Protocol SB 203220/024 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.084)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *02-May-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *15-May-1997*

24.1 STUDY PROTOCOL

24.1.1 Title

A comparison of the renal hemodynamic effects of SB 203220, Eprosartan and Captopril in healthy male volunteers

24.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors in the treatment of hypertension.

24.1.3 Objectives

1. To estimate the relative effect of repeated oral doses of SB 203220, eprosartan, captopril and placebo on effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) in healthy men;
2. To describe the effect of a single oral dose of captopril (25 mg) on effective renal plasma flow and glomerular filtration rate during subchronic administration of eprosartan;
3. To describe the effect of a single oral dose of eprosartan on effective renal plasma flow and glomerular filtration rate during subchronic administration of captopril.

24.1.4 Study design

The study was an open-label, randomized, four period, period-balanced crossover study. Each subject participated (by random allocation to four treatment sequences, ABCD, BACD, CBDA, DCAB) in four study periods separated by at least 2 weeks. During each study period, each subject received one of the following treatments:

1. Regimen A: SB 203220 600 mg (Lot# U93145) orally each morning for 8 days and a single oral dose of captopril (25 mg) on Day 8
2. Regimen B: Eprosartan 300 mg (Lot# U94068) orally every 12 hours or 7 days and a single oral dose of captopril (25 mg) on Day 8
3. Regimen C: Captopril 25 mg (Lot# X94169) orally 3 times daily for 7 days and a single dose on Day 8 plus a single oral dose of eprosartan 300 mg on Day 8
4. Regimen D: Placebo (Lot# U94111) orally every morning for 8 days

Effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) were measured on Days 7 and 8 of each study period using Para-aminohippurate (PAH) clearance (CL_{PAH}) and inulin clearance (CL_{IN}), respectively.

24.1.5 Protocol Amendments

Because of poor (CL_{PAH}) data (in subjects who weighed >90 kg) in Period 1, Protocol amendment #1 (03-Jan-1995) was submitted, in which the maintenance infusion of PAH was adjusted based upon creatinine clearance and weight, and Period 1 was repeated (as Period 5) in all subjects after completion of Period 4 and a 2-week washout period. Amendment 2 consisted of a change in the clinical laboratory performing blood and urine tests.

24.1.6 Population enrolled/analyzed

24-male volunteers 18-45 years of age, and weight ≥50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All doses of study medication were administered under the observation of the study nurse except for the evening dose of eprosartan and the afternoon and evening doses of captopril on Days 1 through 6.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen).

24.1.7 Study procedures

Inulin and PAH clearance tests were performed on Days 7 and 8 of each study period. An iv loading dose of PAH (8 mg/kg) and inulin (50 mg/kg) were given at 6.00 am followed by continuous iv infusions of PAH and inulin. At 8.00 am, the study medication was administered with 240 ml water. PAH and inulin infusions were continued for 6 hours following dosing, with the subject remaining supine throughout except at predetermined periods to void urine. Measurements of supine blood pressure and heart rate, ECG and blood sample collection were made. Subjects

for whom PAH and inulin specimens were available according to protocol were considered as having completed the study. Withdrawals were replaced by another subject assigned to the same sequence of treatments.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, nursing observation, physical examination findings, laboratory findings and 12-lead ECG data during the 5 dosing periods.

24.1.8 **Endpoints:**
The Primary Efficacy Endpoint was CL_{PAH}, a measure of ERPF (effective renal plasma flow). The Secondary Efficacy Endpoint was CL_{IN}, a measure of GFR (glomerular filtration rate). CL_{PAH} and CL_{IN} determinations were performed at -1, -0.5, 0, 0.5, 5, 1.5, 2, 4 and 6 hours post-dose on Days 7 and 8 of each study period.

24..9 **Sample size:**
Based on a within-subject coefficient of variation (CV_W) of 11.7% for CL_{PAH}, to detect differences of at least 20% on a 2-tailed test with 90% power between any 2 treatments for CL_{PAH}, it was estimated that a sample size of 12 would be necessary. No adjustments were made for multiple comparisons. (CV_W for this study ranged from 11.9 to 13.7%).

24.1.10 **Statistical Evaluation:**
Each endpoint was submitted to an ANOVA with terms for subject, period and regimen nested within day. There was additional assessment of first-order carry over prior to dosing on Day 7. Point estimates were computed for the following comparisons of interest:

1. $(\text{RD SB 203220})_{\text{Day 7}} - (\text{RD Placebo})_{\text{Day 7}}$
2. $(\text{RD Eprosartan})_{\text{Day 7}} - (\text{RD Placebo})_{\text{Day 7}}$
3. $(\text{RD Captopril})_{\text{Day 7}} - (\text{RD Placebo})_{\text{Day 7}}$
4. $(\text{RD Eprosartan})_{\text{Day 7}} - (\text{RD captopril})_{\text{Day 7}}$
5. $(\text{RD SB 203220 + SD captopril})_{\text{Day 8}} - (\text{RD SB 203220})_{\text{Day 7}}$
6. $(\text{RD Eprosartan + SD captopril})_{\text{Day 8}} - (\text{RD Eprosartan})_{\text{Day 7}}$
7. $(\text{RD captopril + SD Eprosartan})_{\text{Day 8}} - (\text{RD captopril})_{\text{Day 7}}$

24.1.11 **Investigator , Center and Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 12-Oct-1994 to 10-Feb-1995.

24.2 STUDY POPULATION

24.2.1 **Subject disposition:**
Of 17 subjects screened, one did not meet entrance criteria, 1 did not return after screening, and 1 was an alternate subject not enrolled. 14 (6 black and 8 white) healthy male subjects, 18-45 (mean = 28) years of age, weighing 63.8 to 106.4 (mean = 80.5) kg were randomized. All received at least one dose of study medication as follows:

Treatment	Number of subjects
Regimen A	13
Regimen B	13
Regimen C	13
Regimen D	12

24.2.2 **Withdrawals:**
Four subjects (#003, #006, #008, #011) failed to return for their schedules study periods and were lost to follow-up. Subject #015 replaced #006 (who completed 2 study periods, on Regimens C and B), and Subject #014 replaced #011 (who participated in one study period on Regimen A). Subjects #003 and #008 were not replaced.

24.2.3 **Protocol violations:**
Three subjects (#001, #009, #05) took medications (one dose of Mylanta, topical antibiotic ointment and Motrin and Ventolin MDI, respectively) during the study.

24.3 SAFETY RESULTS

24.3.1 **General considerations:** A total of 30 adverse experiences (AEs) were reported for 9 subjects on study medication.

24.3.2 **Deaths:** There were no deaths during this study.

24.3.3 **Withdrawals:** There was no withdrawals due to adverse experience during this study.

24.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

24.3.5 **Adverse Events:** 30 adverse experiences (AEs) were reported for 9 subjects on study medication as follows:

Treatment	N	Number of AEs	Number of subjects with AEs
Regimen A	13	11	5
Regimen B	13	8	5
Regimen C	13	8	3
Regimen D	12	3	3

The adverse events were mild to moderate in nature and consist of the following:

Regimen A : 1 subject each with abdominal pain, viral infection, flatulence, rash, palpitations, paresthesia, phlebitis, dizziness, myalgia, arthralgia, and asthma;

Regimen B: 2 subjects with dyspepsia and 1 subject each with flatulence, rhinitis, vomiting, pain in left arm, injury and inflammation at injection site;

Regimen C: 2 subjects with flu-like symptoms and 1 subject each with abdominal pain, flatulence, rhinitis, infection right hand, diarrhea and hemorrhoids;

Regimen D: 1 patient each with abdominal pain, taste perversion and upper respiratory infection

24.3.6 **Laboratory findings, ECGs, Vital signs**

There were no pulse rate changes of potential clinical concern as defined by protocol. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) of clinical concern as defined by protocol were observed in 24 instances as follows (they were not sustained and subjects were asymptomatic):

Regimen A: 3 subjects had increased DBP, 2 had decreased DBP;

Regimen B: 4 subjects had decreased DBP, 1 had increased DBP, and 2 each had decreased or increased SBP;

Regimen C: 3 subjects had decreased SBP, 1 had decreased DBP;

Regimen D: 5 subjects had increased DBP, 1 had decreased DBP.

There were no ECG changes (in PR, QRS and QTc intervals) that were of potential concern. No instances of prolongation of QTc were observed.

The laboratory data that were of potential clinical concern according to protocol-defined criteria were as follows:

Regime A: One subject (#007) had hyperkalemia (5.6 mEq/l) on Day 8, 6 hr blood sample;

Regime B: Two subjects (#001 & #015) had hyperglycemia on Day 1, 0 hour samples (being 147 mg/dl and 154 mg/dl, respectively);

Regime C: One subject (#003) had leucocytosis (12.9 x 10^3/mm^3) on Day 8, 6h blood sample; one subject (#008) had elevated ALT (94 IU/L) on Day 1, 0 hr blood sample;

24.4 PHARMACODYNAMIC RESULTS

24.4.1 **Effective renal plasma flow (ERPF) as measured by CL_{PAH}**

In figures Epro-024-1 and Epro-024-2, the pre-dose CL_{PAH} data on days 7 and 8 indicated that steady state levels of PAH could be assumed. The mean CL_{PAH} data were similar on days 7 and 8 for Regimen D (placebo).

CL_{PAH} during Regimen A was indistinguishable from that during placebo on day 7 (on SB 203220 600 mg qd x 7 days) and on day 8 (after addition of single oral dose of captopril 25 mg).

In contrast, the mean CL_{PAH} was consistently, albeit slightly, higher during Regimen B (eprosartan 300 mg q12h for 7 days) than placebo, and addition of a single oral 25 mg dose of captopril on day 8 produced mean CL_{PAH} which were higher than placebo on day 8.

During Regimen C (captopril 25 mg t.i.d for 7 days) the mean CL_{PAH} was lower relative to placebo (markedly at 6 hours post-dose); after addition of eprosartan 300 mg to Regimen C on day 8, the mean CL_{PAH} was similar to placebo but higher than that on day 7 for Regimen C (captopril alone).

Figure Epro-024-1. Time course of CL_{PAH} data on day 7

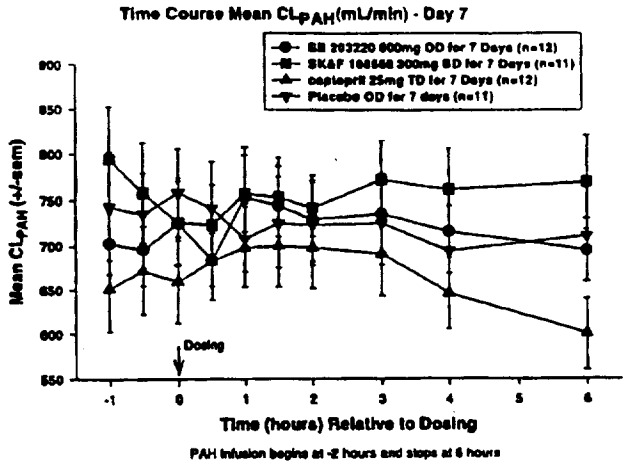
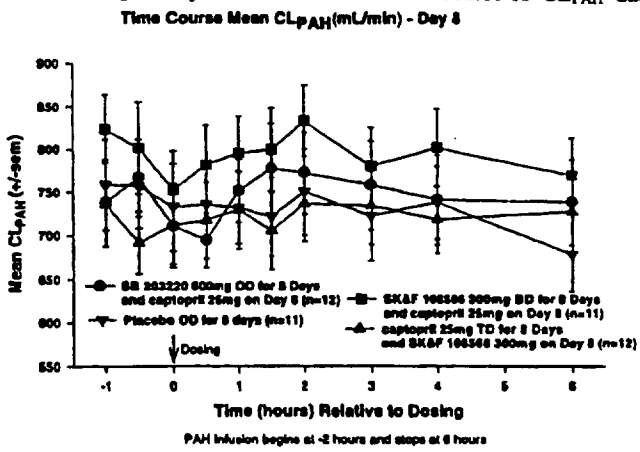


Figure Epro-024-2. Time course of CL_{PAH} data on day 8



24.4.2 Glomerular filtration rate (GFR) as measured by CL_{IN}

The pre-dose CL_{IN} data in figures Epro-024-3 and Epro-024-4 indicated that the steady state levels of inulin may not have been reached prior to dosing, that small incremental increases in mean CL_{IN} after dosing were present for placebo (Regimen D), and the all regimens follow the same pattern and are indistinguishable from each other on body days 7 and 8.

Figure Epro-024-3. Time course of CL_{IN} data on day 7

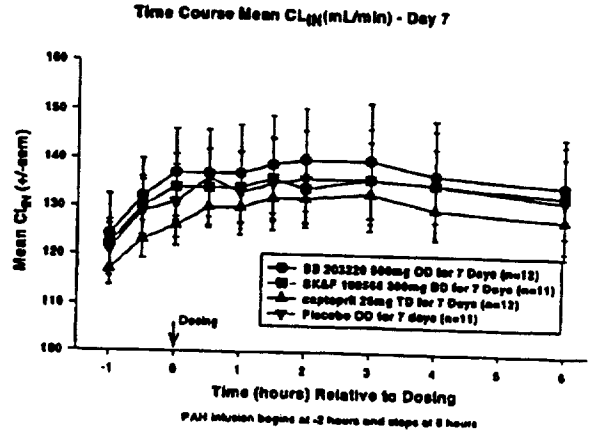
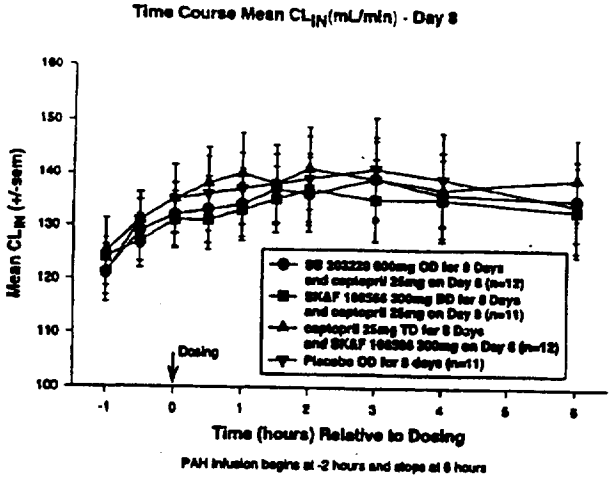


Figure Epro-024-4. Time course of CL_{IN} data on day 8



24.4.3 **Time point comparisons of interest:**

On Day 7 of captopril 25 mg t.i.d, mean CL_{PAH} prior to dosing was significantly lower than that seen with placebo; six hours post-dose, CL_{PAH} was significantly higher for eprosartan than for captopril. The peak post-dose CL_{PAH} responses were similar for all regimens relative to background variability on Day 7.

Comparison of Day 8 to Day 7 CL_{PAH} for each active regimen revealed no significant effect of the addition of a single oral dose of 25 mg captopril to a 7 day regimen of either SB 203220 or eprosartan. The addition of a single oral dose of eprosartan 300 mg on the captopril regimen was not discernible from background variability prior to dosing or for peak post-dose response. However, the 6-hour post-dose response could be differentiated from background variability (128.3 ml/min; 95% CI = 51.5 to 205.0 ml/min).

There was no significant difference for the time point comparisons of interest for the CL_{IN} data.

24.5 **CONCLUSION**

Repeat dose administration of SB 203220, eprosartan and captopril showed no differences in the safety profiles (clinical and laboratory) between the active treatments and placebo.

This study was conducted because of an unexpected finding in Study Protocol 108566/006 that Eprosartan caused a clinically significant rise in effective renal plasma flow (ERPF) in salt-loaded individuals.

ERPF measured on Days 7 and 8 by plasma clearance of para-amino hippurate (CL_{PAH}) was similar following a 7 days course of SB 203220 (600 mg/day) or placebo.

ERPF increased following 7 days of eprosartan (300 mg q 12 h) and decreased following 7 days of captopril (25 mg t.i.d) relative to placebo.

At 6-hours post-dose, the mean CL_{PAH} for captopril was significantly lower than placebo, and the mean CL_{PAH} for eprosartan was significantly higher than for captopril.

Glomerular filtration rate (GFR) measured on Days 7 and 8 by plasma clearance of inulin (CL_{IN}) was not able to be discerned because steady state levels of inulin had not been reached prior to the dosing.

Protocol 025 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.112)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *18-Jun-1997*
DATE COMPLETED *19-Jun-1997*

25.1. STUDY PROTOCOL

25.1.1 **Title** ***A study to evaluate the effect of age and gender on the pharmacokinetics of SK&F 108566 in healthy volunteers***

25.1.2 **Rationale**

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the effect of age and gender on the pharmacokinetics and safety of a single oral dose of eprosartan.

25.1.3 **Objectives**

1. To compare the pharmacokinetics of a single oral dose of eprosartan between young men and elderly men, and between young men and premenopausal women, and,
2. To investigate the plasma protein binding of eprosartan in young male, young female and elderly male subjects.

25.1.4 **Study design**

The study was an open-label, parallel group, single oral dose (200 mg of eprosartan) study of three groups of subjects (A = young men (reference group); B = young women, and C = elderly men). Eligible subjects were administered a single oral dose of eprosartan (200 mg tablets (Lot# U-93234) x 1 tablet) following a light breakfast. Plasma specimens for pharmacokinetic analysis were obtained pre-dose and during 24 hours post-dose.

25.1.5 **Protocol Amendments**

There were no amendments to the protocol.

25.1.6 **Population enrolled/analyzed**

24 healthy, adult volunteers (8 young male, and 8 young female 18-45 years of age (age-matched), and 8 elderly male ≥ 65 years of age), weight > 50 kg and within 20% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled. Female subjects have to be non-pregnant and non-lactating, and were required to have a negative serum pregnancy test, and willing to use an IUD or a barrier method of contraception between screening and follow up.

Compliance: All eprosartan doses were administered by the clinical pharmacology unit personnel.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. A gynecological examination was performed for female subjects unless one has been done within 12 months. Female subjects of child-bearing potential were required to have a negative serum pregnancy test, and were instructed to use an IUD or a barrier method of contraception if engaging in sexual intercourse during the interval between screening and follow-up. Blood (15 ml) and urine samples were obtained for laboratory tests {hematology, chemistry, liver function tests, urinalysis and drug screen, and , for female subjects, serum total human chorionic gonadotropin (hCG)}. Subjects were not permitted to take any prescription or non-prescription medications 1 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and following each dose of study medication.

25.1.7 **Study procedures**

After an 10-hour overnight fast, subjects reported at 7:00 am. Assessment of baseline symptoms and vital signs, and a 12-lead ECG recording were made. Blood and urine samples were taken for clinical laboratory tests, including hCG for female subjects. Subjects were given a light breakfast of cereal, milk, fruit juice (except grapefruit) and muffin at 7:30 am, which was completely consumed within 20 minutes. Within 20 minutes of finishing the meal, subjects were administered a single 200 mg (2 tablets of 100 mg each) oral dose of eprosartan with 240 ml of tepid water. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. No vigorous exercise was permitted. Subjects drank 240 ml water at 2 and 4 hours after dosing. Water, soft drinks without caffeine, fruit juices (except grapefruit juice) were allowed *ad lib* beginning 5 hours after dosing and lunch and dinner were given at 5 and 9-10 hours post dose, respectively. Blood sample (5 ml) collections for

pharmacokinetics were done prior to dose administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours following dosing.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

Subjects returned 7-10 days following administration of eprosartan, at which time safety laboratory tests, including serum hCG for female subjects, were done.

25.1.8 **Pharmacokinetic procedures:**
Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers, frozen at -20°C, and assayed within 5 months. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) for eprosartan in plasma was 10.0 ng/ml based on 0.5 ml aliquots.

Plasma protein binding of eprosartan was determined using an ultrafiltration method with labeled [^{3}H]eprosartan analyzed by liquid scintillation counting to assess the percent fraction unbound.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), $T_{1/2}$, AUC(0-τ), AUC(0-∞). The percent extrapolated was determined by the ratio of [AUC(0-∞) - AUC(0-τ)] to [AUC(0-∞) x 100].

25.1.9 **Endpoints:**
AUC(0-∞) and Cmax were primary endpoints. Clinical monitoring and laboratory safety data were secondary endpoints.

25.1.10 **Sample size:**
Based on a between-subjects coefficients of variation of 32.4% for AUC(0-∞) and 38.5% for Cmax, and a Type I error rate of 5%, a sample size of 8 per group was estimated to provide 90% power to detect difference s of at least 50% between the two groups (young women and the elderly), using a 2-tailed procedure and a critical range symmetric on the $\log_e$ scale. (In this study, the coefficients of variation were 67.0% for AUC(0-∞) and 76.3% for Cmax after $\log_e$ transformation. Based on this finding, 21 subjects per groups would have been necessary. The results from this study, therefore, do not have the required power, and have led to wide 95% confidence intervals.)

25.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 24-Mar-1994 through 09-Aug-1994.

25.2 **STUDY POPULATION**

25.2.1 **Subject disposition:**
24 healthy, adult volunteers (8 young male, and 8 young female, and 8 elderly male ≥ 65 years of age) were enrolled. The young men were 20-39 (mean = 28) years old, weighed 72.0 to 89.9 (mean = 79.1) kg, and were 169-191 (mean = 180) cm tall. The young women were 19-36 (mean = 27) years old, weighed 52.7 to 72.8 (mean = 62.5) kg, and were 152-177 (mean = 165) cm tall. The elderly men were 68-78 (mean = 73) years old, weighed 65.7 to 100.7 (mean = 80.4) kg, and were 165-186 (mean = 177) cm tall.

25.2.2 **Withdrawals:**
There were no withdrawals from this study.

25.2.3 **Protocol violations:**
One subject (#251, elderly man) took nutrition supplements within one week prior to receiving study medication. Subject #280 (young female) had a viral infection 1 day prior to receiving study medication. Subject #281 (young female) had a hemolyzed serum sample that showed a serum potassium of 7.0 mEq/l and total bilirubin of 1.83 mg/dl just prior to dosing.

25.3 **SAFETY RESULTS**

25.3.1 **General considerations:** A total of 14 adverse experiences were reported in 13 subjects.

25.3.2 **Deaths:** There were no deaths during this study.

25.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

25.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

25.3.5 **Adverse Events:** All adverse events were mild to moderate in nature. The AEs are summarized as follows:

1. Elderly Men (2 AEs in 2 subjects): Subject #253 reported backache and subject #255 reported dizziness;
2. Young Men (6 AEs in 5 subjects): Subject #269, #271, #272, #272, and #277 reported headache, and #277 also reported backache.
3. Young Female (6 AEs in 6 subjects): Subjects #264, #266 and #280 reported headache, and #263, #265 and #281 reported dizziness.

25.3.6 **Laboratory findings, ECGs, Vital signs**

There were no changes in pulse rate. 3 elderly men reported blood pressure changes: subject #254 had increased systolic and diastolic blood pressure, subject #257 had decreased diastolic blood pressure on 3 occasions, and subject #260 had decreased diastolic blood pressure. One young male (#273) and one young female (#281) had decreased systolic blood pressure.

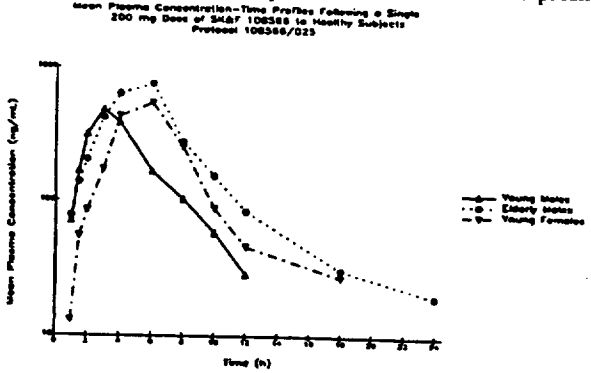
There were no changes in the ECGs that were of potential clinical concern.

5 subjects (1 elderly man and 4 young women) had changes in laboratory parameters outside of potential clinical concern. One elderly man (#251) had a total bilirubin of 2.55 mg/dl at follow up (which decreased to 1.5 mg/dl 18 days later). One female subject (#265) had a serum potassium of 5.6 mEq/l 24 hours after dosing which fell to 3.8 mEq/l one week later. A female subject (#267) had WBC count of 2.7 x 10^3/mm^3 prior to drug administration, which came up to 3.5x10^3/mm^3 one week later. Two females (#263 and #266) had RBCs in their urine which were negative at second urinalysis. There were no other laboratory values of potential clinical concern.

25.4. **PHARMACOKINETIC RESULTS**

Following a single oral dose of 200 mg eprosartan (Figure Epro-025-1) the mean plasma concentration-time profiles for young men, young women and elderly men were characterized by peak plasma concentrations between 2 and 4 hours for young males and females and 3-6 hours for elderly men. Subsequent plasma concentrations of eprosartan declined in a multi-exponential manner. Plasma levels of eprosartan were measurable up to 12-18 hours in young males and young females, and up to 24 hours in elderly men.

Figure Epro-025-1. Mean plasma concentration-time profiles of eprosartan



Total Eprosartan pharmacokinetics:

AUC(0-∞) and Cmax in the elderly were, on average, 2.3 and 2-fold, respectively, higher than those in young males (Table Epro-025-1), the point estimates for the ratio of geometric means in elderly males relative to young males being 2.3 and 1.98, respectively, with a 95% confidence intervals of (1.22, 4.34) and (0.98, 4.00), respectively (Table Epro-025-1). Tmax was delayed in the elderly males compared to young males (Table Epro-025-1), with a median difference of 2.53 hours and 95% confidence interval of (1.00 h, 3.01 h) (Table Epro-025-2).

There was no apparent difference in AUC(0-∞) or Cmax or Tmax or terminal half-life ($T_{1/2}$) values between young males and young females (Tables Epro-025-1 and Epro-025-2).

Table Epro-025-1. Pharmacokinetic values for single oral dose (200 mg) eprosartan in young males, young females and elderly males.

End Point	Young Males	Young Females	Elderly Males
AUC(0-∞) (ng.h/ml)			
Geometric Mean	1828	1817	4215
Mean	2171	2322	4572
Median	1429	1383	4600
S.D.	1544	1806	1653
Cmax (ng/ml)			
Geometric Mean	418	435	828
Mean	498	599	914
Median	349	323	940
S.D.	347	509	353
Tmax (h)			
Mean	2.75	3.52	4.89
Median	3.00	4.00	5.04
S.D.	0.46	0.76	1.25
T1/2 (h)			
Mean	2.81	3.76	6.19
Median	2.89	3.10	5.79
S.D.	0.49	2.04	1.58
fu (%)			
Mean	2.11	2.15	2.17
S.D.	0.31	0.22	0.22
Free AUC(0-∞) (ng.h/ml)			
Geometric Mean	38.2	38.9	91.2
Mean	44.7	49.7	98.5
Median	32.6	30.5	106.8
S.D.	30.5	40.5	34.6
Free Cmax (ng/ml)			
Geometric Mean	8.73	9.32	17.92
Mean	10.19	12.86	19.82
Median	7.95	7.65	19.08
S.D.	6.65	11.23	7.93

Table Epro-025-2. Point Estimates and 95% confidence intervals of comparisons of eprosartan in young females and elderly males compared to young males

Parameter	Comparison	Point Estimate	95% Confidence Interval
AUC(0-∞) †	Young Female : Young Male	0.99	(0.53, 1.87)
	Elderly Male : Young Male	2.31	(1.22, 4.34)
Cmax†	Young Female : Young Male	1.04	(0.51, 2.10)
	Elderly Male : Young Male	1.98	(0.98, 4.00)
Tmax (h)§	Young Female : Young Male	1.00 h	(0.00 h, 1.07 h)
	Elderly Male : Young Male	2.53 h	(1.00 h, 3.01 h)
*T1/2 (h)**	Young Female : Young Male	0.95 h	(-0.63 h, 2.53 h)
	Elderly Male : Young Male	3.38 h	(1.80 h, 4.95 h)
fu (%)	Young Female : Young Male	0.04%	(-0.23%, 0.31%)
	Elderly Male : Young Male	0.06%	(-0.21%, 0.33%)
Free AUC(0-∞) †	Young Female : Young Male	1.02	(0.55, 1.90)
	Elderly Male : Young Male	2.39	(1.29, 4.44)
Free Cmax†	Young Female : Young Male	1.07	(0.53, 2.14)
	Elderly Male : Young Male	2.05	(1.02, 4.12)

† Data presented as the ratio of the geometric means for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)
§ Data presented as the estimated median difference in Tmax for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)
* Data presented as the mean difference in $T_{1/2}$ for digoxin with eprosartan (Regimen B) relative to digoxin alone (Regimen A)

Unbound Eprosartan pharmacokinetics:
There were large variations in the unbound fractions at 12 hours for the elderly males and at 6 hours for young females. No apparent differences were found in the mean fraction unbound between elderly males relative to young males. The mean difference for the elderly relative to young males was 0.06 {95% confidence interval (-0.21, 0.33)}. On the other hand, free AUC(0-∞) and free Cmax values were, on average, 2.3 and 2.05-fold higher, respectively, in the elderly males {95% confidence intervals (1.29, 4.44) and (1.02, 4.12)} compared to young males (Tables Epro-025-1 and Epro-025-2).

No apparent differences were found in the mean fraction unbound between young females relative to young males, the mean difference of young females to young males being 0.04% {95% confidence interval (-0.23%, 0.31%)} (Table Epro-025-2). Similarly, no apparent difference s were observed in free AUC(0-∞) and free Cmax values between young males and young females (Tables Epro-025-1 and Epro-025-2).

There was a large variation with between-subject coefficients of variations about 67% to 76% for AUC(0-∞) and Cmax, with the young female group having consistently higher coefficient of variation than young or elderly males. This resulted in considerable overlap in the range of individual values among all three groups.

25.5 CONCLUSION

Single oral dose administration of eprosartan (200 mg) to healthy male and female volunteers and elderly males did not show any significant differences in adverse experiences. There were no ECG or abnormal laboratory values of potential safety concern.

Following a single oral dose of 200 mg eprosartan, the mean plasma concentration-time profiles were characterized by peak plasma concentrations between 2 and 4 hours for young males and females and 3-6 hours for elderly men. Subsequent plasma concentrations of eprosartan declined in a multi-exponential manner. Eprosartan was highly protein bound to plasma proteins (approximately 98%) with no apparent differences in the mean fraction unbound between elderly males or young females relative to young males.

There was a large variation with between-subject coefficients of variations about 67% to 76% for AUC(0-∞) and Cmax, with the young female group having consistently higher coefficient of variation than young or elderly males. Total and free mean AUC(0-∞), mean Cmax and mean Tmax values in the elderly were > 2-fold larger compared to young males. On the other hand, there was no apparent difference in total and unbound AUC(0-∞) or Cmax, and in Tmax or terminal half-life ($T_{1/2}$) values between young males and young females.

Protocol 026	NDA 20-738	Teveten™ (Eprosartan) Tablets	(Vol. 1.085/86)
DATE OF CORRESPONDENCE:	*11-Oct-1996*	DATE ASSIGNED:	*15-May-1997*
DATE RECEIVED:	*18-Oct-1996*	DATE COMPLETED	*16-May-1997*

26.1 STUDY PROTOCOL

26.1.1 Title

A study to determine the effect of SK&F 108566 on the renal hemodynamics of patients with mild to moderate essential hypertension

26.1.2 Rationale

A substantial proportion (up to 50%) of patients with essential hypertension are "salt-sensitive" or "non-modulators", and have abnormal renal and adrenal responses to changes in sodium intake independent of fluid balance or total body sodium, impaired renal sodium handling and salt-dependent blood pressure elevation. ACE inhibitors appear to be more effective in these non-modulators, because of the importance of intrarenal A-II in their blood pressure response. A-II receptor antagonists also affect the conversion of angiotensinogen to A-I, and offer potential therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. An A-II AT_1 receptor antagonist (eprosartan, which is orally active) is used in this study to determine whether the renal/adrenal effects of ACE inhibitors are related to the ability of these agents to block A-II production.

26.1.3 Objectives

1. To estimate the effect of single and repeated oral doses of eprosartan on the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in patients with mild to moderate hypertension
2. To describe the effect of single and repeated oral doses of eprosartan on urinary electrolyte excretion in patients with mild to moderate hypertension;
3. To assess the safety and tolerability of single and repeated oral doses of eprosartan in patients with mild to moderate hypertension

26.1.4 Study design

The study was a randomized, double-blind, placebo-controlled, two-period, period-balanced crossover study. Adult male subjects with mild to moderate essential hypertension 18-70 years received one of the following during separate study periods:

1. eprosartan (100 mg x 3 tablets (Lot# U94068) q 12 h for 28 days,) or
2. matching placebo (Lot# U94111) q 12 h for 28 days.

Following a minimum 14-day to maximum 6-week washout period, subjects were crossed over to receive the other treatment. Subjects were allocated at random to 1 of two treatment sequences (EP or PE), ensuring period-balance for treatments. Blood and urine samples for determination of effective renal plasma flow (ERPF) using (PAH) clearance (CL_{PAH}), and glomerular filtration rate (GFR) using inulin clearance (CL_{IN}) were obtained on Day 1 and day 28 of each study period. Subjects returned for follow up within 5 - 10 days of Day 28 of the last study period for a physical examination and a safety laboratory evaluation.

26.1.5 Protocol Amendments

There were 3 amendments to the original protocol. In Amendment 1, subjects who smoked were allowed to enroll into the study. Amendment 2 consisted of a change in the clinical laboratory performing blood and urine tests. Amendment 3 removed the requirement for African-American and Caucasian patients to be matched for age and weight, and the formal statistical comparisons between race groups.

26.1.6 Population enrolled/analyzed

25 male subjects 18-70 years of age, and weight > 50 kg and within 25% of ideal weight (based on height) with mild to moderate essential hypertension (average sitting diastolic BP between 90-115 mmHg without treatment at screening at weeks -2 and -1) with negative urine drug screen were enrolled.

Compliance: On study days 1, 7, 14, 21 and 28, morning doses of study medication were administered at the Drug Evaluation Unit. After Day 1, a sufficient supply of study medication was dispensed, and subjects were instructed to take 3 tablets every 12 hours. Compliance was assessed by tablet count.

Pre-study screening: The screening visit (60 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for

laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were given an oral water load of up to 20 ml/kg to determine their ability to provide sufficient urine at a flow rate of at least 3 ml/min to allow for adequate renal function testing. Subjects on antihypertensive medications at screening were instructed to discontinue all medications at least 2 weeks prior to enrollment.

26.1.7 **Study procedures**

Inulin and PAH clearance tests were performed on Days 1 and 28 of each study period.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, nursing observation, physical examination findings, laboratory findings and 12-lead ECG data.

26.1.8 **Evaluation criteria:**

Safety Parameters: Blood pressure, pulse rate, ECG data and clinical laboratory data were reviewed.

Pharmacodynamic Assessments: The Primary Efficacy Endpoints were: ERPF measured by plasma clearance of para-amino hippurate (CL_{PAH}), and GFR measured by plasma clearance of inulin (CL_{IN}). Calculated clearances were not corrected for subject's body surface area. For each primary endpoint, five clearance measures were used in the statistical analysis: pre-dose, average, maximum, maximum percent change from pre-dose and time to maximum. The Secondary Efficacy Endpoints were: clinical safety, laboratory data and urinary electrolyte excretion, in addition to fractional excretion and urinary excretion rates for Na, K, Cl, and uric acid, filtration fraction (CL_{IN}/ CL_{PAH}), and CL_{CR}/CL_{IN} and U_{UA}/U_{CR} ratios.

26.1.9 **Sample size:**

Based on a within-subject coefficient of variation (CV_W) of 12.8% and 11.7% for CL_{PAH} and CL_{IN} respectively, in a previous study, to detect differences of at least 25% on a 2-tailed test with a type I error rate of 5%. and 90% power between placebo and eprosartan, it was estimated that a sample size of 6 within each group would be necessary.

26.1.10 **Investigator , Center and Study Dates:**

Suzanne Swan, MD, Drug Evaluation Unit, Minneapolis Medical Research Foundation, 914 South 8th Street, Minneapolis, MN 55404. Study Dates: 8-Feb-1995 to 5-Mar-1996

26.2 STUDY POPULATION

26.2.1 **Subject disposition:**

Of 25 subjects screened, 10 failed to meet entrance criteria. 15 male subjects, 30-69 (mean = 53±9.6) years of age, weighing 61.8 to 117.3 (mean = 87.9±12.4) kg, and 166-193 (mean = 176±7.1) cm tall, were randomized. 14 of the 15 subjects received at least one dose of study medication; one subject withdrew after randomization (during PAH/inulin infusion) but prior to receiving any study medication. There were 11 patients each who received placebo or eprosartan; 8 patients received both.

26.2.2 **Withdrawals:**

Table Epro-026-1. Subjects withdrawn from the study

Subject Status	Last treatment received		Total number
	Eprosartan	*Placebo*	*of subjects*
Completed study	5	3	8*
Withdrawn			
Adverse experience	1 #001	1 #005	2
Termination by Sponsor	1 #014	0	1
Other	1 #006	2 #004 #010	4** #011
Total withdrawn	3	3	7**

* All subjects received both treatments

** Subject #011 withdrew during first PAH/inulin infusion, prior to dosing with study medication

Seven subjects were withdrawn from the study (Table Epro-026-1). Subject #011 withdrew from the study (due to schedule conflicts) during the initial PAH/inulin infusion prior to dosing with study medication. Subject #006

withdrew after completing eprosartan period in session 1 because of too many i.v. sticks. Subject #004 withdrew after completing placebo period in session 1. Subject #010 withdrew after 17 days of placebo in session 1. Subject #014 was withdrawn after eprosartan for 27 days due to concomitant use of non-steroidal anti-inflammatory drugs.

Two subjects were withdrawn due to adverse experiences. Subject #001 was withdrawn after receiving eprosartan for 17 days because of severe pancreatitis and moderate dehydration requiring hospitalization. Subject #005 on placebo for 26 days was withdrawn from the study due to moderate chest pain.

26.2.3 **Protocol violations:**

The following protocol violations occurred which the sponsor submitted did not effect the safety nor the inferences of the pharmacodynamic analyses performed in this study.

Subject	Description of Protocol Violation
008, 015	creatinine clearance < 70 ml/min at screening; enrolled based upon 24 hour CL_{CR}
014	body weight not within 25% of ideal, took Naprosyn® during the study
005	single dose of study medication taken late, took aspirin during the study
004	subject standing before plasma renin activity sample was drawn
007, 010, 012, 013, 015	individual serum K+ not done due to incorrect sample processing
012	individual urine creatinine assays not done
005, 015	individual pre-dose plasma renin activity assays not done
001, 002, 003, 004	administration of prohibited medication prior to or during the study (Pepcid®, Cata-TTS-3; Procardia®, Vaseretic®, enalapril, hydorchlorothiazide)

26.3 SAFETY RESULTS

26.3.1 **General considerations:** 42 adverse experiences (AEs) were reported for 13 subjects. 20 AEs occurred in 4 subjects while receiving eprosartan, and 22 occurred in 10 subjects receiving placebo.

26.3.2 **Deaths:** There were no deaths during this study.

26.3.3 **Withdrawals due to adverse experiences:** There was two withdrawals due to adverse experience during this study (Table Epro-026-1 above): Subject #001 was withdrawn because of severe pancreatitis and moderate dehydration requiring hospitalization, and Subject #005 was withdrawn due to moderate chest pain.

26.3.4 **Serious, Non-fatal Adverse Events:** There was one serious non-fatal adverse experience during this study. Subject #001 was withdrawn after receiving eprosartan for 17 days because of severe pancreatitis (allegedly following a bout of alcohol intake diagnosis being supported by elevated amylases 231 and 404 units) and moderate dehydration requiring hospitalization. In the CRF at enrollment the patient was checked as having no history of alcoholism, but the narrative of the adverse event stated that this patient had a history of ethanol abuse. The pancreatitis was resolved with conservative treatment, and patient was discharged from hospital after 6 days.

26.3.5 **Adverse Events:** The most common AE following both eprosartan and placebo treatment was headache. The adverse events were mild to moderate in nature, except for the pancreatitis in Subject #001 which was severe resulting in withdrawal from the study. All AEs, except for pre-existing anemia in subject #002, resolved.

26.3.6 **Laboratory findings, ECGs, Vital signs**

There were no changes in mean heart rate, mean systolic blood pressure or mean diastolic blood pressure of potential clinical concern as defined by protocol. Subject #004 (on placebo) and #009 (on eprosartan) had decreases in systolic blood pressure of potential concern, but they are sporadic and asymptomatic. There were no ECG changes (in PR, QRS and QTc intervals) that were of potential concern. No instances of prolongation of QTc > 460 msec were observed.

The laboratory data showed no values for potential clinical concern according to protocol-defined criteria except in one subject (subject #014) who had decreased hemoglobin (from 13.1G/dl at pre-study screening decreased to 11.9 G/dl at Day 28 pre-infusion blood sample and 11.6 G/dl at follow up) and hematocrit (from 39.2% at pre-study screening decreased to 35.2% at Day 28 and 34.5% at follow up). Additional blood samples were not obtained after follow up.

26.4. PHARMACODYNAMIC RESULTS

26.4.1 PAH and Inulin Clearances

The primary endpoints were based on statistical analysis of results on the 8 subjects who completed the study. The observed within-subject coefficients of variation (CV_W%) were comparable to those used in initial sample size and power calculations, and the sponsor proposed that the small sample size of 8 subjects did not appear inadequate for statistical analysis.

There was no substantial differences in effective renal plasma flow or glomerular filtration rate, as measured by average and maximum post-dose PAH and inulin clearance , respectively, between eprosartan and placebo.

Primary endpoint differences within race groups: Only one African-American subject (#002) completed the study. Removal of subject #002 reduced the non-Normality observed in pre-dose CL_{PAH} data on day 1, because this subject exhibited a large difference between regimens relative to other subjects.

Impact of subject dropout on primary endpoint: No notable differences were observed in Mean (SE) CL_{PAH} and CL_{IN} by adding the data of dropouts relative to those based on the 8 subjects who completed the two treatment regimens.

26.4.2 Urine Electrolyte Excretion

Urinary fractional excretion of Na^+, K^+ and uric acid, urinary excretion rates of Na^+, K^+ and uric acid, filtration fraction (CL_{IN}/ CL_{PAH}), CL_{CR}/CL_{IN} and U_{UA}/U_{CR} ratios, were similar after treatment with eprosartan compared to placebo. Overall, this suggests that there were no changes in mean fractional excretion of urine electrolytes and in urine electrolyte excretion rates associated with eprosartan compared to placebo.

26.4.3 Aldosterone and Plasma Renin Activity

There were no apparent changes in mean serum aldosterone concentration nor in plasma renin activity between eprosartan treatment group and placebo group.

There were no correlations between either maximum or average post-dose CL_{PAH} and pre-dose plasma renin activity at either Day 1 or Day 28.

26.5. CONCLUSION

Single or repeat dose administration of eprosartan 300 mg, orally, twice daily for 28 days to subjects with mild to moderate essential hypertension showed no increase in the frequency or severity of adverse experiences compared to placebo. There were 2 withdrawals due to adverse experiences. The protocol violation (history of alcoholism) that was "discovered" after the patient was hospitalized for "pancreatitis" is to be taken into consideration in determining whether pancreatitis could be an adverse event associated with eprosartan. The safety data base should be checked for any more events of (1) pancreatitis and (2) lab reports of anemia after receiving eprosartan.

While hypertensive subjects have reduced effective renal plasma flow compared to healthy volunteers, in this study, no significant change in effective renal plasma flow or glomerular filtration rate was found after administration of eprosartan compared to placebo.

The results indicated that renal blood flow and glomerular filtration were not increased by eprosartan. The sponsor suggested that this lack of increase in renal blood flow after eprosartan treatment could be attributed to the fact that these hypertensive subjects might be in a state of chronic renal vasodilatation already, and did not have the renal reserve necessary to result in an increase in renal blood flow after eprosartan treatment.

There were no apparent natriuretic or kaliuretic effects, and no uricosuric effect of eprosartan.

Protocol 027 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.112)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *17-Jun-1997*
DATE COMPLETED *17-Jun-1997*

27.1. STUDY PROTOCOL

27.1.1 Title *A study to determine the effect of SK&F 108566 on the anticoagulant effect of Warfarin*

27.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. Since hypertension and cardiac disease are frequently found together in the same patient population, it is likely that eprosartan will be prescribed together with Warfarin. Eprosartan is >97% bound to plasma proteins, and may therefore alter warfarin binding to albumin. This may in increase the amount of free warfarin or cause preferential displacement of one of the warfarin enantiomers, resulting in altered anticoagulant effects of warfarin. This study determines if there is any potential interaction between eprosartan and warfarin

27.1.3 Objectives

1. To estimate the effect of eprosartan (SK&F 108566) on the anticoagulant activity of warfarin at steady state,
2. To assess the safety and tolerability of concomitant administration of eprosartan and warfarin, and
3. If an effect on anticoagulant activity were shown, then to investigate the effect of eprosartan on the pharmacokinetics of the S- and R- enantiomers of warfarin.

27.1.4 Study design

The study was a randomized, double-blind (eprosartan dosing phase only), placebo-controlled, parallel group study of the pharmacodynamics with/without pharmacokinetics of warfarin in the absence and presence of eprosartan in 24 male volunteers. After a run-in period of 14 days with warfarin (Coumadin®, Lot# X94139 (1 mg), X94140 (2 mg), X94141 (2.5 mg), X94142 (5 mg) by DuPont Pharmaceuticals) to achieve a stable (variation ≤20%) baseline INR of 1.3 to 1.6 on Days 12, 13 and 14, subjects were randomized to either:

1. Eprosartan (100 mg tablets (Lot# U-94068) x 3) 300 mg twice/day plus warfarin for 7 days, or
2. Matched placebo (Lot# U-94111) 3 tablets twice/day plus warfarin for 7 days.

Subjects continued to take the warfarin dose established during the 14 day run-in period. Subjects received Vitamin K 10 mg (Lot# X94138) by subcutaneous injection at the conclusion of the study to reverse the warfarin effect.

27.1.5 Protocol Amendments

There were no amendments to the protocol.

27.1.6 Population enrolled/analyzed

41 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 20% of ideal weight (based on height), without history of bleeding diatheses or coagulopathy, and a negative urine drug screen within 30 days were screened.

Compliance: Each dose of study medication (warfarin, eprosartan/placebo, Vitamin K) was administered in the clinical pharmacology unit under observation of the nursing staff.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, coagulation profile (including PTT and PT), urinalysis and drug screen). Subjects were not permitted to take prescription or non-prescription medications or aspirin and aspirin-containing compounds during the study, alcohol and tobacco within 72 hours prior to and during the study period, and xanthine and caffeine containing products within 24 hours prior to and during the pharmacokinetic sampling days (Days 13-14 and 21-22).

27.1.7 Study procedures

Warfarin Run-In Phase: Eligible subjects reported at 7:00 am, and remain at the research testing center for the duration of the study. A limited physical examination and assessment of baseline symptoms and vital signs were done. Blood and urine sample collection were made for safety laboratory tests. Warfarin 10 mg was administered

orally with 120 ml water. Subjects fasted 2 hours before and 1 hour after dosing. Standard meals were provided for the duration of the study. Consumption of uncooked vegetable was prohibited during the study. Blood was collected each day just prior to warfarin dosing for determination of PT, and to maintain each subject's INR between 1.3 and 1.6. Dose adjustments were assisted with the computer dosing program (DrugCalc). No dose adjustments >25% were permitted after Day 7. Blood samples were drawn and stored prior to dosing on Days 12 and 13 for confirmation of steady state warfarin enantiomer concentrations, in the event that such analyses were needed.

On Day 14, after an overnight fast and a limited physical examination, blood and urine samples were taken and a 12-lead ECG recording made. The daily warfarin dose was administered orally with 120 ml water and the fasting state maintained for 1 hour. Vital signs were recorded pre-dose, and at 1, 4 and 8 hours post-dose. Blood sample (7 ml) collections for pharmacokinetics were done prior to warfarin dose administration and at ~0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours following warfarin dosing.

Eprosartan/Placebo Dosing Phase: On Day 15, after similar procedures to Day 14, and following warfarin dosing, the study medication (eprosartan 300 mg or placebo 3 tablets) was administered 2 hours after the morning meal. The subject remained fasting for 1 hour after dosing. Vital signs were recorded pre-dose, and at 1, 4 and 8 hours post-dose on Days 15 and 21. Pharmacokinetic samples were drawn and stored prior to and after receiving warfarin dose on Day 21. Subjects who had INR ≥1.9 for 2 successive determinations during the eprosartan/placebo dosing phase were discontinued from the study and received Vitamin K 10 mg subcutaneously.

Post-Treatment Phase: After the last blood sample was collected, each subject received a subcutaneous injection of Vitamin K 10 mg. A complete physical examination, vital signs assessment (sitting blood pressure and heart rate), body weight measurement and a 12-lead ECG were performed. Blood samples were taken for clinical safety laboratory tests. Subjects remained in the research testing center until the PT began to fall from the Day 21 value.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings (Days 1, 14 and 22), 12-lead ECG changes (Day 14 and 22) and vital signs (Days 1, 14, 15, 21 and 22).

27.1.8 **Pharmacokinetic procedures:**

Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C and 2000 rpm for 20 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 3 months. Plasma concentrations of R(+) and S(-) warfarin were to be determined by a stereospecific HPLC assay following coupling of the enantiomers to the optically active reagent carbobenzyl-L-proline.

Pharmacokinetic assay for warfarin were to be done only if:

1. the point estimate of the ratio for INR for warfarin plus eprosartan : warfarin plus placebo was ≤0.80 or ≥1.20 or the 90% confidence interval was not completely contained within the 25% equivalence range for (warfarin + eprosartan) - (warfarin + placebo), or
2. INR was ≥ 1.9 on two consecutive determinations for two or more subjects while on warfarin + eprosartan, or
3. there was a clinically significant bleeding episode in 1 or more subjects randomized to warfarin + eprosartan.

27.1.9 **Endpoints:**

The INR on Day 22 was subjected to ANCOVA with terms for treatment (eprosartan or placebo), the baseline INR (average of INR on Days 12, 13 and 14) as the covariate, and the interaction term between treatment and baseline INR included in the model.

27.1.10 **Sample size:**

Based on residual INR coefficients of variation (CV_{resid}) of 13.1% in a previous study, a sample size of 8 per group would provide 90% power to determine lack of effect of eprosartan on the anticoagulant activity of warfarin using an equivalence range of 25% (i.e., the 90% confidence interval of (warfarin + eprosartan) - (warfarin + placebo) should be contained within the range $-0.25*u_B$, + $0.25*u_B$, where u_B refers to the mean response in the placebo group).

27.1.11 **Investigator , Center and Study Dates:**

David Kazierad, Pharm. D., Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York.
Dates: 03-Oct-1994 to 22-Nov-1994

27.2 **STUDY POPULATION**

27.2.1 **Subject disposition:**

41 healthy male volunteers were screened; 15 failed to meet entrance criteria, and 5 did not come for study initiation. Thus, 21 subjects entered the warfarin run-in phase. 18 subjects, 21-42 (mean = 30) years of age,

weighing 57.5 to 102.0 (mean = 79.3) kg, and 164-188 (mean = 176) cm tall, were randomized. 11 subjects received eprosartan and 7 subjects received placebo.

27.2.2 **Withdrawals:**
3 subjects (#006, 012 and 014) did not meet the criteria ($1.3 \leq INR \leq 1.6$) to continue into the double-blind study medication phase, and were withdrawn prior to randomization.

27.2.3 **Protocol violations:**
The following gives a list of the protocol violations:

Subject Number	Protocol Violation
#005 and #018	INRs were <1.3
#002, #023 and #024	Differences in INRs on Days 12, 13 and 14 were >20%
#010, #019, #020, #021, #022, #023 and #024	Had warfarin doses adjusted on Day 10 (Protocol did not allow dose adjustment after Day 9)
#008	Used Cepacol® lozenges for sore throat during the double-blind phase
#019	Used Neosporin® ointment for a wound on his left index finger during the warfarin run-in phase

27.3 **SAFETY RESULTS**

27.3.1 **General considerations:** A total of 16 adverse experiences were reported in 11 subjects.

27.3.2 **Deaths:** There were no deaths during this study.

27.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

27.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

27.3.5 **Adverse Events:** All were mild to moderate in nature and all resolved during the study. The most common AE was dizziness, reported in 4 subjects who received eprosartan, and none of the subjects on placebo. A list of AEs following treatment with eprosartan or placebo to subjects receiving warfarin is given below:

1. Warfarin plus eprosartan (13 AEs in 8 subjects): Subjects #002, #003, #010 and #019 reported dizziness, #010 also reported headache and somnolence, #021 reported abdominal (left epigastric) pain and chest pain (left breast, aching, intermittent), #022 reported epistaxis, #002 and #017 reported dyspepsia, #007 reported an injury to the right shin, and #019 reported backache;
2. Warfarin plus placebo (3 AEs in 3 subjects): Subject #016 reported epistaxis, #018 reported abdominal discomfort, and # 023 reported scleritis (red left inner sclera).

27.3.6 **Laboratory findings, ECGs, Vital signs**
There were no pulse rate changes of potential clinical concern. During the warfarin run-in phase, subjects #003, #008 and #009 had increased diastolic blood pressure, #015 had increased systolic blood pressure and #018 and #022 had decreased diastolic blood pressure. All of these were asymptomatic. During the double-blind study medication phase, subject #018 on placebo had increased diastolic blood pressure, and subject #022 on eprosartan also had increased diastolic blood pressure on two occasions each, which were not associated with symptoms.

No ECG changes of potential clinical concern were observed during the study.

Only one subject (#006) had clinical safety laboratory values of potential clinical concern, namely increased ALT of 127 IU/l on Day 14 (vs base ALT of 35 IU/l at screening and 24 IU/l upon entry into the warfarin run-in phase). He was not randomized, however, because he did not meet the criteria ($1.3 \leq INR \leq 1.6$). At a repeat blood test 6 days later, his ALT returned to 44 IU/l.

27.4 **INR RESULTS**
The baseline INR for the intent-to-treat analysis was a statistically significant covariate (P=0.0403). The mean INR for subjects given warfarin plus eprosartan was slightly higher than those given warfarin plus placebo (Table Epro-027-1) but the differences were not statistically significant. The adjusted mean INR was 1.42 for warfarin and eprosartan administered concomitantly, and 1.35 for warfarin administered with placebo.

The mean difference in INR for the two blinded study groups was 0.0678 (Table Epro-027-2). An approximation of the ratio between warfarin plus eprosartan versus warfarin plus placebo is obtained by adding 1 to the difference and divided by the placebo adjusted mean. The sponsor submitted that this ratio and its associated 90% confidence intervals fall within the 25% acceptance range (actual figures not provided); thus INR for warfarin plus eprosartan is considered equivalent to INR for warfarin plus placebo.

Upon exclusion of a potential outlier (Subject #020 who had an INR of 2.06 (vs baseline INRs of 1.08, 1,60 and 1.49 on days 12, 13 and 14, and mean baseline INR of 1.63), the baseline INR for the intent-to-treat analysis was no longer a statistically significant covariate (P=0.0860). This did not change the inference (Table Epro-027-2), the approximation ratio now being 1.03 (90% C.I. 0.92, 1.13) which also falls within the 25% acceptance range.

Table Epro-027-1. Mean INR

Comparison	Warfarin + eprosartan (n = 11)	Warfarin + placebo (n = 7)
Baseline INR		
Mean	1.48	1.41
Median	1.47	1.48
S.D.	0.079	0.198
Day 22 INR		
Mean	1.44	1.31
Median	1.39	1.27
S.D.	0.256	0.181

Table Epro-027-2. Mean difference in INR (point estimates) and confidence intervals

Comparison	Point Estimate	95% C.I.
{Eprosartan + warfarin} - {placebo + warfarin}	0.0678	(-0.113, 0.248)
{Eprosartan + warfarin} - {placebo + warfarin}, excluding Subject #020	0.0343	(-0.105, 0.173)

27.5. CONCLUSION

Oral dose administration of eprosartan (300 mg) twice/day to healthy male volunteers taking warfarin for 7 days was not associated with any significant differences in adverse experiences compared to placebo. All adverse experiences were mild to moderate in nature and all resolved during the study. There were no abnormal laboratory values of potential safety concern.

The mean INR for subjects given warfarin plus eprosartan (1.44) was slightly higher than those given warfarin plus placebo (1.31) but the differences were not statistically significant. The approximation ratio between warfarin plus eprosartan versus warfarin plus placebo and its associated 90% confidence intervals fall within the 25% acceptance range. Thus, as measured by the INR, there was no interaction between warfarin and eprosartan with regard to the anticoagulant effect of warfarin.

Protocol 028 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.113)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *13-Jun-1997*
DATE COMPLETED *16-Jun-1997*

28.1 STUDY PROTOCOL

28.1.1 Title

A study to determine the safety and effect of eprosartan on the pharmacodynamics and pharmacokinetics of glyburide in diabetic patients at steady state

28.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages over ACE Inhibitors (absence of side effects such as non-productive cough and angioedema). Since hypertension and diabetes mellitus are frequently found together in the same patient population, it is very likely that eprosartan will be combined with oral hypoglycemic agents for glucose control. Although the binding of glyburide to plasma proteins is non-ionic in nature and therefore more resistant to displacement from protein binding sites, such an interaction is theoretically possible with eprosartan which is >97% bound to plasma protein, and this interaction could enhance the hypoglycemic response to sulfonyureas in NIDDM patients. This study evaluates effect of eprosartan on plasma glucose profiles and, if present, on the steady-state pharmacokinetics of glyburide in patients with diabetes mellitus.

28.1.3 Objectives

1. To establish the concomitant administration of eprosartan and glyburide had no effect on the 24-hour plasma glucose profiles in diabetic patients relative to glyburide plus placebo;
2. To assess the safety and tolerability of concomitant administration of multiple oral doses of glyburide and eprosartan (200 mg bid) to diabetic patients;
3. If an effect on the 24-hour plasma glucose profile was shown, then the effect of eprosartan on the steady state pharmacokinetics of oral glyburide was to be investigated.

28.1.4 Study design

The study was a randomized, double-blind (eprosartan/placebo dosing only), placebo-controlled, two-period, period-balanced, cross-over, pharmacodynamic and pharmacokinetic study in adult male and female patients with non-insulin dependent diabetes mellitus (NIDDM) who were receiving treatment with glyburide: The two treatment periods (each, Days 1 through 7) were separated by a minimum washout period of at least 14 days.

1. Regimen A: Eprosartan 100 mg tablets, (Lot# U94068) x 2, (i.e. 200 mg) twice daily x 7 days
2. Regimen B: Placebo (Lot# U94111) twice daily x 7 days
3. Glyburide (Micronase®) 1.25, 2.5 and 5.0 mg tablets (Lot# X95031, X95030 and X95009, respectively) orally according to their prescribed regimen of 3.75 to 10 mg once daily for at least 7 days before the first study day and during the treatment period.

28.1.5 Protocol Amendments

There were no amendments to the protocol.

28.1.6 Population enrolled/analyzed

24 adults with a history of stable, NIDDM, 18-65 years of age, weight > 50 kg and within 30% of ideal weight (based on height), and a negative urine drug screen within 30 days were screened for enrollment. Patients were to have a stable dosing regimen of glyburide (3.75 to 10 mg/day) with no change in dosing regimen for 30 days, and no change in concomitant medications (e.g., vitamins) for 7 days prior to baseline assessment. Female subjects of child-bearing potential were required to have a negative serum pregnancy test, and must have been using an IUD or a barrier method of contraception or postmenopausal (> 6 months without menstrual period) or surgically sterile.

Compliance: Assessment of outpatient compliance was made by tablet count on Day 0 of period 2, Days 6 and 7 of periods 1 and 2, and at follow up. On Days 1, 6 and 7, the study nurse administered glyburide and the study medication from each patient's assigned bottles.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, a physical examination and a 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Female patients of child-bearing potential had a serum pregnancy test done. Patients were not permitted to take any prescription or non-

prescription medications within 1 week, and probenecid, aspirin or aspirin-containing products, grapefruit juice or grapefruit within 2 weeks prior to and during the study, and alcohol, tobacco, caffeine or a vegetarian diet within 24 hours prior to and during study period. The following medications were not permitted within 30 days prior to and during the study: systemic or inhaled corticosteroids, cyclosporine, cholestyramine, ursodiol, probenecid, phenytoin, cimetidine, trimethoprim, warfarin, ß-blockers, NSAIDs, aspirin and vitamins.

After screening, patients were instructed to discontinue their own glyburide, and were given a bottle of glyburide tablets to be used during the baseline phase, the washout phase, both treatment phases and up to the follow-up visit.

28.1.7 **Study procedures**

Patients reported on the morning of Day-1 prior to taking glyburide. A trough blood sample for plasma glyburide concentration was obtained. The patient returned on the evening of Day-1 and was admitted for a 36 hour stay in the research facility. On Day 0, a 5 ml blood sample was obtained prior to dosing for trough plasma glyburide concentration. Glyburide was administered orally with breakfast, and sitting blood pressure and heart rest were measured at 0, 1 and 4 hours post-dose. At the end of 24 hours, on Study Day 1, patients started the first dosing.

Prior to first dose of study medication, the following were done: baseline signs and symptoms, brief physical examination, sitting blood pressure and heart rate, clinical laboratory tests including urine hCG for women of child bearing potential, blood samples for glyburide concentrations. Patients took glyburide along with eprosartan (200 mg) or matched placebo with breakfast. The medications were administered by the study nurse from each patient's assigned bottles on days when the patients were in the clinic (Days 1, 6, 7 and 8). Patients were discharged from the clinic with a supply of glyburide tablets and eprosartan or placebo tablets, and were instructed to check fasting blood glucose every morning (using a glucometer) and record the results in a daily diary.

Patients were seen again at Day 6 for review of diary, tablet count, adverse experiences and a blood sample for plasma glyburide trough level. They returned the same evening for admission for a 36-hour stay in which the procedures of Day 1 were repeated on Day 7. They also had blood samples for pharmacokinetic analysis (and plasma glucose levels) drawn at: pre-dose, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 16, 20 and 24 hours following administration of glyburide. After 24-hours, blood and urine samples were obtained for clinical laboratory tests, and patients were discharged, being given a supply of glyburide tablets to maintain their current regimen.

After a minimum washout period of 14 days, the procedure was repeated for each patient with the cross over (alternate) study medication (eprosartan or placebo). Patients returned for a follow-up visit 4-7 days after the last dose of study medication for assessment of adverse experiences, tablet count (compliance), review of concomitant medications taken, a limited physical, vital signs, 12-lead ECG and clinical laboratory tests for safety.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

28.1.8 **Pharmacokinetic procedures**:

Blood samples for pharmacokinetics were centrifuged at 4°C and 2000 rpm for 20 minutes, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed later, only if there was evidence that eprosartan affected the pharmacokinetics of glyburide as assessed by the 24-hour glucose profiles.

28.1.9 **Pharmacodynamic procedures**:

On each 24-hour glucose profile day (Day 0 and Day 7 of each study period), plasma glucose levels were obtained at the following times: : pre-dose, 1, 2.5, 4, 5, 6, 7.5, 9, 12, 13, 14.5, 16 and 24 hours post-dosing with glyburide. Blood samples were collected in tubes containing sodium fluoride/potassium oxalate, and glucose levels were determined using an enzymatic method and read biochromatically by spectrophotometry at 340/380 nm.

28.1.10 **Endpoints**:

The primary pharmacodynamic endpoint was the mean 24-hour plasma glucose concentrations {expressed as AUC(0-24) ÷ 24} on Day 0 (for homogeneity of treatment response at baseline) and 7 (for treatment response). Analysis (by ANOVA) of this endpoint used an equivalence range of 30% (i.e., 0.70 to 1.30).

If eprosartan was shown to have an effect on plasma glucose concentrations, then the pharmacokinetic endpoint was the effect of eprosartan on the pharmacokinetics of glyburide using AUC(0-τ).

28.1.11 **Sample size:**
Based on a coefficient of variation of 6.2% on Day 0, and 11.2% on Day 7 for mean plasma glucose concentrations, a sample size of 12 per regimen was estimated to provide 90% power to conclude equivalence (definition = when 90% confidence interval is completely contained within 30% of the glyburide plus placebo regimen) of the two regimens.

28.1.12 **Investigator , Center and Study Dates:**
G. Stephen DeCherney, MD., Medical Research Institute of Delaware, Inc., Newark, Delaware.
Dates: 09-Mar-1995 to 07-Sep-1995.

28.1 STUDY POPULATION

28.2.1 **Subject disposition:**
24 adults with stable non-insulin dependent diabetes mellitus were screened. 12 patients were originally randomized and received at least one dose of study medication. Three patients (#009, #010 and #012) were replaced by patients #013, #016, and #015. Thus, 15 patients 45-64 (mean = 54) years of age, weighing 50.0-104.5 (mean = 87.0) kg, and 149-185 (mean = 172) cm tall, were randomized.

28.2.2 **Withdrawals:**
There were 2 withdrawals. Patient #006 was withdrawn after completing both dosing regimens because he did not return for follow-up procedures. His results were included in the pharmacodynamic analysis. Patient #012 was withdrawn when he was found to use glyburide 15 mg daily, exceeding the protocol-defined limit of 10 mg/day. His results were not included in the pharmacodynamic analysis.

28.2.3 **Protocol violations:**
The following gives a list of protocol violations found in this study:

Patient Number	Protocol Violation
#002, #011, #016	Prior and concomitant medications (Relafan and toradol, i.m. cortisone, aspirin, respectively)
#006	Did not return for follow up
#007, 012	Follow-up visit > 7 days after last dose
#009, 010, 012	Did not meet eligibility criteria - glyburide dosing (on 15 mg/day)
#011	Variation in safety laboratory assay (serum instead of urine pregnancy test was done)
#005, #009	Did not meet eligibility - creatinine clearance <70 ml/min/1.73M^2 (incorrect calculation)
#001, #003, #004, #005, #007, #015	Did not meet revised protocol criteria - corrected creatinine clearances < 70 ml/min/1.73M^2

28.3 SAFETY RESULTS

28.3.1 **General considerations:** No symptoms of hypoglycemia were recorded during the study.

28.3.2 **Deaths:** There were no deaths during this study.

28.3.3 **Withdrawals:** There were no withdrawals from the study due to adverse experiences.

28.3.4 **Serious, non-fatal adverse events:** There was no serious non-fatal adverse experience during this study.

28.3.5 **Adverse events:** Only one adverse experience of mild profuse sweating was reported (by Patient #005 after receiving his final dose of eprosartan). This patient's blood glucose 4 hours before the incident was 152 mg/dl, and 4 hours after the incident was 144 mg/dl. The symptom resolved within 15 minutes without corrective therapy.

28.3.6 **Laboratory findings, ECGs, Vital signs**
No patient in this study exhibited abnormal heart rates. Patient #013 had decreased systolic blood pressure at follow up visit (130 mmHg vs 180 mmHg on baseline Day 1), and patient #003 had decreased pre-dose systolic blood pressure on Day 7 (102 mmHg compared to 138 mmHg pre-dose baseline on Day 1). Both experiences were asymptomatic and transient.

There were no ECG results considered clinically relevant by the investigator. Patient #013 had increased QTc interval at follow-up (460 msec vs 320 msec at screening) which was isolated and asymptomatic, and not accompanied by ST-T wave changes.
No blood glucose values of potential clinical concern were recorded. Patient #001 had a low platelet count pre-dose on Day 1 of second session (73 x 10^3/mm^3). Patient #005 had a low hemoglobin levels (9.9 g/dl) and a low hematocrit (29.6%) at follow up.

28.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

28.4.1 Primary pharmacodynamic endpoints:

The average mean plasma glucose concentrations {expressed as AUC(0-24)÷24} on Day 0 and Day 7 (Table Epro-028-1) were similar between groups. While the diabetic patients exhibited wide fluctuations in plasma glucose concentrations, the fluctuations were similar during both the glyburide + eprosartan and glyburide + placebo regimens. The ANOVA did not reveal a statistically significance sequence or period effect. The approximate point estimates on Day 0 and Day 7 were 0.97 and 0.96 respectively, and the 90% confidence intervals (Table Epro-28-2) were within the range of 0.70-1.30 supporting equivalence.

Table Epro-028-1. Average mean (s.d.) plasma glucose concentration

Day	n	Eprosartan	Placebo
Day 0 (baseline)	12	199 (63.7)	206 (67.1)
Day 7 (post-dose)	12	203 (65.1)	212 (52.0)

Table Epro-028-2. Point Estimates and 95% confidence intervals for mean plasma glucose concentrations

Comparison	Point Estimate†	90% Confidence Interval
Day 0 (baseline)	0.97	(0.83, 1.10)
Day 7 (post-dose)	0.96	(0.90, 1.01)

†Point estimate: expressed as a ratio of the mean response for glyburide + eprosartan to glyburide + placebo

28.4.2 Primary pharmacokinetic endpoints

The sponsor submitted that no evidence of a pharmacodynamic interaction between eprosartan and glyburide was found in the comparison of the mean plasma glucose concentrations (Section 4.1 above). Therefore, glyburide assays and subsequent pharmacokinetic analyses were not performed.

28.5. CONCLUSION

Concomitant oral administration of eprosartan and glyburide to patients with non-insulin dependent diabetes mellitus in this study did not show any serious adverse experiences. Mild profuse sweating was reported by one patient, which was not associated with hypoglycemia and resolved without corrective therapy. There were no abnormal laboratory values of potential safety concern apart from prolonged QTc (460 msec) in one patient, and low hemoglobin and hematocrit in one patient, both at follow-up.

Eprosartan had no effect on the mean 24-hour plasma glucose concentrations in diabetics stabilized on glyburide therapy.

Protocol 029 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.113)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *16-Jun-1997*
DATE COMPLETED *16-Jun-1997*

29.1 STUDY PROTOCOL

29.1.1 Title

A study to evaluate the effect of ranitidine on the pharmacokinetics of eprosartan in healthy young male volunteers

29.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and offer potential therapeutic advantages (absence of side effects e.g., non-productive cough and angioedema) over ACE-inhibitors. A single oral dose of 350 mg eprosartan given with a high-fat meal to 12 healthy male volunteers was associated with increased Cmax and AUC by 80% and 56%, respectively. This study evaluates the influence of gastric pH and the effect of ranitidine (which inhibits basal gastric output by 95%) on the pharmacokinetics and safety of a single dose of eprosartan.

29.1.3 Objectives

1. To estimate the effect of multiple oral doses of ranitidine on the pharmacokinetics of a single oral dose of eprosartan, and,
2. To evaluate the safety and tolerability of concomitant administration of ranitidine and eprosartan.

29.1.4 Study design

The study was a randomized, open-label, two-period, period balanced crossover study of two groups (A and B) separated by a washout period of at least one week, in which each of the young healthy male volunteers received the study medication after an 8-hour fast as follows:

1. Regimen A: A single dose of eprosartan (200 mg tablets (Lot# U-95018) x 2) 400 mg
2. Regimen B: 150 mg ranitidine (Lot# 5ZPT044) orally bid for 3 days run-in period followed by a single oral concomitant dose of eprosartan (200 mg tablets (Lot# U95018) x 2) 400 mg and 150 mg ranitidine on Day 4.

29.1.5 Protocol Amendments

There were no amendments to the protocol.

29.1.6 Population enrolled/analyzed

21 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 10% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All eprosartan doses were administered in the clinical pharmacology unit under the supervision of nursing personnel. Subjects were given bottles containing 5 doses of ranitidine; each bottle was sealed with an electronic (Medication Event Monitoring System) cap that recorded the dates and times the bottle was opened. Subjects were instructed to take one dose every 12 hours.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 2 weeks prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

29.1.7 Study procedures

After an 8-hour overnight fast, subjects reported at 7:00 am. Assessment of baseline symptoms and vital signs, and a 12-lead ECG recording were made. At 8:00 am subjects were administered a single 400 mg (2 tablets of 200 mg each) oral dose of eprosartan with 240 ml of tepid water. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. No vigorous exercise was permitted. Subjects drank 240 ml water at 2 and 4 hours after dosing. Water, soft drinks without caffeine, fruit juices (except grapefruit juice) were allowed *ad lib* beginning 5 hours after dosing and lunch and dinner were given at 5 and 9-10 hours post dose, respectively. Blood sample (5 ml) collections for pharmacokinetics were done prior to dose administration and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours following dosing. Before receiving eprosartan, subjects emptied their bladders and a 20 ml baseline urine sample was collected. After dosing, all urine was collected over 0-12 and 12-24 hour intervals.

For Regimen B (eprosartan and ranitidine), a similar procedure was followed on study Day 4, subjects being administered eprosartan (400 mg) and ranitidine (150 mg) together orally.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

Subjects returned 7-10 days following the last study session, at which time safety laboratory tests were done.

29.1.8 **Pharmacokinetic procedures:**

Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C and 2300 rpm for 10 min, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 3 months. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) for eprosartan in plasma was 10.0 ng/ml based on 0.5 ml aliquots.

The volumes of 12-hour collections of urine were recorded, and 20 ml aliquots stored at -20°C. Eprosartan in urine was assayed using LC/MS/MS. The LLQ for eprosartan in urine was 50.0 ng/ml based on 0.1 ml aliquots.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), $T_{1/2}$, AUC(0-τ), AUC(0-∞). The percent extrapolated was <12% in all profiles for AUC(0-∞) that could be determined. The amount of eprosartan excreted in urine (Ae) was determined from the urinary concentration data and the total urine volume. Renal clearance (CLr) of eprosartan was calculated as Ae(0-24)/AUC(0-24), or, if 24 hour data were not available, as Ae(0-12)/AUC(0-12).

29.1.9 **Endpoints:**

AUC(0-τ) and Cmax were primary endpoints, and CLr was the secondary endpoint for each regimen. Clinical monitoring and laboratory safety data were also secondary endpoints.

29.1.10 **Sample size:**

Based on a coefficient of variation of 23.6% for AUC(0-τ) and 31.2% for Cmax, a sample size of 12 per regimen was estimated to provide 90% power to detect difference s of at least 33% between the two regimens, using a 2-tailed procedure and a critical region of (0.67 to 1.50) on the $\log_e$ scale.

29.1.11 **Investigator , Center and Study Dates:**

Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 20-Jun-1995 through 05-Sep-1995.

29.2 STUDY POPULATION

29.2.1 **Subject disposition:**

21 healthy male volunteers were screened; 1 failed to meet entrance criteria, and 3 decided not to participate for personal reasons. One subject (#011) withdrew after the first session and was replaced by subject #017. Thus, 17 subjects 19-43 (mean = 30) years of age, weighing 58.8 to 91.2 (mean = 74.2) kg, and 159-186 (mean = 176) cm tall, were randomized. 17 subjects received regimen A and 16 subjects received regimen B.

29.2.2 **Withdrawals:**

Subject #011 withdrew (after completing Regimen A) following his involvement in an automobile accident.

29.2.3 **Protocol violations:**

Subjects #010, #012, #013 and #014 during Regimen B were administered ranitidine approximately 30-40 minutes after administration of eprosartan on Day 4 rather than concomitantly as per protocol. The sample collection was stopped, and subjects returned 13-14 days later to repeat the entire session. Pharmacokinetic samples taken (up to 2.5 hr post-dose time point) were not used in any pharmacokinetic parameter calculations.
Subject #003 received a 500 ml 0.9% saline infusion for a vasovagal reaction after dosing with ranitidine and eprosartan on Day 4 of Regimen B in the second session. Subject #011 took 500 mg bid of Motrin for back pain resulting from an automobile accident 9 days after participating in the first session (Regimen A); he withdrew after the first dose of Motrin.

29.3 SAFETY RESULTS

29.3.1 **General considerations:** A total of 13 adverse experiences were reported in 9 subjects.

29.3.2 **Deaths:** There were no deaths during this study.

29.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

29.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

29.3.5 **Adverse Events:** 12 adverse events were mild and 1 was moderate in nature. The most common AE was headache, reported in at least 1 subject in each group. The AEs are summarized as follows:

1. Regimen A (eprosartan alone) (7 AEs in 5 subjects): Subject #005, #010 and #013 reported headache, #011 reported back injury following an automobile accident, and subject #004 reported asthenia, fatigue and malaise;
2. Regimen B (eprosartan plus ranitidine) (2 AEs): Subject #003 reported syncope (required 500 ml 0.9% saline infusion), and #006 reported headache;
3. While on ranitidine alone (4 AEs): Subjects #005 reported headache, #003 reported diarrhea, #009 reported dyspepsia and #016 reported abnormal discoloration of urine.

29.3.6 **Laboratory findings, ECGs, Vital signs**

Subject #003 developed a vasovagal reaction with low systolic blood pressure 2 hours post-dose with ranitidine and eprosartan (93 mmHg vs 124 mmHg at baseline) and received a 500 ml 0.9% saline infusion. His diastolic blood pressure decreased to 51 mmHg and pulse decreased to 53 bpm (vs 68 mmHg and 66 bpm, respectively at baseline.

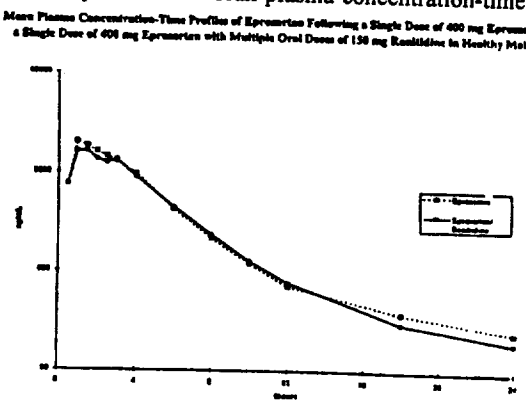
ECGs were not performed during the treatment phase.

There were no changes in laboratory parameters outside of the range for potential clinical concern.

29.4. PHARMACOKINETIC RESULTS

Following single oral doses of 400 mg eprosartan (Figure Epro-029-1) the mean plasma concentration-time profiles were similar. Peak plasma concentrations were reached within 1.5 hours, and the plasma concentrations of eprosartan declined in an apparent mono- or bi-exponential manner. Plasma levels of eprosartan were not measurable at 24 hours in some subjects.

Figure Epro-029-1. Mean plasma concentration-time profiles of eprosartan



Approximately 3% of the dose was excreted in the urine as unchanged eprosartan for both regimens, and the mean Ae (amount of eprosartan excreted in the urine) were not different between the two regimens (Table Epro-029-1). Cmax and AUC(0-τ) were, on average, approximately 7% and 11% lower, respectively for Regimen B (eprosartan and ranitidine) than for Regimen A (eprosartan alone), and the 95% confidence intervals for Cmax and AUC(0-τ) include the value 1 indicating no substantial differences between regimens (Table Epro-029-2).

There was a large variation with between-subject coefficients of variations about 50% and 65% for Regimen A and Regimen B for both Cmax and AUC(0-τ), and the residual or within-subject coefficients of variation for Cmax and AUC(0-τ) being, respectively, 18.9% and 19.4%.

The renal clearance of eprosartan (CLr) was approximately 4% lower in Regimen B than for Regimen A, with the 95% confidence interval of CLr including the value 1 indicating no substantial difference between regimens (Table Epro-02901). The within-subject coefficient of variation for CLr was 57% and between-subject coefficient of variation for CLr were 70% and 40%, respectively, for Regimen A and Regimen B.

Table Epro-029-1. Pharmacokinetic values for eprosartan following single oral dose without and with ranitidine

End Point	Eprosartan	Eprosartan + Ranitidine	Point estimate (95% C.I.)
AUC(0-τ) (ng.h/ml)			
Geometric Mean	7190	6382	0.89 (0.77, 1.03)
Mean	8042	7504	
Median	6597	6283	
S.D.	4128	4635	
Cmax (ng/ml)			
Geometric Mean	1905	1772	0.93 (0.81, 1.07)
Mean	2260	2019	
Median	1755	1556	
S.D.	1465	1173	
Tmax (hr)			
Mean	1.60	1.83	
Median	1.49	1.50	
S.D.	0.71	1.29	
Ae (mg)			
Mean	12.86	11.19	
Median	12.05	9.64	
S.D.	5.74	6.93	
CLr (ml/min)			
Geometric Mean	26.5	25.4	0.96 (0.64, 1.43)
Mean	31.15	27.25	
Median	24.20	24.02	
S.D.	17.44	11.86	

29.5. CONCLUSION

Single oral dose administration of eprosartan (400 mg) to healthy male volunteers with or without ranitidine did not show any significant differences in adverse experiences. One subject developed a fall in systolic blood pressure requiring infusion of 500 ml 0.9% saline. There were no abnormal laboratory values of potential safety concern.

The plasma concentration-time profiles were similar with peak plasma concentrations reached within 1.5 hours, and about 3% of the dose excreted unchanged in the urine, when a single oral dose of eprosartan was given alone or together with ranitidine. The Cmax and AUC(0-τ) were 7% and 11%, respectively lower, and the renal clearance of eprosartan was 4% lower when eprosartan was given together with ranitidine, but these fall within the 95% confidence intervals.

Protocol 034 **NDA 20-738 Teveten™ (Eprosartan) Tablets** *(Vol. 1.114)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *20-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *20-Jun-1997*

34.1 STUDY PROTOCOL

34.1.1 Title

A replicate design study to evaluate the bioequivalence of the clinical trials formulation and the proposed commercial tablet formulation of SK&F 108566 in healthy male volunteers

34.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the bioequivalence of the tablet formulation of 100 mg eprosartan which was used during clinical trials in comparison to a new formulation of 200 mg eprosartan intended for commercial release.

34.1.3 Objectives

1. To compare the bioequivalence of the new tablet formulation intended for commercial release with the old clinical trials tablet formulation of SK&F 108566
2. To assess the safety and tolerability of SK&F 108566 in healthy male volunteers.

34.1.4 Study design

The study was a randomized, open-label, four-period, period balanced crossover study of two groups (A, and B). Each subject participated in four study periods separated by at least 3 days, in which each received:

1. Regimen T: eprosartan 200 mg tablets, (Lot# U94175) the new commercial release formulation) or
2. Regimen R: eprosartan 100 mg tablets, (Lot# U94068) x 2, the old clinical trials formulation)

Each regimen was given orally every 12 hours for 7 doses. Each subject received each regimen during two separate treatment periods for a total of 4 study treatment periods. The treatment periods were administered in one of 4 sequences (RTTR, TTRR, RRTT, TRRT) allocated in a random manner.

34.1.5 Protocol Amendments

The collection time of the safety laboratory assessments was made to allow the safety laboratories to be analyzed in a more efficient manner. The sample preparation methodology was changed to coincide with the standards of practice in the clinical pharmacology unit.

34.1.6 Population enrolled/analyzed

32 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 15% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: Subjects took study medication at the Presbyterian Clinical Research Unit observed by a nurse.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 1 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period until after the 12 hour pharmacokinetic blood sample on Day 4 of each treatment period.

34.1.7 Study procedures

Days 1 - 3: Assessment of baseline symptoms and vital signs were made before administration of the first dose of the first treatment period. Subjects report to the clinical pharmacology unit between 7-8 a.m. and 7-8 p.m. to be administered their dose of study medication. Subjects ate within 1 hour prior to their arrival at the clinical pharmacology unit. Blood and urine samples were taken for clinical laboratory tests within 24 hours of the first dose of the first treatment period. Subjects were allowed to leave after the 2 hour post-dose vital signs. On the morning of Days 2 and 3, a pre-dose blood sample (5 ml) was obtained for pharmacokinetic analysis.

Day 4: Subjects report at 7.00 am. A light breakfast (cereal, milk, juice and muffin) was served, and completely consumed within 20 minutes. Within 30 minutes of start of breakfast, all subjects were administered the study medication with 240 ml of tepid water. Subjects remained sitting for 4 hours post-dose. Subjects drank 240 ml water at 2 and 4 hours post-dose. Water, soft drinks with caffeine or fruit juices (except grapefruit juice) were

permitted *ad lib* 5 hours post-dose, and lunch and dinner were given at 5 and 10 hours post-dose, respectively. Subjects remained in the clinical pharmacology unit until after the 12 hour pharmacokinetic blood sample was obtained. They abstained from strenuous exercise for 24 hours prior to and for 12 hours post-dose on Day 4. Vital signs were obtained pre-dose, and at 1, 2, 6 and 12 hours post-dose. Blood samples (5 ml) for pharmacokinetics were taken prior to dose administration and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours following dosing.

Following the second study session, subjects returned on the morning of Day 5 when blood and urine specimens were taken for clinical laboratory tests. Subjects returned 1 week following the last treatment period, at which time safety laboratory tests were and a 12-lead ECG were done.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

34.1.8 **Pharmacokinetic procedures:**

Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 3 months. Plasma concentrations of eprosartan were determined by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml for a 0.5 ml aliquot.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ) and AUC(0-τ).

34.1.9 **Endpoints:**

AUC(0-τ) and Cmax were primary endpoints, and Tmax was the secondary endpoint. Bioequivalence was determined based on an equivalence range from 0.80 to 1.25 for AUC(0-τ) and Cmax. Clinical monitoring and laboratory safety data were also secondary endpoints.

34.1.10 **Sample size:**

Based on an average within-subject coefficients of variation (CVw) for AUC(0-τ) and Cmax to be 29.4% and 34.6%, respectively, it was estimated that a sample size of 28 would provide at least 90% power to demonstrate equivalence for AUC and Cmax. Equivalence is demonstrated when the 90% confidence intervals for the ratios of T:R for *ln*-transformed AUC(0-τ) and *ln*-transformed Cmax are contained within the range (0.80, 1.25). This range represents a symmetric 20% range on the *ln* scale.

34.1.11 **Investigator , Center and Study Dates:**

Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, Philadelphia, USA. Dates: 03-Oct-1994 to 22-Dec-1994

34.2 **STUDY POPULATION**

34.2.1 **Subject disposition:**

32 male subjects, 20-41 (mean = 28) years of age, weighing 55.2 to 87.2 (mean = 78.4) kg, and 163-197 (mean = 178) cm tall, were screened and randomized. 48% were black and 52% were white.

34.2.2 **Withdrawals:**

Three subjects withdrew from the study. Subject #003 was withdrawn after 6 doses of the test formulation because he complained of chest pain and would not return for follow up examination. Subject #029 was terminated by sponsor after completing 3 treatment periods because the study had met full enrollment. Subject #008 was withdrawn for an adverse experience (anxiety and chest pain) after receiving his third dose.

34.2.3 **Protocol violations:**

Subject #002 took two tablets of Tylenol® 325 mg three times on Day 3 of period one. Subject #025 took one Tylenol® 325 mg during day 1 of the washout period between periods two and three. Subject #033 took one dose of ibuprofen 200 mg on Day 1 of period 1 and amoxillin 250 mg tid for 10 days after completion of period four. Subject #008 received one dose of Maalox 30 mg after he was withdrawn from the study.

34.3 **SAFETY RESULTS**

34.3.1 **General considerations:**

A total of 50 adverse experiences (AEs) were reported for 20 subjects following treatment with the study medication.

34.3.2 **Deaths:** There were no deaths during this study.

34.3.3 **Withdrawals:** Subject #008 had an adverse experience (anxiety and chest pain) following his third dose of the old clinical trials formulation of eprosartan 2 x 100 mg. Screening history, physical examination, laboratory evaluations and 12-lead ECG were normal. The feelings of anxiety (shortness of breath, palpitations, lethargy) and chest pain occurred 6 hours after the first dose. The feelings of anxiety resolved spontaneously after 5 hours. Chest pain was unrelieved by Maalox and lasted about 5 days. 12-lead ECGs on Day 2 and Day 4 were normal and unchanged from the pre-dose ECG. It was thought to be musculoskeletal in origin. The subject was withdrawn from the study.

34.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

34.3.5 **Adverse Events:** All AEs were mild to moderate in nature. Headache was the most frequent AE reported by 6 subjects on the Test regimen and 5 on the Reference regimen.

Regimen T: Subject #001, 003, #009, #013, #014 and #033 reported headache, #003 and #014 reported chest pain, #001 and #011 reported fatigue, #005 reported asthenia, #007, #013, #024 and #025 reported upper respiratory infection, #010 reported palpitation, #010 reported discolored feces, # 010, #014 reported dyspnea, #011 reported dyspepsia, #017 reported pain in jaw, #019 reported dizziness, #033 reported otitis media;

Regimen R: Subject #001, #014, #015, #023, #033 reported headache, #002, #023 reported back pain; #006 and #033 reported dizziness, #007 and #024 reported increased appetite, #007 and #011 reported fatigue, #008 reported anxiety and chest pain (and was withdrawn), #010 reported palpitations and dyspnea, #014 reported discolored feces, #021 reported stiff neck, and #023 reported injury (abrasion to finger).

34.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates. Among subjects receiving the Test regimen, increased systolic blood pressure was recorded 4 times, decreased systolic blood pressure 5 times, and increased or decreased diastolic blood pressure once each. Among subjects receiving the Reference regimen, increased systolic blood pressure was recorded 5 times, decreased systolic blood pressure twice, and decreased diastolic blood pressure 12 times. These blood pressure changes were asymptomatic, and not accompanied by changes in heart rate.

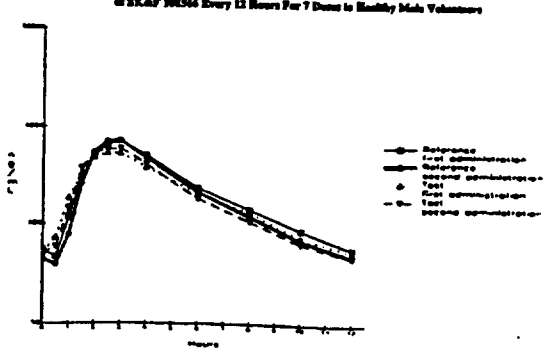
Screening ECGs showed normal intervals (including PR, QRS, QT and QTc). No clinically significant changes were observed when follow-up ECGs were compared to screening ECGs.

During the Test regimen, Subject #005 had two episodes of elevated blood glucose (148 mg/dl and 157 mg/dl compared to a baseline value of 99 mg/dl). During the Reference regimen, Subjects #008 and #026 had elevated blood glucose (144 mg/dl and 153 mg/dl, respectively, compared to baseline values of 93 mg/dl and 92 mg/dl respectively), and Subject #028 had two episodes of decreased Hgb and Hct by about 1.5g/dl and 3-3.6%, respectively from baseline values.

34.4 **PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS**

Following oral doses of the clinical trial formulation and the new commercial release formulation of eprosartan every 12 hours (Figure Epro-034-1), the mean plasma concentration-time profiles were similar. However, the profiles for the test (commercial) formulation were slightly lower than that for the reference (clinical trials) formulation. Peak plasma concentrations were reached within 2-3 hours, and plasma concentrations declined from the peak in a bi-phasic manner. In the majority of subjects, steady-state appeared to have been achieved by Day 3.

Figure Epro-034-1. Time course of plasma concentrations following a single oral dose of eprosartan



AUC(0-τ), Cmax and Tmax were comparable (Table Epro-034-1). The 90% confidence intervals for the comparison of AUC(0-τ) for the Test (commercial release formulation) regimen relative to the Reference (clinical trial formulation) regimen was completely contained within the acceptance range 0.80 to 1.25 (Table Epro-034-2) whereas the 90% confidence interval for Cmax was not contained within the acceptance range (Table Epro-034-2). These results suggest that the commercial tablet formulation had a lower extent of absorption compared to the reference formulation, although the rate of absorption was comparable. Based on the analysis of the primary endpoints, the commercial release formulation cannot be considered bioequivalent to the clinical trials formulation.

Table Epro-034-1. Pharmacokinetic values for eprosartan following single oral doses

End Point	Commercial release formulation (T)	Old clinical trial formulation (R)
AUC(0-τ) (ng.h/ml)		
Geometric Mean	2468	2727
Mean	2655	2981
Median	2552	2662
S.D.	981	1339
Cmax (ng/ml)		
Geometric Mean	684	793
Mean	737	859
Median	705	819
S.D.	274	352
Tmax (hr)		
Mean	2.48	2.63
Median	2.62	2.74
S.D.	0.622	0.511

Table Epro-034-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan formulations

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ)†	T:R	0.91	(0.84, 0.98)
Cmax†	T:R	0.86	(0.78, 0.95)
Tmax§	T-R	-0.20 h	(-0.38 h, 0.12 h)

† Data presented as the ratio of the geometric means for test formulation to reference formulation
§ Data presented as the median difference (T-R) and 90% C.I.

(Note: The calculated between-subject coefficients of variation for AUC(0-τ) and Cmax were 45% for both formulations. The within-subject coefficients of variation for AUC(0-τ) and Cmax for the test formulation were 24.3% and 32.4%, respectively. These values were similar to the within-subject coefficients of variation for the reference formulation, namely, 27.6% and 34.0% for AUC(0-τ) and Cmax, respectively. The residual coefficients of variation observed in this study for AUC(0-τ) and Cmax were 23.6% and 31.2%, respectively. Thus, the sample size used in this study was of sufficient power to assess the bioequivalence of the two formulations.)

34.5. CONCLUSION

Oral dose administration of commercial release formulation of eprosartan (200 mg) and clinical trial formulation (2 x 100 mg) every 12 hours to healthy male volunteers did not show any significant differences in adverse experiences. The most common adverse experience was headache.

Following oral doses of the clinical trial formulation and the new commercial release formulation of eprosartan every 12 hours, the mean plasma concentration-time profiles were similar although the profiles for the test (commercial) formulation were slightly lower. Peak plasma concentrations were reached within 2-3 hours, and plasma concentrations declined from the peak in a bi-phasic manner. In the majority of subjects, steady-state appeared to have been achieved by Day 3.

AUC(0-τ), Cmax and Tmax were comparable. The 90% confidence interval for the comparison of AUC(0-τ) for the Test (commercial release formulation) regimen relative to the Reference (clinical trial formulation) regimen was completely contained within the acceptance range 0.80 to 1.25 whereas the 90% confidence interval for Cmax was not. Based on the analysis of the primary endpoints, the test (commercial release) formulation cannot be considered bioequivalent to the reference (clinical trials) formulation.

Protocol 035 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.115)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *20-Jun-1997*
DATE COMPLETED *23-Jun-1997*

35.1 STUDY PROTOCOL

35.1.1 Title

A study to evaluate the bioequivalence of the clinical trials formulations and the proposed 400 mg commercial tablet formulation of eprosartan in healthy male volunteers

35.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the bioequivalence of the tablet formulation of 100 mg eprosartan, an A-II AT_1 receptor antagonist, which was used during clinical trials in comparison to a new formulation of 400 mg eprosartan intended for commercial release.

35.1.3 Objectives

1. To compare the bioequivalence of the new 400 mg tablet formulation intended for commercial release with the old clinical trials tablet formulation of eprosartan,
2. To assess the safety and tolerability of eprosartan in healthy male volunteers.

35.1.4 Study design

The study was a randomized, open-label, three-period, period balanced, single-dose crossover study of three groups (A, B and C). During each study period, subjects received, with 240 ml tepid water, a single dose of:

1. Regimen A: eprosartan 400 mg tablets, (Lot# U95111) the new commercial release formulation) or
2. Regimen B: eprosartan 100 mg tablets, (Lot# U93235) x 4, the old clinical trials formulation),
3. Regimen C: eprosartan 200 mg tablets, (Lot# U94190) x 2, the old clinical trials formulation),

There was a minimum 7-day washout period between doses. Subjects were randomized to sequence ABC, ACB, BAC, BCA, CAB, CBA.

35.1.5 Protocol Amendments

On 31-Aug-1995, a modification was made to change the lot number for eprosartan 100 mg tablets from U974068 to U93235. On 29-Sep-1995, the planned statistical analysis was revised to include a formal comparison of the 100 mg tablets (Regimen B) to the 200 mg tablets (Regimen C).

35.1.6 Population enrolled/analyzed

79 healthy, non-smoking, adult male volunteers 18-50 years of age, weight > 50 kg and within 15% of ideal weight (based on height), and a negative urine drug screen within 30 days were screened.

Compliance: Subjects took study medication administered by study personnel, the oral cavity being checked following dosing to ensure that the dose was ingested by the subject.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (13 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Subjects were not permitted to take any prescription or non-prescription medications 1 week prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each pharmacokinetic study session.

35.1.7 Study procedures

Subjects report to the clinical pharmacology unit between 7-8 a.m. after an overnight fast since 10 p.m. the previous night. Baseline symptoms and signs were recorded at the first session. A light breakfast (cereal, milk, juice and muffin) was served, and completely consumed within 20 minutes. Within 30 minutes of start of breakfast, all subjects were administered the study medication with 240 ml of tepid water. Prior to dosing, sitting blood pressure and pulse were measured. Subjects drank 240 ml water at 2 and 4 hours after dosing. Water, soft drinks with caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing, and lunch and dinner were given at 5 and 10 hours post dose, respectively. Blood samples for pharmacokinetic analysis were drawn at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours following dosing. Subjects remained in the clinical pharmacology unit for 24 hours after dosing and were discharged after collection of the last pharmacokinetic sample. Subjects abstained from ingestion of xanthine containing drinks or alcohol, and from strenuous exercise for 24 hours prior to and for 24 hours after study drug administration.

eprosartan 400 mg/HCTZ 12.5 mg, and 10 of 128 (7.8%) patients receiving eprosartan 400 mg/HCTZ 25 mg. The second most commonly reported on-therapy adverse experience was myalgia, being found in 29 of 380 (7.7%) patients (7 of 124 (5.6%) patients receiving placebo, 12 of 128 (9.4%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg and 10 of 128 (7.8%) of patients receiving eprosartan 400 mg/HCTZ 25 mg). Dizziness was reported by 17 of 380 (4.5%) patients (2 of 124 (1.6%) patients receiving placebo, 4 of 128 (3.1%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg and 11 of 128 (8.6%) of patients receiving eprosartan 400 mg/HCTZ 25 mg). Only 1 patient (#061.003.00066) receiving eprosartan 400 mg/HCTZ 25 mg reported postural hypotension.

3.5 **Laboratory findings, ECGs, Vital signs**

Only 3 of 376 patients whose vital signs were measured had values of clinical concern: 1 patient (#061.005.00035) on eprosartan 400 mg/HCTZ 12.5 mg had a reduction in systolic blood pressure of clinical concern, and 2 patients (#061.472.00398 and #061.472.00414) on eprosartan 400 mg/HCTZ 25 mg had heart rates (44 bpm and 48 bpm, respectively) of clinical concern.

ECG abnormalities that were not present at baseline and occurred for the first time during the double-blind on-therapy period were observed for 7 patients randomized to placebo, 7 to eprosartan 400 mg/HCTZ 12.5 mg, and 5 to eprosartan 400 mg/HCTZ 25 mg (Table Epro-061-7).

Table Epro-061-7 Number of patients with new ECG findings during the on-therapy period

ECG Abnormality	Placebo UID (n=109)		Eprosartan 400 mg UID HCTZ 12.5 mg UID (n=108)		Eprosartan 400 mg UID HCTZ 25 mg UID (n=113)	
	No.	(%)	No.	(%)	No.	(%)
Conduction						
First degree AV block	0	(0.0)	1	(0.9)	1	(0.9)
Left bundle branch block NOS	1	(0.9)	0	(0.0)	0	(0.0)
Left ventricular hypertrophy	3	(2.8)	1	(0.9)	1	(0.9)
Morphology						
EKG finding of ischemia	0	(0.0)	1	(0.9)	0	(0.0)
Myocardial infarction old	0	(0.0)	1	(0.9)	0	(0.0)
Rhythm						
Sinus bradycardia	1	(0.9)	3	(2.8)	1	(0.9)
Sinus tachycardia	0	(0.0)	0	(0.0)	2	(1.8)
Atrial fibrillation	2	(1.8)	0	(0.0)	0	(0.0)
Total with at least one new onset ECG abnormality	7		7		5	

There was no apparent effect of study medication on atrial rate, ventricular rate, PR interval, QRS interval or QTc in any treatment group, changes between baseline and study endpoint being minimal with the exception of the ECG abnormalities shown in Table Epro-061-8.

Table Epro-061-8 Listing of patients with on-therapy adverse experiences related to heart rate, rhythm or ECG abnormalities

Patient Identification Number	Sex	Age (years)	Days on Double-blind	Adverse Experience (Preferred Term)	Days on Study Med at Onset	Duration	Severity	Relationship	Action
					Placebo UID				
061.004.00410	Female	51	55	Palpitation	15	1 day	Mild	Possibly related	Dose interrupted
					37	1 day	Mild	Possibly related	None
061.002.00156	Female	73	54	ECG abnormal	25 (1)*		Mild	Unrelated	None
061.010.00017	Male	65	53	Fibrillation atrial**	26 (1)*	3 days	Moderate	Unrelated	None
061.052.00228	Female	39	56	Palpitation	30	1 day	Severe	Unrelated	None
061.472.00405	Female	62	52	Fibrillation atrial	23 (1)*		Mild	Unrelated	None
061.571.00432	Male	57	57	ECG abnormal, specific	28 (1)*		Mild	Unrelated	None
					Eprosartan 400 mg/HCTZ 12.5 mg UID				
061.003.00063	Female	52	57	Palpitation	36	10 days	Mild	Unrelated	None
061.472.00347	Female	51	56	Tachycardia	54	1 day	Mild	Possibly related	None
061.574.00472	Female	66	56	ECG abnormal, specific	57 (1)*		Mild	Unrelated	None
					Eprosartan 400 mg/HCTZ 25 mg UID				
061.002.00158	Male	54	61	Palpitation	36	7 days	Mild	Possibly related	None
061.052.00223	Female	48	56	Palpitation	3	12 days	Mild	Unrelated	None
061.574.00369	Male	38	56	Palpitation	44	16 days	Mild	Possibly related	None
061.472.00398	Male	58	56	Bronchospasm	29		Moderate	Possibly related	None

* ( ) indicates the number of days after the last dose of randomized medication.
** This adverse experience was considered by the investigator to be serious.

There were no marked change in baseline and endpoint values for hematology and blood chemistry tests between placebo and eprosartan/HCTZ treatments. 77 of 380 (20.3%) patients had on-therapy laboratory values of clinical concern (25 of 124 (20.2%) on placebo, 28 of 128 (21.9%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg, and 24 of 128 (18.8%) patients receiving eprosartan 400 mg/HCTZ 25 mg. The laboratory parameter most frequently found to be abnormal was fasting blood glucose.

24 of 380 (6.3%) patients reported on-therapy adverse experiences related to clinical laboratory results: (9 of 124 (7.3%) on placebo, 4 of 128 (3.1%) of patients receiving eprosartan 400 mg/HCTZ 12.5 mg, and 11 of 128 (8.6%) patients receiving eprosartan 400 mg/HCTZ 25 mg (Table Epro-061-9). All adverse experiences were mild or moderate in intensity and no patients were withdrawn because of adverse experiences related to laboratory results. Increased creatinine phosphokinase and hypokalemia were the most common on-therapy adverse experiences related to laboratory results.

Subjects returned 1 week following the last treatment period, at which time safety laboratory tests were and a 12-lead ECG were done.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

35.1.8 **Pharmacokinetic procedures:**
Blood samples collected in heparinized tubes and chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 2 months. Plasma concentrations of eprosartan were determined by reverse phase HPLC with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml for a 0.5 ml aliquot.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax), time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), AUC(0-τ), and AUC(0-τ') (where τ' is the time of the last quantifiable concentration in common for all dose levels for each subject, assuming that absorption profiles are similar for all doses and that absorption is complete by the time of τ'). It was not possible to estimate $T_{1/2}$, and AUC(0-∞).

35.1.9 **Endpoints:**
AUC(0-τ) and Cmax were primary endpoints, and AUC(0-τ') and Tmax were the secondary endpoints. Bioequivalence was determined based on an equivalence range from 0.80 to 1.25 for AUC(0-τ) and Cmax.

35.1.10 **Sample size:**
Based on an average within-subject coefficients of variation (CVresid) for AUC(0-τ) and Cmax to be 27.4% and 31.6%, respectively, it was estimated that a sample size of 48 would provide at least 90% power to demonstrate equivalence for AUC and Cmax. Equivalence is demonstrated when the 90% confidence intervals for the ratios of Test:Reference for ln-transformed AUC(0-τ) and ln-transformed Cmax are contained within the range (0.80, 1.25). This range represents a symmetric 20% range on the ln scale. No adjustments were made for multiple comparisons.

35.1.11 **Investigator , Center and Study Dates:**
Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, Philadelphia, USA. Dates: 17-Aug-1995 to 18-Oct-1995.

35.2 **STUDY POPULATION**

35.2.1 **Subject disposition:**
79 healthy male volunteers were screened; 15 failed to meet entrance criteria. 64 subjects, 18-49 (mean = 30) years of age, weighing 55.3 to 109.8 (mean = 77.6) kg, and 163-200 (mean = 178) cm tall, were randomized. 67% were Caucasian, 27% were African-American, 3% were Asian, 2% were Indian and 2% were American Indian. All received at least one dose of the study medication, and 60 subjects completed all treatment sessions A, B and C.

35.2.2 **Withdrawals:**
Four subjects withdrew from the study. Subject #003 was withdrawn after the first treatment session because he was lost to follow-up. Subjects #063 and #067 were withdrawn by sponsor after treatment session 2. Subject #038 was withdrawn due to an adverse experience.

35.2.3 **Protocol violations:**
Subject #021 used topical Psorcon® (diflorasone diacetate) twice daily for skin eruptions, and Subject #038 took Pen Vee K® (500 mg four times daily) for streptococcal pharyngitis. The study was not period balanced because of subject withdrawals.

35.3 **SAFETY RESULTS**

35.3.1 **General considerations:**
A total of 42 adverse experiences (AEs) were reported for 25 subjects, viz., 18 AEs in 14 subjects on Regimen A, 14 AEs in 9 subjects on Regimen B, and 10 AEs in 8 subjects on Regimen C.

35.3.2 **Deaths:** There were no deaths during this study.

35.3.3 **Withdrawals:** Subject #038, a 47 year white male with history of nephrolithiasis, hematuria and passing renal

stones, had an adverse experience (hospitalized for hematuria, dysuria and with ureteric colic related to a kidney stone in his right ureter, and sore throat with fever (Temp 103°F) without cough or runny nose, exudates on his left tonsil and posterior pharynx and bilateral tender anterior cervical lymphadenopathy). The subject was withdrawn from the study. At follow-up visits, the subject reported flank pain, hematuria and passage of stone on four different occasions, almost monthly (in October, November and December 1995 and January 1996).

35.3.4 **Serious, Non-fatal Adverse Events:** There was a serious non-fatal adverse experience during this study, i.e., subject #038 described above.

35.3.5 **Adverse Events:** All AEs were mild (36) to moderate (6) in nature. Headache was the most frequent AE reported by 4 subjects on the Regimen A (new 400 mg formulation), 6 subjects on Regimen B (4 x 100 mg formulation) and 5 on Regimen C (2 x 200 mg formulation):

Regimen A (18 AEs): Subject #022, #023, #046 and #063 reported headache, #004 reported nasal congestion, #006 reported pharyngitis (sore throat), #008 reported fatigue, #009 reported dyspepsia, #020 reported dizziness, #021 reported a rash in the antecubital area, #022 reported paresthesia right hand, #032 reported palpitation, musculoskeletal pain left lower chest and diarrhea, #049 reported syncope, #059 reported toothache, #063 reported nausea and sinusitis (sinus headache);

Regimen B (14 AEs): Subject #005, #016, #020, #023, #037 and #062 reported headache, #028 reported pain in left shoulder #038 reported hematuria, streptococcal sore throat and ureteral colic (for which patient was hospitalized, and withdrawn from the study), #056 reported dizziness and pain in left cephalic area at the venous catheter insertion site, #062 reported nausea and vomiting,

Regimen C (10 AEs): Subject #010, #015, #021 and #023 reported headache, #009 reported dyspepsia, #010 reported diarrhea, #012 reported pharyngitis, #018 reported back pain, #021 reported a rash in the antecubital area and #024 reported dizziness.

35. 3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates or changes in blood pressure of potential clinical concern.

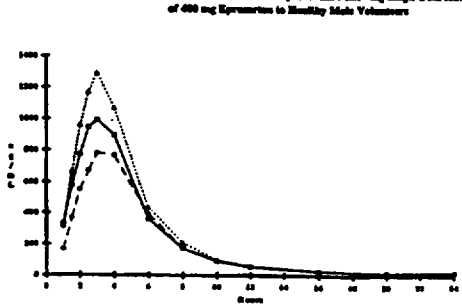
Screening ECGs showed normal intervals (including PR, QRS, QT and QTc). No clinically significant changes were observed when follow-up ECGs were compared to screening ECGs.

Subject #038 had elevated WBC count at screening (10.0 x $10^3/\mu l$, and 11.4 x $10^3/\mu l$ when repeated), and after dosing (13.3 x $10^3/\mu l$). Subject #021 had decreased hematocrit (34.8%), and subject #061 had hypoglycemia (55 mg/dl). Also, subject #038 who was withdrawn for renal stones had hematuria.

35.4. **PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS**

Following single oral doses of the clinical trial formulations and the new 400 mg formulation of eprosartan (Figure Epro-035-1), the mean plasma concentration-time profiles were in general similar except for the 100 mg formulation (Regimen B) in which a slightly slower rate of absorption was observed. Peak plasma concentrations of eprosartan were reached within 2.5 to 4 hours in most subjects. In general, plasma concentrations declined from the peak in a bi-phasic manner. (It is to be noted that samples for subject #049 during Regimens A and B, for subject #050 during Regimens B and C had a large number of NR (not reportable) values in their concentration-time profiles and AUC(0-τ) could not be determined, but both subjects had reliable Cmax and Tmax data. Two subjects (#002 during Regimen A, and #054 during Regimen C) had concentration values >NQ at the zero hour sample and were omitted from the pharmacokinetic analysis.)

Figure Epro-035-1. Time course of plasma concentrations following a single oral dose of eprosartan



The sponsor submitted that no significant sequence or first-order carryover effects were observed for AUC(0-τ), Cmax or AUC(0-τ'). AUC(0-τ), Cmax and Tmax are shown in Table Epro-034-1.

The 90% confidence interval for the comparison of AUC(0-τ) for the Test (400 mg commercial release formulation) regimen relative to the Reference (4 x 100 mg clinical trial formulation) regimen was completely contained within the acceptance range 0.80 to 1.25 (Table Epro-035-2) whereas the 90% confidence interval for Cmax was not contained within the acceptance range (Table Epro-035-2). Also, the 90% confidence intervals for AUC(0-τ) and Cmax did not contain the value 1, suggesting the true ratio of Test:Reference may not be unity. Based on the analysis of the primary endpoints, the test (400 mg commercial release) formulation cannot be considered bioequivalent to the reference (4 x 100 mg clinical trials) formulation.

Table Epro-035-1. Pharmacokinetic values for eprosartan following single oral doses

End Point	Regimen A	Regimen B	Regimen C
AUC(0-τ) (ng.h/ml)			
Geometric Mean	4426	3824	5412
Mean	4872	4170	5829
Median	4420	3915	5301
S.D.	2224	1759	2331
Cmax (ng/ml)			
Geometric Mean	1078	837	1340
Mean	1200	932	1455
Median	1106	785	1341
S.D.	566	445	581
AUC(0-τ') (ng.h/ml)			
Geometric Mean	4341	3721	5283
Mean	4792	4077	5713
Median	4345	3837	5190
S.D.	2227	1769	2356
Tmax (hr)			
Mean	2.78	3.29	2.86
Median	2.98	3.01	2.98
S.D.	0.97	0.91	0.75

For the secondary parameters, the 90% confidence interval for the comparison of AUC(0-τ') for the Test (400 mg commercial release formulation) regimen relative to the Reference (4 x 100 mg clinical trial formulation) regimen was completely contained within the acceptance range 0.80 to 1.25 (Table Epro-035-2). The median difference (of -0.50 h) between the test (400 mg commercial) and reference (4 x 100 mg) formulations for Tmax and the 95% confidence interval did not include the value zero, suggesting that the 4 x100 mg clinical trials (reference) formulation was slighter slower than the 400 mg commercial (test) formulation.

Table Epro-035-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan formulations

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ)†	A:B	1.16	(1.09, 1.24)
Cmax†	A:B	1.30	(1.19, 1.42)
AUC(0-τ')†	A:B	1.17	(1.10, 1.25)
Tmax§	A-B	-0.50 h	(-0.77 h, -0.26 h)
AUC(0-τ)†	A:C	0.83	(0.78, 0.88)
Cmax†	A:C	0.82	(0.75, 0.89)
AUC(0-τ')†	A:C	0.83	(0.78, 0.88)
Tmax§	A-C	-0.01 h	(-0.27 h, 0.24 h)
AUC(0-τ)†	C:B	1.40	(1.32, 1.50)
Cmax†	C:B	1.59	(1.46, 1.74)
AUC(0-τ')†	C:B	1.41	(1.33, 1.51)
Tmax§	C-B	-0.48 h	(-0.53 h, -0.05 h)

† Data presented as the ratio of the geometric means for test formulation to reference formulation
§ Data presented as the median difference for the test - reference, and 90% C.I.

Comparing the test (400 mg commercial) formulation to the other reference (2 x 200 mg clinical trials) formulation, the 90% confidence intervals for AUC(0-τ) and Cmax were not contained within the acceptance range 0.80 to 1.25

(Table Epro-035-2). Here also, the 90% confidence intervals for AUC(0-τ) and Cmax did not contain the value 1, suggesting the true ratio of Test:Reference may not be unity. Based on the analysis of the primary endpoints, the test (400 mg commercial release) formulation cannot be considered bioequivalent to the reference (2 x 200 mg clinical trials) formulation in terms of the primary endpoints in this study.

For the secondary parameters, the 90% confidence interval for the comparison of AUC(0-τ') for the Test (400 mg commercial release formulation) regimen relative to the Reference (2 x 200 mg clinical trial formulation) regimen was not contained within the acceptance range 0.80 to 1.25 (Table Epro-035-2). The median difference (of -0.01 h) between the test (400 mg commercial) and reference (2 x 200 mg) formulations for Tmax and the 95% confidence interval include the value zero, suggesting that the rate of absorption is similar for these two formulations.

Comparing the two reference formulations (4 x 100 mg and 2 x 200 mg), the point estimates and 90% confidence intervals for AUC(0-τ) and Cmax were not contained within the acceptance range 0.80 to 1.25 (Table Epro-035-2). The 90% confidence intervals for AUC(0-τ) and Cmax did not contain the value 1, suggesting the true ratio of Test:Reference may not be unity. Based on the analysis of the primary endpoints, the two reference formulations (4 x 100 mg and 2 x 200 mg) cannot be considered bioequivalent in terms of the primary endpoints in this study.

For the secondary parameters, the 90% confidence interval for the comparison of AUC(0-τ') was not contained within the acceptance range 0.80 to 1.25 (Table Epro-035-2). The median difference (of -0.48 h) between the (2 x 200 mg and 4 x 100 mg) formulations for Tmax and the 95% confidence interval did not include the value zero, suggesting that the rate of absorption of the 4 x 100 mg clinical trials formulation is slower than the 2 x 200 mg formulation.

(Note: The between-subject coefficients of variation for AUC(0-τ) and Cmax were 40 to 50% for each formulation. The within-subject coefficients of variation for AUC(0-τ), Cmax and AUC(0-τ') were 21.2%, 29.7% and 21.5%, respectively. These observed values were lower than that used for the original sample size estimation indicating no adequacies in terms of sample size and power in the assessment of bioequivalence.)

35.5 CONCLUSION

Oral single dose administration of commercial release formulation of eprosartan (400 mg) and two clinical trial formulations (2 x 200 mg and 4x 100 mg) to healthy male volunteers did not show any significant differences in adverse experiences. The most common adverse experience was a mild to moderate headache. One subject with a history of two prior episodes of hematuria and passage of kidney stones developed hematuria with a right ureteric stone again.

Following oral doses of the clinical trial formulations and the new commercial release formulation of eprosartan, the mean plasma concentration-time profiles were generally similar except for the 4 x 100 mg formulation (Regimen B) in which a slightly slower rate of absorption was observed. Peak plasma concentrations of eprosartan were reached within 2.5 to 4 hours in most subjects.

The 90% confidence interval for the comparison of AUC(0-τ) for the Test (400 mg commercial release formulation) regimen relative to the Reference (4 x 100 mg clinical trial formulation) regimen was completely contained within the acceptance range 0.80 to 1.25 whereas the 90% confidence interval for Cmax was not contained within the acceptance range. Comparing the test (400 mg commercial) formulation to the other reference (2 x 200 mg clinical trials) formulation, the 90% confidence intervals for AUC(0-τ) and Cmax were not contained within the acceptance range 0.80 to 1.25. Based on the analysis of the primary endpoints, the test (400 mg commercial release) formulation cannot be considered bioequivalent to either one of the two reference (4 x 100 mg and 2 x 200 mg clinical trials) formulations.

Comparing the two reference formulations (4 x 100 mg and 2 x 200 mg), the point estimates and 90% confidence intervals for AUC(0-τ) and Cmax were not contained within the acceptance range 0.80 to 1.25. The two reference formulations (4 x 100 mg and 2 x 200 mg) cannot be considered bioequivalent in terms of the primary endpoints in this study.

Protocol 043 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.087)*

DATE OF CORRESPONDENCE: *11-Oct-1996*
DATE RECEIVED: *18-Oct-1996*
DATE ASSIGNED: *1-Jul-1997*
DATE COMPLETED *2-Jul-1997*

43.1. STUDY PROTOCOL

43.1.1 Title *Renal response to an angiotensin II antagonist, SK&F 108566, in healthy volunteers*

43.1.2 Rationale

Angiotensin-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study compares the effect of eprosartan, an A-II AT1 receptor antagonist, an ACE inhibitor (captopril), and placebo on effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and adrenal (aldosterone) responses to infusion of angiotensin II.

43.1.3 Objectives

1. To describe the dose range and duration of effects of eprosartan on ERPF (as measured by CL_{PAH}) in healthy male volunteers on a low--salt diet;
2. To compare the effects of eprosartan on ERPF (as measured by CL_{PAH}) in healthy male volunteers during a low salt and during a high salt diet; and,
3. To compare the renal vascular and adrenal responses to eprosartan, captopril and placebo before and during administration of angiotensin II.

43.1.4 Study design

The study was a single dose, crossover study in adult volunteers which was conducted in 3 parts (Parts 1A, 1B and 2) as follows:

Part 1A was an open-label, three-period, dose-ranging study to investigate the effect of increasing oral doses (up to 400 mg) of eprosartan on ERPF (as measured by CL_{PAH}) in subjects maintained on low-salt diet. Subjects received successively higher doses of eprosartan during each of 3 study sessions separated by an interval of at least 2 days.

Part 1B was an open-label, three-period, period-balanced, randomized, crossover study which compared the effect of eprosartan (dose determined in Part 1A) on ERPF (before and during angiotensin II intravenous infusion) in subjects on a low-salt diet (Regimen A) and after salt-loading (Regimen B) to that of placebo on a low-salt diet (Regimen C). Subjects were assigned to sequence ACB or BCA randomly, study sessions being separated by at least 2 days.

Part 2 was a double-blind (except captopril which was open-label), placebo-controlled (for eprosartan only), randomized, three-period, period-balanced, cross over study to compare the effect of single oral doses of the following treatments on ERPF before and during angiotensin II intravenous infusion: A: Eprosartan (dose determined in Part 1A), B: Captopril 25 mg, and C: Placebo. Subjects were assigned randomly to one of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA), study sessions being separated by at least 2 days. Treatments were administered under low-salt or high-salt diet conditions depending on the results of Parts 1A and 1B.

Study medications used were SK&F 108566 oral solution (5 mg per ml, Lot# U-92010), SK&F 108566 oral tablets 50 mg (Lot# U-93225) and matching placebo tablets (Lot# U-94111).

43.1.5 Protocol Amendments

Due to technical difficulties with blinding, the protocol was amended to administer captopril by open-label..

43.1.6 Population enrolled/analyzed

57 healthy adult male and female volunteers 18-50 years of age, weight > 50 kg, a body mass index (BMI) < 33 kg/m^2, and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medication was administered at the clinical research center under the observation of the nursing staff, the oral cavity being examined to assure ingestion of the dose.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical history, 24-hour dietary history to estimate baseline sodium and potassium intake, physical examination, and 12-lead ECG.

After resting supine for 15 minutes measurements of blood pressure and pulse rate were obtained. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). A 24-hour urine specimen was also obtained for urine volume, creatinine, and baseline sodium and potassium excretion. Female subjects of child-bearing potential had to demonstrate a negative hGC to be included in the study.

43.1.7 **Study procedures**

Diet

Low Salt (Part 1A, Regimens A and C of Part 1 B, and Part 2): Subjects were maintained on an isocaloric diet containing 10 mEq sodium and 100 mEq potassium daily beginning 4 days prior to the first study session and continuing through the last study session. 24-hour urine specimens were collected on the day prior to each study session to determine the salt status, and on each day of study confinement to monitor urine sodium excretion.

High Salt (Regimen B of Part 1 B): Subjects were maintained on a high-salt diet (approximately 200 mEq sodium and 100 mEq potassium) for at least 2 days prior to the study session. Subjects previously on a salt-restricted diet received a saline infusion (0.9% sodium chloride injection, 500 ml/h for 4 hours) and were then placed on a high-salt diet for at least 2 days prior to the study session. A 24-hour urine specimen was obtained on the day prior to the study session for urine volume, creatinine, sodium and potassium excretion.

Pre-dosing: Subjects assigned to the low or high salt diet were confined to the clinical research center for the duration of the diet and the study to assure compliance with the diet. Dinner was served, and subjects fasted from food and fluids after 10:00 pm. At 5:15 am the following morning, the subject voided in the bathroom. Subjects then remained supine. An intravenous catheter was placed in both forearm veins. A 12-lead ECG and brief physical examination were performed. Blood and urine samples for safety laboratory studies were collected. Blood pressure and heart rate were measured every 3 minutes prior to initiation of the PAH infusions. The "baseline blood pressure" was defined as the average of these 3 readings taken before the start of PAH and inulin infusions. Subjects were withdrawn if the baseline systolic blood pressure exceeded 140 mmHg, their baseline diastolic blood pressure exceeded 85 mmHg or their baseline heart rate was < 40 bpm.

Clinical monitoring: PAH and inulin clearance tests were performed on the morning of each study period. An i.v. loading dose of PAH (8 mg/kg) and inulin (50 mg/kg) were given at 7:00 am followed by continuous i.v. infusions of maintenance doses of PAH (12 mg/min) and inulin (30 mg/min) for 330 minutes. Single-lead telemetry ECG was monitored continuously until the PAH infusion had been completed. Supine blood pressure and heart rate were measured every 15 minutes. Sitting blood pressure and pulse rate were measured after the subject had rested for at least 15 minutes, and at 6, 8, 12 and 24 hours after dosing. At 8:00 am, study medication was administered with 240 ml of tepid water. The study procedures are given in the flow chart below. A 12-lead ECG was obtained at 5 hours after administration of the study medication or following completion of the angiotensin-II infusion.

In Part 1A, subjects were given successively larger doses of eprosartan orally under low salt conditions, the dose being increased up to 400 mg until further doubling of dose did not increase ERPF in a minimum of 5 subjects.

In Part 1B, single oral doses of 200 mg eprosartan (determined from Part 1A) or placebo were given under low salt conditions, and one session with eprosartan under high salt conditions. Angiotensin II (1 ng/kg/min and 3 ng/kg/min) was administered for 45 minutes to subjects 2 hours after administration of study medication.

Angiotensin II infusion were not administered to subjects if their baseline systolic blood pressure exceeded 140 mmHg or their baseline diastolic blood pressure exceeded 85 mmHg. Angiotensin II infusions were to be terminated if the supine systolic blood pressure increased by >35 mmHg or the supine diastolic BP increased by >30 mmHg or if the supine pulse rate decreased to <40 bpm, and these changes were sustained for > 1 hour of if symptoms related to these changes developed.

Subjects were allowed to void spontaneously, but were not permitted to stand to void during angiotensin-II infusions. They remained supine during the infusions of PAH, inulin and angiotensin II. No fluid or food was permitted for 4 hours after administration of study medication, except 240 ml water at 2 and 4 hours after dosing. Water, soft drinks without caffeine or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing. Meals were served at 5 and 10 hours following the dose of the study medication. A snack was allowed at bedtime.

Blood sample (5 ml) for PAH and inulin were collected at 45 minute intervals during the infusions. Blood samples for aldosterone, plasma renin activity and immunoreactive angiotensin II were obtained prior to and following

infusions of PAH and inulin. A brief physical examination and 12-lead ECG were performed, and blood and urine samples for safety laboratory tests collected at 24 hours following medication.

Adverse experiences (AEs) were elicited by spontaneous reporting by subjects, by nursing observation, physical examination findings, laboratory findings and 12-lead ECG data.

Table Epro-043-1. Flowchart of study procedures

Screening: Medical History, physical examination, 12-lead ECG, safety laboratory tests, urine drug screen, serum hCG (females of child-bearing potential) †

Study Sessions:

Time After Dose (Hours)	-15*	-2	-1	0	0.25	0.75	1.5	1.75	2.25	2.75	3	3.25	4	4.5	5	5.25	6	8	10	12	16	24
Brief History and Physical Examination		✔																				✔
Baseline Symptom/Adverse Experience Assessment				✔																		
Study Medication Administration				✔																		
PAH/Inulin Infusion			X	—	—	—	—	—	—	—	—	—	—	—	—	—	X					
Angiotensin II Infusion (Parts 1B and 2 only)									X	—	—	—	—	—	—	X						
Continuous Single Lead ECG & Supine Vital Signs (Q 15 min)		X	—	—	—	—	—	—	—	—	—	—	—	—	—	X						
PAH & inulin specimens				✔		✔	✔		✔		✔	✔		✔		✔						
Aldosterone, PRA specimens		✔							✔			✔		✔		✔						
12-lead ECG		✔														✔						
Supine Blood Pressure and Pulse Rate																✔						
Safety Lab Studies		✔															✔	✔		✔		✔
Urine hCG †																						✔
Meal Served	✔																					
															✔				✔			

*Prior to first study day only

Follow-up (7 to 10 days after final dose of study medication): Physical examination, safety laboratory studies, serum hCG (females of childbearing potential)

43.1.8 **Assay Methodology:**

PAH, Aldosterone and plasma renin activity were assayed by standard methods.

43.1.9 **Endpoints and Statistical Analyses:**

The Primary Endpoint for pharmacodynamic effect was ERPF as measured by CL_{PAH}. The Secondary Endpoints was GFR as measured by CL_{IN} and serum aldosterone, plasma renin activity and blood pressure. Other endpoints of interest were daily urinary excretion (mEq/day) of sodium and potassium.

43.1.10 **Sample size:**

Part 1A: Sample size was based on feasibility. No formal power calculations were performed.

Part 1B: Based on within-subject coefficient of variation (CV) for CL_{PAH} in subjects treated with placebo and captopril to be 11.4%, it was estimated that a sample size of 6 would provide 90% power to detect a difference of at least 20% in CL_{PAH} between regimens A, B and C, on a two-tailed procedure, with Type I error rate of 5%.

Part 2: Using similar assumptions as above, it was estimated that a sample size of 12 would be required to detect a difference of at least 15% in CL_{PAH} between treatments (eprosartan, captopril and placebo).

43.1.11 **Investigator , Center and Dates:**

Norman K. Hollenberg, MD, PhD, Brigham and Women's Hospital, 75 Francis Street, Boston, MA.
Study Dates: 18-Aug-1994 to 27-Nov-1995.

43.2 STUDY POPULATION

43.2.1 **Subject disposition:**

Of 57 subjects screened, 28 subjects failed to meet entrance criteria or decided not to participate. 9 male subjects entered Part 1A, 6 male subjects were randomized in Part 1B, and 14 (9 male and 5 female) subjects were randomized in Part 2. All subjects received at least one dose of study medication.
There were 67% White, 11% Black, 11% Hispanic and 11% Hispanic (from Columbia) subjects in Part 1A, 76% White, 17% Black and 17% Hispanic subjects in Part 1B, and 64% White and 36% Hispanic subjects in Part 2 of the study. Their demographic data are given in Table Epro-04302 below.

Table Epro-043-2. Demographic characteristics of the study population

Trial Phase	Parameter	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m²)
Part 1A	n	9	9	9	9
	Mean	35	76.2	175	24.7
	SD	8	11.5	9	1.8
	Range	24-48	60.1-90.0	160-189	21.5-27.7
Part 1B	n	6	6	6	6
	Mean	32	85.4	180	26.4
	SD	7	10.3	5	2.9
	Range	25-42	69.6-94.0	173-185	22.7-30.3
Part 2	n	14	14	14	14
	Mean	36	69.9	170	24.1
	SD	9	10.8	10	3.4
	Range	19-48	54.5-93.2	155-188	17.0-29.6

43.2.2 **Withdrawals:**

There were no withdrawals during the study.

43.2.3 **Protocol violations:**

The following table lists the protocol violations in the study, which the sponsor submitted did not affect the safety nor were thought to affect the inferences of the pharmacodynamic analyses performed.

Subject(s)	Description of protocol violation
All subjects in Part 2	Treatment with eprosartan 400 mg instead of 200 mg as determined by protocol during Part 1*
All subjects	Measurement of angiotensin II concentrations not performed
All subjects	Safety laboratory studies performed at another laboratory (with sponsor's agreement)
Part 1A	Each dose was to be tested in ≥ 5 subjects, but only 2 subjects were tested at the 10 mg dose and 3 subjects were tested at the 400 mg dose
#008, #108, #110, #111, #114	Prohibited medications taken within 7 days of start of study
#003, #007, #014, #015, #103, #104, #114	Prohibited concomitant medications taken within 7 days of start of study
All subjects	GGT not done
All subjects	PAH and inulin infusions times were not discontinued at 5.25 hours
All subjects - Part 1B and Part 2	Angiotensin II infusions were not discontinued at 4.5 hours
All subjects - Part 1A	ECG assessment 5.25 hour time point not done
#007	Allowed to continue study with baseline diastolic blood pressure of 91 mmHg
#111	Allowed to continue study with baseline systolic blood pressures of 144 mmHg and 149 mmHg
#003, #005, #006, #007, #008, #009, #010, #011, #012, #013, #014, #016, #101, #102, #103, #106, #107, #110, #112, #113, #114	Specific individual vital signs measurements were not done
#004, #006, #013, #014, #105, #101, #102, #103, #104, #109, #111, #112, #113	Follow up visit not done within 7 to 10 days following final dosing session.
#001, #007, #008, #009, #010, #011, #012, #013, #014, #015, #016, #102, #103, #105, #107, #108, #109, #110, #111, #112, #113	Specific individual blood samples for aldosterone, plasma renin activity, PAH clearance or inulin clearance were not drawn

43.3 SAFETY RESULTS

43.3.1 **General considerations:** In Part 1 A, 2 subjects had prior signs or symptoms: Subject #007 had moderate pain in his middle right finger for which he received Bactrim beginning on Study Day 3, and tetanus diphtheria toxoid beginning on Study Day 4. Subject #008 had 2 episodes of glycosuria (at screening and at follow up, being normal at other time points). There were no prior signs or symptoms in Part 1B. In Part 2, 6 subjects had prior signs or symptoms: Subject #101 had hematuria, #104 had 2 episodes of headache, and #108 and #110 also had headache (all resolved with tylenol), #107 had mild dry skin, #114 had mild stomach upset and constipation (for which he was given Reopen and Milk of Magnesia) and a mild rash (treated with Eucerin Cream).

15 adverse experiences (AEs) were reported for 11 subjects following treatment.

43.3.2 **Deaths:** There were no deaths during this study.

43.3.3 **Withdrawals:** There were no withdrawals due to adverse experiences during this study.

43.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

43.3.5 **Adverse Events:**

All AEs were mild to moderate in nature and resolved without sequale. There was no dose-related increase in the occurrence of AEs.

Part 1A (3 AEs in 2 subjects): Subject #003 reported 5 episodes of nausea and postural hypotension after 1 dose of eprosartan 50 mg (requiring intravenous saline infusion 2 L to resolve the symptoms), and #005 reported mild tachycardia (7 hours after receiving one dose of eprosartan 200 mg tablet):

Part 1B (5 AEs in 2 subjects): Subject #014 reported 2 episodes of mild pruritis and 3 episodes of moderate palpitation after one dose of 200 mg eprosartan tablet and also chest pain and moderate insomnia after treatment with placebo; subject #015 had a mild headache after 1 dose of eprosartan 200 mg;

Part 2 (7 AEs in 7 subjects): Subject #103 reported an allergic reaction to insect bite while on captopril, #104 reported herpes simplex infection while on captopril, #105 reported dizziness after 1 dose of 400 mg eprosartan, #016 reported asthenia after placebo, #108 was reported to have leucopenia while on placebo, #112 reported mild syncope after 1 dose of captopril and #116 reported a rash on captopril

43.3.6 **Laboratory findings, ECGs, Vital signs**

There were no symptomatic or sustained changes in pulse rate or blood pressure associated with the administration of eprosartan. Blood pressure fluctuated during the period of observation, and increases in blood pressure were found in response to the vasopressive effects of angiotensin-II.

There were no baseline ECG findings (in PR, QRS and QTc intervals) that were of potential concern. In Part 2, Subject #105 had QTc of 565 msec at 5.25 hours after administration of 400 mg eprosartan, which decreased to 409 msec 24 hours post dose.

7 subjects had laboratory values of potential clinical concern. In Part 1A, subject #010 had hypoglycemia (fasting blood glucose 47 mg/dl at follow up (vs 72 mg/dl 9 days earlier). In Part 1B, subject #014 had blood glucose concentration of 173 mg/dl post dose eprosartan 200 mg (vs 115 mg/dl predose, and 71 mg/dl at follow up). In Part 2, Subject #102 had urine WBC 15-20/hpf, #103 had serum sodium 123 mEq/l predose (vs prior sodium value of 139 Eq/l), #108 has leucopenia of 2.79 x 10^3/µl predose, #109 had fasting blood glucose 165 mg/dl predose and urine WBC too numerous to count, and #112 had urine WBC 10-20/hpf 24 hours post dose captopril which decreased to 4-6/hpf the following day.

43.4. PHARMACODYNAMIC RESULTS

43.4.1 **Effective Renal Plasma Flow and Glomerular Filtration Rate**

Part 1A: CL_{PAH} increased in a dose-related manner to administration of eprosartan (Figure Epro-043-2), the mean maximum CL_{PAH} being seen with eprosartan 100 mg. For all doses studied, the mean peak CL_{PAH} occurred about 2-3 hours post dose. The mean maximum percentage increase in CL_{IN} was similar for all 5 eprosartan dose levels (being 1.2% for 10 mg, 11% for 50 mg, 6.1% for 100 mg, 7.6% for 200 mg and 7.6% for 400 mg eprosartan).

Part 1B: In Figure Epro-043-3, while the mean predose CL_{PAH} were similar among the three treatment regimens, the mean (±s.d.) maximum percentage difference in post dose CL_{PAH} compared to predose CL_{PAH} values were higher in subjects receiving eprosartan 200 mg on a low salt diet (17.4%±9.6%) versus those receiving eprosartan 200 mg on a high salt diet (4.4%±3.0%) or placebo on a low salt diet (3.1%±5.3%). Eprosartan and low salt diet resulted in an increase in CL_{PAH} to 70 ml/min/1.73m^2 higher than in placebo low salt or eprosartan high salt regimens prior to start of angiotensin II infusion. After infusion of angiotensin II, CL_{PAH} decreased from baseline in the placebo, low salt group in a dose-related manner. Eprosartan (low or high salt diet) blocked the effect of angiotensin II both at 1 ng/kg/min and 3 ng/kg/min. The mean(±s.d.) predose CL_{IN} and the mean(±s.d.) maximum percentage increase in

postdose CL_{IN} compared to predose CL_{IN} appeared similar for all 3 treatment regimens (being 6.6%±5.9% for eprosartan 200 mg low salt, 5.9%±8.9% for eprosartan 200 mg high salt, and 2.9%±5.4% for placebo low salt).

Figure Epro-43-2 Maximum post dose change for CL_{PAH} from baseline (varying doses of eprosartan) Part 1A

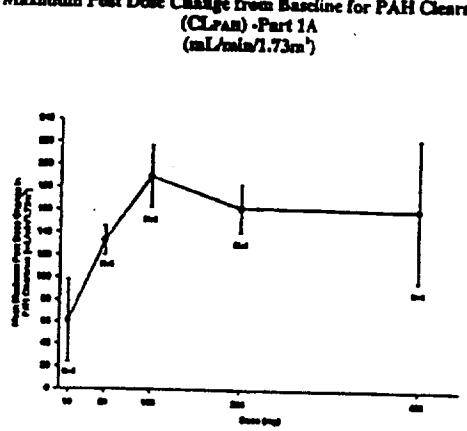
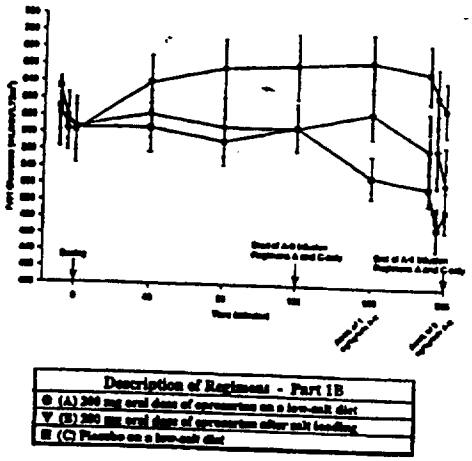


Figure Epro-43-3 Mean CL_{PAH} versus Time (minutes) Part 1 B



Part 2: Figure Epro-043-4 shows that the mean predose CL_{PAH} for the 3 regimens were similar and that CL_{PAH} increased in a similar manner for both eprosartan 400 mg and captopril 25 mg compared to placebo following dosing but prior to angiotensin II infusion. The mean (±s.d.) maximum percentage increase in post dose CL_{PAH} prior to angiotensin II infusion compared to predose CL_{PAH} appeared similar for eprosartan 400 mg (20.0%±8.7%) compared to captopril 25 mg (21.0%±10.3%), both of which appeared greater than placebo (-0.8%±6.2%). During and at the end of angiotensin-II infusion, CL_{PAH} was unchanged following treatment with eprosartan, but decreased markedly during angiotensin II infusion for both captopril and placebo regimens. CL_{PAH} values for the captopril regimen decreased to values similar to the placebo regimen following angiotensin II infusion. These findings demonstrate angiotensin II blockade by eprosartan 400 mg but not by captopril 25 mg or placebo.

In Figure Epro-043-5, the mean(±s.d.) predose CL_{IN} and the mean(±s.d.) maximum percentage increase in postdose CL_{IN} compared to predose CL_{IN} prior to angiotensin II infusion appeared similar for all 3 treatment regimens (being 6.5%±4.8% for eprosartan 400 mg, 4.0%±9.8% for captopril 25 mg, and 2.4%±5.0% for placebo). During and at the end of angiotensin II infusion, the CL_{IN} was higher for subjects on the eprosartan 400 mg treatment compared to those on either captopril 25 mg or placebo.

Figure Epro-043-4 Mean CL_{PAH} versus Time (minutes) (Part 2)

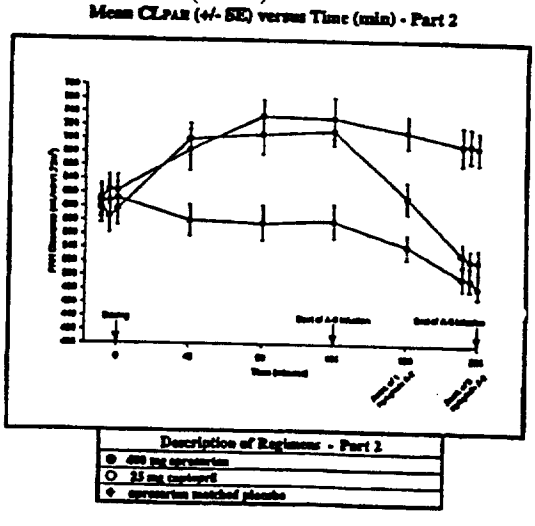
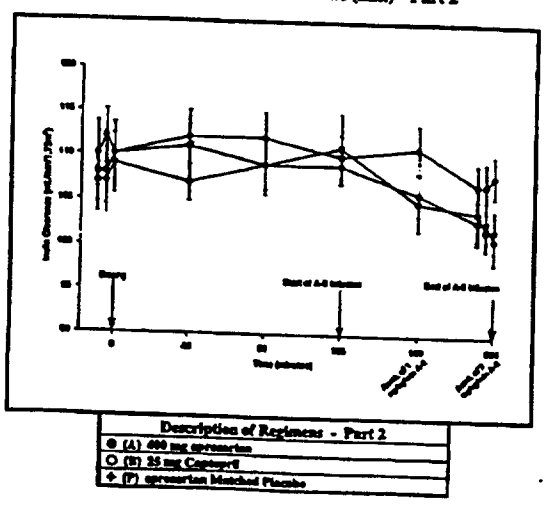


Figure Epro-043-5 Mean CL_{IN} versus Time (minutes) (Part 2)

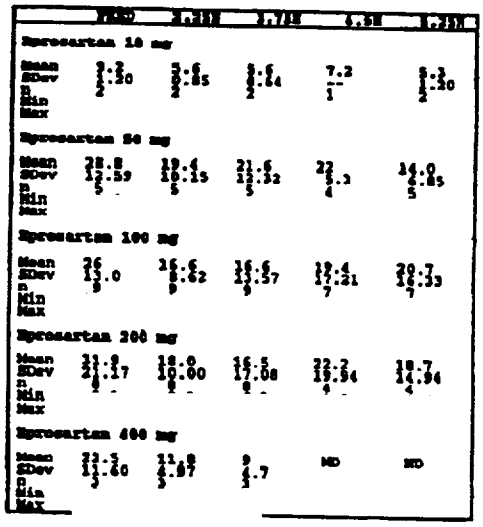


43.4.2 **Serum aldosterone and plasma renin activity**

Part 1A: Mean serum aldosterone levels were decreased compared to mean pre-dose values following single oral doses of eprosartan above 10 mg (Table Epro-043-3). Mean plasma renin activity was increased compared to mean pre-dose values following single oral doses of eprosartan of 50 mg and above (Table Epro-043-4). However, the variability in serum aldosterone values and plasma renin activity were large.

Table Epro-043-3.

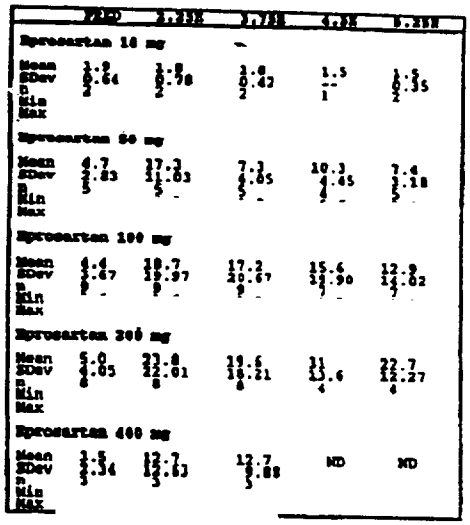
Serum Aldosterone Concentration (ng/dL) - Part 1A



ND = Not Done

Table: Epro-043-4.

Plasma Renin Activity (ng/mL/hr) - Part 1A



ND = Not Done

Part 1B: Mean serum aldosterone levels were elevated in the low salt diet treatment regimens compared to high salt diet regimens (Table Epro-043-5). Eprosartan 200 mg in the low salt diet (prior to angiotensin II infusion) suppressed the mean serum aldosterone concentration (compared to lack of effect of placebo/low salt or eprosartan/high salt regimens).

Angiotensin II infusion further the mean serum aldosterone concentrations in subjects in the placebo/low salt regimen whereas this effect was suppressed in the eprosartan 200 mg/low salt regimen. This suggests blockage of angiotensin II by eprosartan.

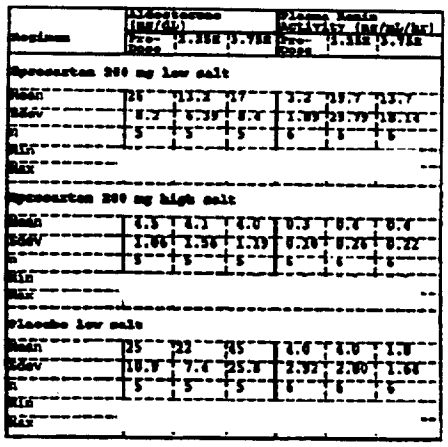
Plasma renin activity was suppressed by angiotensin II infusion in subjects on the placebo/low salt regimen. In subjects receiving eprosartan 200 mg/low salt regimen, the mean plasma renin activity increased in response to eprosartan, and this was not suppressed by infusion of angiotensin II.

Part 2: Mean serum aldosterone levels were elevated prior to dosing because subjects were on low salt diet (Table Epro-043-6). Eprosartan 400 mg and captopril 25 mg (prior to angiotensin II infusion) suppressed the mean serum aldosterone concentrations (compared to lack of effect of placebo).
Angiotensin II infusion further increased the mean serum aldosterone concentrations in subjects receiving placebo or captopril whereas this effect was suppressed in subjects receiving eprosartan 400 mg. This finding was consistent with complete blockade of angiotensin II by eprosartan.

In subjects receiving eprosartan 400 mg and captopril 25 mg, the mean plasma renin activity increased in response to the study medication while placebo did not produce this effect. This increase in plasma renin activity was not suppressed by infusion of angiotensin II in subjects given eprosartan 400 mg, whereas exogenous angiotensin II decreased the plasma renin activity in subjects on captopril 25 mg.

Table Epro-043-5.

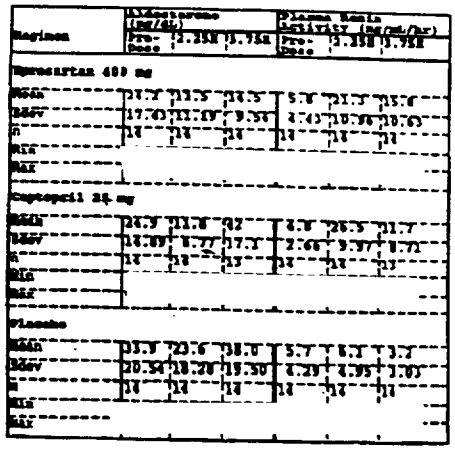
Serum Aldosterone Concentration and Plasma Renin Activity - Part 1B



Note that the 2.25H timepoint was prior to the A-II infusion while the 3.75H timepoint was at the completion of the 3 ng/kg/min A-II infusion for Eprosartan low salt and Placebo regimens

Table Epro-043-6

Serum Aldosterone Concentration and Plasma Renin Activity - Part 2



Note that the 2.25H timepoint was prior to the A-II infusion while the 3.75H timepoint was at the completion of the 3 ng/kg/min A-II infusion.

43.4.3 **Urinary electrolytes and creatinine excretion**

Part 1A: The predose 24-h urinary sodium excretion in these subjects who were maintained on low salt diet ranged from 4.6 to 42 mEq/day. The urine creatinine results indicated adequate collection of 24 hour urine samples.

Following dosing with eprosartan, a mild natriuretic effect was observed without any dose-response, the pooled 24-h urinary sodium excretion being increased, on average, by 17.73 mEq/day (range -0.85 mEq/day to 36.31 mEq/day). Pooled 24-h urinary potassium excretion was also increased, on average, by 8.04 mEq/day (range -22.40 mEq/day to 38.48 mEq/day).

There were a number of protocol violations: subjects #003 and #005 had missing urine collections, and statistical outliers in 24-h urinary sodium excretion values were present with #003, #008, etc. The residual variation for urinary sodium excretion ranged from 39.1% to 49.4%, and for urinary potassium excretion, from 8.0% to 178.6%.

Part 1B: The pre-dose urinary sodium excretion results indicated that subjects receiving high salt diet were salt replete (range 171-569 mEq/24 hours) and those receiving low salt diet were salt depleted (range 5.4 to 29 mEq/day). Urinary potassium excretion was not influenced by the type of diet. Urine creatinine results indicated adequate collection of 24 hour urine samples.

Part 2: The 24 hour urine sodium excretion results (range 2.5 to 48 mEq/day) indicated the subjects (on low salt diet) were appropriately salt depleted. Urinary potassium excretion remained relatively constant. Urine creatinine results indicated adequate collection of 24 hour urine samples.

The 24 hour urinary excretion of sodium following a single oral dose of eprosartan 400 mg (30.19 mEq/day, 95% CI: 25.02, 35.37 mEq/day) was statistically significantly increased compared to placebo (18.77 mEq/day, 95% CI: 13.62, 23.92 mEq/day). The 24 hour urinary excretion of sodium following a single oral dose of captopril 25 mg (21.58 mEq/day, 95% CI: 16.43, 26.73 mEq/day) was between eprosartan and placebo. Daily potassium excretion remain similar between all regimens. The residual variation for urinary sodium excretion ranged from 40.1% to 84.3%, and for urinary potassium excretion, from 14.3% to 220.6%.

43.5 **CONCLUSION**

43.5.1 **Effective Renal Plasma Flow and Glomerular Filtration Rate**

Part 1A: CL_{PAH} increased in response to eprosartan in a dose-related manner, the mean maximum CL_{PAH} being seen with eprosartan 100 mg and the peak $CL_{PAH\,d}$ occurring approximately 2-3 hours post dose. The mean maximum percentage increase in CL_{IN} was similar for all 5 eprosartan dose levels.

Part 1B: The mean predose CL_{PAH} were similar among the three treatment regimens. Eprosartan/low salt regimen resulted in an increase in CL_{PAH} higher than in placebo/low salt or eprosartan/high salt regimens (prior to start of angiotensin II infusion). After infusion of angiotensin II, CL_{PAH} decreased from baseline in the placebo/low salt group in a dose-related manner. Eprosartan (low or high salt diet) blocked the effect of angiotensin II both at 1 ng/kg/min and 3 ng/kg/min. The mean predose CL_{IN} and the mean maximum percentage increase in postdose CL_{IN} compared to predose CL_{IN} appeared similar for all 3 treatment regimens.

Part 2: The mean predose CL_{PAH} for the 3 regimens were similar. CL_{PAH} increased in a similar manner for both eprosartan 400 mg and captopril 25 mg compared to placebo following dosing (prior to angiotensin II infusion). During and at the end of angiotensin-II infusion, CL_{PAH} was unchanged following treatment with eprosartan, but decreased markedly during angiotensin II infusion for both captopril and placebo regimens. CL_{PAH} values for the captopril regimen decreased to values similar to the placebo regimen following angiotensin II infusion. These findings demonstrate angiotensin II blockade by eprosartan 400 mg but not by captopril 25 mg or placebo. The mean predose CL_{IN} and the mean maximum percentage increase in postdose CL_{IN} compared to predose CL_{IN} prior to angiotensin II infusion appeared similar for all 3 treatment regimens. During and at the end of angiotensin II infusion, the CL_{IN} was higher for subjects on the eprosartan compared to those on either captopril or placebo.

43.5.2 **Serum aldosterone and plasma renin activity**

Part 1A: Mean serum aldosterone level was decreased and mean plasma renin activity was increased compared to mean pre-dose values following single oral doses of eprosartan above 10 mg. However, the variability in serum aldosterone and plasma renin activity was large.

Part 1B: Mean serum aldosterone levels were elevated in the low salt diet treatment regimens compared to high salt diet regimens. Eprosartan 200 mg in the low salt diet (prior to angiotensin II infusion) suppressed the mean serum aldosterone concentration (vs no effect with placebo/low salt or eprosartan/high salt regimens). Angiotensin II infusion further increased the mean serum aldosterone concentrations in subjects on the placebo/low salt regimen whereas this effect was suppressed in the eprosartan 200 mg/low salt regimen. This suggests blockage of angiotensin II by eprosartan.

Plasma renin activity was suppressed by angiotensin II infusion in subjects on the placebo/low salt regimen. In subjects receiving eprosartan 200 mg/low salt regimen, the mean plasma renin activity increased in response to eprosartan, and this was not suppressed by infusion of angiotensin II.

Part 2: Mean serum aldosterone levels were elevated prior to dosing in these subjects who were on low salt diet. Eprosartan 400 mg and captopril 25 mg (prior to angiotensin II infusion) suppressed the mean serum aldosterone concentrations. Angiotensin II infusion increased the mean serum aldosterone concentrations in subjects receiving placebo or captopril whereas this effect was suppressed in subjects receiving eprosartan 400 mg. This finding was consistent with complete blockade of angiotensin II by eprosartan.

In subjects receiving eprosartan 400 mg and captopril 25 mg, the mean plasma renin activity increased in response to the study medication while placebo did not produce this effect. This increase in plasma renin activity was not suppressed by infusion of angiotensin II in subjects given eprosartan 400 mg, whereas exogenous angiotensin II decreased the plasma renin activity in subjects on captopril 25 mg.

43.5.3 **Urinary electrolytes and creatinine excretion**

Part 1A: The predose 24-h urinary sodium excretion in the subjects on low salt diet ranged from 4.6 to 42mEq/day. Following dosing with eprosartan, a mild natriuretic effect was observed without a dose-response, the pooled 24-h urinary sodium and potassium excretion being increased by 17.73 mEq/day and 8.04 mEq/day, respectively.

Part 1B: The pre-dose urinary sodium excretion results indicated that subjects receiving high salt diet were salt replete and those receiving low salt diet were salt depleted. Urinary potassium excretion was not influenced by diet.

Part 2: The 24 hour urine sodium excretion results indicated the subjects on low salt diet were appropriately salt depleted. Urinary potassium excretion remained relatively constant. Following a single oral dose of eprosartan 400 mg the 24 hour urinary excretion of sodium was statistically significantly increased compared to placebo. The 24 hour urinary excretion of sodium following a single oral dose of captopril 25 mg was between eprosartan and placebo. Daily potassium excretion remain similar between all regimens.

Protocol SK&F 108566/044 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** ***(Vol. 1.089/90/91/92)***

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *19-May-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *21-May-1997*

44.1. STUDY PROTOCOL

44.1.1 Title

Effects of SK&F 108566 vs captopril on renal hemodynamics in healthy volunteers and in patients with varying degrees of renal insufficiency

44.1.2 Rationale

ACE inhibitors appear to exert a renal protective effect by limiting the hemodynamic changes associated with various forms of chronic progressive renal disease. A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the effects of eprosartan, an A-II receptor antagonist, and captopril, an ACE inhibitor, on renal hemodynamic activity in subjects with normal or impaired renal function compared to placebo.

44.1.3 Objectives

1. To estimate the effect of a single oral dose and repeated daily oral doses of 300 mg of eprosartan or 25 mg captopril or placebo for 7 days (Day 1 through 6 - q 12 h, Day 7 - single dose) on renal hemodynamic parameters {effective renal plasma flow (ERPF) and glomerular filtration rate (GFR)} in male and female subjects with normal renal function, and in male and female patients with varying degrees of renal insufficiency,
2. To assess the safety and tolerability of eprosartan in subjects with normal and impaired renal function.

44.1.4 Study design

The study was a randomized, double-blind (eprosartan vs placebo), placebo-controlled, three-period crossover study. Adult subjects 18-70 years old with normal and varying renal impairment (mild, moderate and severe, based on 24 hour creatinine clearance) received the following during separate study periods:-

1. eprosartan 100 mg (Lot# U94068) x 3 tablets q 12 h for 6 days and a single dose on Day 7, or
2. captopril 25 mg (Lot# X94015) q 12 h for 6 days and a single dose on Day 7, or
3. eprosartan-matched placebo (Lot# U94111) q 12 h for 6 days and a single dose on Day 7.

Subjects were allocated at random to 1 of 6 treatment sequences (ECP, EPC, CEP, CPE, PCE, PEC) in a balanced manner with respect to treatment sequence. The interval between treatment periods was at least 1 week and not more than 2 weeks. Blood and urine samples for determination of ERPF using PAH clearance (CL_{PAH}), and GFR using inulin clearance (CL_{IN}), were obtained on Days 1 and 7 of each of 3 study periods. Subjects returned for follow up within 5 - 10 days of the last study period for a physical examination and a safety laboratory evaluation.

44.1.5 Protocol Amendments

There were 2 amendments to the original protocol. In Amendment 1, captopril was to be administered in an open-label manner because of technical difficulties with blinding. Amendment 2 consisted of a change in the clinical laboratory performing blood and urine tests.

44.1.6 Population enrolled/analyzed

51 adult male and female subjects 18-70 years of age, and weight within 30% of ideal weight (based on height and body frame) with stable renal function (defined as ≤ 25% difference between two determinations of serum creatinine obtained within the 30-day period prior to starting study medication), with negative urine drug screen were enrolled. Subjects were stratified based on the Cockcroft-Gault calculation of creatinine clearance (CL_{CR}) at baseline as follows:

Group A: Normal renal function (CL_{CR} > 80 ml/min/1.73m^2)
Group B Mild renal impairment (CL_{CR} 60 - 80 ml/min/1.73m^2)
Group C: Moderate renal impairment (CL_{CR} 30 - 59 ml/min/1.73m^2)
Group D: Severe renal impairment (CL_{CR} 5 - 29 ml/min/1.73m^2) not requiring renal replacement therapy.

Compliance: The Day 1, 4, and 7 doses of study medication for each treatment period were administered at the Clinical Pharmacokinetics Laboratory. After the Day 1 PAH and inulin clearance measurements were completed, an 11-dose supply of study medication was dispensed in a bottle sealed with an electronic cap that recorded the dates and times the bottle was opened. Subjects were instructed to take one dose every 12 hours.

Pre-study screening: The screening visit (30 days prior to the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood and urine samples were obtained for laboratory tests

(hematology, chemistry, liver function, urinalysis and drug screen). Female subjects of child-bearing potential were required to have a negative serum total chorionic gonadotropin (hCG) test, and were instructed to use an IUD or a barrier method of contraception if engaging in sexual intercourse during the interval between screening and follow-up. Subjects were given an oral water load of up to 20 ml/kg to determine their ability to produce sufficient urine at a flow rate of at least 3 ml/min to allow for adequate renal function testing. Subjects returned the next day with all collected 24-hour urine, and had a blood sample drawn (for calculating creatinine clearance and stratifying them into the study). Diuretics or nifedipine (Procardia®) were withheld for 24 hours prior to Day 1 of each study period.

44.1.7 **Study procedures**

Inulin and PAH clearance tests were performed on Days 1 and 7 of each study period.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, nursing observation, physical examination findings, laboratory findings and 12-lead ECG data.

44.1.8 **Evaluation criteria:**

Safety Parameters: Blood pressure, pulse rate, ECG data and clinical laboratory data were reviewed.

Pharmacodynamic Assessments: The primary endpoints were: ERPF measured by plasma clearance of para-amino hippurate (CL_{PAH}), and GFR measured by plasma clearance of inulin (CL_{IN}). Calculated clearances were not corrected for subject's body surface area. For each primary endpoint, three clearance measures were used in the statistical analysis, namely: average, maximum and time to maximum. The secondary endpoints were clinical safety, laboratory data and fractional excretion and urinary excretion rates for Na^+, K^+, Cl^- and uric acid, filtration fraction (CL_{IN}/ CL_{PAH}), and CL_{CR}/CL_{IN} and U_{UA}/U_{CR} ratios.

44.1.9 **Sample size:**

Based on a within-subject coefficient of variation (CV_W) of 14.9% and 17.0% for CL_{PAH} and CL_{IN}, respectively, in renal transplant recipients with mild to moderate renal insufficiency, to detect differences of 25%-30% on a 2-tailed test with a type I error rate of 5%, and 85% power between any 2 treatments (eprosartan vs placebo, eprosartan vs captopril or captopril vs placebo), with no adjustments made for multiple comparisons, it was estimated that a sample size of 9 per renal impairment group would be necessary.

44.1.10 **Investigator , Center and Study Dates:**

Robert A. Blum, Pharm.D., Millard Fillmore Hospital, 3 Gates Circle, Buffalo, NY 14209.
Study Dates: 01-Nov-1994 to 18-Mar-1996.

44.2 STUDY POPULATION

44.2.1 **Subject disposition:**

Of 51 subjects screened, 16 did not meet entrance criteria. 35 (16 male and 19 female) subjects, 23-70 years of age, weighing 47.8 to 111.8 kg, and 156-187 cm tall, were randomized. All 35 subjects received at least one dose of study medication. 31 subjects each received placebo or eprosartan, and 33 subjects received captopril. Subjects were stratified according to baseline creatinine clearance as follows: 5 subjects had normal renal function and 11, 12 and 7 subjects, respectively, had mild, moderate and severe renal function impairment.

44.2.2 **Withdrawals:**

Table Epro-044-1. Subjects withdrawn from the study

Subject Status	Last treatment received						Total number
	Eprosartan		*Captopril*		*Placebo*		of subjects
Completed study	10		9		11		30*
Withdrawn							
Adverse experience	1	#028	2	#042 #046	1**	#026	4
Protocol violation	0		1	#004	0		1
Total withdrawn	1		3		1		5

* All subjects received all 3 treatments
** Subject #026 withdrawn due to baseline vomiting that continued after dosing.

Five subjects were withdrawn from the study (Table Epro-044-1). Subject #004 had a history of renal cancer and was withdrawn from the study when this violation of exclusion criteria was discovered. This subject had received 5 doses of captopril at withdrawal. Subject #026 was withdrawn due to vomiting that started as a base line event and continued after receiving a single dose of placebo. 3 subjects were withdrawn due to adverse events (Section 3.3).

44.2.3 **Protocol violations:**

The following protocol violations occurred which the sponsor contended did not effect the safety nor the inferences of the pharmacodynamic analyses performed in this study:-

Subject	Description of Protocol Violation
All subjects	Subject allocation to sequence was not conducted in a balanced fashion with respect to treatment sequence within each renal group.
All subjects	Study was ended before full enrollment could be completed.
All subjects	MEMS caps not used to assess subject compliance with study medication administration.
All subjects	No pre-dose PAH or inulin assays were performed
004	Entered study even though subject had a history of kidney cancer (exclusion criteria).*
001, 007, 014, 019, 038, 045, 047	Individual CL_{PAH} assays not done
001, 014, 019, 038, 045	Individual CL_{IN} assays not done
025, 045	Individual urine HCG assays not done
042	Serum HCG assay at follow up not done
001, 019, 045	Individual urine samples for analysis of electrolytes not collected
046	Screening albumin concentration 2.5 g/l (exclusion criterion)**
003, 006	Post-infusion weight not measured
005, 006, 007, 010, 011, 012, 013, 014, 018, 020, 024, 026, 027, 028, 038, 041, 045, 046, 047	Administration of prohibited prior medication or change in concomitant medication regimen or administration of prohibited concomitant medication

*Subject #004 was withdrawn from study after receiving 3 doses of captopril.
**Exception granted by sponsor.

Laboratory data of 24-hour urine collections at screening suggested incomplete urine collections. An estimated creatinine clearance (CL_{CR}) value was calculated from the Cockcroft-Gault formula (uncorrected for body surface area) using the screening serum creatinine value:- Estimated CL_{CR} = $\frac{(140 - age) \times weight\ (kg)}{(72) \times serum\ creatinine\ (mg/dl)}$ (x 0.85 for women)

This estimated CL_{CR} was used to stratify subjects into 1 of 4 renal groups (normal, mild, moderate and severe).

44.3 SAFETY RESULTS

44.3.1 **General considerations:** 55 adverse experiences (AEs) were reported for 23 subjects as follows:

Renal function	Adverse events
Normal	4 AEs occurred in 2 subjects while receiving captopril
Mild impairment	14 AEs occurred in 6 subjects, (6 AEs in 4 subjects while on eprosartan, 5 AEs in 4 subjects while on captopril, and 3 AEs in 2 subjects while on placebo)
Moderate impairment	19 AEs occurred in 8 subjects, (6 AEs in 4 subjects while on eprosartan, 5 AEs in 5 subjects while on captopril, and 8 AEs in 4 subjects while on placebo)
Severe impairment	18 AEs occurred in 7 subjects, (7 AEs in 4 subjects while on eprosartan, 5 AEs in 3 subjects while on captopril, and 6 AEs in 4 subjects while on placebo)

44.3.2 **Deaths:** There were no deaths during this study.

44.3.3 **Withdrawals due to adverse experiences:**

3 subjects were withdrawn due to adverse events. Subject #028, a 58 year old healthy Caucasian male, 72.5 kg, with history of type I diabetes mellitus for 30-35 years, coronary artery disease, hypertension and chronic renal insufficiency, was diagnosed with adenocarcinoma of colon between study periods 1 and 2 after receiving eprosartan. Subject #042, a 45 year old Caucasian female, 56.1 kg, with no history of allergy and no concomitant medications, was withdrawn after developing urticaria, pruritis and rash after receiving captopril for 3 days. Subject #046, a 36 year old healthy Caucasian male, 87.8 kg, with history of type I diabetes mellitus, chronic renal insufficiency, hypertension, hypothyroidism and anemia, (on captopril) was withdrawn after developing edema; the subject progressed to end-stage renal failure requiring hemodialysis, and had to be hospitalized.

44.3.4 **Serious, Non-fatal Adverse Events:** There were 2 serious non-fatal adverse experiences:- Subject #028 was diagnosed with adenocarcinoma of colon between study periods 1 and 2 after receiving eprosartan. Subject #046 (on captopril) progressed to end-stage renal failure requiring hemodialysis and hospitalization.

44.3.5 **Adverse Events:** The adverse events were mild to moderate in nature, except for the two serious, non-fatal AEs mentioned above. For eprosartan, AEs included fatigue, dizziness, abnormal vision and diplopia, headache, vomiting, insomnia, pharyngitis, oliguria and purpura (Subject #017, who had normal platelet counts).

44.3.6 **Laboratory findings, ECGs, Vital signs**

There were no changes in pulse rates of potential clinical concern. There were 218 changes in systolic or diastolic blood pressure (160 were decreases and 58 were increases). Within any of the treatment regimens, there were no differences in the number of changes in systolic or diastolic blood pressure among the subject groups, and they were asymptomatic.

ECG data were obtained only at the screening visit and no further ECG data were reported. At screening there were no findings in PR, QRS and QTc intervals (maximum = 465 msec) that were of potential concern.

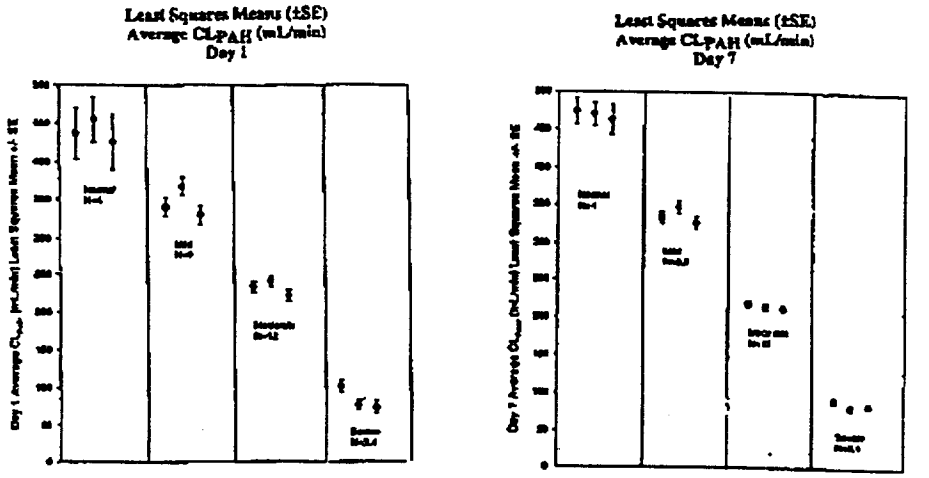
One subject with normal renal function had decreased Hemoglobin (Subject #014; from 12.6 g/dl at screening to 11.9 g/dl after captopril, then 10.9 g/dl after eprosartan and 10.4 g/dl after placebo, and 11.5 g/dl at follow up. Other abnormal laboratory findings in patients with mild, moderate or severe renal impairment were observed to be consistent with their diseased state (decreased hemoglobin and hematocrit, increased blood glucose, etc.).

44.4 PHARMACODYNAMIC RESULTS

44.4.1 PAH and Inulin Clearances

There were no substantial differences in ERPF or GFR as measured by average and maximum post-dose PAH and inulin clearance , respectively, between regimens regardless of renal group, either on Day 1 or Day 7 of dosing. The adjusted (least squares) means and associated standard errors decreased substantially as renal impairment worsened (Figures Epro-044-1 and Epro-044-2).

Figure Epro-044-1. Average CL_{PAH} on Day 1 and Day 7 in subjects with normal and impaired (mild, moderate and severe) renal function on eprosartan, captopril and placebo

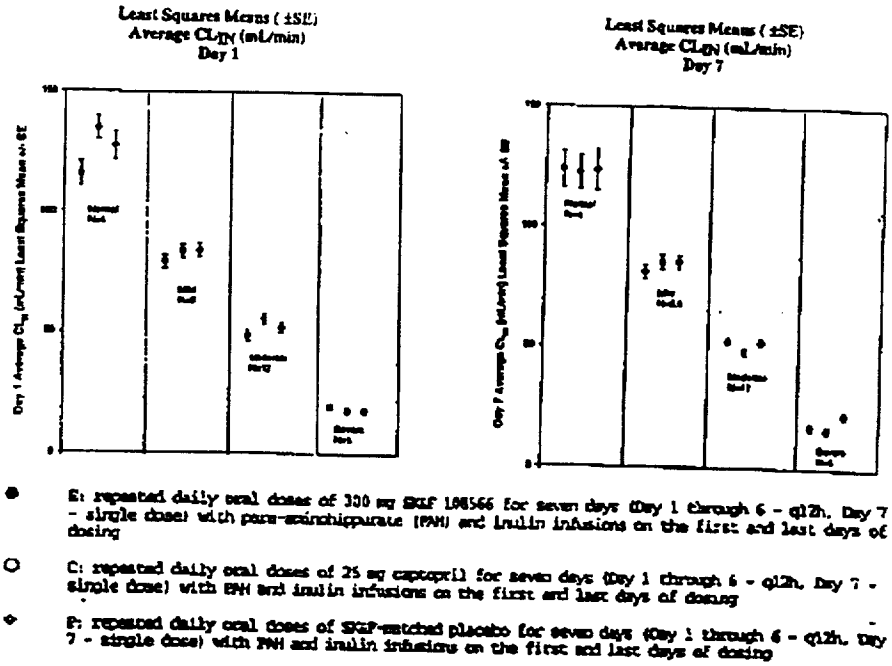


● B: repeated daily oral doses of 300 mg SKF 108566 for seven days (Day 1 through 6 - q12h, Day 7 - single dose) with para-aminohippurate (PAH) and inulin infusions on the first and last days of dosing .

○ C: repeated daily oral doses of 25 mg captopril for seven days (Day 1 through 6 - q12h, Day 7 - single dose) with PAH and inulin infusions on the first and last days of dosing

◆ P: repeated daily oral doses of SKF-enriched placebo for seven days (Day 1 through 6 - q12h, Day 7 - single dose) with PAH and inulin infusions on the first and last days of dosing

Figure Epro-044-2. Average CL_{IN} on Day 1 and Day 7 in subjects with normal and impaired (mild, moderate and severe) renal function on eprosartan, captopril and placebo



44.4.2 **Urine Electrolyte Excretion**

Urinary fractional excretion and urinary excretion rates of Na^+, K^+ and uric acid, the urinary uric acid/urinary creatinine ratio, and CL_{CR}/CL_{IN} ratio, were similar after treatment with eprosartan, captopril or placebo. Overall, the fractional excretion and excretion rates of urinary electrolytes increased with worsening renal function, with no apparent changes in these parameters associated with eprosartan or captopril compared to placebo.

44.4.3 **Statistical issues:**

Of 35 subjects enrolled, 5 were withdrawn (and did not have CL_{PAH} or CL_{IN} data after withdrawal). The study was ended prior to meeting the target enrollment of 9 subjects per renal group. All primary endpoint results were based on the 30 subjects who completed the study, with the exception of CL_{PAH} data for Subject #047, period 3 (placebo), Day 1 which was removed prior to analysis. No adjustments were made for multiple comparisons.

There was imbalance with regard to the number of subjects in each renal group, and treatment sequences within each renal group were imbalanced. Significant period effects were observed for maximum CL_{PAH} on Day 7 in mild and severe renal function groups. Significant carryover effects were noted for average CL_{PAH} on Day 1, for the mild renal group. Inferences were adjusted for such effects in the ANOVA model. Analyses and carryover assessments run with and without the potential statistical outliers did not change the inferences. Because of the small sample sizes for the normal and severe renal groups, and the presence of imbalance in treatment sequences within each renal group, the inferences have to be interpreted with caution.

44.5 **CONCLUSION**

Single or repeat dose oral administration of eprosartan 300 mg twice daily for 7 days or of captopril 25 mg twice daily for 7 days to subjects with normal renal function and those with mild, moderate or severe renal function impairment showed no increase in the frequency or severity of adverse experiences compared to placebo.

In subjects with normal renal function as in those with varying degrees of renal insufficiency, effective renal plasma flow and glomerular filtration rate were similar across regimens (eprosartan, captopril or placebo) under single oral dose (Day 1), and repeat oral dose (Day 7) conditions. Fractional excretion of sodium and urinary sodium excretion rates showed no evidence of sodium retention with eprosartan. Eprosartan had no effects on uric acid excretion in subjects with renal impairment.

Protocol 048 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.093/94)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *06-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *09-Jun-1997*

48.1. STUDY PROTOCOL

48.1.1 Title

Investigation of the safety, pharmacokinetics of single and repeated oral doses of SK&F 108566 (600 mg/day, 800 mg/day and 1200 mg/day) in patients with mild to moderate essential hypertension

48.1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the safety and pharmacokinetics of eprosartan, an A-II AT_1 receptor antagonist, in patients with mild to moderate essential hypertension.

48.1.3 Objectives

1. to evaluate the safety and tolerability of SK&F 108566 administered orally in repeated single daily doses for one week in patients with mild to moderate essential hypertension,
2. to obtain pharmacokinetic data on single and repeated dose administration of SK&F 108566 in patients with mild to moderate essential hypertension
3. to evaluate the short-term (one week) effect of SK&F 108566 on blood pressure and pulse in patients with mild to moderate essential hypertension, and
4. to describe the effect of SK&F 108566 on urine uric acid excretion.

48.1.4 Study design

The study was a randomized, double-blind, placebo controlled, repeated dose, dose-rising, two-period, period balanced crossover study within each of three dose groups (A, B and C) corresponding to three dose levels of SK&F 108566. Following a washout period of 6 weeks, each patient participated in two study periods separated by at least 6 days, in which study medication was administered once daily for 7 days. The dose groups A, B, and C were as follows:

1. Group A: eprosartan (SK&F 108566 oral tablets 100mg, Lot# U93235 x 6 tablets as a single dose) 600 mg once daily
2. Group B: eprosartan (SK&F 108566 oral tablets 100mg, Lot# U93235 x 8 tablets as a single dose) 800 mg once daily
3. Group C: eprosartan (SK&F 108566 oral tablets 100mg, Lot# U93235 x 12 tabs as a single dose) 1200 mg once daily
4. Patients also received matching placebo (Lot# U94031) once daily in a randomized manner.

48.1.5 Protocol Amendments

A protocol amendment was made on 09-May-1994 which added a third treatment regimen (Group C above, with SK&F 108566 1200 mg/day for 7 days) evaluated in 8 additional patients.

48.1.6 Population enrolled/analyzed

24 healthy, non-smoking, adult Caucasian men 18-55 years of age, with mild to moderate essential hypertension (average sitting diastolic blood pressure 95 to 115 mmHg without treatment), weight ≥50 kg and within 25% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medication was administered with 120 ml tepid water by study personnel.

Pre-study screening: The screening visit (60 days prior to start of the study) included a complete medical and medication history, physical examination, and 12-lead ECG. Blood (15 ml) and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Patients with acceptable screening examination were instructed to discontinue all anti-hypertensive medications at least 2 weeks prior to administration of study medication. During this washout phase, patients returned at intervals of 1 week (±1 day) for measurement of blood pressure and pulse rate. Those patients whose average sitting diastolic blood pressure at the week -2 and -1 evaluations was between 95 and 119 mmHg were allowed to participate in the study.

48.1.7 Study procedures

Patients remained at the research facility from the evening prior to first dose of study medication to the morning of day 2 till after the second dose of study medication was administered. A 24-hour urine specimen was also obtained prior to dosing on day 1. Measurements of sitting blood pressure and heart rate, and a 12-lead ECG recording were

made. A blood specimen was obtained to measure plasma renin activity after the patient had been supine for at least 1 hour. A limited physical examination was made, vital signs were obtained, and the study medication administered with 120 ml tepid water. Blood sample (5 ml) collections for pharmacokinetics were done prior to dose administration and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 23.5, 23.75 and 24 hours following dosing, the 24 hour sample being drawn immediately prior to dosing on day 2. Vital signs were recorded immediately before each collection of blood specimen. A 12-lead ECG was obtained prior to dosing and at 2, 4 and 24 hours after the first dose. After obtaining vital signs up to 2 hours after dosing, the patient was allowed to eat breakfast and discharged from the research facility (i.e., 26 hours after the first dosing).

Patients returned each morning for the morning dose of the study medication on days 3 through 6. At the morning visit on day 5 (± 1 day), an Accutracker II ambulatory blood pressure monitoring unit was placed for 24 hours to record blood pressure and pulse rate at 15 minute intervals while the patient was awake, and at 30 minute intervals while he was sleeping. 5 ml blood samples were taken on the morning visits on days 4 and 6 prior to dosing.

Urine was collected and pooled during the 24 hour period prior to dosing on day 7. In the morning of day 7, a blood specimen was obtained to measure plasma renin activity after the patient had been supine for at least 1 hour. Blood samples for pharmacokinetics were drawn as on Day 1. Urine uric acid excretion was also determined to calculate fractional excretion of uric acid at 4 and 24 hours on Days 0, 1 and 7.

Subjects returned 1 week following the last (second) study session, at which time physical examination, recording of vital signs, 12-lead ECG and safety laboratory tests were performed. Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

48.1.8 **Pharmacokinetic procedures**:
Blood samples collected in heparinized tubesand chilled on ice were centrifuged at 4°C, and plasma was transferred to polypropylene containers and frozen at -20°C to be assayed within 7 months. Plasma concentrations of eprosartan were determined by reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) in plasma was 10.0 ng/ml based on a 0.5 ml sample volume.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain the maximum observed plasma concentration (Cmax) and time at which Cmax occurred (Tmax), the apparent terminal elimination rate constant (λ), $T_{1/2}$, AUC(0-τ), AUC(0-∞). The percent extrapolated was < 20% in all with the exception of the following patients: < 30 % in Patients 011 and 013 on Day 7 of 800 mg/day regimen, Patient 040 on Day 1 and Patients 034 and 036 on Day 7 of the 1200 mg/day regimen.

48.1.9 **Endpoints:**
The primary parameters were the clinical monitoring and laboratory safety data, and the plasma concentration data for pharmacokinetics. The secondary parameters were the average sitting diastolic and systolic blood pressure, pulse rate and ambulatory blood pressure.

48.1.10 **Sample size:**
The planned sample size (8 per group) was based on feasibility. No statistical power calculations were performed.

48.1.11 **Investigator , Center and Study Dates:**
Jerry Herron, MD, Arakansas Research Medical Testing Center, Inc., Little Rock, Arkansas, USA.
Study Dates: 06-Jun-1994 to 27-Sep-1994.

48.2 STUDY POPULATION

48.2.1 **Subject disposition:**
24 Caucasian adult male patients with mild to moderate hypertension, 37-55 (mean = 47) years of age, weighing 64 to 96 (mean = 84) kg, and 165-191 (mean = 181) cm tall, were screened and randomized.

48.2.2 **Withdrawals:** No subject withdrew prior to study completion.

48.2.3 **Protocol violations:**
Although not specified in the protocol, all subjects had blood and urine specimens collected and clinical chemistry, hematology and urinalysis tests performed at 24 hours after the first dose of study medication.

Serum uric acid levels at 4 hours post-dose on Day 1, which were specified in the protocol, were not done.

A few patients while receiving placebo (Patients 005, 006, 008 and 034) had measurable concentrations of eprosartan just above the LLQ (which the sponsor suggested may be related to endogenous substances in the plasma).

In the calculations of AUC, the percent extrapolated was <20% in all with the exception of the following patients: Patients 011 and 013 on Day 7 of 800 mg/day regimen, Patient 040 on Day 1 and Patients 034 and 036 on Day 7 of the 1200 mg/day regimen, in whom the percent extrapolated were < 30 %.

Examination of the plasma concentration-time profiles also showed that some of the Patients #005, 011 and 016 were missing the 24-hour post-dose blood samples

48.3 SAFETY RESULTS

48.3.1 **General considerations:** A total of six adverse experiences were reported in 5 subjects.

48.3.2 **Deaths:** There were no deaths during this study.

48.3.3 **Withdrawals:** There were no withdrawals due to adverse experience during this study.

48.3.4 **Serious, Non-fatal Adverse Events:** There was no serious non-fatal adverse experience during this study.

48.3.5 **Adverse Events:** Six adverse events (all mild to moderate in nature) were reported for 5 patients as follows:

1. Group A (eprosartan 600 mg once daily): Patient # 001 reported dizziness and Patient # 008 reported headache.
2. Group B (eprosartan 800 mg once daily): No patients reported AEs.
3. Group C (eprosartan 1200 mg once daily): Patients # 036 and 038 reported headache.
4. Placebo: Patient # 001 reported headache, and Patient # 006 reported dizziness.

48.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates. There were no symptomatic changes in blood pressure. The sponsor submitted that there were no clinically meaningful changes in the 12-lead ECGs and the ECG intervals (including PR, QRS, QT and QTc) noted in any treatment group.

Except for the following patients, there were no apparent changes in any safety laboratory value associated with SK&F 108566, and no values of potential clinical concern were identified: Patient # 006 had an initial hematocrit of 34.9% (normal range = 36-54%) and Patient # 035 had a hematocrit of 35.1-35.3% throughout the study.

Values of urinary excretion of sodium, potassium and creatinine (U_{Na}, U_K, U_{Cr}) and plasma renin activity were similar following administration of eprosartan or placebo with no apparent dose response. There was no change in urine uric acid excretion, fractional excretion of uric acid and Urine Uric Acid to Creatinine Ratios.

48.4. PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

48.4.1 Primary Efficacy Endpoint: Following single and repeat oral doses of eprosartan (Table Epro-048-1) peak plasma concentrations were reached within 1-3 hours: plasma levels were <10% of peak values after 12 hours (<14% for 600 mg/day regimen after 7 days at 18 hours).

In Table Epro-048-2, Tmax was reached within 1.88 to 2.88 hours, with no differences between single and repeated dosing. Mean $t_{1/2}$ ranged from 8.64 to 12.24 hours. A dose-related increase in mean Cmax, AUC(0-τ) and AUC(0-∞) were found. (except for AUCs for the 800 mg dose after 7 days). There was no accumulation with repeated doses. These suggest that eprosartan requires bid dosing.

Although there were slight fluctuations in plasma levels from day to day (Table Epro-048-3), steady-state appears to be reached by Day 4.

Table Epro-048-1. Time course of plasma concentrations following single and repeat oral doses of eprosartan

Time	After first single oral dose of:			After 7 days oral doses of:		
(hour)	*600 mg*	*800 mg*	*1200 mg*	*600 mg*	*800 mg*	*1200 mg*
0	NQ	NQ	NQ	103.0	60.8	145.8
0.25	150.1	111.5	299.8	262.8	275.0	246.6
0.50	555.9	525.1	960.4	515.3	705.7	763.3
0.75	827.5	1174.8	1586.7	934.9	1022.9	1209.3
1.0	1063.1	1474.8	1914.8	903.1	1466.2	1592.4
1.5	1173.4	1718.0	2129.4	1111.1	1674.8	2277.4
2.0	1215.3	1812.7	2058.1	1029.1	1490.6	2302.4
3.0	1239.4	1864.4	1892.5	917.8	1596.3	2359.3
4.0	1183.5	1371.1	1842.2	1133.6	1183.2	2095.0
6.0	534.1	520.1	1209.0	752.1	503.2	1169.8
8.0	256.8	240.0	497.0	443.1	259.3	854.5
12.0	105.8	104.2	272.1	219.9	163.6	478.8
18.0	57.3	72.0	176.4	149.0	102.8	348.2
24.0	41.4	44.2	69.3	70.7	61.9	190.5

NQ = not quantifiable

Table Epro-048-2. Pharmacokinetic values for eprosartan following single and repeat oral doses

End-point	After first single oral dose of:			After 7 days oral doses of:		
	600 mg	*800 mg*	*1200 mg*	*600 mg*	*800 mg*	*1200 mg*
Cmax (ng/ml)						
Mean	1622	2081	2785	1608	2103	2961
Median	1167	1688	2533	1332	1748	2457
S.D.	802	937	1012	726	1502	1432
Tmax (hr)						
Mean	2.53	2.88	2.09	2.56	1.88	2.72
Median	1.50	3.00	1.50	2.25	1.50	3.00
S.D.	1.89	0.64	1.73	1.82	1.09	1.60
AUC(0-τ) (ng.h/ml)						
Mean	7829	9639	14642	9731	9521	19125
Median	6011	6921	13269	9198	9165	20062
S.D.	4477	5476	6838	4381	4975	8632
AUC(0-∞) (ng.h/ml)						
Mean	7895	10520	16310	10786	10443	22423
Median	6451	7179	13755	10204	10246	21695
S.D.	4507	5777	8141	4963	4818	10749
$T_{1/2}$ (h)						
Mean	11.52	7.89	10.43	9.02	8.64	12.24
Median	8.59	5.48	6.29	7.85	8.93	9.22
S.D.	6.98	5.66	6.62	3.13	4.17	6.58
Accumulation Ratio						
Geometric Mean	--	--	--	1.11	0.85	1.14
Minimum	--	--	--	0.72	0.52	0.62
Maximum	--	--	--	1.68	1.93	2.50

Accumulation Ratio = {$AUC_{(0-\tau)}$ on Day 7} ÷{$AUC_{(0-\infty)}$ on Day 1}

Table Epro-048-3. Minimum plasma concentrations (Mean ± SD) of eprosartan

Study	After first single oral dose of:		
Day	*600 mg*	*800 mg*	*1200 mg*
2	41.4 ± 16.3	44.2 ± 17.4	68.1 ±42.14
4	42.2 ± 17.0	94.0 ± 67.0	160.0 ± 67.1
6	75.6 ± 54.1	62.2 ± 38.1	143.7 ± 98.2
7	103.0 ± 104.7	60.8 ± 30.2	145.8 ± 131.5
8	70.7 ± 43.9	55.4 ± 48.2	190.5 ± 141.8

48.4.2 Secondary Efficacy Endpoint

Table Epro-048-4. Change (placebo subtracted) in cuff and ambulatory systolic and diastolic blood pressure following single and repeat oral doses of eprosartan

Day &	After first single oral dose of:			After 7 days oral doses of:		
Time	600 mg	800 mg	1200 mg	600 mg	800 mg	1200 mg
Systolic Cuff Blood Pressure (compared to placebo)						
0h	4.92	0.25	-5.08	1.67	-4.25	5.08
3h	-8.75	-2.00	-7.00	0.00	-1.50	-8.25
24h	1.33	-3.42	1.50	-7.08	-5.92	-7.50
Diastolic Cuff Blood Pressure (compared to placebo)						
0h	0.42	1.25	0.50	0.83	-0.42	2.83
3h	-5.00	-2.25	-2.00	-0.25	-3.00	-2.50
24h	-0.33	2.25	0.25	-2.67	0.17	-1.92
Ambulatory Blood Pressure Monitoring (Systolic) (compared to placebo)						
0-12h				-1.820	1.595	-8.622
12-24h				-1.674	-3.908	-7.304
0-24h				-1.849	-0.524	-8.366
Ambulatory Blood Pressure Monitoring (Diastolic) (compared to placebo)						
0-12h				-2.816	-0.965	-6.049
12-24h				-0.800	-2.989	-5.069
0-24h				-1.699	-1.841	-5.864

There were no symptomatic changes in blood pressure. If a fall in diastolic cuff blood pressure by ≥ 3 mmHg is taken as an acceptable response to treatment, then this response is observed (albeit inconsistently) at 3 hours after dosing, with no apparent treatment response at 24 hours (Table Epro-048-4). This finding also suggests that eprosartan requires bid dosing.

No dose-related response was found in the cuff blood pressure (systolic or diastolic). A dose-dependent lowering of systolic and diastolic blood pressure was found in ambulatory blood pressure monitoring for the 12-24 h period.

48.5 CONCLUSION

Single and repeat dose administration of varying doses (600, 800 and 1200 mg once a day) of eprosartan to patients with mild to moderate essential hypertension did not show any significant differences in adverse experiences compared to placebo. There were no abnormal laboratory values of potential safety concern.

The plasma concentrations reached peak values within 1-3 hours, with $T_{1/2}$ between 8.64 to 12.24 hours. A dose-related increase in mean Cmax, AUC(0-t) and AUC(0-∞) were found (except for AUCs for the 800 mg dose after 7 days). There was no accumulation with repeated doses. There was no accumulation with repeated doses. Steady-state appears to be reached by Day 4. The pharmacokinetic data suggest that eprosartan requires bid dosing.

Diastolic cuff blood pressure was reduced at 3 hours after dosing, with no apparent treatment response at 24 hours. Ambulatory blood pressure monitoring showed dose-dependent lowering of blood pressure during the 12-24 hour period.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA #:	20-738	NDA Volume:	1.1097-1101
DRUG NAME:	Teveten™ (Eprosartan) Tablets		
SPONSOR:	SmithKline Beecham Pharmaceuticals		
TYPE OF DOCUMENT:	New NDA (Clinical Pharmacology Review)		
DATE OF CORRESPONDENCE:	*11-Jul-1997*	DATE ASSIGNED:	*14-Jul-1997*
DATE RECEIVED:	*14-Jul-1997*	DATE COMPLETED	*16-Jul-1997*
MEDICAL OFFICER:	Khin Maung U, M.D.		

1. STUDY PROTOCOL

1.1 Title

Protocol 051: ***A 6-month, double-blind, double dummy, parallel, multicentre study of the action of SK&F 108566 in comparison with enalapril on left ventricular hypertrophy in patients with essential hypertension (DBP ≥95 and ≤114 mmHg)***

1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. Enalapril is a long-acting ACE inhibitor currently marketed for treatment of hypertension and congestive heart failure. In hypertensive patients, an adaptive mechanism to hemodynamic overload of the heart is left ventricular concentric hypertrophy (LVH) by measurement of LVMI, characterized by an increase in left ventricular wall thickness at the expense of chamber volume. ECG evidence of LVH is associated with increased risk of cardiac morbidity and mortality in hypertensive patients. Many antihypertensive agents, including ß-blockers, ACE inhibitors, α methyl dopa and certain calcium antagonists show favorable effects on left ventricular mass and also on its consequence, particularly arrhythmias, left ventricular diastolic function or myocardial ischemia. The best clinical measurement of left ventricular anatomy has been shown to be left ventricular mass indexed (LVMI) by body surface area (the cut-off point being 134 g/m^2 in men and 110 g/m^2 in women). This study evaluates the evolution of LVH by measurement of LVMI (Devereux formula and Penn convention) calculated on echocardiographic parameters in a 6-month, double-blind, double dummy, parallel, multicentre study comparing the efficacy and safety of eprosartan and enalapril in patients with essential hypertension (DBP ≥95 and ≤114 mmHg) and LVH.

1.3 Objectives

The primary objective was to obtain information on the evolution of LVH measured by echocardiography in hypertensive patients with pre-existing LVH taking long term treatment of eprosartan compared with enalapril. The secondary objectives were to obtain information on the evolution of left ventricular diastolic function assessed by echocardiography and Doppler examinations in hypertensive patients with pre-existing LVH, to compare the antihypertensive efficacy and to compare the safety with regard to adverse experiences, laboratory abnormalities and changes in ECGs, following long term use of eprosartan and enalapril.

1.4 Study design

This is a multi-center, double-blind, double-dummy, active (enalapril)-controlled, randomized, parallel group study of patients with essential hypertension (DBP ≥95 and ≤114 mmHg) and LVH (LVMI ≥ 110 g/m^2 for males and ≥90 g/m^2 for females, and septum to posterior wall thickness ratio ≤1.4).

The study consisted of 4 periods: screening, single-blind placebo run-in (3-5 weeks), double-blind treatment (200 mg eprosartan (Lot# U94191 100 mg tablets x 2) bid titrated up to 300 mg and then to 400 mg bid, or 10 mg enalapril (Lot# U94207) qd titrated up to 20 mg (Lot# U94208) qd and then to 40 mg (Lot# U95045) qd, for 12 weeks followed by a 14-week maintenance phase at the titrated dose), and follow-up. Eprosartan placebo (Lot# U94189) and enalapril placebo (Lot# X94158) were given to patients assigned to these placebo treatments. Medications were given with food.

The study design is illustrated in Figure Epro-061-1, and the dose regimens in Table Epro-051-1.

Figure Epro-051-1 Study Design Schematic

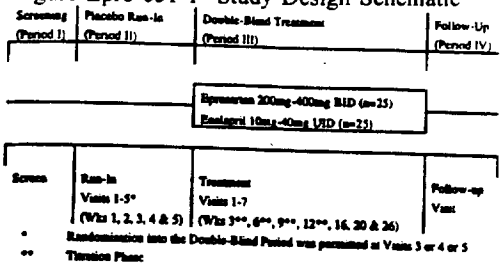


Table Epro-051-1 Dosage Regimen

Dose Level	Eprosartan 100 mg or Placebo Tablets	Enalapril 10 mg, 20 mg or Placebo Capsules
I	2 tablets in the morning and 2 tablets at night of Medication A (100 mg or placebo)	1 Capsule in the morning of Medication Y (10 mg or placebo)
II	3 tablets in the morning and 3 tablets at night of Medication A (100 mg or placebo)	1 Capsule in the morning of Medication X (20 mg or placebo)
III	4 tablets in the morning and 4 tablets at night of Medication A (100 mg or placebo)	2 Capsules in the morning of Medication X (20 mg or placebo)

1.5 **Protocol Amendments**

There were no amendments to the protocol.

1.6 **Population enrolled/analyzed**

126 men and women without child-bearing potential (or women using hormonal or barrier contraceptives or IUCDs) over 18 years age, with essential hypertension (DBP ≥95 and ≤114 mmHg in the last 2 weekly visits, the difference between the average DBP being ≤12 mmHg) and LVH (LVMI ≥ 110 g/m^2 for males and ≥90 g/m^2 for females, and septum to posterior wall thickness ratio ≤1.4) were enrolled. Patients with pregnancy or lactation, secondary forms of hypertension, advanced retinopathy, arrhythmias, clinical evidence of congestive heart failure on treatment with ACE inhibitors, myocardial infarction or a cerebrovascular accident, angina pectoris, unstable diabetes mellitus, clinically significant renal or hepatic disease, alcohol or drug abuse, or chronic/concomitant treatment with drugs known to affect blood pressure, concurrent severe disease (e.g., neoplasm), use of warfarin or other oral anticoagulants, allergy to enalapril were excluded.

Compliance: This was determined by the number of tablets dispensed at each visit and subtracting the returned number of tablets, for each medication. Patients who took <80% or >120% of study medications during 3 consecutive dosing intervals were considered noncompliant.

Pre-study screening: The screening visit (7 days prior to start of the run-in period) included a complete medical and medication history, physical examination including fundoscopy, 12-lead ECG and echocardiographic examination. Blood and urine samples were obtained for laboratory tests (hematology, chemistry, liver function tests, urinalysis and drug screen). Female patients of child-bearing potential must have a negative pregnancy test (ßhCG).

1.7 **Study procedures**

The timing of study visits and procedures conducted at each visit are shown in Table Epro-051-2.

Run-in phase: Patients were seen weekly for sitting diastolic blood pressure (sDBP) and heart rate, adverse experiences, concomitant medications and compliance information. Patients eligible for randomization required an average sDBP ≥95 and ≤114 mmHg in the last 2 weekly visits, the difference between the average DBP being ≤12 mmHg, and also a LVMI at screening of ≥ 110 g/m^2 for males and ≥90 g/m^2 for females, and septum to posterior wall thickness ratio ≤1.4. Eligible patients underwent ECG, cardiopulmonary examination, an echocardiographic examination, body weight and fasting safety laboratory tests, and female patients of child-bearing potential had a negative pregnancy test (ßhCG).

Table Epro-051-2 Study Schedule

		Run-In Period		Treatment Period							
	Screen	Visits 1 & 2	Visits 3, 4 & 5	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Follow Up Visit
Medical History	X										
Physical Examination	X										
Chest X-ray	X										
ECG	X		X*		X		X		X	X	X
CP Examination	X		X*				X			X	X
BPHR	X	X	X	X	X	X	X	X	X	X	X
Echo-cardiography	X		X*							X[#]	
Laboratory Tests	X		X*		X		X		X	X	X
AEs		X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Compliance		X	X	X	X	X	X	X	X	X	
Weight	X		X*		X		X		X	X	X
Randomization			X*								
Dose Titration				X**	X**	X**					
Pregnancy Test	X		X*		(X)		(X)		(X)	X	X

X* - only for those patients who are eligible to be randomised
(X) - only required for women of child bearing potential using barrier methods of contraception or those females of child-bearing potential being withdrawn
X** - only in those patients eligible for dose titration
X' - only patients that have been withdrawn from Visits 5 or 6 and for patients completing the study at Visit 7.

Double-blind treatment phase: This was divided into titration phase and maintenance phase.
Titration phase: Eligible patients were randomized to 1 of 2 medication regimens starting with either eprosartan 200 mg bid or enalapril 10 mg qd (dose Level I) given with food. At the end of weeks 3, 6, 9 and 12 (Visits 1, 2, 3 and 4) patients were assessed for vital signs, adverse experiences and underwent ECG, safety laboratory tests, and female patients of child-bearing potential had a negative pregnancy test (ßhCG). The doses were also titrated upward to Level II (eprosartan 300 mg bid or enalapril 20 mg qd) and then to Level III (eprosartan 400 mg bid or enalapril 40 mg qd) to maintain patient's DBP <90 mmHg. No adjustments of double-blind medication dosage was permitted after Visit 4 (Week 12), any patient requiring an dose reduction being withdrawn from the study. Patients who successfully completed the titration phase at Visit 4 entered the maintenance phase if one of the following conditions were met: (i) sDBP had decreased to <90 mmHg after at least 3 weeks at any dosage, or (ii) sDBP had decreased to ≤100 mmHg and the decreased was at least 5 mmHg from baseline after 3 weeks on dose level III.

Maintenance phase: Patients continued in the study for 14 weeks in this phase provided their BP did not fall into any of the following criteria: (i) Mean sDBP >120 mmHg at any visit; (ii) mean sDBP was between 115-120 mmHg at any visit and had remained within this range upon mandatory return to the clinic within 3 days; (iii) BP had remained at a level unacceptable to the investigator; and (iv) mean sSBP >200 mmHg at 2 consecutive visits.

Follow-up phase: Subjects returned 7-14 days following the last day of study medication, at which time safety laboratory tests, 12 lead ECG, a cardiopulmonary examination, and, for women of child-bearing potential, pregnancy test, were done.

Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

1.8 **Calculations of cardiologic parameters:**

LVMI was calculated (see below) according to the Devereux formulae and the Penn convention from M-mode echocardiographic examinations which were performed, where possible, by the same physician using the same apparatus. A pulsed Doppler examination was also performed for assessment of LV diastolic function. Recordings of echocardiograms and Doppler were done at 110 mm/sec on 3 cycles. An ECG tracing was also recorded. Each recording (15 seconds for each view on VHS or SVHS video tape) was coded for blind readings. A second set of tracings was recorded for use at a subsequent examination.

At the central reading center, measurement of the following echocardiographic parameters was done blindly by 2 observers according to the Penn Convention: (1) Diastolic and systolic interventricular septum thickness ($IVST_d$ and $IVST_s$); (2) Diastolic and systolic left ventricular internal diameter ($LVID_d$ and $LVID_s$), and (3) Posterior wall thickness (PWT) in systole and diastole. Measurements were made on 3 cycles and averaged.

The following parameters were evaluated from the Doppler examinations: (1) isovolumic relaxation time; (2) peak velocity of early left ventricular filling (peak E); (3) peak velocity of late left ventricular filling (peak A); and (4) peak E deceleration time.

From the above parameters, the following calculations were made:

(1) the left ventricular mass (LVM) was calculated from the Devereux and Reicheck formula:
$LVM = 1.04\{(IVST_d + LVID_d + PWT_d)^3 - LVID_d\}^3 - 13.6g.$
LVMI = LVM/body surface area.
(For patients where LVMI for the same echocardiogram differed by ≥10%, a second reading of the paper tracing with the help of videotape recordings wad made by the 2 observers to reach an agreement. If no agreement was made, the echocardiogram of the patient was rejected.)

(2) Peak systolic wall stress (PSWS) was calculated according to the formula of Grassman:
$PSWS = 0.334 \times sSBP \times LVID_s / PWT_s \times (1 + PWT_s/LVID_s)$

(3) Ejection fraction, where $EF = (V_D - V_S)/V_D \times 100$, with
V_D (end diastolic volume) $= 1.047 \times (LVID_d)^3$, and V_S (end systolic volume) $= 1.047 \times (LVID_s)^3$

(4) Fractional shortening, where $FS = (LVID_d - LVID_s)/ LVID_s \times 100$

(5) Ratio of peak E to peak A.

1.9 **Endpoints:**

The primary efficacy endpoint was the change from baseline of the LVMI at month 6 and study endpoint. Comparisons were made using ANOVA or Cochran-Mantel-Haenszel statistic.

The secondary efficacy parameters are the mean changes from baseline of the following parameters:
(1) Ejection fraction
(2) Peak systolic wall stress
(3) LV end systolic and end diastolic volumes
(4) LV fractional shortening
(5) LV diastolic diameter
(6) Peak E/A ratio
(7) Peak E deceleration time
(8) Isovolumic relaxation time
(9) Systolic and diastolic posterior wall thickness
(10) Sitting DBP
(11) Sitting SBP
(12) Sitting heart rate
(13) Proportion of responders in each treatment group (defined as the percent of patients whose sDBP is <90 mmHg or 90-100 mmHg *and* decreased from baseline by at least 10 mmHg)

1.10 **Sample size:**

To detect a difference of 27 g/m^2 in LVMI, assuming a standard deviation of 30 g/m^2, to provide 80% power and a 0.05 level of significance on two-sided testing, the sample size was estimated as 25 evaluable patients per regimen.

1.11 **Investigator , Center and Study Dates:**

The study was carried out in 10 centers in France. The investigators and the centers are given in Table Epro-051-3.
Study dates: 09-Sep-1995 to 06-Aug-1996

Table Epro-051-3 Participating investigators and centers

Centre No.	Investigator	Hospital / Surgery
441	Lelay, Dominique MD	200, Rue Jean Jaurès, Vieux Condé
442	El Soury, Alain MD	1, Rue Pierre Schubert, Saint-Martin D'Hères
443	De La Chevasnerie, Antoine MD	14, Rue de Valmeray, Perigueux
444	Bons, Jean - Philippe MD	40, Bd des Recollets, Toulouse
445	Pons, Eric MD	UCPA-Clinique du Mail, Grenoble
446	Valeix, Pascal PhD	Centre "Les Noisetiers", Vendargues
447	Cottet, Robert MD	1173, Route de Grasse, Antibes
448	Powers, Andre MD	535, Ave. De La Repiemeca, Toulon
449	Boudoual, Serge MD	253, Chem madrague ville, Marseille
450	Pessez, Gilles MD	12, Rue Belle Gabrielle, Le Mans

Data Source: Table 13.8; Appendix A, Appendix B Patient Listing 1 & 2.

2. STUDY POPULATION

2.1 Subject disposition:

126 patients were screened. 58 patients were ineligible (44 were withdrawn at screening (75% did not have LVH), and 14 during the placebo run-in period).

68 patients qualified for randomization to the double-blind treatment period. Of these, two patients were excluded from efficacy evaluation (Patient# 051.446.00822 had no trough blood pressure measurement available, and Patient# 051.449.00839 was excluded due to absence of sufficient source documentation for validation of efficacy data) but were included in safety evaluation. The number (%) of patients who entered each phase of the study is given in Table Epro-051-4. 47 patients (71.2%) completed 6 months of double-blind medication comprising 23 patients (46.9%) in the eprosartan regimen and 24 patients (49.0%) in the enalapril regimen.

Table Epro-051-4

Patient number by study phase and titrated dose

Study Phase	Titrated Dose	Patient Numbers n (%)*
Entered Titration Phase	Eprosartan 200 mg BID	31 (47.0)#
	Enalapril 10 mg QD	35 (53.0)
	Total	66 (100)
Completed Titration Phase	Eprosartan 200 mg BID	16 (34.2)
	Eprosartan 300 mg BID	2 (3.0)
	Eprosartan 400 mg BID	11 (16.7)
	Enalapril 10 mg QD	10 (15.2)
	Enalapril 20 mg QD	12 (18.2)
	Enalapril 40 mg QD	8 (22.9)
	Total	59 (89.4)
Completed Maintenance Phase	Eprosartan 200 mg BID	13 (19.7)
	Eprosartan 300 mg BID	2 (3.0)
	Eprosartan 400 mg BID	7 (22.6)
	Enalapril 10 mg QD	9 (13.6)
	Enalapril 20 mg QD	9 (13.6)
	Enalapril 40 mg QD	5 (7.6)
	Total	47 (71.2)**

* Percentage of patients receiving at least one dose of medication
** Two patients (PIDs 051.447.00838 and 051.447.00837), one from each medication regimen, were "off-drug" at maintenance endpoint (see table 8)
# Includes PIDs 051.446.00822 and 051.449.00839

2.2 Withdrawals:

17 (25.0%) patients were withdrawn (11 (31.4%) in enalapril group and 6 (18.2%) in eprosartan group). 6 (8.8%) patients were withdrawn due to adverse experiences, 5 (7.4%) patients due to lack of efficacy, 2 (2.9%) patients lost to follow up, 1 patient terminated by the sponsor and 3 (4.4%) patients for "other reasons" (Table Epro-051-5).

Table Epro-051-5

Reasons for withdrawal (number (%) of patients)

	Eprosartan (n=33)*		Enalapril (n=35)		Total (n=68)	
	N	%	N	%	N	%
Completed Study	27	81.8	24	68.6	51	75.0
Withdrawal Reason						
Adverse Experiences	3	9.1	3	8.6	6	8.8
Lack of Efficacy	1	3.0	4	11.4	5	7.4
Lost to Follow-up	1	3.0	1	2.9	2	2.9
Other reason	1	3.0	2	5.7	3	4.4
Termination by sponsor	0	0	1	2.9	1	1.5
TOTAL WITHDRAWN	6	18.2	11	31.4	17	25.0

* Includes PIDs 051.446.00822 and 051.449.00839.

2.3 Protocol violations:

Protocol violations (listed in Table Epro-051-6) were not considered as justification for exclusion from the efficacy analysis. The incidence of protocol violations was high (75.8% eprosartan, 74.3% enalapril), predominantly due to noncompliance (33.3% eprosartan, 34.3% enalapril), not taking trough vital signs at specified time points, and taking concomitant medication affecting BP during placebo run-in (27.3% eprosartan vs 22.9% enalapril).

Table Epro-051-6

The number of protocol violators (>5% patients in either medication regimen) by medication regimen and protocol violation

	Eprosartan (n=33)	Enalapril (n=35)	Total (n=68)
At least one violation*	25 (75.8%)	26 (74.3%)	51 (75.0%)
Concomitant medication affecting BP: during run-in	9 (27.3%)	8 (22.9%)	17 (25.0%)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): during treatment	0	2 (5.7%)	2 (2.9%)
Concomitant chronic treatment with NSAIDs (except low-dose aspirin): during treatment	0	2 (5.7%)	2 (2.9%)
Concomitant chronic treatment with other NSAIDs: during treatment	0	2 (5.7%)	2 (2.9%)
Concomitant treatment with MAO inhibitors, tricyclic antidepressants and phenothiazine derivatives: during run-in	3 (9.1%)	0	3 (4.4%)
Concomitant treatment with phenothiazine derivatives: during run-in	2 (6.1%)	0	2 (2.9%)
Concomitant treatment with MAO inhibitors, tricyclic antidepressants and phenothiazine derivatives: during treatment	3 (9.1%)	1 (2.9%)	4 (5.9%)
Concomitant treatment with phenothiazine derivatives: during treatment	2 (6.1%)	0	2 (2.9%)
Noncompliance with study medication; administration of < 80% or > 120% for each of three consecutive visits	11 (33.3%)	12 (34.3%)	23 (33.8%)
Trough vital signs taken between 12:01 and 23:59	11 (33.3%)	17 (48.6%)	28 (41.2%)
Concomitant medication affecting BP: before titration endpoint	1 (3.0%)	2 (5.7%)	3 (4.4%)

*A patient may have had more than one violation and may be counted twice.

2.4 Demography

The demographic characteristics of all patients (non-randomized and randomized) who entered the study are given in Table Epro-051-7.

Table Epro-051-7

Demographic characteristics of all randomised patients

Demography		Eprosartan (n=31)*	Enalapril (n=35)	Total (n=66)
Age (years)	<65	22 (71.0%)	22 (62.9%)	44 (66.7%)
	≥65	9 (29.0%)	13 (37.1%)	22 (33.3%)
Sex	Female	14 (45.2%)	13 (37.1%)	27 (40.9%)
	Male	17 (54.8%)	22 (62.9%)	39 (59.1%)
Race	Black	1 (3.2%)	1 (2.9%)	2 (3.0%)
	Caucasian	29 (93.5%)	33 (94.3%)	62 (93.9%)
	Other	1 (3.2%)	1 (2.9%)	2 (3.0%)
Prior use of antihypertensives	No	10 (32.3%)	8 (22.9%)	18 (27.3%)
	Yes	21 (67.7%)	27 (77.1%)	48 (72.7%)
Severity of hypertension at baseline (sDBP)	< 105 mmHg	26 (83.9%)	27 (77.1%)	53 (80.3%)
	≥ 105 mmHg	5 (16.1%)	8 (22.9%)	13 (19.7%)

NB Only patients with at least one on-therapy trough vital sign are included in the table
* Excludes PIDs 051.446.00822 and 051.449.00839

2.5 Baseline characteristics

The baseline characteristics were similar between the two treatment regimens (Table Epro-051-8). Also, the baseline presenting conditions were similar between the two treatment groups, vascular retinopathy being the most frequently reported condition (36.4% eprosartan vs 31.4% enalapril), with the exception of slightly more patients presenting with elevated cholesterol/triglycerides and menopausal states in the eprosartan regimen and more patients with appendix and female genital surgery in the enalapril regimen.

Table Epro-051-8.

Mean weight, height and vital signs of all randomised patients at baseline

Baseline		Eprosartan (n=31)*	Enalapril (n=35)
Age (years)	Mean ± SEM	61.5 ± 2.2	59.4 ± 2.0
	Range	41.0-87.0	35.0-86.0
BA severity of HTN (mmHg)	Mean ± SEM	99.9 ± 1.0	101.3 ± 0.7
	Range	88.0-113.0	95.0-111.0
Weight (kg)	Mean ± SEM	74.8±2.8	80.8±2.5
	Range	46.0-116.0	57.5-115.0
Height (cm)	Mean ± SEM	166.1±1.7	166.5±1.6
	Range	148.0-187.0	150.0-184.0
Sitting			
Systolic (mmHg)	Mean ± SEM	166.6 ± 2.0	165.3±2.0
	Range	146.0-186.0	141.0-203.0
Diastolic (mmHg)	Mean ± SEM	99.9 ± 1.0	101.3 ± 0.7
	Range	88.0-113.0	95.0-111.0
Heart Rate (bpm)	Mean ± SEM	74.6 ± 1.3	74.5 ± 1.0
	Range	55.0-95.0	60.0-99.0

NB Only patients with at least one on-therapy trough vital sign are included in this table
* Excludes PIDs 051.446.00822 and 051.449.00839

3 SAFETY RESULTS

3.1 Deaths:

There were one death during the study. Sudden death of Patient# 051.449.00841 (86 year-old Caucasian male with Parkinson's disease, disorientation, hypertension, Keith-Wagener Grade 2, LVH and unspecified extrasystoles) occurred 1 day after stopping eprosartan medication he received for 162 days. No autopsy was performed. Concomitant medications included amiodarone (since 1993), haloperidol and thiridiazine (both since 1980).

There was also one death during the placebo run-in period prior to randomization. Patient# 051.446.95925, 68 year-old male with hypertension and a pulmonary neoplasm developed massive bronchial hemorrhage (post-endoscopy), septic shock (blood cultures positive for Staphylococcus aureus), and died.

3.2 Withdrawals due to Adverse Experiences:

There were 6 withdrawals due to adverse experiences (not including the patient who died), 2 in the eprosartan regimen and 4 in the enalapril regimen (Table Epro-051-9).

Table Epro-051-9 Adverse events leading to withdrawal (number (%) of patients)

Adverse experience	Eprosartan (n = 33)		Enalapril (n = 35)	
Abdominal pain	1 (3.0%)	#051.446.00822	0	
Breakage of nail	1 (3.0%)	#051.449.00872	0	
Depression	0		1 (2.9%)	#051.443.00809
Cough	0		1 (2.9%)	#051.443.00810
Myalgia	0		1 (2.9%)	
Vertigo	0		1 (2.9%)	

3.3 Serious, Non-fatal Adverse Events:

There were 3 patients with serious, adverse experiences, all in the enalapril regimen. Patient# 51.441.00804 reported claudication in the lower extremities (diagnosis = right femoral artery stenosis) after 102 days of study medication, lasting 12 days. Patient# 051.448.00846 had a liver biopsy done (diagnosis = chronic viral hepatitis C, and septal fibrosis without cirrhosis) after 55 days of study drug administration. Patient# 051.449.00835 reported a subocclusive intestinal syndrome (relieved with colonic washout) following 1 day after enalapril administration lasting for 4 days. This last patient eventually withdrew from the study due to lack of efficacy.

Two patients had serious, adverse experiences during the placebo run-in period. Patient# 051.449.00842 was hospitalized for asymptomatic bradycardia after 37 days of placebo, which was resolved after a pacemaker was implanted. Patient# 051.447.95884 underwent surgery with knee prosthesis for pre-existing right knee arthrosis 21 days after placebo run-in medication, for which placebo was stopped, and the patient withdrawn from the study.

3.4 Adverse Events:

Adverse experiences were more frequent in the enalapril regimen (62.9%) compared to eprosartan regimen (45.5%), this being mainly due to increased incidence in the enalapril regimen of cough (14.3%), back pain (8.6%) and myalgia (8.6%), none of which were reported in the eprosartan regimen. The incidence of other adverse experiences (headache, vertigo, hyperglycemia, pharyngitis, etc.) were low and similar between both regimens. In the enalapril regimen, the frequency of cough increased with increasing dose. In the eprosartan regimen, the highest incidence of AEs occurred at the lowest dose (200 mg bid).

Only 1 patient (# 051.444.00814) required a change in dose due to an AE. This patient reported malaise and hypotension after 134 days of treatment, and had enalapril dose reduced from 40 mg qd to 20 mg qd.

3.5 Laboratory findings, ECGs, Vital signs

In Table Epro-051-10, of AEs related to vital signs/ECG, a total of 7 AEs were reported in the enalapril regimen, representing 6 patients (17.1%), and 3 AEs were reported in the eprosartan regimen representing 3 patients (9.1%). In the eprosartan regimen, all AEs relating to vital signs/ECGs occurred at the lowest dose (200 mg bid).

There were 2 patients in the eprosartan regimen and 1 in the enalapril regimen who had trough vital sign values on-therapy recorded as falling outside the pre-defined values of potential clinical concern.. Patient# 051.441.00802 on eprosartan had a single low sSBP of 58 mmHg for Day 182+, and patient# 051.447.00859 had single low sDBP values of 54 mmHg (Day 86-121) and 58 mmHg (Day 122-181). Patient# 051.449.00871 in the enalapril regimen had elevated sitting heart rates of 126, 130 and 134 bpm (mean = 130 bpm) between days 1 - 22.

Table Epro-051-10

Number (%) of patients with adverse experiences related to vital signs/ECGs

	Eprosartan		
Body System* Preferred Term	200 mg BID n=33 (%)	300 mg BID n=13 (%)	400 mg BID n=11 (%)
Cardiovascular General	1 (3.0)	0	0
Heart disorder	1 (3.0)	0	0
Heart Rate and Rhythm	2 (6.1)	0	0
Extrasystoles	2 (6.1)	0	0
	Enalapril		
Body System* Preferred Term	10 mg UID n=35 (%)	20 mg UID n=24 (%)	40 mg UID n=11 (%)
Cardiovascular General	1 (2.9)	0	1 (9.1)
ECG abnormal	1 (2.9)	0	0
Hypotension	0	0	1 (9.1)
Heart Rate and Rhythm	0	3 (12.5)	1 (9.1)
Bradycardia	0	0	1 (9.1)
Supraventricular extrasystoles	0	1 (4.2)	0
Atrial fibrillation	0	1 (4.2)	0
Tachycardia	0	1 (4.2)	0
Supraventricular tachycardia	0	1 (4.2)	0

* The number of patients within a body system are not additive, since a patient can have more than one AE within a body system

There was a larger number of patients who had new on-therapy ECG abnormalities in the enalapril regimen (25.7%) compared to the eprosartan regimen (25.7%), due mainly to sinus tachycardia. The mean values of PR-, QRS- and QTc- intervals were within the pre-defined ranges of potential clinical concern at all 3 time-points. A slightly higher incidence of QTc interval abnormalities on-therapy (Week 6 and/or Week 12) was found with eprosartan (18.2%) , compared to enalapril (11.4%), and at month 6 (eprosartan = 12 patients, 66.7%, vs enalapril = 5 patients, 26.3%).

4. EFFICACY RESULTS

4.1 Statistical considerations

Analysis was done on all patients who had received at least one dose of randomized medication and had at least one trough vital sign measurement during the on-therapy period. Of 68 randomized patients, 25 (11 eprosartan and 14 enalapril) patients had evaluable echocardiographic data. The study was powered for 25 patients per treatment group. Thus, with only 25 (50%) of the total number of required evaluable patients, this study could not be expected to detect statistically significant differences . The reasons given for the 43 (19 eprosartan, 24 enalapril) patients being excluded from echocardiographic evaluation are as follows: (i) baseline or on-therapy echocardiogram unsatisfactory, unreadable, axis changed or Doppler data missing (5 eprosartan, 4 enalapril); (ii) post-baseline echocardiogram conducted >1 day post end of therapy (1 eprosartan, 4 enalapril); (iii) duplicate calculation of baseline or on-therapy LVMI remained >10% on re-reading (6 eprosartan, 8 enalapril); and (iv) baseline and/or on-therapy echocardiogram not done (7 eprosartan, 8 enalapril).

4.2 Primary Efficacy Parameters

Table Epro-051-11 shows that at study endpoint, LVMI was similar to baseline in the eprosartan regimen (mean change being -1.5 g/m^2) and decreased in the enalapril regimen (-7.6 g/m^2). At month 6, a decrease in LVMI from baseline was found in both medication regimens, being larger for the enalapril regimen (-11.9 g/m^2) compared to the eprosartan regimen (-3.6 g/m^2). The difference between medication regimens in change from baseline in LVMI at study endpoint or 6 month time-point was not statistically significant.

Table Epro-051-11

LVMI (g/m^2) (mean ± SEM) at baseline and change from baseline at month 6 and study endpoint

LVMI (g/m^2)	Eprosartan	Enalapril
Baseline	(n=13)	(n=15)
Mean ± SEM	126.5± 8.4	123.7± 5.9
Month 6	(n = 9)	(n= 8)
Mean ± SEM	123.6± 12.7	103.3± 7.5
Month 6 change	(n = 9)	(n= 8)
Mean ± SEM	-3.6 ± 7.6	-11.9± 4.1
Study endpoint	(n=11)	(n=15)
Mean ± SEM	122.7± 10.6	116.5± 6.7
Study endpoint change	(n=11)	(n=14)
Mean ± SEM	-1.5± 6.4	-7.6± 5.4

4.3 Secondary Efficacy Parameters

In Table Epro-051-12, peak systolic wall stress (PSWS) decreased in the eprosartan regimen to a greater degree compared to the enalapril regimen at both month 6 and study endpoint. On the other hand, LV end diastolic volume was found to decrease more in the enalapril regimen compared to eprosartan at both month 6 and study

endpoint. The isovolumic relaxation time at both 6 month and study endpoint increased from baseline in the eprosartan regimen, whereas it decreased from baseline in the enalapril regimen. None of the differences between the two treatment regimens for any of the changes from baseline in LVMI-related parameters was statistically significant.

Table Epro-051-12

LVMI-related variables (mean ± SEM) at baseline and change from baseline at month 6 and study endpoint

Ejection fraction (%)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
PWMI (g/m^2 dense)		
Baseline		
Mean ± SEM		
Month 6 endpoint		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
LV End Diastolic Volume (cm^3)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
LV End Diastolic Volume (cm^3)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
LV Fractional Shortening (%)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
LV Diastolic Dimension (cm)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
RA Ratio		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
Peak E Deceleration Time (ms)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
Isovolumic Relaxation Time (ms)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
Diastolic PWT (cm)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		
Systolic PWT (cm)		
Baseline		
Mean ± SEM		
Month 6		
Mean ± SEM		
Month 6 change		
Mean ± SEM		
Study endpoint		
Mean ± SEM		
Study endpoint change		
Mean ± SEM		

There were significant regimen-by-center interactions at titration and maintenance endpoints for sDBP and at maintenance and study endpoints for sitting heart rate. At titration, maintenance and study endpoints, similar and clinically significant decreases in sDBP and sSBP from baseline were found in both regimens (Table Epro-051-13). Sitting heart rate was similar to baseline values at all 3 time-points for both regimens.

Table Epro-051-13

Trough sDBP, sSBP and sitting Heart Rate (mean ± SEM) at baseline (b/l) and change from baseline at titration, maintenance and study endpoints

sDBP (mmHg)	Eprosartan	Enalapril
Baseline	(n=31)	(n=35)
Mean ± SEM	99.9±1.0	101.3±0.7
Titration endpoint	(n=31)	(n=35)
Mean ± SEM	83.8±1.6	88.1±1.7
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-16.1±1.3	-13.1±1.7
Maintenance endpoint	(n=29)	(n=28)
Mean ± SEM	83.0±1.8	84.2±1.2
Change from b/l	(n=29)	(n=28)
Mean ± SEM	-16.1±1.6	-17.0±1.1
Study endpoint	(n=31)	(n=35)
Mean ± SEM	83.6±1.9	87.4±1.6
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-16.3±1.7	-13.8±1.5
sSBP (mmHg)		
Baseline	(n=31)	(n=35)
Mean ± SEM	166.6±2.0	165.3±2.0
Titration endpoint	(n=31)	(n=35)
Mean ± SEM	147.2±2.6	149.2±2.9
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-19.4±2.4	-16.1±2.7
Maintenance endpoint	(n=29)	(n=28)
Mean ± SEM	147.7±3.1	141.2±2.6
Change from b/l	(n=29)	(n=28)
Mean ± SEM	-18.8±3.1	-22.9±2.4
Study endpoint	(n=31)	(n=35)
Mean ± SEM	147.7±3.0	146.1±2.9
Change from b/l	(n = 31)	(n = 35)
Mean ± SEM	-18.9±2.9	-19.3±2.6
Sitting Heart Rate (bpm)		
Baseline	(n=31)	(n=35)
Mean ± SEM	74.6±1.3	74.3±1.8
Titration endpoint	(n=31)	(n=35)
Mean ± SEM	70.8±1.4	73.8±2.0
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-3.8±1.3	-0.7±1.7
Maintenance endpoint	(n=29)	(n=28)
Mean ± SEM	72.1±1.4	71.6±1.8
Change from b/l	(n=29)	(n=28)
Mean ± SEM	-2.4±1.2	-2.9±1.7
Study endpoint	(n=31)	(n=35)
Mean ± SEM	72.0±1.3	72.5±1.9
Change from b/l	(n=31)	(n=35)
Mean ± SEM	-2.6±1.1	-1.9±1.8

The proportion of responders (sDBP decreased to <90 mmHg or 90-100 mmHg and decrease from baseline by ≥10 mmHg) was greater in the eprosartan regimen compared to enalapril regimen (by 12.8% and 12.0%, respectively) at both titration and study endpoints (Table Epro-051-14).

Table Epro-051-14

Results of the Cochran-Mantel-Haenszel analysis of the number (%) of randomised patients who respond (patients with sDBP < 90 mmHg or 90-100 mmHg and decreased from baseline (b/l) by ≥ 10 mmHg)

Time Point	Response	Eprosartan (n=31)	Enalapril (n=35)
Titration Endpoint	No response	4 (12.9%)	9 (25.7%)
	<90 mm Hg	25 (80.6%)	24 (68.6%)
	≥ 10mmHg decrease from b/l	2 (6.5%)	2 (5.7%)
	Total responders	27 (87.1%)	26 (74.3%)
Difference / Relative Risk Ratio (95% CI) and p-value			12.8% / 1.12 (0.87, 1.45) 0.314
Study Endpoint	No response	6 (19.4%)	11(31.4%)
	<90 mm Hg	23 (74.2%)	22 (62.9%)
	≥ 10mmHg decrease from b/l	2 (6.5%)	2 (5.7%)
	Total responders	25 (80.6%)	24 (68.6%)
Difference / Relative Risk Ratio (95% CI) and p-value			12.0% / 1.13 (0.86, 1.50) 0.309

4.4 Efficacy Subgroup Analysis

Mean and changes in LVMI from baseline at month 6 and study endpoints for subgroups (age, sex, race, prior use of antihypertensive agents, severity of hypertension) showed a statistically significant ($P<0.05$) difference between medication regimens for patients with prior use of antihypertensive therapy: a greater decrease in LVMI from baseline was found in the enalapril group compared to the eprosartan regimen (Table Epro-051-15). However, the number of patients in each medication regimen by subgroup was too small to allow making valid statistical inferences.

Subgroup analysis for the secondary endpoint parameters revealed significant regimen-by-center interaction for age <65 years at titration endpoint, for age ≥65 years at maintenance and study endpoints, for females, Caucasians and prior use of antihypertensive agents at titration and maintenance endpoints, and for the subgroup of patients by severity of baseline hypertension at maintenance endpoint (Table Epro-051-16). The number of patients in each medication regimen by subgroup was too small, however, to allow any valid conclusions to be drawn.

Table Epro-051-15.

Results of analysis of variance for the change from baseline in mean LVMI (g/m^2) at month 6 and study endpoint by subgroup - least squares means and 95% confidence intervals (95% CI)

Subgroup	Eprosartan	Enalapril	Difference (95% CI)	P-value
< 65 years				
Month 6	(n=6)	(n=6)		
Mean ± SEM	-11.0 ± 7.7	-23.8 ± 7.7	-12.8 (-39.0, 13.5)	0.279
Study endpoint	(n=7)	(n=9)		
Mean ± SEM	-6.7 ± 11.9	-14.3 ± 8.8	-7.6 (-42.3, 27.1)	0.627
≥ 65 years				
Month 6	(n=3)	(n=3)		
Mean ± SEM	15.7 ± 18.1	-3.0 ± 13.2	-18.7 (-81.3, 44.0)	0.413
Study endpoint	(n=4)	(n=5)		
Mean ± SEM	19.9 ± 16.0	1.3 ± 10.9	-18.7 (-81.3, 44.0)	0.413
Males				
Month 6	(n=5)	(n=5)		
Mean ± SEM	-0.3 ± 9.5	-19.7 ± 9.5	-20.0 (-47.4, 7.4)	0.125
Study endpoint	(n=6)	(n=9)		
Mean ± SEM	-3.5 ± 9.5	-13.5 ± 6.3	-9.9 (-31.0, 15.0)	0.445
Females				
Month 6	(n=4)	(n=3)		
Mean ± SEM	-19.0 ± 15.7	-13.0 ± 14.0	6.0 (-60.9, 72.9)	0.794
Study endpoint	(n=5)	(n=6)		
Mean ± SEM	-7.8 ± 12.4	-3.2 ± 9.4	4.6 (-38.6, 47.8)	0.781
Caucasian				
Month 6	(n=9)	(n=8)		
Mean ± SEM	-9.0 ± 8.4	-17.1 ± 7.6	-8.2 (-28.8, 12.5)	0.406
Study endpoint	(n=11)	(n=13)		
Mean ± SEM	-1.5 ± 6.48	-9.5 ± 5.56	#	#
Prior use of antihypertensives				
Month 6	(n=5)	(n=6)		
Mean ± SEM	9.8 ± 10.2	-12.1 ± 6.4	-22.0 (-42.9, -1.1)	0.042*
Study endpoint	(n=6)	(n=12)		
Mean ± SEM	8.6 ± 9.1	-13.4 ± 5.1	-22.0 (-43.4, -0.6)	0.045*
No prior use of antihypertensives				
Month 6	(n=4)	(n=0)		
Mean ± SEM	-18.7 ± 14.2	-	-	-
Study endpoint	(n=5)	(n=2)		
Mean ± SEM	-5.8 ± 15.7	-4.8 ± 28.7	1.0 (-481.8, 483.8)	0.983
Baseline sDBP < 105mmHg				
Month 6	(n=6)	(n=7)		
Mean ± SEM	-11.8 ± 9.4	-15.9 ± 8.2	-4.1 (-27.5, 19.2)	0.703
Study endpoint	(n=10)	(n=11)		
Mean ± SEM	-3.4 ± 10.0	-10.5 ± 7.8	-7.0 (-31.3, 17.2)	0.541

Significant medication regimen-by-center interaction
& Indicates raw mean and SEM
* Significance whereby $p < 0.05$

Table Epro-051-16

Results of analysis of variance for the mean change from baseline in sDBP at titration, maintenance and study endpoints by subgroup - least squares means and 95% confidence intervals (95% CI)

Subgroup	Eprosartan	Enalapril	Difference (95% CI)	P-value
< 65 years				
Titration Endpoint	(n=22)	(n=22)		
Mean ± SEM	-15.8± 1.7&	-12.3 ± 2.4&	#	#
Maintenance Endpoint	(n=20)	(n=17)		
Mean ± SEM	-13.5 ± 2.0	-14.9 ± 1.9	-1.4 (-6.2, 3.4)	0.563
Study Endpoint	(n=22)	(n=22)		
Mean ± SEM	-11.9 ± 2.7	-10.3 ± 2.5	1.6 (-4.2, 7.7)	0.550
≥ 65 years				
Titration Endpoint	(n=9)	(n=13)		
Mean ± SEM	-16.4 ± 3.4	-14.8 ± 2.6	-1.6 (-6.6, 9.9)	0.675
Maintenance Endpoint	(n=9)	(n=11)		
Mean ± SEM	-19.4 ± 3.4&	-18.9 ± 1.3&	#	#
Study Endpoint	(n=9)	(n=13)		
Mean ± SEM	-19.4 ± 3.4&	-15.5 ± 2.1&	#	#
Males				
Titration Endpoint	(n=17)	(n=22)		
Mean ± SEM	-14.9± 2.6	-13.1 ± 2.3	1.8 (-4.4, 7.9)	0.562
Maintenance Endpoint	(n=16)	(n=16)		
Mean ± SEM	-13.7 ± 2.3	-14.2 ± 2.1	-0.5 (-6.1, 5.1)	0.848
Study Endpoint	(n=17)	(n=22)		
Mean ± SEM	-12.5 ± 2.9	-10.9 ± 2.6	1.5 (-5.3, 8.4)	0.650
Females				
Titration Endpoint	(n=14)	(n=13)		
Mean ± SEM	-18.1± 2.5&	-15.4± 2.3&	#	#
Maintenance Endpoint	(n=13)	(n=12)		
Mean ± SEM	-18.0± 2.4&	-12.3± 1.6&	#	#
Study Endpoint	(n=14)	(n=13)		
Mean ± SEM	-18.6 ± 2.7	-17.0 ± 2.4	0.9 (-5.4, 7.2)	0.761
Caucasian				
Titration Endpoint	(n=29)	(n=33)		
Mean ± SEM	-16.3 ± 1.4&	-13.4± 1.7&	#	#
Maintenance Endpoint	(n=27)	(n=36)		
Mean ± SEM	-16.8± 1.5&	-17.5± 1.0&	#	#
Study Endpoint	(n=29)	(n=33)		
Mean ± SEM	-15.2 ± 2.2	-13.0 ± 1.9	2.3 (-2.4, 6.9)	0.332
Prior use of antihypertensives				
Titration Endpoint	(n=21)	(n=27)		
Mean ± SEM	-16.2 ± 1.9&	-12.1 ± 2.0&	#	#
Maintenance Endpoint	(n=19)	(n=30)		
Mean ± SEM	-15.7 ± 2.3&	-16.7 ± 1.4&	#	#
Study Endpoint	(n=21)	(n=27)		
Mean ± SEM	-14.8 ± 3.1	-11.8 ± 2.4	3.0 (-3.8, 9.8)	0.376
No prior use of antihypertensives				
Titration Endpoint	(n=10)	(n=6)		
Mean ± SEM	-14.7± 2.2	-16.8 ± 2.3	-2.1 (-8.2, 3.9)	0.464
Maintenance Endpoint	(n=10)	(n=6)		
Mean ± SEM	-13.9 ± 1.3	-15.8 ± 1.3	-2.0 (-5.4, 1.5)	0.234
Study Endpoint	(n=10)	(n=6)		
Mean ± SEM	-13.9 ± 1.2	-15.8 ± 1.3	-2.0 (-5.4, 1.5)	0.234
Baseline sDBP < 105mmHg				
Titration Endpoint	(n=26)	(n=27)		
Mean ± SEM	-15.0± 2.3	-12.0 ± 2.0	2.9 (-1.7, 7.6)	0.208
Maintenance Endpoint	(n=26)	(n=22)		
Mean ± SEM	-16.0± 1.7&	-16.0± 1.3&	#	#
Study Endpoint	(n=26)	(n=27)		
Mean ± SEM	-14.3 ± 2.5	-11.4 ± 2.1	-2.9 (-2.0, 7.8)	0.238
Baseline sDBP ≥ 105mmHg				
Titration Endpoint	(n=5)	(n=6)		
Mean ± SEM	-17.8± 5.9	-11.3 ± 4.7	6.6 (-11.3, 24.4)	0.403
Maintenance Endpoint	(n=3)	(n=6)		
Mean ± SEM	-16.7± 4.8&	-20.8± 0.3&	#	#
Study Endpoint	(n=5)	(n=6)		
Mean ± SEM	-17.2 ± 5.6	-12.6 ± 4.5	4.6 (-12.4, 21.7)	0.579

Significant medication regimen-by-center interaction
& Indicates raw mean and SEM

5. CONCLUSION

At the doses used, eprosartan and enalapril showed no differences in clinical and laboratory safety profiles and in ECGs. No excessive lowering of blood pressure and no effect on heart rate were found. Adverse events were more frequent in the enalapril regimen (62.9%) compared to eprosartan regimen (45.5%) due mainly to increased incidence of cough (14.3%, which was dose-related), back pain (8.6%) and myalgia (8.6%) in the enalapril regimen.

LVMI was similar to baseline in the eprosartan regimen (mean change being -1.5 g/m^2) and decreased in the enalapril regimen (-7.6 g/m^2) at study endpoint. At month 6, a decrease in LVMI from baseline was found in both medication regimens, being larger for enalapril (-11.9 g/m^2) compared to eprosartan (-3.6 g/m^2). The difference between medication regimens in change of LVMI from baseline was not statistically significant at either time point.

Eprosartan, compared to enalapril, caused a greater decrease in peak systolic wall stress (PSWS) and increase in isovolumic relaxation time at both month 6 and study endpoint from baseline. On the other hand, LV end diastolic volume was found to decrease more in the enalapril regimen compared to eprosartan at both month 6 and study endpoint. None of these differences between the two treatment regimens was statistically significant.

For both regimens, similar and clinically significant decreases in sDBP and sSBP from baseline were found at titration, maintenance and study endpoints, whereas sitting heart rate was similar to baseline at all 3 time-points. The proportion of responders (sDBP decreased to <90 mmHg or 90-100 mmHg and decrease from baseline by ≥10 mmHg) was greater in the eprosartan regimen compared to enalapril regimen at both titration and study endpoints.

The lack of statistically significant findings in this study may be due to having a total of only 25 patients with evaluable echocardiographic data rather than the total of 50 patients (25 patients per group) required to provide 80% power to detect a rather large change in LVMI of 27 g/m^2.

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