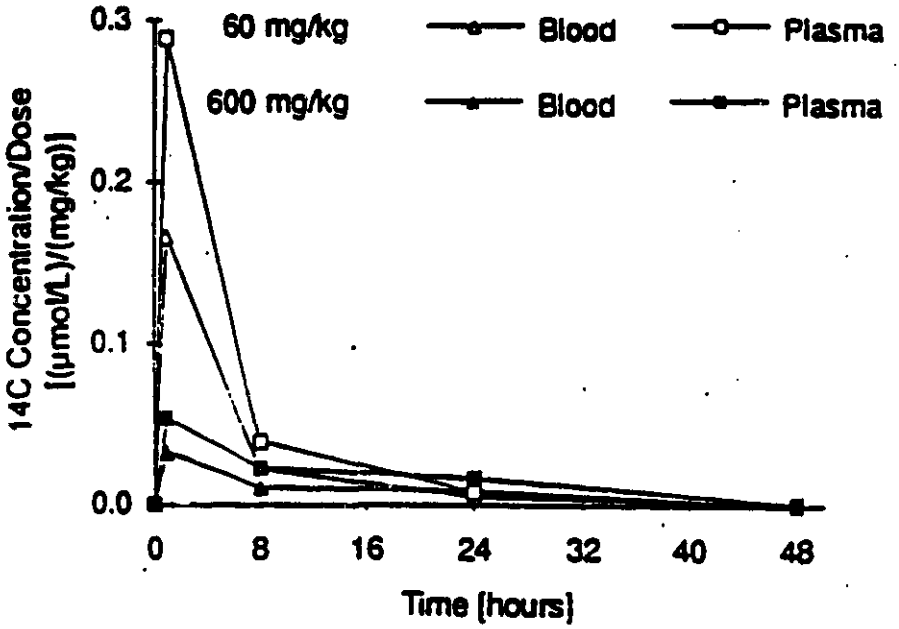


Fig. 3.4.9.1.: Specific concentra' ; of radioactive substances in blood and plasma after a single oral dose of [^{14}C]CGP 4. .3. Means of 3-5 animals/time-point.

The pattern of distribution of radioactivity throughout the body of the dam was similar at all time-points. As in the previous study (section #3.4.8), stomach, liver, kidney and small intestine showed higher distribution of labelled drug substance than did the remaining investigated organs and tissues. The radioactive concentrations detected in the female reproductive organs, the ovary, the uterus and the mammary glands were comparable and approximately 1/3 of that in the blood. The lowest levels were observed in the brain and were below the limit of detection 24 hr postdose (Table 3.4.9.1).

At all investigated time-points (excluding 48 hr time-point) ^{14}C concentrations were found in most of the placentas and the levels were roughly comparable to those found in other organs and tissues. ^{14}C levels were detected in fetuses of all dams (averaged about 3% of that in the maternal blood) at 1 hr, in fetuses of 1 dam at 8 hr and in fetuses of no dams at 24 hr. Reliable estimates of ^{14}C levels in amniotic fluid could not be made since the samples were contaminated with blood.

TABLE 3.4.9.1

MEAN DISTRIBUTION OF [^{14}C]CGP 48933 IN RATS AND UPTAKE INTO THE FETUS 1, 8, 24 and 48 HOURS AFTER SINGLE ORAL DOSE OF 60 MG/KG [^{14}C]CCGP 48933 ON DAY 13 OF GESTATION. TEST #947012

	^{14}C Concentration (nmol/gm)			
Sample	1 HR	8 HR	24 HR	48 HR
Blood	9.98	1.34	0.31	0.03
Plasma	17.33	2.36	0.50	0.02
Salivary	2.08	0.22	0.08	0.01
Thyroid	2.14	0.96	0.13	0.00
Thymus	0.92	0.15	0.03	0.00
Lung	4.29	0.64	0.16	0.00
Heart	2.28	0.30	0.08	0.00
Aorta	2.25	0.61	0.00	0.00
Liver	58.11	21.52	7.90	3.53
Pancreas	2.01	0.24	0.05	0.00
Spleen	0.99	0.21	0.07	0.02
Adrenal	2.72	0.41	0.11	0.00
Kidney	19.81	4.44	1.43	0.17
White fat	0.94	0.11	0.03	0.00
Axillary lymph nodes	2.45	0.40	0.11	0.00
Ovary	3.60	0.53	0.13	0.00
Muscle	0.62	0.10	0.04	0.00
Sciatic nerve	1.90	0.36	0.03	0.00
Bone marrow	2.38	0.27	0.07	0.00
Stomach	98.74	54.45	7.83	0.18
Small intestine	72.27	8.00	2.52	0.07
Skin	2.30	0.74	0.09	0.00
Brown fat	2.04	0.32	0.05	0.00
Eye	0.77	0.23	0.02	0.00
Brain	0.36	0.05	0.00	0.00
Uterus	3.65	0.60	0.15	0.00
Mammary gland	3.12	0.56	0.09	0.00
Placenta	2.99	0.87	0.23	0.04
Foetus	0.37[a]	0.02[a]	NS	<0.01

a: Several samples were below the limit of detection

TABLE 3.4.9.2
EXCRETION OF RADIOACTIVE SUBSTANCES IN URINE AND FECES OF PREGNANT RATS AFTER ORAL ADMINISTRATION OF 60 MG/KG [^{14}C]CGP 48933 ON DAY 13 OF GESTATION. TEST #947012

	Excretion in % of administered radioactivity								
Time interval	Urine				Faeces				Urine and feces
Hr	RA10	RA11	RA12	Mean	RA10	RA11	RA12	Mean	Mean
0- 8	1.12	1.05	1.54	1.23	--	--	--	-	1.23
8-24	1.44	1.33	0.91	1.23	81.04*	92.86*	70.43*	81.44*	82.67
24-48	0.10	0.10	0.78	0.32	13.91	2.77	23.14	13.27	13.60
0-48	2.65	2.48	3.23	2.78	94.95	95.63	93.57	94.72	97.50

* : Feces samples were collected in one fraction between 0 and 24 hours after administration

The radioactivity was excreted to an extent of 98% of the administered dose in the feces and urine within 2 days postdose (Table 3.4.9.2). The residual concentrations of radioactive substance(s) in almost all investigated organs and tissues were at or below the limit of detection at 48 hr post dose. Residual concentrations substantially above the background were only found in the liver, kidneys, stomach (2 of 3 dams) and small intestine. The recovery of radioactivity in the contents of the stomach and the small intestine at various time-points represent the unabsorbed material. The proportions of the dose (range in %) found in the contents of these two tissues are as follows:

	1 hr	8 hr	24 hr
Stomach:	43-64%	3-12%	up to 4% of the dose
Small intestine:	26-41%	3-10%	up to 1.3% of the dose

In summary, the extent and/or rate of absorption of 60 mg/kg ^{14}C-CGP 48933 orally administered to pregnant rats on day 13 of gestation, as in the previous study was low. The concentrations of radioactive substance(s) were highest in kidneys, stomach, small intestine and liver. Radioactivity was detectable in mammary glands, suggesting the possible excretion with the milk in lactating animals. Unlike in the previous study, the label was detectable in fetuses on day 13 of gestation (at 1 hour time-point, fetal ^{14}C levels corresponded to about 3% of maternal blood levels). The study indicates that CGP 48933 and/ or its metabolites are transferable to the embryo-fetal compartment of pregnant rats during the period of organogensis.

3.4.10. Transfer of Radioactive Substances to the Embryo-Fetal Compartment of Mice After Oral Administration of 60 mg/kg [^{14}C]CGP 48933

Location of Data: Vol. 38

Testing Facility: Division of Preclinical Safety/Drug Metabolism, Ciba-Geigy Ltd., Basle, Switzerland.

Identification No.: Report #DMET(EU) 4/1995, Test #947015

Study Dates: May/June 1994 to March/April 1995 (dosing dates not given)

GLP Compliance: Studies were NOT done in accordance with GLP regulations

Animals: Female mice of strain Tif:RAIf(SPF) were 9 weeks of age and weighed 39-46 gm on day 13 of gestation.

Mode of Administration/Dosage Levels: Suspensions of [^{14}C]CGP 48933 (batch #Mo-20.8 B20) in 0.5% sodium CMC and 0.5% Tween 80 in water contained 6.1 mg drug/g . Each animal received orally (by gavage) 60 mg [^{14}C]CGP 48933/kg body weight on day 13 of gestation.

Observations and Measurements: The distribution of radiolabelled substance(s) in selected organs and tissues, including blood and plasma, were made 1, 4, 8 and 24 hours post dose on day 13 of gestation (n=3 at all time- points). Animals were not subjected to whole body autoradiography and no excretion experiments were carried out.

Results: The pattern of distribution of radioactivity throughout the body of the dam was similar at all time-points and was roughly comparable to the pattern seen in pregnant rats after administration of the same dose (see section #3.4.9). As in rats, liver and kidney (stomach and small intestine were not studied) showed higher distribution of labelled drug than the remaining investigated organs and tissues .

The ^{14}C concentrations in plasma were highest at 1 hr and decreased with time. They were below the limit of detection 24 hr post dose. The plasma concentrations at all time points were approximately 2-fold higher than those in blood. A comparison of the specific ^{14}C plasma AUC's estimated in this study at various time points with those obtained in a kinetics study in male mice after oral doses of 3, 200 and 600 mg/kg (section #2.5) and in a study in pregnant rats at an oral dose of 60 mg/kg (section #3.4.9) indicates that the systemic availability of the 60 mg/kg dose in pregnant mice is very low. The mean AUC values [normalized to (µmol/l).h/(mg/kg)] in these studies were as follows:

Pregnant mice, 60 mg/kg (this study):			0.11
Section #2.4	Male mice,	3 mg/kg:	0.73
		200 mg/kg:	0.34
		600 mg/kg:	0.20
Section #3.4.9	Pregnant rat,	60 mg/kg:	1.70

The above data suggest a low systemic availability of [^{14}C]CGP 48933 in pregnant mice compared to pregnant rats or male mice.

Concentrations of radioactivity detected in the ovary, the uterus and the mammary glands were comparable or lower than those in the blood. The lowest levels were observed in the brain. The ^{14}C concentrations declined by about half in most of the organs and tissues between 1 and 4 hr post dose. Again, the levels halved between 4 and 8 hr post dose and after 24 hr, the ^{14}C levels fell below the limit of detection in all investigated organs and tissues except the liver, in which the levels were still high in all animals, and the uterus in which levels were detectable in one mouse (Table 3.4.10.1).

At time-points up to 24 hr post dosing, ^{14}C concentrations were found in most of the placentas and the levels were roughly comparable to those found in other organs and tissues or lower than those in the blood. The mean ^{14}C concentrations of 5 fetuses from each animal (15 fetuses/time-point), though low (2% of the maternal blood at 1 hr post dose), remained approximately constant over the 24 hr observation period, while the radioactive susbstance(s) in the maternal blood, organs and tissues declined between 1 and 24 hr post dose (Table 3.4.10.1).

TABLE 3.4.10.1

MEAN DISTRIBUTION OF [^{14}C]CGP 48933 IN MICE AND UPTAKE INTO THE FETUS 1, 8, 24 and 48 HOURS AFTER SINGLE ORAL DOSE OF 60 MG/KG [^{14}C]CGP 48933 ON DAY 13 OF GESTATION. TEST #947015

	^{14}C Concentration (nmol/gm)			
Sample	1 HR	8 HR	24 HR	48 HR
Blood	0.54	0.25	0.14	0.01
Plasma	0.99	0.49	0.27	<0.01
Salivary	0.16	0.07	0.03	0.00
Thymus	0.11	0.05	0.04	0.00
Lung	0.35	0.19	0.10	<0.01
Heart	0.17	0.09	0.05	0.01
Aorta	0.46	0.00	0.03	0.00
Liver	11.32	9.25	6.16	0.18
Pancreas	0.15	0.29	0.03	0.00
Spleen	0.10	0.12	0.06	0.00
Adrenal	0.28	0.30	0.16	0.00
Kidney	2.89	1.14	0.83	0.02
White fat	0.06	0.12	0.00	0.00
Ovary	0.21	0.18	0.12	0.01
Muscle	0.06	0.09	0.05	<0.01
Skin	0.19	0.07	0.05	0.00
Brown fat	0.11	0.06	0.05	0.00
Eye	0.04	0.03	0.06	0.00
Brain	0.03	0.01	0.01	0.00
Uterus	0.26	0.17	0.09	0.04
Mammary gland	0.10	0.08	0.03	0.00
Foetus[a]	0.01[c]	0.01[c]	0.01[c]	0.02[c]
Placenta[b]	0.15	0.11	0.07	0.02

a: Means of 5 fetuses for each individual animal.

b: Means of 5 placentas for each individual animal.

c: In many samples, the values were below the limit of detection

3.4.11. Transfer of Radioactive Substances to the Embryo-Fetal Compartment of Rabbits After Oral Administration of 10 mg/kg [^{14}C]CGP 48933

Location of Data: Vol. 38

Testing Facility: Division of Preclinical Safety/Drug Metabolism, Ciba-Geigy Ltd., Basle, Switzerland.

Identification No.: Report #DM(EU) 11/1994, Test #937031

Study Dates: October 1993 (dosing date(s) not given)

GLP Compliance: Study was **NOT** done in accordance with GLP regulations

Animals: Two pregnant Himalayan rabbits were 6 months of age and weighed 2.6 and 2.9 kg on day 17 of gestation.

Mode of Administration/Dosage Levels: 73.6 mg [^{14}C]CGP 48933 (batch #Mo-20.8 B-7) were suspended in 7.32 gm suspension in 0.5% sodium CMC and 0.5% Tween 80 in water resulting in a concentration of 10 mg [^{14}C]CGP 48933/g suspension. One rabbit weighing 2.6 kg received 2.7 gm (10.38 gm/kg) and the other weighing 2.9 kg received 3.2 gm (11.03 mg/kg) suspension orally (by gavage) on day 17 of gestation. The dose (10 mg/kg) chosen for this study was the highest dose level used in the teratogenicity study in rabbits.

Observations and Measurements: Blood samples were collected from the ear vein at 0.5, 2, 4, 6 and 24 hr post dose. Excretion of radioactivity in urine was measured in 24 hr samples. The distribution of radiolabelled substance(s) in selected organs and tissues, including amniotic fluid, placenta and fetuses, was determined after killing and dissecting both animals 24 hr post dose. Animals were not subjected to whole body autoradiography.

Results: After oral administration of 10 mg/kg [^{14}C]CGP 48933, the radioactive material(s) appeared in the systemic circulation in the first sampling period, 30 min post dose. Thereafter, the ^{14}C concentrations remained approximately constant up to 6 hr in one rabbit and declined slowly to about half the initial levels in the other rabbit. However, in both rabbits, the plasma ^{14}C concentrations increased between 6 and 24 hr, peaking (Cmax) at 24 hr, suggesting that oral absorption was still ongoing (Table 3.4.11.1). Blood ^{14}C concentrations were in parallel to those in the plasma and were 50-70% of the plasma ^{14}C concentrations. Though the study does not permit a precise estimate of oral absorption, absorption must be at least as high as the percent dose excreted with the 0-24 hr urine, which was 25% in rabbit #6012 and 8% in rabbit #6268. It may be noted that the AUC for radioactive substance(s) in rabbit #6268 is approximately 4 times lower than that in rabbit #6012 (see Table 3.4.11.1). The overall rate of oral absorption seemed low in comparison to rats for which the ^{14}C concentrations in blood and plasma reached Cmax at about 15 min and declined to values of about 2-3% of Cmax within 24 hr.

TABLE 3.4.11.1
CONCENTRATIONS OF CGP48933 [µmol/L] AND RADIOACTIVE SUBSTANCES IN PLASMA OF PREGNANT RABBITS AFTER ORAL ADMINISTRATION OF 10 MG/KG [^{14}C]CGP48933 ON DAY 17 OF GESTATION. TEST #937031

Time	Animal #RB 6012		Animal #RB 6268	
[hr]	CGP48933	Total ^{14}C	CGP48933	Total ^{14}C
0.5	13.3	12.2	7.1	5.8
2	16.2	14.7	4.9	4.3
4	15.5	13.7	3.2	2.9
6	15.2	14.2	3.0	2.7
24	20.8	20.8	4.1	5.2
AUC[a]	412	395	89	93

a: $AUC_{(0\text{-}24\ h)}$ [(µmol/L). h], concentration at t=0 was taken as 0.

Highest concentration of radioactivity was found in kidneys followed (in descending order) by blood, plasma and liver (Table 3.4.11.2). In contrast, in the rat and mouse the highest concentration was found in the liver followed (in descending order) by kidneys, blood and plasma. This explains the higher proportion of the dose excreted renally by rabbits (8-25% in 24 hr) than by rats (1.3%). The distinct uptake of radioactivity into the mammary glands suggests that the compound may be excreted with the milk in lactating animals.

The ^{14}C concentrations in placentas and mammary glands were 20-30% of that found in the maternal blood. The ^{14}C concentration in amniotic fluid was below the limit of detection. Similarly, the radioactive material was not detected in the fetuses of one rabbit (#6268) which generally had low exposure; however, a low concentration of ^{14}C was detected in the fetuses of the other rabbit. This suggests that the extent of transfer of radioactivity from the doe to the fetus was low, about 3.2% of the concentration in the maternal blood.

In summary, after oral administration of 10 mg/kg [^{14}C]CGP 48933 to pregnant rabbits on day 17 of gestation, the extent of absorption was at least 8% in one animal and at least 25% in another. The does were continuously exposed to CGP 48933 during the 24 hr observation period. The transfer of ^{14}C substances to the embryo-fetal compartment during the period of organogenesis could not be ascertained with any degree of precision since concentrations of CGP 48933 in maternal plasma were very different for the two does.

TABLE 3.4.11.1

DISTRIBUTION OF [^{14}C]CGP 48933 IN RABBITS AND UPTAKE INTO THE FETUS 24 HOURS AFTER SINGLE ORAL DOSE OF 10 MG/KG [^{14}C]CCGP 48933 ON DAY 17 OF GESTATION. TEST #937031

	^{14}C Concentration (nmol/gm)	
Sample	RB 6012	RB 6268
Blood[a]	15.08	3.50
Plasma[a]	20.81	5.30
Lung	4.95	1.03
Muscle	.44	.09
White fat	.72	.19
Liver	10.43	4.01
Kidney	27.70	11.82
Endbrain	.22	.09
Ovary	4.08	.96
Uterus	4.47	1.03
Mammary gland[a]	4.90	1.34
Amniotic fluid	.03[c]	NS[b]
Placenta[b]	2.92	.99
Foetus[b]	.17	NS
Foetal brain[a]	.11	NS
Foetal liver[a]	.20	.06

NS: not significant

a: Mean of 2 samples

b: Mean of 4.samples

c: Mean of 3 samples, NS in two samples, concentration in the third sample 0.09 nmol/g

3.4.12. ^{14}C Concentrations in Milk and Plasma After Oral Administration of 3 mg/kg [^{14}C]CGP 48933 to Lactating Rats

Location of Data: Vol. 38

Testing Facility: Division of Preclinical Safety/Drug Metabolism, Ciba-Geigy Ltd., Basle, Switzerland.

Identification No.: Report #DMET(EU) 18/1995, Protocol #957018

Study Dates: August 1995 (dosing date not given)

GLP Compliance: Study was NOT done in accordance with GLP regulations

Animals: Female rats (of strain, Tif:RAIf(SPF)) weighed 285-473 gm on day 13 after parturition. Age not given.

Mode of Administration/Dosage Levels: 0.3 mg [^{14}C]CGP 48933 (batch #Mo-20.8 B-20) was dissolved in 1 gm of phosphate buffer pH 7. Each of 6 non-fasting lactating animals received 10 gm solution/kg body weight (corresponds to a dose of 3 mg drug/kg body weight) orally (by gavage) on day 13 after parturition.

Observations and Measurements: The litter size had been reduced to 6 pups per litter immediately after parturition and was further reduced to 4 pups per litter at 24 hr (before dosing) in order to obtain enough milk for analysis. Milk and plasma were collected from 3 animals at 15 min, 4 and 24 hr post dose and 3 animals at 1, 8 and 48 hr post dose. The pups were separated from the dams 2 hr before and during milking. Oxytocin (4 IU/kg) was given i.p. to increase the milk production. Blood samples were taken sublingually by sticking a deep lingual vein with a fine needle under anesthesia. Milk was collected immediately afterwards. Radioactivity in milk and plasma samples was measured by liquid scintillation counting.

Results: After oral administration of 3 mg/kg [^{14}C]CGP 48933, the radioactive material(s) appeared in the systemic circulation and milk in the first sampling period, 15 min post dose. In the plasma, the maximum mean ^{14}C concentration was observed at 15 min post dose and declined thereafter and was at the limit of detection 48 hr post dose (Table 3.4.12.1).

In the milk, the maximum mean ^{14}C concentration was observed between 4 and 8 hr post dose (interindividual variability was large). The levels were near the limit of detection 48 hr post dose (Table 3.4.12.1), indicating that test substance and its metabolites are eliminated vitrtually completely from both milk and plasma. Transfer of CGP 48933 and/or metabolites into the milk was slow since maximum mean ^{14}C concentrations were observed in plasma 15 min, and in milk 4 hr after administration of [^{14}C]CGP 48933.

TABLE 3.4.12.1

CONCENTRATIONS OF RADIOACTIVE SUBSTANCES IN PLASMA AND MILK OF LACTATING RATS AFTER ORAL ADMINISTRATION OF 3 MG/KG [^{14}C]CGP48933 ON DAY 13 OF PARTURITION. PROTOCOL #957018

TIME (H)	RA1	RA2	RA3	RA4	RA5	RA6	MEAN ± SE
Plasma [ng eq./ml]							
0.25	2831	274	352	-	-	-	1152 ± 1028
1	-	-	-	370	570	180	373 ± 138
4	62	148	143	-	-	-	117 ±34
8	-	-	-	98	130	88	105 ± 16
24	7	9	5	-	-	-	7 ± 1
48	-	-	-	NS	3	NS	1 ± 1
Milk [ng eq./ml]							
0.25	4	NS	14	-	-	-	6 ± 5
1	-	-	-	7	M	NS	4 ± -
4	7	27	106	-	-	-	47 ±37
8	-	-	-	45	17	25	29 ± 10
24	2	7	15	-	-	-	8 ± 5
48	-	-	-	7	2	NS	3 ± 3

S.E.: Standard error; NS: Not significant, assigned a value of 0 for calculation of mean and S.E.; M: no sample obtained.

4. OVERALL SUMMARY AND EVALUATION

Pharmacodynamics

CGP 48933 is a non-peptidic, competitive, potent, orally-effective, specific antagonist of angiotensin active at the AT_1 angiotensin II receptor. It was developed by Ciba-Geigy Corporation for the treatment of hypertension and congestive heart failure.

CGP 48933 exhibited a high affinity for the AT_1 receptor in binding to human adrenal cortex, rat aortic smooth muscle cells and rat adrenal glomerulosa. CGP 48933 bound with a slightly lower affinity to dog aorta (IC_{50} 56 nM) and dog adrenal glomerulosa (IC_{50} 126 nM). This suggests the presence of different AT_1 subtypes in dog, rat and human. The binding affinity of CGP 48933 for AT_2 receptors (human uterus) was more than 10,000 times lower than for AT_1 receptors. CGP 48933 had no or negligible binding affinity at various neurotransmitter receptor sites or calcium channel binding sites. In isolated vascular smooth muscle studies, CGP 48933 was a selective and competitive antagonist of angiotensin II. The impairment of endothelial regulation of peripheral vascular resistance in SHR vascular beds was eliminated after treatment with CGP 48933. Thus, therapy with CGP 48933 appears to improve vascular endothelial responsiveness to ease local blood flow to vital organs.

In conscious, normotensive rats, oral administration of CGP 48933 at a dose of 10, but not 3, mg/kg reduced basal blood pressure by 29%. However, both 3 and 10 mg/kg CGP 48933 reduced pressor responses induced by angiotensin II (0.4 µg/kg, i.v.), by 53% and 87%, respectively. The pressor response to norepinephrine was not reduced by either of the doses. In the renal hypertensive rat, the decrease in b.p. after either oral or i.v. administration of CGP 48933 was dose dependent. With i.v. administration (0.01 to 10 mg/kg, single bolus), the peak hypotensive effect was observed at 10 min, followed by a brief recovery toward initial values. This was slowly followed by a secondary prolonged fall in b.p., taking an hour to develop into a maximum effect; blood pressure reduction persisted for up to 24 hour. The mechanism of this biphasic effect is not clear from the study. With oral administration (1 to 10 mg/kg, single dose), peak hypotensive effect developed after 4 hr and blood pressure reduction persisted for more than 24 hr. Administration of either CGP 48933 (2 mg/kg, p.o.) or the diuretic hydrochlorothiazide (10 mg/kg, p.o.) alone to SHR resulted in a similar, moderate decrease in b.p. The combination of the two drugs was clearly more effective. The effect on b.p. was additive.

Angiotensin II plays a key role in controlling sodium balance by regulating the synthesis and excretion of aldosterone. In conscious female rats, 100 mg/kg CGP 48933 p.o. reduced urinary volume and decreased sodium and chloride excretion. Also, angiotensin II controls renin release through feedback mechanisms. Administration of CGP 48933 to sodium restricted rats significantly increased both angiotensin II and renin levels 4, 6 and 24 hr after treatment. The increase in renin levels, despite the high levels of angiotensin II, shows the effective blockade of the angiotensin II receptor that mediates the negative feedback. The decrease in b.p. induced by CGP 48933 and the concomitant increase in sympathetic nerve activity (manifested by increase in heart rate, which was blocked by pretreatment with propranolol) may represent additional

mechanisms involved in the stimulation of renin release. The low-sodium-induced 10-fold increases in aldosterone levels (in comparison to animals on a normal-sodium diet) were further elevated by CGP 48933. On the other hand, in normal or sodium-depleted rats, CGP 48933 blocked the rise in plasma aldosterone levels induced by a challenge dose of angiotensin II. This effect was also observed *in vitro* in bovine adrenal glomerulosa cells. This suggests that low-sodium-induced aldosterone release is not mediated via the angiotensin II adrenal receptor and that factors other than angiotensin II are important in controlling aldosterone secretion.

In sodium depleted dogs, i.v. administration of CGP 48933 (3 mg/kg) caused an immediate reduction in b.p. that lasted for an hour. Plasma angiotensin II levels showed an immediate and approximately 4-fold increase within 15 min after drug administration and slowly returned to control values 60 min after drug administration. In renal hypertensive dogs, CGP 48933, administered acutely at doses of 10 and 30 mg/kg p.o., reduced systolic blood pressure by 29 and 68 mmHg, respectively, 5 hr after dosing (peak effect). The relatively short duration of action of CGP 48933 in the dog may be a consequence of its low affinity for AT_1 receptors in this animal species compared to rat. Intravenous (0.1 to 1 mg/kg) and oral administration (0.1 to 3 mg/kg) caused a dose-related fall in b.p. in sodium-depleted marmosets. The effect persisted for up to 2 hr with i.v. and up to 5 hr with oral administration. These results suggest that CGP 48933 is shorter lived in both marmoset and dog than in rat.

Pharmacokinetics

Following oral administration of radiolabeled drug to mice, rats and marmosets, valsartan (CGP 48933) was rapidly absorbed with uptake of radioactivity most rapid and highest in liver. The estimated absolute bioavailability of test substance in mice was about 25% at 3 mg/kg, decreasing to 13% at 200 mg/kg and 9% at 600 mg/kg. The proportion of the dose absorbed also decreased with increasing dose. In rats, the bioavailability was 73% at 10 mg/kg. A radiotracer study in bile cannulated rats indicated 20 to 50% absorption at 3 mg/kg. The estimated bioavailability of CGP 48933 in the marmoset at a dose of 100 mg/kg was about 2% in males and 9% in females. A radiotracer study in marmosets showed 20 and 50% absorption of CGP 48933, based on plasma ^{14}C levels, after oral doses of 60 and 400 mg/kg, respectively. Based on renal excretion data, an absorption of 29% after 60 mg/kg and 39% after 400 mg/kg was estimated. In clinical studies, mean absolute bioavailability of the 80 mg capsule of valsartan (CGP 48933) was found to be 23%. Approximately linear increases in Cmax and AUC with increasing doses were observed over the dosing range of 40 to 200 mg. Test substance reached its maximum plasma concentration approximately 2 hours postdosing.

The elimination of the test compound was rapid and complete in mice and rats but sluggish and incomplete after 4 days in marmosets with both oral and i.v. dosing. Excretion in all three species, irrespective of the dose and route of administration, was primarily fecal (60-95% of the dose), more a reflection of biliary excretion of absorbed material than fecal excretion of unabsorbed compound. Renal excretion accounted for less than 2% of the dose in rats, 2 to 8% in mice and up to 16% of the dose in marmosets. CGP 48933 excretion in humans is also primarily fecal (approximately 70% of administered dose as unchanged drug), a reflection of extensive biliary

excretion. Only 10% of the dose is excreted in urine as unchanged drug. Thus, in man, approximately 20% of an administered dose of CGP 48933 is metabolized.

The *in vitro* oxidative metabolism of CGP 48933 by postmitochondrial liver fractions from mouse, rat, rabbit, dog, marmoset and man was very low with (minor) metabolite peaks (P2 and P3) seen only in the marmoset and man. Incubation of postmitochondrial liver fractions of rat with UDPGA enabled *in vitro* glucuronidation of CGP 48933. This resulted in detection of a major metabolite peak P4. Rat hepatocytes and rat liver slices metabolized CGP 48933 to yield one of the two major metabolites (peak P4). This metabolite (acyl glucuronide of CGP 48933) was also excreted with the bile (91-100% after i.v., 18-65% after oral dosing) but it was conspicuously absent from the feces (absence might be due to hydrolysis in the intestine and/or the feces). The extracts of the feces and the urine of marmosets contained (at low doses only) a second major metabolite (peak P3), which was also observed in the *in vitro* incubation with marmoset liver fraction. This metabolite is formed by oxidative biotransformation and was not cleavable by enzymatic or basic hydrolysis. It was also observed in the human pharmacokinetic study and was characterized as a valeryl-4 hydroxy analog (metabolite M1 or CGP 71580). This major human metabolite (constitutes 23.3% of the bioavailable dose) was not found in any other species and according to the sponsor, M1 does not contribute to the pharmacological activity of CGP 48933 and biotransformation of CGP 48933 to M1 can be considered as a minor elimination process. In the mouse, both the urine and fecal extracts contained predominantly unchanged CGP 48933, three major metabolites (peaks P1, P2 and P5), only two of which have been characterized, and several minor metabolites (Fig. 4.1).

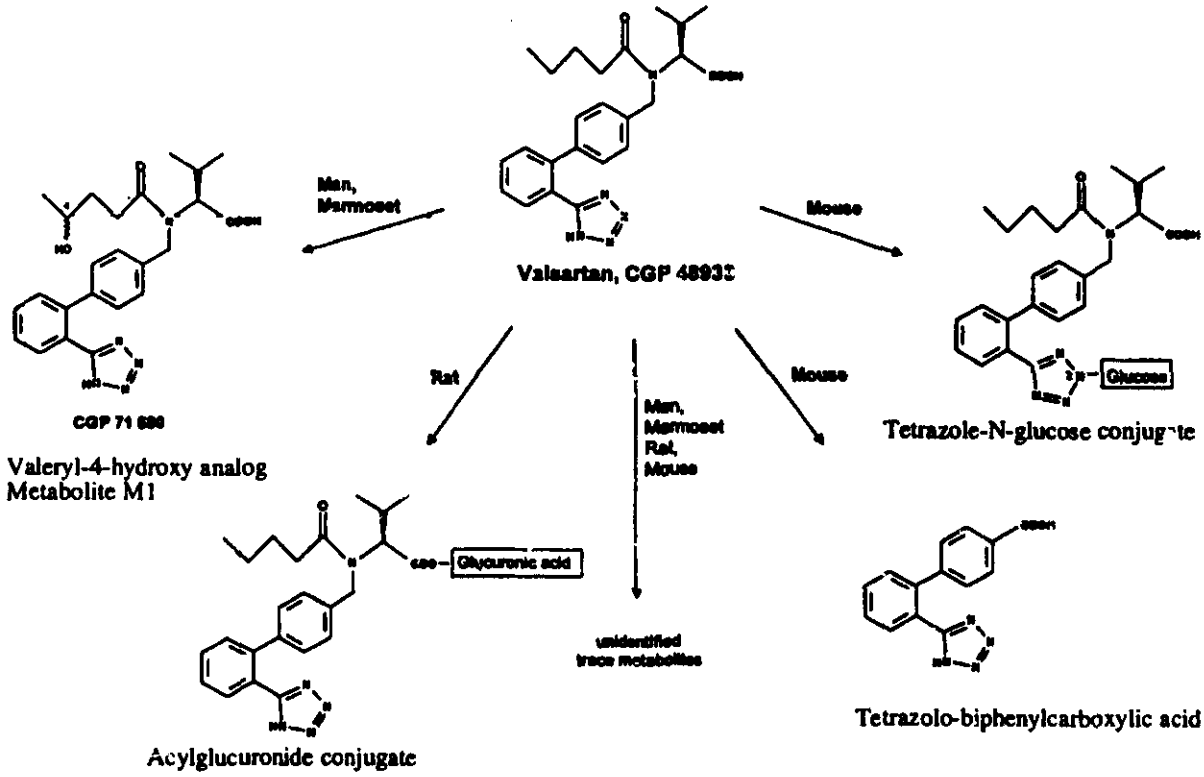


Fig. 4.1.: Scheme of biotransformation pathways of CGP 48933 (valsartan) in animals and man

CGP 48933 binds predominantly to serum albumin (88-98%). The binding of CGP 48933 to proteins of human serum and plasma, and to proteins of rat, dog and rabbit serum and marmoset plasma, was comparable. In the mouse, protein binding was about 10% less than that observed in the other (including human) species.

Acute Toxicity

The acute oral single-dose toxicity of CGP 48933 was determined in rats and marmosets at doses of 2000 mg/kg and 1000 mg/kg, respectively. There were no deaths and no gross lesions were seen during necropsy. Whereas no clinical signs of toxicity were observed in rats, emesis was observed in marmosets.

Subchronic and Chronic Toxicity

The long-term toxicity of CGP 48933 was studied in a series of daily oral dosing studies of up to 12 months in rats and marmosets, and daily intravenous dosing studies of 14 days in rats and marmosets.

No deaths were noted in rats treated with oral CGP 48933 doses of up to 600 mg/kg/day for 14-days or 3-months, or up to 200 mg/kg/day for 12 months. Treatment-related, dose-dependent decreases in body weight gain and food consumption were observed only in the 12-month study. A significant dose-dependent increase in water consumption followed by increased urine volume was seen in all studies and reflects the blockade of angiotensin-II-induced aldosterone formation and sodium reabsorption produced by CGP 48933. The threshold dose for these effects was >20 mg/kg/day in the 12-month study.

A dose-dependent increase in mean blood urea was observed in all three studies. In the 3-month study, red cell parameters dropped in both sexes at the 600 mg/kg/day dose level to produce mild anemia. This effect was observed as only a minor change in rats receiving 200 mg/kg/day in the 12-month study. Dose-dependent decreases in absolute and relative heart and liver weights relative to concurrent control were noted for males at all dose levels in both 3- and 12-month studies. These reductions possibly reflect the pharmacological activity of the compound since there were no drug-related histopathological findings for these organs. A minimal increase in incidence of renal tubular hyperplasia of proximal straight tubules in the outer medulla was observed in 6/10 males given 600 mg/kg/day and 2/10 males given 200 mg/kg/day for 3 months. Two male rats receiving 600 mg/kg/day also showed a minimal increase in tubular basophilia within the cortex and medulla, generally accompanied by basement membrane thickening. Renal tubular hyperplasia was, however, not seen in rats given 600 mg/kg/day for 12 months. Hypertrophy of renin-producing cells resulting in hypertrophy of the renal glomerular afferent arterioles occurred in most of the animals that had received 200 mg/kg/day for 6 or 12 months, and in animals that had received 200 or 600 mg/kg/day for 3 months. The juxtaglomerular apparatus exists in mammalian kidneys for the regulation of blood pressure. Antihypertensive agents of this class have been shown to induce morphological changes in the kidney, characterized by either hypertrophy or hyperplasia of the juxtaglomerular cells. Microscopic examination of

kidneys from recovery group animals showed that these effects of CGP 48933 are completely reversible.

The most prominent finding in the 3 month oral administration study in marmosets was moderate to severe toxic nephropathy. This resulted in moribund sacrifices of four animals receiving 600 mg/kg/day and one receiving 200 mg/kg/day. An additional high dose animal with nephropathy was sacrificed late in the recovery period. Deaths were not observed in either the 1 year study in which the high dose was 120 mg/kg/day or the 14-day study in which the high dose was 600 mg/kg/day, suggesting a dose and time-dependent drug-related finding. Nephropathy was present in all high dose animals at terminal sacrifice in the 3-month study but in none of the animals in the 12 month study. However, renal arteriolar hypertrophy occurred in all high dose animals in both 3- and 12-month studies. As noted in our discussion of the rat studies, these effects are known to reflect the pharmacological activity of the compound. Also, seen at the high dose in the 3-month marmoset study were stomach ulcer, adrenal cortical hypertrophy, and moderate to marked hepatic lipid vacuolation. Decreases in body weight gain and food consumption were evident in marmosets receiving 200 or more mg/kg/day in 3-month study only. Vomiting was frequently observed in most high dose animals in all three studies and the severity was related to the dose and duration of the study. Slight to very marked increases in blood urea (up to 1103%), creatinine (up to 98%) and alkaline phosphatase (up to 82%) were observed in all animals that had received 120 or more mg/kg/day, though they were most severe in the 3-month study. In that study, all marmosets in the high dose group and to a lesser extent in the mid dosage group exhibited a moderate anemia that correlated with the severity of increased levels of renal extra-medullary hemopoiesis. No abnormalities were detected at urinalysis in any of the studies.

The sponsor has conducted 14-day intravenous toxicity studies with CGP 48933 in rats and marmosets. In both studies, no treatment-related effects were observed at the highest tested doses (100 mg/kg/day in rats, 60 mg/kg/day in marmosets.)

Genotoxicity

The genotoxic potential of CGP 48933 was investigated *in vitro* in microbial mutagenesis assays (*Salmonella typhimurium* and *Escherichia coli* tester strains), in the Chinese hamster lung (V79 cell) mutagenesis assay, in a structural chromosomal aberration assay in Chinese hamster ovary and in one *in vivo* assay for clastogenic effects in rat bone marrow (micronucleus test). CGP 48933 was non genotoxic in all tests. Table 4.1 lists the maximum concentrations/doses of CGP 48933 used in each of these assays.

TABLE 4.1.

GENOTOXICITY ASSAY	MAXIMUM CONCENTRATION OR DOSE WITH & WITHOUT S9
Ames test (*S. typhymurium, E. coli*)	5000 µg/plate (+/- S9)
Chinese hamster V79 cell mutation assay	5550 µg/ml (- S9), 1388 µg/ml (+ S9)
Chinese hamster ovary cell chromosomal aberration assay	655 µg/ml (- S9), 1310 µg/ml (+ S9)
Rat bone marrow (*in vivo*) micronucleus assay	3125 mg/kg

Reprotoxicity

In male rats, administration of CGP 48933 (up to 200 mg/kg/day) for 90 days prior to mating and during mating had no effects on mating or fertility indices, reproductive performance of pregnant F_0 females, or prenatal development of the F_1 generation. In the same study, administration of CGP 48933 resulted in an overall (treatment days 0-126) dose-dependent reduction in body weight gain for males at 50 and 200 mg/kg/day, but these reductions (7 and 18% of control gain, respectively) were not statistically significant. On the other hand, body weight gain from day 49 to day 63 was significantly lower ($P < 0.05$) and body weight loss from day 91 to day 98 significantly higher ($P < 0.05$) than control for the high dose male group.

Table 4.2. summarizes CGP 48933 dosage thresholds for adverse effects in reproductive toxicity studies in rats, rabbits and mice (excluding effects in male rats). Administration of CGP 48933 to rats from premating through lactation, at doses up to 200 mg/kg/day, or only during organogenesis or during late gestation and lactation, at doses up to 600 mg/kg/day, did not result in deaths, abortions or gross lesions in parental animals. A decrease in body weight gain relative to concurrent control was observed during the treatment period in all three rat studies at doses of 200 or more mg/kg/day. Food intakes were also reduced in segment I and III studies. There was no effect of test substance on F_0 fertility parameters as assessed by numbers of corpora lutea, implants, live fetuses/litter, and pre- and postimplantation losses. The F_1 generation was, however, significantly affected in rat studies in which parental animals were treated with 600 mg CGP 48933/kg/day during organogenesis or late gestation and lactation. This treatment was associated with a decrease in fetal weight and pup birth weight. Although incidence of dilated brain ventricles was increased at 600 mg/kg/day (10.7% *versus* 5.7% in control), incidence was neither statistically different from concurrent control, nor outside the historical control range (1.5 to 17.4%). Dilation of brain ventricles (categorized as a variation) was also observed in fetuses when parental rabbits were treated with CGP 48933 at doses as low as 10 mg/kg/day. Dilation of brain ventricles, the sponsor claims, is a common finding in segment II studies, associated with low fetal weights, and generally disappears within a few days after birth. Thus, the finding is not drug-related. Significant increases in pup mortality on postnatal days 0-4 (both sexes) and 4-21 (male pups only) and decreases in pup body weight gain throughout the lactation period were seen at 600 (but not 200) mg CGP 48933/kg/day. Another possible effect on postnatal development of

TABLE 4.2

DOSAGE THRESHOLDS* FOR ADVERSE EFFECTS OF CGP 48933 IN RAT, RABBIT AND MOUSE REPRODUCTION STUDIES

Test #/Review section #	924222/3.4.1	916067/3.4.2	936207/3.4.3	916070/3.4.4	934168/3.4.5	936133/3.4.7
Species (strain)	Rat (SD)	Rat (SD)	Rat (SD)	Rabbit (DB)	Rabbit (NZ)	Mouse (CD-1)
Dose (mg/kg/day by gavage)	10, 50, 200	60, 200, 600	60, 200, 600	2, 5, 10	2, 5, 10	60, 200, 600
Days of drug administration	See below[a]	GD 6-15	GD 15-LD 20	GD 6-18	GD 7-19	GD 6-15
Day of necropsy	GD 20, LD 21	GD 20	GD 20[e], LD 21	GD 28	GD 29	GD 18
Maternal Toxicity						
1. Mortality	>200	>600	>600	>10	2-5[m]	>600
2. ↓ weight gain	50-200[b]	60-200[d]	200-600[f]	>10	>10	>600
3. ↓ food intake	50-200[c]	> 600	200-600[g]	>10	<2[n]	>600
4. ↓ corpora lutea + ↓ implants	>200	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Embryo/Fetal Toxicity						
1. ↓ survival	>200	>600	Not examined	5-10[j]	>10[p]	>600
2. ↓ fetal/pup birth body weight	>200	200-600	200-600	>5[k]	>10	>600
3. Dilated brain ventricles	Not examined	200-600[q]	Not examined	2-5[q,k]	>10	>600
4. Thickened ribs	>200	>600	Not examined	2-5[k]	>10	>600
Neonatal Toxicity						
1. ↓ survival	>200	Not applicable	200-600[h]	Not applicable	Not applicable	Not applicable
2. ↓ body weight gain	>200		200-600[i]			
3. Postnatal development						
delayed ear canal opening	10-50 (♀)		200-600 (♂)			
delayed pinna detachment	>200		200-600			

SD: Sprague-Dawley; DB. Dutch Belted; NZ: New Zealand white. *When two doses are given, the first is the highest dose at which an effect was not seen and the second is the lowest dose at which an effect was seen.

a: 14 days prior to mating with treated males, during mating and until day 19 of gestation (c-sectioned animals) or through day 20 of lactation (natural delivery animals); b: premating days 0-14, GD 0-20; c: premating days 0-14 and GD 0-6; d: GD 15-20; e: necropsy was limited to assessment of fetal kidney; f: GD 15-20; g: GD 15-20 and LD 0-7; h: significant reductions on postnatal days 0-4 for both sexes and on days 4-21 for male pups; i: throughout the lactation period; j: non-dose dependent but significant increase in the incidence of resorptions in both high and mid dose groups; k: only 4 dams with live young (13 fetuses) survived to term in the 10 mg/kg/day group; l: observed in 2 fetuses/2 does, 4 fetuses/3 does, 5 fetuses/4 does and 1 fetus at 0, 2, 5 and 10 mg/kg/day, respectively; m: two deaths, one each at mid and high doses; n: dose-dependent decrease on GD 7 to 8; p: mean resorption and postimplantation loss higher than control in the high dose group but difference from control not statistically significant; q: high dose incidence not significantly different from concurrent control incidence and within historical control range.

the F_1 generation was an apparent delay in pinna detachment at 600 (but not 200) mg/kg/day. Although ear canal opening was also delayed at this dose level, the delay was limited to male pups in the segment III (600 mg/kg/day) and female pups in the segment I (50 or more mg/kg/day) studies (see Table 4.2). As with ACE inhibitors, the rabbit showed unusual sensitivity to CGP 48933 with respect to dose and maternal toxicity and reproductive parameters. Increases in the incidence of resorption and postimplantation loss at doses of 5 or more mg/kg/day were noted in both rabbit studies, although in one of these studies the increases were not statistically significant due to large standard deviations for both treated and control groups. Rabbit fetal weights were not influenced by test substance. No adverse effect of CGP 48933 was documented in the mouse developmental toxicity study, but lack of effect may simply reflect the drug's relatively poor bioavailability in the mouse compared to rats and rabbits (see below).

Pregnancy did not alter the pharmacokinetic profile of CGP 48933 in rats. Tissue distribution studies of [^{14}C]CGP 48933 in the pregnant rat, rabbit and mouse showed that radioactivity was confined primarily to maternal blood and excretory organs (kidney, liver and small intestine). Distinct ^{14}C concentrations were found in the mammary glands, placenta, brain and fetuses of all species. Thus, the test substance can cross the blood-brain barrier and is also transferable to the embryo-fetal compartment. Concentrations of CGP 48933 in placenta and mammary glands were similar and ranged from 19 to 30% of that found in maternal blood, the lowest concentration being in the mouse. The ^{14}C concentrations in fetuses were 1.9, 3.2 and 3.7% of the maternal blood 1 hr post dose in the mouse, the rabbit and the rat, respectively. Transfer of CGP 48933 and/metabolites into the milk in the rat was slow; maximum mean ^{14}C concentrations were observed in plasma 15 min, and in milk 4 hr after administration of radioactive test substance. The levels were near the limit of detection 48 hr post dose. Ninetyeight percent of administered radioactivity was excreted in the feces and urine within 48 hr post dose in pregnant rats. The absorption of test substance in pregnant rabbits is more prolonged than in pregnant rats. The systemic availability of ^{14}C tagged compound was 15-fold lower for pregnant mice than for pregnant rats.

NOTE: This review does not address the (rat and mouse) carcinogenicity studies conducted with valsartan. The results and adequacy of those studies are addressed in a separate review by Dr. Anthony G. Proakis.

5. LABELING

Those sections in the proposed labeling that refer to preclinical studies that were covered by this review were reviewed and considered acceptable with the following exception:

Under WARNINGS: *Fetal/Neonatal Morbidity and Mortality*

The sponsor's proposed text summarizing the results of studies in rats, rabbits and mice (line nos. 302 to 329) reads as follows:

> "No teratogenic effects were observed when TRADENAME was administered to pregnant mice[37] and rats[38] at oral doses up to 600 mg/kg/day and to pregnant rabbits[39] at oral doses up to 10 mg/kg/day. These doses in mice, rats, and rabbits, respectively, represent 220, 220, and 4 times the maximum recommended human dose based on mg/kg, and 18, 36, and 1 times based on mg/m^2. These calculations assumed an oral dose of 160 mg/day for a 60-kg woman. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) was observed at doses of 5 and 10 mg/kg/day, which was associated with maternal toxicity as the rabbit is highly susceptible to the hypotensive effects of this and related compounds.
>
> It is not known whether TRADENAME is excreted in human milk. In the drug metabolism studies, oral administration of radiolabeled valsartan to lactating rats resulted in excretion of valsartan and/or metabolites with the milk[40]. Offspring from rats treated with TRADENAME at oral doses of 600 mg/kg/day during the last trimester of pregnancy as well as lactation showed a slightly reduced survival rate and a slight delay in developmental milestones[41]. These effects on the offspring were associated with decreased maternal weight gain and decreased food consumption. There was no drug-related effect on the offspring at doses up to 200 mg/kg/day, which is 75 times (based on mg/kg) or 12 times (based on mg/m^2) the maximum recommended human dose. These calculations assumed an oral dose of 160 mg/day for a 60-kg woman."

The above text does not include the effects of valsartan on rat fetal weight or pup birth weight. These effects were observed when parental rats were treated with valsartan at oral doses of 600 (but not 200) mg/kg/day during organogenesis or late gestation and lactation. The above text does include a statement regarding excretion of valsartan in rat and human milk. That statement is already included under PRECAUTIONS, Nursing Mothers, and should be deleted from WARNINGS. The following statement incorporates our recommended changes:

> "No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in

fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, materr ally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200, and 2 mg/kg/day in mice, rats, and rabbits represent 220, 73, and 0.8 times, respectively, the maximum recommended human dose (MRHD) on a mg/kg basis or about 18, 12, and 0.2 times the MRHD on a mg/m^2 basis. (Calculations assume an oral dose of 160 mg/day and a 60-kg patient.)"

6. RECOMMENDATION

This new drug application for valsartan is approvable with recommended changes in labeling (see page 131).

9/30/'96
G. Jagadeesh, Ph.D.

cc:
Original NDA 20,665
HFD-110
HFD-110/CSO
HFD-110/G. Jagadeesh
HFD-110/T. Proakis
HFD-024/J. DeGeorge
HFD-345/
Accepted by: ---------- on 9-30-96
gj/9/30/96 /NDA20665.org; .pkz (compressed file)

K. Bongiovanni
AUG 28 1996

NDA # 20,665

REVIEW AND EVALUATION OF RODENT CARCINOGENICITY STUDIES

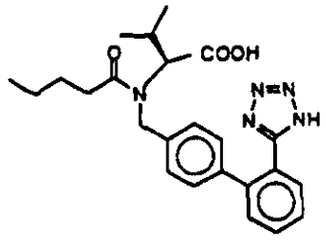
Anthony G. Proakis, Ph.D.
8/28/96

ORIGINAL SUBMISSION DATE: 12/28/95
CENTER RECEIPT DATE: 12/28/95
REVIEWER RECEIPT DATE: 2/09/96

PRODUCT: Valsartan (CGP 48933) Capsules

SPONSOR: Ciba Pharmaceuticals Division
CIBA-GEIGY Corporation
Summit, NJ

CHEMISTRY: Valsartan is described as (S)-N-valeryl-N-{[2'-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl}-valine. Its molecular weight is 435.5 and its empirical formula is $C_{24}H_{29}N_5O_3$.



PHARMACOLOGICAL CLASS: Antihypertensive (Angiotensin II Antagonist)

PROPOSED INDICATION: Hypertension.

FORMULATION AND DOSAGE: Valsartan has been formulated into capsules containing 80 or 160 mg valsartan; crospovidone, NF; magnesium stearate, NF; povidone, USP; sodium lauryl sulfate, NF, and purified water, USP serve as excipient. The recommended starting dose is 80 mg once daily; the dosage may be increased to 160 mg once daily if additional antihypertensive effect is required.

STUDIES REVIEWED: Sponsor submitted reports of 3-month dose rangefinding (dietary) toxicity studies in rats and mice and 24-month carcinogenicity (dietary) studies in rats and mice. These reports are contained in Vols. 14-16, 22-24 and 39 of the application.

3-Month Dose Rangefinding Study in Rats

Study Facility: Ciba-Geigy Ltd., Stein, Switzerland
Study No.: 916188
Study Dates: Initiation of Treatment= 1/29/92
Terminal Sacrifice= 4/30/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Tif:RAIF (Sprague-Dawley derived) rats (M=162-186g; F=142-161g)

Drug Administration: Valsartan (CGP 48933, Batch # 800291) was administered orally in the diet (admixed with pelleted food). The drug-containing pellets were prepared for week 1 and biweekly thereafter. Control animals were fed pelleted food without the test article.

Dose Levels: 0, 60, 200 and 600 mg/kg/day (5/sex/group for main test; 15/sex/group for blood drug level determinations).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were measured prior to treatment and at weekly intervals. Food consumption was measured weekly. Clinical chemistry and hematology analyses were carried out on blood samples obtained by orbital sinus puncture from surviving animals in the main study at the end of the treatment period. At termination of treatment, surviving control and treated animals were killed and examined macroscopically. Sections from major organs and tissues were fixed on slides and subjected to microscopic examination. Blood samples (~0.7 ml) were collected from the orbital sinus of animals from the satellite groups during treatment days 7-8 and 90-91 for measurement of plasma valsartan levels.

Results: Average achieved doses ranged from 91%-97% of intended daily doses.

Achieved Doses

	Sex	Intended Daily Dose (mg/kg)		
		60	200	600
Achieved Daily Dose (mg/kg)	M F	58 58	187 182	583 580

Mortality: No rats died during the study.

Clinical Signs: Tremor of the head was observed in 2/5 high dose females beginning week 6 of treatment. No other clinical signs of toxicity were noted following treatment.

Other Treatment-Related Effects: Body weights of females from all treated groups and high dose males were lower than control during Weeks 5-13. Food consumption among treated females was slightly lower than control from Weeks 11-13 of treatment. Food consumption for all treated females over the entire dosing period was 7% to 9% lower than control. Food consumption in males was not appreciably affected by valsartan treatment. Hematologic parameters (RBC count, Hct, Hb) among valsartan-treated animals (all dose levels) were lower than control. Plasma urea and creatinine were increased above control values in mid and high dose males; treated females were generally unaffected. The relativ liver weights in high dose males and females were lower than control; relative adrenal weight was significantly higher than control in high dose males only.

Valsartan Associated Findings in Rats

Measurement		Sex	Control Value	% Difference From Control		
				60 mg/kg/day	200 mg/kg/day	600 mg/kg/day
Body Weight (gm)	Wk -1	M	174	-1.1	-1.1	-2.2
		F	153	0.0	0.0	-0.6
	Wk 5	M	376	+0.8	-0.4	-1.9
		F	251	-8.3	-8.1	-10.5
	Wk 10	M	453	+1.9	+2.2	+0.8
		F	285	-6.4	-7.7	-9.7
	Wk 13	M	476	-7.2	-7.3	-9.0
		F	298	-8.0	-8.1	-9.1
Food Consumption[a] (gm/rat/week)		M	148	+1.5	+6.7	-4.4
		F	127	-17.8	-19.2	-19.6
Hematology[b]						
RBC Count		M	8.6	-9.6	-10.8*	-16.3*
(X 10^6 /ul)		F	7.8	-6.9*	-5.5	-9.0*
Hematocrit		M	44.4	-5.0	-8.3*	-12.6*
(%)		F	42.5	-5.6*	-5.9	-7.8*
Hemoglobin		M	9.3	-6.4	-9.9*	-13.7*
(mmol/l)		F	9.0	-5.8	-6.9*	-9.2*
Serum Chemistry[a]						
Blood Urea		M	5.71	-6.8	+167*	+277*
(mmol/l)		F	5.47	-3.7	+17	+7.1
Creatinine		M	49.2	-3.3	+23	+41*
(umol/l)		F	47.3	-8.4	-0.5	+3.3
Organ Weight						
Absolute Liver Wt.		M	17.0	-3.7	-5.2	-26.7*
(gm)		F	10.6	-16.0	-20.7	-21.0*
Absolute Adrenal Wt.		M	65.5	-9.0	+7.9	+11.5
(mg)		F	3.5	-8.1	+17.2	-17.4
Relative Liver Wt.		M	37.3	-2.9	-6.6	-17.5*
(mg/kg)		F	36.9	-6.6	-10.8	-13.8
Relative Adrenal Wt.		M	0.14	-6.9	+6.9	+26.9*
(mg/kg)		F	0.33	+1.5	-7.6	-10.7

[a] Values represent average % differences from control for Weeks 11-13. [b] Values derived from measurements made during Week 14. * Significant difference from control ($p<0.05$).

Gross and Microscopic Pathology: No treatment-related findings were noted following macroscopic examination. Microscopic examination showed increased incidences of renal pathology compared to control.

Renal Finding	Sex	# Rats Showing Finding / # Rats Examined			
		0 (Control)	60	200	600
Lymphocyte Infiltration of Renal Cortex	M F	0/5 0/5	0/5 0/5	1/5 0/5	2/5 1/5
Polymorphonuclear Infiltration of Renal Papilla	M	0/5	0/5	0/5	1/5
Renal Tubular Atrophy	M F	0/5 3/5	1/5 1/5	1/5 2/5	3/5 5/5
Basophilic Renal Tubule	M	0/5	0/5	0/5	1/5

Valsartan Blood Levels: Plasma concentrations of valsartan were determined for the low and high dose groups (60 and 600 mg/kg/day) during weeks 2 and 13 of treatment. Within the 22-hr sampling time, a total of 3 samples (8 hrs apart) were obtained from each rat, requiring a total of 12/sex/group; the remaining rats/group were used as spares. Plasma levels and AUC values increased with increasing dose, were comparable in males and female rats and did not show evidence of accumulation after repeated dosing.

Valsartan Plasma Levels (umol/L)

Sampling Time (hr)[a]	600 mg/kg/day[b]				600 mg/kg/day[b]			
	Week 2		Week 13		Week 2		Week 13	
	Male	Female	Male	Female	Male	Female	Male	Female
0	3.16	2.54	1.70	1.25	24.41	10.10	22.06	17.76
2	2.25	1.88	2.74	3.19	13.04	28.71	12.07	28.91
4	2.17	1.56	2.21	2.40	15.88	29.51	10.53	27.43
6	1.30	2.33	1.18	1.20	20.29	21.30	19.61	20.22
8	3.37	2.97	2.33	1.77	29.36	9.04	18.82	8.63
10	2.19	1.66	4.45	3.24	10.93	24.33	14.35	27.00
12	0.96	1.03	3.36	3.69	8.55	21.45	9.85	31.69
14	1.42	2.06	1.39	1.26	17.02	18.27	17.41	20.41
16	3.40	3.10	2.24	2.24	32.27	13.61	26.14	21.52
18	2.30	3.21	4.38	3.97	13.09	20.53	12.38	28.87
20	1.70	1.52	2.83	3.07	12.52	20.25	6.26	20.35
22	2.23	2.56	1.03	1.33	21.46	13.09	13.09	18.82

[a] First sample taken ~ 1 hour after start of 12-hour light period.
[b] Each value represents the mean from 3 rats.

Valsartan AUC Values

Sex	Time	Dose mg/kg/day	AUC[0-24 hr] umol*hr/L
Males	Week 2 Week 13	60 60	47.5 57.0
Males	Week 2 Week 13	600 600	391.8 329.0
Females	Week 2 Week 13	60 60	47.7 54.6
Females	Week 2 Week 13	600 600	440.3 506.6

24-Month Carcinogenicity Study in Rats

Study Facility: Ciba-Geigy Ltd., Stein, Switzerland
Study No.: 926007
Study Dates: Initiation of treatment: 8/24/92
Termination of treatment and necropsy: 8/29/94 to 9/13/94

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Tif: RAIf (Sprague-Dawley derived) rats (4-5 weeks old; M= 83-123 gm; F=82-118 gm one week prior to initiation of treatment)

Drug Administration: Valsartan (Batch # 800292 & 800592) was administered in the diet admixed with pelleted food provided *ad libitum;* control animals received pelleted food without the test article. Diets were prepared at about monthly intervals. Diets were analyzed for test article stability and homogeneity periodically (11 times) during the study.

Dose Levels: 0, 10, 50 and 200 mg/kg/day; allocation of animals/dose group is as follow:

Animal Allocation

#/Sex/Group	Evaluation Parameters					
	Survival	Macroscopic Exam	Histopathology (Carcinogenicity)	Hematology	Blood Chemistry	Blood Drug Levels
50	X	X	X			
10		X	X	X	X	
10		X				X

Observations/Measurements: Animals were observed once to twice daily for mortality and clinical signs of toxicity. Body weights were measured prior to treatment, at weekly intervals for the first 3 months and monthly thereafter. Food consumption was measured weekly for the first 3 months and monthly thereafter. Water consumption was measured monthly. Ophthalmologic exams were conducted in male and female rats from the high dose group and control group prior to initiation of treatment and at 6, 12, 18 and 24 months of treatment. Hematology and blood chemistry determinations and urinalysis were conducted on 10 rats/sex/dose group during weeks 13, 27, 53, 78 and 105. At the end of the treatment period, the surviving control and treated animals (from the 50/sex/group original main group plus 10/sex/group from the hematology/lab chemistry subgroup) were bled under ether anesthesia and subjected to macroscopic examination and major organs weighed. Sections of major tissues and organs were fixed on slides and examined microscopically for histopathology. Complete necropsy and histopathology were performed on all animals which died or were sacrificed in moribund condition prior to

study termination unless prevented by advanced autolysis or cannibalism. The statistical method of Peto et.al. (IARC Monograph, Supplement 2, 1980) was used in the analysis of the histopathology data for significance of carcinogenicity findings. Plasma drug levels were determined from blood samples obtained by orbital puncture from 5 rats/sex/dose group in the satellite groups at 7AM, 5PM and at 7PM during weeks 2, 27, 53, 79 and 105 of treatment; the remaining 5/sex/group were retained as spares.

Results: Average achieved doses ranged from 96%-97% of the intended daily doses.

Achieved Doses

	Sex	Intended Daily Dose (mg/kg)		
		10	50	200
Achieved Daily Dose* (mg/kg)	M	9.7	48.2	191.4
	F	9.6	47.9	191.8

* Value corrected for amount of test article recovered by analysis of diet

Animal Survival: Treatment had no effect on the survival of male and female rats to terminal necropsy.

Animal Survival

Dose Group (mg/kg/day)		# Surviving to Terminal Necropsy	
		Males (n=50)	Females (n=50)
Control	(0)	26	32
Valsartan	(10)	28	35
	(50)	24	36
	(200)	28	36

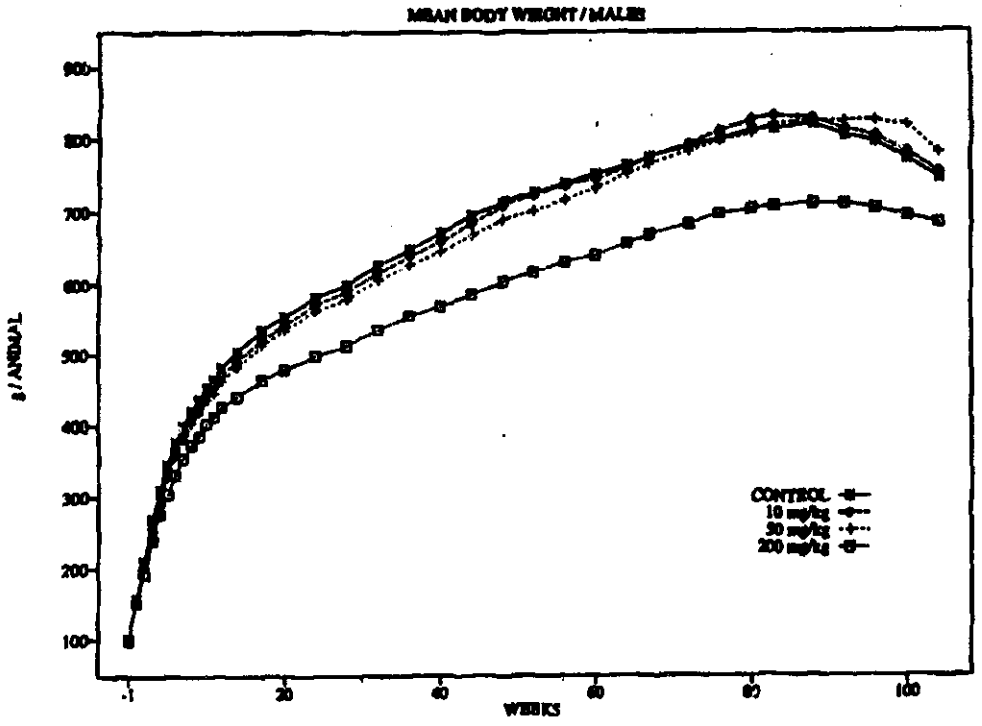
Body Weight: High dose males showed a lower rate of body weight gain resulting in mean body weights approximately 12-14.6% lower than control for most of the study; at study initiation (Wk -1), mean body weight of high dose males was 2.4% lower than control and at study termination mean body weight of surviving high dose males was 8.1% lower than control. Mean values for treated females were comparable to control throughout the treatment period.

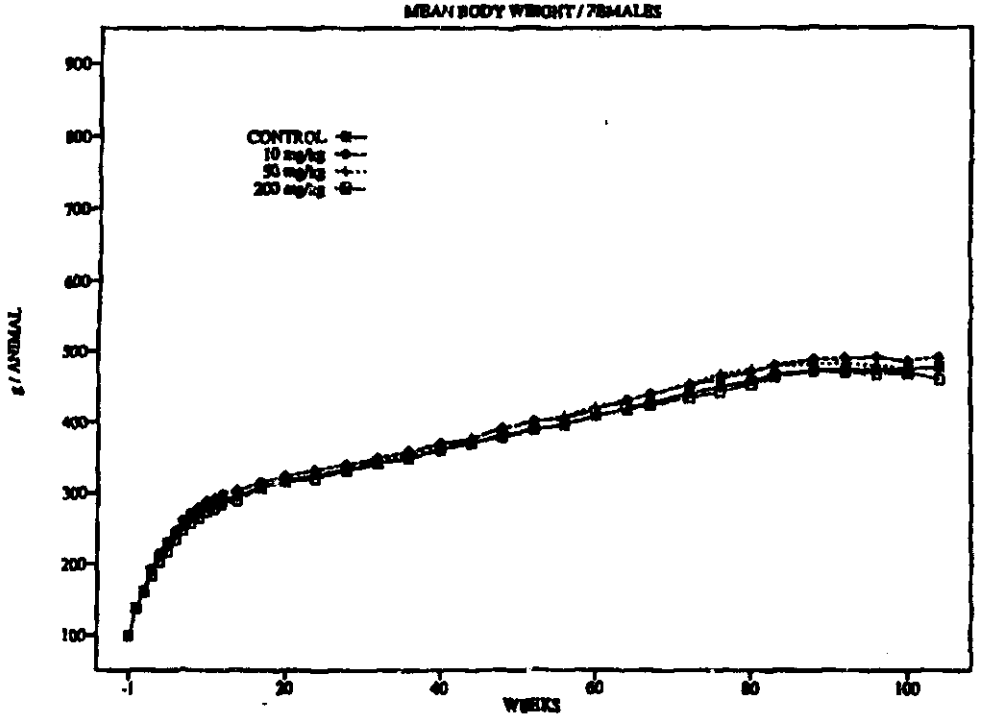
Mean Body Weight, gm (% Difference from Control)

Dose Group (mg/kg/day)	Males Week 1	Males Week 28	Males Week 56	Males Week 80	Males Week 104
Control (0)	158	600	739	813	746
Valsartan (10)	155	590	737	825	755
(50)	157	580	717	807	781
(200)	152* (-3.8%)	513* (-14.5%)	631* (-14.6%)	703* (-13.5%)	685 (-8.1%)
	Females Week 1	Females Week 28	Females Week 56	Females Week 80	Females Week 104
Control (0)	136	332	396	457	477
Valsartan (10)	137	340	405	470	491
(50)	137	332	409	473	474
(200)	137	331	398	452	459

* Significantly lower than control ($P<0.01$)

Body Weight Curves for Males and Females





Food Consumption: Overall (Weeks 1 to 104) food intake by high dose males was approximately 8% lower than that of the control group. Food intake among all other treated groups (low and mid dose males and all females) was not appreciably different from respective controls.

Water Consumption: From the start of treatment and throughout the study, high dose males consumed markedly larger (11%-63%) quantities of water than did the control group. Smaller differences from control that were seen with other treated groups were attributed to normal variation.

Ophthalmological Examination: The incidences of changes to the eyes were similar for treated and control rats.

Hematology: RBC counts, hemoglobin and hematocrit for high dose males and females were consistently lower than control throughout the study. Slightly lower than control reductions in these parameters were noted in valsartan treated mid dose males and females.

Hematologic Findings in Rats

Measurement	Sex	Control Value	% Difference from Control		
			10 mg/kg	50 mg/kg	200 mg/kg
RBC Count, x 10^6/µl					
Week 13	M	8.6	+1.0	-6.1*	-10.0*
Week 53		8.0	+0.9	-8.3*	-13.3*
Week 105		7.5	0.0	-0.2	-7.4
Week 13	F	8.1	-2.3	-5.8	-9.1*
Week 53		7.7	-1.7	-5.5	-8.3
Week 105		7.5	-10.9	-9.0	-8.1*
Hemoglobin, mmol/l					
Week 13	M	9.6	-0.6	-3.1	-6.9*
Week 53		8.9	-0.2	-7.1*	-13.2*
Week 105		8.5	+1.0	+1.2	-8.9
Week 13	F	9.2	-1.2	-3.5	-6.6*
Week 53		8.8	-1.0	-3.5	-6.2
Week 105		9.1	-10.5	-7.5	-9.8*
Hematocrit, %					
Week 13	M	47	-0.4	-3.4	-8.6*
Week 53		44	-0.9	-6.1*	-12.7*
Week 105		40	+1.0	+1.2	-13.1
Week 13	F	45	-3.5	-4.9*	-8.6*
Week 53		44	-2.1	-2.8	-6.2
Week 105		41	-9.1	-6.6	-6.9*

* Significantly different from control ($p<0.01$)

Blood Chemistry: Elevations from control blood urea and creatinine levels among high dose males were the most prominent valsartan-related blood analyses findings; no treatment related effects in females were observed.

Blood Chemistry Findings in Male Rats

Measurement	Control Value	% Difference from Control		
		10 mg/kg/day	50 mg/kg/day	200 mg/kg/day
Blood Urea, mmol/l				
Week 13	7.2	-7.9	-2.4	+68.5*
Week 27	6.0	-3.5	+12.5	+79.6*
Week 53	4.9	+6.7	+29.4	+113.0*
Week 105	5.6	+5.1	-22.3	+48.5
Creatinine, µmol/l				
Week 13	58.5	-3.0	+8.9	+35.3*
Week 27	69.2	-3.7	+11.6	+30.2*
Week 53	62.9	-7.7	+2.2	+4.4
Week 105	63.9	-10.4	-20.7	+14.0

* Significantly different from control (P<0.01)

Urinalysis: Significantly higher than control volumes of more dilute urine were excreted by high dose males during the first 78 weeks of the study. The urine outputs by mid and low dose males and all treated females were comparable to that of control levels.

Urine Output in Male Rats

Measurement	Control Value	% Difference from Control		
		10 mg/kg/day	50 mg/kg/day	200 mg/kg/day
Urine Volume, ml/kg				
Week 13	5.98	-9.0	+39.3	+73.7*
Week 27	4.32	-6.2	+39.9	+174.8*
Week 53	5.34	+15.7	+34.4	+110.3*
Week 78	7.71	-4.7	+11.7	+46.2*
Week 105	10.55	-31.2	-17.2	-0.1

* Significantly different from control (P<0.01)

Organ Weights: Lower than control absolute and relative liver weights were noted in high dose males and females.

Absolute and Relative Liver Weights

Measurement	Sex	Control Value	% Difference from Control		
			10 mg/kg/day	50 mg/kg/day	200 mg/kg/day
Absolute Liver Wt. (gm)	M	21.99	0.0	-1.8	-17.9*
	F	16.78	-1.5	-1.5	-16.3*
Relative Liver Wt. (gm/kg)	M	31.82	-2.8	-8.1	-12.3*
	F	38.35	-6.8	-3.2	-14.3*

* Significantly different from control (p<0.01)

Macroscopic Examination: Increases above control incidences of animals with renal cysts were observed in mid and high dose females and in high dose males. The sponsor states that this finding represents characteristic, spontaneous, age-related changes that occur in this colony of rats. Because this effect appears to be dose-related, the sponsor regards the renal cysts as treatment related. The increased incidence of renal cysts were concentrated among those animals that survived to scheduled sacrifice.

Macroscopic Findings in Rats

Measurement	Sex	# Rats Affected/# Rats Examined			
		0 mg/kg/day	10 mg/kg/day	50 mg/kg/day	200 mg/kg/day
Renal Cyst	M	4/70	3/70	2/70	16/70[a]
	F	1/70	1/70	5/70	12/70[a]

[a] Cysts in 12 males and in 10 females were detected at time of scheduled sacrifice.

Histopathology: Neoplastic Lesions

Sponsor's analysis showed no increase above control in the incidences of benign, primary malignant and metastatic malignant tumors (Summary of Primary Tumors located in Appendix I). There were no significant differences between valsartan-treated groups and control in the number of tumors/animal or in the number of tumor bearing animals.

Tumor Data[a]

Measurement	Sex	Treatment Group (mg/kg/day)			
		0 (control)	10	50	200
No. Tumors/Animal	M	1.68	1.53	1.42	1.37
	F	1.50	1.15	1.13	1.27
No. Tumor-Bearing Animals	M	52	49	46	44
	F	51	42	54	47

[a] Results based on 60 rats/group examined

FDA/CDER statistical analysis revealed that none of the tested tumor types showed a statistically significant positive trend or an increase in the incidence in valsartan treated groups compared with the control group (Statistical Review and Evaluation, Appendix III).

Histopathology: Non-Neoplastic Lesions

Valsartan-related effects were observed in the kidneys and adrenal cortex. Renal effects ascribed to valsartan treatment included cyst formation, lymphocytic infiltration, chronic progressive nephropathy, edema of the renal papilla and dilatation of the renal pelvis. The increase above control incidences were observed primarily in high dose males and, to a lesser extent, in mid dose males and high and mid dose females. A slightly higher than control incidence of hyperplasia of the adrenal cortex was noted in all valsartan-treated male groups but not in females.

Non-Neoplastic Lesions

Tissue/Lesion	Sex	Dose Level/Incidence (# Animals Affected; n=60)			
		0 (control)	10 mg/kg/d	50 mg/kg/d	200 mg/kg/d
Kidney	M				
Cyst formation		7	3	15	45
Lymphocytic infiltration		41	37	44	56
Chronic progressive nephropathy		48	46	51	60
Calcification		2	3	50	37
Edema of renal papilla		0	0	0	7
Dilatation of renal pelvis		1	1	1	3
Adrenal Cortex					
Hyperplasia		11	17	22	22
Kidney	F				
Cyst formation		3	3	17	32
Lymphocytic infiltration		22	16	30	47
Chronic progressive nephropathy		37	36	37	55

Valsartan Blood Levels: After repeated oral doses of valsartan, plasma concentrations and AUC values of the parent drug increased with increasing dose in male and female rats. The plasma levels of valsartan were higher in males than in females. In some instances, plasma levels of drug tended to increase with treatment duration; however, no consistent trend for drug accumulation was noted with increasing dose.

Valsartan Plasma Levels

Sex/Dose Group (mg/kg/day)		Time of Sample	Valsartan Plasma Levels (umol/L)*				
			Week 2	Week 27	Week 53	Week 78	Week 105
Males	10	7 AM	1.05	1.28	1.13	1.37	1.95
		5 PM	1.21	0.77	0.61	0.46	0.86
		7 AM	0.86	1.02	0.67	1.09	0.86
	50	7 AM	3.69	5.43	6.25	5.33	9.16
		5 PM	1.61	2.43	4.30	3.12	5.67
		7 AM	2.84	3.89	5.65	5.09	6.45
	200	7 AM	24.35	15.39	11.69	21.90	19.77
		5 PM	11.71	10.77	9.31	15.15	15.33
		7 AM	16.41	11.43	13.77	16.09	17.89
Females	10	7 AM	0.32	1.11	0.63	5.03	1.81
		5 PM	0.32	0.62	ND	1.08	1.43
		7 AM	0.11	0.47	0.89	1.40	1.16
	50	7 AM	1.55	4.90	1.97	4.59	8.24
		5 PM	0.49	2.28	0.57	2.94	4.22
		7 AM	1.93	3.93	1.42	3.28	5.01
	200	7 AM	13.77	8.82	17.38	15.20	14.71
		5 PM	5.87	4.21	6.61	5.53	10.96
		7 AM	8.66	3.78	9.78	9.48	11.09

* Each value represents the mean from 5 rats/dose group/ time interval/sample week; the same rats/dose group were used for all time intervals within a sample week and in subsequent weeks except when spare animals were necessary. ND= not detected; below detection limit (0.01 umol/L)

Valsartan $AUC_{0-24\ hr}$ Values

Dose Group (mg/kg/day	Sex	$AUC_{0-24\ hr}$ (umol*hr/L)				
		Week 2	Week 27	Week 53	Week 78	Week 105
10	M	25.8	22.8	17.7	20.0	25.7
50		57.6	83.5	122.4	99.7	161.4
200		377.1	289.2	266.6	403.9	407.8
10	F	6.2	16.3	9.4	47.9	34.3
50		27.1	79.4	26.6	81.2	126.9
200		199.9	121.1	234.7	208.7	282.7

3-Month Dose Rangefinding Study in Mice

Study Facility: Ciba-Geigy Ltd., Stein, Switzerland
Study No.: 916190
Study Dates: Initiation of Treatment= 1/22/92
Terminal Sacrifice= 4/23/92

GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Tif: MAGf (SPF), hybrids of NIH x MAG (M= 23.3-29.9g, F=21.0-26.8g at initiation of treatment).

Drug Administration: Valsartan (CGP 48933, Batch # 800291) was administered orally in the diet (admixed with pelleted food). The drug-containing pellets were prepared for week 1 and biweekly thereafter. Control animals were fed pelleted food without the test article.

Dose Levels: 0, 60, 200 and 600 mg/kg/day (5/sex/group for main test; 48/sex/group for blood drug level determinations).

Observations/Measurements: Animals were observed daily for mortality and clinical signs of toxicity. Body weights were measured prior to treatment and at weekly intervals. Clinical chemistry and hematology analyses were carried out on blood samples obtained by orbital sinus puncture from surviving animals in the main study at the end of the treatment period. At termination of treatment, surviving control and treated animals were killed and examined macroscopically. Sections from major organs and tissues were fixed on slides and subjected to microscopic examination. Complete necropsy and histopathology were performed on all animals which died or were sacrificed in moribund condition prior to study termination unless prevented by advanced autolysis or cannibalism Blood samples were collected from the orbital sinus of animals from the satellite groups during treatment days 7-8 and 90-91 for measurement of plasma valsartan levels.

Results: Average achieved doses ranged from 95%-108% of intended daily doses.

Achieved Doses in Mice

	Sex	Intended Daily Dose (mg/kg)		
		60	200	600
Achieved Daily Dose (mg/kg)	M	57	192	613
	F	63	200	646

Mortality: One high dose male died on Day 57 of treatment. One low dose male, 3 high dose males and one high dose female died under anesthesia before terminal blood sampling.

Clinical Signs: Clinical signs of toxicity, which included lethargy, piloerection, micturition and hunched back, were confined to a single high dose male, with first onset 2 days before the animal died (Day 57).

Other Treatment-Related Effects: Body weight did not significantly differ from control throughout the treatment period. Food consumption was slightly lower than control (statistically different from control at weeks 11-13) with all valsartan dose levels in females but food consumption in males did not significantly differ from control. Hematologic parameters (RBC counts, hematocrit, hemoglobin) were significantly lower in mid and high dose males; females were unaffected by valsartan treatment. Increases in blood urea and creatinine above control levels were seen in males from all valsartan-treated groups. In, females, blood urea levels were lower than control; however, effects on serum creatinine were mixed. A dose-related increase in relative kidney weight was noted in males but relative kidney weight in treated females was generally lower than control (not dose-related).

Gross and Microscopic Pathology: There were no treatment-related macroscopic findings. Microscopic examination showed higher than control incidence of hepatocellular hypertrophy in treated males; the effect was noted in all high dose males and to a lesser frequency in low and mid dose treated groups. Higher than control incidence of hepatic necrosis was noted in mid and high dose males and females. Atrophy of the thymic cortex was limited to high dose females.

Valsaretan Associated Findings in Mice

Measurement		Sex	Control Value	% Difference From Control		
				60 mg/kg/day	200 mg/kg/day	600 mg/kg/day
Body Weight (gm)	Wk -1	M	26.1	+1.3	+0.7	+1.5
		F	23.8	-3.7	+0.6	-2.2
	Wk 5	M	36.7	+1.3	-0.6	+0.8
		F	26.4	-1.4	+1.4	-0.9
	Wk 10	M	43.4	+0.2	-0.8	-1.5
		F	28.4	-0.2	+0.8	-0.6
	Wk 13	M	45.5	+2.4	-1.0	-3.9
		F	30.0	-0.4	0.0	+0.3
Food Consumption[a] (gm/rat/week)		M	37.6	+8.9	+3.0	+13.2
		F	53.7	-19.1*	-31.4*	-19.8*
Hematology[b]						
RBC Count		M	10.7	-0.8	-3.2	-12.2*
($X 10^6$/ul)		F	9.6	+10.0	+9.9	-0.3
Hematocrit		M	50.2	-3.8	-7.6*	-9.2*
(%)		F	45.6	+11.2*	+5.7	-0.7
Hemoglobin		M	9.7	-3.6*	-8.6*	-12.1*
(mmol/l)		F	8.9	+11.3*	+6.9	-1.9
Serum Chemistry[a]						
Blood Urea		M	7.2	+40.0*	+54.1*	+135*
(mmol/l)		F	11.9	-45.3	-54.2*	-10.8
Creatinine		M	25.3	+21.4*	+32.7	+31.3*
(umol/l)		F	25.5	-14.9*	+1.3	+11.2
Organ Weight						
Absolute Kidney Wt.		M	582	+0.5	+3.1	+11.1
(mg)		F	453	-10.8	-9.5	-6.4
Relative Kidney Wt		M	12.9	+11.7	+14.0	+25.6*
(mg/gm)		F	16.4	-14.0	-8.9	-9.8

[a] Values represent average % differences from control for Weeks 11-13. [b] Values derived from measurements made during Week 14. * Significant difference from control ($p<0.05$).

Microscopic Pathology in Mice

Pathologic Finding	Sex	Incidence[a]			
		0 (Control)	60 mg/kg	200 mg/kg	600 mg/kg
Hepatic Hypertrophy	M	1/5	3/5	2/5	5/5
Hepatic Necrosis	M	0/5	0/5	2/5	1/5
	F	0/5	0/5	3/5	3/5
Thymic Cortex Atrophy	F	0/5	0/5	0/5	2/5

[a] No occurence of hepatic hypertrophy in females or thymic cortex atrophy in males in control and treated groups.

Valsartan Plasma Levels: Plasma concentrations of valsartan were determined for the low and high dose groups (60 and 600 mg/kg/day) during weeks 2 and 13 of treatment. Valsartan was detected in the plasma in only one male mouse (1.82 umol/L at the end of the 13th week) dosed at 60 mg/kg/day. In the other 47 males and 48 females of this group, valsartan levels were below the limit of detection (< 0.05 umol/L). In mice treated with 600 mg/kg/day, 7/24 male mice and 10/24 female mice showed detectable levels (mean of 0.73 and 1.18 umol/l, respectively) of valsartan at the end of the first week of treatment. After 13 weeks of treatment, 8/24 male mice and 1/24 female mice showed detectable levels of valsartan (mean of 0.49 and 3.17 umol/l, respectively). AUC values could not be determined from the limited number of plasma level values.

24-Month Carcinogenicity Study in Mice

Study Facility: Ciba-Geigy Ltd., Stein, Switzerland
Study No.: 926006
Study Dates: Initiation of treatment = 7/13/92
Termination of treatment and necropsy= 7/11/94 to 7/18/94
GLP Compliance: Statement indicates that this study was conducted in compliance with GLP regulations.

Animals: Tif: MAGf (SPF), hybrids of NIH X MAG (M=22.2-30.9 gm; F=20.6-27.9 gm at 1 week prior to the initiation of treatment).

Drug Administration: Valsartan (Batch # 800292) was administered orally in the diet admixed with pelleted food and provided *ad libitum*; control animals received pelleted food without the test article. Diets were prepared at about monthly intervals. Diets were analyzed for test article stability and homogeneity periodically (12 times) during the study.

Dose Levels: 0, 10, 40 and 160 mg/kg/day

Animal Allocation

#/Sex/Group		Evaluation Parameters				
Control	Treatment	Survival	Carcinogenic Potential	Hematology	Blood Chemistry	Blood Drug Levels
50	50	X	X			X (24 Mo.)*
10	10		X	X		
10	10		X		X	
5	15					X (6 Mo.)
5	15					X (12 Mo.)
5	15					X (18 Mo.)
5	5	X		Spares	Spares	Spares

* Blood was obtained from 5/sex/control group and 15/sex/treated groups prior to terminal sacrifice for blood drug level determination.

Observations/Measurements: Animals were observed once to twice daily for mortality and clinical signs of toxicity. Body weights were measured prior to initiation of treatment, at weekly intervals for the first 3 months and monthly thereafter. Food consumption was measured weekly for the first 3 months and monthly thereafter. Hematologic and clinical chemistry analyses were carried out in blood obtained by orbital sinus puncture in 10 mice/sex/dose group during weeks 26, 53, 78 and 105. Blood samples were also obtained by the same technique from mice in the satellite test group for determination of blood drug levels during weeks 26, 53, 78 and 105. At the end of the treatment period, the surviving control and treated animals allocated for carcinogenicity evaluation were bled under ether anesthesia and subjected to macroscopic examination and the major organs weighed. Sections of major tissues and organs were fixed on slides and examined microscopically for histopathology.Complete necropsy and histopathology were performed on all animals allocated for carcinogenicity evaluation which died or were sacrificed in moribund condition prior to study termination unless prevented by advanced autolysis or cannibalism The statistical method of Peto et. al. (IARC Monograph, Supplement 2, 1980) was used to analyze histopathology data for significance of neoplastic findings.

Results:

Achieved Doses: Average achieved doses ranged between 98% to 102% of the intended daily doses.

Achieved Doses in Mice

	Sex	Intended Daily Dose (mg/kg)		
		10	40	160
Achieved Daily Dose* (mg/kg)	M	10.12	39.99	162.8
	F	9.82	39.39	161.3

* Value corrected for amount of test article recovered by analysis of diet.

Animal Survival: Treatment had no effect on the survival of male and female mice to terminal necropsy.

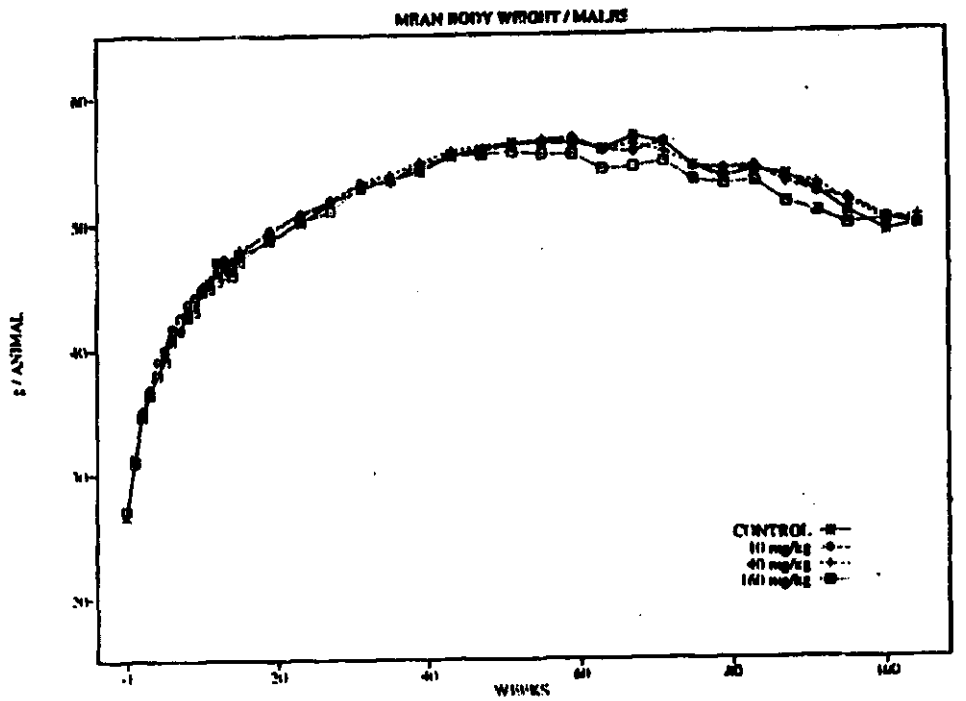
Animal Survival*

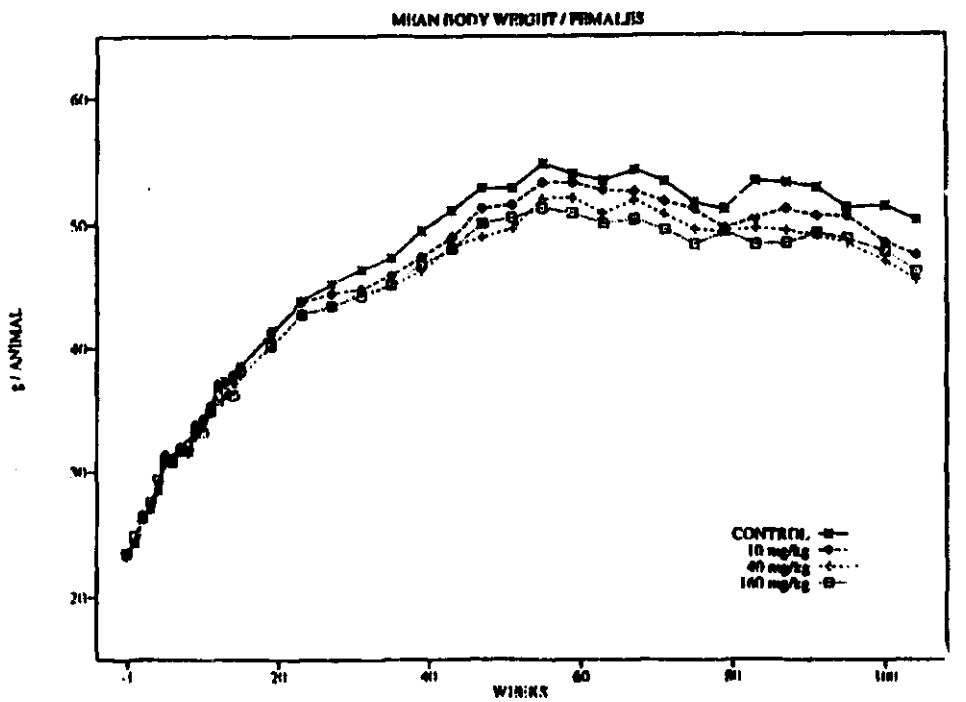
Dose Group (mg/kg/day)		# Surviving to Terminal Necropsy	
		Males	Females
Control	(0)	27	33
Valsartan	(10)	32	31
	(40)	30	25
	(160)	27	34

* Based on initial 55/sex/group

Body Weight: Mean body weights for treated males were similar to those of the control group throughout the study. Body weights and body weight gains in mid and high dose females were slightly lower than control by the end of the first 13 weeks and continued through to study termination. Body weight gains among low dose females were slightly lower than control over the second year of the study.

Body Weight Curves for Male and Female Mice





Body Weights in Mice

Dose Group (mg/kg/day)	Mean Body Wt, gm (% Difference from Control)			
	Males Week -1	Males Week 13	Males Week 51	Males Week 104
Control (0)	26.6	46.6	56.3	49.6
Valsartan (10)	27.1	47.3	56.1	49.8
(40)	26.8	47.1	56.3	50.3
(160)	27.1	46.1	55.6	49.6
	Females Week -1	Females Week 13	Females Week 51	Females Week 104
Control (0)	23.4	37.4	52.9	50.3
Valsartan (10)	23.3	37.1	51.6	47.5
(40)	23.4	36.1	49.7 (-6.0%)*	45.5 (-9.5%)
(160)	23.4	36.3	50.6 (-4.4%)*	46.2 (-8.2%)

* Significantly different from control ($p<0.01$)

Body Weight Gain in Female Mice

Treatment Interval	Body Weight Gain, gm (% difference from control)			
	0 (Control)	10 mg/kg/d	40 mg/kg/d	160 mg/kg/d
Week -1 to 13	13.99	13.76 (-1.6%)	12.76 (-8.8%)	12.85 (-8.2%)
Week -1 to 51	29.53	28.30 (-4.2%)	26.37 (-10.7%)	27.12 (-8.2%)
Week -1 to 104	26.98	24.23 (-10.2%)	22.19 (-17.8%)	22.73 (-15.8%)

Food Consumption: Food consumption in valsartan-treated male and female groups was comparable to that of control.

Hematology: Reductions from control of up to 5% were noted in hematologic parameters (RBC counts, hematocrit and hemoglobin) among high dose treated males and females.

Blood Chemistry: Blood chemistry values were generally similar for treated and control mice. Isolated increases above control blood urea and creatinine levels were noted among high dose males and females; but no consistent increases were seen throughout the study.

Organ Weights: Organ weight measurements revealed similar absolute and relative organ weights between treated and control groups.

Gross Pathology: Macroscopic examination revealed slightly higher than control incidences of lung nodules and kidney cysts in mid and high dose male mice and increased incidence of enlarged mesenteric lymph nodes in mid and high dose female mice.

Macroscopic Findings in Mice

Macroscopic Finding	Sex	Incidence, # Animals with Lesion			
		0 mg/kg/d (n=70M, 70F)	10 mg/kg/d (n=69M, 69F)	40 mg/kg/d (n=70M, 69F)	160 mg/kg/d (n=69M, 68F)
Lung Nodule	M	11	12	22	19
Kidney Cyst	M	18	16	20	24
Enlarged Mesenteric Lymph Node	F	9	8	11	15

Histopathology: Neoplastic Lesions

Sponsor's analysis revealed no significant differences between valsartan-treated groups and control in the number of tumors/animal or in the number of tumor-bearing animals (Summary of Primary Tumors Located in Appendix II).

Tumor Data*

Measurement	Sex	Treatment Group (mg/kg/day)			
		0 (control)	10	50	200
No. Tumors/Animal	M F	2.19 1.74	2.04 1.68	2.11 1.48	2.05 1.72
No. Tumor-Bearing Animals	M F	56 58	54 62	53 54	57 58

* Results based on 69-70M and 68-70F/group examined.

The sponsor's analysis showed that the pooled incidence of mammary gland tumors was significantly increased (Jonckheere's trend test; p=0.0288) in high dose females.

Mammary Gland Tumors

Mammary Tumor	Incidence, # Females with Tumors			
	0 mg/kg/d (n=70)	10 mg/kg/d (n=69)	40 mg/kg/d (n=69)	160 mg/kg/d (n=68)
Initial Carcinoma	0	0	0	1
Carcinoma	2	0	0	1
Adenoacanthoma	2	2	3	6
TOTAL	4	2	3	8 (11.8%)

The sponsor's historical incidence of mammary gland neoplasias in untreated females, derived from 11 studies of 24 months duration, is as follows:

Sponsor's Historical Control Incidence of Mammary Gland Tumors

	Incidence (mice with MG tumor/# examined)	% Incidence
Range (Single Study)		
Low	1/60	1.7%
High	10 /80	12.5%
Total (Combined Studies)	44/717	6.1%

Adenomas of the caecum were detected in 3/69 high dose males *vs* 0/70 in the control group. This finding was coincident with a decrease in the number of caecum carcinomas (4/70 in controls *vs* 0/69 in high dose male group). When the total (adenoma plus carcinoma) incidence for high dose treatment is compared to control, no treatment-related tumorigenic effect on the caecum is evident.

The sponsor's analysis showed the occurrence of hepatoblastoma to be significantly increased (Jonckheere's trend test; p=0.0435) above control in high dose males (1, 0, 0, 3 for C, LD, MD and HD, respectively); however, the incidence of animals bearing any malignant primary tumor of the liver (20 in control *vs* 17 in high dose male group) and of animals with any benign or malignant primary tumor of the liver (38 tumors in control *vs* 24 in high dose group) presented no evidence of a treatment-related increased incidence of liver neoplasia.

The sponsor's analysis showed a significantly (Jonckheere's trend test; P=0.0256) increased incidence of adenomas of the Harderian glands in high dose females; however, the incidence seen in high dose females fell within the sponsor's historical control range.

Harderian Gland Histopathology in Female Mice

Tumor Type	Incidence (# Females with Lesion (% Incidence))			
	0 (n=70)	10 (n=69)	40 (n=69)	160 (n=68)
Adenoma	4 (5.7%)	1 (1.4%)	3 (4.3%)	7 (10.3%)
Historical Control				
Range (Single Study)				
Low	1/59 (1.7%)			
High	14/85 (16.5%)			
Total (Combined Studies)	60/713 (8.4%)			

The occurrence of secondary (systemic) infiltration of malignant lymphoma was increased

The occurrence of secondary (systemic) infiltration of malignant lymphoma was increased above control in various organs (mesenteric and axillary lymph nodes, lung, liver, salivary glands, kidney and urinary bladder) and decreased in other organs (skeletal muscle, heart, aorta and small intestine) of treated males and females compared to control. Malignant lymphomas are systemic neoplasias infiltrating a variable pattern of organs. The sponsor states that the severity of the disease is unrelated to the number and/or distribution of secondary infiltrated organs. Also, no treatment-related increase in the primary tumor, malignant lymphoma of the lymphoreticular tissue, was observed and, therefore, no toxicologic relevance was ascribed to these secondary infiltrations.

FDA/CDER statistical analysis revealed that none of the tested tumor types showed a statistically significant positive trend or an increase in the incidence in the treated groups when compared with the control group (Statistical Review and Evaluation, Appendix III).

Histopathology: Non-Neoplastic Lesions

Valsartan treatment was associated with a higher than control incidence (0, 1, 1, 3 for C, LD, MD and HD, respectively) of focal, acute hemorrhage of the gastric mucosa in male mice. In one high dose animal, the hemorrhage was coincident with a gastric ulcer.

The incidence of hyperplasia of the urinary bladder epithelium was higher in high dose males (11/68) than in control males (6/70). In the majority of the mice affected (control or treated), the hyperplasia was associated with inflammatory processes in the urinary bladder and, in the absence of primary tumors of the urinary bladder of treated males, was considered to have no toxicological relevance

Microscopic examination of the kidneys did not validate the higher than control incidence of kidney cysts that was detected during gross examination. The microscopic incidence of renal cysts noted in valsartan-treated groups was similar to that seen in control groups (male incidence=32, 24, 26, 31; female incidence=3, 0, 6, 1 for C, LD, MD and HD, respectively).

Valsartan Blood Levels

Except in a few mice, valsartan was not detected in the plasma at the lowest dose level (10 mg/kg/day). Plasma concentrations of valsartan increased with increasing doses of 40 and 160 mg/kg/day. There were no striking differences between plasma valsartan concentrations of male and female mice.

Valsartan Plasma Levels[a]

Sex/Dose Group (mg/kg/day)		Valsartan Plasma Conc. (umol/L)			
		Week 26	Week 59	Week 78	Week 105
Males	10	ND	0.02	ND	ND
	40	0.04	0.13	0.25	0.07
	160	0.39	0.42	0.37	0.39
Females	10	ND	0.10	ND	ND
	40	0.02	0.16	0.14	0.13
	160	0.44	0.76	0.49	0.68

[a] Values represent the mean from 15/sex/group/sampling week (5/sex/group/sample wk at each of 3 sample periods, 10AM, 8PM and at 2PM).

ND= Not detected; below detection limit (0.01 umol/L)

SUMMARY AND EVALUATION

The Rat Study

Dose selection for the rat carcinogenicity study was based on a 3-month dose rangefinding dietary study in which 3 dose levels (60, 200 and 600 mg/kg/day) of valsartan were evaluated. Dose levels of 200 and 600 mg valsartan/kg/day, respectively, caused lower than control mean body weights in females (approx 9% and 10% lower during weeks 5 to 13 of treatment) and in males (approx 9% lower at week 13 of treatment), lower than control mean values for hematologic parameters (5.5% and 16.3% lower for RBC counts, 5.9% and 12.6% lower for hematocrit and 6.9 and 13.7% lower for hemoglobin) in males and females and higher than control mean values for blood urea (167% and 277% higher) and serum creatinine (23% and 41% higher) in males. The 60 mg/kg/day dose of valsartan caused small to negligible effects on these parameters. Relative liver weights in high dose males and females were lower than control. Relative adrenal weight in high dose males was significantly higher than control. The sponsor regarded the reduction from control body weight, decreased hematologic parameters, elevations of blood urea and serum creatinine and increased incidence of renal lesions seen with the 600 mg/kg/day dose as effects not compatible with long term animal survival. Although these effects were observed to a lesser degree with the 200 mg/kg/day dose level, the sponsor regarded this dose as a maximally tolerated dose and an appropriate high dose for the carcinogenicity study. Although the sponsor did not seek concurrence from the division prior to the initiation of the carcinogenicity study, the criteria used (effect on body weight, renal lesions) for selection of the high dose are reasonable and are consistent with current ICH Guidelines on High Dose Selection for Carcinogenicity Studies.

In the 24-month rat carcinogenicity study, dietary administration of valsartan at dose levels up to 200 mg/kg/day elicited no clinical signs of toxicity and did not adversely affect survival. The average achieved doses of valsartan were within 96% - 97% of the intended daily doses. Mean plasma concentrations and AUC values of the parent drug increased with increased dose in both males and females. Mean body weight values in high dose males were approximately 12%-14.6% lower than control values throughout most of the study (a reduction from control body weight was also seen in males at the same dose at the end of 13 weeks in the dose-rangefinding study). Lower than control hematologic parameters were noted in males and females receiving 50 and 200 mg valsartan/kg/day. This effect, common to ACE inhibitors and angiotensin II antagonists, is the result of reductions in plasma erythropoietin presumably due to the decreased influence of angiotensin II on the kidney. High dose males showed higher than control serum urea and creatinine concentrations. Gross examination revealed higher than control incidences of renal cysts in high dose males and females. Microscopic examination showed higher than control incidences of renal cysts, lymphocytic infiltration and chronic progressive nephropathy in high dose males and females. The treatment-related effects on body weight, blood chemistry and renal histology in high dose animals supports the sponsor's choice of 200 mg/kg/day as the high dose based on a maximally tolerated dose.

The sponsor's overall analysis of animals with benign, primary malignant and metastatic tumors did not reveal a valsartan-related increase of neoplasias. Analysis of the tumor data by FDA/CDER statisticians, likewise, showed no treatment-related increases of neoplasias

The Mouse Study

Dose selection for the mouse carcinogenicity study was based on a 3-month dose rangefinding dietary study in which 3 dose levels (60, 200 and 600 mg/kg/day) were evaluated. Doses of 60 to 600 mg/kg/day had no effect on body weight. Doses of 200 and 600 mg/kg/day reduced hematologic parameters (RBC counts, hematocrit and hemoglobin) from control levels. Blood urea and serum creatinine were elevated above control in all male dose groups. Relative kidney weight was higher than control in high dose males. Doses of 200 and 600 mg/kg/day were associated with higher than control incidence of hepatic hypertrophy (males only) and hepatic necrosis (males and females). Higher than control incidence of atrophy of the thymic cortex was noted in females treated with 600 mg valsartan/kg/day. Based on the hepatocellular necrosis, elevations of blood urea and serum creatinine and reduced hematologic parameters, the dose of 200 mg valsartan/kg/day was regarded by the sponsor to have exceeded a maximally tolerated dose (MTD). Therefore, the sponsor selected 160 mg valsartan/kg/day as an appropriate high dose for the 2-year carcinogenicity study in mice. (The sponsor did not seek concurrence from division prior to initiating the 2-year study.) This dose is approximately 50X the maximum recommended clinical dose on a body-weight basis.

In the 24 month mouse carcinogenicity study, dietary administration of valsartan dose levels up to 160 mg/kg/day elicited no clinical signs of toxicity and did not adversely affect survival. The average achieved valsartan doses were within 98%-102% of the intended daily doses. Plasma concentrations of parent drug increased dose-dependently with 40 and 160 mg/kg/day; valsartan was detected in the plasma in only a few mice at the lowest dose level (10 mg/kg/day). Mean body weights and body weight gains in mid and high dose females were lower (4.4% and 9.5%, respectively, for body weight and 15.8% and17.8%, respectively, for weight gain) than control, particularly during the second year of treatment. Valsartan treatment had no adverse effects on food consumption, hematology, blood chemistry or organ weights.

The sponsor's analysis showed no significant differences between valsartan-treated and control groups in the number of tumors/animal or in the number of tumor-bearing animals. Slightly higher than control incidences of adenoma of the caecum (HD males) and Harderian glands (HD females) were considered to be unrelated to valsartan treatment based on sponsor's historical control incidence or analysis under pooled

mammary gland neoplasias. In addition, no significant increase above control incidence for mammary gland tumors was noted when the tumor types were analyzed separately. Analysis of the tumor data by the FDA/CDER statistical reviewer revealed no evidence of tumorigenicity by valsartan at dietary levels up to 160 mg/kg/day.

LABELING

Under PRECAUTIONS, *Carcinogenesis, Mutagenesis, Impairement of Fertility,* the sponsor's proposed carcinogenesis statement reads as follows:

" There was no evidence of carcinogenicity when TRADENAME was administered orally to mice and rats for 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats, respectively, are 70 and 87 times the maximum recommended human dose based on mg/kg or 6 and 14 times based on mg/m^2. These calculations assumed an oral dose of 160 mg/day for a 70-kg patient."

That text should be revised to read as follows:

"There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats, respectively, are 70 and 87 times the maximum recommended human dose (MRHD) on a mg/kg basis or about 6 and 14 times the MRHD on a mg/m^2 basis. (Calculations assume an oral dose of 160 mg/day and a 70-kg patient.)"

Anthony G. Proakis, Ph.D.
Pharmacologist

Original NDA #20,665
HFD-110
HFD-110/CSO
HFD-110/AProakis
HFD-110/GJagadee h
HFD-345/EButler
Accepted by ...GR on 8/21/96

APPENDIX I

Summary of Primary Tumors in Rats

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Removal code : all Observation period : all

Selected experimental group(s): all*

Selected animals: all*

Selected findings : all

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Treatment ended in observation period, selected	70	70	70	70
Examined macroscopically	70	70	70	70
Examined microscopically*				
S1	39	42	41	43
MS	11	4	6	9
FD	10	14	13	8
Total	60	60	60	60

* Comment:
Except animals of experimental group III (10 animals/sex/group) which were not requested for microscopical examination according to the study protocol. Note: Experimental Group III refers to satellite toxicokinetic animals (10/sex/group) used for blood drug level determinations.

Abbreviations used in pathology tables

S1, S2....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
PRIMARY SITE UNCERTAIN				
SARCOMA, NOT OTHERWISE SPECIFIED				
FD	1	0	0	0
Total	1	0	0	0
MALIGNANT MESOTHELIOMA				
S1	0	0	1	0
Total	0	0	1	0
HISTIOCYTIC SARCOMA				
FD	1	0	1	0
Total	1	0	1	0
SKIN				
KERATOACANTHOMA				
S1	0	0	1	0
Total	0	0	1	0
SQUAMOUS CELL CARCINOMA				
FD	0	0	1	0
Total	0	0	1	0
SUBCUTANEOUS TISSUE				
SARCOMA, NOT OTHERWISE SPECIFIED				
FD	1	0	0	0
Total	1	0	0	0
FIBROMA				
S1	3	2	1	0
MS	1	0	0	0
Total	4	2	1	0
FIBROSARCOMA				
MS	1	1	0	0
Total	1	1	0	0
MALIGNANT FIBROUS HISTIOCYTOMA				
S1	0	1	0	0
Total	0	1	0	0

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
SUBCUTANEOUS TISSUE (continued)				
LIPOMA				
S1	0	0	0	1
MS	0	0	0	1
Total	0	0	0	2
MALIGNANT NEURINOMA				
S1	1	0	0	0
Total	1	0	0	0
MAMMARY GLAND				
CARCINOMA, INITIAL				
S1	5	3	3	2
Total	5	3	3	2
CARCINOMA				
S1	4	1	5	5
MS	1	0	0	1
FD	2	1	1	3
Total	7	2	6	9
ADENOMA				
S1	3	1	1	2
FD	1	1	1	0
Total	4	2	2	2
FIBROSARCOMA				
S1	0	0	0	1
Total	0	0	0	1
MAMMARY FIBROMA				
S1	1	0	1	1
Total	1	0	1	1
FIBROADENOMA				
S1	9	17	12	7
MS	7	2	5	8
FD	4	5	2	2
Total	20	24	19	17

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
LYMPHORETICULAR TISSUE				
MALIGNANT LYMPHOMA				
FD	0	0	0	1
Total	0	0	0	1
HAEMATOPOIETIC TISSUE				
MYELOID LEUKAEMIA				
S1	0	0	0	1
FD	0	0	0	1
Total	0	0	0	2
MESENTERIC LYMPH NODE				
HAEMANGIOMA				
S1	2	0	4	0
Total	2	0	4	0
ANGIOSARCOMA				
S1	0	0	0	1
Total	0	0	0	1
SKELETAL MUSCLE				
RHABDOMYOSARCOMA				
S1	1	0	0	0
Total	1	0	0	0
SALIVARY GLAND				
CARCINOMA				
FD	0	0	1	0
Total	0	0	1	0
LIVER				
BENIGN HEPATOMA				
S1	0	0	2	0
Total	0	0	2	0

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
LIVER (continued)				
HEPATOCELLULAR CARCINOMA				
S1	0	1	0	0
Total	0	1	0	0
VAGINA				
SQUAMOUS CELL CARCINOMA, INITIAL				
S1	0	0	1	0
Total	0	0	1	0
LEIOMYOMA				
S1	1	0	0	0
Total	1	0	0	0
UTERUS				
CARCINOMA				
S1	0	1	0	0
Total	0	1	0	0
LEIOMYOSARCOMA				
MS	1	0	0	0
Total	1	0	0	0
OVARY				
TUBULAR ADENOMA				
S1	0	1	1	0
MS	0	0	1	0
FD	0	0	0	1
Total	0	1	2	1
CYSTADENOMA				
S1	0	1	0	0
Total	0	1	0	0
BENIGN GRANULOSA/THECA CELL TUMOUR				
S1	0	1	2	2
MS	1	0	0	0
FD	0	0	0	1
Total	1	1	2	3

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group		1	2	3	4
Exposure : mg/kg		0	10	50	200
Animals initially in study		70	70	70	70
Examined microscopically		60	60	60	60
ADENOHYPOPHYSIS					
ADENOMA					
	S1	15	14	15	15
	MS	3	0	1	3
	FD	2	5	5	2
	Total	20	19	21	20
ADRENAL CORTEX					
ADENOMA					
	S1	3	1	9	4
	MS	1	0	0	0
	Total	4	1	9	4
ADRENAL MEDULLA					
BENIGN MEDULLARY TUMOUR					
	S1	0	0	1	1
	FD	1	0	1	0
	Total	1	0	2	1
MALIGNANT MEDULLARY TUMOUR					
	S1	0	0	0	1
	Total	0	0	0	1
THYROID GLAND					
CARCINOMA					
	S1	0	0	2	1
	Total	0	0	2	1
ADENOMA					
	S1	0	2	0	1
	MS	0	0	0	1
	Total	0	2	0	2
C-CELL ADENOMA					
	S1	3	2	2	2
	MS	1	0	0	1
	FD	1	1	1	0
	Total	5	3	3	3

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
THYMUS				
SQUAMOUS CELL CARCINOMA				
FD	0	1	0	0
Total	0	1	0	0
BENIGN THYMOMA				
S1	1	0	0	1
Total	1	0	0	1
THYMIC LYMPHOMA				
FD	0	0	1	0
Total	0	0	1	0
PANCREATIC ISLET				
CARCINOMA				
S1	1	0	0	0
Total	1	0	0	0
ADENOMA				
S1	3	1	1	1
FD	1	1	0	0
Total	4	2	1	1
CEREBRAL MENINGES				
BENIGN GRANULAR CELL TUMOUR				
S1	1	0	1	0
Total	1	0	1	0
BRAIN				
MALIGNANT ASTROCYTIC GLIOMA				
S1	0	1	0	0
Total	0	1	0	0

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
PERITONEUM				
LIPOMA				
MS	1	0	0	0
Total	1	0	0	0

Summary tables of tumour occurrence

GENERAL OCCURRENCE OF PRIMARY TUMOURS IN MALES

Removal code : all Observation period : all

Selected experimental group(s): all*

Selected animals: all*

Selected findings : all

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Treatment ended in observation period, selected	70	70	70	70
Examined macroscopically	70	70	70	70
Examined microscopically*				
S1	33	33	32	32
AD	0	0	1	2
MS	9	13	10	4
FD	18	14	17	22
Total	60	60	60	60

* Comment:
Except animals of experimental group III (10 animals/sex/group) which were not requested for microscopical examination according to the study protocol.

Abbreviations used in pathology tables

S1, S2....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

GENERAL OCCURRENCE OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
NUMBER OF MALES WITH ONE TUMOUR				
S1	10	8	14	11
AD	0	0	0	1
MS	6	7	5	2
FD	7	6	5	5
Total	23	21	24	19
NUMBER OF MALES WITH TWO TUMOURS				
S1	9	9	3	9
AD	0	0	0	1
MS	3	4	4	1
FD	4	3	3	8
Total	16	16	10	19
NUMBER OF MALES WITH THREE TUMOURS				
S1	5	9	5	3
AD	0	0	1	0
MS	0	1	1	1
FD	2	1	2	0
Total	7	11	9	4
NUMBER OF MALES WITH FOUR TUMOURS				
S1	4	0	1	0
FD	1	0	0	0
Total	5	0	1	0
NUMBER OF MALES WITH FIVE TUMOURS				
S1	1	0	2	0
Total	1	0	2	0
NUMBER OF MALES WITH SIX TUMOURS				
S1	0	0	0	1
MS	0	1	0	0
Total	0	1	0	1

GENERAL OCCURRENCE OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
NUMBER OF MALES WITH SEVEN TUMOURS				
S1	0	0	0	1
Total	0	0	0	1
NUMBER OF TUMOURBEARING MALES				
S1	29	26	25	25
AD	0	0	1	2
MS	9	13	10	4
FD	14	10	10	13
Total	52	49	46	44

GENERAL OCCURRENCE OF PRIMARY TUMOURS IN FEMALES

Removal code : all Observation period : all

Selected experimental group(s): all*

Selected animals: all*

Selected findings : all

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Treatment ended in observation period, selected	70	70	70	70
Examined macroscopically	70	70	70	70
Examined microscopically*				
S1	39	42	41	43
MS	11	4	6	9
FD	10	14	13	8
Total	60	60	60	60

* Comment:
Except animals of experimental group III (10 animals/sex/group) which were not requested for microscopical examination according to the study protocol.

Abbreviations used in pathology tables

S1, S2....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

GENERAL OCCURRENCE OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	50	60	60
NUMBER OF FEMALES WITH ONE TUMOUR				
S1	12	14	16	17
MS	8	3	5	5
FD	2	4	8	4
Total	22	21	29	26
NUMBER OF FEMALES WITH TWO TUMOURS				
S1	16	13	14	10
MS	1	0	1	2
FD	5	4	2	2
Total	22	17	17	14
NUMBER OF FEMALES WITH THREE TUMOURS				
S1	3	1	6	3
MS	0	0	0	2
FD	1	1	1	1
Total	4	2	7	6
NUMBER OF FEMALES WITH FOUR TUMOURS				
S1	1	2	1	1
MS	2	0	0	0
Total	3	2	1	1
NUMBER OF TUMOURBEARING FEMALES				
S1	32	30	37	31
MS	11	3	6	9
FD	8	9	11	7
Total	51	42	54	47

SUMMARY OF PRIMARY TUMOURS IN MALES

Removal code : all Observation period : all

Selected experimental group(s): all*

Selected animals: all*

Selected findings : all

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Treatment ended in observation period, selected	70	70	70	70
Examined macroscopically	70	70	70	70
Examined microscopically*				
S1	33	33	32	32
AD	0	0	1	2
MS	9	13	10	4
FD	18	14	17	22
Total	60	60	60	60

* Comment:
Except animals of experimental group III (10 animals/sex/group) which were not requested for microscopical examination according to the study protocol. Note: Experimental Group III refers to satellite toxicokinetic animals (10/sex/group) used for blood level determination.

Abbreviations used in pathology tables

S1, S2....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
PRIMARY SITE UNCERTAIN				
MALIGNANT NEURINOMA				
S1	0	0	0	1
Total	0	0	0	1
SKIN				
KERATOACANTHOMA				
S1	0	0	1	2
MS	0	1	0	0
Total	0	1	1	2
SQUAMOUS CELL CARCINOMA				
MS	0	1	0	0
FD	0	0	0	1
Total	0	1	0	1
SUBCUTANEOUS TISSUE				
UNDIFFERENTIATED SARCOMA				
FD	0	1	0	0
Total	0	1	0	0
FIBROMA				
S1	5	5	5	3
MS	4	10	5	4
FD	3	1	6	6
Total	12	16	16	13
FIBROSARCOMA				
S1	1	0	0	0
MS	2	1	2	0
FD	0	0	1	0
Total	3	1	3	0
BENIGN FIBROUS HISTIOCYTOMA				
S1	0	0	1	0
Total	0	0	1	0
LIPOMA				
S1	2	2	0	1
FD	1	1	0	0
Total	3	3	0	1

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
SUBCUTANEOUS TISSUE (continued)				
ANGIOSARCOMA				
Si	0	0	0	1
Total	0	0	0	1
NEURINOMA				
Si	0	0	0	1
FD	1	0	0	0
Total	1	0	0	1
MALIGNANT NEURINOMA				
Si	0	0	0	1
Total	0	0	0	1
MAMMARY GLAND				
LIPOMA				
Si	0	0	0	1
Total	0	0	0	1
FIBROADENOMA				
Si	1	0	1	0
AD	0	0	1	0
MS	1	0	0	0
FD	0	1	0	2
Total	2	1	2	2
LYMPHORETICULAR TISSUE				
MALIGNANT LYMPHOMA				
MS	1	0	0	0
FD	1	2	0	0
Total	2	2	0	0
HAEMATOPOIETIC TISSUE				
MYELOID LEUKAEMIA				
FD	1	0	0	0
Total	1	0	0	0

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
SPLEEN				
HAEMANGIOMA				
S1	0	1	1	0
MS	0	1	0	0
Total	0	2	1	0
MESENTERIC LYMPH NODE				
HAEMANGIOMA				
S1	3	3	3	2
MS	0	2	1	0
Total	3	5	4	2
SKELETAL MUSCLE				
RHABDOMYOSARCOMA				
MS	1	0	0	0
Total	1	0	0	0
LUNG				
CARCINOMA				
FD	0	0	1	0
Total	0	0	1	0
LIVER				
CHOLANGIOCARCINOMA				
MS	0	1	0	0
Total	0	1	0	0
BENIGN HEPATOMA				
S1	0	2	0	0
MS	0	1	0	0
Total	0	3	0	0
HEPATOCELLULAR CARCINOMA				
FD	0	1	0	0
Total	0	1	0	0

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
EXOCRINE PANCREAS				
CARCINOMA				
S1	1	0	0	0
Total	1	0	0	0
ADENOMA				
S1	4	3	1	0
FD	0	0	1	0
Total	4	3	2	0
SMALL INTESTINE				
MUCINOUS CARCINOMA				
FD	1	0	0	0
Total	1	0	0	0
KIDNEY				
CARCINOMA				
FD	1	0	0	0
Total	1	0	0	0
SARCOMA, NOT OTHERWISE SPECIFIED				
FD	0	0	0	1
Total	0	0	0	1
LIPOSARCOMA				
FD	0	0	1	0
Total	0	0	1	0
PROSTATE				
ADENOMA				
S1	1	1	1	1
FD	1	1	0	0
Total	2	2	1	1
TESTIS				
BENIGN INTERSTITIAL CELL TUMOUR				
S1	0	1	0	2
MS	0	0	1	0
FD	1	1	0	1

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
TESTIS (continued)				
Total	1	2	1	3
MALIGNANT INTERSTITIAL CELL TUMOUR				
S1	1	0	0	0
AD	0	0	0	1
Total	1	0	0	1
ADENOHYPOPHYSIS				
ADENOMA				
S1	17	11	11	10
AD	0	0	1	1
MS	3	1	2	1
FD	8	4	2	4
Total	28	15	16	16
ADRENAL CORTEX				
CARCINOMA				
FD	0	0	0	2
Total	0	0	0	2
ADENOMA				
S1	10	7	8	11
MS	0	2	1	0
FD	0	1	3	2
Total	10	10	12	13
ADRENAL MEDULLA				
BENIGN MEDULLARY TUMOUR				
S1	4	2	2	6
AD	0	0	0	1
MS	0	0	1	0
FD	1	0	0	0
Total	5	2	3	7
MALIGNANT MEDULLARY TUMOUR				
S1	1	3	2	2
Total	1	3	2	2

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
THYROID GLAND				
ADENOMA				
S1	0	1	1	1
Total	0	1	1	1
C-CELL ADENOMA				
S1	5	3	5	2
AD	0	0	1	0
MS	0	3	0	2
FD	1	0	1	1
Total	6	6	7	5
C-CELL CARCINOMA				
S1	2	1	0	1
Total	2	1	0	1
THYMUS				
BENIGN THYMOMA				
S1	0	0	1	0
MS	0	0	1	0
Total	0	0	2	0
PANCREATIC ISLET				
CARCINOMA				
S1	1	3	0	0
FD	2	0	1	0
Total	3	3	1	0
ADENOMA				
S1	3	1	5	0
MS	0	0	1	0
FD	1	0	0	0
Total	4	1	6	0
CEREBRAL MENINGES				
HAEMANGIOMA				
S1	0	0	0	1
Total	0	0	0	1

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	50	200
Animals initially in study	70	70	70	70
Examined microscopically	60	60	60	60
CEREBRAL MENINGES (continued)				
BENIGN GRANULAR CELL TUMOUR				
S1	0	2	0	0
MS	0	0	1	0
FD	0	1	0	1
Total	0	3	1	1
BRAIN				
MIXED GLIOMA				
S1	1	0	0	0
Total	1	0	0	0
MALIGNANT ASTROCYTIC GLIOMA				
S1	1	1	0	0
FD	1	0	0	0
Total	2	1	0	0
PERITONEUM				
LIPOMA				
S1	0	0	0	1
Total	0	0	0	1

APPENDIX II

Summary of Primary Tumors in Mice

SUMMARY OF PRIMARY TUMOURS IN MALES

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Treatment ended in observation period, selected	90	120	120	120
Advanced autolysis, no samples taken	0	1	0	0
No samples taken, technical reasons	0	0	0	1
Autopsy not requested by protocol	20	50	50	50
Examined macroscopically	70	69	70	69
Examined microscopically				
S4	29	33	33	33
AD	6	3	7	2
MS	3	3	0	2
FD	32	30	30	32
Total	70	69	70	69

Abbreviations used in pathology tables

S1, S2....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	70	69
PRIMARY SITE UNCERTAIN				
SARCOMA, NOT OTHERWISE SPECIFIED				
FD	0	0	0	1
Total	0	0	0	1
OSTEOGENIC SARCOMA				
FD	1	0	0	0
Total	1	0	0	0
SUBCUTANEOUS TISSUE				
SEBACEOUS CARCINOMA				
MS	1	0	0	0
Total	1	0	0	0
LIPOSARCOMA				
S4	0	0	1	0
Total	0	0	1	0
ANGIOSARCOMA				
FD	0	1	0	0
Total	0	1	0	0
LYMPHORETICULAR TISSUE				
MALIGNANT LYMPHOMA				
S4	13	16	15	20
AD	1	0	0	0
FD	3	4	3	3
Total	17	20	18	23
HAEMATOPOIETIC TISSUE				
MYELOID LEUKAEMIA				
FD	0	1	3	1
Total	0	1	3	1
SPLEEN				
ANGIOSARCOMA				
FD	1	0	0	1
Total	1	0	0	1

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	70	69
SKELETAL MUSCLE				
RHABDOMYOSARCOMA				
FD	0	0	1	0
Total	0	0	1	0
LUNG				
CARCINOMA				
S4	2	3	1	2
AD	0	0	1	0
MS	0	1	0	0
FD	4	2	2	3
Total	6	6	4	5
ADENOMA				
S4	6	11	14	11
AD	2	0	2	1
MS	0	0	0	1
FD	7	3	7	8
Total	15	14	23	21
TOOTH, NOS				
BENIGN ODONTOGENIC TUMOUR				
S4	0	1	1	0
Total	0	1	1	0
LIVER				
BENIGN HEPATOMA				
S4	9	5	8	3
AD	2	0	1	1
MS	1	0	0	0
FD	6	6	12	3
Total	18	11	21	7
HEPATOCELLULAR CARCINOMA				
S4	11	15	7	11
AD	2	1	1	0
FD	6	3	3	3
Total	19	19	11	14

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	70	69
LIVER (continued)				
HEPATOBLASTOMA				
S4	0	0	0	1
FD	1	0	0	2
Total	1	0	0	3
ANGIOSARCOMA				
S4	1	1	0	0
FD	1	1	0	2
Total	2	2	0	2
STOMACH				
MALIGNANT MAST CELL TUMOUR				
FD	0	0	1	0
Total	0	0	1	0
GLANDULAR STOMACH				
ADENOMA				
S4	0	1	0	1
Total	0	1	0	1
SMALL INTESTINE				
ADENOMA				
S4	0	0	0	1
Total	0	0	0	1
LARGE INTESTINE				
ADENOMA				
S4	0	2	0	0
Total	0	2	0	0
CAECUM				
ADENOMA				
S4	0	0	0	2
MS	0	0	0	1
FD	0	0	1	0
Total	0	0	1	3

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	70	69
CAECUM (continued)				
MUCINOUS CARCINOMA				
S4	1	0	0	0
FD	3	3	3	0
Total	4	3	3	0
KIDNEY				
ADENOMA				
S4	1	1	0	1
Total	1	1	0	1
URINARY BLADDER				
TRANSITIONAL CELL CARCINOMA				
AD	1	0	0	0
Total	1	0	0	0
PROSTATE				
CARCINOMA				
S4	1	1	0	0
Total	1	1	0	0
ADENOMA				
S4	2	0	0	1
FD	0	0	0	1
Total	2	0	0	2
LEIOMYOMA				
S4	0	0	1	0
Total	0	0	1	0
SEMINAL VESICLE				
CARCINOMA				
S4	0	1	0	0
Total	0	1	0	0
ADENOMA				
S4	1	1	1	0
FD	0	0	0	1

SUMMARY OF PRIMARY TUMOURS IN MALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	70	69
SEMINAL VESICLE (continued)				
Total	1	1	1	1
LEIOMYOMA				
S4	0	0	2	0
Total	0	0	2	0
LEIOMYOSARCOMA				
S4	0	1	1	0
FD	1	0	1	2
Total	1	1	2	2
BENIGN GRANULAR CELL TUMOUR				
S4	1	0	0	1
Total	1	0	0	1
TESTIS				
BENIGN INTERSTITIAL CELL TUMOUR				
S4	0	1	1	0
Total	0	1	1	0
HAEMANGIOMA				
FD	0	0	1	0
Total	0	0	1	0
ADENOHYPOPHYSIS				
ADENOMA				
S4	0	0	0	1
Total	0	0	0	1
ADRENAL CORTEX				
ADENOMA				
S4	1	0	0	2
FD	0	2	0	1
Total	1	2	0	3

SUMMARY OF PRIMARY TUMOURS IN MALES

Group		1	2	3	4
Exposure : mg/kg		0	10	40	160
Animals initially in study		90	120	120	120
Examined microscopically		70	69	70	69
THYROID GLAND					
ADENOMA					
	S4	1	0	0	0
	Total	1	0	0	0
C-CELL ADENOMA					
	S4	0	0	1	0
	Total	0	0	1	0
PANCREATIC ISLET					
ADENOMA					
	FD	2	1	0	1
	Total	2	1	0	1
HARDERIAN GLAND					
CARCINOMA					
	FD	0	1	0	0
	Total	0	1	0	0
ADENOMA					
	S4	11	14	12	14
	AD	2	0	1	1
	MS	1	0	0	0
	FD	7	5	2	7
	Total	21	19	15	22

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Removal code : all Observation period : all

Selected experimental group(s): all

Selected animals: all

Selected findings : all

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Treatment ended in observation period, selected				
Advanced autolysis, no samples taken	90	120	120	120
No samples taken, technical reasons	0	1	1	1
Autopsy not requested by protocol	0	0	0	1
Examined macroscopically	20	50	50	50
Examined microscopically	70	69	69	68
S4				
AD	39	37	34	37
MS	2	5	5	2
FD	1	0	0	0
Total	28	27	30	29
	70	69	69	68

Abbreviations used in pathology tables

S1, S2....	scheduled sacrifice(s)
MS	moribund sacrifice
FD	found dead
AD	accidental death

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group		1	2	3	4
Exposure : mg/kg		0	10	40	160
Animals initially in study		90	120	120	120
Examined microscopically		70	69	69	68
PRIMARY SITE UNCERTAIN					
CARCINOMA					
	FD	1	0	0	1
	Total	1	0	0	1
SKIN					
BASAL CELL CARCINOMA					
	FD	0	1	0	0
	Total	0	1	0	0
SUBCUTANEOUS TISSUE					
FIBROSARCOMA					
	FD	1	0	0	1
	Total	1	0	0	1
MAMMARY GLAND					
CARCINOMA, INITIAL					
	S4	0	0	0	1
	Total	0	0	0	1
CARCINOMA					
	S4	0	0	0	1
	MS	1	0	0	0
	FD	1	0	0	0
	Total	2	0	0	1
ADENOMA					
	S4	0	0	1	0
	Total	0	0	1	0
ADENOACANTHOMA					
	S4	0	0	1	3
	FD	2	2	2	3
	Total	2	2	3	6

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	69	68
LYMPHORETICULAR TISSUE				
MALIGNANT LYMPHOMA				
S4	26	19	15	14
AD	0	3	0	0
FD	16	16	17	22
Total	42	38	32	36
HAEMATOPOIETIC TISSUE				
MYELOID LEUKAEMIA				
MS	1	0	0	0
FD	2	0	0	2
Total	3	0	0	2
SPLEEN				
SARCOMA, NOT OTHERWISE SPECIFIED				
FD	0	1	0	0
Total	0	1	0	0
ANGIOSARCOMA				
S4	0	2	0	0
FD	0	0	1	1
Total	0	2	1	1
MESENTERIC LYMPH NODE				
HAEMANGIOMA				
FD	1	0	0	0
Total	1	0	0	0
BONE				
OSTEOGENIC SARCOMA				
FD	0	1	0	0
Total	0	1	0	0
LUNG				
CARCINOMA				
S4	0	1	1	0
AD	0	0	0	1
FD	4	5	1	1

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	69	66
LUNG (continued)				
Total	4	6	2	2
ADENOMA				
S4	9	8	6	6
AD	0	2	1	0
FD	2	2	2	3
Total	11	12	9	9
LIVER				
BENIGN HEPATOMA				
S4	5	7	4	5
AD	0	1	0	0
FD	1	3	1	3
Total	6	11	5	8
HEPATOCELLULAR CARCINOMA				
S4	2	2	0	1
FD	0	1	1	0
Total	2	3	1	1
HAEMANGIOMA				
S4	1	1	1	1
Total	1	1	1	1
ANGIOSARCOMA				
S4	0	0	1	0
Total	0	0	1	0
HISTIOCYTIC SARCOMA				
S4	0	0	0	1
Total	0	0	0	1
SMALL INTESTINE				
ADENOMA				
S4	0	1	0	0
Total	0	1	0	0

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	69	68
LARGE INTESTINE				
MUCINOUS CARCINOMA				
FD	0	1	0	0
Total	0	1	0	0
CAECUM				
CARCINOMA				
S4	0	0	0	1
Total	0	0	0	1
ADENOMA				
S4	0	0	1	0
AD	0	1	0	0
FD	1	0	0	0
Total	1	1	1	0
MUCINOUS CARCINOMA				
S4	0	0	0	1
Total	0	0	0	1
URINARY BLADDER				
LEIOMYOSARCOMA				
S4	0	1	0	0
Total	0	1	0	0
UTERUS				
ADENOMA				
S4	1	0	0	0
Total	1	0	0	0
SARCOMA, NOT OTHERWISE SPECIFIED				
S4	0	1	0	0
Total	0	1	0	0
LEIOMYOMA				
S4	2	4	3	4
AD	0	1	0	0
FD	1	2	0	0
Total	3	7	3	4

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group	1	2	3	4
Exposure : mg/kg	0	10	40	160
Animals initially in study	90	120	120	120
Examined microscopically	70	69	69	68
UTERUS (continued)				
LEIOMYOSARCOMA				
S4	2	1	0	0
FD	0	0	0	2
Total	2	1	0	2
HAEMANGIOMA				
S4	1	0	0	0
FD	0	0	0	1
Total	1	0	0	1
ANGIOSARCOMA				
FD	0	0	0	1
Total	0	0	0	1
BENIGN GRANULAR CELL TUMOUR				
FD	0	0	1	0
Total	0	0	1	0
OVARY				
SARCOMA, NOT OTHERWISE SPECIFIED				
FD	0	0	0	1
Total	0	0	0	1
LEIOMYOSARCOMA				
AD	0	0	1	0
Total	0	0	1	0
HAEMANGIOMA				
S4	1	0	0	1
AD	0	0	1	0
FD	2	2	3	2
Total	3	2	4	3
ANGIOSARCOMA				
S4	1	0	0	1
Total	1	0	0	1

SUMMARY OF PRIMARY TUMOURS IN FEMALES

Group		1	2	3	4
Exposure : mg/kg		0	10	40	160
Animals initially in study		90	120	120	120
Examined microscopically		70	69	69	68
ADENOHYPOPHYSIS					
ADENOMA					
	S4	5	7	5	7
	AD	0	1	0	0
	FD	2	0	4	0
	Total	7	8	9	7
THYROID GLAND					
C-CELL ADENOMA					
	FD	0	1	1	0
	Total	0	1	1	0
BRAIN					
MALIGNANT EPENDYMOMA					
	S4	0	0	1	0
	Total	0	0	1	0
HARDERIAN GLAND					
CARCINOMA					
	S4	1	1	0	0
	Total	1	1	0	0
ADENOMA					
	S4	1	1	1	7
	AD	1	0	0	0
	FD	2	0	2	0
	Total	4	1	3	7
PERITONEUM					
FIBROSARCOMA					
	S4	1	0	0	0
	Total	1	0	0	0

Summary tables of tumour occurrence

APR 17 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-665 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 04-10-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-28-95	12-28-95	01-04-96

NAME & ADDRESS OF APPLICANT:

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

DRUG PRODUCT NAME:

Proprietary: not yet decided on
Nonproprietary/USAN: valsartan
Code Name/#: CGP 48933
Chem.Type/Ther.Class: 1S

Patent Status: US # 5,399,578 to Ciba-Geigy Corporation expires March 21, 2012

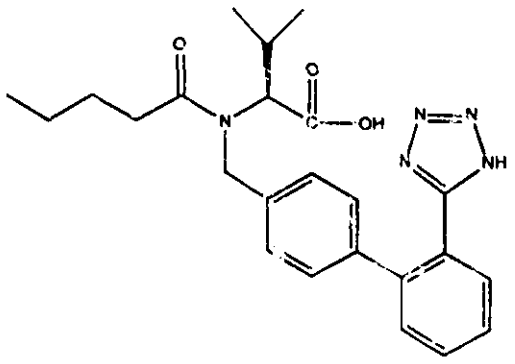
PHARMACOL.CATEGORY/INDICATION: hypertension

DOSAGE FORM: CHG
STRENGTHS: 80 mg and 160 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

STRUCTURAL FORMULA, CHEMICAL NAME: N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine; CAS Number - 13782-53-4

MOLECULAR FORMULA: $C_{24}H_{29}N_5O_3$

MOLECULAR WEIGHT: 435.5



SUPPORTING DOCUMENTS:

Letters of Authorization are provided for all Type III DMFs. A review of the DMFs through Excalibur and Comis indicates an absence of any significant concerns pertaining to the containers, closures and packaging materials for the valsartan capsules.
One Type IV DMF is referenced, DMF The relevant technical information is also provided in the NDA. Therefore a review is not necessary.

RELATED DOCUMENTS (if applicable):

CONSULTS:

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS: Approvable
Recommend that this application be marked approvable and the deficiencies noted in this review be conveyed to the applicant.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/C. Coughlin/12/5/94
HFD-110/CSO
HFD-810/CHoiberg

R/D Init by: RWolters/

File: 20-665 rev.1 last saved on 4/17/96 at 1:47 PM

4/17/96

Christopher S. Coughlin, Ph.D. 4-17-96

JUN 20 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #. 20-665 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 06-17-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENTS	04-09-96	04-12-96	04-19-96
	05-30-96	05-31-96	06-06-96
	05-31-96	06-04-96	06-07-96

NAME & ADDRESS OF APPLICANT:

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary: Diovan
Nonproprietary/USAN: valsartan
Code Name/#: CGP 48933
Chem.Type/Ther.Class: 1S

Patent Status: US # 5,399,578 to Ciba-Geigy Corporation expires March 21, 2012

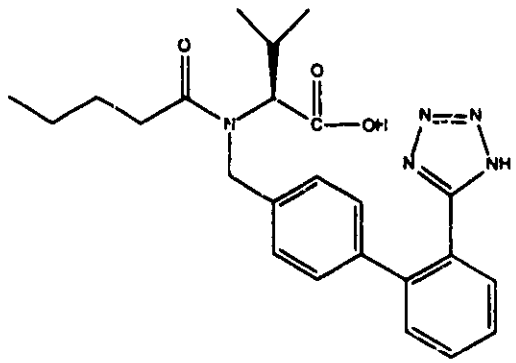
PHARMACOL.CATEGORY/INDICATION: hypertension

DOSAGE FORM: CHG
STRENGTHS: 80 mg and 160 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

STRUCTURAL FORMULA, CHEMICAL NAME: N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine; CAS Number - 13782-53-4

MOLECULAR FORMULA: $C_{24}H_{29}N_5O_3$

MOLECULAR WEIGHT: 435.5



SUPPORTING DOCUMENTS:

See listing of DMFs in Review 1.

RELATED DOCUMENTS (if applicable):
IND Ciba Geigy Valsartan

CONSULTS:
The Environmental Assessment review is being handled by the EA team.
A consult from the Labeling and Nomenclature regarding the proposed tradename has been sent and received back indicating that Diovan is an acceptable tradename.

REMARKS/COMMENTS:
The 04-09-96 amendment provides the proposed tradename of Diovan. A consult has been received back from the Labeling and Nomenclature committee indicating that this is acceptable.
The 05-30-96 amendment is a reply to a letter sent about the EA section. A copy has been provided to Nancy Sager.
The 05-31-96 amendment is a reply to our deficiency letter resulting form the first CMC review.

CONCLUSIONS & RECOMMENDATIONS: Approvable
Recommend that this application be marked approvable for CMC issues. Remaining issues include the submission of additional stability data to support expiration dating, EA review, Inspection results, and Methods Validation.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/C. Coughlin
HFD-110/CSO
HFD-810/CHoiberg

Christopher S. Coughlin, Ph.D. 6-20-96

R/D Init by: RWolters/

6/3/96

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-665 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 09-17-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENTS	07-31-96	08-05-96	08-08-96
	09-06-96	09-09-96	09-11-96

NAME & ADDRESS OF APPLICANT:

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary: Diovan
Nonproprietary/USAN: valsartan
Code Name/#: CGP 48933
Chem.Type/Ther.Class: 1S

Patent Status: US # 5,399,578 to Ciba-Geigy Corporation expires March 21, 2012

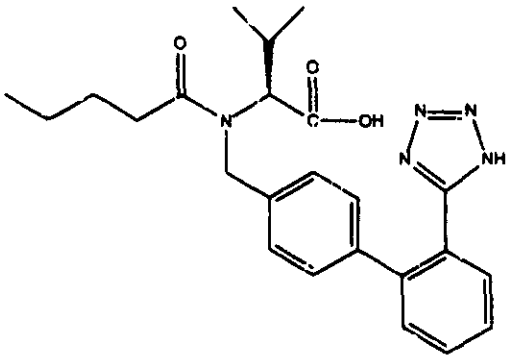
PHARMACOL.CATEGORY/INDICATION: hypertension

DOSAGE FORM: CHG
STRENGTHS: 80 mg and 160 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

STRUCTURAL FORMULA, CHEMICAL NAME: N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine; CAS Number - 13782-53-4

MOLECULAR FORMULA: $C_{24}H_{29}N_5O_3$

MOLECULAR WEIGHT: 435.5



SUPPORTING DOCUMENTS:

See listing of DMFs in Review 1.

RELATED DOCUMENTS (If applicable):
IND Ciba Geigy Valsartan

CONSULTS:
The Environmental Assessment review is being handled by the EA team.
A consult from the Labeling and Nomenclature regarding the proposed tradename has been sent and received back indicating that Diovan is an acceptable tradename.

REMARKS/COMMENTS:
The 07-31-96 amendment provides additional stability data as well as updates of the drug substance and product specifications(several impurity limits have been tightened.)
The 09-06-96 amendment provides results of photostability testing on the drug product.

CONCLUSIONS & RECOMMENDATIONS: Approvable
Recommend that this application be marked approvable for CMC issues with a 24 month expiry period. Remaining issues include the EA review, Inspection results, and Methods Validation.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/C. Coughlin
HFD-110/CSO

9-17-96
Christopher S. Coughlin, Ph.D.

R/D Init by: RWolters/

9/18/96

K Brannam
NOV 8 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-665 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 11-07-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENTS	10-22-96	10-23-96	10-25-96
	10-29-96	10-30-96	10-31-96
	10-30-96	10-31-96	11-6-96

NAME & ADDRESS OF APPLICANT:

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary: Diovan
Nonproprietary/USAN: valsartan
Code Name/#: CGP 48933
Chem.Type/Ther.Class: 1S

Patent Status: US # 5,399,578 to Ciba-Geigy Corporation expires March 21, 2012

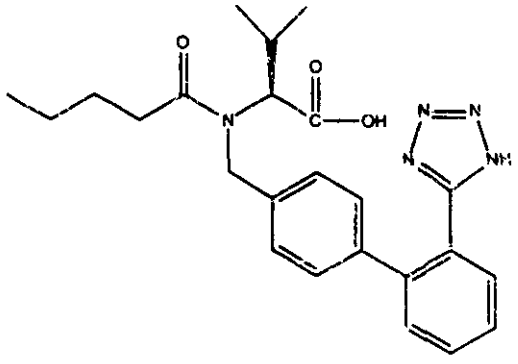
PHARMACOL.CATEGORY/INDICATION: hypertension

DOSAGE FORM: CHG
STRENGTHS: 80 mg and 160 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

STRUCTURAL FORMULA, CHEMICAL NAME: N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine; CAS Number - 13782-53-4

MOLECULAR FORMULA: $C_{24}H_{29}N_5O_3$

MOLECULAR WEIGHT: 435.5



SUPPORTING DOCUMENTS:

See listing of DMFs in Review 1.

RELATED DOCUMENTS (if applicable):
IND . Ciba Geigy Valsartan

CONSULTS:
The Environmental Assessment review is being handled by the EA team.
A consult from the Labeling and Nomenclature regarding the proposed tradename has been sent and received back indicating that Diovan is an acceptable tradename.
An Acceptable EER was received back in October, a copy of which is attached.

REMARKS/COMMENTS:
The 10-22-96 amendment provides a response to EA questions. A copy has been forwarded to the EA team which is handling the review.
The 10-29-96 amendment provides an additional piece of information for the EA review.
The 10-30-96 amendment concerns the dissolution specification. Ciba's original proposed dissolution spec was a Q= after 45 min. The biopharm reviewer requested a change to a Q= after 45 min. Ciba has come back with a proposal for a Q= after 30 min. They state that they have already reached an agreement with the Irish Health Authority on this spec and would like to have it standard worldwide. Additionally, they provide a reprint of an article in PharmEuropa Vol 8, No. 3, which suggests a Q value of for conventional release dosage forms. A look at their Development Pharmaceutics report in vol. 1.5 of the NDA provides dissolution profiles for the clinical and final formulations of the 80 mg and 160 mg capsules, as well as for the biobatch used in Protocol 47. There does not appear to be any difference in the dissolution values at 30 min versus those at 45 min. For the 80 mg capsules, the minimum value at 30 min is % versus at 45 min. For the 160 mg capsules, the minimum value at 30 min is versus at 45 min. From a strictly dissolution point of view, I do not see a problem with the new proposed spec, the product will probably be about equally dissolved at both time points. However, in consultation with Dr. Parekh, the current biopharm reviewer, we decided that the spec should remain at Q= in 45 min. Two main reasons are given. First, the original biopharm review stated that the spec should be set at Q= in 30 min, but this was revised to 45 min since all of the stability data were performed at 45 min. And second, the current FDA draft guideline on dissolution recommends a Q=. Given that meeting this spec of Q= in 45 min should not be a problem, I recommend that it remain.

CONCLUSIONS & RECOMMENDATIONS: Approvable
Recommend that this application be marked approvable for CMC issues with a 24 month expiry period. It is recommended that the dissolution specification should remain at Q= in 45 minutes. Remaining issues include the EA review, and Methods Validation.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/C Coughlin
HFD-110/CSO

11-7-96
Christopher S. Coughlin, Ph.D.

R/D Init by: RWolters

File: 20-665 rev.4 last saved on 11/7/96 at 11:34 AM

11/8/96

DEC 24 1996

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-665 **CHEM.REVIEW #:** 5 **REVIEW DATE:** 12-19-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENTS	11-14-96	11-18-96	11-19-96
	12-11-96	12-12-96	12-17-96

NAME & ADDRESS OF APPLICANT:

Ciba Pharmaceuticals Division
Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

DRUG PRODUCT NAME

Proprietary: Diovan
Nonproprietary/USAN: valsartan
Code Name/#: CGP 48933
Chem.Type/Ther.Class: 1S

Patent Status: US # 5,399,578 to Ciba-Geigy Corporation expires March 21, 2012

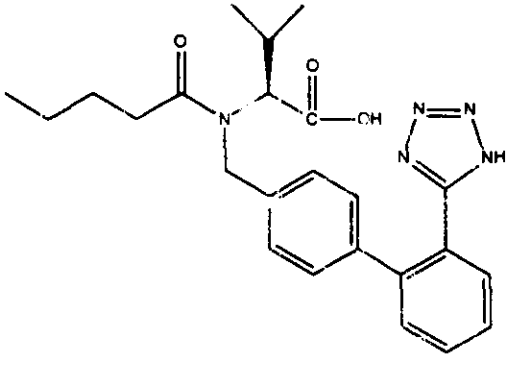
PHARMACOL.CATEGORY/INDICATION: hypertension

DOSAGE FORM: CHG
STRENGTHS: 80 mg and 160 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: Rx

STRUCTURAL FORMULA, CHEMICAL NAME: N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine; CAS Number - 137862-53-4

MOLECULAR FORMULA: $C_{24}H_{29}N_5O_3$

MOLECULAR WEIGHT: 435.5



SUPPORTING DOCUMENTS:

See listing of DMFs in Review 1.

RELATED DOCUMENTS (if applicable):
IND Ciba Geigy Valsartan

CONSULTS:
The Environmental Assessment review is being handled by the EA team which has issued a FONSI dated 12-3-96.
A consult from the Labeling and Nomenclature regarding the proposed tradename has been sent and received back indicating that Diovan is an acceptable tradename.
An Acceptable EER was received back in October.

REMARKS/COMMENTS:
The 11-14-96 amendment provides an amendment to the EA submission. Apparently, the EA submission inadvertently included Ciba's facility at Summit, New Jersey as a site for packaging of the finished dosage form. They do not intend to use this site for this purpose and have deleted it from the EA. These facts have already been noted by the EA reviewer and an amended FONSI has been issued.
The 12-11-96 amendment provides copies of the final printed labeling excluding the package insert. It is noted that they intend to only supply samples of valsartan 80 mg in bottles containing 3 capsules. The labeling is acceptable. All of the container labels indicated the manufacture is performed in Switzerland, as we asked, the graphics seem clear and no extra "advertising " text is included on the physician sample cartons.

CONCLUSIONS & RECOMMENDATIONS: Approvable
Recommend that this application be marked approvable for CMC issues with a 24 month expiry period. The only outstanding CMC issue the Methods Validation which should not holdup approval.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/C. Coughlin
HFD-110/CSO

Christopher S. Coughlin, Ph.D. 12-19-96

R/D Init by: RWolters/ 12/24/96

File: Coughlin HD:Documents:1996:NDA:20-665 rev.5

ENVIRONMENTAL ASSESSMENT

and

FINDING OF NO SIGNIFICANT IMPACT

for

Diovan™
(Valsartan)
Capsules
NDA 20-665

Ciba-Geigy Corporation

U. S. FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Cardio-Renal Drug Products
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-665

Diovan™

(Valsartan)

Capsule

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact of this action and has concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Diovan™, Ciba-Geigy Corporation prepared an environmental assessment (attached) in accordance with [21 CFR 25.31a(a)] which evaluates the potential environmental impact of the manufacture, use and disposal of the product. The maximum expected environmental concentration is at a level that normally relieves the applicant from completing format items 7, 8, 9, 10, 11, and 15 in accordance with the Tier 0 approach specified in the *Guidance for Industry for the submission of an Environmental Assessment in Human Drug Applications and Supplements*.

Valsartan is a chemically synthesized drug which is administered as a capsule in the treatment of hypertension. The drug substance will be manufactured by Ciba-Geigy, Werke Schweizerhalle, Switzerland, Ciba-Geigy Limited Werk Stein, Stein, Switzerland. The finished drug product will be manufactured at Ciba-Geigy Limited Werk Stein, Stein, Switzerland and used in hospitals, clinics and by patients in their homes.

Valsartan may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Drug substance and product that fail specification, pass expiration period, or are returned from the field are destroyed

by high temperature incineration by approved and regulated facilities. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

12/3/96
Date

PREPARED BY
Carl J. Berninger, Ph.D.
Environmental Scientist
Environmental Assessment Team
Center for Drug Evaluation and Research

12/3/96
Date

CONCURRED
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

Attachments: Environmental Assessment (FOI copy)
Material Safety Data Sheet (drug substance)

Ciba-Geigy Limited
Basle, Switzerland

ciba

Environmental Assessment Information

21 CFR 25.31a(a)

Diovan (valsartan) capsules, 80 mg and 160 mg

Table of Contents

List of Non-confidential Appendices

Appendix	
Appendix I	Description and map of environmental settings of Ciba facility - Suffern, New York (Section 4.3.3.)
Appendix II	*Deleted - information no longer applicable*
Appendix III	Environmental protection certificate (Section 6.4.)
Appendix IV	Statement of compliance (Section 6.4.)
Appendix V	Material Safety Data Sheet (Section 6.5.)
Appendix VI	Curriculum Vitae for preparers (Section 12.)

List of Confidential Appendices

Appendix	
Appendix 1	Valsartan Capsule NDA Application Technical Summary: Part D. *Chemistry, Manufacturing and Controls Summary*
Appendix 2	Description of environmental settings: Ciba overseas facility (Section 4.3.1.)
Appendix 3	Description of environmental settings: Ciba overseas facility (Section 4.3.2.)
Appendix 4	Identification of contract manufacturer of product intermediate and Self-certification of compliance (Section 4.3.1.)
Appendix 5	Description of environmental settings of contract packaging facilities (Section 4.3.3.)
Appendix 6	Description of environmental settings of waste disposal facilities (Section 4.5.)
Appendix 7	Ciba monograph: Valsartan (Section 5.3.)
Appendix 8	Fifth year production forecast for Valsartan capsules, 80 mg and 160 mg (Section 6.6.)
Appendix 9	Calculation of the Expected Introduction Concentration (EIC) for Valsartan entering the aquatic environment from patient use (Section 6.6.)

Executive summary

The National Environmental Policy Act (NEPA) requires federal agencies to prepare environmental impact statements (EIS) detailing the environmental impact of, and alternatives to, proposals for major federal actions that significantly affect the quality of the human environment. Pursuant to these statutory requirements, procedures for implementation have been issued by the Council on Environmental Quality (CEQ) in 40 CFR Parts 1500-1508.

The Food and Drug Administration (FDA), as a federal agency, has accordingly issued supplemental regulations to implement these requirements in 21 CFR 25.1-50. Section 25.20 states that all actions by the FDA are subject to environmental consideration and must be individually examined for environmental impact unless excluded as a class by categorical exclusion under Section 25.24. This document has been prepared according to the format outlined in 21 CFR 25.31a(a), "Environmental assessment for proposed approvals of FDA-regulated products - Format 1".

Ciba Pharmaceuticals Division has filed an NDA for Diovan (valsartan) capsules. Diovan capsules contain the drug substance Valsartan, an effective antihypertensive agent which produces clinically significant reductions in blood pressure that persist over 24 hours when administered once daily. It is effective regardless of age, gender or racial origin.

An environmental assessment has been prepared for Diovan capsules, following the format specified. Approval of the NDA for Diovan capsules will have no impact upon compliance with current emission requirements at any of the overseas manufacturing facilities or the packaging facilities within the United States. It was also concluded from the information provided in this assessment that the maximum anticipated levels of Valsartan in the environment occurring as a result of this indication would be less than 1 part per billion, and thus qualifies for a Tier 0 approach. Accordingly, format items 7, 8, 9, 10, 11 and 15 have not been included.

Because of the therapeutic benefits associated with the availability and use of Valsartan capsules, it is the conclusion of Ciba Pharmaceuticals Division that approval is preferable to non-approval, and requests that the FDA issue a **"Finding of No Significant Impact"** for Valsartan NDA.

Environmental Assessment Information

An environmental assessment has been prepared in accordance with the requirements stated in 21 CFR Part 25.31a(a) for Diovan capsules.

1. Date

November 12, 1996 (corrected)

2. Name of applicant

Ciba-Geigy Corporation
Pharmaceuticals Division

3. Address

556 Morris Avenue
Summit, New Jersey 07901 - 1398

4. Description of the proposed action

4.1. Requested approval

Ciba Pharmaceuticals Division has filed a New Drug Application (NDA) for Diovan (valsartan) capsules. Valsartan (CGP 48933) is a member of a new class of antihypertensive agents which inhibit the renin-angiotensin system by direct blockade of angiotensin II receptors. By contrast, ACE inhibitors block the action of angiotensin I converting enzyme (ACE) and prevent the formation of angiotensin II. However, ACE is also responsible for the degradation of bradykinin, and a blockade of this activity may lead to increased levels of kinin in plasma and tissues. This effect has been implicated in the pathogenesis of both the cough and angioneurotic edema that are side effects of ACE inhibitor therapy. Direct blockade of angiotensin II receptors is considered to be a more specific mechanism of inhibiting the renin-angiotensin system without producing these side effects. Valsartan acts as a potent, selective and competitive antagonist of angiotensin II at the AT_1 receptor subtype. Valsartan is orally active, has a very good safety and tolerability profile, and is effective regardless of age, gender or racial origin. In general, dosage adjustment is not necessary in the elderly or in renally or hepatically impaired patients. Clinical studies have demonstrated that patients on Valsartan

have statistically less cough than patients treated with ACE-inhibitors. Diovan is available as capsules for oral administration, containing either 80 mg or 160 mg of Valsartan.

For further information regarding the subject of this assessment, please refer to the *Chemistry, Manufacturing and Controls Summary* provided for your convenience in Confidential Appendix 1 of this document. This section is identical to documentation found in the overall summary of NDA.

4.2. Need for action

Approval of this NDA will result in the distribution of Diovan capsules throughout the United States. Approval will offer patients safe and effective therapy in the treatment of hypertension. Because of the therapeutic benefits associated with the availability and use of Valsartan to this patient population, approval is justified and preferable to non-approval.

4.3. Sites of production and environmental settings

4.3.1. Manufacture of bulk drug substance

As noted in the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1) of this NDA, the bulk drug substance Valsartan is manufactured by:

CIBA-GEIGY, Ltd.
Ciba Pharmaceuticals Division
CH-4002 Basel, Switzerland

Specifically, Valsartan drug substance will be chemically manufactured at the following site in Basel, Switzerland:

CIBA-GEIGY
Werke Schweizerhalle
CH-4133 Schweizerhalle
Switzerland

A description of the environmental setting for this facility is provided in Confidential Appendix 2.

Additionally, Valsartan drug substance can be milled at the following site in Basel, Switzerland:

Ciba-Geigy Limited Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

A description of the environmental setting for this facility is provided in Confidential Appendix 3.

For technical reasons, one of the intermediate products is manufactured by a contract manufacturer. This information is classified as confidential business information, and therefore, the identification of this facility is provided in Confidential Appendix 4.

4.3.2. Manufacture of finished dosage form

As noted in the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1) of this NDA, finished dosage form manufacture occurs at the following facility:

Ciba-Geigy Limited Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

As previously mentioned, a description of the environmental setting for this manufacturing facility is provided in Confidential Appendix 3.

4.3.3. Packaging of finished dosage form

Drug product packaging will occur either at the following Ciba facility:

Ciba-Geigy Corporation
Pharmaceuticals Division
25 Old Mill Road
Suffern, New York 10901 - 7914

or at the following contract facilities:

Corning National Packaging, Inc. - DMF #7955
6575 Snowdrift Road
Allentown, PA 18106-9528

Packaging Coordinators, Inc. - DMF #11520
3001 Red Lion Road
Philadelphia, PA 19124

PACO Pharmaceutical Services - DMF #3347
1200 Paco Way
Lakewood, NJ 08701

Sharp Corporation - DMF #397
Ridge Pike and Carland Road
Conshohocken, PA 19428

An environmental setting description and map for the Ciba facility at Suffern, NY are provided in Non-confidential Appendix I. Descriptions of the environmental settings for the contract packaging facilities are provided in Confidential Appendix 5.

4.4. Sites of product use and environmental settings

Diovan capsules will be marketed throughout the United States as a solid oral dosage form administered once daily for the reduction of blood pressure. Diovan capsules will be available to patients through prescription only.

4.5. Sites of product disposal and environmental settings

Ciba publishes, on a quarterly basis, a report entitled *"Hazardous & Chemical Waste Disposal Sites"*. All hazardous waste disposal facilities listed in this report are recommended for approval by Ciba-Geigy Corporation only after Ciba personnel complete and submit an inspection and audit report. A list of non-hazardous disposal facilities is also provided, and it is the Corporation's recommendation that these facilities also be audited once every two years. The Pharmaceuticals Division makes a practice of auditing all non-hazardous waste disposal facilities. Ciba Pharmaceuticals Division notifies its contract packaging facilities as to which disposal facilities are currently approved by Ciba.

All waste generated by the packaging of Diovan capsules, as well as all returned or rejected production material, is classified as non hazardous waste. Solid process residuals (returned or rejected production material, laboratory waste) will be shipped from Ciba for off-site incineration at permitted incineration facilities. The sites and descriptions of the environmental settings of the incineration facilities currently used by Ciba are provided in Confidential Appendix 6.

5. Identification of chemical substances that are the subject of the proposed action

5.1. Drug product

Trade name: Diovan capsule

5.2. Drug substance

Common name: Valsartan

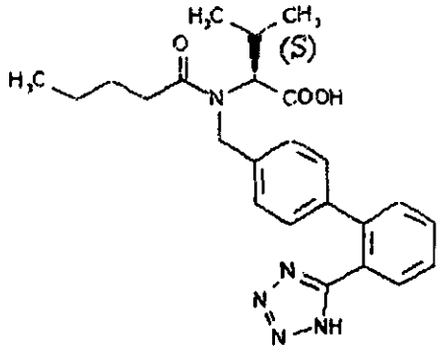
Chemical name: (S)-N-valeryl-N-{[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl}-valine

CAS number: 137682-53-4

Molecular formula: $C_{24}H_{29}N_5O_3$

Molecular weight: 435.5

Structural formula:



Description:

Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and basic aqueous solutions. It is slightly soluble in water and sparingly soluble in aqueous solutions with pH less than seven.

For further information on the physical and chemical properties of the drug substance Valsartan, please refer to the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1) of this NDA.

5.3. Impurities

Manufacture of the drug substance, Valsartan, is controlled so that the total amount of the D-enantiomer of Valsartan does not exceed 2.0% and the total amount of other related substances does not exceed 0.8%. Please refer to *Ciba monograph: Valsartan (CGP 48933)* (Confidential Appendix 7) for information on the identification and concentration of the impurities which may be present in the drug substance Valsartan.

6. Introduction of substances into the environment

6.1. Sites of production

6.1.1. Manufacture of bulk drug substance

Valsartan drug substance will be chemically manufactured at the following facilities:

CIBA-GEIGY
Werke Schweizerhalle
CH-4133 Schweizerhalle
Switzerland

Additionally, Valsartan drug substance can be milled at the following site in Basel, Switzerland:

Ciba-Geigy Limited Werk Stein
Schaffhauserstrasse
CH-4332 Stein
Switzerland

For technical reasons, one of the intermediate products is manufactured by a contract manufacturer. The identity of this contract manufacturer is considered classified confidential business information.

6.1.2. Manufacture of finished dosage form

The finished dosage form, Diovan 80 mg and 160 mg capsules, will be manufactured at the following facility:

Ciba-Geigy Limited Werk Stein
Schaffhauserstrasse
CH-4332 Stein, Switzerland

Information on the manufacture of Diovan capsules, its composition, and a schematic of the capsule manufacturing procedure are contained in Attachments IV and V of the *Chemistry, Manufacturing and Controls Summary* (Confidential Appendix 1).

6.1.3. Packaging of finished dosage form

Packaging operations will take place at Ciba's facility in Suffern, NY or at the following contract packaging facilities:

Corning National Packaging, Inc. - DMF #7955
6575 Snowdrift Road
Allentown, PA 18106-9528

Packaging Coordinators, Inc. - DMF #11520
3001 Red Lion Road
Philadelphia, PA 19124

PACO Pharmaceutical Services - DMF #3347
1200 Paco Way
Lakewood, NJ 08701

Sharp Corporation - DMF #397
Ridge Pike and Carland Road
Conshohocken, PA 19428

6.2. Substances expected to be emitted and controls exercised

6.2.1. Air emissions and controls

Ciba - Suffern, New York

The only air emissions associated with the packaging of Diovan (valsartan) capsules are particulates and fugitive volatile organic compounds (VOCs). The total amount of particulate emissions generated during the packaging of Diovan capsules will be trace (0.55 lbs/year) having been controlled by dust collectors with a 99.9% capture efficiency for incoming particulates. (This amount is based upon a number of worst-case assumptions, including the assumption that *all* batches of Diovan capsules for the peak production year will be packaged at the Suffern facility. Currently, the Suffern facility is permitted to emit up to 9 lbs of particulates annually.)

Insignificant quantities of fugitive VOCs are generated during the cleaning of the packaging lines with isopropyl alcohol. Since the site's total annual permitted VOC emission (23 tons) is below the New York State significant source threshold, Suffern is classified as a minor source (not a Title V facility) and therefore, no applicable control device is required. With average annual VOC emissions of approximately 8 tons, Suffern will continue to be in compliance with EPA and NYSDEC regulations, even with the additional 0.12 tons of VOC emissions associated with the cleaning of the packaging equipment for Diovan capsules.

The emissions of particulates and VOCs for the packaging of Diovan capsules during the forecasted peak production year (see section 6.6. and Confidential Appendix 8) will be in compliance with the Suffern facility's permitted emission levels.

6.2.2. Waste water discharges and controls

Ciba - Suffern, New York

Process and domestic waste water is conveyed from the facility via a gravity sewerage system to an on-site sewerage pumping station. This flow is then directed to the Village of Suffern publicly-owned treatment works (POTW). The Village system is designed to process 1.8 million gallons per day (MGD). The average flow from the facility is approximately 118,000 gallons per day (GPD). The POTW regulates the Suffern facility for its discharge through a state-authorized pre treatment permit program. This program regulates the facility for flow,

pH, biochemical oxygen demand (BOD), total suspended solids (TSS), oil, grease, metals, toluene and methylene chloride. Reporting is submitted on a semi-annual basis.

6.2.3. Solid waste and controls

Ciba - Suffern, New York

All rejected production material from the packaging of Diovan capsules is sent off-site for incineration at facilities which must operate in conformance with permits issued under the authority of the applicable Federal, state and local regulations. All facilities utilized for the disposal of solid process residuals are inspected by Ciba personnel on an annual basis to ensure conformance with Federal and state regulations. All packaging components which can be recycled will be sold.

Returned goods

Products returned to Ciba Pharmaceuticals Division by the customer are evaluated by the Quality Control Department. Those materials which must be discarded are tested and evaluated so as to properly classify them. Those that must be managed in accordance with applicable Federal, state and local regulations are appropriately managed and shipped off-site to disposal facilities as described in section 4.5. [Sites of product disposal and environmental settings]. Incineration is the method of choice for destruction of wastes.

Contract packaging facilities

Contract packaging facilities are required to dispose of any non hazardous solid waste (i.e., product packaging materials) generated at facilities approved by Ciba, and that the method of destruction be incineration.

Incineration facilities

Only incineration facilities approved by Ciba are used for the disposal of returned or rejected products as well as wastes generated during product packaging. The incineration of returned and rejected materials generates residual solids which are disposed of by the individual disposal sites in accordance with their operating permits in permitted landfills. Expected air emission from pollution control equipment associated with the incineration of packaging wastes are water vapor, carbon monoxide, carbon dioxide and small quantities of nitrous oxides. The incineration of discarded packaging materials will also generate waste water. This water is treated by the incineration facility before discharge in accordance with the operating permits issued by the state in which the facility is located. Whenever possible, discarded packaging components are sold to a reclaimer/recycler.

6.3. Citation of compliance with applicable emission requirements

6.3.1. Citations for waste water

Ciba - Suffern, New York

Aqueous emissions must be in compliance with the Clean Water Act. New York is authorized by the Federal government to regulate these emissions under *6 NYCRR*. The Suffern facility discharges waste water to the Village of Suffern POTW under a permit issued by the Village of Suffern. The POTW, in turn, operates under a State Pollutant Discharge Elimination System (SPDES) permit issued by the State of New York under Title NYCRR.

6.3.2. Citations for solid waste

Ciba - Suffern, New York

All solid wastes must be disposed of in accordance with the applicable regulations included in NYCRR. Since all solid wastes are sent off-site for disposal, this requires the use of licensed transporters and permitted disposal facilities.

Contract packaging facilities

Contract packaging facilities must conform to all applicable Federal, state and local regulations, and must manage waste materials according to Ciba standards. All solid wastes generated by the contract packaging facilities listed in Section 4.3.3. are sent only to those incineration facilities approved by Ciba. Non hazardous solid waste may be returned by the contract packager to the Ciba Summit facility for disposal, or directly routed to one of the disposal facilities as described in Section 4.5. All disposal facilities on Ciba's approved list utilize incineration as the method of treatment.

6.4. Certification of compliance

An environmental protection certificate was obtained from the Canton of Basel-Landschaft for the production of Valsartan active substance. A copy of this certificate is provided in Non-confidential Appendix III.

An environmental protection certificate was obtained from the Canton of Aargau for the manufacture of Valsartan capsules. A copy of this certificate is provided in Non-confidential Appendix III.

A statement of compliance regarding environmental permits required by the contract manufacturer of one of the intermediate products for Valsartan active substance is provided in Confidential Appendix 4, as this information has been classified as confidential business information.

A statement of compliance by Ciba regarding environmental permits required for the packaging of Diovan (valsartan) capsules at the Suffern, New York facility is provided in Non-confidential Appendix IV.

6.5. Compliance with OSHA Hazard Communication Standard

In accordance with the requirements of the Occupation Health and Safety Administration (OSHA) Hazard Communication Standard, 29 CFR 1910.1200, Ciba Pharmaceuticals Division has established a Hazard Communication/Right-to-Know program at the Suffern, New York site which covers all employees. Under this program, all chemicals are first evaluated to determine whether they meet the OSHA criteria for hazardous chemicals. All containers are then labeled with the chemical name, CAS number, and information regarding the nature of hazards associated with that substance. Material Safety Data Sheets (MSDSs) are available for all chemicals handled at the plant, with MSDSs prepared internally for those materials used in the production of finished dosage forms. These are available in each area where the substance is used, as well as in a central location. The program also provides the required employee training, which includes hazard recognition, interpretation of information on MSDSs and labels, the safe handling of selected classes of hazardous materials, and proper use of personal protective equipment.

To demonstrate compliance with the Federal and state occupational health requirements, an MSDS for Valsartan drug substance is included in Non-confidential Appendix V.

6.6. Quantities and concentrations expected to enter the environment

The concentration of Valsartan expected to be released into the environment as a result of prescription of the drug product Diovan capsules for the treatment of hypertension was determined based upon market research. The marketing forecast for Valsartan capsules during the peak year is provided in Confidential Appendix 8.

Based upon a forecasted peak year maximum sales (and therefore, production), the Expected Introduction Concentration (EIC) for the drug substance Valsartan has been calculated. The EIC value, the supporting calculations and the assumptions made for this calculation are provided in Confidential Appendix 9.

It was concluded from the information provided in this Appendix that the maximum anticipated levels of Valsartan in the environment occurring as a result of this indication would be less than 1 part per billion. Since this qualifies for a Tier 0 approach, format items 7, 8, 9, 10, 11 and 15 have not been included.

12. List of preparers

A curriculum vitae, documenting the qualifications and credentials for each of the contributors to this environmental assessment, is provided in Non-confidential Appendix VI.

13. Certification

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for preparation of the environmental assessment.

11/12/96

Joseph A. LoMenzo, Ph.D. Date
Executive Director, Health, Safety & Environment

14. References

1. Center for Drug Evaluation and Research (CDER), November 1995. *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements.*

Appendices

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Environmental Assessment Information

Appendix I

Appendix I

Description and map of environmental settings of Ciba facility: Suffern, NY
(Section 4.3.3.)

Ciba-Geigy Corporation
Pharmaceuticals Division
25 Old Mill Road
Suffern, New York 10901-7914

This Ciba pharmaceutical manufacturing facility is located in the Villages of Suffern and Montebello, Rockland County, New York (combined population 14,950) on 162 acres, approximately 30 miles northwest of New York City. The manufacturing facility, which resides within the boundaries of the Village of Suffern, consists of two main buildings, a new docking facility, an automated warehouse structure and several auxiliary buildings with a combined total floor space of approximately 454,000 square feet. The site is bounded by the New York State Thruway on the north, Hemion Road on the east, the Conrail Piermont Line on the south and the Plaza Material Corp. quarry on the west. Wooded ridges on its east and west sides border a flat valley where the facility, parking area and landscaped area lie. The site employs an average workforce of approximately 550 people. The surrounding neighborhood includes retail businesses, light industry and private residences. The topography of the region is varied. The climate is temperate, with an average annual rainfall of 43.5 inches. A map of the facility follows.

Terrain - The developed portion of the site, approximately 33 acres, is generally flat, with an average elevation of approximately 320 feet above sea level. The nature of the soil is characterized as glacial deposits, consisting of sand, gravel and a till mixture of sand, gravel, boulders and clay, with sandstone and shale bedrock.

Water Resources - The Suffern facility is located in a drainage basin with a total of 295 acres. During storm events, stormwater runoff from this basin is channeled naturally through the Ciba's property, eventually discharging through a culvert under Route 287, to Lake Antrim, which eventually feeds into the Mahwah River. Stormwater runoff from the facility is directed to this system through a standard gravity-flow conduit system designed specifically for stormwater runoff conveyance. Four (4) distinct wetland areas have been delineated at the site, totaling 18.6 acres. None of these areas fall under the NY State Department of Environmental Conservation (NYSDEC) regulations governing wetlands protection (12.4 acres or greater). However, three of these four wetlands areas do fall under both Federal Clean Water Act (CWA) regulations and the US Army Corps of Engineer Environmental Protection Regulations.

Process and domestic wastewater are conveyed from the facility via a gravity sewerage system to an on-site sewerage pumping station. This flow is then directed to the Village of Suffern publicly owned treatment works (POTW) at an average flowrate of 118,000 gallons per day (GPD). This POTW is designed to process 1.8 million gallons per day (MGD). The POTW regulates the Suffern facility for its discharge through a Federally-authorized pretreatment permit program. This program regulates the facility for flow, pH, biochemical oxygen demand (BOD), total suspended solids (TSS), oil, grease, metals toluene and methylene chloride. Reporting is submitted on a semi-annual basis. All domestic and fire protection water is purchased from the Village of Suffern, which operates a well field, and is interconnected with the Spring Valley Water Company for supplemental purposes.

Air Quality - Suffern is part of the air quality geographical area regulated under the New York -New Jersey - Connecticut Interstate Air Quality Control Region of the Environmental Protection Agency (EPA). Locally, Suffern air quality is regulated by both the NYSDEC and the Rockland County Department of Health. Enforcement issues are handled jointly.

Regional air quality designations are given in Part 81 of the 40 Code of Federal Regulations (CFR). Suffern is currently in compliance with the National Ambient Air Quality Standards (NAAQS) for particulate matter, nitrogen dioxide, sulfur oxides and carbon monoxide. However, Suffern, along with the entire State of New York, is in non-compliance with the NAAQS for ozone.

Emissions of regulated substances into the air are reported to Federal, state and local authorities under Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA). SARA Title III requires affected facilities to track and submit emission inventories annually. Ciba-Geigy Corporation has been meeting the requirements of SARA Title III since the inception of the program in 1987 and will continue to comply. New York is required to submit to the EPA a State Implementation Plan (SIP) detailing how New York meets all Federal air quality requirements. Ciba fully complies with the SIP outlined by New York. The Clean Air Act Amendments of 1990 promulgated many new air regulations. New York is currently revising their SIP to reflect these new regulations. Ciba intends to fully comply with the new SIP.

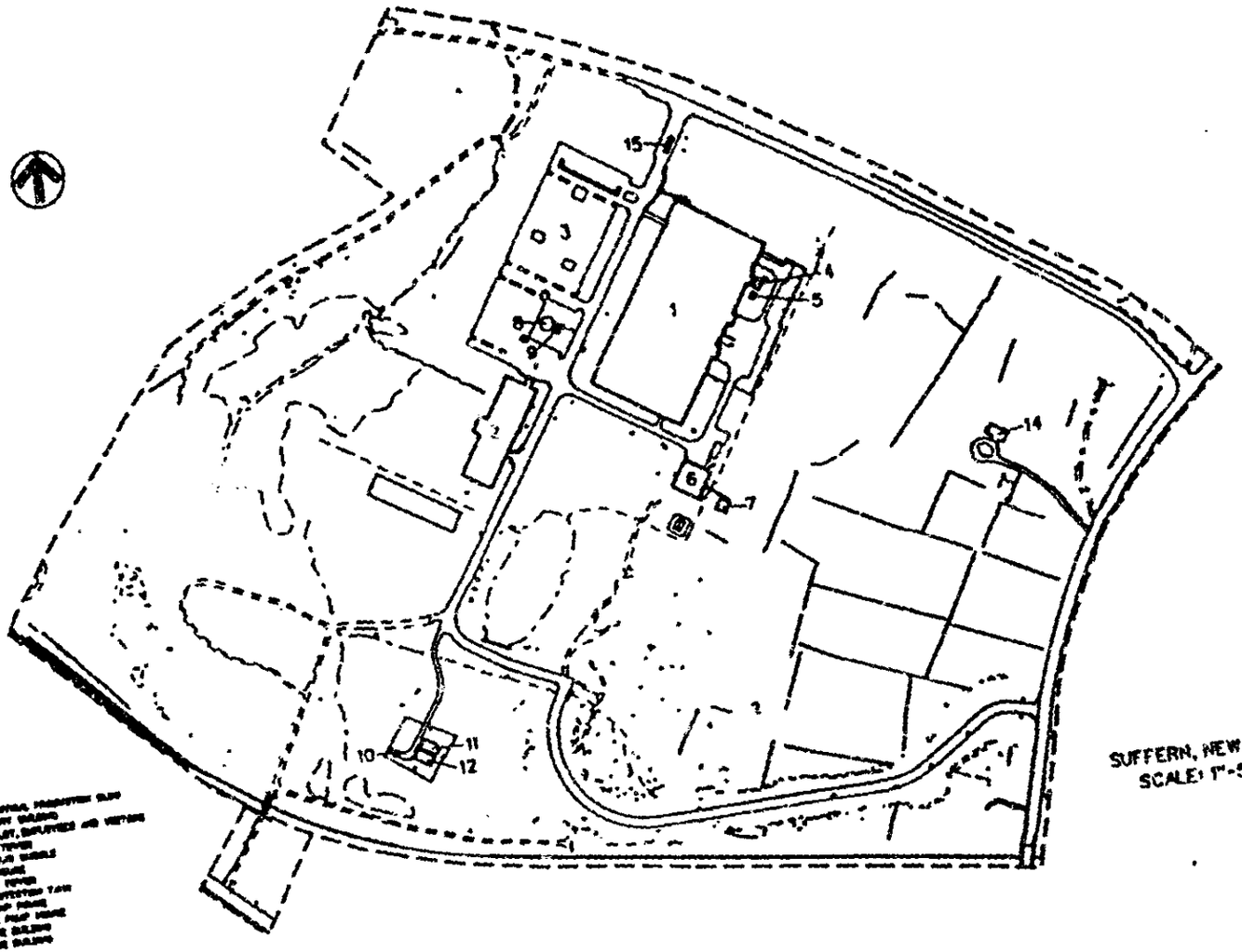
In the State of New York, air emissions are regulated under Title 6 of the New York State Codes, Rules and Regulation (NYCRR). As required by these regulations, Ciba maintains an active air permit program. All permits have been, and will continue to be, renewed and updated as process/facility changes occur. New permits will be obtained as required. Where appropriate, Ciba has installed state-of-the-art pollution controls to minimize air emissions. In

addition, stack tests have been, and will continue to be, performed for all relevant emission points to ensure compliance.

In the County of Rockland, air emissions are regulated under Article XII of the Sanitary Code of the County of Rockland. As required by County regulations, Ciba maintains an active air permit program. All permits have been, and will continue to be, renewed and updated as changes occur.

Map

Suffern, New York



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Environmental Assessment Information

Appendix II

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Environmental Assessment Information

Appendix III

4410 Liestal, Rheinstrasse 29
Telefon 061 925 51 11
Telefax 061 925 69 48

Bau- und Umweltschutzdirektion
Kanton Basel-Landschaft

Liestal

Liestal, den 18. Dezember 1995

Umweltschutzbescheinigung

(Gültig bis 31. Dezember 1997)

Environmental protection certification

(Valid until 1997-12-31)

Die Bau- und Umweltschutzdirektion bestätigt, dass die Firma

CIBA-GEIGY
WERKE SCHWEIZERHALLE AG
POSTFACH 1130, CH-4133 PRATTELN

über sämtliche Bewilligungen verfügt, die aufgrund der eidgenössischen und kantonalen Umweltschutzgesetzgebung für ihren Betrieb zur Herstellung von Valsartan nötig sind. Im weiteren kann bestätigt werden, dass bei regelmässigen Kontrollen, welche die kantonalen Behörden im Betrieb 2060 durchführen, bis jetzt keine nennenswerten Verstösse gegen die Umweltschutzgesetzgebung festgestellt worden sind.

The department for construction and environmental protection confirms that the company

CIBA-GEIGY
WERKE SCHWEIZERHALLE AG
POSTFACH 1130, CH-4133 PRATTELN

has all the permits required by both federal and cantonal swiss environmental protection laws and regulations to operate a plant for the production of Valsartan. This document furthermore confirms that regular inspections of the 2060 plant by local authorities up to now have never shown any noteworthy infringements against environmental protection regulations.

Die Bau- und Umweltschutzdirektion ist im Kanton Basel-Landschaft für den Vollzug aller relevanten Gesetze und Verordnungen des eidgenössischen und kantonalen Umweltrechts zuständig.

The department for construction and environmental protection is the authority that is competent on the territory of the canton of Basel-Land to enforce the relevant federal and cantonal laws and regulations on the protection of the environment.

Die Vorsteherin der Bau- und Umweltschutzdirektion
The Minister for Construction and Environmental Protection

Elsbeth Schneider-Kenel

BAUDEPARTEMENT DES KANTONS AARGAU
Abteilung Umweltschutz

Entfelderstrasse 16
Telefon 064 21 27 28 neu ab 4.11.96: 062 835 34 31
Telefax 064 21 17 90 neu ab 4.11.96: 062 835 34 39
Marcel Schmid

5001 Aarau, 17. Oktober 1995
Switzerland

Federal Drug
Administration

U.S. A.

ENVIRONMENTAL PROTECTION CERTIFICATE

1. The company CIBA-GEIGY ltd. operates facilities for pharmaceutical manufactering at the following address

   CIBA-GEIGY ltd. Werk Stein
   Schaffhauserstrasse
   CH-4232 Stein, Switzerland

2. These production facilities may only operate in accordance with permits issued by the responsible authorities. In the permits are laid down the purpose for which buildings and plants may be used and the legal conditions with which the company must comply.

3. The above described permits cover the preparation of pharmaceutical products containing active substance of

   VALSARTAN (80 & 100mg)

4. All buildings and plants of the company CIBA-GEIGY ltd. Werk Stein must comply with the federal and cantonal laws and regulations concerning safety, protection of the environment and working conditions. Compliance is enforced by the cantonal authorities.

5. The relevant departments of the cantonal authorities perform periodic inspections.

6. On the basis of the inspections performed it can be confirmed that there exists no indication of violation of the applicable laws and regulations.

BAUDEPARTEMENT
Chef Abteilung Umweltschutz

i. V. Hazel Klimke

Dr. Jürg W. Tschopp

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Environmental Assessment Information

Appendix IV

Pharmaceuticals Division

Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901-1398
Telephone 908 277 5000

Statement of Compliance

Ciba states that it is compliance with, or on a schedule to be in compliance with, all requirements set forth in all applicable Federal, state and local statutes and regulations, as well as permits, consent decrees and administrative orders applicable to the packaging of Diovan® (valsartan) capsules at our Pharmaceutical production facility in Suffern, New York.

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CGP 48 933 - Valsartan

Environmental Assessment Information

Appendix V

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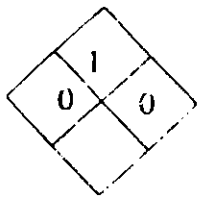

MATERIAL SAFETY DATA SHEET

CIBA-GEIGY CORPORATION
PHARMACEUTICALS DIVISION
556 Morris Avenue
Summit, NJ 07901-1398

24 Hour Emergency Telephone Numbers:
Chemical Emergency Response Center: 1-800-888-8372
Medical Emergency: 1-908-277-5000

For Non-Emergency Situation/Technical Information: 1-908-277-5397 (9:00 AM - 5:00 PM E.S.T.)

SECTION 1. PRODUCT IDENTIFICATION

PRODUCT NAME:	**Valsartan**
Ciba ID No.:	145765.4
CLASSIFICATION:	Class I Compound
SYNONYMS:	Diovan™ Active Ingredient, CGP 48933
THERAPEUTIC CATEGORY:	Antihypertensive agent (angiotensin II inhibitor)
GENERIC NAME:	None
CHEMICAL NAME:	(S)-N-valeryl-N-{[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl}-valine
CHEMICAL FORMULA:	$C_{24}H_{29}N_5O_3$
MOLECULAR WEIGHT:	435.5

SECTION 2. COMPOSITION/INFORMATION ON INGREDIENTS

COMPOSITION	CAS #	CONCENTRATION (% BY WT.)
Valsartan	137862-53-4	> 99%

SECTION 3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW

****

PRACTICALLY NON-TOXIC/ORAL
MAY DECREASE BLOOD PRESSURE
MAY BE HARMFUL BY INHALATION
AVOID CONTACT WITH EYES AND SKIN
AVOID BREATHING DUST

****

PRIMARY ROUTE(S) OF ENTRY: Inhalation

EFFECTS OF OVEREXPOSURE:

Skin: Not known. Studies have not been performed to assess skin irritation potential.

Eye: Not known. Studies have not been performed to assess eye irritation. Systemic effects from absorption is possible.

Inhalation: Not known. Studies have not been performed to assess acute inhalation toxicity. Systemic effects from absorption is possible.

Ingestion: Although this material has been found to be well-tolerated in animals after oral administration, its pharmacological mode of action suggests that it might possibly induce a variety of undesired effects.

TARGET ORGAN EFFECTS: Not known.

REPRODUCTIVE HAZARDS: There are no reported adverse effects on reproductive function or fetal development.

CARCINOGENICITY: Studies have not been performed to assess carcinogenic potential.

ACGIH:	Not listed
EPA:	Not listed
IARC:	Not listed
MAK:	Not listed
NIOSH:	Not listed
NTP:	Not listed
OSHA:	Not listed

MUTAGENICITY: Devoid of mutagenic potential in four test systems (see Section 11).

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: None known.

SECTION 4. EMERGENCY AND FIRST AID MEASURES

Skin Contact: Wash contaminated area with soap and water.

Eye Contact: Flush with running water for 15 minutes holding eyelids open.

Inhalation: Remove to fresh air. Restore and/or support breathing as needed.

Ingestion: Get medical attention immediately.

SECTION 5. FIRE FIGHTING MEASURES

Flash Point: Not applicable **Method Used:** Not applicable

Flammable Limits (% in air)
Lower: Not applicable Upper: Not applicable

Autoignition Temperature: Not applicable

Extinguishing Media: Use media suitable for fire in surrounding area.

Special Fire Fighting Procedures and Precautions: Evacuate area and fight fire from safe distance.

Fire and Explosion Hazards: Contaminated water from fire hoses or sprinklers must be prevented from draining into waterways, sewers, or the ground water. Appropriate measures must be taken for containment. Combustion can lead to the formation of poisonous and irritant decomposition products..

Fire-Fighting Equipment: Wear full protective clothing and a pressure-demand self-contained breathing apparatus.

Decomposition Products: Carbon and nitrogen oxides, as well as other poisonous or irritant gases and vapors can be formed following thermal decomposition or combustion.

NFPA Ratings: Health = 0 Flammability = 1 Reactivity = 0 Special Hazard = None
Hazard Rating Scales: 0 = Minimal 1 = Slight 2 = Moderate 3 = Serious 4 = Severe U = Unknown

SECTION 6. ACCIDENTAL RELEASE MEASURES

Steps to be taken if Material is Released or Spilled: Using appropriate protective equipment, sweep up and containerize spilled material. Avoid contamination of soils, sewage systems and waterways.

SECTION 7. HANDLING AND STORAGE

Storage Temperature (Min./Max.): Store material between 2°C and 30°C.

Shelf Life: Not known.

Special Sensitivity: Protect from light and warm, damp air.

Handling and Storage Precautions: Store in tightly sealed containers and protect from excessive heat and sources of ignition.

SECTION 8. EXPOSURE CONTROLS/PERSONAL PROTECTION

Protection: Safety glasses with side shields.

Skin Protection: Wear protective gloves if direct handling of material is expected. If in solution, selection of gloves depends upon vehicle.

Respiratory Protection: A NIOSH-approved half-face respirator equipped with dust filters must be worn for open handling of material. HEPA cartridges offer a greater level of protection.

Ventilation Requirements: Local exhaust ventilation should be used for dusty operations involving quantities greater than one kilogram.

Additional Measures: Handle as a Class I compound *(see Safety Procedure G-14)*. Avoid contact with eyes, skin and personal clothing.

Exposure Limits (Definition of terms):

ACGIH:	American Conference of Governmental Industrial Hygienists
Ceiling:	Ceiling Value
DTEL:	Derived Target Exposure Limit
MAK:	Federal Republic of Germany Maximum Concentration Values in the Workplace
NIOSH:	National Institute for Occupational Safety and Health
OSHA:	Occupational Safety and Health Administration [USA]
PEL:	Permissible Exposure Limit
PIEL:	Permissible Internal Exposure Limit [Ciba internal]
REL:	Recommended Exposure Limit
Skin (notation):	absorbed through skin
STEL:	Short Term Exposure Limit
TLV:	Threshold Limit Values
TWA:	Time-Weighted Average

Component	Exposure Limit
Valsartan	PIEL = 1 mg/m^3 (Ciba internal provisional 8 hr. TWA)

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance :	fine powder	**Odor Threshold:**	none
Color:	white	**Odor Characteristics:**	odorless
pH:	3.8 @ 0.18 g/l, 25°C (aq. sol.)	**Vapor Pressure:**	$< 1 \times 10^{-3}$ torr
Boiling Point:	not applicable	**Vapor Density:**	not applicable
Melting/Freezing Pt:	105 - 110°C (221 - 230°F)	**Specific Gravity:**	0.978
Solubility:	0.18 g/l in water (25°C);	**Partition Coefficient:**	-1.10 at 22°C
	> 300 g/l in 96% ethanol (26°C)	**Combustibility:**	brief ignition and
	> 500 g/l in methanol (26°C)		rapid extinction
Ignition Point:	410°C: whirled dust method	**Hazard Class (milling):**	SKM 1
Dust Explosion Class:	ST 2H	**Hazard Class (drying):**	SKT 1
Self-ignition:	none up to 105°C		

SECTION 10. STABILITY AND REACTIVITY

Stable (yes/no): Yes. Decomposition occurs at 170°C. 1% aqueous solution is stable (at pH 7.4) for at least 3 weeks at 50°C.

Hazardous Polymerization: Will not occur.

Conditions and Materials to Avoid: Protect from excessive heat and moisture. Avoid storage of material below 2°C and above 30°C.

Incompatibility: Avoid contact with acids, bases, and oxidizing agents.

Hazardous Decomposition Products: Thermal decomposition or combustion results in the formation of carbon and nitrogen oxides, as well as other poisonous or irritant gases and vapors.

SECTION 11. TOXICOLOGICAL INFORMATION

Eye Irritation: No data available.

Skin Irritation/Sensitization: No data available.

Oral Toxicity: LD_{50} > 2000 mg/kg (rat)
LD_{50} = 1000 mg/kg (marmoset)

Dermal Toxicity: No data available.

Inhalation Toxicity: No data available.

Subchronic:

In short-term studies over periods of 14 days in rats and marmosets and 3 months in rats, treatment with Valsartan in daily oral doses of 60, 200, or 600 mg/kg was generally well tolerated. The most prominent findings were elevated blood urea levels at doses ≥ 200 mg/kg in rats and at 600 mg/kg in marmosets.

Marmosets treated for 3 months with daily oral doses of 30, 60, 200, and 600 mg/kg displayed dose-related toxic effects at doses of 200 mg/kg and above. The high dose was reduced to 400 mg/kg after 23 days. The main pathological effects took the form of changes in renal function with increased blood urea and creatinine levels.

Repeated daily intravenous administration of Valsartan over 14 days at doses of 10, 30, or 100 mg/kg in rats and 6, 20, or 60 mg/kg in marmosets was generally well tolerated.

Chronic/Carcinogenicity:

The results of 6- and 12-month oral studies in rats receiving 20, 60, and 200 mg/kg and in marmosets receiving 12, 40, and 120 mg/kg body weight indicated good tolerability. A few minor symptoms were presumed to be due to the pharmacological activity of the compound. In rats, some kidney values were altered at 60 and 200 mg/kg.

Mutagenicity:

Negative in the following tests: Ames test; *Salmonella - E. coli* /liver microsome test; *in vitro* gene-mutation test with V79 cells (embryonic lung fibroblasts) of the Chinese hamster; *in vitro* chromosome aberration test in ovarian cells of the Chinese hamster; *in vivo* micronucleus test in rats.

Reproductive Effects:

No teratogenic effects were detectable in the fetuses of rats and mice given doses up to and including 600 mg/kg daily, nor in those of rabbits given 10 mg/kg, the highest dose tolerated without toxic reactions in the dams. Treatment with doses up to and including 200 mg/kg also had no effect on the fertility or reproductive performance of one generation of rats and their offspring.

SECTION 12. ECOLOGICAL INFORMATION

Ecotoxicological Information

Microbial growth inhibition:

Species	Minimum Inhibitory Concentration (mg/L)
Aspergillus niger	> 1000
Trichoderma viride	> 1000
Clostridium perfringens	> 1000
Bacillus subtilis	1000
Nostoc sp.	200

Freshwater Invertebrates:	EC_{50} = 580 mg/L	Species: *Daphnia magna*
	NOEC = 280 mg/L	Species: *Daphnia magna*
Fish toxicity:	LC_{50} > 100 mg/l (96 hours)	Species: trout

Chemical Fate Information

Valsartan is not biodegradable (method of OECD guideline No. 301/B). When properly introduced into adequately prepared biological sewage-treatment plants, no reduction in the aerobic decomposition capacity of activated sludge is to be anticipated. Contamination of soil, drains, and surface waters should be avoided. Bioaccumulation in fish or other aquatic organisms, although unlikely to occur, cannot be ruled out.

SECTION 13. DISPOSAL CONSIDERATIONS

Waste Disposal Method: All wastes must be disposed of in accordance with local, state and federal laws and regulations. (Contact local or state environmental agency for specific rules).

EPA Hazardous Waste Number: None.

SECTION 14. TRANSPORTATION INFORMATION

DOT Shipping Name:	Drugs, N.O.I. NMFC Item 60000
DOT Hazard Class:	None
DOT Identification:	None
Packing Group:	None
Hazard Label:	None
Special Requirements:	None
Exceptions:	None
Non-Bulk Requirements:	None
Bulk Requirements:	None
Max. Passgr. Air/Rail:	None
Max. Cargo Only Air/Rail:	None
Reportable Quantity (lbs.):	None
Stowage:	None
Other Requirements:	None
Product Label:	None
Packing Group:	None

SECTION 15. REGULATORY INFORMATION

OSHA (Occupational Safety & Health Administration):	This Material Safety Data Sheet contains the information required by the Federal OSHA Hazard Communication Standard (29 CFR 1910.1200).
OSHA PSM (Product Safety Management):	Not listed
NJ TCPA (Toxic Catastrophe Prevention Act):	This product contains NONE of the substances subject to the reporting requirements of Section N.J.A.C. 7:31 of this act.
TSCA (Toxic Substance Control Act):	Not listed

CERCLA (Comprehensive Response Compensation & Liability Act): Not listed

SARA Title III (Superfund Amendments & Reauthorization Act):

Section 302 Extremely Hazardous Substances: Not applicable (R&D exemption)

Section 311/312 Hazard Categories: None

Section 313 Toxic Chemicals: Not listed

RCRA (Resource Conservation & Recovery Act): Not listed

Other State Regulatory Information:

New Jersey: NJ RTK Threshold Planning Quantity = 10,000 lbs.

Other USA Regulations: None

California Proposition 65: The following statement is made in order to comply with the California Safe Drinking Water and Toxic Enforcement Act of 1986: *This material is not known to the State of California to cause cancer or reproductive toxicity.*

Canada: WHMIS Ingredient Disclosure List
Not listed

EEC Classification (European Economic Community):

Warning Symbol: Xn
Risk Codes: R20
Safety Codes: S24/25

SECTION 16. OTHER INFORMATION

Reason for Issue: Added tradename under Synonyms.

Supersedes Date:	**29 Aug 95**		
Written By:	C. Perino	**Date:**	29 Aug 95
Approved By:	J. Sinno	**Date:**	30 Apr 96

To the best of our knowledge, the information contained herein is accurate. However, Ciba-Geigy Corporation does not assume any liability whatsoever for the accuracy or completeness of the information contained herein except for the product's administration/use as intended. Final determination of the suitability of any material is the sole responsibility of the user. All materials may present unknown hazards and should be used with caution. Although certain hazards are described herein, we cannot guarantee that these are the only hazards which exist.

Non - Confidential

CGP 48 933 - Valsartan

Environmental Assessment Information

Appendix VI

CURRICULUM VITAE

Francis J. Gasparini

Research Scientist III

ACADEMIC RECORD

Institution	Date	Degree	Major Field
Colgate University	1969	BA	Chemistry
State University of New York at Albany	1971		Biochemistry
Columbia University	1976	Ph.D.	Biochemistry

PROFESSIONAL EXPERIENCE

(Position Listed in Reverse Chronological Order)

CIBA-GEIGY Corporation, Pharmaceuticals Division

Research Scientist III, Physical & Analytical Chem./Analytical Development - US 1993 - Present
Research Scientist II, Physical and Analytical Chemistry 1989 - 1993

Montefiore Medical Center and the Albert Einstein College of Medicine

Clinical Endocrine Core Laboratory
Director 1983 - 1989
Neuroendocrine Laboratory
Assistant Director 1980 - 1983

The Roosevelt Hospital, Columbia University

Endocrine Biochemistry
Research Scientist 1979 - 1980

The Rockefeller University

Endocrine Biochemistry
Post Doctoral Fellow 1976 - 1979

PROFESSIONAL AND HONORARY SOCIETIES

The Endocrine Society
American Association for the Advancement of Science
New York City Dept. of Health, Clinical Laboratory Supervisor's License

PUBLICATIONS

Gasparini, F. J., Hochberg, R. B., and Lieberman, S., "Biosynthesis of Steroid Sulfates by the Boar Testes," Biochemistry, 15, 3969, (1976).

Gasparini, F. J., Wolfson, A., Hochberg, R. B., and Lieberman, S., "Side-chain Cleavage of Some Cholesterol Es J. Biol. Chem., 254, 6650 (1979).

Bradlow, H. L. an Gasparini, F. J., "Current Status of Prostate Androgen Receptors," Annals of Clinical and Laboratory Science, 9, 299 (1979).

Weinberg, U., Gasparini, F. J., and Weitzman, E. D., Ontogeny of Melatonin Metabolism in the Rat. In Melatonin Rhythm Generating System," D. C. Klein, Ed., S. Karger, Basel, Switzerland, 1982, 193-203.

Halbreich, U., Asnis, G., Goldstein, S., Ryan, J. and Gasparini, F. J., "Need for "deadaptation" of Health Research Volunteers Admitted to Hospital," Lancet, 1(8431), 756 (1985).

Zern, M., Halbreich, U., Bacon, K., Galanter, M., Kang, B. and Gasparini, F. J., "Relationship Between Serum Cortisol, Liver Function, and Depression in Detoxified Alcoholics," Alcoholism - Clinical & Experimental Research, 10, 320 (1986).

Starosta, Z., Gasparini, F. J., Shapiro, L. E., and Surks, M. I., "Diminished Hepatic L - Triiodothyronine Nuclear Receptor Concentration in Rats Bearing the Walker 256 Carcinoma is not Due to a Generalized Decrease in Nonhistone Protein Synthesis," Endocrinology, 123, 1172 (1988).

Weinberg, U., Gasparini, F. J. and Weitzman, E. D., "The Developmental Pattern of in vitro Rat Liver Melatonin Degrading Activity," Endocrinology, 108, 1081 (1981).

Halbreich, U., Goldstein, S., Asnis, G., and Gasparini, F. J., "The Afternoon Cortisol Test (ACT): Representation of the Mean 24 Hour Plasma Levels of Cortisol With a Single short Continuous Blood Sample," J. Clinical Neuropharmacology, 7(1), 274 (1984).

Steve J. Lesko, CSP
Environmental Compliance Officer/Waste, HS&E

EMPLOYMENT

Mr. Lesko has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since May 1994. As Environmental Compliance Officer/Air, Mr. Lesko has the responsibility of regulatory compliance for all medical, hazardous and non-hazardous pharmaceutical wastes for the Summit site. In addition to the Environmental Compliance Officer/Waste responsibilities, Mr. Lesko is also currently responsible for managerial and daily operations of the Environmental section for the Division.

Prior to assuming the above-noted responsibilities, Mr. Lesko was employed by Ciba Corporation, Pharmaceuticals Division and held the position's of Compliance Auditor and Industrial Hygienist since November, 1988. Before joining Ciba, Mr. Lesko worked as an Industrial Hygienist for Beecham Laboratories, an Associate Industrial Hygienist for Clayton Environmental Laboratories and as an Industrial Hygiene Technologist for Princeton Testing Laboratories.

PROFESSIONAL ACTIVITIES

Mr. Lesko is a member of the national and local sections of the American Industrial Hygiene Association and the American Society of Safety Engineers, and the Environmental Auditing Roundtable.

EDUCATION

Mr. Lesko holds a Bachelors degree in Biology from the Ramapo College of New Jersey and is currently pursuing a Masters degree in Environmental Science from the New Jersey Institute of Technology (expected graduation May, 1996).

CERTIFICATIONS AND LICENSES

Mr. Lesko also holds the designation of a Certified Safety Professional (CSP) from the American Society of Safety Engineers.

Peter Leung
Environmental Compliance Officer/Air, HS&E

EMPLOYMENT

Mr. Leung has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since June 1991. As Compliance Officer/Air, Mr. Leung has the responsibility of regulatory compliance for all air emissions for the Summit site. Prior to joining Ciba, Mr. Leung worked for Stone and Webster Engineering Corporation as an environmental engineer.

PROFESSIONAL ACTIVITIES

Mr. Leung is a member of the American Institute of Chemical Engineers and the Air and Waste Management Association.

EDUCATION

Mr. Leung holds a Bachelor degree in Chemical Engineering from The Cooper Union, School of Engineering.

Lisa A. Lumia
Technical Coordinator, Drug Regulatory Affairs

EMPLOYMENT

Since June 1984, Ms. Lumia has been employed by Ciba Corporation, Pharmaceuticals Division in Suffern, New York. As a Technical Coordinator, Ms. Lumia is responsible for the preparation and maintenance of control documents for marketed and investigational compounds; organization and compilation of the chemistry, manufacturing and controls section of Original INDs and NDAs and subsequent submissions to support the IND or NDA; and the preparation of responses to FDA concerns regarding technical issues.

PROFESSIONAL ACTIVITIES

Ms. Lumia is a member of the American Association of Pharmaceutical Scientists.

EDUCATION

Ms. Lumia holds a Bachelors degree in biology from Lafayette College, Easton, Pennsylvania.

Christopher R. Perino
Occupational Toxicologist, HS&E

EMPLOYMENT

Mr. Perino has been employed by Ciba Corporation, Pharmaceuticals Division in Summit, New Jersey since November 1992. As an Occupational Toxicologist, Mr. Perino has the responsibility of OSHA Hazard Communication compliance for the Pharmaceuticals Division. Prior to joining Ciba, Mr. Perino worked for Gibraltar Biological Laboratories as Manager of Toxicology and Administration.

PROFESSIONAL ACTIVITIES

Mr. Perino is a member of the Occupational Toxicology Roundtable, Society of Toxicology (Mid-Atlantic chapter) and the Society for Chemical Hazard Communication.

EDUCATION

Mr. Perino holds a Masters degree in Biology from Montclair State College and a Bachelors degree in Biology from Villanova University.

PUBLICATIONS

Chemical TIMES & TRENDS: 21-28, Oct..1991.
Chemical TIMES & TRENDS: 28-31, Jan. 1992.

Joyce Ann Sinno, Ph.D.
Environmental/Occupational Toxicologist, HS&E

EMPLOYMENT

Dr. Sinno has been employed by Ciba Corporation since November 1990 as Environmental/ Occupational Toxicologist for the Pharmaceuticals Division. In addition to responsibilities associated with her position as Occupational Toxicologist, Dr. Sinno's environmental responsibilities include the preparation of Environmental Assessments for NDA and IND submissions. Dr. Sinno was previously employed by Pfizer Pharmaceuticals.

PROFESSIONAL ACTIVITIES

Dr. Sinno is a member of the Society of Environmental Toxicology and Chemistry (SETAC), the Mid-Atlantic Chapter of the Society of Toxicology (MASOT), and the American Industrial Hygiene Association (AIHA).

EDUCATION

Dr. Sinno holds a Bachelors degree and a Masters degree in Pharmaceutical Toxicology and a doctoral degree in Biochemical Toxicology from St. John's University College of Pharmacy and Allied Health Professions.

PUBLICATIONS

Biol. Trace Element Res. **20**: 153-160, 1989.

END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

NDA 20665

Group Leader
and
Division Director's
memos

DF

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products

Date: 6 November 1996
From: Robert R. Fenichel, HFD-110
Subject: valsartan (DIOVAN, Ciba), NDA 20-665
To: Raymond J. Lipicky, HFD-110

DEC 20 1996

With this application, the sponsor proposes to market 80- and 160-mg tablets of valsartan for the treatment of hypertension. This version of this memo supersedes a version that was distributed yesterday; the new version incorporates various latebreaking news and navigational aids suggested by Kathleen Bonglovanni.

Chemistry

Methods validation has not yet been completed, but all other chemistry-related matters have been settled to Dr. Coughlin's satisfaction. The manufacturing facility passed its EER inspection this month, and a copy of the report is present in the package. The proposed trade name (DIOVAN) is acceptable to the committee that worries about such things.

Biopharmaceutics

The absolute bioavailability of valsartan from oral DIOVAN is only 23%, and most of the bioavailable drug is excreted unchanged in the bile. One inactive hydroxylated metabolite ("M1") accounts for most of the valsartan that is metabolized, and the site of this transformation has not been identified. The usual P450 suspects appear (from observed drug-drug noninteractions) to be innocent

Valsartan's effects (if any) upon the metabolism of other drugs have been only shallowly investigated. Coadministered valsartan is known not to affect the pharmacodynamics *[sic]* of warfarin or the pharmacokinetics of digoxin, amlodipine, indomethacin, glibenclamide, or atenolol. Measurable effects on the pharmacokinetics of HCTZ and furosemide were clinically trivial. Some suggestions for further workup are contained in Dr. Parekh's memo dated 22 October.

Valsartan is a chiral compound, apparently not racemized in the body. Its pharmacokinetics are approximately linear throughout the range of 80–320 mg, its apparent volume of distribution is about 0.2 L/kg, and its elimination half-life is 5–7 hours. Since less than 15% of orally-administered valsartan is eliminated renally, the pharmacokinetics are not much affected by renal dysfunction. On the other hand, the AUC of valsartan was increased up to fourfold in patients with hepatic dysfunction.

About 10% of bioavailable valsartan remains unaccounted for.

When valsartan is administered with food, the AUC and C_{max} are reduced by 41% and 53%, respectively. In Protocol 17, patients were randomized to receive valsartan 80 mg in the fed or fasted states. After 8 weeks of therapy, the placebo-corrected trough reduction in seated DBP was about 50% larger in the fasted group; this pharmacodynamic difference was not statistically significant, but it certainly was consistent with the known pharmacokinetics.

The tested and to-be-marketed formulations were found to be appropriately similar.

With labeling changes that she listed, Dr. Zia-Amirhosseini believed that the application was approvable.

Pharmacology/Toxicology

In *in vitro* studies, valsartan bound to AT_1 receptors with exquisite specificity, although affinities varied from species to species by about 2 orders of magnitude. Binding to other neurotransmitter receptors, including AT_2 receptors, was 4 orders of magnitude weaker.

Bioavailability of enteral valsartan varied from species to species but was generally less than 50%. As in humans, most of the bioavailable drug was excreted unchanged; the human metabolite M1 was found in marmosets, but rodents' metabolism of valsartan produces only several different metabolites not found in humans, some identified and some not.

The general and reproductive toxicology studies were reviewed by Dr. Jagadeesh, and the carcinogenicity studies were reviewed by Dr. Proakis. These studies brought forth no surprises. With some minor labeling changes that they listed, Drs. Jagadeesh and Proakis believed that the application was approvable.

The methods and results of the carcinogenicity trials were discussed and approved at CAC meetings on 17 September and 22 October.

Efficacy

The clinical trials are elegantly described in Dr. Ganley's review dated 4 October. Over 2300 hypertensive patients were exposed to valsartan in randomized, placebo-controlled trials, and another 2000 or so exposures were accrued in other populations and settings. The hypertensive patients studied were the usual middle-aged gang, mainly white and mainly male.

The primary endpoint was generally the placebo-corrected change in seated diastolic blood pressure at trough; one trial used supine pressure measurements instead of seated ones. As shown in Dr. Ganley's Table SE.1 on page 15 of his review of 4 October, valsartan was associated with modest, dose-related reductions in blood pressure throughout the range (10–320 mg/day) of doses tested. The weighted-average placebo-corrected reductions in (usually seated) blood pressure are shown in the table on the next page. In the individual trials, drug

Weighted Averages by Dose
Placebo-corrected reduction in seated* BP at Endpoint*

	dose (mg/day)					
	10	20	40	80	160	320
patients	25	244	282	1040	310	150
BP reduction	1.3/0.8	5.6/2.8	6.2/2.6	7.0/4.4	7.4/4.6	9.0/6.4

* All but one; see Dr. Ganley's tables for details.

from pages 15 & 18 of Dr. Ganley's review of 4 Oct

effects larger than 2 mm Hg were usually statistically significant, and those larger than 4 mm Hg were always statistically significant.

In women, valsartan appeared to be more effective in some trials, but *less* effective in others. Similarly, there was no convincing association between efficacy and age or (perhaps surprisingly) race.

An all-comer parallel-group comparison of once-daily versus twice-daily dosing was not performed, but Protocol 50 followed patients who had failed to respond adequately to once-daily valsartan 80 mg. These patients were randomly assigned to receive 160 mg/day, either once daily or as 80 mg bid. There was a trend for better response to the twice-daily regimen, but the difference was statistically and clinically insignificant ($<< 1$ mm Hg).

Protocol 19 was a 702-patient, 8-week, randomized, double-blind trial in patients whose blood pressure was inadequately controlled after 4 weeks of treatment with valsartan 80 mg/day. These patients were randomized to continue with valsartan 80 mg/day, to double the valsartan to 160 mg/day, to add hydrochlorothiazide 12.5 mg/day, or to add hydrochlorothiazide 25 mg/day. As shown in the table below, the valsartan monotherapy arms were not significantly different from each other, but 80/12.5 was significantly more effective than either, and 80/25 was significantly more effective still.

Safety & ADRs

Protocol 33 was a 129-patient, 6-week, double-blind, randomized, parallel-group trial comparing valsartan 80 mg/day, lisinopril 10 mg/day, and HCTZ 25 mg/day in patients who had histories of ACE-inhibitor-induced cough, reproduced during a lisinopril challenge and disappearing on rechallenge. The

Protocol 19
Reduction from Baseline in Seated BP at Endpoint

valsartan (mg)	80.0	160.0	80.0	80.0
HCTZ (mg)	0.0	0.0	12.5	25.0
patients	179	171	176	176
Reduction in BP	3.8/5.3	5.9/5.7	9.3/7.8	15.7/10.4

from pages 89-90 of Dr. Ganley's review of 4 Oct

trial was intended to show that valsartan does not induce cough in patients who do cough in response to ACE inhibitors. As described on pages 105-107 of Dr. Ganley's review of 4 October, Protocol 33 was spectacularly successful, with a 69% incidence of cough in the lisinopril group and incidences less than half that size (and indistinguishable from each other) in the valsartan and HCTZ groups.

In addition, ACE inhibitors (sometimes enalapril, sometimes lisinopril) appeared as positive controls in some of the placebo-controlled trials, so it was possible to make various direct comparisons of valsartan and the ACE inhibitor, looking at the incidences of some adverse effects of interest. As in Protocol 33 (and as predicted on biological grounds), cough was more frequent in the ACE-inhibitor patients (7.9%) than in those who received valsartan (2.3%) or placebo (1.5%). The apparent difference persists* when various kindred ADRs ("Upper Respiratory Tract Infection," "Pharyngitis," and so on) are pooled with "Coughing," and the same differential was seen with enalapril as with lisinopril. Dr. Ganley perceives a subtle dose-related increase in cough in the valsartan patients,† but I do not find the data convincing.

There were no unequivocal cases of angioedema or renal failure associated with valsartan. Nevertheless, considering the experience with losartan, Dr. Ganley recommends (pages 9 and 10 of his review of 4 October) that the angioedema and renal-failure labeling of valsartan should be similar to that of losartan.

Other adverse reactions were seen with roughly equal incidences in the valsartan, ACE-inhibitor, and placebo groups, and without apparent relation to age, race, or gender. The same was true of adverse reactions leading to withdrawal and of most abnormal laboratory results. Neutropenia is the one possible exception.

Dr. Ganley has had difficulty in obtaining adequate information regarding observed cases of neutropenia. Such data as are available are summarized in his supplemental review dated 7 October. Among the 6000 or so patients studied, 10 were neutropenic ($< 10^9$ cells/L) at baseline, and 23 were found to be neutropenic at some time during treatment. On a per-patient basis, neutropenia was somewhat more common in the valsartan exposed patients, although this difference did not achieve statistical significance.‡ The data we have been given are not sufficient to use patient-days of exposure as the denominator, and use of this denominator would presumably favor valsartan, since the control agents were generally restricted to short trials.

Because a reasonable number of these patients were neutropenic at baseline (before exposure to study drugs), and because some of the on-treatment cases reverted to normal neutrophil counts while continuing to receive treatment, one may speculate that some or all of the observed cases were laboratory errors or random variations. On the other hand, several of the nadir counts were the

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* See Dr. Ganley's review of 4 October, page 6.

† See his Table SS.11 on page 10 of his review of 4 October.

‡ My quick calculations from Dr. Ganley's Table 1 show $\chi^2_1 \approx 1.9$ $(0.1 < P < 0.2)$ for valsartan vs. others including valsartan combinations, $\chi^2_1 \approx 1.4$ $(0.2 < P < 0.3)$ for valsartan (monotherapy or combinations) vs. others.

last observations recorded for the involved patients, whose subsequent courses are unknown.

Dr. Ganley has requested additional information from the sponsor, but my own inclination would be to let it drop.

Treatment×Race Interaction

To decide what the labeling of DIOVAN should say about the interaction of treatment and race, we'll need to decide whether we are Bayesians or frequentists.

The Bayesian prior is easy to describe. Presumably because hypertensive blacks are often hypertensive despite low plasma renin, drugs that suppress the renin-angiotensin system have had somewhat less antihypertensive efficacy in blacks than in nonblacks. This is reflected in the approved labels of the various ACE inhibitors and of losartan. In the labeling of at least one fixed-dose combination (benazepril/amlodipine (LOTREL, Ciba)), it is asserted that in blacks the ACE-inhibitor component contributes nothing to the combination's antihypertensive efficacy.

Are there enough data here to overcome our expectations? Some of the data are laid out in Table SE.5 on page 17 of Dr. Ganley's review of 4 October. That table shows that there were 6 trial×dose combinations in which more than a few blacks were enrolled; the 6 cells included 830 whites and 140 blacks. In 5 of the 6 cells, the placebo-corrected valsartan-associated SeDBP reductions in blacks were numerically *greater* than those seen in whites randomized to the same therapy; overall, the average drug effect in blacks was 29% greater than that seen in whites.

Should this label swing to the opposite extreme, and assert that valsartan is more effective in blacks? Dr. Nuri points out* that the tabulated drug effects do not represent differences in the response to valsartan. Instead, the drug effects are dominated by differential responses to *placebo*. Should we revert to the prior?

Recommendations

DIOVAN should be approved for the treatment of hypertension, alone or in combination with other drugs.

The labeling, as extensively marked up in the included copy marked "MARKED UP," is in pretty good shape. Most of my comments are included in the markup, but some are here, keyed to circled red letters marked on the marked-up copy

A. One of the other markers-up has in various places† resolved the treatment×race question by saying, in

* See pages 11-14 of his review dated 23 August.

† At lines 174, 193-198, and 238, and in the insertion at line 247.

effect, that this interaction has not been studied. In fact, there were RCTs that included 830 whites and 140 blacks. The results of these trials are difficult to interpret, but it's just not true that there is an open question here, likely to be resolved predictably and unambiguously by some easily-described trial. I think we're stuck with the fact that

> Antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In randomized, controlled trials of DIOVAN that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally more effective in blacks, when the measure of efficacy was the extent of superiority to placebo. Blacks' response to placebo in these trials was significantly less than that of whites, which numerically accounts for the unexpected overall finding. There is no simple interpretation of these findings in terms of differential efficacy by race.

and that's what I'd say, probably in place of lines 193-198.

B. I crossed out the sentences on lines 208-211 and 227-230. I'm a little uncomfortable putting into labeling *any* trial data that suggest a predictable magnitude of effect; non-placebo-corrected data are (to me) out of the question.

C. The paragraph inserted just above line 402 seems ill-conceived. Valsartan is scarcely metabolized at all, so I'm not sure that any study of that metabolism is worthwhile. What's worth studying, and probably worth mentioning, is the possibility that valsartan, without being metabolized itself, might inhibit or induce enzymes, thereby affecting the disposition of other drugs.

D. The two paragraphs and the accompanying table at lines 468-478 take up much too much space. Why not just

> In trials in which valsartan was compared to an ACE inhibitor and to placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the

groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidence of cough in those randomized to valsartan (or to placebo) was less than half the incidence in those randomized to receive ACE inhibitors.

E. Dr. Zia-Amirhosseini wanted to add "The effect of race on the pharmacokinetics of valsartan has not been studied" to the **Clinical Pharmacology** section at line 126, but this would be a mistake, not because it would be unprecedented, but because it is ill-conceived. Racial distinctions are made in labeling because Phase III trials are usually unable to get any closer to phenotypic variations. PK information, on the other hand, is necessarily obtained from a small number of patients who can be characterized with great precision, so there's no reason to settle for race as a descriptor.

F. The inserted paragraphs starting at line 385 and continuing until just before the one just before line 402 are immensely bulkier than they need to be. How about

No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, furosemide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and digoxin did not affect the pharmacokinetics of valsartan or the peak concentration (C_{max}) or time to C_{max} (t_{max}) of digoxin; the effect (if any) of valsartan on the AUC of digoxin has not been determined.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

Coadministration of valsartan and cimetidine did not change the pharmacokinetics of cimetidine, but the

AUC and C_{max} of valsartan were increased by 17% and 49%, respectively.

cc: NDA 20-665
HFD-110/RFenichel
HFD-110/CGanley
HFD-111/KBonglovanni
HFD-710/WNuri

DF

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : NOV 21 1996

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 Lipicky

SUBJECT: Approvability of NDA 20-665, Diovan (valsartan), Ciba-Geigy.

DEC 20 1996

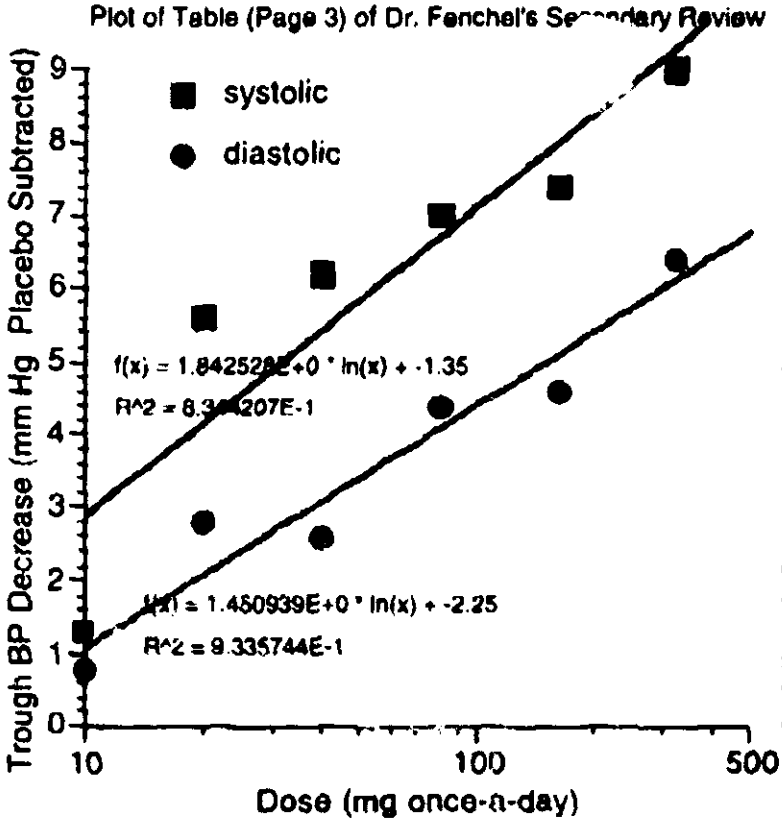
TO : Director, Office of Drug Evaluation I, HFD-100

Introduction

This memorandum and attached documentation represent the Division's recommendation that NDA 20-665 be approved. Our marked-up draft labelling is attached, as is an approvable letter for your signature. There are no clinical issues that are unresolved (except for, perhaps, the response of blacks). Establishment inspections have been completed and are satisfactory, environmental assessment (as of 11/18/96) is not done (review of a response to a deficiency letter is in progress), methods validation has not been completed. Otherwise, there is nothing outstanding. None of the outstanding items prohibit signing the approvable letter.

Efficacy

Without question, valsartan lowers blood pressure (systolic and diastolic); 10 placebo-controlled trials involving 2330 patients with mild-to-moderate hypertension clearly demonstrate that effect. It is unfortunate that the highest dose studied was only 320 mg (once-a-day). As can be seen from the figure (to the left), the trough blood pressure response is nicely related to the log of the orally administered dose. The effect growing larger, the larger the dose. The largest mean effect remaining "modest", but larger than we sometimes see with other NDAs.



There were no dose-limiting side effects (except for a hint of dose-relatedness for cough and dizziness [Table SS.7, page 8 of Dr. Ganley's review). It is not at all clear, form the data on blood pressure and side-effects, why the dose should be limited to 320 mg, but no greater doses were studied. Three studies (Protocols 09, 10, 31 and 11) measured blood pressure at trough as well as other times in the dosing interval. A summary of these data can be found on page 5 of Dr. Ganley's review. On a whole,

especially at lower doses, once-a-day dosing does not seem to cover the entire dosing interval. Not too surprising, since the terminal half-life is in the order of 7 to 9 hours. Peak blood pressure effects are seen about 6 hours after taking a dose, and the peak plasma concentration is also at about 4 to 6 hours (taken with food, earlier in the fasted state). Protocol 50 produced results that support labelling that would say "total daily dose of xxx mg, administered once-a-day or in two divided doses."

The above summary is not consistent with what the sponsor desires (they want the upper limit of dose to be 160 mg and a clear statement in labelling that says twice-a-day is no better than once-a-day), nor is it consistent with either Dr. Fenichel's nor Dr. Ganley's interpretation of the data (my surmise, since neither edited the dosage and administration section of sponsor supplied draft labelling). To amplify my interpretation, I offer a graph (attached as a separate sheet of paper, labelled Appendix I).

Plotted on that page are the placebo-subtracted change from baseline for casual, cuff, trough systolic and diastolic blood pressures (at the designated "endpoint" as well as at the end of the trials). The data were derived from an "intent to treat" analysis conducted by Dr. Nuri. The 4 trials represented (Studies 10, 11, 23 and 31) are all of the placebo-controlled, parallel dose ranging trials that were submitted. For comparative purposes, but a side-light from the major features of the plots, are the results of Study 17 (which compared the blood pressure effects of valsartan in a group that took valsartan, once-a-day, with food or in the fasted state).

Only one study (Study 31) used a dose greater than 160 mg. Only one study (Study 31) found statistically significant differences from placebo for all dosing groups. Numerically, only one study (Study 31) had numerically greater decreases in blood pressure at each increasing dose. None of the studies (including Study 31) had a statistically significantly greater effect at the highest dose studied, compared to the next lowest dose. I think, the graphic (above) that depicts the overall weighted average by dose at endpoint (the table on page 3 of Dr. Fenichel's review) is the "best" representation of what the studies found. Were one to rely on single trials for the "best" representation, one might conclude that 40 mg (Study 11, diastolic) has the greatest effect, or that 80 mg (Study 23, systolic) has the greatest effect. Point by point comparisons are, in my view, inappropriate. What is true, I think, is that the larger the dose the greater is the effect, over the entire dose range studied. So, from an effect point of view, there is no reason to limit the dose allowed to 160 mg (should one elect that option, the implicit statement is that doses greater than 160 mg have no greater effect). Such a statement is not, in my view, consistent with the overall data. Of course, there were not many patients who received 320 mg (only 150 randomized to that group). Nonetheless, there appear to be no dose-related adverse effects and on-a-whole, there were more adverse effects observed in the placebo population, and there is a large number (4543 patients) who have been exposed to valsartan. So, I see no reason for caution.

One trial (Study 50) did a "half-hearted" comparison of once-a-day to twice-a-day administration. I agree with Dr. Nuri's statement that the design of the trial did not allow a rigorous comparison between these two dosing intervals. Study 50 randomized 734 patients (a large trial), was parallel in design and was placebo-controlled. The study was powered to detect a 3 mm Hg change in sitting diastolic blood pressure (180 patients per group, assuming 90% power and a standard deviation of 8 mm Hg.). Patients were randomized to one of 4 groups. All patients were titrated starting at valsartan 80 mg once-a-day, lisinopril 10 mg once-a-day or placebo, for 4 weeks. For patients who were judged to be not responsive (sitting diastolic greater than or equal to 90 mm Hg), the dose was doubled (160 mg valsartan or 20 mg lisinopril). When judged to be unresponsive one valsartan group received 80 mg twice-a-day, the other 160 mg once-a-day. This second regimen was continued for 8 more weeks. Analyses at the end of 12 weeks were based on intent-to treat, on the change from baseline for each randomized group. Indeed, there were no statistically significant differences between active therapy groups, although each group was

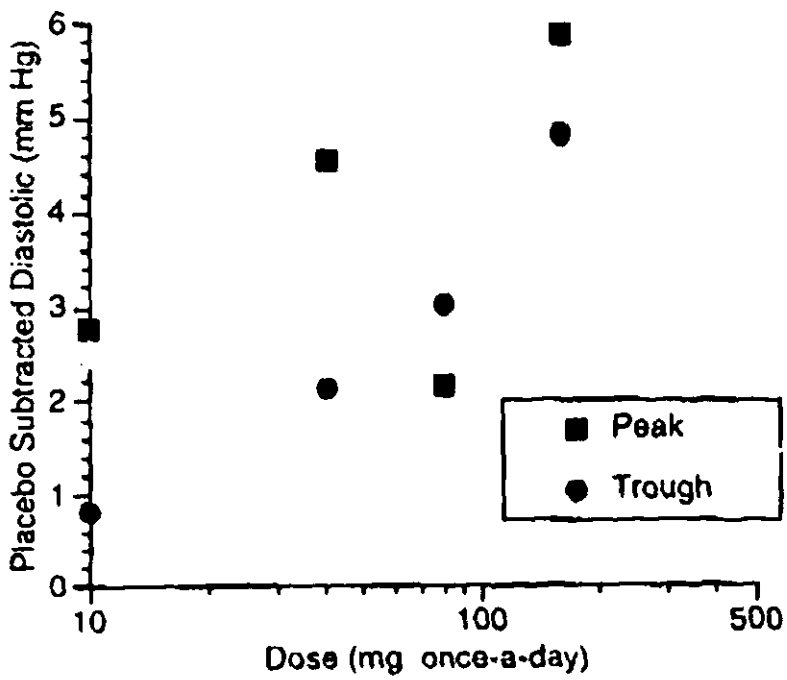
statistically significantly different from placebo. The groups of titrated patients (about 65% of the valsartan groups needed titration) had a further decrease in blood pressure (about 1 mm Hg for placebo, and about 4 mm Hg for valsartan and lisinopril groups). The greater effect that could be attributed to titration was not different between the groups. Retrospectively (if we had agreed to this design) , I cannot conclude from this trial that once-a-day and twice-a-day are equally effective, at trough.

The ABPM studies (mainly Study 31), as well as peak-to-trough studies (Studies 09 and 10) are the only data available that allow some sort of intuition regarding once-a-day *vs* twice-a-day. To my eye (and there is no existing quantitative method that can help), Figure 31.2b (page 65 of Dr. Ganley's review), the 20 and 80 mg dose of valsartan (administered once-a-day) loses a little toward the end of the dosing interval (the 20 mg dose losing more than the 80 mg dose). Only the 320 mg dose clearly does not lose some magnitude of effect during the tail of the dosing interval.

Trough/peak ratios (Table SE.9., page 19 of Dr. Ganley's review) are incorrectly calculated. The trough/peak ratio calculation should be performed on placebo subtracted data (i.e., on drug effect), if such calculation is performed at all. If the drug effect is used for the calculation the table looks as follows (using the numbers in Table SE.9..

Treatment	Peak Change	Trough Change	Trough/Peak Ratio
valsartan 10 mg	2.77 mm	0.83 mm	30%
valsartan 40 mg	4.57 mm	2.13 mm	47%
valsartan 80 mg	2.17 mm	3.03 mm	140%
valsartan 160 mg	5.87 mm	4.83 mm	82%

The table above is not too illuminating and helps very little. The following graph helps a little. It plots the peak Change and Trough Change as a function of dose.



Like other dose-response data in the application, everything orders nicely as a function of dose; except for the 80 mg dose, which clearly is an anomaly. I think the plot (ignoring the 80 mg dose) is consistent with the notion that at low doses (e.g., 10 mg) little of the peak effect is left at trough and as the dose increases, more and more of the peak is retained. This, to me, confirms the intuitive look at the ABPM data. ABPM and Peak/Trough taken together strongly suggest that valsartan is not a once-a-day drug over the entire dosing interval studied. Once-a-day is an acceptable regimen. It is not the only regimen that should be advised. Twice-a-day has been studied and is safe.

Dr. Fenichel points out (page 5 of his secondary review) the basis for decision making regarding the blood pressure response to valsartan in blacks. This issue needs revisiting sometime (somehow, but it is not clear what the somehow operations would be). In our most recent ACE inhibitor approval, it was clear (to me and Dr. Stockbridge, but not to you) that blacks responded as well to that ACE inhibitor as did whites (in fact in an all black, dose-response trial, the dose-response in blacks was identical to that in whites; but this latter identity was an across studies comparison). Our current labelling and the community's perception of less response to ACE inhibitors in blacks is one that is derived from subgroup analysis that produces results consistent with models of mechanism of hypertension. Our labelling of losartan was "Bayesian" and I think the labelling of valsartan should conform the "Bayesian" thinking process.

There is a large food effect (page 13 of Dr. Zia-Amirhosseini's review, a substantial decrease in the bioavailability of valsartan when taken with food). In keeping with that effect, in a single study (Protocol 17; a placebo-controlled trial involving 285 patients), the mean decrease in blood pressure was numerically less (about 2 mm Hg less) in the group taking 80 mg with food than in the group taking 80 mg in a fasted state; although both groups had a response that was greater than that in the placebo population. Labelling should say that a fasting state is preferred.

I think I have very little else to add to the thinking process that is present in the attached reviews. Valsartan is certainly an antihypertensive agent and can be administered once or twice-a-day over the entire daily dose range studied.

Safety

All told there were 4543 patients exposed to valsartan (4190 monotherapy and 353 combination therapy), with 3710 in controlled trials and 2330 (formal tables only include 2316 patients; this difference in numbers is not significant, nor is it resolved, nor should it be resolved) in placebo-controlled trials of 4 days to 12 weeks duration. The bulk of patients were exposed for less than 30 days, 626 were exposed to 180 days or longer and 224 were exposed for 365 days or longer; at the time of NDA submission. A Safety Update was submitted on 4/25/96 and reviewed; an additional Safety Update was just submitted (dated November 13, 1996) and is currently under review . At the time of the first Safety Update, 253 patients had entered the second year of open-label follow-up and 131 had completed two years of follow up.

As can be seen from 21 pages of adverse events reported in placebo-controlled trials (Dr. Ganley's 11/196, Medical Officer Review Addendum dated 11/1/96), valsartan was essentially not differentiable from placebo for either total or any specific adverse event. In fact, for the most common adverse effects (headache and dizziness), headache was more common in the group receiving placebo (incidence of 13.5%) than in the group receiving valsartan (incidence of 9.8 %); for dizziness the incidence was almost identical (3.5 % for placebo and 3.6 % for valsartan).

There were 12 deaths reported (as of 3/31/96) and 2 more (in the 4/25/96 Safety Update) for a total of 14 deaths. Narrative summaries of the 12 deaths reported in the original submission are in the appendix of Dr. Ganley's review and the 2 deaths of the reported in the first Safety Update are summarized in Dr. Ganley's 10/15/96 review. There is no signal that can be perceived in these events.

One controlled-trial (Protocol 33) was a head-to-head comparison of valsartan and lisinopril in a patient population selected for having typical ACE inhibitor cough. The incidence of cough was the major end-point. The results clearly differentiated valsartan from lisinopril (the incidence of cough in the valsartan group was both less than the incidence of cough in the lisinopril group as well as being indistinguishable from that of the HCTZ group. All of the results of all of the other trials are consistent with the findings of this single trial. Valsartan, like losartan, is free of this side effect.

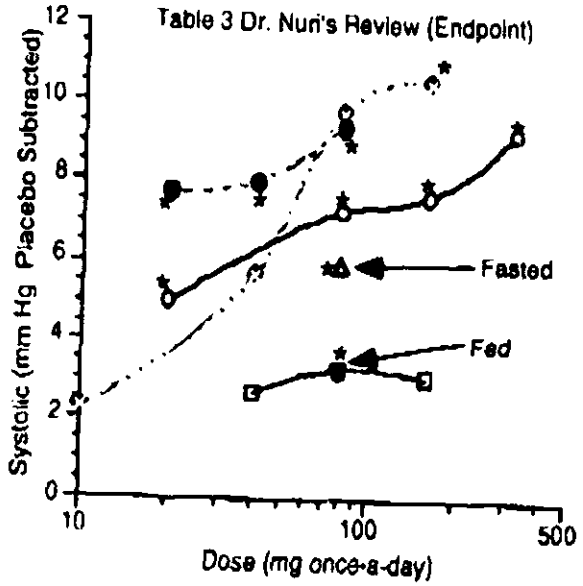
In his original (10/8/96) review, Dr. Ganley was concerned about neutropenia. The sponsor in a submission dated 10/23/96 provided more information and in a review (dated 11/5/96) Dr. Ganley concluded that there was no signal present (as did Dr. Fenichel and as do I).

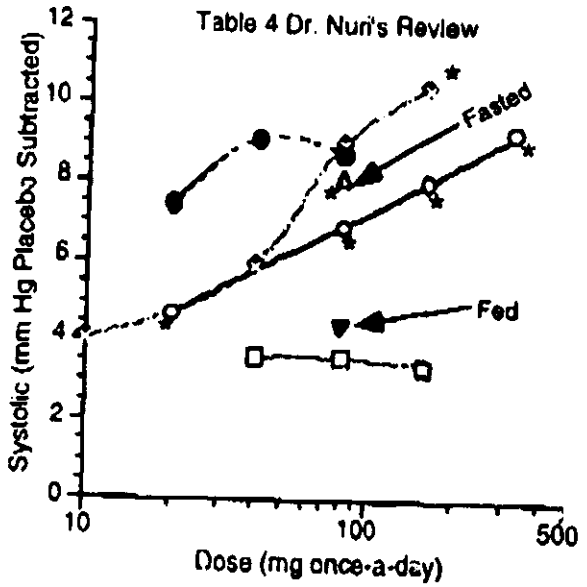
Summary

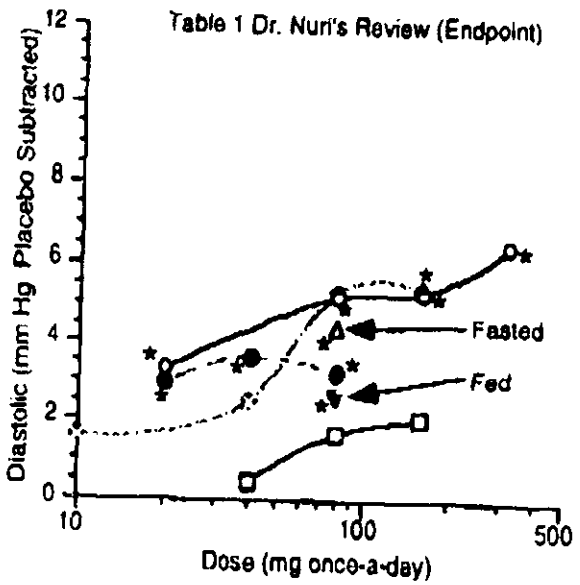
There is no reason that I can find prohibiting your signing the approvable letter. Your comments regarding labelling are invited.

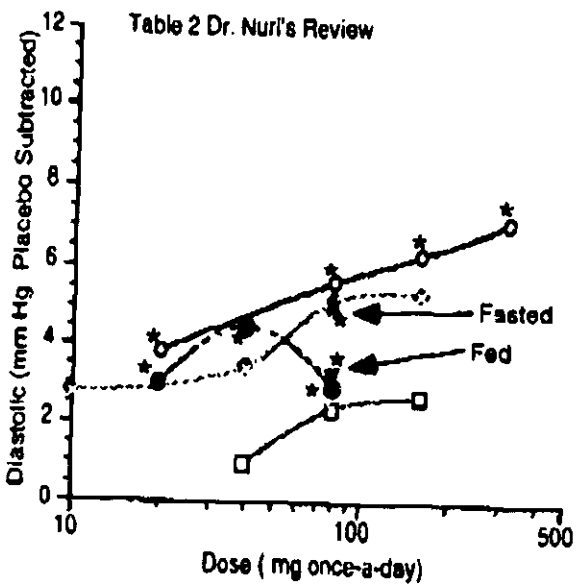
cc
Orig.
HFD-110
HFD-110/Project Manager
HFD-110/RLipicky

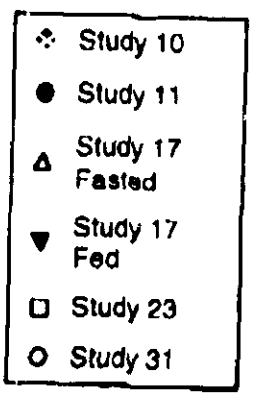
Appendix I











Summary of Studies 10, 11, 17, 23 and 31.
The data were taken from Dr. Nuri's Statistical Review (dated 8/23/96).
The Figure legend is to the left.
The "*" on the above graphs show those data points that were statistically differentiable from placebo.