DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

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SPONSOR:	SmithKline Beecham Pharmaceuticals		
TYPE OF DOCUMENT:	New NDA (Clinical Pharmacology Review)		
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1. STUDY PROTOCOL

1.1 Title

Protocol 061: ***An 8-week, double-blind, double-dummy, placebo-controlled, parallel group, multicenter comparison of regimens of oral SK&F 108566 and hydrochlorothiazide given in combination in patients with mild to moderate essential hypertension (DBP ≥ 95 & ≤ 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. Hydrochlorothiazide (HCTZ) is a diuretic used as a standard therapy for hypertension, and is often used in combination with other antihypertensive agents. This study evaluates the efficacy and safety of adding eprosartan to HCTZ therapy in those patients whose blood pressure is not controlled with HCTZ alone.

1.3 Objectives

1. To compare the antihypertensive efficacy of eprosartan 400 mg once daily in combination with HCTZ 12.5 or 25 mg once daily in patients with mild to moderate hypertension (average sitting diastolic blood pressure ≥ 95 and ≤ 114 mmHg).
2. To assess the safety of eprosartan and HCTZ in combination with regard to adverse experiences, laboratory abnormalities and electrocardiograms (ECGs).

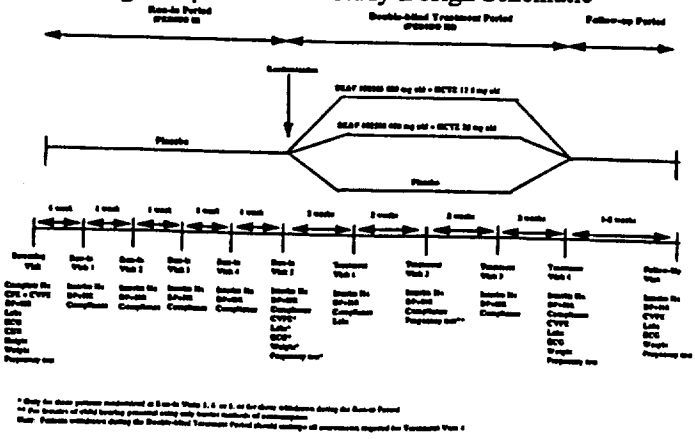
1.4 Study design

This is a Phase III, multi-center, double-blind, double-dummy, placebo-controlled, parallel group study of patients with mild to moderate essential hypertension who were randomized to receive for 8 weeks:

1. placebo (eprosartan placebo = Lot# U95146, HCTZ placebo = Lot# U95233)
2. eprosartan 400 mg (Lot# U95111) and HCTZ 12.5 mg (Lot# U 95234)
3. eprosartan 400 mg (Lot# U 95111) and HCTZ 25 mg (Lot# U 95235)

The study design is illustrated in Figure Epro-061-1 below:

Figure Epro-061-1. Study Design Schematic



After completing the double-blind treatment period, patients may enter an open-label, long-term study (protocol #105) or return within 7-14 days for follow-up visit.

1.5 **Protocol Amendments**

Amendment 1 (applied only to Canada). Sections of protocol pertaining to safety limits for withdrawal, and reasons for withdrawal were modified to conform to Canadian requirements.

Amendment 2 (applied only to France): Sections of protocol pertaining to safety limits for withdrawal, and reasons for withdrawal were modified to conform to Canadian requirements.
Amendment 3 (applied only to the US and Canada): Section of protocol pertaining to the procedure for reporting serious adverse experiences was modified to include the new office and emergency telephone numbers for contacting the Medical Monitor in North America. The procedure for emergency identification of double-blind medication was changed.

1.6 **Population enrolled/analyzed**

519 patients with newly diagnosed mild to moderate hypertension (average sitting diastolic blood pressure ≥ 95 and ≤ 114 mmHg) including women without child bearing potential or using hormonal or barrier contraceptives or IUCDs, at least 18 years of age without secondary hypertension, arrhythmias, clinical evidence of congestive heart failure, 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, were enrolled.

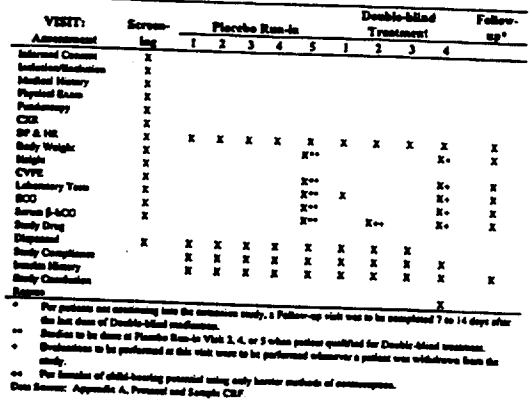
Compliance: This was determined by the number of tablets dispensed at each visit and subtracting the returned number of tablets.

Pre-study screening: All antihypertensive medication except HCTZ were discontinued at the screening visit or up to 7 days after the screening visit. Treatment with concomitant antihypertensive agents and other excluded medications (MAO inhibitors, tricyclic antidepressants, phenothiazine derivatives, sympathomimetic amines, NSAIDS (except low dose aspirin up to 325 mg/day), warfarin and other anticoagulants, etc., was not allowed.

1.7 **Study procedures**

The schedule for assessment of efficacy and efficacy parameters is given in Table Epro-061-1.

Table Epro-061-1. Schedule of study assessments



As shown in table, the study consisted of a screening period, a placebo run-in period of 3-5 weeks during which sitting blood pressure was recorded weekly and then randomized at the last visit, a double-blind period of 8 weeks during which each patient took the randomized medication and sitting blood pressures recorded every 2 weeks, and a follow-up visit 7-14 days after completion of the double-blind treatment period.

1.8 **Efficacy assessments:**

The primary efficacy parameter was the mean change from baseline to study endpoint in sitting diastolic blood pressure (SitDBP). Baseline was defined as the mean of the last two qualifying visits of the placebo run-in period.

The secondary efficacy criteria were as follows:

- Mean change from baseline in sitting systolic blood pressure (SitSBP)

- Mean change from baseline from sitting heart rate (SitHR)
- Proportion of responders in each treatment group (i.e., percent of patients whose SitDBP was <90 mmHg or ≤100 mmHg and decreased from baseline by at least 10 mmHg) using Cochran-Mantel-Haenszel statistic, adjusting for center or subgroup interaction by Breslow-Day test.

Comparisons of SitDBP were made for each of the following subgroups: age (<65 and ≥65 years), sex, race (Black, Caucasian, Oriental, Other), prior use of antihypertensives (Yes, No), and severity of hypertension at baseline (SitDBP <105 and ≥105 mmHg), using ANOVA

1.9 **Safety assessments:**

Safety assessments include adverse experiences, physical examinations, results of clinical laboratory tests (blood chemistry, hematology and urinalysis), BP and HR, and ECGs (at screening, at entry to double-blind treatment, at treatment visit 4, and at follow up or withdrawal from study) while "on therapy" (defined as the period starting from the first dose of randomized medication and including the 24-hour period after the last dose of randomized medication).

1.10 **Sample size:**

To detect a 5 mmHg difference in change from baseline between any 2 regimens, assuming a standard deviation of 8 mmHg, to provide 90% power and a 0.05 level of significance on two-sided testing with a Hochberg procedure of Bonferroni adjustment for the 3 comparisons, the sample size was estimated to be 70 evaluable patients per medication regimen.

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

27 investigators in 5 countries (2 in the Netherlands, 3 in Canada, 3 in France, 6 in the United Kingdom and 13 in the United States) participated in the study. The medical monitor was Marcus B. Saltzman, MD, SmithKline Beecham Pharmaceuticals, Collegeville, Pennsylvania. Study Dates: 15-Jan-1996 to 14-Aug-1996.

2. STUDY POPULATION

2.1 **Subject disposition:**

519 patients were screened. 13 (2.5%) withdrew prior to receiving single-blind placebo run-in medication (2=protocol violation, 1= lost to follow-up, 10 = "other reasons"). 126 (24.9%) were not randomized (21=withdrawn due to adverse experiences, 21=protocol violations, 6=lack of efficacy, 1=lost to follow up and 77="other reasons").

Of 380 patients who qualified for randomization, 124 received placebo, 128 received eprosartan 400 mg/HCTZ 12.5 mg and 128 patients received eprosartan 400 mg/HCTZ 25 mg.

4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and they were no included in analysis. 352 (92.6%) patients completed the 8-week study; 28 (7.4%) patients were withdrawn.

2.2 **Withdrawals:**

28 (7.4%) patients were withdrawn (10 in placebo group, 8 in eprosartan 400 mg/HCTZ 12.5 mg group, and 10 in eprosartan 400 mg/HCTZ 25 mg group). 10 (2.6%) patients were withdrawn due to adverse experiences, 9 (2.4%) patients due to lack of efficacy, 2 patients lost to follow up, 4 patients due to protocol violations and 3 patients for "other reasons" (Table Epro-061-2).

Table Epro-061-2. The number and percentage of randomized patients who completed the study or were withdrawn by the reason for study withdrawal

	Placebo UID		Eprosartan 400 mg UID HCTZ 12.5 mg UID		Eprosartan 400 mg UID HCTZ 25 mg UID		Total	
Study Conclusion	(n = 124)		(n = 128)		(n = 128)		(n = 380)	
Reason	No.	(%)	No.	(%)	No.	(%)	No.	(%)
COMPLETED STUDY	114	(91.9)	120	(93.8)	118	(92.2)	352	(92.6)
EARLY TERMINATION	10	(8.1)	8	(6.3)	10	(7.8)	28	(7.4)
Withdrawal Reason								
Adverse Experiences	1	(0.8)	3	(2.3)	6	(4.7)	10	(2.6)
Lack of Efficacy	5	(4.0)	1	(0.8)	3	(2.3)	9	(2.4)
Lost to Follow-up	0	(0.0)	2	(1.6)	0	(0.0)	2	(0.5)
Other reasons	3	(2.4)	0	(0.0)	0	(0.0)	3	(0.8)
Protocol violation, including non-compliance	1	(0.8)	2	(1.6)	1	(0.8)	4	(1.1)

2.3 Protocol violations:

The most frequently occurring protocol violations (≥4.5% in any medication group) are summarized in Table Epro-061-3. The incidences of individual protocol violations were consistent across the 3 treatment groups and are therefore not expected to affect the outcome of the study. Including these frequently occurring protocol violations, 321 (84.5%) randomized patients had at least one protocol violation (106 (85.5%) in placebo group, 108 (84.4%) in eprosartan 400 mg/HCTZ 12.5 mg group, and 107 (83.6%) in eprosartan 400 mg/HCTZ 25 mg treatment group). The most common protocol violation was not taking study medication 22-24 hours before scheduled trough (pre-dose) vital sign measurements that occurred in 234 (61.6%) of randomized patients.

Table Epro-061-3

Frequency of Protocol Violations: Number (%) of Randomized Patients With At Least one Violation and Distribution of the Most Frequent (Incidence ≥4.5% in any Treatment Group) Types of Violations

	Placebo UID		EPROSARTAN 400 mg UID				TOTAL	
			HCTZ 12.5 mg		HCTZ 25 mg			
	(n = 124)		(n = 128)		(n = 128)		(n = 380)	
Protocol Violation	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Patient medication not taken 22 - 24 hours before pre-dose vital sign measurements*	84	(67.7)	71	(55.5)	79	(61.7)	234	(61.6)
Concomitant medication affecting BP: during Placebo Run-in	13	(10.5)	6	(4.7)	9	(7.0)	28	(7.4)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): within 7 days prior to Screening	10	(8.1)	14	(10.9)	7	(5.5)	31	(8.2)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): during Placebo Run-in	11	(8.9)	15	(11.7)	10	(7.8)	36	(9.5)
Concomitant chronic treatment with NSAIDs (except low-dose aspirin): during Placebo Run-in	10	(8.1)	12	(9.4)	10	(7.8)	32	(8.4)
Concomitant chronic treatment with aspirin (except low-dose aspirin): during Placebo Run-in	2	(1.6)	6	(4.7)	3	(2.3)	11	(2.9)
Concomitant chronic treatment with other NSAIDs: during Placebo Run-in	9	(7.3)	7	(5.5)	7	(5.5)	23	(6.1)
Concomitant chronic treatment with sympathomimetic amines or NSAIDs (except low-dose aspirin): during treatment	9	(7.3)	18	(14.1)	15	(11.7)	42	(11.1)
Concomitant chronic treatment with NSAIDs (except low-dose aspirin): during treatment	9	(7.3)	14	(10.9)	14	(10.9)	37	(9.7)
Concomitant chronic treatment with aspirin (except low-dose aspirin): during treatment	3	(2.4)	6	(4.7)	3	(2.3)	12	(3.2)
Concomitant chronic treatment with other NSAIDs: during treatment	7	(5.6)	9	(7.0)	11	(8.6)	27	(7.1)
Concomitant treatment with MAO inhibitors, Tricyclic antidepressants and Phenothiazine derivatives: during Placebo Run-in	2	(1.6)	7	(5.5)	3	(2.3)	12	(3.2)
Trough vital signs taken between 12:01 and 23:59	5	(4.0)	9	(7.0)	8	(6.3)	22	(5.8)
Antihypertensives (at least one) during the Placebo Run-in period	13	(10.5)	6	(4.7)	9	(7.0)	28	(7.4)
Number of patients with no violations	18	(14.5)	20	(15.6)	21	(16.4)	59	(15.5)
Number of patients with at least one violation **	106	(85.5)	108	(84.4)	107	(83.6)	321	(84.5)

Note: A patient may have had more than one violation and may be counted twice.
**The number of patients include the 60 patients listed in Section 11.0, Errata. These patients may or may not have other violations and therefore are not subtracted from the total

2.4 Demography

The demographic characteristics of all patients (non-randomized and randomized) who entered the study are given in Table Epro-061-4.

Table Epro-061-4. Demographic characteristics of all non-randomized and randomized patients

			Randomized			
				Eprosartan 400 mg UID		
Demographic	Screening Only (n = 13)	Run-in Only (n = 126)	Placebo UID (n = 124)	HCTZ 12.5 mg UID (n = 128)	HCTZ 25 mg UID (n = 128)	Total (n = 380)
Age (years)						
<65 years	8 (61.5)	93 (73.8)	94 (75.8)	111 (86.7)	105 (82.0)	310 (81.6)
≥65 years	5 (38.5)	33 (26.2)	30 (24.2)	17 (13.3)	23 (18.0)	70 (18.4)
Mean ± SDM	59.1 ± 3.6	56.0 ± 1.1	55.6 ± 1.0	53.1 ± 0.9	55.1 ± 1.1*	54.6 ± 0.6*
Range	55 - 77	22 - 85	35 - 82	22 - 85	28 - 85	28 - 85
Sex						
Male	8 (61.5)	68 (67.6)	75 (60.5)	67 (52.3)	73 (56.3)	214 (56.3)
Female	5 (38.5)	66 (52.4)	49 (39.5)	61 (47.7)	55 (43.8)	166 (43.7)
Race						
Black	3 (23.1)	25 (18.3)	25 (13.1)	12 (9.4)	12 (9.4)	29 (10.3)
Caucasian	10 (76.9)	102 (79.4)	99 (79.8)	105 (84.4)	111 (86.7)	315 (82.7)
Oriental	0	2 (1.6)	2 (1.6)	3 (2.3)	2 (1.6)	7 (1.8)
Other**	0	1 (0.8)	0 (0.5)	3 (2.3)	3 (2.3)	16 (4.2)
Weight (kg)						
Mean ± SDM	83.6 ± 3.3+	80.2 ± 1.7	86.6 ± 1.5	86.4 ± 1.5	84.1 ± 1.6*	85.7 ± 1.8*
Range	69.4 - 110.0	45.3 - 144.4	56.8 - 139.7	64.5 - 137.4	64.5 - 134.5	64.5 - 139.7
Height (cm)						
Mean ± SDM	171.8 ± 2.8+	168.5 ± 1.0	169.8 ± 0.9	169.9 ± 1.0	168.5 ± 1.0*	169.4 ± 0.6*
Range	160.0 - 182.4	137.0 - 198.1	147.3 - 202.7	144.5 - 203.7	147.0 - 192.0	144.5 - 203.7

* Four patients randomized to eprosartan 400 mg/HCTZ 25 mg (PIDs: 061.052.00213, 061.374.00277, 061.472.00040, and 061.573.00457) did not have on-therapy trough vital sign data, and therefore are not included in descriptive statistics for age, weight, and height.
** Other races included Hispanic, Asian, Mediterranic, White/Caucasian, 1/2 Japanese, Filipino, Guyanese, Mid-eastern, and East Indian.
+ Weight and height was available for only 10 of the 13 "Screening-only" patients.

2.5 Baseline characteristics

The sitting diastolic blood pressure was between 95 and 104 mmHg for the majority (311 or 81.8%) of randomized patients, and between 105 and 114 mmHg for the remaining (69 or 18.2%) patients. Most (294 or 77.4%) of the randomized patients had a history of prior use of antihypertensive agents (94 of 124 (75.4%) patients on placebo, 98 of 128 (76.6%) patients on eprosartan 400 mg/HCTZ 12.5 mg and 102 of 128 (79.7%) on eprosartan 400 mg/HCTZ 25 mg).

Table Epro-061-9

Listing of Patients with On-therapy Adverse Experiences Related to Laboratory Results

Patient Identification Number	Adverse Experience	Days on Study Meds at Onset	Severity	Relationship	Lab Test (Reference Range)*	Baseline Value	Highest or Lowest Value [Day]	Last Value [Day]
				Placebo				
061.002.00152	Creatine phosphokinase increased	60 (1)	Moderate	Possibly related				
061.005.00133	Creatine phosphokinase increased	62 (1)	Mild	Possibly related				
061.006.00044	Diabetes	28	Mild	Unrelated				
061.007.00055	Gout	25	Mild	Unrelated				
061.011.00104	Lymphopenia	14	Mild	Unrelated				
061.012.00211	Pyuria	15	Mild	Unrelated				
061.052.00227	Hepatic enzymes increased	15	Moderate	Unrelated				
061.052.00228	Hematuria	57 (1)	Mild	Unrelated				
	Hypokalemia	57 (1)	Mild	Unrelated				
061.053.00262	Urinary tract infection**	7 44	Moderate	Unrelated				
				Eprosartan 400 mg/HCTZ 12.5 mg QD				
061.004.00006	Urinary tract infection	9	Mild	Unrelated				
061.006.00044	Gout	4	Moderate	Unrelated				
061.008.00081	Creatine phosphokinase increased	57 (1)	Mild	Possibly related				
061.574.00469	Hyperglycemia	15	Mild	Possibly related				
				Eprosartan 400 mg/HCTZ 25 mg QD				
061.002.00026	Hypokalemia	57 (1)	Moderate	Related				
061.002.00158	Hypokalemia	16	Mild	Related				
061.002.00161	Hypokalemia**	1	Mild	Related				
		32 (1)	Moderate	Related				
	Creatine phosphokinase increased	32 (1)	Moderate	Possibly related				
061.003.00086	SGPT (ALAT) increased**	1 15	Mild Mild	Not related Not related				
	Hyperuricemia	15	Mild	Related				
061.006.00045	Urinary tract infection	14	Mild	Not related				
061.007.00060	Creatine phosphokinase increased**	96 57 (1)	Moderate Mild	Possibly related				
061.052.00196	Hypokalemia	57 (1)	Mild	Possibly related				
061.275.00302	BUN increased	13	Mild	Possibly related				
	Creatine phosphokinase increased**	13	Mild	Possibly related				
	NPN increased	13	Mild	Possibly related				
061.471.00301	Leukocytosis	15	Mild	Unrelated				
061.472.00353	Gout	24	Moderate	Possibly related				
061.571.00431	Creatine phosphokinase increased	48	Mild	Unrelated				

* References ranges for fasting glucose are age-dependent and reference ranges for creatine phosphokinase are gender-dependent.

** The same adverse experience occurred at least twice during the study.

Key: Investigator-designated Severity: Mild, Moderate, or Severe. Investigator-designated Relationship: Unrelated, Possibly Related, or Related. Days on study medications are presented relative to the first dose of randomized medication, numbers in ( ) indicate the number of days after the last dose of randomized medication.

4. EFFICACY RESULTS

4.1 Statistical considerations

This study was overpowered because it enrolled more patients (approximately 126 per group were randomized) than were needed (70 patients per group) to detect a difference of 5 mm Hg between two treatment groups. Thus, the statistically significant differences in efficacy parameters detected at study endpoint may be due to over-enrollment.

4.2 Primary Efficacy Parameter

The reduction in mean sitting diastolic blood pressure from baseline to endpoint ranged in a dose-related (to HCTZ) manner from 5.4 mmHg for the placebo group to 12.2 mmHg for the eprosartan 400 mg/HCTZ 25 mg once/day treatment group (Table Epro-061-10), the differences between active treatment groups and placebo being statistically significant. Table Epro-061-10 also shows that the reduction in SitDBP due to placebo effect was 5.4 mmHg, that due to HCTZ was 2.4 mmHg for the 12.5 mg dose and 4.8 mmHg for the 25 mg dose, leaving a relatively small reduction in SitDBP of 2.0 mmHg attributable to the eprosartan 400 mg once/day dose.

Analysis of SitDBPs at each visit showed that the maximum response was achieved at Week 6 with eprosartan 400 mg/HCTZ 12.5 mg treatment, and at Week 8 with eprosartan 400 mg/HCTZ 25 mg treatment.

Table Epro-061-10. Mean (±SE) trough sitting diastolic blood pressure at baseline and study endpoint, and mean change from baseline in trough sitting diastolic blood pressure at study endpoint (95% Bonferroni confidence intervals)

	MEDICATION REGIMEN		
SitDBP (mmHg)	Placebo (n=124)	Epro+HCTZ 12.5mg (n=128)	Epro + HCTZ 25 mg (n=124†)
Baseline	101.0 ± 0.3	101.3 ± 0.4	99.8 ± 0.3
Study Endpoint	95.6 ± 0.8	91.5 ± 0.7	87.6 ± 0.7
Change from Baseline	-5.4 ± 0.8	-9.8 ± 0.7	-12.2 ± 0.6
Difference from placebo (95% CI) p-value		-4.4 (-6.7, -2.1) < 0.0001*	-6.9 (-9.1, -4.6) < 0.0001*
Difference from epro + 12.5 mg HCTZ (95% CI) p-value			-2.5 (-4.7, -0.2) 0.0095*

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

4.3 **Secondary Efficacy Parameters**

Decreases from baseline to study endpoint in mean sitting systolic blood pressure ranged from 5.5 mmHg for the placebo group to 16.3 mmHg for the eprosartan 400 mg/HCTZ 25 mg once/day regimen (Table Epro-061-11), the differences between active treatment groups and placebo being statistically significant. There was no change in sitting heart rate. Table Epro-061-11 also shows that the reduction in SitSBP due to placebo effect was 5.5 mmHg, that due to HCTZ was 2.3 mmHg for the 12.5 mg dose and 4.6 mmHg for the 25 mg dose, leaving a reduction in SitSBP of 6.2 mmHg attributable to the eprosartan 400 mg once/day dose.

Table Epro-061-11. Mean (±SE) trough sitting systolic blood pressure and heart rate at baseline and study endpoint, and mean change from baseline in trough sitting diastolic blood pressure at study endpoint (95% Bonferroni confidence intervals)

	MEDICATION REGIMEN		
Vital Signs	Placebo (n=124)	Epro+HCTZ 12.5mg (n=128)	Epro + HCTZ 25 mg (n=124†)
SitSBP (mmHg)			
Baseline	155.8 ± 1.4	154.1 ± 1.3	154.2 ± 1.3
Study Endpoint	150.3 ± 1.5	140.0 ± 1.4	137.9 ± 1.4
Change from Baseline	-5.5 ± 1.1	-14.0 ± 1.1	-16.3 ± 1.1
Difference from placebo (95% CI) p-value		-8.6 (-12.3, -4.9) < 0.0001*	-10.9 (-14.6, -7.1) < 0.0001*
Difference from epro + 12.5 mg HCTZ (95% CI) p-value			-2.3 (-6.0, -1.5) 0.145
SitHR (bpm)			
Baseline	74.1 ± 0.7	74.5 ± 0.7	74.1 ± 0.8
Study Endpoint	74.1 ± 0.9	73.9 ± 0.8	72.8 ± 0.9
Change from Baseline	0.1 ± 0.7	-0.6 ± 0.6	-1.2 ± 0.6

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure,
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

The total percentages of patients who responded at endpoint were also dose related to HCTZ, being 29% in placebo group, 55.5% in eprosartan 400 mg/HCTZ 12.5 mg once/day group and 73.4% in the eprosartan 400 mg/HCTZ 25 mg once/day group (Table Epro-061-12), the differences between placebo and each of the active treatment groups being statistically significant (by Cochran Mantel Haenszel analysis). Here, too, in a dose related (to HCTZ) manner, the percentage of responders due to placebo effect was 29%, that due to HCTZ was 17.9% for the 12.5 mg dose and 35.8% mmHg for the 25 mg dose, leaving a meager 8.6% percentage of responders attributable to the eprosartan 400 mg once/day dose.

Analyses of subgroups showed that eprosartan 400 mg/HCTZ 25 mg once/day treatment reduced the SitDBP significantly compared to placebo for all subgroups except patients whose race was classified as "Other", and for

those patients with baseline SitDBP ≥105 mmHg. Subgroups containing larger number of patients (all subgroups except Oriental patients and patients whose race was classified as "Other") showed a dose related (to HCTZ) responder rate ranging from 13.3-43.3% in placebo group, 51.0-82.4% for eprosartan 400 mg/HCTZ 12.5 mg treatment group to 66.7-82.6% for eprosartan 400 mg/HCTZ 25 mg treatment group.

Table Epro-061-12. Number (%) of patients who responded (Patients with SitDBP < 90 mmHg, or 90-100 mmHg and decreased from baseline by at ≥ 10 mmHg) at study endpoint (Cochran Mantel Haenszel Analysis)

	MEDICATION REGIMEN					
Response	Placebo (n=124)		Epro+HCTZ 12.5mg (n=128)		Epro + HCTZ 25 mg (n=124†)	
Endpoint	No.	(%)	No.	(%)	No.	(%)
<90 mmHg	30	(24.2)	57	(44.5)	77	(62.1)
90-100 mmHg**	6	(4.8)	14	(10.9)	14	(11.3)
Total	36	(29.0)	71	(55.5)	91	(73.4)
Relative Risk (95% CI) p-value			1.59 (1.22, 2.08) < 0.001*		2.62 (1.87, 3.68) < 0.001*	
Relative Risk (95% CI) p-value					-1.66 (-1.11, 2.51) 0.003*	

n = number of patients with a baseline value and study endpoint value
* Indicates significance at 0.05 using modified Bonferroni procedure; ** The decrease must have been at least 10 mmHg from baseline.
† 4 patients (#061.052.00217, #016.274.00277, #061.472.00340, and #061.573.00457) randomized to eprosartan 400 mg/ HCTZ 25 mg did not have any trough (pre-dose) vital signs taken after randomization and were not included in analysis.

5. CONCLUSION

At the doses used, eprosartan/HCTZ combinations showed no differences from placebo in clinical and laboratory safety profiles. No excessive lowering of blood pressure and no effect on heart rate were found.

There was a dose-related (to HCTZ) statistically significant reduction in sitting diastolic blood pressure compared to placebo. However, the reduction in SitDBP attributable to eprosartan 400 mg once/day was small (2 mmHg) compared to that due to placebo effect (5.4 mmHg) and HCTZ 12.5 mg (2.4 mmHg) and 25 mg (4.8 mmHg). Secondary efficacy parameters (sitting systolic blood pressure and percentage of patients who responded at endpoint) also showed the same trend, with a reduction in sitting systolic blood pressure of 6.2 mmHg (compared to 5.5 mmHg for placebo) and a responder rate of 8.6% (compared to 29% for placebo) attributable to eprosartan 400 mg once/day. Over-enrollment of patients (124-128 patients per group rather than the required 70 patients per group) may have contributed to the finding of spurious statistical significance in the efficacy parameters between the eprosartan/HCTZ treatment groups and the placebo treatment group.

Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

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Protocol SB 203220/069 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.095)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *02-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *03-Jun-1997*

69.1 STUDY PROTOCOL

69.1.1 Title *A study of the renal hemodynamic effects of Eprosartan and Losartan in normal healthy male volunteers*

69.1.2 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 in the treatment of hypertension and congestive heart failure. Losartan, in single dose studies in normal volunteers and hypertensive patients, had no effects on ERPF or GFR, but had a uricosuric effect leading to lowering of serum uric acid.

69.1.3 Objectives

1. To compare the effect of a single oral dose of eprosartan to a single oral dose of losartan on effective renal plasma flow (ERPF) and urine uric acid excretion;
2. To describe the effect of a single oral dose of eprosartan or a single oral dose of losartan on glomerular filtration rate (GFR) and urinary electrolyte excretion; and,
3. To assess the safety and tolerability of a single oral dose of eprosartan and a single oral dose of losartan in normal, healthy male volunteers.

69.1.4 Study design

The study was an open-label, randomized, two period, period-balanced crossover study under salt-replete (given salt supplementation) conditions. Each subject received a single oral dose of 400 mg eprosartan (two 200 mg tablets, Lot# U95118) or Cozaar® (Losartan) 50 mg (Lot# X95149), separated by a washout period of at least 7 days.

69.1.5 Protocol Amendments

There were no amendments to the protocol.

69.1.6 Population enrolled/analyzed

Although intended to enroll 24, only 17 healthy, non-smoking male volunteers 18-50 years of age, and weight > 50 kg and within 15% of ideal weight (based on height), and a negative urine drug screen within 30 days were enrolled.

Compliance: All study medication was administered by study personnel, each subject's oral cavity being examined after each dose to ensure ingestion of the study medication.

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). A 24-hour urine specimen was also obtained for sodium and potassium excretion; instructions regarding dietary sodium supplements were based on the 24 hour urinary sodium and potassium excretion results.

69.1.7 Study procedures

Based upon the dietary history obtained at screening, subjects received instructions to take a 2500 calorie diet containing about 200 mEq sodium and 100 mEq potassium for at least 5 days prior to each study session. They were also given up to 3 g sodium chloride (1 g tablets, Eli Lilly & Co.) one to two times daily, and up to 30 mEq potassium chloride (10 mEq K-Dur® tablets, Key Pharmaceuticals) 1 to 3 times daily during the 5 days prior to and throughout the study. No salt supplementation was given during the PAH and inulin infusions.
Inulin and PAH clearance tests were performed on the morning of each study period. An iv loading dose of PAH (8 mg/kg) and inulin (50 mg/kg) were given at 6.00 am (2 hours before study medication administration) followed by continuous iv infusions of PAH and inulin up to 4 hours post-dose. The subjects drank 240 ml of water at this time. At 8.00 am, the study medication was administered with 240 ml water. PAH and inulin infusions were continued for 4 hours following dosing, with the subject remaining supine throughout except at predetermined periods to void urine and drink water. They were not allowed to stand until after blood samples for plasma renin activity (PRA) and aldosterone were drawn. They also remain fasted until the end of the PAH and inulin infusions.

Measurements of supine blood pressure and heart rate, ECG and blood sample collection were made. Blood sample (5 ml) collections were done at -1, -0.5, 0, 0.5, 1, 1.5, 2, 3, 4 hours for PAH and inulin concentrations. and at -1, 0, 1, 2, 3 and 4 hours for sodium, potassium chloride, creatinine and uric acid concentrations. Urine was collected at -2.5 to -1, -1 to 0, 0 to 1, 1 to 2, and 2 to 3 hours, and analyzed for sodium, potassium, chloride, creatinine and uric acid concentrations.

Subjects returned 5 - 7 days following the last study session, at which time safety laboratory tests were performed. Adverse experiences (AEs) were elicited by spontaneous reporting by subjects, by nursing observation, physical examination findings, laboratory findings and 12-lead ECG data.

69.1.8 **Endpoints:**

The Primary Efficacy Endpoints were CL_{PAH}, a measure of effective renal plasma flow, fractional excretion of uric acid (Fe_{UA}), urine uric acid to creatinine ratio (UUA/UCr) and the safety and tolerability of eprosartan and losartan..

The Secondary Efficacy Endpoints were CL_{IN}, a measure of glomerular filtration rate, urinary excretion rates and fractional excretion for Na^+, K^+ and Cl^-, plasma renin activity and aldosterone levels and the ratio of creatinine clearance to inulin clearance (CL_{CR} /CL_{IN}).

69.1.9 **Sample size:**

Based on a within-subject coefficient of variation (CV_W) of 11.9% for CL_{PAH} observed in a previous protocol (# SB 203220/024), to detect differences of at least 20% on a 2-tailed test with a Type I Error rate of 5% and 90% power between the 2 treatments, it was estimated that a sample size of 12 would be necessary. Also, based on average between-subject coefficient of variation (CV_b) of 21.2% for Fe_{UA} observed in a previous protocol (# SK&F 108566/007), to detect differences of at least 30% on a 2-tailed test with a Type I Error rate of 5% and 90% power between the 2 treatments, it was estimated that a sample size of 12 would be necessary.

69.1.10 **Statistical Evaluation:**

Each primary endpoint was submitted to an ANOVA with terms for sequence, subject, period and regimen.

69.1.11 **Investigator , Center and Dates:**

Bernard Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 25-Sep-1995 to 17-Nov-1995.

69.2 STUDY POPULATION

69.2.1 **Subject disposition:**

Of 17 subjects screened, one did not meet entrance criteria and 4 had schedule conflicts. 12 (8 black, 2 white, 1 Indian and 1 Iranian) healthy male subjects, 21-33 (mean = 26) years of age, weighing 53.6 to 95.3 (mean = 74.9) kg, and 170-193 (mean = 178) cm tall, were randomized. All received study medication as follows:

Treatment	Number of subjects
Regimen A (single oral dose of 400 mg eprosartan)	12
Regimen B (single oral dose of 50 mg losartan)	12

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

69.2.3 **Protocol violations:**

(1) Vital signs were not assessed immediately prior to administration of study medication.

(2) Urine was not collected for the 3 to 4 hour post-dose interval during both sessions. Excretion rates for sodium, potassium, chloride, urine uric acid and creatinine, fractional excretion for sodium, potassium, chloride and uric acid and UUA/UCr could not be calculated for this time period.

(3) Statistical analyses of Fe_{UA} and UUA/UCr following administration of eprosartan and losartan were performed using 0-3 hour post-dose data instead of 0-4 hour post-dose data; the maximal separation between the effects of eprosartan and losartan on urine uric acid excretion may not have been captured due to this protocol violation.

69.3. SAFETY RESULTS

69.3.1 **General considerations:** There were no adverse experiences (AEs) were reported during this study.

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

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

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

69.3.5 **Adverse Events:** There were no adverse experiences (AEs) were reported during this study.

69.3.6 **Laboratory findings, ECGs, Vital signs**

There were no pulse rate changes of potential clinical concern as defined by protocol. Changes in diastolic blood pressure (DBP) of clinical concern as defined by protocol were observed in 3 instances as follows (they were not sustained and subjects were asymptomatic):

Eprosartan: 2 subject (#006 and #012) had increased DBP
Losartan:: 1 subject (#011) had decreased DBP

There were no baseline ECG findings (in PR, QRS and QTc intervals) that were of potential concern. ECGs were not performed during the study treatment phase or follow-up.

Two laboratory data that were of potential clinical concern according to protocol-defined criteria were observed at follow up: viz., Subject #005 had low hemoglobin (11.9 g/dl) and Subject #006 had a low hematocrit (35.8%).

69.4. **PHARMACODYNAMIC RESULTS**

There were no statistically significant sequence or period effects, or violation of model assumptions in the pre-dose or maximum post-dose data for CL_{PAH}, urine sodium and potassium excretion rates, Fe_{UA} and UUA/UCr. Table Epro-069-1 shows that the mean CL_{PAH} and urinary excretion rates of sodium and potassium were not different between losartan and eprosartan. The fractional excretion of urine uric acid (Fe_{UA}) and urine uric acid to urine creatinine ratio (UUA/UCr) increased significantly following losartan compared to eprosartan, which were more pronounced at 1-2 and 2-3 hour urine collections (Figure Epro-069-1).

Figure Epro-69-1. Comparison of time course of Fe_{UA} following single oral dose of losartan and eprosartan

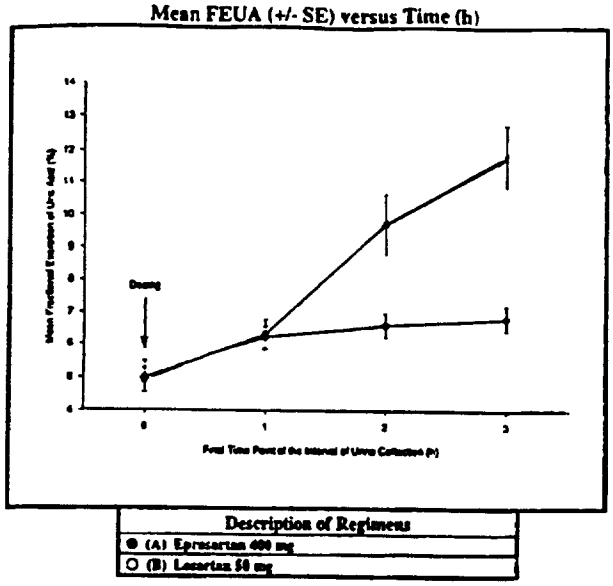


Figure Epro-069-2 shows that the pre- and post-dose CL_{IN} data (which were a measurement of GFR) following eprosartan and losartan were similar with respect to their effect on GFR. However, the data on only 12 subjects lack the statistical power to enable drawing any valid inferences. Mean urinary chloride excretion rate, mean sodium,

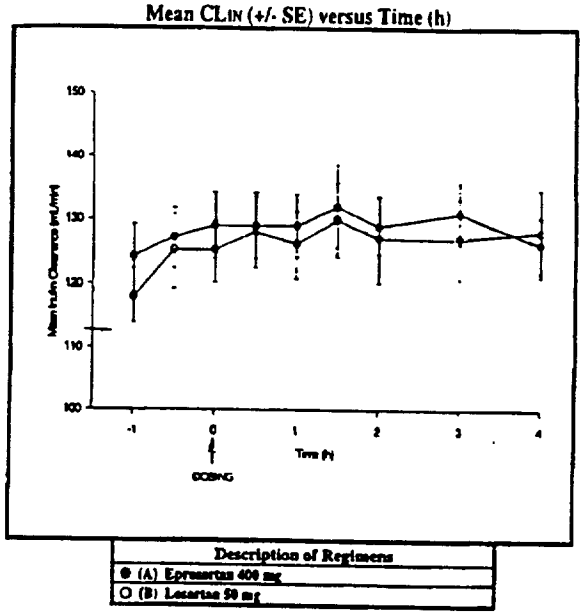
potassium or chloride fractional excretion, mean plasma renin activity and mean serum aldosterone levels were not different in the subjects between period of receiving eprosartan and that of receiving losartan.

Table Epro-069-1. Mean (SD) maximum post-dose primary endpoint data between regimens

Parameter	Eprosartan (n=12)	Losartan (n=12)	Difference (95% C.I.)	P value†
CL_{PAH} (ml/min)	1027 (231)	954 (113)	73.75 (-71.07, 218.57)	0.2492
Fe_{UA} (%)	6.9 (1.3)	12.0 (3.5)	-5.13 (-6.91, -3.34)	0.0054
UUA/UCr ratio	0.403 (0.095)	0.676 (0.202)	-0.27 (-0.38, -0.16)	0.0119
Urinary Na^+ excretion rate (mEq/min)	4.1714 (1.592)	3.3988 (0.876)	0.77 (-0.51, 2.06)	0.6772
Urinary K^+ excretion rate (mEq/min)	1.5174 (0.700)	1.3366 (0.458)	0.18 (-0.32, 0.68)	0.3709

†: ANOVA

Figure Epro-69-2. Comparison of time course of CL_{IN} following single oral dose of losartan and eprosartan



69.5 CONCLUSION

Single oral dose administration of eprosartan and losartan showed no differences in the safety profiles (clinical and laboratory).

While Study Protocol 108566/006 suggested that eprosartan may cause a clinically significant rise in effective renal plasma flow (ERPF) in salt-loaded individuals, in this study ERPF as measured by plasma clearance of para-amino hippurate (CL_{PAH}) was not increased significantly after a single dose of eprosartan compared to losartan.

Urine uric acid excretion as determined by fractional excretion of urine uric acid (Fe_{UA}) and urine uric acid to urine creatinine ratio (UUA/UCr) increased significantly following losartan compared to eprosartan.

There were no differences in the effect of losartan and eprosartan on glomerular filtration rate (GFR) as measured by plasma clearance of inulin (CL_{IN}), urinary excretion of sodium and potassium, and plasma renin activity and serum aldosterone levels.

Protocol 086 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol.1.116)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *23-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *24-Jun-1997*

86.1 STUDY PROTOCOL

86.1.1 Title *A study of the effect of food on eprosartan pharmacokinetics in healthy male volunteers*

86.1.2 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 food on eprosartan pharmacokinetics following an 800 mg dose which is anticipated to be the largest dose to be recommended for the treatment of hypertension. Because eprosartan pharmacokinetics are not dose proportional at doses greater than 200 mg, the effect of food on the highest commercial dose was investigated.

86.1.3 Objectives

1. To estimate the difference between the pharmacokinetics of a single oral dose of 800 mg (2 x 400 mg tablets) of eprosartan under fasting conditions and following a standard high fat meal in healthy male volunteers, and
2. To evaluate the safety and tolerability of oral eprosartan.

86.1.4 Study design

The study was a randomized, open-label, two-period, period balanced crossover study of two groups (A, and B). Subjects were allocated at random to one of two sequences: AB or BA. Each subject participated in two study periods separated by at least one week, in which each received the study medication as a single oral dose of:

1. Regimen A: eprosartan 800 mg, (Lot# U95111, 400 mg tablet x 2) administered to fasted subjects, or
2. Regimen B: eprosartan 800 mg, (Lot# U95111, 400 mg tablet x 2) administered following a standard high fat meal.

86.1.5 Protocol Amendments

There were no amendments to the protocol.

86.1.6 Population enrolled/analyzed

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

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history, and physical examination. 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 weeks prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

86.1.7 Study procedures

After an overnight fast, patients reported to the clinical pharmacology unit at 7:00 am. Assessment of baseline symptoms and vital signs were made. The fed group was given a standardized high-calorie, high-fat breakfast (2 eggs cooked in butter, 2 strips of bacon, 2 pieces of toast, 2 teaspoons (10 grams) of butter, 4 ounces (113 grams) of hash brown potatoes and 8 ounces (240 ml) of whole milk) equivalent to 1020 calories (58 g carbohydrate, 33 g protein, 58-75 g fat). The meal was given at 7:30 am, and completely consumed within 20 minutes. Subjects allocated to the fed or fasted groups were physically separated during the consumption of the breakfast. At 8:00 am (within 20 minutes of fed subjects finishing the meal), all subjects were administered the study medication with 240 ml of tepid water. No food or drink was permitted for 5 hours after dosing. Subjects drank 240 ml water at 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 9-10 hours post dose, respectively. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. Prior to dosing and 2 hours post-dosing, sitting blood pressure and pulse rate were obtained. 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, 16, 20, 24 and 30 hours following dosing. Subjects were permitted to leave the center after the 24 hour pharmacokinetics sample was drawn, but had to return for the 30 hour blood sample.

Subjects returned 1 week following the last study session, at which time safety laboratory tests were done.

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

86.1.8 **Pharmacokinetic procedures:**
Following collection, blood samples 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 a reversed-phase HPLC method with UV detection. The lower limit of quantification (LLQ) in plasma was 10 ng/ml based on 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). Because of the variability and/or limited measurable quantities of plasma concentrations in the terminal phase, $T_{1/2}$ and AUC(0-∞) could not be estimated.

86.1.9 **Endpoints:**
Not defined in the protocol, but it could be assumed that AUC(0-τ) and Cmax were primary endpoints, and Tmax was the secondary endpoint, and that clinical monitoring and laboratory safety data were also secondary endpoints.

86.1.10 **Sample size:**
Based on an average within-subject coefficients of variation (CVw) for AUC and Cmax to be 33.3% and 35.0%, respectively, it was estimated that a sample size of 20 would provide at least 90% power, on a two-tailed procedure, with Type I error rate of 5% and a symmetric 30% range on the ln-scale, to detect a difference of at least 30% between the fed and fasted regimens.

86.1.11 **Investigator , Center and Study Dates:**
G. Stephen DeCherney, MD, Medical Research Institute of Delaware, Inc., 4755 Ogletown-Stanton Rd., Suite 419, Newark, DE 19718. Dates: 28-Nov-1995 to 29-Dec-1995.

86.2 STUDY POPULATION

86.2.1 **Subject disposition:**
36 healthy male volunteers were screened; 14 failed to meet entrance criteria (including 5 subjects who had a body weight >15% of ideal, 4 subjects who had abnormal blood counts, 3 subjects who had abnormal clinical chemistry values, 1 subject who had a positive urine drug screen and 1 subject who did not return following screening). 20 male subjects (2 being held in reserve after the initial enrollment was met), 20-40 (mean = 29) years of age, weighing 59.8 to 97.0 (mean = 82.2) kg, and 163-192 (mean = 181) cm tall, were screened and randomized. 40% were black and 60% were white. All 20 subjects completed the study.

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

86.2.3 **Protocol violations:**
No protocol violations were reported. One subject (#011) had Gilbert's syndrome (screening bilirubin was 2.1 mg/dl, and follow up serum bilirubin was 2.2 mg/dl)

86.3 SAFETY RESULTS

86.3.1 **General considerations:**
There were no signs or symptoms present prior to the initial dose of the study, and only one subject reported an adverse experience (mild dizziness) during the study.

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

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

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

86.3.5 **Adverse Events:**
One subject (#007) reported a mild dizziness approximately 2 hours after dosing (fasted regimen) without changes in vital signs. It resolved without treatment.

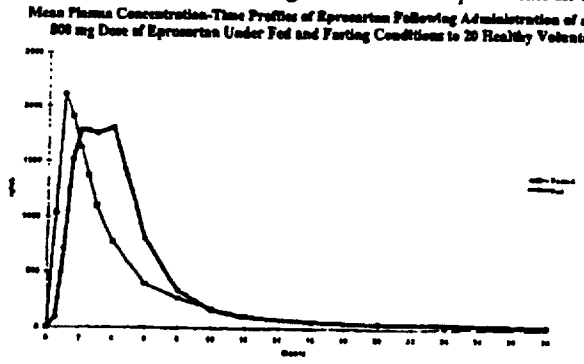
86.3.6 **Laboratory findings, ECGs, Vital signs**
No patient in this study exhibited abnormal heart rates of potential clinical concern. Two subjects experienced decreases in diastolic blood pressure > 20 mmHg (Subject # 012 and #018) 2 hours following administration of eprosartan as Regimen A (fasted state). Subject #015 had decreased diastolic blood pressure 2 hours following administration of eprosartan as Regimen B (fed state). All events were asymptomatic.

Screening ECGs showed normal intervals (including PR, QRS, QT and QTc). No post-dose ECGs were done.

There were no clinically important changes from baseline in the clinical laboratory safety data following the administration of eprosartan.

86.4 **PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS**
Following single oral doses of 800 mg of eprosartan (Figure Epro-086-1), peak plasma concentrations were reached within 1 to 2 hours in the fasted state and within 2 to 4 hours in the fed state. In general, plasma concentrations declined from the peak in a bi-exponential manner. (It is to be noted that the plasma concentration value (1162.9 mg/ml) at the 1.5 hour timepoint for Subject #012 during Regimen A was not consistent with the other plasma concentrations in his concentration-time profile and was deleted from the pharmacokinetic analysis. The sponsor thought there was a mix-up of samples collected at the 6 hour timepoint for Subject #015 (Regimen B) and Subject #016 (Regimen A), and switched the concentration values at the 6 hour timepoint for these two subjects.)

Figure Epro-086-1. Time course of plasma concentrations following a single oral dose of eprosartan in fed and fasted states



In Table Epro-086-1, the AUC(0-τ) was 20% larger, and the Cmax was 7% less when 800 mg (2 x 400 mg) eprosartan was given after a high fat meal compared to the fasted condition. The 95% confidence interval (Table Epro-086-2) for AUC(0-τ) does not include the value 1.00 indicating a food effect on AUC(0-τ), whereas the 95% confidence interval for Cmax includes the value 1 indicating no substantial difference. The high fat meal caused a delay in Tmax as the median difference between eprosartan in the fed state to eprosartan in the in the fasted state was 1.75 hours. The 95% confidence interval for Tmax does not include the value zero suggesting that the rate of absorption is different in the fed and fasted states. Overall, the results demonstrate that administration of eprosartan with a high fat meal delayed the rate of absorption, but the extent of absorption was slightly increased - on the average - by 20%. (Note: In a previous study of 300 mg eprosartan, too, a high fat meal slightly delayed the rate of absorption, but increased the extent of absorption.)

Table Epro-086-1. Pharmacokinetic values for eprosartan following single oral doses of eprosartan in fed and fasted states

End Point	Eprosartan 800 mg fasted	Eprosartan 800 mg fed
AUC(0-τ) (ng.h/ml)		
Geometric Mean	7980	9542
Mean	8456	10102
Median	8092	9605
S.D.	3068	3591
Cmax (ng/ml)		
Geometric Mean	2388	2214
Mean	2508	2312
Median	2036	2075
S.D.	841	745
Tmax (hr)		
Mean	1.45	3.15
Median	1.25	3.50
S.D.	0.58	0.96

Table Epro-086-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan in fed and fasted states

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ)†	B:A	1.20	(1.01, 1.41)
Cmax†	B:A	0.93	(0.77, 1.12)
Tmax§	B-A	1.75 h	(1.00 h, 2.50 h)

† Data presented as the ratio of the geometric means for eprosartan in regimen B (fed) : regimen A (fasted)
§ Data presented as the median difference of eprosartan in regimen B (fed) - regimen A (fasted) and 95% C.I.

(Note: The between-subject coefficients of variation for ln-transformed AUC(0-τ) were 35% for both regimens, and for ln-transformed Cmax were 30% for both regimens. The within-subject coefficients of variation for AUC(0-τ) and Cmax were 25.4% and 29.3%, respectively. These values were slightly lower than that used for the original sample size estimation indicating no inadequacies in terms of sample size.)

86.5 CONCLUSION

Single oral dose administration of 800 mg eprosartan in fed and fasted states was not associated with adverse events, apart from one subject with mild dizziness. There were no laboratory values of potential safety concern.

Following single oral doses of 800 mg of eprosartan, peak plasma concentrations were reached within 1 to 2 hours in the fasted state and within 2 to 4 hours in the fed state. In general, plasma concentrations declined from the peak in a bi-exponential manner. The AUC(0-τ) was 20% larger, and the Cmax was 7% less when 800 mg eprosartan was given after a high fat meal compared to the fasted condition. The 95% confidence interval for AUC(0-τ) does not include the value 1.00 indicating a food effect on AUC(0-τ), whereas the 95% confidence interval for Cmax includes the value 1 indicating no substantial difference. The high fat meal caused a delay in Tmax by 1.75 hours on the average. The 95% confidence interval for Tmax does not include the value zero suggesting that the rate of absorption is different in the fed and fasted states. The results suggest that administration of eprosartan with a high fat meal delayed the rate of absorption, but the extent of absorption was slightly increased - on the average - by 20%.

Protocol 089	**NDA 20-738**	**Teveten™ (Eprosartan) Tablets**	*(Vol. 1.117)*
DATE OF CORRESPONDENCE:	*11-Oct-1996*	DATE ASSIGNED:	*19-Jun-1997*
DATE RECEIVED:	*18-Oct-1996*	DATE COMPLETED	*20-Jun-1997*

89.1 STUDY PROTOCOL

89.1.1 **Title** ***A study to evaluate the bioequivalence of the 100 mg clinical trials tablet and the proposed 300 mg commercial tablet formulation of eprosartan in healthy male volunteers***

89.1.2 **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 300 mg eprosartan intended for commercial release.

89.1.3 **Objectives**

1. To assess the bioequivalence of the new eprosartan 300 mg tablet formulation intended for commercial release with the old eprosartan 100 mg clinical trials tablet formulation
2. To assess the safety and tolerability of eprosartan in healthy male volunteers.

89.1.4 **Study design**

The study was a randomized, open-label, two-period, period balanced crossover study of two groups (A, and B). Each subject participated in two study periods separated by at least one week, in which each received, within 30 minutes of a standard breakfast after an overnight fast, the study medication as a single oral dose of:

1. Regimen A: eprosartan 300 mg tablets, (Lot# U95110) the new commercial release formulation) or
2. Regimen B: eprosartan 100 mg tablets, (Lot# U94068) x 3, the clinical trials formulation)

89.1.5 **Protocol Amendments**

There were no amendments to the protocol.

89.1.6 **Population enrolled/analyzed**

48 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: All study medication was administered with 120 ml tepid water by study 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. 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 weeks prior to and during the study, and alcohol, tobacco and caffeine within 24 hours prior to and during each study period.

89.1.7 **Study procedures**

After an overnight fast, patients reported to the clinical pharmacology unit at 7:00 am. Assessment of baseline symptoms and vital signs, and a 12-lead ECG recording were made. A standard breakfast (cereal, milk, juice and muffin) was given at 7:30 am, and completely consumed within 20 minutes. At 8:00 am (within 30 minutes of start of breakfast), all subjects were administered the study medication with 240 ml of tepid water. Subjects remained sitting for at least 5 hours after dosing. No food or drink was permitted for 4 hours after dosing. 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 9-10 hours post dose, respectively. Subjects remained in the clinical pharmacology unit for 24 hours after dosing. 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, 16, 20 and 24 hours following dosing.

Subjects returned 1 week following the last study session, at which time safety laboratory tests were done.

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

89.1.8 **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 a method based on protein precipitation with methanol, followed by LC/MS/MS analysis employing positive-ion electrospray ionization. The lower limit of quantification (LLQ) in plasma was 20 ng/ml and the upper limit of quantification (ULQ) was 5000 ng/ml for a 50 µl 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). Because of variability in plasma concentrations in the terminal phase and/or limited measurable plasma concentrations in the terminal phase, $T_{1/2}$ and AUC(0-∞) could not be estimated.

89.1.9 **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.

89.1.10 **Sample size:**
Based on an average within-subject coefficients of variation (CVw) for AUC and Cmax to be 25.9% and 31.2%, 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 A:B for AUC and Cmax are contained within the range (0.80, 1.25). This range represents a symmetric 20% range on the ln scale.

89.1.11 **Investigator , Center and Study Dates:**
Jerry Herron, Arkansas Research Medical Testing Center, 1207 Rebsamen Park Road, Little Rock, Arkansas 72202.
Dates: 17-Jan-1996 to 12-Feb-1996

89.2 STUDY POPULATION

89.2.1 **Subject disposition:**
48 male subjects, 20-45 (mean = 33) years of age, weighing 68.1 to 104.5 (mean = 82.4) kg, and 168-190 (mean = 180) cm tall, were screened and randomized. 48% were black and 52% were white.

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

89.2.3 **Protocol violations:**
No protocol violations were noted.

89.3 SAFETY RESULTS

89.3.1 **General considerations:**
There were no signs or symptoms present prior to the initial dose of the study, and only one subjected reported an adverse experience (mild headache) during the study.

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

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

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

89.3.5 **Adverse Events:**

One subject (#047) reported a mild headache of 4 hours duration on the day after receiving Regimen A (commercial eprosartan 300 mg tablet) during session 2.

89.3.6 **Laboratory findings, ECGs, Vital signs**

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

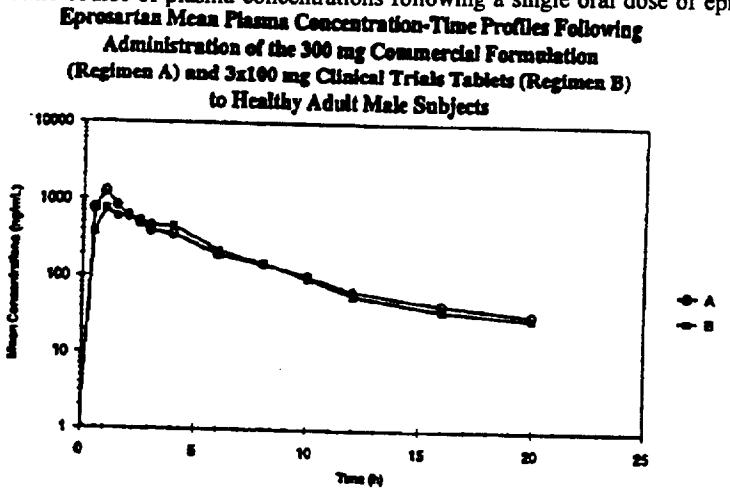
Screening ECGs showed normal intervals (including PR, QRS, QT and QTc). No post-dose ECGs were done.

Three subjects had asymptomatic borderline elevated WBC counts on end-of-study laboratory tests: subjects #036 and #046 each had WBC count 14.2 x $10^3/mm^3$, and subject #033 had a WBC count of 14.0 x $10^3/mm^3$.

89.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Following single oral doses of the clinical trial formulation and the new commercial release formulation of eprosartan (Figure Epro-089-1), the mean plasma concentration-time profiles were similar except for the first 2 hours following drug administration. Peak plasma concentrations were reached within 1 hour and plasma concentrations declined from the peak in a mono- or bi-phasic manner. (It is to be noted that samples at 10 & 16 h time points for subject #030 during Regimen A, at 8 h time point for subject #017 during Regimen B, and at 6 and 12 h time points for subject #018 during Regimen B were used up due to chromatographic problems, and were designated "non-reportable" in the analysis.)

Figure Epro-089-1. Time course of plasma concentrations following a single oral dose of eprosartan



In Table Epro-089-1, the AUC(0-τ) was 15% larger, and the Cmax was 31% higher with the 300 mg commercial tablet compared to 3 x 100 mg tablets. The 90% confidence intervals (Table Epro-089-2) for the comparisons of the primary pharmacokinetic parameters (AUC(0-τ) and Cmax) for the test (Regimen A commercial release formulation 300 mg relative to Regimen B - old clinical trial formulation 3 x 100 mg) are not contained in the acceptance range 0.80 to 1.25, and do not contain the value 1 suggesting that the true ratios may not be unity. The 95% confidence interval for Tmax contains 0 as a plausible value for the true median difference between Regimen A and Regimen B.

These results suggest that the 300 mg commercial tablet formulation was absorbed faster (larger point estimate for Cmax than observed for AUC(0-τ) with 0.25 hr median difference in Tmax) than the 3 x 100 mg clinical trials formulation, and that they cannot be considered bioequivalent.

(Note: The calculated between-subject coefficients of variation for ln-transformed AUC(0-τ) were 57% for both regimens, and for ln-transformed Cmax were 76% and 60% for regimens A and B, respectively. Analysis performed by removing an outlier (Subject #046) did not change the inferences. The calculated within-subject coefficients of variation for AUC(0-τ) and Cmax were 36% and 52%. These suggest a larger variability than that encountered in previous studies. Based on these observed coefficients of variations, a sample size of 56 and 118 subjects would be needed to provide at least 90% power to demonstrate equivalence for AUC(0-τ) and Cmax, respectively.)

Table Epro-089-1. Pharmacokinetic values for eprosartan following single oral doses

End Point	Commercial release formulation (A)	Old clinical trial formulation (B)
AUC(0-τ) (ng.h/ml)		
Geometric Mean	3610	3152
Mean	4118	3788
Median	3812	3321
S.D.	2247	3750
Cmax (ng/ml)		
Geometric Mean	1028	784
Mean	1280	926
Median	1034	779
S.D.	927	676
Tmax (hr)		
Mean	1.29	1.55
Median	1.00	1.00
S.D.	1.22	0.97

Table Epro-089-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan formulations

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ)†	A:B	1.15	(1.02, 1.29)
Cmax†	A:B	1.31	(1.11, 1.55)
Tmax§	A-B	-0.25 h	(-0.50 h, 0.00 h)

† Data presented as the ratio of the geometric means for A:B
§ Data presented as the median difference (A-B) and 95% C.I.

89.5 CONCLUSION

Single oral dose administration commercial release formulation of eprosartan (300 mg) and clinical trial formulation (3 x 100 mg) to healthy male volunteers did not show any significant differences in adverse experiences. There were no abnormal laboratory values of potential safety concern.

Following single oral doses of the clinical trial formulation and the new commercial release formulation of eprosartan, the mean plasma concentration-time profiles were similar except for the first 2 hours. Peak plasma concentrations were reached within 1 hour and plasma concentrations declined from the peak in a mono- or bi-phasic manner.

The AUC(0-τ) was 15% larger, and the Cmax was 31% higher with the 300 mg commercial tablet compared to 3 x 100 mg tablets. The 90% confidence intervals for AUC(0-τ) and Cmax are not contained in the acceptance range 0.80 to 1.25, suggesting that the 300 mg commercial tablet formulation and the 3 x 100 mg clinical trials formulation cannot be considered bioequivalent.

Protocol 090 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.096/97/98)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *21-May-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *25-Jun-1997*

90.1 STUDY PROTOCOL

90.1.1 Title *A six-week, double-blind study to compare the effects of eprosartan and placebo on proteinuria in patients with Type II diabetes mellitus*

90.1.2 Rationale

Microalbuminuria is the first sign of diabetic renal disease, frequently accompanied by mild hypertension. Measures to reduce blood glucose values close to the normal range, and use of ACE inhibitors to treat hypertension have been shown to delay the onset and slow the progression of diabetic nephropathy. A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects e.g., non-productive cough and angioedema) over ACE-inhibitors. This study evaluates the safety and efficacy of eprosartan, an A-II AT_1 receptor antagonist, on proteinuria in patients with Type II diabetes mellitus compared to placebo.

90.1.3 Objectives

1. The primary objective was to evaluate the effect of eprosartan (300 mg twice daily) on proteinuria in patients with Type II diabetes mellitus compared to placebo after six weeks of double-blind treatment
2. The secondary objective was to evaluate the safety of eprosartan in diabetic patients with proteinuria and to compare the safety of eprosartan and placebo with regard to adverse experiences, laboratory test abnormalities, vital signs, and ECG changes in these patients.

90.1.4 Study design

The study was a randomized, double-blind, parallel comparison of twice daily doses of eprosartan 300 mg and placebo, and consisted of 5 periods: screening, placebo run-in (1-2 weeks), double-blind treatment (6 weeks), open-label treatment (eprosartan x 6 weeks) and follow up (1-2 weeks). (The report submitted did not include the open-label period.)

Male and female patients ≥18 years with Type II diabetes mellitus and average urinary protein excretion ≥300 and ≤3000 mg/24 hour with or without hypertension were randomized, following a single-blind placebo run-period, to receive one of the following during the double-blind study period:

1. eprosartan (100 mg x 3 tablets (Lot# U95116) q 12 h for 6 weeks,) or
2. matching placebo (Lot# U94209) q 12 h for 6 weeks.

90.1.5 Protocol Amendments

A protocol amendment was made prior to enrollment, which reduced the minimal amount of 24-hour urine protein required for entry (from 500 mg/24 hours to 300 mg/24 hours), and excluded the use of ACE inhibitors for at least 2 weeks prior to the screening visit and not permitted during the trial.

90.1.6 Population enrolled/analyzed

155 adult male and female patients > 18 years of age, with well-controlled stable Type II diabetes mellitus of ≥12 months duration with HbA_{1C} < 9% at screening, with no or mild controlled essential hypertension and a positive dipstick value of ≥1+ protein at screening, 12-hour urinary protein excretion ≥300 and ≤3000 mg/24 hr, and serum creatinine < 3 mg/dl at screening and qualifying visits, were enrolled

Compliance: At each clinic visit, the number of tablets dispensed was recorded, and patients were instructed to return any unused drug at the next visit. Compliance was assessed by tablet count. Taking <80% or >120% of the study medication at each visit for 2 consecutive visits was considered noncompliant.
Pre-study screening: The screening visit included a complete medical history, physical examination including fundoscopy, 12-lead ECG, fasting blood and urine samples for laboratory studies (hematology, chemistry, liver function tests and urinalysis), a urine dipstick for protein, and a chest X-ray obtained within the previous 6 months.

90.1.7 Study procedures

Patients who had a positive dipstick for urinary protein at screening started single-blind placebo and collected 2 consecutive 24-hour urine samples within 2 weeks. If the 24-hour urinary protein was between 300 mg and 3000 mg, the patient was randomized into the double-blind period and assigned to eprosartan or placebo for 6 weeks, with

clinic visits every 2 weeks, and 2 consecutive 24-hour urine collections repeated at the end of Week 6. After completion, patients had the option to enter the open-label eprosartan treatment period for an additional 6 weeks, again with clinic visits every 2 weeks, and 2 consecutive 24-hour urine collections repeated at the end of Week 12. Following this, patients had the option of entering a 1-year open-label extension study or to come back for follow up 1-2 weeks later for safety assessments. Patients who completed the 6-week double-blind treatment phase including the 2 assessments of 24-hour urinary protein excretion at Week 6 were considered to have completed the study.

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

90.1.8 **Evaluation criteria:**

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

Pharmacodynamic Assessments: The Primary Efficacy Endpoints was the percent change from baseline in 24-hour urinary protein excretion (by analysis of variance) at Week 6 of the double-blind treatment period. Terms for center, regimen and center-by-regimen interaction were included in the model. Using an intent-to-treat analysis, patients with protocol violations were included in all analyses. The Secondary Efficacy Endpoints were: urinary albumin (similar to that on the primary efficacy parameter) and urinary creatinine.

90.1.9 **Sample size:**

Assuming a standard deviation of 40.0% for percent change from baseline, 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, a sample size of 60 evaluable patients per medication regimen was estimated to be necessary.

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

The study was conducted at 13 centers by 13 investigators in the US. Of the 13 investigators, one investigator (Dr. Robert A. Fiddes of Southern California Research Institute, Whittier, CA) was responsible for 19 of 45 patients given placebo, and 20 of 40 patients given eprosartan being randomized into the clinical trial, in contrast to low enrollment rates in other centers (Table Epro-090-1). Also, all withdrawals (4 in the placebo group and 6 in the eprosartan group) were from the same Dr. Fiddes's center; none of the other centers had withdrawals. Because this disproportionate number of enrollees and withdrawals in one center could cause bias in statistical analysis, subgroup analyses will be done (1) with patients from Dr. Fiddes's center and (2) with patients from all other centers as a group, to determine if the results were consistent with the overall findings.

Table Epro-090-1. Distribution of patients by Center/Investigator

Center		Placebo		Eprosartan		Total	
Number	*Investigator*	*R*	*C*	*R*	*C*	*R*	*C*
001	*Fiddes*	19	15	20	14	39	29
002	*Weinberg*	2	2	2	2	4	4
003	*Heatley*	4	4	3	3	7	7
004	*DeCherney*	1	1	0	0	1	1
005	*Rendell*	6	6	4	4	10	10
006	*Peiris*	1	1	0	0	1	1
007	*Bakris*	3	3	2	2	5	5
008	*Lukas*	2	2	3	3	5	5
009	*Boren*	1	1	1	1	2	2
011	*Lewin*	3	3	3	3	6	6
012	*Rosenblatt*	1	1	1	1	2	2
013	*McAllister*	1	1	1	1	2	2
014	*Patron*	1	1	0	0	1	1
	ALL	45	41	40	34	85	75

R = number of randomized patients; C = number of patients who completed the study.

90.2. STUDY POPULATION

90.2.1 **Subject disposition:**

Of 155 patients screened, 21 withdrew before the single-blind placebo period. 49 did not qualify for randomization. 85 patients (eprosartan 40, placebo 45) qualified for randomization and received at least one dose of study

medication. Of the 85 randomized patients, 75 (eprosartan 34, placebo 41) completed the 6-week double-blind treatment phase including 2 assessments of 24-hour urinary protein excretion at Week 6. One patient had endpoint assessment after Week 6; thus, only 74 patients were included in the efficacy analysis.

90.2.2 **Withdrawals:**

10 patients were withdrawn from the study (Table Epro-090-2), all from one center by one investigator (Dr. Fiddes). Two patients each on placebo and eprosartan were withdrawn because of adverse experiences. There was no further explanation regarding the 1 patient who was "lost to follow up" and 5 patients withdrawn for "other reasons".

Table Epro-090-2. Patients withdrawn from the study

Patients' Status	Treatment received		Total number
	Placebo	*Eprosartan*	*of patients*
Randomized	45	40	85
Completed study	41 (91.1%)	34 (85.0%)	75 (88.2%)
Withdrawn			
Adverse experience	2 (4.4%)	2* (5.0%)	4 (4.7%)
Lost to follow up	0	1 (2.5%)	1 (1.2%)
Other reasons	2 (4.4%)	3 (7.5%)	5 (5.9%)
Total withdrawn	4 (8.9%)	6 (15.0%)	10 (11.8%)

*Only 1 patient withdrew for an AE; the other patient #00057 died while on therapy.

90.2.3 **Protocol violations:**

The following protocol violations (Table Epro-090-3) occurred which the sponsor contended did not effect the safety nor the inferences of the efficacy analyses performed in this study.

Table Epro-090-3. Protocol violators from the study

Patients' Status	Treatment received		Total number
	Placebo	*Eprosartan*	*of patients*
Repeated use of prohibited concomitant medications within 2 weeks of screening visit	1 (2.2%)	1 (2.5%)	2 (2.4%)
Concomitant medication affecting BP: during placebo run-in	5 (11.1%)	2 (5.0%)	7 (8.2%)
Concomitant medication affecting BP: during treatment	5 (11.1%)	6 (15.0%)	11 (12.9%)
Mean urinary protein <300 mg or >3000 mg/24 hr at qualifying visit	2 (4.4%)	7 (17.5%)	9 (10.6%)
Creatinine ≥3 mg/dl at screening or qualifying visit	1 (2.2%)	1 (2.5%)	2 (2.4%)
Losartan or ACE inhibitor 2 weeks before screening or during study	11 (24.4%)	13 (32.5%)	24 (28.2%)

90.3 SAFETY RESULTS

90.3.1 **General considerations:**

20 patients each in the eprosartan and placebo groups reported 1 or more adverse experiences (AEs)

90.3.2 **Deaths:**

Patient # 090.001.00057, on eprosartan 300 mg q 12 h, experienced a myocardial infarction on Day 32 of double-blind treatment and died.

90.3.3 **Withdrawals due to adverse experiences:**

10 patients were withdrawn from the study (Table Epro-090-2). Two patients each on placebo and eprosartan were withdrawn because of AEs. Patient #090.001.00059 (67 yr. male on 35th day of placebo) was withdrawn due to pulmonary edema and coronary artery disease. Fatigue was the reason for withdrawal for Patient #090.001.00084 (53 yr. male on 41st day of placebo). Patient #090.001.00061 (43 yr. male on 42nd day of eprosartan) was withdrawn because of syncope. Patient # 090.001.00057 (71 yr. male on 32nd day of eprosartan) experienced a myocardial infarction and died. There was no further explanation regarding the 1 patient who was "lost to follow up" and 5 patients withdrawn for "other reasons".

90.3.4 **Serious, Non-fatal Adverse Events:**

There was one serious adverse experience during this study. Patient # 090.001.00057, on eprosartan, experienced a myocardial infarction on Day 32 of double-blind treatment, and died.

90.3.5 **Adverse Events:**

The most common AEs following both eprosartan and placebo treatment were dizziness (placebo 6.7%, eprosartan 15.0%), fatigue (placebo 4.4%, eprosartan 7.5%) and diarrhea(placebo 6.7%, eprosartan 2.5%). The AEs were mild to moderate in nature, and no patient required a dose reduction because of AEs.

90.3.6 **Laboratory findings, ECGs, Vital signs**

No randomized patient in this study exhibited abnormal heart rates. 7 patients on placebo and 13 patients on eprosartan had decreased sitting diastolic blood pressure (<60 mmHg)

Abnormal blood pressures were found in 5 patients on placebo and 10 patients on eprosartan at various times during the double-blind treatment period. While it was mentioned in text that 8 of 45 patients on placebo and 9 of 40 patients on eprosartan experienced ECG changes during the double-blind treatment period, the type of changes and data regarding PR, QT, QTc intervals, etc. were not presented.

At baseline, laboratory test (hematology and blood chemistry) values in most patients were within normal limits. The mean values for hematology and blood chemistry were within reference ranges at both baseline and endpoint, except for fasting blood glucose (consistent with the diagnosis of the patients enrolled).

Patient #090.009.00044 on placebo had low fasting blood glucose (75-84 mg/dl). Patient #090.011.00054 on eprosartan had hypoglycemia (58-85 mg/dl). Patient #090.008.0046 on eprosartan had hyperkalemia (5.7 mEq/l vs baseline of 4.0 mEq/l), and #090.001.00115 on eprosartan had neutropenia (13.4% vs baseline of 55.4%). One (#090.009.00042) of 40 patients (2.5%) who received eprosartan experienced leucopenia (WBC count 3.7 x $10^3/\mu l$ (from baseline value of 6.2 x $10^3/\mu l$) and elevated alkaline phosphatase of 141 (baseline value also 141) IU/l. One of 45 patients (2.2%) who received placebo (#090.009.00044) had elevated serum creatinine of 2.2 mg/dl (baseline creatinine = 1.9 mg/dl).

90.4 PHARMACODYNAMIC RESULTS

90.4.1 Primary Efficacy Endpoint

Overall, patients on placebo had mean percentage increase in urinary protein from base line by 34% at Week 6, while those in the eprosartan regimen had a mean percentage decrease of 1% (Table Epro-090-4). Due to lack of power (not enrolling the required 60 patients per group), the results were not significant (P=0.0597).

Table Epro-090-4. Percentage change from baseline in urinary protein at Week 6 (by ANOVA)

	All Patients		High Proteinuria Pts		From Center 001		From all other centers	
Parameter	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*
N	40	35	17	9	15	17	25	18
Mean	33.8	-1.1	22.2	-34.1	19.3	-1.3	38.4	-8.8
SE	15.7	18.8	13.3	21.1	15.1	14.2	20.9	27.3
P value	0.0597		0.0254		0.3275		0.1206	

In a subset of patients in whom the urinary proteinuria was > 1000 mg/24 hr, a statistically significant reduction (P = 0.0254) in urinary protein was observed in the eprosartan regimen compared to placebo (Table Epro-090-4). The eprosartan group showed a 34% decrease in proteinuria while the placebo group showed an increase of 22%.

Comparing Center 001 (that had 39 of the total of 85 randomized patients) to the remaining centers (Table Epro-094-4), the percent change in proteinuria from baseline of patients receiving placebo (increased by 19%) vs eprosartan (reduced by 1%) in Center 001 was less than that observed in the other centers where patients on placebo had increased proteinuria by 38% compared to patients on eprosartan who had decreased proteinuria by 9%.

90.4.2 Secondary Efficacy Endpoint

In Table Epro-090-5, urinary albumin was reduced in patients in the eprosartan group (about 5%) in contrast to patients in the placebo group in whom urinary albumin was increased (30 %), but the differences were not statistically significant (P=0.0827).

Table Epro-090-5. Percentage change from baseline in urinary albumin at Week 6 (by ANOVA)

	All Patients		From Center 001		From all other centers	
Parameter	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*	*Placebo*	*Eprosartan*
N	39	33	15	15	24	18
Mean	30.0	-4.7	16.5	-0.9	35.0	-13.9
SE	16.7	20.1	16.6	16.6	21.7	28.3
P value	0.0827		0.4644		0.1238	

Here, too, comparing Center 001 to the remaining centers (Table Epro-094-5), the percent change in albuminuria from baseline of patients receiving placebo (increased by 17%) vs eprosartan (reduced by 1%) in Center 001 was less than that observed in the other centers where patients on placebo had increased proteinuria by 35% compared to patients on eprosartan who had decreased proteinuria by 14%.

90.5 CONCLUSION

Eprosartan given in twice daily doses of 300 mg to diabetic patients with proteinuria showed no increase in the frequency or severity of adverse experiences compared to placebo. 34 of 40 (85%) eprosartan patients and 41 of 45 (91%) placebo patients completed the study. One patient died of acute myocardial infarction after 32 days of receiving 300 mg eprosartan. Ten randomized patients (6 on eprosartan and 4 on placebo) were withdrawn from the study. Four patients (2 eprosartan, 2 placebo) were withdrawn due to adverse experiences.

Analysis of the primary efficacy parameter showed that patients on placebo had mean percentage increase in urinary protein from base line by 34%, while those on eprosartan had a mean percentage decrease of 1%. Due to lack of power (not enrolling the required 60 patients/group), the results were not significant (P = 0.0597). In a subset of patients who had proteinuria > 1000 mg/24 hr, a statistically significant reduction (P = 0.0254) in urinary protein was observed in patients on eprosartan (34%) compared to an increase in proteinuria by 22% in patients receiving placebo. Urinary albumin was reduced in patients on eprosartan (by about 5%) in contrast to an increased (30 %) urinary albumin in patients on placebo, but the differences were not statistically significant (P = 0.0827).

Patients in Center 001 (that had 39 of the total of 85 randomized patients) showed less distinctive differences between placebo and eprosartan. The percent change in proteinuria from baseline of patients receiving placebo (increased by 19%) vs eprosartan (reduced by 1%) in Center 001 was less than that observed in the other centers where proteinuria increased by 38% in patients on placebo compared a reduction in proteinuria by 9% in patients on eprosartan. Also, the percent change in albuminuria from baseline of patients receiving placebo (increased by 17%) vs eprosartan (reduced by 1%) in Center 001 was less than that observed in the other centers where albuminuria increased by 35% in patients on placebo compared to a reduction in albuminuria by 14% in patients on eprosartan.

Protocol 092 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.118)*

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

92.1 STUDY PROTOCOL

92.1.1 **Title** ***A study to evaluate the bioequivalence of the proposed 300 mg commercial tablet formulation versus the clinical trials tablet and of eprosartan in healthy male volunteers***

92.1.2 **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 300 mg eprosartan intended for commercial release.

92.1.3 **Objectives**

1. To assess the bioequivalence of the new eprosartan 300 mg tablet formulation intended for commercial release with the clinical trials tablet formulation
2. To assess the safety and tolerability of eprosartan in healthy male volunteers.

92.1.4 **Study design**

The study was a randomized, open-label, two-period, period balanced crossover study of two groups (A, and B). Each subject participated in two study periods separated by at least one week, in which each received, within 30 minutes of a standard breakfast after an overnight fast, the study medication as a single oral dose of:

1. Regimen A: eprosartan 300 mg tablet (Lot# U95110) the new commercial release formulation) or
2. Regimen B: eprosartan 100 mg tablet (Lot# U94191) x 1 plus 200 mg tablet (Lot# U94190) x 1 , the clinical trials formulation)

92.1.5 **Protocol Amendments**

There were no amendments to the protocol.

92.1.6 **Population enrolled/analyzed**

48 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: All study medication was administered with 120 ml tepid water by study 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. 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 study period.

92.1.7 **Study procedures**

After an overnight fast, patients reported to the clinical pharmacology unit at 7:00 am. Assessment of baseline symptoms and vital signs, and a 12-lead ECG recording were made. A standard breakfast (cereal, milk, juice and muffin) was given at 7:30 am, and completely consumed within 20 minutes. At 8:00 am, all subjects were administered the study medication with 240 ml of tepid water. Subjects remained sitting for at least 5 hours post-dose. No food or drink was permitted 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 9-10 hours post-dose, respectively. Subjects remained in the clinical pharmacology unit for 24 hours post-dose. Blood sample (5 ml) collections for pharmacokinetics were done pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hours post-dose. Subjects returned 1 week following the last study session for safety laboratory tests. Adverse experiences (AEs) were elicited by spontaneous patient reporting, results of laboratory findings, 12-lead ECG changes and vital signs.

92.1.8 **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 1 months. Plasma concentrations of eprosartan

were determined by a method based on protein precipitation with methanol, followed by LC/MS/MS analysis employing positive-ion electrospray ionization. The lower limit of quantification (LLQ) in plasma was 20 ng/ml and the upper limit of quantification (ULQ) was 5000 ng/ml for a 50 µl 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). Because of variability in plasma concentrations in the terminal phase and/or limited measurable plasma concentrations in the terminal phase, $T_{1/2}$ and AUC(0-∞) could not be estimated.

92.1.9 **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.

92.1.10 **Sample size:**
Based on an average within-subject coefficients of variation (CVw) for AUC and Cmax to be 25.9% and 31.2%, 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 A:B for AUC and Cmax are contained within the range (0.80, 1.25). This range represents a symmetric 20% range on the ln scale.

92.1.11 **Investigator , Center and Study Dates:**
Jerry Herron, Arkansas Research Medical Testing Center, 1207 Rebsamen Park Road, Little Rock, Arkansas 72202. Dates: 17-Jan-1996 to 12-Feb-1996.

92.2 **STUDY POPULATION**

92.2.1 **Subject disposition:**
48 male subjects, 18-42 (mean = 33) years of age, weighing 63.6 to 97.7 (mean = 80.4) kg, and 165-190 (mean = 178) cm tall, were screened and randomized. 38% were black and 63% were white.

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

92.2.3 **Protocol violations:** No protocol violations were noted.

92.3. **SAFETY RESULTS**

92.3.1 **General considerations:**
There were no signs or symptoms present prior to the initial dose of the study, and only one subjected reported an adverse experience (mild heartburn) during the study.

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

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

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

92.3.5 **Adverse Events:**
One subject (#002) reported a mild heartburn 8.5 hours receiving Regimen A (commercial eprosartan 300 mg tablet) during session 1, which resolved after 1 hour and 15 minutes.

92.3.6 **Laboratory findings, ECGs, Vital signs**
No patient in this study exhibited abnormal heart rates. There were no changes in blood pressure.

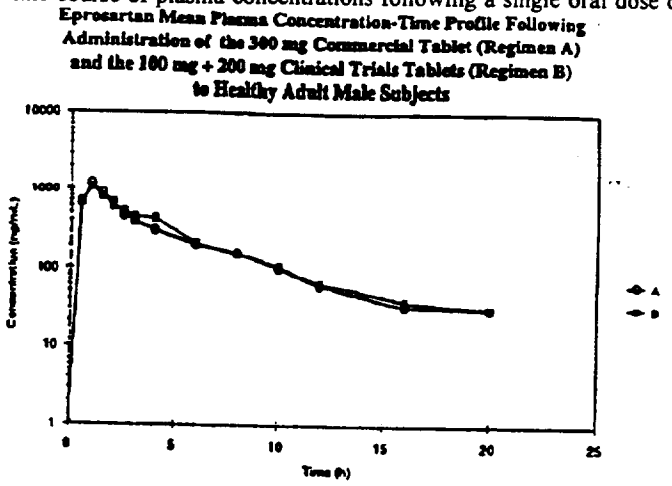
Screening ECGs showed normal intervals (including PR, QRS, QT and QTc). No post-dose ECGs were done.

Seven subjects (#002, #003, #007, #012, #026, #036 and #039) had asymptomatic elevated WBC counts at the follow-up visit approximately 7 days after the last dose of eprosartan; all returned to normal on repeat testing. Two subjects (#003 and #027) had increased WBCs in the urine (>15/hpf) at the follow-up visit.

92.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Following single oral doses of the clinical trial formulation and the new commercial release formulation of eprosartan (Figure Epro-092-1), the mean plasma concentration-time profiles were similar. Peak plasma concentrations were reached within 1 hour and plasma concentrations declined from the peak in a mono- or bi-phasic manner.

Figure Epro-092-1. Time course of plasma concentrations following a single oral dose of eprosartan



In Table Epro-092-1, AUC(0-τ) and Cmax were approximately similar between the 300 mg commercial tablet and the clinical trial 1 x 100 mg plus 1 x 200 tablets. Based on the point estimates for AUC(0-τ), Cmax and Tmax (Table Epro-092-2), the rate and extent of absorption appeared to be similar between the two formulations. However, the 90% confidence intervals (Table Epro-092-2) for the comparisons of the primary pharmacokinetic parameters (AUC(0-τ) and Cmax) for the test (Regimen A commercial release formulation relative to Regimen B - clinical trial formulation) exceed the upper end of the acceptance range 0.80 to 1.25 and therefore, the 300 mg commercial tablet formulation has not been demonstrated to be bioequivalent to the 100 mg + 200 mg clinical trials tablet formulations. The 95% confidence interval for Tmax contains 0 as a plausible value for the true median difference between regimens A and B.

Subjects #010, #015 and #042 were identified as potential statistical outliers for AUC(0-τ) based on the residual plots. Also subjects #010, #041 and #042 for Cmax based on the residual plots. A second analysis performed on a reduced data set without the outliers did not change the inferences on Cmax, but for AUC(0-τ), while the point estimate remained unchanged, the resulting 90% confidence interval became completely contained within the equivalence range 0.80 to 1.25 (Table Epro-092-2). However, a significant sequence effect was also observed for AUC(0-τ) based on the reduced data set. All conclusions are based on the full data set.

Table Epro-092-1. Pharmacokinetic values for eprosartan following single oral doses

End Point	Commercial release formulation (A)	Old clinical trial formulation (B)
AUC(0-τ) (ng.h/ml)		
Geometric Mean	3331	3217
Mean	4000	4199
Median	3544	3163
S.D.	3387	6270
Cmax (ng/ml)		
Geometric Mean	1087	1037
Mean	1279	1226
Median	1156	1025
S.D.	734	972
Tmax (hr)		
Mean	1.25	1.48
Median	1.00	1.00
S.D.	0.84	1.31

The significant sequence effect for AUC(0-τ) was examined by use of an unpaired t-test comparing Regimen A to Regimen B within each period separately, and by a paired t-test comparing Regimen A to Regimen B within each sequence separately. The point estimates of ratios of adjusted geometric means of Regimen A relative to Regimen B, and the corresponding 90% confidence intervals were calculated (Table Epro-092-3) which showed a relatively large discrepancy in adjusted geometric means between sequence AB and BA, suggesting a true sequence effect.

Table Epro-092-2. Point Estimates and 90% confidence intervals of comparisons of eprosartan formulations.

Parameter	Comparison	Point Estimate	90% Confidence Interval
AUC(0-τ)†	A:B	1.04	(0.84, 1.28)
*AUC(0-τ)†**	A:B	1.04	(0.90, 1.20)
Cmax†	A:B	1.05	(0.86, 1.27)
*Cmax†***	A:B	1.10	(0.94, 1.29)
Tmax§	A-B	0.00 h	(-0.25 h, 0.25 h)

† Data presented as the ratio of the geometric means for A:B; § Data presented as the median difference (A-B) and 95% C.I.; * Subjects #010, #015, #041 and #042 removed; ** Subjects #010, #041 and #042 removed

Table Epro-092-3. Point Estimates and 90% confidence intervals for AUC(0-τ) using the reduced data set

Parameter	Period I Adjusted Geometric Means	Period II Adjusted Geometric Means	90% Confidence Interval
Sequence AB	2944 (A)	2954 (B)	1.00 (0.79, 1.26)
Sequence BA	3379 (B)	3679 (A)	1.09 (0.90, 1.32)
PE and 90% C.I.	0.87 (0.70, 1.09)	1.25 (1.04, 1.50)	

AUC(0-τ) reduced data set: Subjects #010, #015, #041 and #042 removed

(Note: The calculated between-subject coefficients of variation for ln-transformed AUC(0-τ) were 65% for both regimens for the full data set, and 47% and 38% for Regimen A and Regimen B, respectively, for the reduced data set. The between-subject coefficients of variation for ln-transformed Cmax were 67% and 61% for Regimens A and B, respectively, for the full data set, and 60% and 43% for Regimens A and B, respectively, for the reduced data set. The calculated within-subject coefficients of variation for AUC(0-τ) and Cmax were 68% and 62%, respectively, for the full data sets, and 42% for AUC(0-τ) and 47% for Cmax for the reduced data set. These suggest a larger variability than that encountered in previous studies. Based on these observed coefficients of variations, a sample size of 200 and 166 subjects would have been needed to provide at least 90% power to demonstrate equivalence for AUC(0-τ) and Cmax, respectively.)

Despite the increased variability due to statistical outliers, there still remained an inadequacy in terms of sample size for this study. The reason that the bioequivalence was not demonstrated may be in part due to lack of statistical power which did not allow differentiation of a real difference in bioavailability between the formulations.

92.5 CONCLUSION

Single oral dose administration commercial release formulation of eprosartan (300 mg) and clinical trial formulation (1 x 100 mg + 1 x 200 mg) to healthy male volunteers did not show any significant differences in adverse experiences. There were no abnormal laboratory values of potential safety concern.

Following single oral doses of the clinical trial formulation and the new commercial release formulation of eprosartan, the mean plasma concentration-time profiles were similar. Peak plasma concentrations were reached within 1 hour and plasma concentrations declined from the peak in a mono- or bi-phasic manner.

Based on the point estimates for AUC(0-τ), Cmax and Tmax of the intent-to-treat population, the rate and extent of absorption appeared to be similar between the two formulations. However, the 90% confidence intervals for AUC(0-τ) and Cmax exceed the upper end of the acceptance range 0.80 to 1.25 suggesting that the 300 mg commercial tablet formulation cannot be considered bioequivalent to the 100 mg + 200 mg clinical trials tablet formulations. The reason that the bioequivalence was not demonstrated may be in part due to lack of statistical power from an inadequate sample size in the presence of large between-subject and within-subject variations.

Protocol 094 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.099/100)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *10-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *11-Jun-1997*

94.1 STUDY PROTOCOL

94.1.1 Title

An investigation of the effects of fluconazole on the pharmacokinetics, urine uric acid excretion, safety and tolerability of eprosartan and losartan in healthy male volunteers

94.1.2 Rationale

Losartan, an Angiotensin II AT_1 receptor, is associated with increased urinary excretion of uric acid, and undergoes extensive hepatic metabolism via the cytochrome P450 system (CYP2C9 and CYP3A4). Eprosartan is not associated with increase uric acid excretion, and is predominately eliminated by excretion of unchanged drug. Fluconazole is a known inhibitor of CYP2C9, and increases plasma concentrations of drugs that are metabolized via CYP2C9 such as warfarin, phenytoin, tolbutamide, etc. This study was conducted to evaluate the effects of fluconazole on the metabolism, pharmacokinetics and urine uric acid excretion rates of eprosartan and losartan.

94.1.3 Objectives

To estimate the effect of steady state fluconazole on the pharmacokinetics of repeat oral doses of eprosartan, losartan and E-3174 and to evaluate the effect of single and repeat oral doses of eprosartan and losartan, with and without fluconazole, on urine uric acid excretion.

94.1.4 Study design

The study was an open-label, placebo-controlled, parallel group study. Subjects were randomly assigned to receive either eprosartan, losartan or placebo for 20 days (Days 1-20) along with fluconazole treatment on Days 11-20:

1. Regimen A: Eprosartan 300 mg tablets, (Lot# U95110) twice daily x 20 days
2. Regimen B: Cozaar® (Merck), 50 mg tablets (Lot# X96036) x 2, (100 mg) once daily x 20 days
3. Regimen C: Placebo (Lot# U95146) once daily x 20 days
4. Fluconazole (Diflucan®) 200 mg tablets (Lot# X96029) orally once daily from Day 11 through Day 20 to all subjects.

94.1.5 Protocol Amendments

There were no amendments to the protocol.

94.1.6 Population enrolled/analyzed

48 healthy, non-smoking, adult male volunteers 18-50 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.

Compliance: All study medication was administered with 60 ml tepid water by study personnel. On Days 2-9 and 11-19, subjects who received eprosartan were instructed to return to the clinical research unit at approximately 12 hour intervals, while subjects who received losartan or placebo were instructed to return at approximately 24 hours intervals to receive their dose of study medication. On Days 1, 10 and 20, subjects were given study medications as inpatients under the same schedule.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history and a physical examination. 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 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.

94.1.7 Study procedures

Subjects reported at 5:00 p.m. the night before Day 0. After dinner at 6:00 p.m., they underwent an overnight fast. The next morning at 7 am, blood and urine collections were made. Assessment of baseline symptoms and vital signs was made and the study medication administered orally with 60 ml tepid water. (It was not mentioned in the protocol or study report when breakfast was given.) Every day, subjects eat identical meals (lunch, dinner and snack) consisting of at least 1 meat dish, with 240 ml of water. All fluids were restricted except during meals.

Subjects remained in the clinical pharmacology unit for 24 hours after dosing. No vigorous exercise was permitted. Sitting blood pressure and pulse measurements were obtained prior to dosing and at 2, 4, and 6 hours post-dose.

Blood sample (5 ml) collections for uric acid and creatinine concentrations were done pre-dose and at 0, 1, 2, 3, 4, 5, 6, 12, and 24 hours post-dose. Urine samples were also collected coinciding with the blood sample collections. The evening dose of eprosartan was given 12 hours after the morning dose. After the collection of the 24 hour sample and administration of the next morning dose of study medication, the subject was discharged from CRU.

Subjects returned on the evening of study Day 9. On Day 10, they underwent the same procedure as Day 1, together with blood samples for pharmacokinetic analysis drawn pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and - for losartan regimen - 24 hours. Placebo treated subjects did not have blood samples drawn for pharmacokinetics. Urine collections were made as before. Subjects were discharged on the morning of Day 11. Medication with fluconazole was started. The procedures were repeated with subjects reporting on the evening of Day 19.

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

94.1.8 **Pharmacokinetic procedures:**

Blood samples for pharmacokinetics were centrifuged at 4°C and 2300 rpm for 10 minutes, 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) in plasma for eprosartan was 10 ng/ml for a 0.5 ml aliquot, and for losartan LLQ was 5.0 ng/ml for a 1.0 ml aliquot. Urine and serum uric acid were measured by a spectrophotometric method utilizing the uricase reaction, and creatinine by the modified Jaffe method.

Concentration-time data analysis was performed using a non-compartmental pharmacokinetic analysis program to obtain Cmax, Tmax, the apparent terminal elimination rate constant (λ), $T_{1/2}$, AUC(0-τ), AUC(0-∞). All non quantifiable (NQ) values before the first measurable concentration were set to zero, and all NQ values after the last measurable concentration were removed from computation if <50% of subject had measurable concentrations, or, if > 50% of subjects had measurable concentrations, any NQ values were set to 1/2 LLQ (5 ng/ml for eprosartan, 2.5 ng/ml for losartan and E-3174).

94.1.9 **Endpoints:**

Pharmacodynamic endpoints were undissociated urine uric acid, UUA/UCr, total excretion of urine uric acid and urine creatinine, and serum uric acid concentrations of Days 0, 1, 10 and 20. The pharmacokinetic endpoints were the effect of steady-state fluconazole on the pharmacokinetics of repeated oral doses of eprosartan, losartan and E-3174 (Day 20 vs Day 10) using AUC(0-τ) and Cmax.

94.1.10 **Sample size:**

A sample size of 12 per regimen was estimated to provide 90% power to detect differences of at least 30% between Days 20 and 10 in the losartan and eprosartan regimens with a Type I error rate of 5% on a two-tailed procedure.

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

David Kazierad, Pharm. D., Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York. Dates: 19-Feb-1996 to 06-Apr-1996.

94.2 STUDY POPULATION

94.2.1 **Subject disposition:**

91 male subjects were screened; 43 failed to meet entrance criteria or withdrew prior to enrollment. 48 subjects 19-50 (mean = 32) years of age, weighing 54.5 to 100.0 (mean = 81.2) kg, and 154.9-190.5 (mean = 178.2) cm tall, were randomized and received at least one dose of study medication.

94.2.2 **Withdrawals:**

Table Epro-094-1. Subjects withdrawn from the study

Subject Status	Treatment received			Total number
	Regimen A	*Regimen B*	*Regimen C*	*of subjects*
Completed study	14	16	14	44
Withdrawn				
Adverse experience	1 #026	0	0	1
Protocol violation	1 #008	0	2 #017 #047	3
Total withdrawn	2	0	2	4

There were 4 withdrawals (Table Epro-094-1): Subject #008 did not return after receiving 3 doses of eprosartan. Subject #017 was on placebo and withdrew on Day 18 due to a death in his family. Subject #047 was withdrawn after the 12th day due to noncompliance. Subject #026 was withdrawn after receiving eprosartan 300 mg bid for 10 days followed by eprosartan 300 mg bid plus fluconazole 200 mg qd for 2 days when he developed an adverse experience (moderate insomnia, moderate nausea and mild diarrhea).

94.2.3 **Protocol violations:**

Two subjects (#028 and #046) took prohibited medications (Polymixin B (Polytrim®) eye drops and multivitamin, respectively), which were not thought to affect the results of the study.
Non-compliance, due to absence at dosing sessions, was noted for the following subjects:

Subject #024: Losartan and fluconazole not administered on Day 12
Subject #029: Morning dose of eprosartan not administered on Day 6
Subject #047: Placebo not administered on Day 7, and placebo and fluconazole not administered on Day 12.

94.3. SAFETY RESULTS

94.3.1 **General considerations:**

Six subjects experienced baseline events prior to dosing which dissolved without treatment except the conjunctivitis in subject #028.

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

94.3.3 **Withdrawals:**

There were one withdrawal due to adverse experience. Subject #026 was withdrawn after receiving eprosartan 300 mg bid for 10 days followed by eprosartan 300 mg bid plus fluconazole 200 mg qd for 2 days when he developed an adverse experience (moderate insomnia, moderate nausea and mild diarrhea). His adverse experiences resolved 3 days after discontinuation of study medications.

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

94.3.5 **Adverse events:**

53 adverse events were reported for 28 subjects. The most frequent AEs were upper respiratory tract infection in 11 subjects (4 each with eprosartan and losartan, 2 with placebo and 1 with placebo and fluconazole), and headache in 6 subjects (2 with losartan, 1 with losartan and fluconazole, and 3 with placebo). All AEs were mild to moderate in nature, none required treatment, and all resolved spontaneously (except the untreated, ongoing ear disorder in Subject #018 during dosing with eprosartan and fluconazole) including the mild transient syncopal episodes reported by Subject #010 after receiving eprosartan and fluconazole, and by Subject #016 after receiving losartan and fluconazole, and the insomnia associated with withdrawal for Subject #026.

94.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates. While there were 21 events of change in blood pressure (increase or decrease in systolic or diastolic) they were asymptomatic and transient.

Two laboratory values of potential concern were observed in one patient: microscopic hematuria (15-25 rbc/hpf) attributable to subject's history of kidney stones, and elevated blood glucose (155 mg/dl) which could be related to borderline diabetes. Both laboratory parameters were normal at a repeat laboratory analysis.

94.4. PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

94.4.1 **Primary pharmacodynamic endpoints:**

Co-administration of fluconazole with eprosartan, losartan or placebo was not associated with significant differences in the level of undissociated uric acid. However, there was a large number of urine collections with undissociated uric acid concentrations exceeding the equilibrium concentration (95 mg/L) of uric acid (36-59% of all collections contained undissociated uric acid > 95 mg/L, and 88-100% of subjects had at least one collection with an undissociated urine uric acid concentration > 95 mg/L). These results were not consistent with those from a previous study involving normal subjects, and could be due to fluid restriction imposed on Days 0, 1, 10 and 20 that could have led to concentrated urine samples.

UUA/UCr ratios were similar in all regimens on Day 0. UUA/UCr ratios did not change following eprosartan in single or repeat dose, or co-administered with fluconazole compared to the placebo regimen. Losartan, however,

was associated with a statistically significant increase in UUA/UCr ratio (compared to placebo) following a single dose (Day 1), repeat dose (Day 10), or repeat co-administration of losartan and fluconazole (Table Epro-094-2).

Table Epro-094-2. Mean (SD) Observed Maximum UUA/UCr

Regimen	Day 0	Day 1	Day 10	Day 20
A	0.486 (0.080)	0.544 (0.097)	0.493 (0.086)	0.430 (0.096)
B	0.470 (0.089)	0.761 (0.199)	0.587 (0.139)	0.555 (0.200)
C	0.463 (0.094)	0.468 (0.065)	0.455 (0.091)	0.419 (0.064)

The mean total excretion of urine uric acid and creatinine were similar between regimens on Days 0, 1, 10 and 20, with no differences between regimens following repeat dosing of eprosartan or losartan with or without co-administration of fluconazole (Table Epro-094-3). This may be due to lack of completeness of 24-h urine collections.

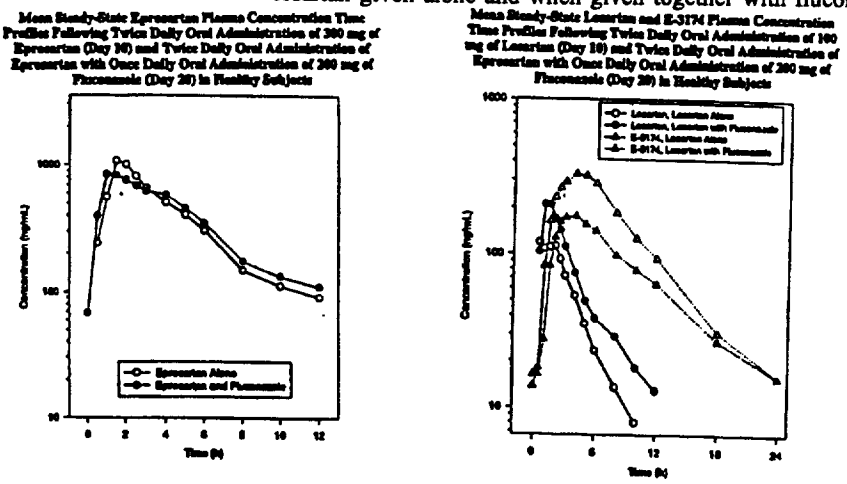
Table Epro-094-3. Mean (SD) Total Daily Excretion of Urine Uric Acid (mg) and Urine Creatinine (mg)

Regimen	Day 0	Day 1	Day 10	Day 20
Urine Uric Acid (mg)				
A	625.2 (151.0)	689.6 (144.5)	663.7 (173.7)	626.0 (161.3)
B	672.6 (134.6)	734.4 (220.7)	662.7 (236.5)	686.8 (229.2)
C	610.2 (208.7)	702.5 (198.2)	620.9 (161.1)	644.7 (146.2)
Urine Creatinine (mg)				
A	1748.3 (400.5)	1862.5 (392.3)	1798.2 (545.0)	1945.8 (446.1)
B	1887.5 (353.9)	1784.9 (405.7)	1771.2 (500.1)	1921.5 (572.3)
C	1818.3 (424.1)	1959.1 (465.3)	1733.6 (454.4)	1841.0 (472.5)

Losartan and eprosartan lower the mean serum uric acid concentrations slightly (vs to placebo). Co-administration with fluconazole did not influence the effects of either eprosartan or losartan on mean serum uric acid concentrations.

4.2 Primary pharmacokinetic endpoints

Figure Epro-094-1. Steady state plasma concentration-time profiles for eprosartan and losartan given alone and when given together with fluconazole



The steady state concentration-time data (Fig Epro-094-1) following eprosartan (Day 10) and eprosartan plus fluconazole (Day 20) showed that the mean concentration-time profiles followed a similar course, with plasma concentrations declining in a mono- or bi-phasic manner and measurable for 12 hours. The steady state concentration-time data following losartan (Day 10) and losartan plus fluconazole showed higher losartan concentrations when fluconazole was added compared to losartan alone, whereas E-3174 concentrations were lower when losartan was administered with fluconazole than losartan was given alone.

In Table Epro-094-4, the AUC(0-τ) for eprosartan increased by 4% following administration of fluconazole together with eprosartan, and the Cmax decreased by 11%. However, the changes were within the 95% confidence intervals (Table Epro-094-5), and therefore, there were no substantial difference in pharmacokinetics when eprosartan was administered alone and with fluconazole. Following administration of losartan with fluconazole, losartan AUC(0-τ) was increased by 66% (Table Epro-094-4) which was statistically significant (the 95% confidence intervals did not

contain the value 1, Table Epro-094-5), and the Cmax increased 30%. On the other hand, E-3174 AUC(0-τ) and Cmax were decreased by 43% and 56%, respectively (Table Epro-094-4), which was statistically significant (the 95% confidence intervals did not contain the value 1, Table Epro-094-5). These findings suggest that losartan metabolism was inhibited by fluconazole, a CYP2C9 inhibitor whereas eprosartan pharmacokinetics were not changed by fluconazole.

Table Epro-094-4. Pharmacokinetic values for eprosartan, losartan and E-3174 singly and together with fluconazole.

	Eprosartan	Eprosartan+ Fluconazole	Losartan	Losartan + Fluconazole	E-3174	E-3174 + Fluconazole
	Day 10	*Day 20*	*Day 10*	*Day 20*	*Day 10*	*Day 20*
AUC(0-τ) (ng.h/ml)						
Geometric Mean	3878	4046	471	783	2771	1574
Mean	4331	4505	483	818	2857	1676
Median	3880	4479	481	755	2552	1461
S.D.	1967	2096	114	261	770	620
Cmax (ng/ml)						
Geometric Mean	1134	1013	220.2	286.2	406.6	178.3
Mean	1254	1133	246.2	322.8	425.1	195.3
Median	1271	1165	221.0	302.0	430.0	173.0
S.D.	547	464	124.9	157.3	112.3	85.5
Tmax (h)						
Mean	1.86	1.82	1.62	1.50	3.69	3.76
Median	1.74	1.50	1.50	1.50	3.00	3.50
S.D.	0.79	1.10	0.99	0.68	1.57	1.24

Table Epro-094-5. Point Estimates and 95% confidence Intervals of comparisons of eprosartan, losartan and E-3174

Parameter	Comparison	Point Estimate	95% Confidence Interval
Eprosartan			
AUC(0-τ)†	Day 20 : Day 10	1.04	0.87, 1.25
Cmax†	Day 20 : Day 10	0.89	0.67, 1.19
Tmax§	Day 20 : Day 10	0.00 h	-0.52, 0.50 h
Losartan			
AUC(0-τ)†	Day 20 : Day 10	1.66	1.44, 1.92
Cmax†	Day 20 : Day 10	1.30	0.92, 1.84
Tmax§	Day 20 : Day 10	-0.30 h	-0.75, 0.50 h
E-3174			
AUC(0-τ)†	Day 20 : Day 10	0.57	0.52, 0.62
Cmax†	Day 20 : Day 10	0.44	0.39, 0.49
Tmax§	Day 20 : Day 10	0.25 h	-0.74, 0.99 h

† Data presented as the ratio of the geometric means for Day 20: Day 10.
§ Data presented as the estimated median difference (Day 20 - Day 10) and 95% confidence intervals

5. CONCLUSION

Oral administration of eprosartan and losartan to healthy male volunteers in this study did not show any serious adverse experiences apart from one subject who withdrew due to insomnia. There were no abnormal laboratory values of potential safety concern.

Eprosartan did not exhibit significant uricosuric effect relative to placebo after single, repeat or repeat combination dosing with fluconazole. Losartan alone in a single dose or repeat doses, or co-administered with fluconazole significantly increased urine uric acid excretion (UUA/UCr ratio) compared to placebo or eprosartan.

Co-administration of fluconazole with losartan significantly increased the steady-state AUC of losartan and decreased the steady-state AUC of E-3174, which was presumed attributable to inhibition of CYP2C9 of the Cytochrome P450 system. Fluconazole administration did not alter the steady-state pharmacokinetics of eprosartan (consistent with the fact that eprosartan does not undergo oxidative metabolism in humans).

Protocol 095 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.101/102)*

DATE OF CORRESPONDENCE: *11-Oct-1996* DATE ASSIGNED: *11-Jun-1997*
DATE RECEIVED: *18-Oct-1996* DATE COMPLETED *12-Jun-1997*

95.1. STUDY PROTOCOL

95.1.1 **Title** ***An investigation of the effects of ketoconazole on the pharmacokinetics, urine uric acid excretion, safety and tolerability of eprosartan and losartan in healthy male volunteers***

95.1.2 **Rationale**

Losartan, an Angiotensin II AT_1 receptor, is associated with increased urinary excretion of uric acid, and undergoes extensive hepatic metabolism via the cytochrome P450 system (CYP2C9 and CYP3A4). Eprosartan is not associated with increase uric acid excretion, and is predominately eliminated by excretion of unchanged drug. Ketoconazole is a known inhibitor of CYP3A4, and increases plasma concentrations of drugs that are metabolized via CYP3A4 such as terfenadine, midazolam, etc. This study was conducted to evaluate the effects of ketoconazole on the metabolism, pharmacokinetics and urine uric acid excretion rates of eprosartan and losartan.

95.1.3 **Objectives**

To estimate the effect of steady state ketoconazole on the pharmacokinetics of repeat oral doses of eprosartan, losartan and E-3174 and to evaluate the effect of single and repeat oral doses of eprosartan and losartan, with and without ketoconazole, on urine uric acid excretion.

95.1.4 **Study design**

The study was an open-label, placebo-controlled, parallel group study. Subjects were randomly assigned to receive either eprosartan, losartan or placebo for 10 days (Days 1-10) along with ketoconazole treatment on Days 6-10:

1. Regimen A: Eprosartan 300 mg tablets, (Lot# U95110) twice daily x 10 days
2. Regimen B: Cozaar® (Merck), 50 mg tablets (Lot# X96036) x 2, (100 mg) once daily x 10 days
3. Regimen C: Placebo (Lot# U95146) once daily x 10 days
4. Ketoconazole (Nizoral®) 200 mg tablets (Lot# X96028) orally once daily from Day 6 through Day 10 to all subjects.

95.1.5 **Protocol Amendments**

There were no amendments to the protocol.

95.1.6 **Population enrolled/analyzed**

82 healthy, non-smoking, adult male volunteers 18-50 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 screened for enrollment.

Compliance: All study medication was administered with 60 ml tepid water by nursing staff, the oral cavity being examined to assure ingestion of medication. On Days 2-4 and 6-9, subjects who received eprosartan were instructed to return to the clinical research unit at approximately 12 hour intervals, while subjects who received losartan or placebo were instructed to return at approximately 24 hours intervals to receive their dose of study medication. On Days 0, 1, 5 and 10, subjects were given study medications as inpatients under the same schedule.

Pre-study screening: The screening visit (30 days prior to start of the study) included a complete medical and medication history and a physical examination. 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 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.

95.1.7 **Study procedures**

Subjects reported at 5:00 p.m. the night before Day 0. After dinner at 6:00 p.m., they underwent an overnight fast. The next morning at 7 am, blood and urine collections were made. Assessment of baseline symptoms and vital signs was made and the study medication administered orally with 60 ml tepid water. (It was not mentioned in the protocol or study report when breakfast was given.) Every day, subjects eat identical meals (lunch, dinner and snack) consisting of at least 1 meat dish, with 240 ml of water. All fluids were restricted except during meals.

Subjects remained in the clinical pharmacology unit for 24 hours after dosing. No vigorous exercise was permitted. Sitting blood pressure and pulse measurements were obtained prior to dosing and at 2, 4, and 6 hours post-dose. Blood sample (5 ml) collections for uric acid and creatinine concentrations were done prior to dose administration and at 0, 1, 2, 3, 4, 5, 6, 12, and 24 hours following dosing. Urine samples were also collected coinciding with the blood sample collections. The evening dose of eprosartan was given 12 hours after the morning dose. After the collection of the 24 hour sample and administration of the next morning dose of study medication, the subject was discharged from CRU.

Subjects returned on the evening of study Day 4 and on Day 5, underwent the same procedure as Day 0, together with blood samples for pharmacokinetic analysis at the following periods: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and - for losartan regimen - 18 and 24 hours. Placebo treated subjects did not have blood samples for pharmacokinetics drawn. Urine collections were made as mentioned before. Subjects were discharged on the morning of Day 6. Medication with ketoconazole was started. The procedures were repeated with subjects reporting on the evening of Day 9.

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

95.1.8 **Pharmacokinetic procedures**:
Blood samples for pharmacokinetics were centrifuged at 4°C and 2300 rpm for 10 minutes, 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) in plasma for eprosartan was 10 ng/ml for a 0.5 ml aliquot, and for losartan LLQ was 5.0 ng/ml for a 1.0 ml aliquot. Urine and serum uric acid were measured by a spectrophotometric method utilizing the uricase reaction, and creatinine by the modified Jaffe method.

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-∞). All non quantifiable (NQ) values before the first measurable concentration were set to zero, and all NQ values after the last measurable concentration were removed from computation if <50% of subject had measurable concentrations, or, if > 50% of subjects had measurable concentrations, any NQ values were set to 1/2 LLQ (5 ng/ml for eprosartan, 2.5 ng/ml for losartan and E-3174).

95.1.9 **Endpoints:**
Pharmacodynamic endpoints were undissociated urine uric acid, UUA/UCr, total excretion of urine uric acid and urine creatinine, and serum uric acid concentrations on Days 0, 1, 5 and 10. The pharmacokinetic endpoints were the effect of steady-state ketoconazole on the pharmacokinetics of repeated oral doses of eprosartan, losartan and E-3174 (Day 10 vs Day 5) using AUC(0-τ) and Cmax.

95.1.10 **Sample size:**
A sample size of 12 per regimen was estimated to provide 90% power to detect differences of at least 30% between Days 10 and 5 in the losartan and eprosartan regimens with a Type I error rate of 5% on a two-tailed procedure.

95.1.11 **Investigator , Center and Study Dates:**
David Kazierad, Pharm. D., Clinical Pharmacokinetics Laboratory, Millard Fillmore Hospital, Buffalo, New York.
Dates: 13-Feb-1996 to 18-Mar-1996

95.2 STUDY POPULATION

95.2.1 **Subject disposition:**
82 male subjects were screened; 34 failed to meet entrance criteria or withdrew prior to enrollment, and 2 more withdrew before dosing. 46 subjects 18-47 (mean = 31) years of age, weighing 57.7 to 99.5 (mean = 80.0) kg, and 165.1-193.0 (mean = 177.6) cm tall, were randomized and received at least one dose of study medication.

95.2.2 **Withdrawals:**
There were 6 withdrawals (Table Epro-095-1). Subjects #022 and #034 were withdrawn prior to dosing. Subject #002 received eprosartan for 6 days plus a single dose of ketoconazole on Day 6 before being withdrawn due to noncompliance. Subject #003 received losartan daily and ketoconazole from Days 6-9 and was withdrawn due to a

family crisis. Subject #012 received 2 doses of placebo and was withdrawn due to a work schedule conflict. Subject #019 was withdrawn due to an adverse experience (moderate nausea and vomiting) on Day 8 in Regimen A. All data for these subjects were included in pharmacodynamic analysis but not in the pharmacokinetic analysis.

Table Epro-095-1. Subjects withdrawn from the study

Subject Status	Treatment received			Total number
	Regimen A	*Regimen B*	*Regimen C*	*of subjects*
Completed study	13	14	15	42
Withdrawn				
Adverse experience	1 #019	0	0	1
Protocol violation	1 #002	1 #003	1 #012	3
Total withdrawn	2	1	1	4

95.2.3 **Protocol violations:**

Two subjects (#029 and #037) took prohibited medications (250 mg cephalexin orally for 2 days for prophylaxis of a hand wound, and 4-Way Nasal Spray® (Bristol-Myers) intranasally for cold symptoms, respectively), and Subject #032 ate a chocolate brownie within 24 hours of Day 0. Subject #045 had microscopic pyuria which resolved without treatment, and Subject #037 had elevated blood glucose (146 mg/dl).

Non-compliance, due to absence at dosing sessions, was noted for the following subjects:

Subject #002: Morning dose of eprosartan not administered on Day 4
Subject #029: Placebo not administered on Day 4, and placebo and ketoconazole not administered on Day 8
Subject #039: Placebo and ketoconazole not administered on Day 7
Subject #045: Evening doses of eprosartan not administered on Days 2 and 6.

95.3 SAFETY RESULTS

95.3.1 **General considerations:**

Four subjects experienced mild baseline events prior to dosing which dissolved without treatment after dosing except the mild rash experienced by Subject #045.

95.3.2 **Deaths:**

There were no deaths during this study.

95.3.3 **Withdrawals:**

There were one withdrawal due to adverse experience. Subject #019 was withdrawn after receiving eprosartan 300 mg bid for 8 days and ketoconazole 200 mg qd on Days 6-8 when he developed moderate nausea, vomiting and a mild headache and mild diarrhea, all of which were resolved the day after the withdrawal.

95.3.4 **Serious, non-fatal adverse events:**

There was no serious non-fatal adverse experience during this study.

95.3.5 **Adverse events:**

14 adverse events were reported for 11 subjects. The most frequent AE was headache (1 during eprosartan plus ketoconazole, 2 during losartan plus ketoconazole and 1 during placebo), followed by diarrhea (1 during eprosartan plus ketoconazole, 1 during losartan), upper respiratory tract infection (1 during eprosartan and 1 during eprosartan plus ketoconazole), dizziness (1 on eprosartan), vomiting (1 on eprosartan plus ketoconazole) and back pain (1 on placebo). All AEs were mild to moderate in nature, none required treatment, and all resolved spontaneously.

95.3.6 **Laboratory findings, ECGs, Vital signs**

No patient in this study exhibited abnormal heart rates. While there were 54 events of change (6 increased and 48 decrease in systolic or diastolic) blood pressure they were asymptomatic and transient.

One laboratory value of potential concern were observed in one patient: elevated blood glucose (146 mg/dl) which could be related to borderline diabetes.

95.4 PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

95.4.1 Primary pharmacodynamic endpoints:

Co-administration of ketoconazole with eprosartan, losartan or placebo was not associated with significant differences in the level of undissociated uric acid. However, there was a large number of urine collections with undissociated uric acid concentrations exceeding the equilibrium concentration (95 mg/L) of uric acid (33-54% of all collections contained undissociated uric acid > 95 mg/L, and 80-100% of subjects had at least one collection with an undissociated urine uric acid concentration > 95 mg/L). These results were not consistent with those from a previous study involving normal subjects, and could be due to fluid restriction imposed on Days 0, 1, 5 and 10 that could have led to concentrated urine samples.

UUA/UCr ratios were similar in all regimens on Day 0. UUA/UCr ratios did not change following eprosartan in single or repeat dose, or co-administered with ketoconazole compared to the placebo regimen (Table Epro-095-2). Losartan was associated with a statistically significant increase in UUA/UCr ratio (compared to placebo or eprosartan) following a single dose (Day 1), repeat dose (Day 5), or repeat co-administration of losartan and ketoconazole (Day 10).

Table Epro-095-2. Mean (SD) Observed Maximum UUA/UCr

Regimen	Day 0	Day 1	Day 5	Day 10
A	0.437 (0.070)	0.503 (0.125)	0.449 (0.084)	0.461 (0.095)
B	0.474 (0.093)	0.760 (0.147)	0.623 (0.188)	0.627 (0.238)
C	0.401 (0.089)	0.427 (0.041)	0.442 (0.068)	0.435 (0.105)

The mean total excretion of urine uric acid and creatinine were similar between regimens on Days 0, 1, 5 and 10, following repeat dosing of losartan or eprosartan with or without co-administration of ketoconazole (Table Epro-095-3). This finding may be due to lack of completeness of urine collections over a 24 hour period.

Table Epro-095-3. Mean (SD) Total Daily Excretion of Urine Uric Acid (mg) and Urine Creatinine (mg)

Regimen	Day 0	Day 1	Day 5	Day 10
Urine Uric Acid (mg)				
A	542.8 (107.6)	674.3 (208.9)	699.0 (234.0)	694.3 (239.6)
B	565.7 (163.6)	716.2 (212.6)	686.0 (184.5)	646.0 (248.2)
C	545.5 (146.6)	621.6 (162.5)	689.0 (186.3)	601.4 (192.1)
Urine Creatinine (mg)				
A	1698.0 (371.6)	1812.2 (476.0)	1947.0 (421.8)	1973.7 (463.6)
B	1757.3 (366.9)	1691.2 (462.2)	1833.7 (424.9)	1760.0 (587.7)
C	1746.8 (306.1)	1777.5 (402.2)	1949.6 (450.8)	1851.8 (606.6)

Losartan lowered the mean serum uric acid concentrations (compared to placebo) after a single dose (Day 1) and following repeat dose (Day 5). Eprosartan did not lower mean serum uric acid relative to placebo. Co-administration with ketoconazole did not influence the effects of either eprosartan or losartan on mean serum uric acid levels.

95.4.2 Primary pharmacokinetic endpoints

Following eprosartan or losartan (Day 5), and eprosartan or losartan plus ketoconazole (Day 10), the mean concentration-time profiles of eprosartan, losartan and E-3174 (Fig Epro-095-1) followed a similar course, with maximum plasma concentrations achieved at 1.5 hours, 2 hours and 3-4 hours, respectively, and then declining in an apparent biexponential manner over 12 hours.

In Table Epro-095-4, steady state AUC(0-τ) and Cmax for eprosartan were 3% and 20% lower, respectively, following administration of ketoconazole compared with eprosartan alone. However, the changes were within the 95% confidence intervals (Table Epro-095-5), and therefore, there were no substantial difference in pharmacokinetics when eprosartan was administered alone and with ketoconazole. Following administration of losartan with fluconazole, losartan AUC(0-τ) was 1% higher (Table Epro-095-4) and the Cmax was 9% lower, being within the 95% confidence intervals (Table Epro-095-5) with no statistically significant differences when losartan was administered alone and with ketoconazole. E-3174 AUC(0-τ) and Cmax were 7% and 13% higher, respectively

(Table Epro-09-4) following co-administration of losartan with ketoconazole compared to losartan alone. This was not statistically significant (being within the 95% confidence intervals, Table Epro-095-5). These findings suggest that metabolism of eprosartan and losartan was not altered by ketoconazole, a CYP3A4 inhibitor, and also that in humans, CYP3A4 does not play a predominant role in the first pass or systemic conversion of losartan to E-3174.

Figure Epro-095-1. Steady state plasma concentration-time profiles for eprosartan and losartan given alone and when given together with ketoconazole

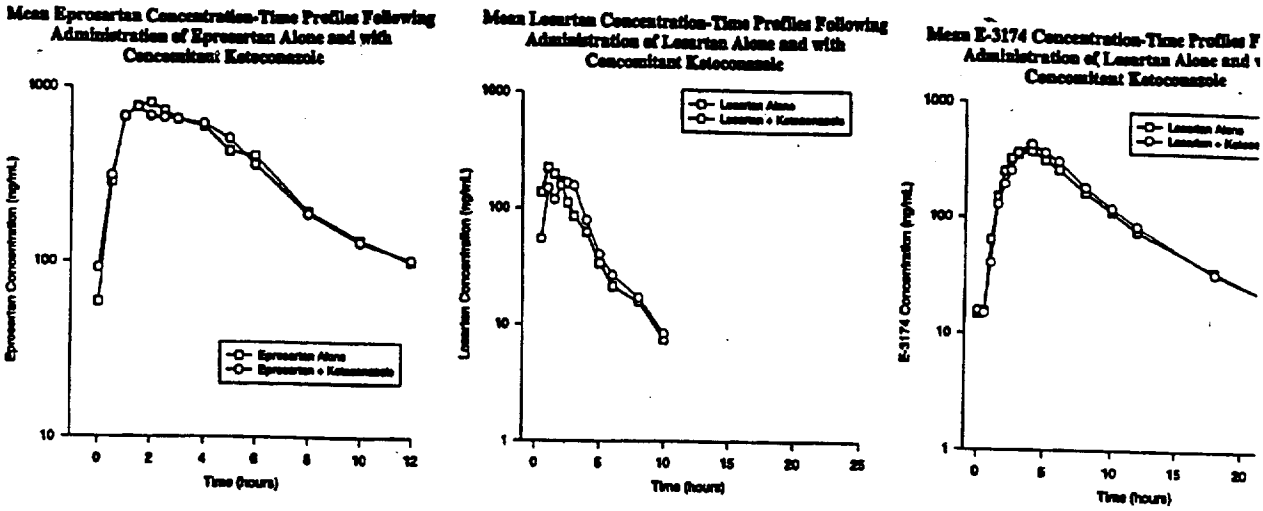


Table Epro-095-4. Pharmacokinetic values for eprosartan, losartan and E-3174 singly and together with ketoconazole

	Eprosartan	Eprosartan+ Ketoconazole	Losartan	Losartan + Ketoconazole	E-3174	E-3174 + Ketoconazole
	Day 5	*Day 10*	*Day 5*	*Day 10*	*Day 5*	*Day 10*
AUC(0-τ) (ng.h/ml)						
Geometric Mean	4230	4107	580	585	2660	2846
Mean	4470	4406	633	627	2817	2986
Median	4006	3671	591	588	2906	2888
S.D.	1686	1852	255	241	939	949
Cmax (ng/ml)						
Geometric Mean	1164	929	296.5	269.9	393	444
Mean	1193	1028	336.8	300.1	431	478
Median	1191	981	311.5	281.5	425	422
S.D.	285	537	167.0	143.4	187	205
Tmax (h)						
Mean	1.81	2.19	1.78	1.93	3.21	3.54
Median	1.50	1.50	1.50	2.00	3.00	4.00
S.D.	0.92	1.25	1.17	0.78	1.51	1.17

Table Epro-095-5. Point Estimates and 95% confidence Intervals of comparisons of eprosartan, losartan and E-3174

Parameter	Comparison	Point Estimate	95% Confidence Interval
Eprosartan			
AUC(0-τ)†	Day 10 : Day 5	0.97	0.74, 1.28
Cmax†	Day 10 : Day 5	0.80	0.59, 1.08
Tmax§	Day 10 : Day 5	0.25 h	-0.50 h, 1.25 h
Losartan			
AUC(0-τ)†	Day 10 : Day 5	1.01	0.90, 1.13
Cmax†	Day 10 : Day 5	0.91	0.70, 1.18
Tmax§	Day 10 : Day 5	0.25 h	-0.98 h, 1.00 h
E-3174			
AUC(0-τ)†	Day 10 : Day 5	1.07	0.96, 1.19
Cmax†	Day 10 : Day 5	1.13	0.98, 1.30
Tmax§	Day 10 : Day 5	0.25 h	-0.50 h, 1.01 h

† Data presented as the ratio of the geometric means for Day 10: Day 5.
§ Data presented as the estimated median difference (Day 10 - Day 5) and 95% confidence intervals

95.5 CONCLUSION

Oral administration of eprosartan and losartan to healthy male volunteers in this study did not show any serious adverse experiences. There were no abnormal laboratory values of potential safety concern.

Eprosartan did not exhibit significant uricosuric effect relative to placebo after single, repeat or repeat combination dosing with ketoconazole. Losartan alone in a single dose or repeat doses, or co-administered with ketoconazole significantly increased urine uric acid excretion (UUA/UCr ration) compared to placebo or eprosartan.

The steady-state pharmacokinetics of eprosartan, losartan and E-3174 were similar following co-administration of ketoconazole compared with eprosartan or losartan alone, suggesting that inhibition of CYP3A4 of the Cytochrome P450 system did not alter the metabolism of eprosartan (which does not undergo oxidative metabolism in humans) or losartan (consistent with published reports).

Protocol 099 **NDA 20-738** **Teveten™ (Eprosartan) Tablets** *(Vol. 1.108/109)*

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

99.1. STUDY PROTOCOL

99.1.1 **Title** ***An evaluation of the pharmacokinetics of a single oral dose of eprosartan in hemodialysis-dependent patients with end stage renal disease compared to volunteers with normal renal function***

99.1.2 **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) while providing a renal protective effect. This study evaluates the pharmacokinetics of a single 400 mg oral dose of eprosartan in patients with end stage renal disease maintained on hemodialysis compared to volunteers with normal renal function.

99.1.3 **Objectives**

1. To compare the pharmacokinetics of eprosartan in hemodialysis-dependent patients with end stage renal disease between hemodialysis treatments (non-dialysis day) relative to age- and weight-matched volunteers with normal renal function;
2. To compare protein binding characteristics of eprosartan in hemodialysis-dependent patients with end stage renal disease between hemodialysis treatments (non-dialysis day) relative to age- and weight-matched volunteers with normal renal function;
3. To determine hemodialysis clearance and protein binding characteristics of eprosartan during dialysis (dialysis day); and
4. To assess the safety and tolerability of eprosartan in patients with end stage renal disease maintained on hemodialysis.

99.1.4 **Study design**

The study was an open-label, parallel-group, single dose study in hemodialysis-dependent patients with end stage renal disease and age (± 5 years)- and weight (± 5 kg)- matched volunteers with normal renal function (creatinine clearance (CLCr) > 80 ml/min). Volunteers completed one study session, and hemodialysis patients completed two study sessions one on a non-dialysis day and again on a dialysis day after a 14-day washout period.

Each participant took a single oral dose of eprosartan (Batch # U95113, 400 mg tablets) 400 mg on the morning of study day. (On dialysis day, hemodialysis patients were dosed 3 hours prior to start of hemodialysis). Blood samples were obtained for pharmacokinetic analysis prior to and for 24 hours after the dosing. For hemodialysis patients, dialysate was collected during the hemodialysis on the dialysis day to calculate hemodialytic clearance.

99.1.5 **Protocol Amendments**

The original protocol was amended on 30 Oct-1996 to remove the exclusion criterion dealing with total bilirubin, ALT, AST restrictions for hemodialysis patients and volunteers.

99.1.6 **Population enrolled/analyzed**

15 hemodialysis patients and 18 volunteers with normal renal function between 18-70 years, weighing ≥ 50 kg and within 30% of ideal body weight based on height and gender, and a negative urine drug screen within 30 days were screened. Hemodialysis patients had to be on stable hemodialysis treatment for ≥3 months and be able to tolerate a hemodialysis treatment lasting 4 hours with blood flow rates between 400 and 500 ml/min.

Compliance: Each dose of study medication was administered in the clinical pharmacology unit or Vivra Renal Care under the observation of the nursing staff. The oral cavity of each subject was examined by the study nurse following dosing to assure that the dose was actually ingested by the subject.
Pre-study screening: The screening visit (30 days prior to the study) included a complete medical and medication history, and physical examination. Blood samples were obtained from hemodialysis patients and volunteers for laboratory tests (hematology, chemistry, liver function) and urine samples from volunteers for urinalysis and drug screen. Female subjects of child-bearing potential were required to have a negative serum pregnancy test.

99.1.7 **Study procedures**

Hemodialysis-dependent patients with end stage renal disease

Patients were permitted to continue on prescribed medication during the study. Concomitant medications were held from midnight the night preceding administration of eprosartan until 5 hours after dosing (with the exception of insulin, erythropoietin and 1,25 di-hydroxyvitamin D which were administered on the patient's usual schedule).

Non-dialysis day: Patients reported to the clinical pharmacology unit (after breakfast) at 7:00 am on the morning after their last hemodialysis treatment. Baseline signs and symptoms were recorded. Blood samples were collected for clinical laboratory tests. Serum hCG had to be negative for women of child bearing potential within 48 hours prior to dose administration. The 400 mg dose of eprosartan was administered approximately 24 hours after the start of the last hemodialysis treatment.

Dialysis day: Patients ate breakfast before reporting at Vivra Renal Care about 4 hours prior to start of their hemodialysis treatment. Baseline signs and symptoms were recorded. Blood samples were collected for clinical laboratory tests. Blood pressure, heart rate and symptoms and signs were assessed prior to dosing and at 1, 2, 3, 4, 6 and 24 hours after dosing. The 400 mg dose of eprosartan was administered approximately 3 hours prior to the start of the hemodialysis treatment. Approximately 1 hour after completion of the hemodialysis treatment, patients were transported to the clinical pharmacology unit. Meals were offered at 8 and 12 hours after dosing. Patients were not permitted to exceed their usual daily fluid intake during the study day.

Volunteers with normal renal function

Volunteers were not permitted to take prescription or non-prescription medications. They reported to the clinical pharmacology unit (after breakfast) at 7:00 am. Baseline signs and symptoms were recorded. Blood and urine samples were collected for clinical laboratory tests. Serum hCG had to be negative for women of child bearing potential within 48 hours prior to dose administration. The 400 mg dose of eprosartan was administered, and volunteers drank 240 ml of water at 2 and 4 hours after dosing.

All study participants

Water, soft drinks without caffeine, or fruit juices (except grapefruit juice) were permitted *ad lib* 5 hours after dosing. Lunch was given 5 hours after dosing and dinner at 9-10 hours after dosing. Special meal arrangements were made for hemodialysis patients to maintain compliance with their usual dietary restrictions. Participants abstained from strenuous physical exercise, ingestion of drinks and foods containing xanthine (e.g., chocolate), alcohol and tobacco.

In volunteers and in hemodialysis patients (non-dialysis day) blood samples for pharmacokinetic analysis were obtained prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours following dosing. In hemodialysis patients on dialysis day, blood samples were obtained were prior to dosing and at 0.5, 1, 1.5, 2, 3 (immediately pre-dialysis), 7.5, 8, 9, 10, 12, 18, and 24 hours following dosing. Pre-dialyzer (arterial line) and post-dialyzer (venous line) blood samples were obtained at 4, 5, 6 and 7 hours after drug administration. Dialysis elluent was collected prior to the start of hemodialysis and then in the intervals 0-1, 1-2, 2-3 and 3-4 hours after initiation of hemodialysis. On each study day, all participants had additional blood specimens (7 ml) drawn at 3 and 7 hours post-dosing for the determination of the *ex vivo* plasma protein binding of eprosartan.

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

99.1.8 **Pharmacokinetic procedures:**

Blood samples for pharmacokinetics kept 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 reversed phase HPLC assay method with UV detection. The lower limit of quantification (LLQ) in plasma for eprosartan was 9.77 ng/ml for a 0.5 ml aliquot.

Dialysate concentrations of eprosartan were quantified by solid-phase extraction followed by reversed phase HPLC assay method with UV detection. LLQ for eprosartan was 9.85 ng/ml for a 0.5 ml aliquot of dialysate.

The *ex vivo* 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), AUC(0-τ), and the unbound AUC(0-τ) and the unbound Cmax. It was not

possible to estimate $T_{1/2}$ and AUC(0-∞). The amount of eprosartan in the dialysate (Ae) was determined from the dialysate concentration data and the total dialysate volume. The apparent dialytic clearance (CL_{hd}) was calculated from Ae/AUC where AUC was the area under the curve during the 4 hour dialysis session.

99.1.9 **Sample size:**

Based on a between-subject coefficient of variation (CV_b) for dose-normalized Cmax (41.9%) and AUC (48.39%) at the 400 mg dose level in Study SK&F 108566/008, to detect differences of ≥50% on a 2-tailed test with a type I error rate of 5%, symmetric critical range on the $\log_e$ scale, and 85% power, it was estimated that a sample size of 10 per group would be necessary.

99.1.10 **Evaluation criteria:**

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

The primary pharmacokinetic parameters were AUC(0-τ) and Cmax of eprosartan for hemodialysis patients (non-dialysis day) and volunteers with normal renal function. Secondary pharmacokinetic endpoints were mean percent fraction unbound, Tmax, unbound Cmax, and unbound AUC(0-τ) of eprosartan for the same groups.

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

Bernard E. Ilson, MD, SmithKline Beecham Clinical Pharmacology Unit, Presbyterian Medical Center, University of Pennsylvania Health System, Philadelphia, PA. Study Dates: 22-Oct-1996 to 04-Dec-1996.

99.2 STUDY POPULATION

99.2.1 **Subject disposition:**

Of 15 hemodialysis patients screened, 5 did not meet entrance criteria and 1 withdrew consent to participate. Nine (89% male and 11% female, 100% black) patients, 27-59 (Mean = 43) years of age, weighing 54.1 to 106.3 (mean = 79.9) kg, and 160-190 (mean = 175) cm tall participated. All 9 patients completed the non-dialysis day study and 8 patients completed the dialysis day study.

Of 18 volunteers screened, 4 did not meet entrance criteria, 1 did not participate due to a personal emergency, 1 failed to arrive on the scheduled study day and 2 volunteers were alternates who were not needed. 10 (100% male, and 80% white and 20% black) volunteers, 34-58 (Mean = 43) years of age, weighing 65.7 to 102.6 (mean = 84.6) kg, and 169-191 (mean = 178) cm tall participated.

99.2.2 **Withdrawals:**

One hemodialysis patient (#010) was withdrawn after completing the non-dialysis day due to early termination of the study by the sponsor.

99.2.3 **Protocol violations:**

Subject#	Protocol Violation
#002	Received 40μg IM vaccination with Hepatitis B surface antigen (Recombivax®) 5 days prior to the dialysis day study
#003	Received 40μg IM vaccination with Hepatitis B surface antigen (Recombivax®) 1 day prior to the non-dialysis day study
#004	Consumed chocolate-covered almond candy 30 minutes prior to dosing for the dialysis day study
#005	Received 40μg IM vaccination with Hepatitis B surface antigen (Recombivax®) 7 days after completing the non-dialysis day study
#008	Received 25 mg iron dextran (Infed®) IV and 100 mg iron dextran (Infed®) IV between the non-dialysis day and dialysis day. Also received 50 mg diphenhydramine (Benedryl®) for pruritus during hemodialysis on the dialysis day.

99.3 SAFETY RESULTS

99.3.1 **General considerations:** 9 adverse experiences (AEs) were reported for 7 study participants.

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

99.3.3 **Withdrawals due to adverse experiences:**
There were no withdrawals due to adverse experiences.

99.3.4 **Serious, Non-fatal Adverse Events:**
There were no serious non-fatal adverse experiences.

99.3.5 **Adverse Events:**
3 hemodialysis patients reported 3 AEs (#004 reported hypotension, #007 and #008 each reported headache), all occurring on dialysis study day. There were no AEs reported by hemodialysis patients on non-dialysis study day.

4 volunteers with normal renal function reported 6 AEs (#102, #106, #107 and #110 each reported headache, and #110 also reported nausea and rash).

99.3.6 **Laboratory findings, ECGs, Vital signs**
There were no changes in pulse rates of potential clinical concern. 3 hemodialysis patients had changes in blood pressure on dialysis day study: Patient #003 had increased systolic BP (187 mmHg 2 hours post-dose vs 156 mmHg at baseline), #004 had decreased systolic BP (117 mmHg and 102 mmHg 4 and 6 hours post-dose vs 159 mmHg at baseline) and #005 had decreased systolic BP (116 mmHg and 104 mmHg 4 and 6 hours post-dose vs 148 mmHg at baseline). These were all asymptomatic.

There were no laboratory values of potential clinical concern in volunteers except Patient #109 who had a pre-dose potassium of 5.7 mEq/l and a pre-dose serum bilirubin of 1.9 mg/dl. The serum potassium returned to within reference range at 24 h post-dose sample (4.7 mEq/l). The total bilirubin decreased to 1.2 mg/dl at 24 h post-dose sample. In hemodialysis patients, there were abnormal laboratory values consistent with end stage renal disease: elevated BUN and creatinine, decreased hemoglobin and hematocrit. These abnormal findings are summarized in Table Epro-099-1.

Table Epro-099-1

Hemodialysis Patients Who had Clinical Laboratory Values of Potential Clinical Concern Not Necessarily Related to End Stage Renal Disease

Subject	Laboratory Value	Comments/Etiology
001	K^+ of 5.6 mEq/L at +24 hours NDD	ESRD
	Elevated serum glucose (154-315 mg/dL) throughout study	Diabetes mellitus
	Elevated GGT (64-84 IU/L) at screen and throughout study	Not clinically significant
003	K^+ of 6.0 mEq/L at study screen	ESRD
	K^+ of 5.8 mEq/L at pre-dose DD	ESRD
	Elevated GGT (99-140 IU/L) at screen and throughout study	Not clinically significant - Hepatitis C positive
004	WBCs 2.3-2.5 (x 10^3/µL) during NDD and at pre-dose DD	Not clinically significant
	Thrombocytopenia (70-90 x 10^3/µL) at screen and throughout study	Possibly related to underlying disease
	Elevated GGT (147-220 IU/L) at screen and throughout study	Not clinically significant - Hepatitis C positive
	Elevated AST (111 IU/L) at +24 hours DD	Not clinically significant
	Elevated Total Bilirubin (1.7 mg/dL) at study screen	Not clinically significant
006	K^+ of 5.7 mEq/L at 24 hours NDD	ESRD
	Glucose of 57 mg/dL at study screen	Fasting sample
007	K^+ of 5.6 mEq/L at screen; 4.8-7.0 throughout study	ESRD
008	Elevated GGT (67-87 IU/L) at screen and throughout study	Not clinically significant
	Albumin of 3.2 g/dL at pre-dose NDD	ESRD/malnutrition
010*	K^+ of 6.2 mEq/L at 24 hours NDD	ESRD
	WBCs 3.1 (x 10^3/µL) at study screen	Not clinically significant
	Elevated GGT (355-409 IU/L) at screen and throughout NDD*	Not clinically significant
	Elevated ALT (84 IU/L) at +24 hours NDD	Not clinically significant
	Elevated Alk Phos (136-151 IU/L) at screen and throughout NDD*	ESRD (renal osteodystrophy)

ESRD = End Stage Renal Disease NDD = Non-Dialysis Day DD = Dialysis Day
*Subject 010 was withdrawn prior to completion of the dialysis day due to early termination of the study.

99.4 PHARMACOKINETIC RESULTS

99.4.1 Pharmacokinetics of eprosartan in volunteers with normal renal function and hemodialysis patients (Non dialysis day study)

Following administration of a single dose of 400 mg eprosartan, maximum plasma concentrations of eprosartan were observed between 1-3 hours post-dose in volunteers with normal renal function, and 1-4 hours post-dose in hemodialysis patients (Figure Epro-099-1). Concentration-time profiles declined in a mono- or bi-phasic manner in most participants following Cmax.

In Table Epro-099-2, AUC(0-τ) was increased, on average, by about 60% in hemodialysis patients compared to volunteers with normal renal function. There was considerable overlap between individual AUC(0-τ) values, with a wide confidence interval. The Cmax was approximately similar between the two groups of participants, with considerable overlap in the individual Cmax values. The median difference and 90% confidence interval for Tmax between hemodialysis patients and volunteers with normal renal function include the value zero suggesting that the rate of absorption is similar for the two groups.

The mean percent fraction unbound of eprosartan was significantly increased in hemodialysis compared to volunteers with normal renal function (3.02% vs 1.74%, respectively). Unbound AUC(0-τ) was, on average, about 172% larger in hemodialysis patients relative to volunteers with normal renal function. Here, too, there was considerable overlap between individual AUC(0-τ) values, with a wide confidence interval. The unbound Cmax increased, on average, by about 73% with considerable overlap of individual Cmax values. (When patients #003, #004 and #006 who were statistical outliers with extreme unbound AUC(0-τ) and unbound Cmax values were excluded, the mean unbound Cmax was similar between groups.)

Table Epro-099-2. Mean (SD) pharmacokinetic parameters for eprosartan and unbound eprosartan following single oral 400 mg dose to subjects with normal renal function and hemodialysis patients

Parameter		Non-Dialysis Day (n=9)	Volunteers (n=10)	Point estimate (95% CI)
Eprosartan				
AUC(0-τ) (ng.h/ml)	Mean	15075	6672	1.60[a] (0.78, 3.25)
	Median	7545	6138	
	SD	17375	3071	
	Geometric Mean	9652	6047	
	CV (%)	119.9	49.8	
Cmax (ng/ml)	Mean	2180	1780	1.01[a] (0.60, 1.71)
	Median	1662	1611	
	SD	1626	585	
	Geometric Mean	1724	1703	
	CV (%)	82.7	31.1	
Tmax (h)*	Median	1.55 (1.03 - 4.02)	1.49 (1.02 - 3.05)	0.45 h[b] (-0.45 h, 1.52 h)
	Mean	2.13	1.66	
	SD	1.00	0.63	
Unbound Eprosartan				
%fu (ex vivo)	Mean	3.02	1.74	1.27[c] (0.83, 1.72)
	Median	2.97	1.78	
	SD	0.64	0.17	
Unbound AUC(0-τ) (ng.h/ml)	Mean	506	116	2.72[a] (1.28, 5.79)
	Median	506	104	
	SD	716	55	
	Geometric Mean	286	135	
	CV (%)	135	50.4	
Unbound Cmax (ng/ml)	Mean	68.6	31.0	1.73[a] (0.99, 2.99)
	Median	39.5	26.4	
	SD	64.9	10.7	
	Geometric Mean	51.0	29.6	
	CV (%)	88.1	32.4	

* Tmax data presented as median (range); [a] data presented as the ratio of geometric means (Non-Dialysis Day : Normal)
[b] data presented as the median difference (Non-Dialysis Day : Normal)
[c] data presented as the difference in arithmetic means (Non-Dialysis Day : Normal)

The effects observed between-subjects with normal renal function and hemodialysis patients with end stage renal disease are characterized by wide confidence intervals due to increased variability in the hemodialysis group. Between-subject variability in hemodialysis patients (119.9% for AUC and 82.7% for Cmax) was relatively larger than in volunteers with normal renal function (49.8% for AUC and 31.1% for Cmax).

Similarly, between- subject variability in hemodialysis patients (135.0% for unbound AUC and 88.1% for unbound Cmax) was relatively larger than in volunteers with normal renal function (50.4% for unbound AUC and 32.4% for unbound Cmax). The sponsor proposed that impact of this difference in variability on statistical inference was found to be negligible employing Satterthwaite's procedure.

99.4.2 **Pharmacokinetics of eprosartan in hemodialysis patients (Non-dialysis day and Dialysis day study)**

Following administration of a single dose of 400 mg eprosartan, maximum plasma concentrations of eprosartan were observed between 1-4 hours post-dose in hemodialysis patients (Figure Epro-099-2), and the concentration-time profiles declined in a mono- or bi-phasic manner following Cmax. There was no increase ("rebound effect") of eprosartan plasma concentrations upon cessation of hemodialysis.

In Table Epro-099-3, AUC(0-τ) and Cmax were was increased, on average, by about 35% on dialysis day compared to non-dialysis day. Tmax was delayed on the dialysis day in all but 1 patient, the median Tmax occurring about 2.5 hours later on the dialysis day compared to non-dialysis day. The findings suggest an increased extent and duration of absorption causing increased bioavailability of eprosartan on the dialysis day.

The pre-dialysis (3 hr post-dose) percent fraction unbound of eprosartan (3.19%) was almost similar to that at 3 hours (2.81%) and 7 hours (3.26%) post-dose on the non-dialysis day, whereas the post-hemodialysis (7-hour post-dose) percent unbound fraction on the dialysis day (2.01%) was decreased. This increase in plasma protein binding immediately after dialysis may be due to removal of an endogenous component that accumulates between dialysis sessions and causes displacement of eprosartan from binding sites. This increased in protein binding after dialysis may also contribute to the increased total AUC.

CL_{hd} of eprosartan, determined by dialysate measurement, was 11.22 ml/min. This suggests that eprosartan, being highly protein bound, is not cleared by hemodialysis, and that the contribution of CL_{hd} to systemic clearance was small (about 10%) in patients with negligbile renal function from end stage renal disease.

Table Epro-099-3. Mean (SD) pharmacokinetic parameters for eprosartan and unbound eprosartan following single oral 400 mg dose to hemodialysis patients (Non-Dialysis day and Dialysis day)

Parameter		Non-Dialysis Day (n=9)§	Dialysis Day (n=8)
AUC(0-τ) (ng.h/ml)	Mean	15075	20593
	Median	7545	13346
	SD	17375	17423
	Geometric Mean	9652	15352
	CV (%)	119.9	96.2
Cmax (ng/ml)	Mean	2180	2900
	Median	1662	2203
	SD	1626	1520
	Geometric Mean	1724	2564
	CV (%)	82.7	57.3
*Tmax (h)**	Median	1.55 (1.03 - 4.02)	3.98 (1.98 - 7.50)
	Mean	2.13	4.27
	SD	1.00	1.64
%fu (3h)	Mean	2.81	3.19
	Median	2.54	3.26
	SD	0.83	0.78
%fu (7h)	Mean	3.26	2.01
	Median	3.05	1.90
	SD	0.72	0.43
CL_{hd} (ml/min)	Mean	—	11.22
	Median	—	9.95
	SD	—	7.10

* Tmax data presented as median (range)

§ Subject #002 did not have a reportable %fu value at 7 hour sample time-point on the Non-Dialysis Day

Figure Epro-099-1

Mean Plasma Eprosartan Concentration-Time Profiles Following Oral Administration of 400 mg Eprosartan

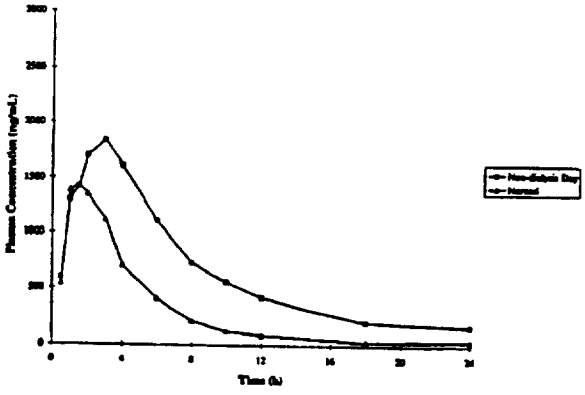
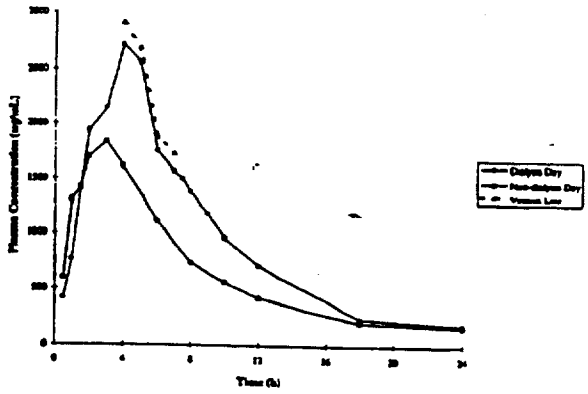


Figure Epro-099-2

Mean Plasma Eprosartan Concentration-Time Profiles Following Oral Administration of 400 mg Eprosartan



On dialysis days, patient underwent dialysis from 3 to 7 hours post-dose

99.5 CONCLUSION

Single oral 400 mg dose of eprosartan administered to volunteers with normal renal function and hemodialysis-dependent patients with end stage renal disease showed no increase in the frequency or severity of adverse experiences, headache being the most frequently reported adverse experience.

Plasma concentrations of eprosartan reached peak values between 1-3 hours post-dose in volunteers with normal renal function, and 1-4 hours post-dose in hemodialysis patients, the median Tmax being approximately 1.5 hours for both groups. There was a high degree of variability in pharmacokinetics of hemodialysis patients with end stage renal disease. AUC(0-τ) was increased by about 60% in hemodialysis patients compared to volunteers with normal renal function while the Cmax was approximately similar between the two groups.

The mean percent fraction unbound of eprosartan was significantly increased in hemodialysis compared to volunteers with normal renal function (3.02% vs 1.74%, respectively). Unbound AUC(0-τ) and unbound Cmax increased by about 172% and 73%, respectively, in hemodialysis patients relative to volunteers with normal renal function.

On dialysis day, AUC(0-τ) and Cmax were was increased by about 35% compared to non-dialysis day. The median Tmax occurred about 2.5 hours later on the dialysis day compared to non-dialysis day.

The post-hemodialysis (7-hour post-dose) percent unbound fraction on the dialysis day (2.01%) was decreased compared to pre-dialysis value (3.19%) and 7 hour post-dose on non-dialysis day (3.26%), indicating an increase in plasma protein binding immediately after dialysis.

CL_{hd} of eprosartan, determined by dialysate measurement, was 11.22 ml/min. Eprosartan, being highly protein bound, is not cleared by hemodialysis, the contribution of CL_{hd} to systemic clearance being small (about 10%) in these hemodialysis patients end stage renal disease.

D. Wrucco

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

AUG 8 1997

NDA #:	20-738	NDA Volume:	1.1097-1101
DRUG NAME:	Teveten™ (Eprosartan) Tablets	Doc ID	BM (M20.1-20.5)
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

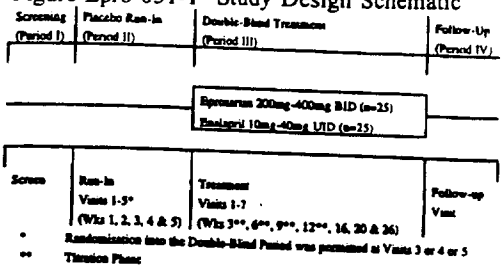


Table Epro-051-1 Dosage Regimen

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
BP/HR	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
Randomisation			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	Lelièv, Dominique MD	200, Rue Jean Jaurès, Vieux Condé
442	El Sawy, Alain MD	1, Rue Pierre Schubert, Saint-Martin D'Heres
443	De La Chevasnerie, Antoine MD	14, Rue de Valmeray, Perigny
444	Boca, Jean - Philippe MD	40, Bd des Recollets, Toulouse
445	Puec, Eric MD	UCPE-Clinique du Mail, Grenoble
446	Valriet, Pascal PhD	Centre "Les Nations", Vandoeuvre
447	Cudac, Robert MD	1173, Route de Grasse, Antibes
448	Perret, Andre MD	535, Ave. De La Renaissance, Toulon
449	Boudoual, Serge MD	253, Chem. undergrave ville, Marseille
450	Pesque, Gilles MD	13, 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 UID	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 UID	10 (15.2)
	Enalapril 20 mg UID	12 (18.2)
	Enalapril 40 mg UID	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 UID	9 (13.6)
	Enalapril 20 mg UID	9 (13.6)
	Enalapril 40 mg UID	5 (7.6)
	Total	47 (71.2)**

* Percentage of patients rec...ng at least one dose of medication
** Two patients (PIDs 051.447.00858 and 051.447.00837), one from each medication regimen, were "off-drug" at maintenance endpoint (see table 8)
# Excludes 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%)	3 (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 this 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
DIAsystolic 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±3.8	80.8±2.5
	Range	46.0-116.0	57.9-115.0
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 ± 1.3
	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=35 (%)	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 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	(n=13) 70.4 ± 2.0	(n= 15) 71.1 ± 1.6
Month 6		
Mean ± SEM	(n=9) 69.4 ± 2.3	(n=9) 74.3 ± 2.5
Month 6 change		
Mean ± SEM	(n=9) -1.6 ± 1.9	(n=9) 3.1 ± 1.5
Study endpoint		
Mean ± SEM	(n=11) 70.5 ± 2.0	(n=16) 74.8 ± 1.6
Study endpoint change		
Mean ± SEM	(n=11) 0.1 ± 2.0	(n=15) 1.4 ± 1.8
PEWS (ms^2 /beat)		
Baseline		
Mean ± SEM	(n=13) 95.9 ± 2.6	(n=15) 84.9 ± 3.6
Month 6 endpoint		
Mean ± SEM	(n=9) 85.7 ± 5.0	(n=9) 94.6 ± 6.9
Month 6 change		
Mean ± SEM	(n=9) -17.1 ± 5.7	(n=9) -0.1 ± 5.7
Study endpoint		
Mean ± SEM	(n=11) 85.7 ± 4.3	(n=15) 75.9 ± 4.3
Study endpoint change		
Mean ± SEM	(n=11) -10.0 ± 4.7	(n=14) -9.0 ± 5.7
LV End Systolic Volume (cm^3)		
Baseline		
Mean ± SEM	(n=13) 45.3 ± 4.4	(n=15) 36.6 ± 4.4
Month 6		
Mean ± SEM	(n=9) 42.7 ± 7.0	(n=9) 32.6 ± 5.0
Month 6 change		
Mean ± SEM	(n=9) -1.7 ± 1.5	(n=9) -4.3 ± 2.1
Study endpoint		
Mean ± SEM	(n=11) 41.3 ± 4.7	(n=16) 34.3 ± 3.7
Study endpoint change		
Mean ± SEM	(n=11) -3.0 ± 1.5	(n=15) -3.1 ± 2.1
LV End Diastolic Volume (cm^3)		
Baseline		
Mean ± SEM	(n=13) 146.9 ± 11.0	(n=15) 127.9 ± 10.9
Month 6		
Mean ± SEM	(n=9) 140.0 ± 12.4	(n=9) 125.3 ± 11.3
Month 6 change		
Mean ± SEM	(n=9) -5.4 ± 7.5	(n=9) -11.4 ± 7.8
Study endpoint		
Mean ± SEM	(n=11) 136.7 ± 10.7	(n=16) 123.4 ± 9.2
Study endpoint change		
Mean ± SEM	(n=11) -5.8 ± 5.4	(n=15) -3.9 ± 7.0
LV Posterior Wall Thickness (in)		
Baseline		
Mean ± SEM	(n=13) 33.6 ± 1.5	(n=15) 30.9 ± 1.4
Month 6		
Mean ± SEM	(n=9) 33.3 ± 2.2	(n=9) 34.4 ± 1.8
Month 6 change		
Mean ± SEM	(n=9) -0.6 ± 1.6	(n=9) 1.4 ± 1.3
Study endpoint		
Mean ± SEM	(n=11) 34.1 ± 1.9	(n=16) 34.9 ± 1.3
Study endpoint change		
Mean ± SEM	(n=11) 0.7 ± 1.6	(n=15) 0.2 ± 1.3
LV Diastolic Dimension (cm)		
Baseline		
Mean ± SEM	(n= 13) 5.2 ± 0.1	(n= 15) 5.0 ± 0.1
Month 6		
Mean ± SEM	(n=9) 5.1 ± 0.2	(n=9) 4.9 ± 0.1
Month 6 change		
Mean ± SEM	(n=9) -0.1 ± 0.1	(n=9) -0.1 ± 0.1
Study endpoint		
Mean ± SEM	(n=11) 5.0 ± 0.2	(n=16) 5.0 ± 0.1
Study endpoint change		
Mean ± SEM	(n=11) -0.0 ± 0.1	(n=15) -0.0 ± 0.1
E/A Ratio		
Baseline		
Mean ± SEM	(n=13) 1.4 ± 0.1	(n=15) 1.2 ± 0.1
Month 6		
Mean ± SEM	(n=10) 1.4 ± 0.1	(n=9) 1.3 ± 0.1
Month 6 change		
Mean ± SEM	(n=10) 0.0 ± 0.1	(n=9) -0.0 ± 0.1
Study endpoint		
Mean ± SEM	(n =13) 1.4 ± 0.1	(n=16) 1.4 ± 0.1
Study endpoint change		
Mean ± SEM	(n =13) 0.0 ± 0.1	(n=15) -0.1 ± 0.1
Peak E Deceleration Time (ms)		
Baseline		
Mean ± SEM	(n=13) 193.2 ± 9.2	(n=15) 190.7 ± 7.1
Month 6		
Mean ± SEM	(n=10) 183.0 ± 8.8	(n=7) 183.4 ± 19.6
Month 6 change		
Mean ± SEM	(n=10) -9.2 ± 11.0	(n=7) -15.7 ± 19.0
Study endpoint		
Mean ± SEM	(n=13) 201.8 ± 9.3	(n=14) 179.3 ± 11.3
Study endpoint change		
Mean ± SEM	(n=13) -7.5 ± 10.0	(n=13) -11.8 ± 13.3
Isovolumic Relaxation Time (ms)		
Baseline		
Mean ± SEM	(n=13) 123.2 ± 6.1	(n=13) 126.1 ± 7.4
Month 6		
Mean ± SEM	(n=10) 126.0 ± 15.1	(n=6) 107.8 ± 13.0
Month 6 change		
Mean ± SEM	(n=10) 10.4 ± 14.1	(n=6) -9.4 ± 17.4
Study endpoint		
Mean ± SEM	(n=12) 128.1 ± 12.8	(n=13) 120.3 ± 8.2
Study endpoint change		
Mean ± SEM	(n=12) 5.2 ± 13.4	(n=9) 1.3 ± 19.4
Diastolic PWT (ms)		
Baseline		
Mean ± SEM	(n=13) 1.0 ± 0.0	(n=13) 1.1 ± 0.0
Month 6		
Mean ± SEM	(n=9) 1.0 ± 0.1	(n=6) 1.0 ± 0.1
Month 6 change		
Mean ± SEM	(n=9) 0.0 ± 0.0	(n=6) -0.0 ± 0.0
Study endpoint		
Mean ± SEM	(n=11) 1.0 ± 0.1	(n=15) 1.0 ± 0.0
Study endpoint change		
Mean ± SEM	(n=11) 0.0 ± 0.0	(n=14) -0.0 ± 0.0
Systolic PWT (ms)		
Baseline		
Mean ± SEM	(n=13) 1.4 ± 0.0	(n=13) 1.5 ± 0.0
Month 6		
Mean ± SEM	(n=9) 1.3 ± 0.0	(n=6) 1.4 ± 0.1
Month 6 change		
Mean ± SEM	(n=9) -0.0 ± 0.0	(n=6) -0.1 ± 0.0
Study endpoint		
Mean ± SEM	(n=11) 1.4 ± 0.0	(n=15) 1.4 ± 0.0
Study endpoint change		
Mean ± SEM	(n=11) 0.0 ± 0.0	(n=14) -0.1 ± 0.0

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=5)		
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	-5.5 ± 9.5	-13.5 ± 6.3	-8.0 (-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=5)		
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	-17.3 ± 7.6	-8.3 (-28.8, 12.5)	0.406
Study endpoint	(n=11)	(n=5)		
Mean ± SEM	-1.5 ± 6.4&	-9.5 ± 5.5&	#	#
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 row 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=32)	(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	-10.2 ± 2.5	1.8 (-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&	-18.0 ± 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± 2.5&	#	#
Maintenance Endpoint	(n=13)	(n=12)		
Mean ± SEM	-18.0± 2.4&	-17.3± 1.6&	#	#
Study Endpoint	(n=14)	(n=13)		
Mean ± SEM	-18.6 ± 2.7	-17.6 ± 2.4	0.9 (-5.4, 7.2)	0.761
Caucasian				
Titration Endpoint	(n=39)	(n=33)		
Mean ± SEM	-16.3 ± 1.4&	-13.4± 1.7&	#	#
Maintenance Endpoint	(n=27)	(n=26)		
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=26)		
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 ± 1.2	-15.8 ± 1.3	-2.0 (-5.4, 1.5)	0.234
Study Endpoint	(n=10)	(n=8)		
Mean ± SEM	-13.9 ± 1.2	-15.8 ± 1.3	-2.0 (-5.4, 1.5)	0.234
Baseline sDBP < 105mmHg				
Titration Endpoint	(n=36)	(n=37)		
Mean ± SEM	-15.0± 2.3	-12.0 ± 2.0	2.9 (-1.7, 7.6)	0.208
Maintenance Endpoint	(n=36)	(n=22)		
Mean ± SEM	-16.0± 1.7&	-16.0± 1.3&	#	#
Study Endpoint	(n=36)	(n=27)		
Mean ± SEM	-14.3 ± 2.5	-11.4 ± 2.1	-2.9 (-7.0, 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=8)		
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 row 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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D. W. Hazel

AUG 7 1997

MEDICAL OFFICER REVIEW

NDA #:	20-738
DRUG NAME:	Eprosartan
SPONSOR:	Smith-Kline-Beecham
TYPE OF DOCUMENT:	New NDA
DATE RECEIVED:	10-11-96
DATE REVIEW COMPLETED:	*7-30-97*
MEDICAL OFFICER:	Isaac W. Hammond,

Submissions

Date Received	File # (volume)	Information
10-11-96	20-738	NDA

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

General Information

Name of Drug

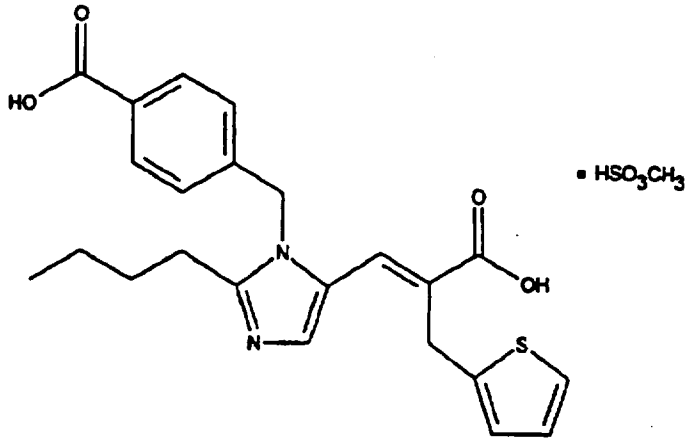
Generic: Eprosartan

Trade: TEVETEN™

Chemical: (E)-∝-{{2-Butyl-1-{(4-carboxyphenyl)]-1H-imidazol-5-yl] methylene]-2-thiophenepropanoic acid monomethanesulfonate

Structural Formula:

Eprosartan mesylate



Molecular Formula: Salt: $C_{23}H_{24}N_2O_4S \cdot CH_4O_3S$

Molecular Weight: 520.625

Pharmacologic Category: Angiotensin II Receptor Antagonist (AT_1 subtype)

Proposed Indication: Hypertension

Dosage Form: 300 mg, and 400 mg tablets

Route of Administration: Oral
Related Drugs: Irbesartan, Losartan, Tasosartan, Valsartan

Resume

Eprosartan is a selective non-peptide angiotensin II receptor antagonist (a non-biphenyl tetrazole AT_1 subtype). It has no optical isomerism or polymorphism. It is soluble in neutral and alkaline pH but is poorly soluble at acid pH which may contribute to the absolute bioavailability of approximately 13%. Approximately 90% of oral dose is excreted in the feces and about 7% in the urine. There are no active metabolites

Eprosartan 200 mg twice daily to 400 mg twice daily were effective in decreasing diastolic blood pressure. However, some patients respond favorably to eprosartan at the highest dose studied (1200 mg once daily). Eprosartan appeared to be comparably effective in all age groups. The data is unclear whether this is an effective monotherapy for blacks and female patients.

Table of Contents

Study Location

SUMMARY

Patient Exposure

A total of 20 clinical trials evaluating the efficacy of eprosartan have been initiated in different patient populations. Open label extensions of controlled trials are counted as separate trials. The NDA contains information on 11 trials completed and 9 ongoing with interim reports, information from these trials are not included. The trials have been sponsored and monitored by SmithKline Beecham. The 9 trials on efficacy include the following:

- 7 controlled trials in hypertensive subjects (Protocols 010, 011, 013, 016, 017, 045, 049);
- 4 active controlled trials in hypertensive subjects (Protocols 014, 041, 047, 053);
- 2 active control trials evaluating incidence of cough (Protocol 014, 053);

The total number of patients with essential hypertension randomized to eprosartan in the 11 double-blind, placebo/active controlled trials was 1794. The dose of eprosartan in these studies ranged from 25 mg to 1200 mg. The duration of double-blind therapy ranged from 4 to 13 weeks. Table S.1 lists the number of patients exposed to eprosartan in each type of trial.

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

Category	Protocol Numbers	No. Of Trials	Eprosartan	Total
Placebo Controlled	010, 011, 013, 016, 017, 045, 049	7	1324	1710
Active Controlled	014, 041, 047	3	424	844
Placebo & Active Controlled	053	1	46	136
Controlled Trials Total		**11**	**1794**	**2690**

The demographic characteristics of the patients randomized in these trials are listed in Table S.2.

Table S.2. Demographic Characteristics of All Randomized Patients

	Treatment Group				
Patient Data	Placebo N (%)	Eprosartan N (%)	Enalapril N (%)	Procardia XL N (%)	Total N (%)
Total Patients	449 (100)	1778 (100)	368 (100)	102 (100)	2697 (100)
Age (years)					
Mean	57.2	56.9	56.1	53.6	56.7
Std. Dev.	12.2	11.7	11.1	10.5	11.7
Range	24 - 93	20 - 93	24 - 86	31 - 74	20 - 93
Age (years)					
<65	303 (67.5)	1250 (70.3)	280 (76.1)	82 (80.4)	1915 (71.0)
≥65	146 (32.5)	528 (29.7)	88 (23.9)	20 (19.6)	782 (29.0)
Race					
Black	50 (11.1)	199 (11.2)	26 (7.1)	22 (21.6)	297 (11.0)
White	355 (79.1)	1466 (82.5)	311 (84.5)	76 (74.5)	2208 (81.9)
Other	44 (9.8)	113 (6.4)	11 (8.4)	4 (3.9)	192 (7.1)
Sex					
Female	170 (37.9)	677 (38.1)	170 (46.2)	40 (39.2)	1057 (39.2)
Male	279 (82.1)	1101 (61.9)	198 (53.8)	62 (60.8)	1640 (60.8)

Efficacy

Diastolic Blood Pressure

The sponsor performed 7 placebo controlled trials in patients with essential hypertension. The double-blind treatment period ranged from 4 to 13 weeks. The doses ranged from 25 mg to 1200 mg. The studies can be divided into either placebo controlled studies (010, 011, 013, 016, 017, 045, 049), active controlled studies (041, 047) or both placebo and active controlled studies (053). The primary evidence of efficacy (i.e., decreases sitDBP) is provided by 4 double-blind, parallel dose trials (010, 011, 013, 049). Table S.3 summarizes the changes in sitDBP in the double-blind parallel dose trials.

Table S.3 Mean Changes (mm Hg) in sitDBP at Endpoint in Placebo Controlled Trials

			Eprosartan BID Regimen							Eprosartan QD Regimen			
Protocol		Placebo	25	50	100	150	200	300	400	400	600	800	1200
010	N	22		24	24	22	22						
	Mean	-3.4		-5.9	-1.8	-4.9	-9.5						
	Std. Dev	4.9		5.8	5.8	6.1	6.3						
	Cor. Mean			-2.5	1.6	-1.5	-6.1*						
011	N	87	86		82		86	81	86				
	Mean	-2.8	-5.1		-4.8		-6.8	-7.2	-8.0				
	Std. Err	0.7	0.8		0.8		0.7	0.7	0.8				
	Cor. Mean		-2.4*		-2.0*		-4.0*	-4.4*	-5.2*				
013+	N	83					76			76			
	Mean	-3.9					-5.4			-7.2			
	Std. Dev	0.8					0.8			0.8			
	Cor. Mean						-1.5			-3.3			
049	N	72								70	73	72	71
	Mean	-3.7								-4.6	-6.0	-5.3	-6.9
	Std. Err	1.0								0.9	0.9	0.8	0.9
	Cor. Mean									-0.9	-2.3*	-1.7	-3.3*

* = statistically significant difference compared to placebo
Cor. Mean = Placebo Subtracted Average Difference
+ = Baseline minus Week 3 (This was done because of study design)

Isaac W. Hammond, MD, Ph.D

Sitting Diastolic Blood Pressure - Subgroup Analysis

The change in DBP in placebo controlled trials was evaluated among subgroup based on demographic variables. There are limitations in most of the studies such that each study may not be useful for each analysis. Table S.4 lists the placebo subtracted change in sitDBP at endpoint as a function of age.

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Table S.4 Placebo Subtracted Change in SitDBP (Placebo Controlled Trials) By Age

			Eprosartan BID Regimen														Eprosartan QD Regimen							
Prot. #		N	25	N	50	N	100	N	150	N	200	N	300	N	400	N	400	N	600	N	800	N	1200
010	<65			20	-3.2	17	1.6	17	-4.1	19	-7.0												
	≥65			6	-1.4	9	-1.3	5	6.1	3	-1.4												
011	<65	77	-2.9*			71	-1.9			73	-4.8*	68	-4.7*	68	-6.2*								
	≥65	13	2.0			15	-5.2			17	-0.7	16	-2.6	22	-4.1								
049	<65															54	-2.1	52	-2.8	16	-2.4	54	-3.9*
	≥65															18	-4.3*	21	-2.8	32	-4.2	16	-1.4

Data Source: Appendix 3.13.3.2

Table S.5 lists the placebo subtracted change in sitDBP at endpoint as a function of race. When data from all studies are combined, black subjects represent approximately 10% of all subjects randomized into treatment groups, so we are unable to draw any conclusions from the data. Examination of the change in sitDBP for blacks appear to be less than the change observed for white subjects.

Table S.3 Mean Changes (mm Hg) in sitDBP at Endpoint in Placebo Controlled Trials

			Eprosartan BID Regimen							Eprosartan QD Regimen			
Protocol		Placebo	25	50	100	150	200	300	400	400	600	800	1200
010	N	22		24	24	22	22						
	Mean	-3.4		-5.9	-1.8	-4.9	-9.5						
	Std. Dev	4.9		5.8	5.8	6.1	6.3						
	Cor. Mean			-2.5	1.6	-1.5	-6.1*						
011	N	87	86		82		86	81	86				
	Mean	-2.8	-5.1		-4.8		-6.8	-7.2	-8.0				
	Std. Err	0.7	0.8		0.8		0.7	0.7	0.8				
	Cor. Mean		-2.4*		-2.0*		-4.0*	-4.4*	-5.2*				
013+	N	83					76			76			
	Mean	-3.9					-5.4			-7.2			
	Std. Dev	0.8					0.8			0.8			
	Cor. Mean						-1.5			-3.3			
049	N	72								70	73	72	71
	Mean	-3.7								-4.6	-6.0	-5.3	-6.9
	Std. Err	1.0								0.9	0.9	0.8	0.9
	Cor. Mean									-0.9	-2.3*	-1.7	-3.3*

* = statistically significant difference compared to placebo
Cor. Mean = Placebo Subtracted Average Difference
+ = Baseline minus Week 3 (This was done because of study design)

Isaac W. Hammond, MD, Ph.D

Sitting Diastolic Blood Pressure - Subgroup Analysis

The change in DBP in placebo controlled trials was evaluated among subgroup based on demographic variables. There are limitations in most of the studies such that each study may not be useful for each analysis. Table S.4 lists the placebo subtracted change in sitDBP at endpoint as a function of age.

Table S.4 Placebo Subtracted Change in SitDBP (Placebo Controlled Trials) By Age

			Eprosartan BID Regimen														Eprosartan QD Regimen							
Prot. #		N	25	N	50	N	100	N	150	N	200	N	300	N	400	N	400	N	600	N	800	N	1200
010	<65			20	-3.2	17	1.6	17	-4.1	19	-7.0												
	≥65			6	-1.4	9	-1.3	5	6.1	3	-1.4												
011	<65	77	-2.9*			71	-1.9			73	-4.8*	68	-4.7*	68	-6.2*								
	≥65	13	2.0			15	-5.2			17	-0.7	16	-2.6	22	-4.1								
049	<65															54	-2.1	52	-2.8	16	-2.4	54	-3.9*
	≥65															18	-4.3*	21	-2.8	32	-4.2	16	-1.4

Data Source: Appendix 3.13.3.2

Table S.5 lists the placebo subtracted change in sitDBP at endpoint as a function of race. When data from all studies are combined, black subjects represent approximately 10% of all subjects randomized into treatment groups, so we are unable to draw any conclusions from the data. Examination of the change in sitDBP for blacks appear to be less than the change observed for white subjects.

Table S.5 Placebo Subtracted Change in SitDBP (Placebo Controlled Trials) By Race

			Eprosartan BID Regimen													Eprosartan QD Regimen							
Protocol		N	25	N	50	N	100	N	150	N	200	N	300	N	400	N	400	N	600	N	800	N	1200
010	Blk..			1	-1.1	4	2.3	6	6.0	5	0.0												
	NBlk			25	-3.8	22	0.0	16	-5.0	17	-8.2												
011	Blk.	7	+			13	+			13	+	8	+	3	+								
	NBlk	83	-2.6*			73	-2.4*			77	-4.0*	76	-4.2*	87	-5.7*								
049	Blk.															17	-2.0	17	-3.3	11	-1.0	15	-2.6
	NBlk															55	-2.9	56	-2.9	60	-3.2*	55	-4.7*

Data Source: Appendix 3.13.3.2

+ = Cannot be Calculated because of center* drug interaction

Table S.6 lists the placebo subtracted change in sitDBP at endpoint as a function of Sex. In protocol 010, the study enrolled only male subjects. This was one of the first few studies carried out by the sponsor. At that time of the study, toxicologic studies needed to ensure that the drug could be used in females were not completed so females were not included. In study protocol 049, the change in sitDBP could not be calculated because of center by drug interaction. This leaves us with only one study (011) that provides data for the true comparison of the effect of eprosartan among male and females, so it may be inappropriate to comment on the efficacy of this drug among females.

Table S.6 Placebo Subtracted Change in SitDBP (Placebo Controlled Trials) By Sex

			Eprosartan BID Regimen														Eprosartan QD Regimen							
Protocol		N	25	N	50	N	100	N	150	N	200	N	300	N	400	N	400	N	600	N	800	N	1200
010	F				♀		♀		♀		♀												
	M			26	-2.2	26	1.6	22	-1.5	22	-6.0												
011	F	37	-4.8*			31	-4.2*			30	-3.8*	32	-4.2*	27	-6.1*								
	M	53	-0.9			55	-0.9			60	-3.7*	52	-4.2*	63	-5.5*								
049	F															20	+	26	+	32	+	36	+
	M															52	-1.5	47	-3.1*	39	-0.8	34	-3.3*

Data Source: Appendix 3.13.3.2

♀ = No Females in Study

+ = Cannot be calculated because of Center * Drug interaction

Sitting Systolic Blood Pressure

Table S.7 lists the mean changes in sitSBP at endpoint in placebo controlled trials.

Table S.7 Placebo Subtracted Change in SitBBP at Endpoint in Placebo Controlled Trials

	Eprosartan BID Regimen							Eprosartan QD Regimen			
Protocol	25	50	100	150	200	300	400	400	600	800	1200
010		-1.9	-2.3	-1.9	-8.2						
011	-0.8		-3.3		-6.6*	-7.6*	-8.2*				
049								-4.1*	-7.5*	-4.9*	-9.5*

Data Source: Table 14.2.1, Appendix 3.13.3.2

Response Rate

A successful response was defined as sitDBP < 90 mm Hg or ≥ 10 mm Hg change from baseline. Table S.8 list the response rates at endpoint for the placebo controlled trials that did not have a dose titration. In studies with multiple eprosartan dose groups (protocols 010, 011, 016, 017, 045, 049), there is

generally an increase in response with increases in dose.

Table S.8 Response Rates at Endpoint in Parallel Dose Placebo Controlled Trials

		Eprosartan BID Regimen							Eprosartan QD Regimen			
Protocol	Placebo	25	50	100	150	200	300	400	400	600	800	1200
010	9.1		42.3	15.4	27.3	54.5						
011	19.8	30.0		33.7		37.0	42.4	45.6				
016	30.8		45.3	51.0								
017	60.9			65.9		73.6						
045	20.0								25.8			
049	23.6								27.8	28.8	36.1	43.7

Twice Daily Dosing

The only study to compare twice daily dosing with once daily dosing was protocol 013. Protocol 013 is randomized, double-blind, placebo controlled, dose titration, parallel trial. Patients with sitting DBP ≥ 95 and ≤ 114 mm Hg at baseline were randomized to placebo, eprosartan 200 mg bid or 400 mg qd. After 3 weeks of treatment, patients who continue to have elevated blood pressure had their dose increased (to either 300 mg bid or 600 mg qd, "level 2"). After another 3 weeks at the level 2 dose, patients who continue to have elevated blood pressure had their dose increased again to either 400 mg bid or 800 mg qd, "level 3", and re-evaluated after another 3 weeks. Approximately 55/70 78.6% of patients given bid dosing required dose titration compared to 65/73 (89.0%) of the once daily patients . Overall, 63/154 (40.9%) of patients treated with eprosartan responded to treatment. Table S.8 Lists the mean change in sitDBP at different time points for these patients. There is no significant difference between once a day and twice a day dosing.

Table S.8 Mean Change in sitDBP for patients who had dose titration in Protocol 013

	Week 3		Week 6		Week 9		Study Endpoint	
	N	Mean	N	Mean	N	Mean	N	Mean
Placebo	83	-3.8	74	-5.1	69	-4.4	86	-4.2
Eprosartan 200 → 400 mg BID	76	-5.4	71	-10.0	69	-9.0	77	-9.2
Eprosartan 400 → 800 mg QD	76	-7.1	75	-9.5	72	-8.4	77	-9.4

Trough-Peak Effect

Protocols 011 and 049 collected blood pressure measurements at trough and at time points other than trough. In protocol 049, the maximum decline in sitDBP occurred at 2 hours post dosing (compared to trough baseline) at week 4. So the 2 hour post dose Trough-Peak values measured at week 4 are reported in Table S.10 Protocol 049 also reported trough-to-peak ratios at 8 weeks, this data is reported in Table S.11

Time to Steady State

Protocols 011 and 049 provided data to determine time to steady state. The two studies showed that steady state blood pressure control can be reached in two weeks

Table S.10 Placebo Subtracted Change in SitDBP at Week 4 in Placebo Controlled Trials

	Eprosartan BID Regimen					Eprosartan QD Regimen			
	25	100	200	300	400	400	600	800	1200
Peak Chg.	-7.1	-7.2	-9.9	-10.3	-9.5	-8.1	-9.0	-9.9	-11.1
Trough Chg.	-4.4	-5.6	-6.6	-7.3	-6.6	-5.7	-5.1	-6.3	-7.2
Trough/Peak Ratio	0.20	0.60	0.50	0.59	0.52	0.56	0.24	0.46	0.52

Data Source: Table 14.23.1, Appendix 3.13.3.2

Table S.11 Placebo Subtracted Change in SitDBP at Week 8 in Protocol 049

	Eprosartan BID Regimen					Eprosartan QD Regimen			
	25	100	200	300	400	400	600	800	1200
Peak Chg.						-7.9	-11.6	-7.4	-10.5
Trough Chg.						-4.4	-6.2	-4.9	-6.7
Trough/Peak Ratio						0.08	0.24	0.19	0.34

Data Source: Table 14.23.1

PLACEBO CONTROLLED TRIALS

Study #	Design	Measure of Efficacy	Treatment Groups	N
010**	-r, db, pc, p, 4 weeks Tx period - hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg).A US study - Male Only	ABPM	- placebo - eprosartan 50 mg bid - eprosartan 100 mg bid - eprosartan 150 mg bid - eprosartan 200 mg bid	22 26 26 22 22
011*	-r, db, pc, p, 8 weeks Tx period - hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg).Canadian and US study	- change in average sitting DBP	- placebo - eprosartan 25 mg bid - eprosartan 100 mg bid - eprosartan 200 mg bid - eprosartan 300 mg bid - eprosartan 400 mg bid	93 91 87 90 86 91
013*	-r, db, pc, dt, p, 13 weeks Tx period -hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg).European Dose Titration study	- change in average sitting DBP	- placebo - eprosartan 200 mg bid - eprosartan 300 mg bid - eprosartan 400 mg bid - eprosartan 400 mg qd - eprosartan 600 mg qd - eprosartan 800 mg qd	86 79 78
016**	-r, db, pc, p, 4 weeks Tx period -hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg). -eprosartan was added to 25 mg HCTZ US study	- change in average sitting DBP	- placebo - eprosartan 50 mg bid + HCTZ - eprosartan 100 mg bid + HCTZ	52 53 51
017**	-r, db, pc, p, 9 weeks Tx period -hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg). European study - involving only Elderly in dose titration.	- change in average sitting DBP	- placebo - eprosartan 100 mg bid - eprosartan 200 mg bid	47 92 91
045**	-r, db, pc, p, 4 weeks Tx period -hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg). A US study - Male Only	ABPM	- placebo - eprosartan 400 mg qd	30 31
049*	-r, db, pc, mc, p, 8 weeks Tx period - hypertensive patients (mean sitting DBP ≥ 95 and ≤ 114 mm Hg).A US study	- change in average sitting DBP	- placebo - eprosartan 400 mg qd - eprosartan 600 mg qd - eprosartan 800 mg qd - eprosartan 1200 mg qd	74 72 73 73 72

qd = once daily; bid = twice daily; r = randomized; db = double-blind; pc = placebo controlled; Tx = treatment; mc = multi center; p = parallel; ac = active control; dt=dose titration * = pivotal trial; ** = supporting trial

Active Controlled Trials

Study #	Design	Measure of Efficacy	Treatment	N
014	-r,db,ac,p,26 wks Tx period - hypertensive pts (mean sitting DBP ≥ 95 and ≤ 114 mm Hg). Europe, N. America, S. Africa	-change in average sitting DBP	-eprosartan 200 mg bid -eprosartan 300 mg bid -epro. 300 + HCTZ 25 qd -enalapril 5 mg qd -enalapril 10 mg qd -enalapril 20 mg qd -enal. 20 qd + HCTZ 12.5 qd -enal. 20 qd + HCTZ 25 qd	264 264
041	-r,db,ac,p,26 wks Tx period - hypertensive pts (mean sitting DBP ≥100 and ≤ 114 mm Hg). A US study	-change in average sitting DBP	-eprosartan 200 mg bid -eprosartan 300 mg bid -nifedipine 60 mg qd -nifedipine 90 mg qd -epro. 300 bid + nifed. 60 qd -nifed. 90 qd + epro. 100 bid -nifed. 90 qd + epro. 200 bid	101 97
047	-r,db,ac,p,10 wks Tx period - hypertensive pts (mean sitting DBP ≥115 and ≤ 125 mm Hg). Europe, S. Africa	-change in average sitting DBP	-eprosartan 200 mg bid -eprosartan 300 mg bid -eprosartan 400 mg bid -epro. 300 bid + HCTZ 25 qd -enalapril 10 mg qd -enalapril 20 mg qd -enalapril 30 mg qd -enalapril 40 mg qd -enal 40 qd + HCTZ 25 qd	59 59
053	-r,db,ac,p,10 wks Tx period -A US study	-change in average sitting DBP	-placebo -eprosartan 300 mg bid -enalapril 20 mg qd	45 46 45