Protocol 010. A Four-Week, Double-blind, Parallel, Dose-Range Multi center Comparison of Oral Eprosartan Twice Daily with Placebo in Male Patients with Mild to Moderate Hypertension

Protocol

Design & Objective

This was a double-blind, randomized, parallel, dose-range comparison of twice daily doses of Eprosartan 50, 100, 150 and 200 mg and placebo consisting of four phases: screening, placebo run-in, 4 weeks double-blind treatment, and follow-up. The primary objective of the study was to demonstrate the effect of four dose levels of eprosartan in reducing blood pressure using 24-hour ambulatory monitoring (ABPM) in male patients with mild to moderate hypertension (defined as sitting diastolic BP between 95 and 115 mm Hg). The secondary objectives of this study were to assist in delineating doses for Phase III clinical trials and to assess activity over a 24-hour period through ABPM; to further define the safety of through observation of adverse events, laboratory abnormalities, and changes in ECGs; and to describe the population pharmacokinetics of eprosartan in patients with hypertension. The pharmacokinetic/ pharmacodynamic objective was to describe the relationship between plasma concentration and therapeutic response and/or adverse events in patients receiving eprosartan. The study included male patients only because the required toxicity studies were not completed at the time of the study, so females were not allowed to participate in the study.

Eligibility Criteria

Inclusion Criteria

1. Men between 18 and 75 years of age (inclusive).
2. Patients with essential hypertension (as defined below) at the end of the placebo run-in period defined as:
   - average sitting DBP ≥ 95 mm Hg and ≤ 114 mm Hg at three consecutive weekly visits and
   - the difference between the highest and lowest average sitting DBP values for the last three visits did not exceed 10 mm Hg; and the difference between the averages at the last two visits did not exceed 5 mm Hg.
3. Patients with newly diagnosed essential hypertension, or those previously treated patients from whom antihypertensive therapy could be safely withdrawn for the duration of the study.

Exclusion Criteria

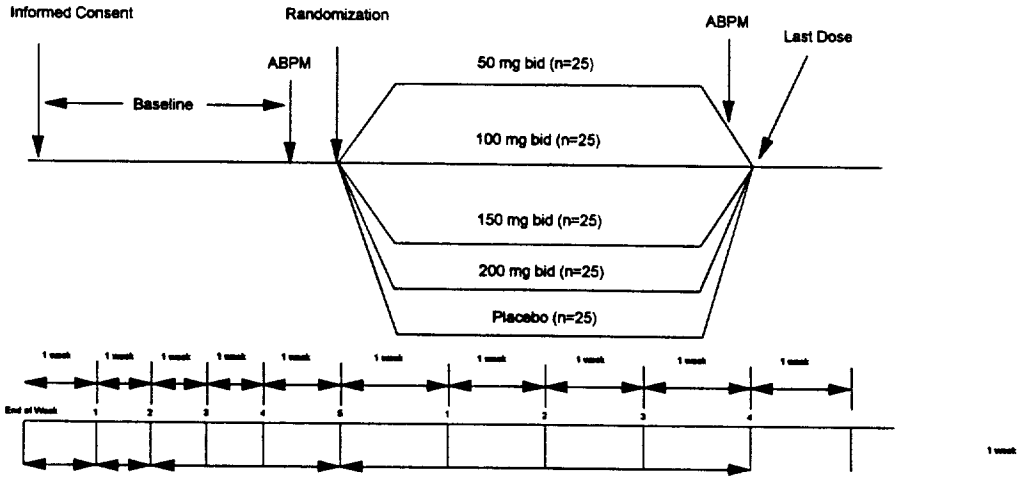
1. secondary forms of hypertension
2. advanced hypertensive retinopathy
3. mean sitting SBP >200 mm Hg
4. advanced atrio-ventricular conduction defect unless a pacemaker is in place
5. significant ventricular tachyarrhythmias requiring therapy
6. bradycardia (resting sitting heart rate <50 bpm) after withdrawal of previous antihypertensive medications
7. signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days
8. congestive heart failure (CHF) on treatment with ACE inhibitors or diuretics, patients with untreated reduced ejection fraction may be included
9. angina pectoris treated with regular doses of nitrates, beta blockers, or calcium channel blockers
10. diabetes mellitus that is unstable despite treatment with insulin or oral hypoglycemic agents
11. clinically significant renal or hepatic disease, serum creatinine >2.5 mg/dl (220 micromol/L), ALT, AST, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range
12. leukocyte count <3000/mm^3 or platelet count <100,000/mm^3
13. other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality that, in the opinion of the investigator, could preclude participation or survival

14. active alcohol or drug abuse
15. use of warfarin or other oral anticoagulants within 30 days before the screening visit
16. use of an investigational drug within 30 days before enrollment into this study or within five half-lives of the investigational drug (the longer period will apply)
17. concomitant administration of any medication known to affect blood pressure
18. concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low dose aspirin up to 325 mg per day). Patients must have discontinued such drugs for at least 7 days before the screening visit
19. concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazine derivatives
20. patients sensitive to eprosartan or other drugs in its class
21. patients who have received randomized medication in a previous trial of eprosartan

Description of Phases

The study consisted of four phases including screening, placebo run-in, double-blind treatment, and follow-up. After the initial screening visit, subjects entered a three-to five-week single-blind, placebo run-in phase to establish baseline parameters. When subjects qualified for inclusion they were randomized into one of the five treatment regimens for four weeks; twice daily doses of eprosartan 50 mg, 100 mg, 150 mg, or 200 mg, or placebo. Efficacy and safety assessments using ABPM, were again performed at the end of the 4-week treatment period. One week post-treatment, safety was assessed at a follow-up visit. The study design is presented in Figure 10.1

Figure 10.1 Study Design with Phases of Study



Primary & Secondary Endpoints

The primary efficacy parameter was the mean ambulatory blood pressure (MABP) measured from 0 to 12 hours after the morning dose of study medication. The MABP was defined as the mean of all programmed readings

during the specified period for ABPM recordings that have met all "successful reading criteria": Successful Reading Criteria for 24-Hour ABPM Recording:

- At least 80% of programmed recordings of BP are acceptable
- No consecutive lapses of recording 2 hours. (A lapse was defined as an hour of recording with less than two successful readings.)

The secondary efficacy parameters are as follows:

- MABP over hours 13-24.
- MABP over hours 0-24.
- MABP over 3- hour period starting with hour 0
- Peak/trough ratio of placebo-adjusted MABP for 0-12 and 13-24 hour intervals
- Percent of period (0-12 hours) that systolic and diastolic BPs were greater than 140 mm Hg and 90 mm Hg, respectively.
- Mean areas under the BP (systolic and diastolic) curves where recorded pressures exceeded (140 mm Hg and 90 mm Hg, respectively) when patients are awake, and where pressures exceed (120 mm Hg and 80 mm Hg, respectively when patients are asleep.
- Mean clinic BP (cuff readings) and heart rate.
- Proportion of responders in each treatment group, defined as those patients whose mean sitDBP was reduced to <90 mm Hg or by 10 mm Hg.

The baseline value for ABPM was defined as the MABP recording at the end of the placebo run-in phase, corresponding to the same intervals as the primary and secondary efficacy parameters. The baseline value for clinic BP and heart rate was defined as the average of the three values obtained prior to the qualifying ABPM at the end of run-in, and before the first dose of randomized study medication was administered.

Committees

There were no steering, safety, events or executive committees involved in this protocol

Statistical Methods

Efficacy:

Demographic variables (categorical data) were compared using the Chi-square test, while the analysis of variance was used to analyze blood pressure and other continuous variables. The model included center, regimen and Center-by-Regimen interaction terms. The sample size of 25 per group was established to provide 85% power to detect a difference of 5 mm Hg in change from baseline. This assumed a standard deviation of 6.5 mm Hg and used 0.05 level of significance. These were the protocol specified tests.

Interim Analysis

No interim analysis was planned or carried out for this study.

Results

Due to methodological difficulties, peak to trough ratios were not calculated. With this intent-to-treat protocol, all available patients' data were used. Since some of the patients had an inadequate number of BP readings, calculations of percent of time were not used.

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 10.1

Table 10.1 Patient Disposition

No. of Patients	Placebo	Eprosartan BID Regimen				Total
		50 mg	100 mg	150 mg	200 mg	
Screened						118
Randomized	22	26	26	22	22	118
Completed treatment	22	24	24	22	22	114
Premature discontinuations	0	2	2	0	0	4
Evaluated for ITT	22	24+	24	22	22	114

+One patient did not have valid daytime ABPM readings due to equipment failure, Since the primary efficacy parameter is mean ABPM measured from 0 to 12 hours after the morning dose, this patient's data are not included in these analyses.

Data Source: Appendix 3.1.1, 3.1.3.2, 3.1.4.1

Demographic characteristics

Patient demographic information includes age and race are summarized in Table 10.2. All patients enrolled in the study were male because the required toxicity studies were not completed at the time of the study, so females were not allowed to participate in the study. The study was conducted by 18 investigators in the United States. While the majority of the patients in each treatment group were white, the ratio of white to black patients did not differ significantly among the groups.

Table 10.2 Demographic characteristics of all patients by regimen

			Eprosartan BID Regimen				
		Placebo	50 mg	100 mg	150 mg	200 mg	Total
Sample Size		n=22	n=26	n=26	n=22	n=22	N=118
Age (years)		55.3±11.8	54.3±9.9	56.0±12.4	55.8±8.8	51.1±10.1	54.5±10.7
Age Range		38-79	35-70	20-73	38-70	29-67	20-79
Race n(%)	Black	5(22.7)	1(3.8)	4(15.4)	6(27.3)	5(22.7)	21(17.8)
	Caucasian	12(54.5)	23(88.5)	21(80.8)	14(63.6)	17(77.3)	87(73.7)
	Other	5(22.7)	2(7.7)	1(3.8)	2(9.1)	0	10 (8.5)

+ Represent data for randomized patients only

Data Source: Section 13.0, App. 3.2.2 and 3.2.3

Efficacy Results

The primary efficacy parameter was defined as MABP measured from 0 to 12 hours after morning dose of study medication. Baseline visit was defined as the end of the placebo run-in phase, and end of study was defined as the last visit on double blind medication. Table 10.3 presents a summary of the analysis of MABP measured from 0 to 12 hours after the morning dose of study medication. The ANOVA test, which was the protocol specified

test, was used to test the overall statistical significance of the blood pressure change. Mean ambulatory diastolic blood pressure was found to be significantly decreased from baseline, but the results was driven by the highly significant effect of the following two doses (150 mg and 200 mg). The overall ANOVA was significant with a p=0.0184.

Table 10.3 Mean (±SD) ambulatory blood pressure (MABP) at baseline and endpoint measured 0 - 12 hrs.

MABP (mm Hg)		Eprosartan BID Regimen			
0 - 12 hours	Placebo n=22	50 mg n=24	100 mg n=24	150 mg n = 22	200 mg n = 22
Diastolic					
Baseline	94.0±6.2	94.2±6.3	94.8±5.1	94.3±4.4	95.0±5.6
Endpoint	93.6±7.7	90.4±7.2	93.0±5.2	89.2±6.0	89.2±7.7
Change	-0.4±6.5	-3.8±5.9	-1.8±5.3	-5.1±5.7	-5.8±8.0
Placebo Subtracted		-3.4	-1.4	-4.7*	-5.4**
Systolic					
Baseline	156.6±9.7	159.0±14.7	160.5±9.9	158.0±12.0	158.5±10.1
Endpoint	155.5±10.3	152.3±16.2	156.9±12.3	152.5±11.4	149.9±13.6
Change	-1.1±8.1	-6.7±10.9	-4.6±9.1	-5.5±7.6	-8.6±8.2
Placebo Subtracted		-5.6	-3.5	-4.4	-7.5**

* p=0.0075 ** p=0.0049
Data source Appendix 3.3.1, 3.3.3

Secondary Efficacy

The secondary efficacy parameters were defined as the mean change from baseline: MABP over hours 13-24, MABP over hours 0-24, MABP over 3- hour period starting with hour 0, peak/trough ratio of placebo-adjusted MABP for 0-12 and 13-24 hour intervals, percent of period (0-12 hours) that systolic and diastolic BPs were greater than 140 mm Hg and 90 mm Hg, respectively, mean areas under the BP (systolic and diastolic) curves where recorded pressures exceeded (140 mm Hg and 90 mm Hg, respectively) when patients are awake, and where pressures exceed (120 mm Hg and 80 mm Hg, respectively when patients are asleep, mean clinic BP (cuff readings) and heart rate, proportion of responders in each treatment group, defined as those patients whose mean sitDBP was reduced to < 90 mm Hg or by 10 mm Hg. Tables 10.4 to 10.7 present summaries of selected secondary efficacy parameters.

Table 10.4 presents a summary of MABP at baseline and at endpoint measured from 12 to 24 hours. A comparison of MABP measured 12 - 24 hours, using the protocol specified ANOVA test, showed that there were no statistically significant decrease in blood pressure (DBP, p=0.3352; SBP, p=0.2046).

Table 10.4 Mean (±SD) ambulatory blood pressure (MABP) at baseline and endpoint measured 12 - 24 hrs.

MABP (mm Hg)		Eprosartan			
12 - 24 hours	Placebo n=22	50 mg n=24	100 mg n=24	150 mg n = 22	200 mg n = 22
Diastolic					
Baseline	86.8±6.0	83.7±8.3	89.2±7.7	84.5±8.1	86.4±7.8
Endpoint	85.1±8.2	81.5±8.3	84.7±8.8	80.5±7.2	81.2±6.9
Change	-1.7±7.0	-2.2±6.9	-4.5±5.4	-4.1±8.1	-5.2±6.2
Placebo Subtracted		-0.5	-2.8	-2.4	-3.5
Systolic					
Baseline	144.9±10.1	145.0±15.8	153.0±13.3	145.1±14.6	146.0±13.7
Endpoint	142.5±10.3	138.9±14.9	144.9±15.1	138.2±12.6	139.1±13.8
Change	-2.4±9.3	-6.2±10.4	-8.1±8.4	-7.0±11.5	-6.9±7.9
Placebo Subtracted		-3.8	-5.7	-4.6	-4.5

Data source Appendix 3.13.2.2

Table 10.5 presents a summary of MABP at baseline and at endpoint measured from 0 to 24 hours. A comparison of the MABP measured 0 - 24 hours, using the protocol specified ANOVA test, showed that there were no statistically significant decrease in blood pressure (DBP, p=0.0641; SBP, p=0.0793).

Table 10.5 Mean (±SD) ambulatory blood pressure (MABP) at baseline and endpoint measured 0 - 24 hrs.

MABP (mm Hg)		Eprosartan			
0 - 24 hours	Placebo n=22	50 mg n=24	100 mg n=24	150 mg n = 22	200 mg n = 22
Diastolic					
Baseline	90.4±5.0	88.8±6.4	91.8±6.0	89.5±5.3	90.5±6.0
Endpoint	89.2±7.0	86.3±6.8	89.0±6.0	85.0±5.9	85.3±6.5
Change	-1.2	-2.5	-2.8	-4.5	-5.2
Placebo Subtracted		-1.3	-1.6	-3.3	-4.0
Systolic					
Baseline	150.8±8.2	152.0±14.3	156.7±10.8	151.5±12.4	152.2±10.7
Endpoint	149.0±8.9	145.5±13.9	151.3±12.5	145.5±11.3	144.5±12.8
Change	-1.8	-6.5	-5.4	-6.0	-7.7
Placebo Subtracted		-4.7	-3.6	-4.2	-5.9

Data source Appendix 3.3.1, 3.3.3 and 3.5.1

Table 10.6 presents a summary of mean clinic trough sitting vital signs at baseline and at endpoint. Blood pressure recordings were obtained using the mercury sphygmomanometer. A comparison of the clinic sitting diastolic blood pressures, using the ANOVA test, showed that there was a statistically significant decrease in diastolic blood pressure with p=0.0005. The multiple comparison test, however, showed that the highly significant result of the ANOVA was driven by one significantly effective dose (200 mg bid). Sitting systolic blood pressure and heart rate was not significantly decreased.

Table 10.6 Mean (±SD) Clinic Sitting vital signs at baseline and endpoint.

MABP (mm Hg)		Eprosartan Twice Daily			
0 - 12 hours	Placebo n=22	50 mg n=24	100 mg n=24	150 mg n = 22	200 mg n = 22
Diastolic					
Baseline	102.1±4.5	101.0±4.4	103.0±5.4	101.4±5.0	102.5±4.7
Endpoint	98.7±6.6	95.1±7.8	101.2±7.4	96.5±6.4	93.0±6.5
Change	-3.4±4.9	-5.9±5.8	-1.8±5.8	-4.9±6.1	-9.5±6.3
Placebo Subtracted		-2.5	+1.6	-1.5	-6.1*
Systolic					
Baseline	152.0±10.0	151.9±11.8	161.4±15.5	153.9±15.8	153.7±13.7
Endpoint	147.5±12.4	145.4±17.1	155.3±14.6	148.5±13.6	141.0±14.1
Change	-4.5	-6.5	-6.1	-5.4	-12.7
Placebo Subtracted		-2.0	-1.6	-0.9	-8.2
Heart Rate					
Baseline	72.7±6.6	76.6±10.3	74.0±8.1	70.2±9.5	72.2±7.8
Endpoint	75.2±6.4	76.3±10.9	75.3±6.8	70.7±10.6	72.5±8.6
Change	+2.5	-0.3	+1.3	+0.5	+0.3
Placebo Subtracted		+2.8	+1.2	+2.0	+2.2

* p=0.001 ** p=0.0156 Data source Appendix 3.4.1 and 3.6.1

Table 10.7 presents a summary of the percent responders to eprosartan at endpoint. The data indicates that 54.5% of the subjects taking the effective dose responded to the drug.

Table 10.7 Number (%) of clinical responders at endpoint

		Eprosartan			
	Placebo n=22	50 mg n=24	100 mg n=24	150 mg n = 22	200 mg n = 22
All Patients	2(9.1)	11(42.3)	4(15.4)	6(27.3)	12(54.5)

responder was defined as patient whose mean sitDBP was reduced to <90 mm Hg or if > 90 mm Hg but declined by 10 mm Hg.

Conclusion:

Based on the review of this study, it was concluded that the minimum effective dose of eprosartan for significant reduction of blood pressure among men, was 200 mg given twice daily.

Reviewer's Comments

It was expected that this drug which is proposed to be dosed once daily, will have a blood pressure effect that is sustained over a 24 hour period. It was noted that even when dosed twice daily, the effect on blood pressure from 0 to 12 hours was significant. However, the effect from 13 to 24 hours was not significant. This observation should be reconciled with clinical pharmacology studied in deciding on the dosing interval for this drug.

Protocol 011. An 8-Week, Double-Blind, Parallel, Dose Range, Multicenter, North American Comparison of Oral Eprosartan 25 to 400 mg Twice Daily With Placebo in Patients with Essential Hypertension (DBP ≥95 and ≤114 mm Hg).

Protocol

Design & Objective

This was a prospective, randomized, multicenter, double blind, placebo controlled, parallel, Phase III, study in patients with essential hypertension. Patients were randomized to receive eprosartan (25, 100, 200, 300, or 400 mg twice daily) or placebo. The primary Objective of the study was to demonstrate the antihypertensive effect of eprosartan at doses of 25, 100, 200, 300, and 400 mg twice daily compared with placebo in patients with essential hypertension and an average SitDBP ≥95 mm Hg and ≤114 mm Hg. The secondary objectives were to further define the safety of eprosartan through observation of adverse experiences, laboratory abnormalities, standing BP and heart rate (HR), and changes in ECGs and to describe the population pharmacokinetics of eprosartan in patients with hypertension.

Inclusion Criteria

1. Men, or women without child-bearing potential (post menopausal, i.e., 6 months without menstrual period; surgically sterile), or women using hormonal or barrier contraceptives or intrauterine contraceptive devices; all of whom were at least 18 years of age and had given their written informed consent to participate.
2. Patients with essential hypertension (as defined below) at the end of the placebo run-in period defined as:
   - average sitting DBP ≥ 95 mm Hg and ≤ 114 mm Hg at three consecutive weekly visits and
   - the difference between the highest and lowest average sitting DBP values for the last three visits did not exceed 10 mm Hg; and the difference between the averages at the last two visits did not exceed 5 mm Hg.
3. Patients with newly diagnosed essential hypertension, or those previously treated patients from whom antihypertensive therapy could be safely withdrawn for the duration of the study.

Exclusion Criteria

1. pregnancy or lactation
2. secondary forms of hypertension
3. advanced hypertensive retinopathy
4. mean sitting SBP >200 mm Hg
5. advanced atrio-ventricular conduction defect unless a pacemaker is in place
6. significant ventricular tachyarrhythmias requiring therapy
7. bradycardia (resting sitting heart rate <50 bpm) after withdrawal of previous antihypertensive medications
8. signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days
9. congestive heart failure (CHF) on treatment with ACE inhibitors or diuretics, patients with

untreated reduced ejection fraction may be included

10. angina pectoris treated with regular doses of nitrates, beta blockers, or calcium channel blockers
11. diabetes mellitus that is unstable despite treatment with insulin or oral hypoglycemic agents
12. clinically significant renal or hepatic disease, serum creatinine >2.5 mg/dl (220 micromol/L), ALT, AST, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range
13. leukocyte count <3000/mm^3 or platelet count <100,000/mm^3
14. other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality that, in the opinion of the investigator, could preclude participation or survival
15. active alcohol or drug abuse
16. use of warfarin or other oral anticoagulants within 30 days before the screening visit
17. use of an investigational drug within 30 days before enrollment into this study or within five half-lives of the investigational drug (the longer period will apply)
18. concomitant administration of any medication known to affect blood pressure
19. concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low dose aspirin up to 325 mg per day). Patients must have discontinued such drugs for at least 7 days before the screening visit
20. concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazine derivatives
21. patients sensitive to eprosartan or other drugs in its class
22. patients who have received randomized medication in a previous trial of eprosartan

Description of Phases

The study consisted of four periods including Screening, Placebo Run-in, Double-blind Treatment, and Follow-up. After screening, subjects entered a 4-6 week single blind placebo run-in period to establish baseline parameters. The double-blind treatment period consisted of 8 weeks, where subjects were randomized to treatment with eprosartan 25 mg bid, 100 mg bid, 200 mg bid, 300 mg bid, 400 mg bid or placebo The Baseline Visit was defined as the end of the Placebo Run-in Period (Week 4, 5, or 6), when the patient qualified for randomization to receive double-blind medication. At study completion, patients could either enter an open-label, long-term, extension study (protocol 050) or return within 7 to 14 days for a Follow-up Visit. The study design is schematically presented below in Figure 11.1.

Primary & Secondary Efficacy Parameter

The primary efficacy variable was defined as the mean change from Baseline in sitting diastolic blood pressure at trough. The secondary efficacy variables are as follows:

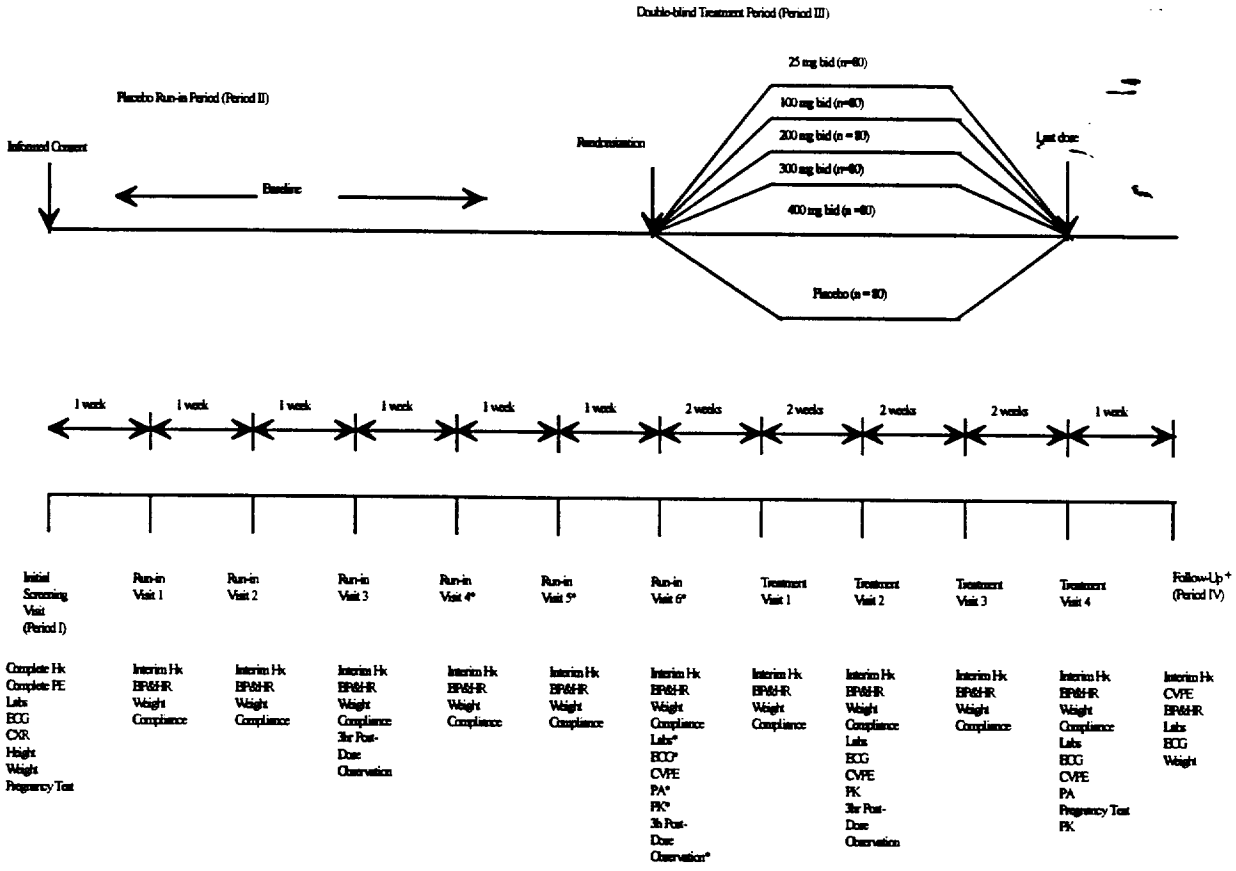
- Mean change from baseline in SitDBP (peak measurement).
- Mean change from baseline in StaDBP (peak and trough measurements).
- Mean change from baseline in SitSBP and StaSBP (peak and trough measurements).
- Mean change from baseline in SitHR and StaHR (peak and trough measurements).
- Proportion of responders in each treatment group, defined as the percentage of patients with SitDBP <90 mm Hg or 90-100 mm Hg and decreased from baseline by at least 10 mm Hg.
- Trough to peak ratio of efficacy defined in terms of the primary efficacy index.
- Mean change from baseline in fasting lipid values (total cholesterol, HDL, LDL, triglycerides), glucose, and electrolytes in the total patient data set and in the subset of patients with baseline values above the reference range.
- Proportion of patients with persistent nonproductive (dry) cough in each treatment group

Committees

There were no steering, safety, events or executive committees involved in this protocol.

NDA 20-738

Figure 11.1. Study Design with Phases of Study



*PA, Labs, ECG, PK, and 3hr post-dose observation will be performed at Run-in Visit 4, 5 or 6, whenever the patient qualifies for randomization.
+Only for patients not continuing into extension study.
CVPE = Cardiovascular Pulmonary Exam
PK = Pharmacokinetics Assessment
PA = Pulmonary Assessment
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Statistical Methods

Efficacy:

An analysis of variance was used to calculate pairwise comparisons of the differences in treatment groups, along with Bonferroni confidence intervals. The model included treatment, center, and treatment-by-center interaction, unless the interaction was not significant (P>.10), in which case the interaction term was removed. Comparisons were made between each dose of eprosartan and placebo and also between the 300 mg and 400 mg doses for the difference in mean change from baseline at endpoint. The sample size of 80 evaluable patients per group was estimated to provide 90% power to detect a difference of 5 mm Hg in change from Baseline. This assumed a standard deviation of 8 mm Hg and used 0.05 level of significance, two-sided testing, and a Bonferroni adjustment for each active group compared to placebo and 300 mg twice daily compared to 400 mg twice daily.

Interim Analysis

No interim analysis was planned or carried out for this study.

Study Procedures

Table 11.1 presents the Schedule of Assessments carried out as part of the study.

Table 11.1 outlines the schedule for assessment of efficacy and safety parameters.

		Placebo Run-in (Period II)						Double-blind Treatment (Period III)				Post-Treatment Follow-up*
Assessment Visit No.	**Screening (Period I)**	1	2	3	4	5	6	1	2	3	4	**(Period IV)**
Informed Consent	x											
Inclusion/Exclusion	x											
Complete History	x											
Baseline Signs/Symptoms	x											
Physical Exam	x											
Funduscopy	x											
Prior Medications	x											
Pregnancy Test (Serum - hCG)	x										x	
Clinical Laboratory Tests	x				x++	x++	x++		x		x	x
ECG	x				x++	x++	x++		x		x	x
Chest x-ray**	x											
Height	x											
Weight	x	x	x	x	x	x	x	x	x	x	x	x
Interim History		x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications		x	x	x	x	x	x	x	x	x	x	x
BP & HR (Pre-dose)	x	x	x	x	x	x	x	x	x	x	x	x
BP & HR (Post-dose)				x	x++	x++	x++		x			
ABPM+					x++	x++	x				x	
PK (Pre-dose)									x		x	
PK (Post-dose)					x++	x++	x++		x			
PK Profile+											x	
CVPE	x				x++	x++	x++		x		x	x
Pulmonary Assessment					x++	x++	x++				x	
Study Drug Compliance		x	x	x	x	x	x	x	x	x	x	
Adverse Experiences		x	x	x	x	x	x	x	x	x	x	x

* Only for patients not continuing into the extension study.

** Chest x-ray performed within 12 months prior to screening was acceptable.

\+ Only selected sites performed the ABPM and PK supplemental studies.

++ Performed at Placebo Run-in Visit 4, 5, or 6, whenever patients became eligible to enter Period III.

Data Source: Protocol 011 is presented in Appendix A, Part 1.

Results

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 11.2.

Table 11.2 Patient disposition

No of patients:	Placebo	Eprosartan BID Regimen					Total
		25 mg	100 mg	200 mg	300 mg	400 mg	
Screened							788
Entered run-in							736
Randomized	93	91	87	90	86	91	538
Completed treatment	81	86	79	82	78	81	487
Follow-up*	35	32	22	30	27	29	175

* Follow-up was designed only for subjects not entering open label extension study.
Data Source: Tables 13.2, 13.3.1, 13.3.2, 15.10.

Demographic characteristics

The study was conducted by 34 investigators at 29 centers in the United States and 5 centers in Canada. Nine centers participated in the supplemental ABPM study and four in the PK profile study. The ABPM data was used in a substudy, and therefore not included in this review. The mean age was , 57.6±0.9 (ranged: 21-85 years) for subjects that were not randomized, compared to 54.7±1.1 (ranged: 20-86 years) for those 538 subjects who were randomized. A summary of patient demographic characteristics are presented in Table 11.3. There were significant differences in several demographic variables including; age, race and gender between the groups.

Table 11.3 Demographic characteristics of all patients by regimen

		Nonrandomized			Eprosartan bid Regimen				
Characteristic		Screened Only	Run-in Only	Placebo	25 mg	100 mg	200 mg	300 mg	400 mg
Sample Size		n=52	n=198	n=93	n=91	n=87	n=90	n=86	n=91
Age (years) (mean±SEM)		54.8±1.7	57.6±0.9	53.8±1.0	54.4±1.1	54.7±1.2	54.9±1.1	54.9±1.2	55.6±1.1
Age Range (years)		23 - 80	21 - 85	33 - 76	28 - 81	23 - 83	20 - 78	30 - 81	29 - 86
Race	Black	6	20	10	7	13	13	9	3
	Caucasian	45	167	74	80	70	73	73	82
	Oriental	0	1	5	0	1	1	2	0
	Other	1	10	4	4	3	3	2	6
Sex	Female	23	67	33	37	31	30	32	28
	Male	29	131	60	54	56	60	54	63

Data Source: Tables 13.7.1, 13.11, 13.12.1

EFFICACY RESULTS

Investigators

Thirty-four investigators participated in this study. They were chosen for their interest in the study and their ability to enter eligible patients. Five investigational sites were located in Canada and 29 investigational sites were located in the USA. One investigator in the US (Benjamin Levy, M.D., Center #026) was withdrawn from participation in the study by the sponsor for administrative reasons. Dr Levy did not enrol any subjects for the study. Based on information made available by the criminal investigational division of the agency, another investigator in the US (Robert A. Fiddes, M.D., J.D. #013) was withdrawn from participation in the study by the agency. Therefore, data from these investigational sites were not included in the analyses presented in this report; which is different from what was submitted by the sponsor.

The primary efficacy parameter was defined as the mean change from baseline sitting diastolic blood pressure at trough. Baseline Visit was defined as the end of the Placebo Run-in Period (Week 4, 5, or 6) and end of study was defined as the trough sitting diastolic blood pressure at visit 4 of the double blind period. Table 11.4 contains a summary of analysis involving trough sitting diastolic blood pressure. Eprosartan decreased sitting diastolic blood pressure significantly in all groups that were treated with medication, and the differences achieved statistical significance after correcting for the placebo effect. The doses studied ranged from 25 mg bid to 400 mg bid.

Table 11.4 Mean ± SEM Trough Sitting Diastolic Blood Pressure at Baseline and at End of Study

		Eprosartan Regimen				
Sitting DBP	Placebo (n=87)	25 mg bid (n=86)	100 mg bid (n=82)	200 mg bid (n=86)	300 mg bid (n=81)	400 mg bid (n=86)
Baseline	100.9±0.5	99.8±0.5	100.7±0.5	100.1±0.4	101.3±0.5	101.±0.5
End of Study	98.1±1.0	94.6±1.0	95.9±1.0	93.3±0.8	94.1±0.9	93.0±1.0
Change from Baseline	-2.8±0.7	-5.2±0.8	-4.8±0.8	-6.8±0.7	-7.2±0.7	-8.0±0.8
Least Squares Mean Difference from Placebo	p-value	-2.4 0.0146	-2.0 0.0344	-4.0 0.000142	-4.4 0.000031	-5.2 0.00000112

n = the number of patients with a Baseline value and study endpoint value.

* Indicates significance at 0.05 using modified Bonferroni procedure.

Data Source: Tables 14.1.1.; 14.17.1

The secondary efficacy parameters were defined as the mean change from baseline; sitting systolic blood pressure at trough, sitting heart rate at trough, standing diastolic blood pressure at trough, standing systolic blood pressure at trough, and standing heart rate at trough. Baseline visit was defined as the end of the placebo Run-in period (Weeks 4, 5, or 6) and the end of study was defined as the above listed variables at visit 4 of the double blind period. Table 11.5 presents a summary of the analyses involving the above listed variables. Eprosartan decreased all blood pressure measures significantly in all groups treated with medication, exhibited a dose response relationship to these blood pressure variables. However, eprosartan did not affect heart rate. The doses studied ranged from 25 mg bid to 400 mg bid.

Table 11.5 Mean ± SEM Trough Diastolic Blood Pressure at Baseline and Study Endpoint

		Eprosartan Regimen				
Vital Sign	Placebo (N=87)	25 mg bid (n=86)	100 mg bid (n=82)	200 mg bid (n=86)	300 mg bid (n=81)	400 mg bid (n=86)
Sitting SBP (mm Hg)						
Baseline	152.9±1.5	150.1±1.3	152.9±1.5	151.7±1.5	155.1±1.4	153.1±1.5
Study Endpoint	151.0±1.6	147.3±1.6	147.7±1.8	143.1±1.6	145.3±1.8	142.9±1.7
Change from Baseline	-1.9±1.2	-2.8±1.2	-5.3±1.3	-8.6±1.1	-9.8±1.5	-10.3±1.5
Δ from Placebo(p-value)		-0.8(0.650)	-3.3(0.071)	-6.6(.0003)	-7.6(.0001)	-8.2(.0001)
SitHR (bpm)						
Baseline	74.6±0.8	73.5±0.8	72.8±0.9	73.7±0.9	74.2±0.9	74.1±0.9
Study Endpoint	73.1±0.9	73.3±1.0	73.1±1.0	72.9±1.0	74.4±1.0	74.2±1.0
Change from Baseline	-1.5±0.6	-0.1±0.7	0.3±0.9	-0.8±0.8	0.2±0.6	0.1±0.8
Δ from Placebo(p-value)		1.3(0.229)	1.8(0.086)	0.7(0.484)	1.5(0.156)	1.6(0.133)
StaDBP (mm Hg)						
Baseline	102.1±0.6	100.5±0.5	101.4±0.5	101.0±0.6	102.3±0.6	102.1±0.5
Study Endpoint	100.2±1.0	96.9±0.9	97.5±0.9	94.8±0.8	96.5±0.9	94.8±1.0
Change from Baseline	-1.8±0.7	-3.6±0.8	-3.9±0.8*	-6.2±0.7	-5.8±0.8	-7.3±0.9
Δ from Placebo(p-value)		-1.8(0.101)	-2.2(0.049)	-4.3(.0001)	-4.1(.0002)	-5.5(.0001)
StaSBP (mm Hg)						
Baseline	152.4±1.5	149.0±1.3	152.4±1.5	151.0±1.6	154.7±1.5	152.9±1.5
Study Endpoint	151.7±1.7	147.0±1.6	147.9±1.7	142.6±1.7	146.0±2.0	143.2±1.8
Change from Baseline	-0.7±1.3	-2.0±1.3	-4.7±1.3	-8.4±1.2	-8.7±1.6	-9.7±1.4
Δ from Placebo(p-value)		-1.3(0.474)	-4.1(0.031)	-7.6(.0001)	-8.0(.0001)	-8.9(.0001)
StaHR (bpm)						
Baseline	77.3±0.9	76.7±0.9	75.9±0.9	77.3±0.9	77.5±1.0	77.0±0.9
Study Endpoint	76.4±1.0	76.6±1.1	75.8±1.0	76.3±1.0	78.0±1.2	76.6±1.0
Change from Baseline	-0.9±0.7	-0.1±0.8	-0.1±0.9	-1.0±0.7	0.5±0.8	-0.3±0.8
Δ from Placebo(p-value)		0.6(0.603)	0.8(0.463)	-0.2(0.868)	1.2(0.266)	0.4(0.679)

Data Source Table 14.18.1, 14.19, 14.20, 14.21, 14.22

* Indicates significance at 0.05 using modified Bonferroni procedure

Subgroup Efficacy Analysis

Age, Gender, and Race:

In this protocol, even though the primary efficacy parameter was defined as sitting diastolic blood pressure. In the subgroup analyses, it was not the reported parameter. The sponsor reported response rates and used the cochran-Mantel test to compare the groups. The data were re-analyzed as defined in the protocol (using the primary efficacy parameter), numeric differences, consistent with those reported in Table 11.5, but did not achieve statistical significance, probably because of lack of statistical power.

Trough-Peak

Trough-peak differences in sitting diastolic blood pressure were evaluated as per study protocol and the results using group means are presented below in Table 11.6. The sponsor did not present the protocol stated analysis of variance for peak-trough ratios. The placebo subtracted trough-peak ratio was defined as;

$$PlaceboSubtractedTrough-PeakRatio=\frac{(Trough_{Epro.Txed}-Trough_{Epro.B})-(Trough_{PlaceboTxed}-Trough_{PlaceboB})}{(Peak_{Epro.Txed}-Peak_{Epro.B})-(Peak_{PlaceboTxed}-Peak_{PlaceboB})}$$

Table 11.6 Mean ± SEM Placebo Subtracted Trough-Peak Ratios in Sitting Diastolic Blood Pressure at Baseline and at Week 4

	Eprosartan Regimen				
Sitting DBP	25 mg bid (n=88)	100 mg bid (n=80)	200 mg bid (n=83)	300 mg bid (n=78)	400 mg bid (n=85)
Mean	0.59	0.77	0.74	0.79	0.71

n = the number of patients with a Baseline value and study endpoint value.
Data Source: Tables 14.23.1.

The placebo subtracted ratios ranged from 0.59 for 25 mg bid to 0.79 for 300 mg bid. There was lack of consistency in the trend of these ratios.

Conclusion:

This study demonstrates that when given twice daily eprosartan at doses of 25 mg to 400 mg, effectively lowers diastolic blood and systolic blood pressure by statistically significant amounts with no effect on heart rate. Subgroup analyses as well as trough-peak ratios analyzed per protocol, did not yield statistically significant differences.

Protocol 013. A 13-Week, Double-Blind, Parallel, Multi-Center, Multi-Country Comparison of the Efficacy and Safety of Oral Eprosartan Taken Either Once Daily or Twice Daily with Placebo in Patients with Essential Hypertension (DBP ≥ 95 and ≤ 114 mm Hg).

Protocol

Design & Objective

This was a prospective, randomized, dose-titration, multi-center, double-blind, placebo-controlled, parallel group study in patients with essential hypertension with sitting diastolic blood pressure between 95 and 114 mm Hg. The primary objective of the study was to demonstrate the antihypertensive efficacy of oral eprosartan given once daily compared with twice daily. The secondary objectives were to evaluate the effect of eprosartan on fasting serum concentrations of lipids, glucose, and electrolytes; to further define the safety of eprosartan through observation of adverse experiences (AEs), laboratory abnormalities, and changes in electrocardiograms (ECGs) and to attempt to describe the relationship between plasma concentrations of eprosartan and efficacy assessments. In the ABPM sub-study the objective was to investigate the effect of the 2 eprosartan regimens, compared to placebo, on blood pressure using 24-hour ambulatory monitoring.

Inclusion Criteria

1. Men, or women without child-bearing potential (post menopausal, i.e., 6 months without menstrual period; surgically sterile), or women using hormonal or barrier contraceptives or intrauterine contraceptive devices; all of whom were at least 18 years of age and had given their written informed consent to participate.
2. Patients with essential hypertension (as defined below) at the end of the placebo run-in period defined as:
   - average sitting DBP ≥ 95 mm Hg and ≤ 114 mm Hg at three consecutive weekly visits and
   - the difference between the highest and lowest average sitting DBP values for the last three visits did not exceed 10 mm Hg; and the difference between the averages at the last two visits did not exceed 5 mm Hg.
3. Patients with newly diagnosed essential hypertension, or those previously treated patients from whom antihypertensive therapy could be safely withdrawn for the duration of the study.

Exclusion Criteria

1. pregnancy or lactation
2. secondary forms of hypertension
3. advanced hypertensive retinopathy
4. mean sitting SBP >200 mm Hg
5. advanced atrio-ventricular conduction defect unless a pacemaker is in place
6. significant ventricular tachyarrhythmias requiring therapy
7. bradycardia (resting sitting heart rate <50 bpm) after withdrawal of previous antihypertensive medications
8. signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days
9. congestive heart failure (CHF) on treatment with ACE inhibitors or diuretics, patients with untreated reduced ejection fraction may be included
10. angina pectoris treated with regular doses of nitrates, beta blockers, or calcium channel blockers
11. diabetes mellitus that is unstable despite treatment with insulin or oral hypoglycemic agents
12. clinically significant renal or hepatic disease, serum creatinine >2.5 mg/dl (220 micromol/L), ALT, AST, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range
13. leukocyte count <3000/mm^3 or platelet count <100,000/mm^3
14. other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory

abnormality that, in the opinion of the investigator, could preclude participation or survival
15. active alcohol or drug abuse
16. use of warfarin or other oral anticoagulants within 30 days before the screening visit
17. use of an investigational drug within 30 days before enrollment into this study or within five half-lives of the investigational drug (the longer period will apply)
18. concomitant administration of any medication known to affect blood pressure
19. concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low dose aspirin up to 325 mg per day). Patients must have discontinued such drugs for at least 7 days before the screening visit
20. concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazine derivatives
21. patients sensitive to eprosartan or other drugs in its class
22. patients who have received randomized medication in a previous trial of eprosartan
23. Hypertension due to current use of oral contraceptive agents.

Description of Phases

The study consisted of four periods; screening, placebo run-in, double-blind treatment, and follow-up. After screening, subjects entered a 4-6 week single blind placebo run-in period to establish baseline parameters. The double-blind treatment period consisted of 9 weeks double blind dose titration phase, where subjects were randomized to treatment with either eprosartan 400 mg qd or 200 mg bid placebo (Level 1). Dosage was titrated to 600 mg qd or 300 mg bid or placebo (Level 2), or subsequently to 800 mg qd or 400 mg bid or placebo (Level 3), if blood pressure is not controlled. Blood pressure control was defined as sitting DBP at trough <90 mm Hg; or ≤ 100 mm Hg with a decrease from baseline by at least 10 mm Hg. After completion of the dose titration period, a 4 week maintenance period was initiated only for those whose sitting diastolic blood pressure has been controlled at a given dose level. Subjects whose sitting diastolic blood pressure were not controlled at the end of the dose titration period were withdrawn from the study for lack of efficacy. Following withdrawal at week 9 of titration period or completion of the double blind treatment phase (week 13) subjects could consent to enter a long term extension study (protocol 052) which began on the same day as the week 9 or 13 visit. Those subjects not participating in the extension study were required to return for a follow up visit after 7-14 days. The study design is schematically presented in Figure 13.1 .

Primary & Secondary Endpoints

The primary efficacy parameter was mean change from baseline in sitting DBP measured at trough (pre-dose) at week 13. The secondary parameters were mean change from baseline in the following:

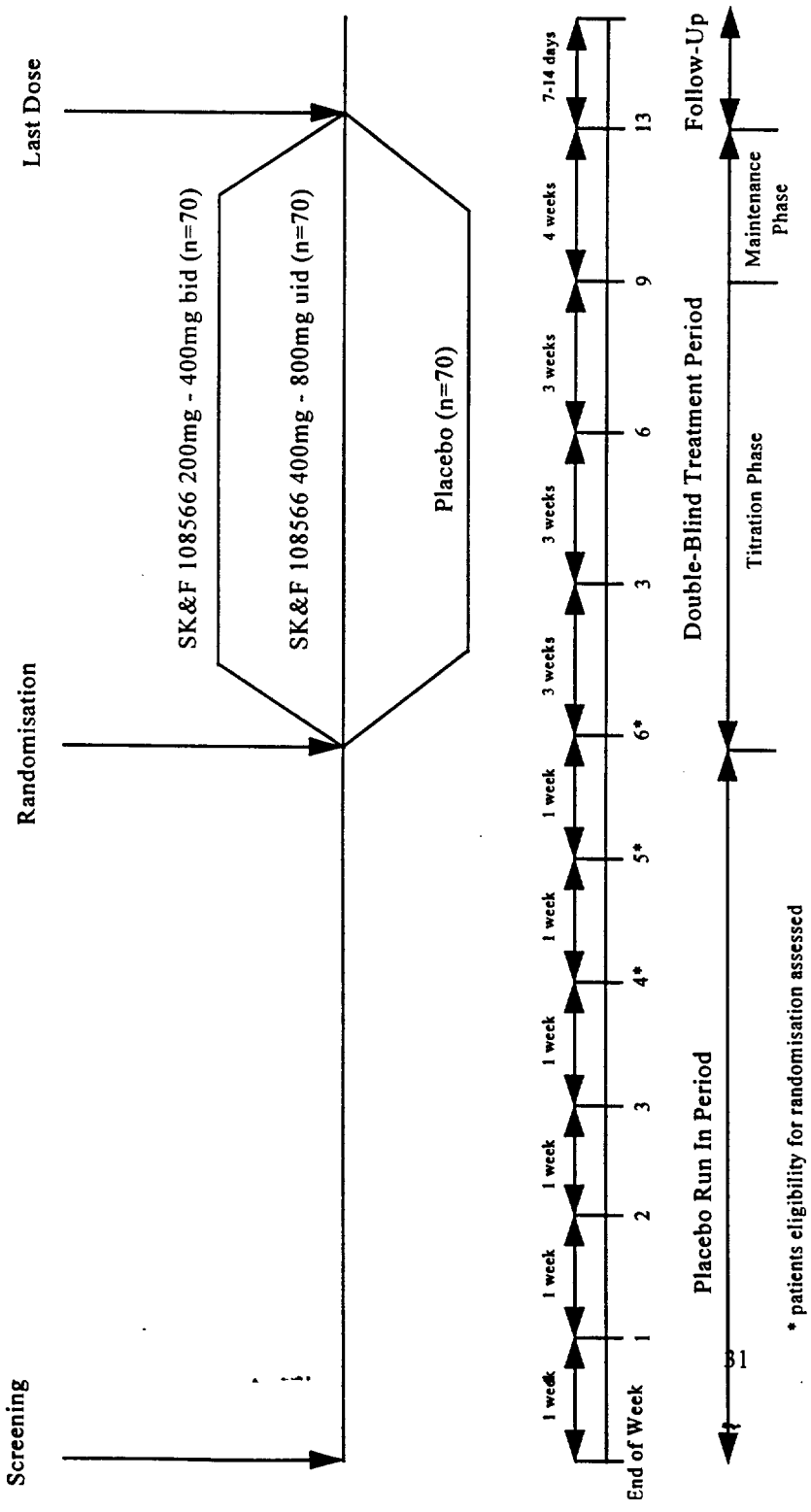
- sitting DBP at peak (3-hours post-dose),
- sitting systolic blood pressure (SBP) and heart rate (HR) at peak and trough,
- standing DBP, SBP and HR at peak and trough,
- proportion of responders on each medication regimen (that is, the percent of patients whose sitting DBP at trough was < 90 mm Hg; or ≤ 100 mm Hg and decreased from baseline by at least 10 mm Hg),
- trough to peak ratio of efficacy defined in terms of the primary efficacy variable and mean change from baseline in lipid values (total cholesterol, HDL, LDL, triglycerides) and serum glucose.

Committees

There were no steering, safety, events or executive committees involved in this protocol.

NDA 20-738

Figure 13.1 Study Design with Phases of Study



Isaac W. Hammond, MD, Ph.D

Statistical Methods

Efficacy:

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 interval were included in the analysis. The sample size of ~~70~~ evaluable patients on each medication regimen provided 90% power to detect a 5 mm Hg difference in the change from baseline between any two medication regimens. This assumed a standard deviation of 8 mm Hg and used a 0.05 level of significance, two-sided testing, with a Bonferroni adjustment for the three comparisons.

An analysis of variance (PROC GLM in SAS) was used to compare differences between regimens, along with Bonferroni confidence intervals. The model included terms for center, regimen and regimen-by-center interaction. The corrected trough to peak ratio representing the proportion of peak effect which remained at trough was calculated at week 9 for each eprosartan regimen and was corrected for both the placebo run-in effect for that patient group and for the effect seen at week 9 for the placebo regimen.

Interim Analysis

No interim analysis was planned or carried out for this study.

Results

Patient Disposition

The disposition of patients who participated in the study protocol is summarized in table 13.1.

Table 13.1 Patient disposition

No of patients:	Placebo	Eprosartan Regimen		Total
		Twice Daily	Once Daily	
Screened				311
Entered run-in				308
Randomized	86	79	78	243
Completed Week 13 treatment	28	36	47	111
Premature discontinuations	58	43	31	132
Evaluated for efficacy	86	77	77	240
Follow-up*	38	36	28	102

* Follow-up was designed only for subjects not entering open label extension study.

Data Source: Tables 13.3, 13.4.1, 13.10.1 and 15.18

Demographics characteristics

Subjects were recruited from 27 european centers. The number of subjects randomized per center ranged from 1 to 48. The mean age 57.1±0.7 years for subjects that were randomized, compared to 58.1±1.1 years for those 68 subjects who were screened but were not randomized. Variations in demographic and clinical variables between randomized and nonrandomized subjects were not statistically significant. A summary of demographic variables for randomized subjects is provided in Table 13.2.

Table 13.2 Demographic characteristics of all randomized patients by regimen

			Eprosartan Regimen		
Characteristic		Placebo	Twice Daily	Once Daily	TotalEfficacy Results
Sample Size		(n = 86)	(n = 79)	(n = 78)	(n = 243)
Age (years) (mean±SEM)		57.8±1.2	54.5±1.1	59.1±1.1	57.1±0.7
Age Range (years)		24 - 83	27 - 78	30 - 82	24 - 83
Race	Black	0	3 (3.8)	2 (2.6)	5 (2.1)
	Caucasian	82 (95.3)	74 (93.7)	71 (91.0)	227 (93.4)
	Oriental	4 (4.7)	2 (2.5)	5 (6.4)	11 (4.5)
Sex	Male	46 (53.5)	48 (60.8)	42 (53.8)	136 (56.0)
	Female	40 (46.5)	31 (39.2)	36 (46.2)	107 (44.0)

Efficacy

Efficacy analysis included all subjects who received at least one dose of randomized medication, and had at least one trough vital sign measurement during the on-therapy interval. This criteria was defined in the NDA document (vol. 220, p 19 of 241). Application of this criteria to the data led to the disqualification of only one subject (013.133.00012) from the efficacy analysis. Whereas, the sponsors NDA report excluded three subjects from the efficacy analysis. As a result of this discrepancy the efficacy analyses were repeated excluding only subject 013.133.00012. In disqualifying only this one subject, we were expected to have 242 subjects in the analyses, but the data included only 238 subjects. The sponsor is reviewing the data to identify and explain the missing four subjects. Using the protocol defined analysis of variance (PROC GLM in SAS) the three groups were compared at week 3 of the double blind treatment period (when all subjects were on the lowest dose of treatment medication), and at week 9 of the double blind treatment period (when all subjects were at the highest dose of medication). The sponsor provided comparison at the end of study was meaningless, because the data included only responders. One hundred and eleven (45.7%) randomized subjects were responders. The results of our analysis using change in trough sitting diastolic blood pressure at week 3 is provided in Table 13.3

Table 13.3 Mean ±SEM Trough Sitting Diastolic Blood Pressure at Baseline and Week 3 of Treatment for Patients with vitals at both periods.

Sitting DBP	Placebo (n = 84)	Eprosartan Regimen	
		Twice Daily (n = 78)	Once Daily (n = 76)
Baseline	102.8 ± 0.5	102.7 ± 0.6	102.3 ± 0.5
Week 3	99.1 ± 1.0	97.5 ± 1.1	95.2 ± 1.0
Change from Baseline	-3.7 ±	-5.2	-7.2
Difference from Placebo		1.5	3.5*

n = number of subjects with baseline value and week 3

* Indicates significance at 0.05 using modified Bonferroni procedure

The ANOVA was statistically significant with a p-value < 0.0001. There was a significant center interaction, but no drug-by-center interaction as suggested by sponsor. In the multiple comparison procedure which was carried out as part of the testing, eprosartan 400 mg once daily dose showed a statistically significant decrease in trough sitting diastolic blood pressure from placebo.

Summary of the analysis involving the change in trough sitting diastolic blood pressure at week 9 of double-blind treatment (after dose titration) is provided in Table 13.4. At the end of the dose titration period both the once daily and twice daily dosing of eprosartan produced statistically significant decreases in sitting diastolic blood pressure.

Table 13.4 Mean ±SEM Trough Sitting Diastolic Blood Pressure at Baseline and Week 9 for Patients with trough measurements at both periods.

Sitting DBP	Placebo (n = 69)	Eprosartan Regimen	
		Twice Daily (n = 69)	Once Daily (n = 72)
Baseline	102.6 ± 0.5	102.6 ± 0.6	102.2 ± 0.5
Week 9	98.2 ± 1.2	93.4 ± 1.1	93.9 ± 1.0
Change from Baseline	-4.4	-9.2	-8.3
Difference from Placebo		4.8*	3.9*

n = number of subjects with baseline value and week 9 value
* Indicates significance at 0.05 using modified Bonferroni procedure

The least square mean trough sitting diastolic blood pressure decline by dose of eprosartan at week 9 is summarized in Table 13.5.

Table 13.5 Ranked Least Squares Mean Trough Sitting Diastolic Blood Pressure Decline by dose of Eprosartan at Week 9 (Patients with Week 9 Measurements)

	Eprosartan						
	200 mg BID n=15	300 mg BID n=18	400 mg BID n=37	400 mg QD n=18	600 mg QD n=19	800 mg QD n=36	Placebo n=71
Mean DBP Δ	-17.6	-7.4	-5.9	-12.6	-11.7	-4.2	-3.5
Placebo Corrected	-13.1	-3.9	-2.4	-9.1	-8.2	-0.7	-

Δ= change

Secondary Efficacy Parameters

Results of the secondary efficacy parameters are summarized below in Table 13.6

Table 13.6 Mean ± SEM Trough Vital Signs at Baseline and Week 9 for Patients with Measurements at both periods.

Vital Sign Measurement	Placebo	Eprosartan Regimen	
		Twice Daily	Once Daily
Sitting SBP (mm Hg)	(n=69)	(n=69)	(n=72)
Baseline	160.0±1.6	158.8±1.4	160.4±1.7
Week 9	155.3±2.3	146.1±1.9	150.9±1.9
Change from Baseline	-4.7	-12.7*	-9.5*
Sitting Heart Rate (bpm)	(n=69)	(n=69)	(n=72)
Baseline	73.8±1.0	74.2±1.1	72.9±1.0
Week 9	74.0±1.3	73.8±1.1	71.8±1.0
Change from Baseline	+0.2	-0.4	-1.1
Standing DBP (mm Hg)	(n=69)	(n=69)	(n=73)
Baseline	104.2±0.6	104.8±0.7	104.2±0.7
Week 9	101.2±1.3	96.1±1.1	95.7±1.1
Change from Baseline	-3.0	-8.7*	-8.5*
Standing SBP (mm Hg)	(n=69)	(n=69)	(n=73)
Baseline	158.3±1.6	159.4±1.4	160.3±1.6
Week 9	155.2±2.3	145.7±1.9	150.1±1.9
Change from Baseline	-3.1	-13.7*	-10.2*
Standing Heart Rate (bpm)	(n=69)	(n=69)	(n=72)
Baseline	77.4±1.0	78.4±1.1	77.1±1.0
Week 9	78.9±1.3	76.7±1.1	75.5±1.0
Change from Baseline	+1.5	-1.7	-1.6

* Indicates significance at 0.05 using modified Bonferroni procedure

Data Sources: Sitting Systolic Blood Pressure - Table 14.18.1
Sitting Heart Rate - Table 14.19
Standing Diastolic Blood Pressure - Table 14.20
Standing Systolic Blood Pressure - Table 14.21
Standing Heart Rate - Table 14.22

The results of the analysis of variance for secondary efficacy parameters indicated that both systolic and diastolic blood pressure were reduced significantly, however, heart rate was not significantly affected.

Subgroup Efficacy Analysis
Age:

A comparison of sitting diastolic blood pressure (primary endpoint) by age (between subjects <65 years and those ≥65 years) 3 weeks after randomization, showed that a significant decline in DBP was present only among younger subjects. There was a decline in DBP among older subjects but their numbers were not enough to give statistical power for detection of such change between the two groups. The data is presented in Table 13.7.

Table 13.7 Mean ± SEM Trough Diastolic Blood Pressure at Baseline and Week 3 by Age Groups.

	Age < 65 Years			Age ≥ 65 Years		
Vital Sign	Placebo	Twice Daily	Once Daily	Placebo	Twice Daily	Once Daily
Sitting DBP (mm Hg)	(n=60)	(n=66)	(n=52)	(n=23)	(n=10)	(n=24)
Baseline	103.0±0.7	103.2±0.6	102.6±0.6	101.8±1.0	98.6±1.1	101.3±1.0
Study Endpoint	98.9±1.1	98.2±1.1	95.7±1.2	98.5±1.9	90.9±2.7	93.5±1.9
Change from Baseline	-4.1	-5.0*	-6.9*	-3.3	-7.7	-7.8

Data Source Table 14.17.2
* Indicates significance at 0.05 using modified Bonferroni procedure

At the end of the titration period (ie. 9 weeks of therapy), the decline in sitting diastolic blood pressure was again confined to the younger subjects. The decline in sitting diastolic blood pressure among older subjects was consistent with that found in the younger subgroup. However, the differences did not achieve statistical significance among the older subjects, probably because the subgroup sample sizes were too small to provide enough statistical power for detection of the differences observed. The data is presented in Table 13.8.

Table 13.8 Mean ± SEM Trough Diastolic Blood Pressure at Baseline and Week 9 by Age Groups.

	Age < 65 Years			Age ≥ 65 Years		
Vital Sign	Placebo	Twice Daily	Once Daily	Placebo	Twice Daily	Once Daily
Sitting DBP (mm Hg)	(n=51)	(n=60)	(n=49)	(n=23)	(n=10)	(n=24)
Baseline	103.0±0.7	103.2±0.6	102.6±0.6	101.8±1.0	98.6±1.1	101.3±1.0
Study Endpoint	98.4±1.4	93.7±1.1	94.4±1.3	98.5±1.9	90.9±2.7	93.5±1.9
Change from Baseline	-5.6	-9.5*	-8.2*	-3.3	-7.7	-7.8

Data Source Table 14.17.2
* Indicates significance at 0.05 using modified Bonferroni procedure

Gender:

Comparison of sitting diastolic blood pressure at week 3 of treatment by gender showed that there was no statistically significant decline in DBP among subjects by sex. The data is presented in Table 13.9.

Table 13.9 Mean ± SEM Trough Diastolic Blood Pressure at Baseline and Week 3 by Gender.

	Female			Male		
Vital Sign	Placebo	Twice Daily	Once Daily	Placebo	Twice Daily	Once Daily
Sitting DBP (mm Hg)	(n=38)	(n=30)	(n=36)	(n=45)	(n=46)	(n=40)
Baseline	102.2±0.9	101.9±0.9	101.6±0.7	103.0±0.7	103.1±0.7	102.7±0.8
Study Endpoint	97.3±1.4	95.1±1.8	91.8±1.3	100.0±1.4	98.6±1.3	97.9±1.3
Change from Baseline	-4.9	-6.8	-9.8	-3.0	-4.5	-4.8

Data Source Table 14.17.3
* Indicates significance at 0.05 using modified Bonferroni procedure

After 9 weeks of treatment with eprosartan statistically significant decline in sitting diastolic blood pressure was detected only among female subjects. The decline is sitting diastolic blood pressure among male subjects was not statistically significant. The data is presented in Table 13.10.

Table 13.10 Mean ± SEM Trough Diastolic Blood Pressure at Baseline and Week 9 by Gender.

	Female			Male		
Vital Sign	Placebo	Twice Daily	Once Daily	Placebo	Twice Daily	Once Daily
Sitting DBP (mm Hg)	(n=30)	(n=26)	(n=33)	(n=39)	(n=43)	(n=39)
Baseline	102.2±0.9	101.9±0.9	101.6±0.7	103.0±0.7	103.1±0.7	102.7±0.8
Study Endpoint	96.7±1.9	90.2±2.1	91.6±1.2	99.4±1.6	95.3±1.2	95.8±1.5
Change from Baseline	-5.5	-11.7*	-10.0*	-3.6	-7.8	-6.9

Data Source Table 14.17.3
* Indicates significance at 0.05 using modified Bonferroni procedure

Race:

There were not enough blacks or other racial subjects randomized in the study to provide any meaningful comparison of primary efficacy endpoint in this study. Data source Table 14.17.3

Trough- Peak Differences

The trough- peak ratio in sitting diastolic blood pressure were evaluated and the results are presented in Table 13.11. The trough to peak ratio is defined as:

$$Trough-PeakRatio=\frac{Trough_{Treatment}-Trough_{Baseline}}{Peak_{Treatment}-Peak_{Baseline}}$$

Where Trough values are group means and Peak values are also group means ;
and the placebo subtracted trough to peak ratio is defined as:

$$PlaceboSubtractedTrough-PeakRatio=\frac{(Trough_{Epro.Tred}-Trough_{Epro.B})-(Trough_{PlaceboTred}-Trough_{PlaceboB})}{(Peak_{Epro.Tred}-Peak_{Epro.B})-(Peak_{PlaceboTred}-Peak_{PlaceboB})}$$

Where Trough values are group means and Peak values are also group means.

Table 13.11 Placebo Subtracted Trough-Peak Ratios in Sitting Diastolic Blood Pressures

Tx. Group	n	Peak hour 1	Peak hour 2	Peak hour 3
Placebo	60			
Once Daily	60	0.88	0.75	0.67
Twice Daily	66	1.20	0.91	0.87

Note: DBP values are group means (mm Hg). The apparent trough: peak ratio for each regimen is corrected for the run-in mean values for that regimen and the corrected trough: peak ratio for each regimen is corrected for the run-in mean values for that regimen and placebo regimen mean values.
Data Source: Table 14.29.1

Response rate

The proportion of subjects who responded at study endpoint to the treatment by eprosartan is summarized in Table 13.12. Response was defined in 2 ways: 1) patients whose sitting DBP <90 mm Hg, and 2) patients whose sitting DBP 90-100 mm Hg and decreased from baseline by at least 10 mm Hg.

Table 13.12 Results of the Cochran-Mantel-Haenzel Tests of Response Rates Between Medication Regimen at Study Endpoint

	Placebo	Twice Daily	Once Daily
Response 1) 2) No Response	22/86 (25.6%) 19/86 (22.1%) 3/86 (3.5%) 64/86 (74.4%)	27/77 (35.1%) 20/77 (26.0%) 7/77 (9.1%) 50/77 (64.9%)	36/77 (46.8%) 30/77 (39.0%) 6/77 (7.8%) 41/77 (53.2)
Contrast	Twice Daily vs Once Daily	Twice Daily vs Placebo	Once Daily vs Placebo
Relative-Risk Ratio and 95% CI	0.61 (0.32, 1.16)	0.56 (0.24, 1.30)	0.35 (0.17, 0.74)
CMH p-value	0.065	0.098	0.0009

Conclusion

This study showed that eprosartan is effective in reducing blood pressure in only (40.9%) of the subjects randomized into the study. The data indicates that once daily dosing was indistinguishable from twice daily dosing. Eprosartan was equally effective in reducing blood pressure in younger and older subjects, male and female subjects. However the efficacy of eprosartan in noncaucasian subjects remains unanswered. **It should be noted that dose titration is expected to make the two treatment groups look alike.**

Reviewers Comments

This study provides an interesting insight into the dosing of eprosartan. This study utilized a dose titration scheme, at the end of the dose titration period, it was noted that there appears to be a inverse relationship between increasing dose of eprosartan and blood pressure lowering effect. Because of the dose titration, we can only compare 200 mg BID to the 400 mg QD. Examination of data summarized in Table 13.4 showed that twice daily dosing of eprosartan produced a larger decline in sitDBP at week 3. Table 13.6 also indicates that twice daily dosing produces a larger blood pressure decline than once daily dosing. It was concluded that twice daily dosing was superior to once daily dosing.

Protocol 016. A 4-Week, Double-Blind, Parallel, Placebo-Controlled, Multicenter Trial of Oral Eprosartan Added to Hydrochlorothiazide Therapy in Patients with Essential Hypertension (DBP ≥95 and ≤114 mm Hg).

Protocol

Design & Objective

This was a Phase III, multicenter, double-blind, parallel group study in patients with essential hypertension. The study consisted of four periods: Screening, HCTZ Run-in, Double-blind Treatment, and Follow-up. The primary objective of the study was to assess the relative antihypertensive efficacy and safety of eprosartan 50 and 100 mg twice daily when added to the treatment regimen of patients with essential hypertension whose BP is uncontrolled (average sitting diastolic BP ≥95 and ≤114 mm Hg [Korotkoff V]) with 25 mg of HCTZ once daily. The secondary objectives were; to further define the safety of eprosartan through observation of adverse experiences, laboratory abnormalities, and changes in ECGs, and to compare the effects of the combined regimens to HCTZ plus placebo for fasting serum concentrations of lipids, glucose, and electrolytes.

Eligibility Criteria

Inclusion Criteria

1. Men, or women without child-bearing potential (post menopausal, i.e., 6 months without menstrual period; surgically sterile), or women using hormonal or barrier contraceptives or intrauterine contraceptive devices; all of whom were at least 18 years of age and had given their written informed consent to participate.
2. Patients with essential hypertension (as defined below) at the end of the HCTZ run-in period defined as:
   - average sitting DBP ≥ 95 mm Hg and ≤ 114 mm Hg at three consecutive weekly visits, and
   - the difference between the highest and lowest average sitting DBP values for the last three visits did not exceed 10 mm Hg; and the difference between the averages at the last two visits did not exceed 5 mm Hg.
3. Patients with newly diagnosed essential hypertension, or those previously treated patients from whom antihypertensive therapy could be safely withdrawn for the duration of the study.

Exclusion Criteria

1. Pregnancy or lactation.
2. Secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, or pheochromocytoma.
3. Advanced hypertensive retinopathy (ie, Keith-Wagener Grade III or IV).
4. Average sitting SBP >210 mm Hg.
5. Advanced atrioventricular conduction defects (ie, second or third degree heart block) unless a pacemaker is in place.
6. Significant ventricular tachyarrhythmias requiring therapy.
7. Bradycardia (resting SitHR <50 beats/minute) after withdrawal of previous antihypertensive medications (except HCTZ).
8. Signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days.
9. Congestive heart failure (CHF) on treatment with ACE-I or diuretics (except for HCTZ, 25 mg per day, which is allowed). Patients with untreated reduced ejection fraction may be included.
10. Angina pectoris treated with regular doses of nitrates, b-blockers, or calcium channel blockers.
11. Diabetes mellitus that is unstable (repeated episodes of ketoacidosis, hyperglycemic coma, or hypoglycemic shock) despite treatment with insulin or oral hypoglycemic agents.
12. Clinically significant renal or hepatic disease: serum creatinine >2.5 mg/dL (220 micromol/L); ALT, AST, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the

laboratory reference range.

13. Leukocyte count <3000/mm3 or platelet count <100,000/mm3.
14. Other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality which, in the opinion of the investigator, could preclude participation or survival.
15. Active alcohol or drug abuse.
16. Use of warfarin within 30 days prior to screening.
17. Use of an investigational drug within 30 days of enrollment into this study or within five half-lives of the investigational drug (the longer period will apply).
18. Concomitant administration of any medication known to affect BP.
19. Concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low-dose aspirin). Patients must be off such drugs for at least 1 week prior to the Screening Visit.
20. Concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, and phenothiazine derivatives.
21. Hypertension due to the current use of oral contraceptive agents.
22. Sensitivity to eprosartan or other drugs in its class or to thiazide diuretics.
23. Treatment with randomized medication in a previous trial of eprosartan.

Description of Phases

A schedule of assessments (Table 16.1) and a flow chart (Figure 16.1) are provided to outline the phases and procedures used in the study. The trial consisted of four (4) phases: screening, hydrochlorothiazide (HCTZ) run-in, double-blind treatment, and follow-up. After screening, subjects entered a 4-5 week run-in period to establish baseline parameters. During this period subjects received open label HCTZ 25 mg once daily and single blind placebo for eprosartan twice daily. The double blind treatment period consisted of 4 weeks of dosing, where subjects were randomized to treatment with eprosartan 50 mg bid plus HCTZ 25 mg once daily, or eprosartan 100 mg bid plus HCTZ 25 mg once daily, or placebo bid plus HCTZ 25 mg once daily. The mercury sphygmomanometer was used as the primary measurement device. Baseline was defined as the mean of the last two visits during the HCTZ run-in phase. At the end of study, patients had the option of entering an open-label, long-term protocol (Protocol 039) or return for follow-up visit off therapy.

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Table 16.1 Schedule of Assessments for efficacy and safety parameters

		Run-in					Double-Blind Period				Follow-up .
VISIT:	Screen	1	2	3	4	5	1	2	3	4	
Assessment											
Informed Consent	X										
Inclusion/Exclusion	X										
Medical History	X										
Physical Exam	X										
Funduscopy	X										
CXR	X										
BP & HR	X	X	X	X	X	X	X	X	X	X	X
Post-dose (1, 2, 3 hrs)						X**			X**		
Body Weight	X	X	X	X	X	X	X	X	X	X	X
Height	X										
CVPE	X					X+		X		X++	X
Laboratory Tests	X					X+		X		X++	X
Lipid Profile	X					X+		X		X++	X
ECG	X					X+				X++	
Serum b-hCG	X									X++	
Study Drug Dispensed	X	X	X	X	X	X+	X	X	X		
Study Compliance		X	X	X	X	X	X	X	X	X	
Interim History		X	X	X	X	X	X	X	X	X	X
Study Conclusion											
Reason										X	

* For patients not continuing into the extension study, a follow-up visit was to be completed 7 to 14 days after the last dose of double-blind medication.

*** On Dosing Day 1 and Visit 3, a dose of double-blind medication was administered in the office and post-dose vital signs taken after 1, 2, and 3 hours.

\+ Studies to be done at Run-in Visit 4 or 5 when patient qualified for double-blind treatment.

++ Evaluations to be performed at this visit were to be performed whenever a patient was withdrawn from the study.

Data Source: Appendix A, Protocol and Sample CRF.

Primary & Secondary Endpoints

The primary efficacy variable was defined as the mean change from baseline in sitting diastolic blood pressure (DBP) at trough. The secondary efficacy variables were defined as:

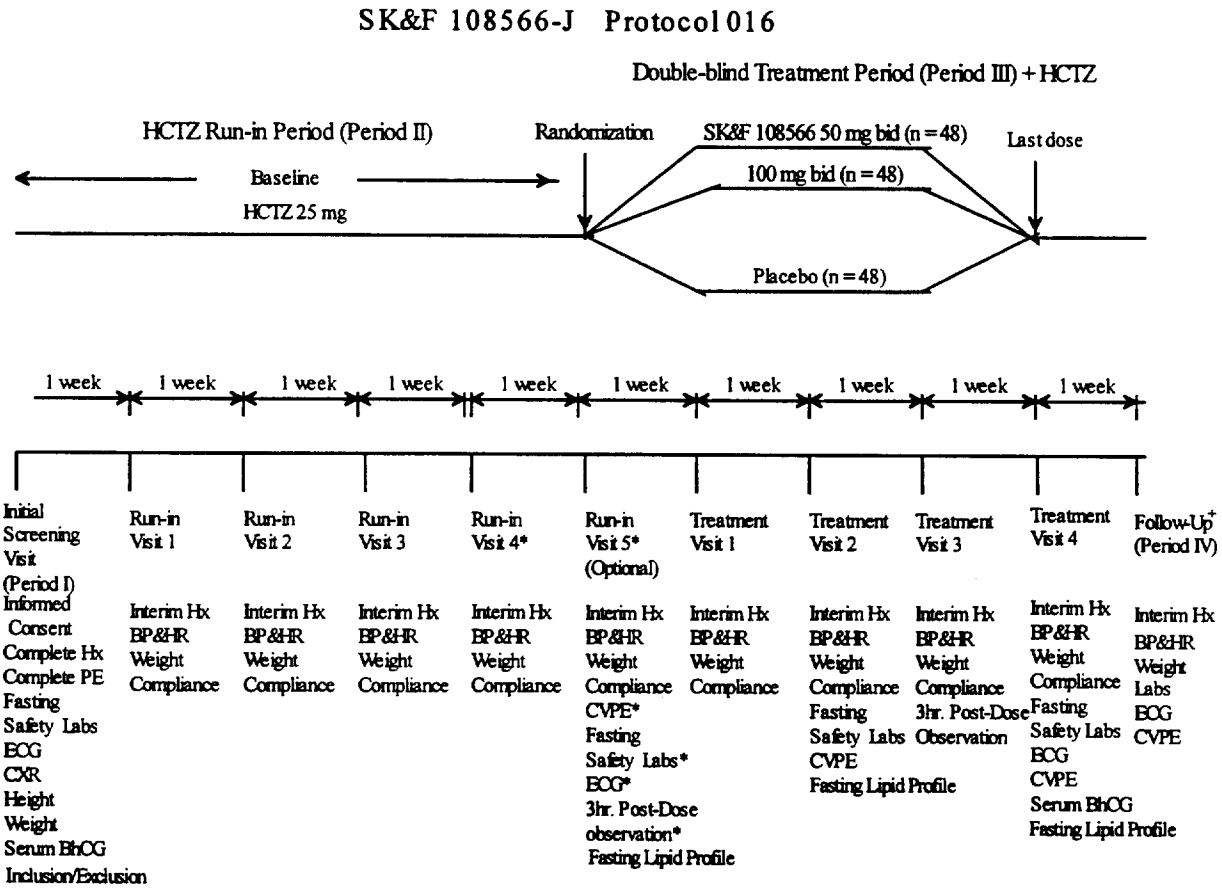
- Mean change from baseline for SitSBP.
- Mean change from baseline for SitHR.
- Mean change from baseline for StaDBP.

- Mean change from baseline for StaSBP.
- Mean change from baseline for StaHR.
- Response rate.
- Mean change from baseline for glucose, lipids (total cholesterol, HDL, LDL, and triglycerides), and electrolytes.

Committees

There were no steering, safety, events or executive committee involved in this protocol.

Figure 16.1 Study Design



*Labs ECG, CVPE, and 3 hr post-dose observation will be performed when the patient qualifies for randomization
+For patients not continuing into the extension study, a follow-up visit was to be completed 7 to 14 days after the last dose of double-blind medication.
CVPE = Cardiovascular pulmonary exam

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Statistical Analysis Plan

A minimum of 144 patients were to be randomized to achieve 48 evaluable patients per medication regimen (156 patients were randomized). This sample was estimated to detect a 7 mm Hg difference based on an estimated standard deviation of 8.5 mm Hg and a type I error rate of .05 with three two-sided multiple pairwise comparisons and a power of .95. The modified Bonferroni procedure due to Hochberg was applied in the analysis

of the primary efficacy parameter: mean change from baseline for SitDBP. Under the Hochberg procedure, the largest p-value is compared to 0.05. If it is less than or equal to 0.05, than all p-values are statistically significant. If not, the next largest p-value is compared to 0.025 (0.05/2). If it is less than or equal to 0.025, then it and all smaller p-values are significant at the 0.05 level. If not, this procedure is continued for the third largest p-value, which must be less than 0.0167 (0.05/3).

There are three comparisons of interest: eprosartan 50 mg vs placebo, eprosartan 100 mg vs placebo, and eprosartan 50 mg vs 100 mg. Multiple comparisons of differences between regimens using the modified Bonferroni procedure were performed, and the Analysis of variance (ANOVA) was applied. The model included medication regimen, center, and regimen-by-center interaction. If there was no significant (P>0.10) regimen-by-center interaction, the interaction term was removed, and the reduced model was used. The analysis was applied to the intent-to-treat population at each visit and at endpoint. However, conclusions are based on the intent-to-treat analysis at endpoint. Patients who took the first dose of double-blind medication and had blood pressure measured only after that dose (peak observation) were not to be included in this analysis. (No patient fit this category.)

Results

Disposition

The disposition of patients who participated in this protocol is summarized in Table 16.2

Table 16.2 Patient Disposition

	Placebo + HCTZ	Eprosartan BID + HCTZ 25 Mg Once Daily		Total
		50 mg	100 mg	
# Screened				274
# Seen During Run-in Period				259
# Randomized	52	53	51	156
# Completing Study (%)*	50	50	49	149
# Not Completing Study	2	3	2	7

Data Source: Tables 13.2,13.5

Demographic

Subjects were recruited from 13 centers. The number of subjects randomized per center ranged from 3 to 22. The mean age was 54.3±10.6 for subjects who were randomized, compared to 56.7±12.6 or those 103 subjects who were not randomized. Variations in demographic and clinical variables between randomized and nonrandomized subjects were not statistically significant. A summary of patient demographic characteristics are presented in Table 16.3.

Table 16.3 Patient Demography

			Eprosartan BID Regimen		
		Placebo	50 mg	100 mg	Total
		n=52	n=53	n=51	n=156
Age (years)		54.3±11.0	53.1±9.9	52.8±11.0	53.4±10.6
Age Range (years)		29 - 78	30 - 74	31 - 82	29 - 82
Sex	Male	39(75.0)	39(73.6)	34(66.7)	112(71.8)
	Female	13(25.0)	14(26.4)	17(33.3)	44(28.2)
Race	Black	13(25.0)	12(22.6)	8(15.7)	33(21.2)
	Caucasian	36(69.2)	36(67.9)	37(72.5)	109(69.9)
	Other	3(5.8)	5(9.5)	6(11.8)	14(9.0)

Data Source: Table 13.10, 13.11

Primary Efficacy Evaluation

The primary efficacy parameter in this study was the change from baseline in sitting DBP at trough. Baseline was defined as the mean of the last two qualifying visits during the run-in phase. Summary of the mean change in primary efficacy analysis is presented in Table 16.4. The results show that eprosartan 50 mg plus HCTZ 25 mg and eprosartan 100 mg plus 25 mg HCTZ decreased sitting diastolic blood pressure. However, the differences did not achieve statistical significance. The ANOVA p-value was 0.1967.

Table 16.4 Mean Change in Sitting Diastolic Blood Pressure

GROUPS	N	Baseline	Endpoint	Change	Placebo Subtracted	p value
Placebo	52	100.4±*	95.5±1.2	-4.9		
Eprosartan 50 mg	53	101.0±*	93.2±1.2	-7.9	-3.0	0.026
Eprosartan 100 mg	51	100.7±*	93.0±1.2	-7.7	-2.7	0.038

Data Source Table 14.1

* Std. Dev indeterminable because of center by treatment interaction.

Secondary Efficacy Evaluation

Secondary efficacy parameters were not reviewed because the primary efficacy parameter was not statistically significant. So all the alpha designated for the study was spent in the testing of the primary efficacy parameter, making the review of secondary efficacy parameter unacceptable. The secondary efficacy variables included; mean change from baseline for SitSBP, mean change from baseline for SitHR, mean change from baseline for StaDBP, mean change from baseline for StaSBP, mean change from baseline for StaHR, response rate, mean change from baseline for glucose, lipids (total cholesterol, HDL, LDL, and triglycerides), and electrolytes.

Conclusions

Based on the review of this study, it was concluded that when added to HCTZ 25 mg once daily, eprosartan regimens of 50 mg and 100 mg twice daily did not reduce blood pressure significantly.

Protocol 017. A 9-Week, Double-Blind, Parallel, Dose titration, Multi-Center, Multi-Country Comparison of Oral Eprosartan Twice Daily with Placebo in Elderly Patients with Essential Hypertension (DBP ≥95 and ≤114 mm Hg).

Protocol

Design & Objective

This was a phase III, prospective, randomized, multi-center, double-blind, placebo controlled, three parallel group study with dose titration among elderly patients (age ≥65 years) with essential hypertension (DBP ≥ 95 and ≤ 114 mm Hg). The primary objective of the study was to demonstrate and compare the antihypertensive efficacy of two dosing regimens of eprosartan (100 mg and 200 mg) to placebo in elderly patients with essential hypertension with average sitting diastolic blood pressure (DBP) ≥ 95 and ≤ 114 mm Hg. The secondary objectives were to further define the safety of eprosartan and to describe the population pharmacokinetics of eprosartan, and to attempt to describe the relationship between plasma concentrations and efficacy assessments.

Eligibility Criteria

Inclusion Criteria

1. Men, or women who were 65 years of age or older and had given their written informed consent to participate.
2. Patients with essential hypertension at the end of the placebo run-in period defined as:
   - average sitting DBP ≥95 mm Hg and ≤114 mm Hg at three consecutive weekly visits

   and
   - the difference between the highest and lowest average sitting DBP values for the last three visits did not exceed 12 mm Hg; and the difference between the averages at the last two visits did not exceed 8 mm Hg.
3. Patients with newly diagnosed essential hypertension, or those previously treated patients from whom antihypertensive therapy could be safely withdrawn for the duration of the study.

Exclusion Criteria

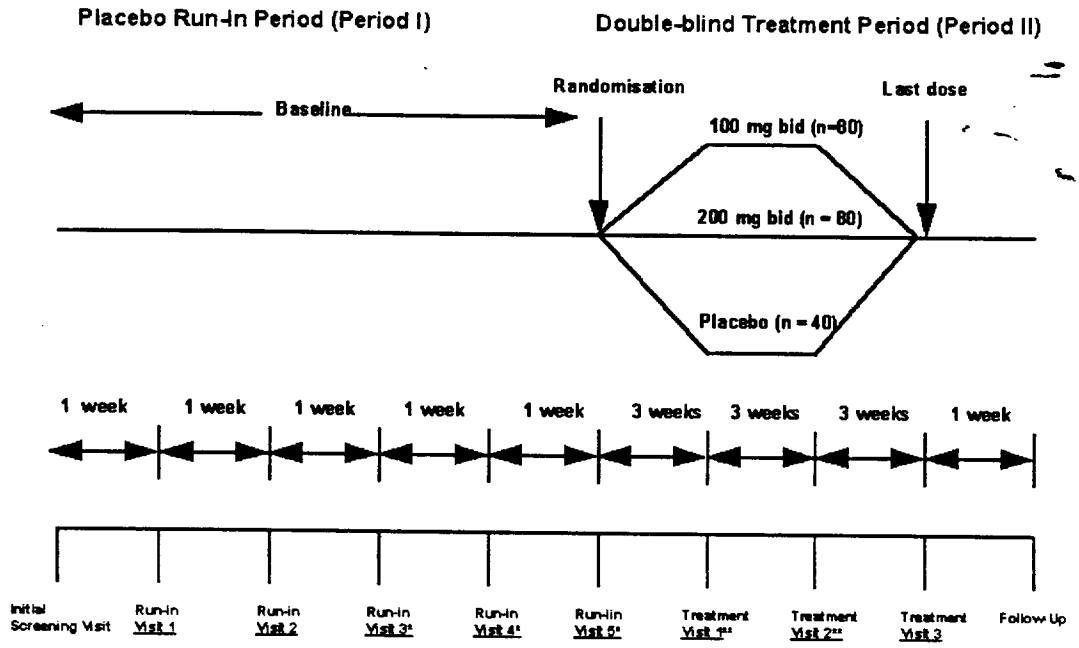
1. Secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, or pheochromocytoma.
2. Advanced hypertensive retinopathy (i.e. Keith-Wagener Grade III or IV).
3. Average sitting SBP > 200 mm Hg.
4. Advanced atrioventricular conduction defects (i.e., second or third degree heart block) unless a pacemaker was in place.
5. Significant ventricular tachyarrhythmias requiring therapy.
6. Bradycardia (resting sitting heart rate < 50 beats/minute) after withdrawal of previous antihypertensive medications.
7. Signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days.
8. Congestive heart failure on treatment with ACE-inhibitors or diuretics. Patients with untreated reduced ejection fraction were permitted.
9. Angina pectoris prevented by the use of regular doses of beta blockers, calcium channel blockers or nitrate. Prophylaxis of angina with transdermal glycerol trinitrate was permitted provided that it had been prescribed at a constant dose for at least 4 weeks prior to the screening visit.
10. Diabetes mellitus that was unstable (repeated episodes of ketoacidosis, hyperglycemic coma, or hypoglycemic shock) despite treatment with insulin or oral hypoglycemic agents.
11. Presence of clinically significant renal or hepatic disease: serum creatinine > 2.5 mg/dl (220 mmol/l); alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range.
12. Leukocyte count < 3000/mm3 or platelet count < 100,000/mm3

13. Other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality which, in the opinion of the investigator, could have precluded participation or survival.
14. Active alcohol or drug abuse.
15. Use of warfarin or other oral anticoagulants within 30 days prior to screening.
16. Use of an investigational drug within 30 days of enrollment into this study or within 5 half-lives of the investigational drug (the longer period will apply).
17. Concomitant administration of any medication known to affect blood pressure, including diuretic therapy.
18. Concomitant chronic treatment (i.e. longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine. Patients must have been off of such drugs for at least 1 week prior to the screening visit.
19. Concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, and phenothiazine derivatives.
20. Patients sensitive to eprosartan or other drugs in its class.
21. Patients who had received randomized medication in a previous trial of eprosartan.

Description of Phases

The study consisted of four periods: Screening, placebo run-in, double-blind treatment, and follow-up. After the screening period, subjected were entered into a placebo run-in phase. At the end of the placebo run-in period, baseline parameters and evaluable variables were established. Subjects meeting the eligibility criteria for entry into the study were randomized into three parallel groups (placebo, 100 mg, and 200 mg) for treatment. The randomization schema involved an assignment ratio of 1:2:2 respectively. The subjects in the three groups were followed for a period of 9 weeks. Subjects were evaluated every 3 weeks and their drug dosage adjusted upwards if their blood pressure was not controlled according to a predefined criteria (DBP < 90 mm Hg or decreased by 10 mm Hg). The Level I treatment assignments were as follows - placebo, 100 mg bid, 200 mg. After 3 weeks at level I, subjects whose blood pressure was not controlled were titrated to placebo, 200 mg bid, 300 mg bid (Level II). After 3 weeks on level II dosage, subjects not controlled were titrated to placebo, 300 mg bid, 300 mg bid respectively (level III). The mercury column sphygmomanometer was used as the primary measurement device. Baseline trough DBP was defined as the mean of the last two qualifying visits of the placebo run-in period. The primary endpoint of the study was defined as the end of week 3 during the double-blind treatment period, when subjects were on level I dose levels. At the end of the study, patients had the option of continuing in an open label extension protocol study or return for follow-up visit off therapy. The follow-up visit was scheduled for subjects who did not enter the open label extension study (protocol 040). These subjects returned 7 to 14 days after the last day of coded medication. A flow chart outlining the phases of the study is shown in Figure 17.1.

Figure 17.1 Study Design with Phases of study



KEY: * Patients qualify for randomisation ** Dosage titration permitted

Primary & Secondary Endpoints

The primary efficacy variable was defined as the mean change from baseline in sitting diastolic blood pressure (DBP) at trough measured at week 3 of the double-blind treatment period. Secondary efficacy variables were defined as:

- mean change from baseline in sitting systolic blood pressure (SBP) at peak and trough,
- mean change from baseline in sitting DBP at peak,
- mean change from baseline in sitting heart rate at peak and trough,
- mean change from baseline in standing DBP at peak and trough,
- mean change from baseline in standing systolic blood pressure (SBP) at peak and trough,
- mean change from baseline in standing heart rate at peak and trough,

Committees

There were no steering, safety, events or executive committees involved in this protocol.

Statistical Analysis Plan

Changes in blood pressure, heart rate and other continuous variables were assessed by the Analysis of Variance (ANOVA). Categorical demographic and clinical characteristics were assessed by the Chi square test. The type I error was set at α=0.05 for all formal hypothesis. The sample size of 80 evaluable patients on each eprosartan regimen and 40 patients on the placebo regimen (a 2:2:1 randomization) provided 80% power to detect a 5 mm Hg difference in a change from baseline between any two medication regimens. This assumed a standard deviation of 8 mm Hg and used a 0.05 level of significance, two-sided testing, with a Bonferroni adjustment for the three comparisons.

Interim Analysis

No interim analysis was planned or carried out for this study.

Results

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 17.1. The number of subjects evaluated for efficacy represent subjects who had at least one post baseline trough measurements.

Table 17.1 Patient disposition

No. Of patients	Placebo	Eprosartan BID Regimen		Total
		100 mg	200 mg	
Screened				279
Entered run-in				274
Randomized	47	92	91	230
Completed treatment	45	84	87	216
Evaluated for efficacy	46	88	91	225
Follow-up	14	35	31	80

Data Source: Tables 13.4, 13.5.1, 13.6.1 and 15.17

Demographic characteristics

Subjects were recruited from 16 european centers. The number of subjects randomized per center ranged from 3 to 37. A review of the demographic characteristics for non-randomized and randomized patients at baseline did not indicate any marked differences in the two populations. A summary of demographic variables for randomized subjects is provided in Table 17.2

Table 17.2 Patient Demography

			Eprosartan BID Regimen	
		Placebo	100 mg	200 mg
		n=47	n=92	n=91
Age (years)		72.6±0.9	72.5±0.7	71.7±0.6
Age Range (years)		65 - 93	65 - 93	63 - 93
Sex	Male	17(36.2)	43(46.7)	35(38.5)
	Female	30(63.8)	49(53.3)	56(61.5)
	Caucasian	47(100)	91(98.9)	91(100)

Data Source: Tables 13.10.1 and 13.15.1

Efficacy

The primary efficacy parameter was defined as the mean change from baseline sitting diastolic blood pressure at trough. Baseline was defined as the mean of the last two qualifying visits during the placebo run-in period, and week 3 evaluation of defined parameters were used to determine change during the double blind treatment period. Summary of the mean change in primary efficacy analysis is presented in Table 17.3 below. The results showed that eprosartan 100 mg and the 200 mg doses failed to produced a statistically significant decrease in

sitting diastolic blood pressure over the placebo effect.

Table 17.3 Mean Change in Sitting Diastolic Blood Pressure at Week 3

GROUPS	N	Baseline	Endpoint	Change	Placebo Subtracted	p value
Placebo	46	100.9±0.6	92.3±1.1	-8.6±1.0	---	
Eprosartan 100 mg	88	101.0±0.4	91.7±1.0	-9.3±0.9	-0.7	0.620
Eprosartan 200 mg	91	101.2±0.5	89.9±0.8	-11.3±0.8	-2.7	0.050

Data Source Tables 14.1.1, 14.8.1 and 14.14.1

A summary of the effect of eprosartan of sitting trough diastolic blood pressure at each time point and study endpoint is summarized in Table 17.4.

Table 17.4 Results of analysis of variance for the mean change from baseline in the sitting DBP at each time point and study endpoint -- least squares means and 95% Bonferroni confidence intervals (95% CI)

Medication regimen	n	Mean Change from Baseline	Contrast	Difference (95% CI)	p value
Week3					
Placebo	46	-7.8			
100 mg	88	-8.4	with placebo	-0.7 (-3.9, 2.6)	0.620
200 mg	91	-10.4	with placebo	-2.6 (-5.8, 0.6)	0.050
			with 100 mg	-2.0 (-4.6, 0.7)	0.074
Week 6					
Placebo	45	-9.7			
100 mg	86	-10.5	with placebo	-0.7 (-4.3, 2.8)	0.621
200 mg	90	-11.1	with placebo	-1.4 (-4.9 , 2.1)	0.340
			with 100 mg	-0.7 (-3.6, 2.2)	0.575
Week 9					
Placebo	44	-9.6			
100 mg	85	-10.9	with placebo	-1.3 (-4.9, 2.3)	0.368
200 mg	86	-11.8	with placebo	-2.2 (-5.8, 1.4)	0.139
			with 100 mg	-0.9 (-3.8, 2.1)	0.476
Study endpoint					
Placebo	46	-8.7			
100 mg	88	-10.9	with placebo	-2.2 (-6.0, 1.5)	0.155
200 mg	91	-11.8	with placebo	-3.1 (-6.9, 0.7)	0.047
			with 100 mg	-0.9 (-4.0, 2.2)	0.492

Data Source: Table 14.1.1

A summary of the effect of eprosartan of sitting systolic blood pressure at each time point and study endpoint is summarized in Table 17.5.

Table 17.5 Results of analysis of variance for the mean change from baseline in trough sitting SBP at each time point and study endpoint -- least squares means and 95% Bonferroni confidence intervals (95% CI)

Medication regimen	n	Mean Change from Baseline	Contrast	Difference (95% CI)	p value
Week3					
Placebo	46	-8.1			
100 mg	88	-10.0	with placebo	-1.9 (-7.5, 3.7)	0.409
200 mg	91	-13.2	with placebo	-5.1 (-10.7, 0.4)	0.028
			with 100 mg	-3.2 (-7.8, 1.4)	0.092
Week 6					
Placebo	45	-9.5			
100 mg	86	-13.6	with placebo	-4.0 (-10.2, 2.1)	0.0114
200 mg	90	-14.9	with placebo	-5.4 (-11.6, 0.8)	0.035
			with 100 mg	-1.4 (-6.4, 3.7)	0.519
Week 9					
Placebo	44	-10.1			
100 mg	85	-13.7	with placebo	-3.6 (-10.4, 3.2)	0.204
200 mg	86	-17.0	with placebo	-6.9 (-13.8, -0.1)	0.015*
			with 100 mg	-3.4 (-9.0, 2.3)	0.152
Study endpoint					
Placebo	46	-9.0			
100 mg	88	-13.8	with placebo	-4.8 (-11.7, 2.1)	0.095
200 mg	91	-17.6	with placebo	-8.6 (-15.5, -1.7)	0.003*
			with 100 mg	-3.8 (-9.5, 1.9)	0.106

KEY * Indicates significance at 0.05 using modified Bonferroni procedure.
Data Source: Table 14.2.1

Subgroup Efficacy Analysis

Secondary efficacy parameters were not reviewed because the primary efficacy parameter was not statistically significant. So all the alpha designated for the study was spent in the testing of the primary efficacy parameter, making the review of secondary efficacy parameter unacceptable. The secondary efficacy variables included; mean change from baseline for SitSBP, mean change from baseline for SitHR, mean change from baseline for StaDBP, mean change from baseline for StaSBP, and mean change from baseline for StaHR.

Conclusion:

Based on the review of this study, it was concluded that eprosartan 100 mg and 200 mg doses given twice daily did not reduce blood pressure significantly.

Reviewers Comments

The results of this study are not consistent with the results from other studies included in the NDA submission. After three weeks of treatment with 200 mg bid of eprosartan no significant reduction in sitting diastolic blood pressure was observed. The number of subjects treated with 200 mg of eprosartan in this study was 91. In protocol 010 the same 200 mg bid dose of eprosartan reduced sitting diastolic blood pressure significantly after 4 weeks, with a group size of 22. Similarly, a significant sitting diastolic blood pressure reduction with 200 mg bid of eprosartan was observed in protocol 011, with a group size of 86. There was also a significant reduction in sitting diastolic blood pressure using the same 200 mg bid dose of eprosartan in protocol 013, with a group size of 15. Secondly, in protocol 049, it was noted that the blood pressure decline obtained after two weeks of treatment, seem to be the maximum blood pressure decline even if treatment was continued for up to 8 weeks. So that three weeks treatment with 200 mg bid dose of eprosartan was expected to significantly reduce sitting diastolic blood pressure.

Protocol 045. A Four Week, Double-Blind, Parallel, Multicenter Comparison of Oral Eprosartan 400 mg Once Daily with Placebo in Male Patients with Mild to Moderate Hypertension (sitting diastolic BP between 95 and 114 mm Hg).

Protocol

Design & objectives

The study was a prospective, double-blind, randomized, parallel, dose-range comparison of once daily doses of eprosartan 400 mg and placebo and consisted of four phases: screening, placebo run-in, double-blind treatment, and follow-up. The primary objective was to demonstrate the trough effect of 400 mg eprosartan administered once daily to reduce blood pressure using 24-hour ambulatory monitoring (ABPM) in male patients with mild to moderate hypertension (sitting diastolic BP between 95 and 114 mm Hg). The secondary objectives were to: assess the activity of 400 mg eprosartan over 24 hours when administered once daily with food, further define the safety of eprosartan through observation of adverse events, laboratory abnormalities, and changes in ECGs, and describe the population pharmacokinetics of eprosartan in patients with hypertension

Eligibility Criteria

Inclusion Criteria

1. Men between 18 and 85 years of age (inclusive).
2. Mild to moderate essential hypertension defined as an average sitting diastolic blood pressure (SitDBP) of ≥95 and <115 mm Hg without treatment confirmed by a mean daytime diastolic blood pressure, (MDDBP) defined as the 12-hour period beginning with the morning office dose of medication of ≥87 mm Hg and 35% of daytime readings ≥90 mm Hg on ABPM.
3. Newly diagnosed essential hypertension, or previously treated hypertension in individuals in whom antihypertensive therapy could be safely withdrawn for the duration of the study.

Exclusion Criteria

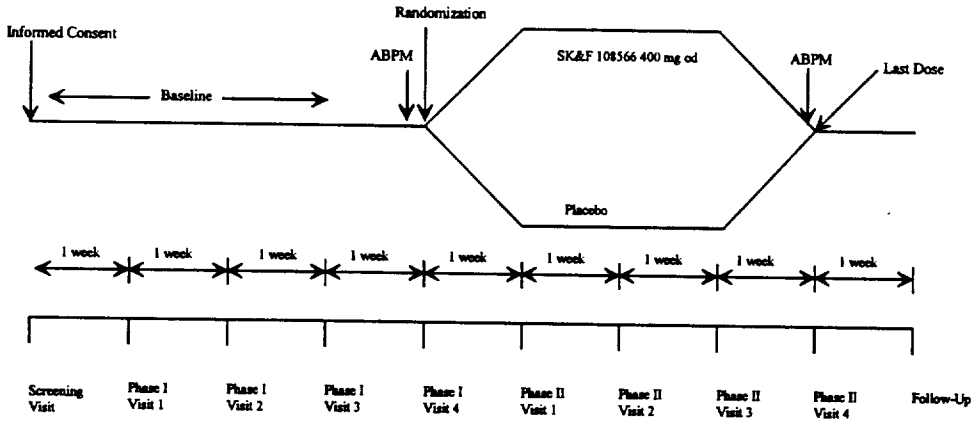
1. Secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, renal artery stenosis, or pheochromocytoma.
2. Advanced retinopathy (i.e. Keith-Wagener Grade III or IV).
3. Advanced atrioventricular conduction defects (i.e. second or third degree heart block) unless controlled by a pacemaker.
4. Significant ventricular tachyarrhythmias requiring therapy.
5. Bradycardia (resting sitting heart rate <50 beats/minute) after withdrawal of previous antihypertensive medications.
6. Signs, symptoms, or history of congestive heart failure, angina pectoris, myocardial infarction, or a cerebrovascular accident within the past 90 days.
7. Diabetes mellitus requiring insulin therapy or oral hypoglycemic therapy unless oral hypoglycemic therapy was stable for three months prior to the screening visit.
8. Presence of clinically significant renal or hepatic disease: serum creatinine >2 mg/dL (220 micromol/L); ALT, AST, total bilirubin, or alkaline phosphatase more than twice the upper limit of the laboratory reference range.
9. Leukocyte count <3000/mm3 or platelet count <100,000/mm3.
10. Use of warfarin within 30 days prior to screening.
11. Active alcohol or drug abuse.
12. Use of an investigational drug within 30 days of enrollment into this study or within five half-lives of the investigational drug (the longer period applied).
13. Patients who worked third (night) shift.
14. Concomitant administration of any medication known to affect blood pressure.
15. Concomitant chronic treatment (i.e. longer than 7 days) with sympathomimetic amines, e.g. phenylephrine or pseudoephedrine. Use of such drugs was prohibited for at least 1 week prior to the screening visit.

16. Other concurrent severe disease, e.g. neoplasm or significant laboratory value(s) which, in the opinion of the investigator, could preclude participation or survival.
17. Previous participation in a trial of eprosartan where double-blind medication had been administered.

Description of Phases

The study consisted of four phases: screening, placebo run-in, double-blind treatment, and follow-up (Figure 45.1). At the initial screening visit, a complete history and physical examination were performed including laboratory analyses, ECG, and chest x-ray (CXR); this was followed by a 2- to 4-week, single-blind, placebo run-in phase (Phase II), during which interim history, vital signs, and compliance information were collected. Laboratory tests, ECG, and ABPM were performed at the last placebo run-in visit (baseline), when the patient qualified for randomization to either once daily doses of eprosartan 400 mg or placebo. During the double-blind treatment phase (Phase III), patients were seen weekly to collect interim history, vital signs, and compliance information. Efficacy and safety assessments, including ABPM, were again performed at the end of the 4-week treatment. Safety was assessed at a follow-up visit approximately one week after the last dose of double-blind medication.

Figure 45.1 Study Design with Phases of Study



Primary & Secondary Endpoints

The primary efficacy parameter was the mean ambulatory blood pressure (MABP) measured during 20 to 24 hours after the morning dose of study medication (trough level) at endpoint. The MABP is defined as the mean of all programmed readings during the specified period for ABPM recordings that have met all "successful reading criteria": Successful Reading Criteria for 24-Hour ABPM Recording

- At least 80% of programmed recordings of BP are acceptable
- No consecutive lapses of recording 2 hours. (A lapse was defined as an hour of recording with less than two successful readings.)
- At least 12 readings were recorded during the period from 20 to 24 hours post-dose.

The secondary parameters are as follows:

- MABP over hours 0-24.
- MABP over 4-hour periods, starting with hour 0.
- Peak and trough values of clinic BP.
- Peak/trough ratio of placebo-adjusted MABP for 0-24 hour interval.
- BP load (percent of period (0-12 hours) that systolic and diastolic BPS were >140 mm Hg and >90 mm Hg respectively; percent of period (13-24 hours) that systolic and diastolic BPS were > 120 mm Hg and >80 mm Hg, respectively).

- Mean areas under the systolic and diastolic BP curves where recorded pressures exceeded 140 mm Hg and 90 mm Hg, respectively, when patients were awake and where pressures exceeded 120 mm Hg and 80 mm Hg, respectively when patients were asleep.
- Mean clinic BP (cuff readings) and heart rate.
- Proportion of responders in each treatment group (ABP responders defined as patients whose MDDBP was reduced to <87 mm Hg or by ≥ 10 mm Hg; clinical responders defined as patients whose mean SitDBP was reduced to <90 mm Hg or by ≥ 10 mm Hg).

In addition to what is stated in the protocol, the area under the curve (AUC) was calculated using the trapezoid rule where missing values were linearly interpolated. The baseline value for ABPM was the MABP, based on recordings at the end of the placebo run-in phase, corresponding to the same intervals as the primary and secondary efficacy parameters. The baseline value for clinic BP and heart rate was the average of the three values obtained after the conduct of a valid qualifying ABPM at the end of run-in before the first dose of randomized study medication was administered.

Statistical Methods

For data analysis, the intent-to-treat endpoint has been defined as the last observation recorded during double-blind treatment. Target sample size calculation was based on ABPM data, a standard deviation of 6.5 mm Hg was assumed for MABP derived according to the procedures presented in the protocol. For a difference of 5 mm Hg in blood pressure between the treatment groups, it was estimated that a sample size of 36 per group would be required to establish statistical significance (two-tail) at $\alpha = 0.05$ and power = 0.90.

The study was terminated after only 61 of the expected 80 patients were randomized. No reason was stated in the application, however in response to a telephone inquiry, Linda Rebar (Regulatory Affairs) related that the study was terminated because of slow enrollment and eagerness to review data. Assuming the true standard deviation of 6.5 mm Hg, a sample size of 24 patients in the placebo treatment group and 26 patients in the eprosartan 400 mg treatment group with both a baseline and endpoint ABPM had a power of 78% to detect a difference of 5 mm Hg, for a two-tailed test at the 0.05 level of significance.
No per protocol analysis was performed. A subgroup analysis of efficacy was to be performed. Due to the low numbers of patients in some of the subgroups including race (black: eprosartan, six of 31 patients; placebo, four of 30 patients), age (≥65 years: eprosartan, seven of 31 patients; placebo, five 30 patients), and severity of hypertension (105-114 mm Hg: eprosartan, seven of 31 patients, placebo, four of 30 patients), an analysis of the subgroups was not performed on the efficacy parameters. In addition, the peak-to-trough ratio of placebo-adjusted MABP for the 0-24 hour interval was not calculated.

Results

Patient Disposition

The disposition of patients who participated in this study protocol is summarized in Table 45.1.

Table 45.1 Patient Disposition

	Placebo	Eprosartan 400 mg	Total
# Screened			109
# Randomized	30	31	61
# Completing Study(%)	30 (100)	31 (100)	61 (100)
# for Follow-up(%)	29 (96.7)	30 (96.8)	59 (96.7)

Data Source: Appendix 3.1.2

Demographics Characteristics

Subjects were recruited from 6 centers. The number of subjects randomized per center ranged from 5 to 16. There were no statistically significant differences in the age of randomized subjects compared to non-randomized subjects. The mean age was 54.3 years (range 40 to 73 years) in the eprosartan 400 mg treatment group and 52.1 years (range 26 to 67 years) in the placebo treatment group. There were no statistically significant differences in racial composition between the two groups.

Efficacy Evaluation

As described earlier, no Per-Protocol analysis was performed due to "the small number of protocol violations and the small number of patients in the study". Instead an intent-to-treat analysis was performed. The results shown are for patients who were randomized and had at least one on-therapy assessment. The ABPM results include those patients who underwent a successful ABPM at both baseline and week 4 and thus completed the study by definition. The endpoint observation is defined as the last assessment recorded during the double-blind treatment period. Of the 61 patients randomized, 51 patients (eprosartan 400 mg, 26; placebo, 25) had a successful ABPM at baseline and endpoint.

Primary Efficacy Parameter

The primary efficacy parameter in this study was the change from baseline in MABP over the period of hours 20-24 after the dose of study medication. Baseline and endpoint mean measurements of ABPM and change from baseline taken at 20-24 hours during the 24-hour monitoring period are found in Table 45.2. MABP measured at trough (20-24 hours after dosing) decreased at endpoint to a greater degree in patients treated with eprosartan than placebo treated patients when compared to the same monitoring period at baseline. This was found for both diastolic (eprosartan: -4.0 ± 6.9 mm Hg; placebo: -0.3 ± 8.1 mm Hg) and systolic (eprosartan: -5.0 ± 10 mm Hg; placebo: -0.8 ± 14.3 mm Hg) measurements. These differences did not achieve statistically significance.

Table 45.2. Mean (±S.D.) Ambulatory Blood Pressure (MABP) at Baseline and Endpoint at 20-24 Hours Post-Dose

		Systolic Blood Pressure (mm Hg)			Diastolic Blood Pressure (mm Hg)		
Group	n	Baseline	Endpoint	Change	Baseline	Endpoint	Change
Placebo	24	150.3±15.1	149.5±17.2	-0.8±14.3	92.6±8.6	92.3±9.3	-0.3±8.1
Eprosartan	26	149.0±11.8	144.0±13.0	-5.0±10.0	94.2±7.4	90.2±6.7	-4.0±6.9

Data Source: Appendix 3.3.3, and 3.13.2.2

Secondary Parameters of Efficacy

Secondary efficacy parameters were not reviewed because the primary efficacy parameter was not statistically significant. So all the alpha designated for the study was spent in the testing of the primary efficacy parameter, making the review of secondary efficacy parameter unacceptable according to statistical principles. The secondary efficacy parameters included MABP measured at 0-12, 12-24, 0-24, and every four hours from 0-20 hours, mean clinic blood pressure and heart rate, trough/peak ratio of clinic blood pressure, and the number of responders in each treatment group.

Conclusion:

Based on the review of this study, it was concluded that eprosartan 400 mg did not significantly reduce blood pressure. The study was terminated before the target sample size was achieved and the analyses presented were not those defined in the study protocol. The intent-to-treat analysis which was carried out is a much preferred analysis, but the difference did not achieve statistical significance. This may have been due to the lack of statistical power. The lack of statistically significant difference in the primary efficacy parameter of this study presents a special concern in the review of this drug. The sponsor is requesting a once daily dosing of this drug, but carried out only two studies using once daily regimen. The first of which is this protocol (protocol 045), which did not yield

statistical significant difference. On the other hand, there were five studies using twice daily dosing regimen.

There was a discrepancy in the study design and the title. According to the title the study was carried out as stated, but in the design of the study it was stated that this was supposed to be a dose-range comparison. There was no dose range component to the study, it will be presumed that this was a typographical error. Another concern with this study is that it was designed specifically to evaluate eprosartan in males, not females. No reason was offered for the exclusion of females.

It was concluded that this study should be ignored (at best), in the overall decision regarding this new drug application, or considered a negative study. This is because there were too many deficiencies in the study that makes the results not acceptable:

1. Early termination of the study, without any documented reason. The study design did not have any stopping rules.
2. Lack of statistical power.
3. Ignoring the protocol specified analysis and parameters in the submission. This led to a concern that the results of the protocol defined analyses were probably not significant, which was confirmed by reanalysis of the data.
4. Design of the study stated that this was supposed to be a dose range study, but the study had no dose-range component.
5. The study was carried out in males only, making the results not generalizable to the general population, for who the drug is intended.
6. No statistically significant differences were observed.

Protocol 049. An 8-week, double-blind, parallel, dose range, multicenter, comparison of Eprosartan 400, 600, 800 and 1200 mg once daily with placebo in patients with essential hypertension (DBP ≥ 95 and ≤ 114 mm Hg).

Protocol

Design & Objectives

This was a multicenter, randomized, double-blind, placebo controlled, parallel, multi dose study in patients with essential hypertension. The primary objective was to determine the *antihypertensive effect* of doses ranging from 400 to 1200 mg once daily in patients with essential hypertension and average sitting DBP ≥ 95 and ≤ 114 mm Hg. The secondary objectives were to: assess the safety of once daily doses of eprosartan through observation of adverse experiences, laboratory abnormalities, sitting heart rate, standing vital signs, and changes in electrocardiograms (ECG); evaluate the effect of eprosartan on fasting serum glucose concentration, lipid profile, and electrolytes; and to describe the population pharmacokinetics of once daily doses of eprosartan in patients with hypertension.

Inclusion Criteria

1. men or women ≥ 18 years of age who have given informed consent to participate, women of child bearing potential must use some form of contraception
2. patients with essential hypertension having a mean sitting DBP of ≥ 95 and ≤ 114 mm Hg without treatment at the end of the placebo run-in period
3. newly diagnosed patients with essential hypertension, or previously treated patients from whom antihypertensive therapy can be safely withdrawn for the duration of the study

Exclusion Criteria

1. pregnancy or lactation
2. secondary forms of hypertension
3. advanced hypertensive retinopathy
4. mean sitting SBP >200 mm Hg
5. advanced atrio-ventricular conduction defect unless a pacemaker is in place
6. significant ventricular tachyarrhythmias requiring therapy

7. bradycardia (resting sitting heart rate <50 bpm) after withdrawal of previous antihypertensive medications
8. signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days
9. congestive heart failure (CHF) on treatment with ACE inhibitors or diuretics, patients with untreated reduced ejection fraction may be included
10. angina pectoris treated with regular doses of nitrates, beta blockers, or calcium-channel blockers
11. diabetes mellitus that is unstable despite treatment with insulin or oral hypoglycemic agents
12. clinically significant renal or hepatic disease, serum creatinine >2.5 mg/dl (220 micromol/L), ALT, AST, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range
13. leukocyte count <3000/mm^3 or platelet count <100,000/mm^3
14. other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality that, in the opinion of the investigator, could preclude participation or survival
15. active alcohol or drug abuse
16. use of warfarin or other oral anticoagulants within 30 days before the screening visit
17. use of an investigational drug within 30 days before enrollment into this study or within five half-lives of the investigational drug (the longer period will apply)
18. concomitant administration of any medication known to affect blood pressure
19. concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low dose aspirin up to 325 mg per day). Patients must have discontinued such drugs for at least 7 days before the screening visit
20. concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazine derivatives
21. patients sensitive to eprosartan or other drugs in its class
22. patients who have received randomized medication in a previous trial of eprosartan

Description of Phases

A flow chart outlining the phases of the study is shown in Figure 11.1. The trial consisted of a four (4) week placebo run-in period followed by an 8 week double blind treatment period. Patients who had a trough sitting diastolic blood pressure (DBP) between 95 mm Hg and 114 mm Hg at the end of the placebo run-in period were randomized to placebo, eprosartan 400 mg, eprosartan 600 mg, eprosartan 800 mg or eprosartan 1200 mg once daily dosing. The mercury sphygmomanometer was used as the primary measurement device. Baseline trough DBP was defined as the mean of the last two qualifying visits in the placebo run-in period. Study endpoint was defined as the last available record for randomized patients who received at least one dose of study medication during the double-blind treatment period and had at least one efficacy measurement taken at trough. At the end of the study, patients had the option of continuing in an open label extension protocol study or return for follow-up visit off therapy. The follow-up visit was scheduled for subjects who did not enter the open-label extension study. Subjects returned 7 to 14 days after the last day of coded medication.

Primary & Secondary Endpoints

The primary efficacy variable was defined as the mean change from baseline in sitting diastolic blood pressure (DBP) at trough. Secondary efficacy variables were defined as:

- mean change from baseline in sitting DBP at peak,
- mean change from baseline in sitting systolic blood pressure (SBP) at peak and trough,
- mean change from baseline in sitting heart rate at peak and trough,
- mean change from baseline in standing DBP at peak and trough,
- mean change from baseline in standing SBP at peak and trough,
- mean change from baseline in standing heart rate at peak and trough,
- proportion of responders in each treatment group, that is, the percent of subjects whose sitting DBP is

between 91 mm Hg and 100 mm Hg, and decreased by at least 10 mm Hg,
- trough to peak ratio of efficacy defined in terms of the primary efficacy index, and
- mean change from baseline in fasting lipid values (total cholesterol, HDL, LDL, triglycerides) and glucose in the total patient data set and in the subset of patients with baseline values above the normal range.

Committees

There were no steering, safety, events or executive committees involved in this protocol.

Statistical Analysis Plan

Changes in blood pressure, heart rate and other continuous variables were assessed by the Analysis of Variance (ANOVA). Categorical demographic and clinical characteristics were assessed by the Chi square test. The type I error was set at α=0.05 for all formal hypothesis. Sample size of 77 subjects per treatment group provides 90% power to detect a 5 mm Hg difference in a change from baseline. This assumed a standard deviation of 8 mm Hg (which corresponds to SEM=0.912) and used an α=0.05 with two-sided testing and Bonferroni adjustment for each active group compared to placebo and 800 mg compared to 1200 mg.

Interim Analysis

No interim analysis was planned or carried out for this study.

Results

Disposition

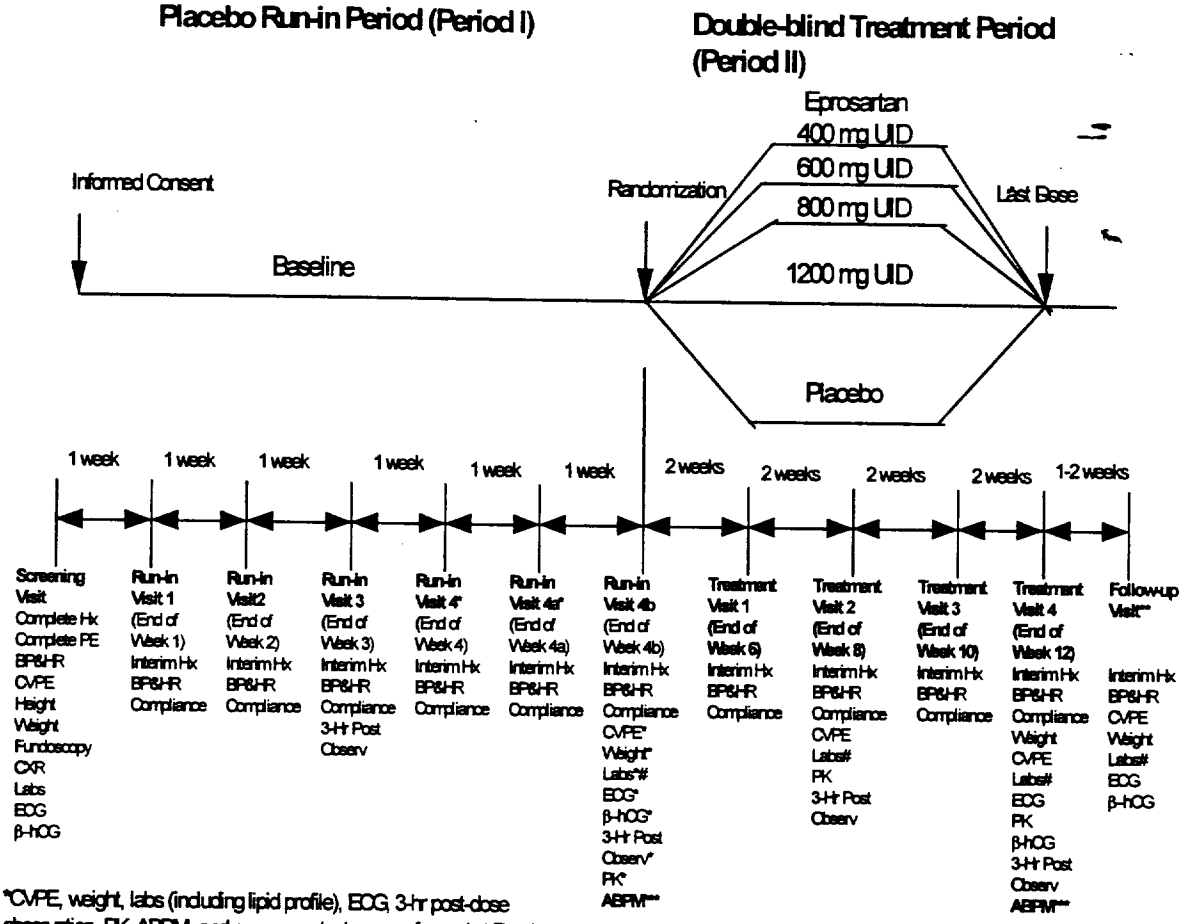
The disposition of patients who participated in this protocol is summarized in Table 49.1 below.

Table 49.1 Patients Disposition

	Placebo	Eprosartan				Total
		400 mg	600 mg	800 mg	1200 mg	
# Screened						607
# Randomized	74	70	73	73	72	362
# Completing Study (%)*	62 (83.8)	63 (87.5)	71 (97.3)	66 (90.4)	69 (95.8)	331 (90.9)
# Returning for Follow-up (%)**	24 (32.4)	27 (37.5)	23 (31.5)	30 (41.0)	27 (37.5)	131 (35.9)
# Not Completing Study	12	9	2	7	3	33

* Percentages are based on the number of patients who entered Period II.
** Based on the number of patients who did not enter open label extension study.
Data Source: Tables 13.2, 13.3.1, 13.3.2, 15.10, and Appendix B, Patient Listing 4.

Figure 49.1 Study Design with Phases of Study



*CVPE, weight, labs (including lipid profile), ECG, 3-hr post-dose observation, PK, ABPM, and pregnancy test was performed at Run-in Visit 4, 4a, or 4b, whenever the patient qualified for randomization.
**Only for patients who did not continue into extension study.
#LABS - include lipid profile
PK = Pharmacokinetics Assessment
CVPE = Cardiovascular Pulmonary Examination
Hx = History

***ABPM At end of Run-in, if ABPM monitoring had been unsuccessful, patients were rescheduled within 48 hours. The first dose of randomized medication followed completion of a a successful reading for baseline ABPM. Treatment Visit 4 ABPM was scheduled either two days before or one day after the final visit. If ABPM was unsuccessful, rescheduling occurred within 48 hours and study medication continued until successful ABPM was obtained.

Demographics

Subjects were recruited from 32 centers. The number of subjects randomized per center ranged from 3 to 38. The mean age was 55.7 ± 11.4 years for subjects that were randomized, compared to 55.1 ± 12.5 for those 243 subjects who were screened but not randomized. Variations in demographic and clinical variables between randomized and nonrandomized subjects were not statistically significant. A summary of patient demographic characteristics are presented in Table 49.2.

Table 49.2 Patient Demography

	Placebo	Eprosartan				Total
		400 mg	600 mg	800 mg	1200 mg	
# Caucasians Randomized	50 (67.6)	48 (66.7)	53 (72.6)	53 (72.6)	52 (72.2)	256 (70.3)
# Males Randomized (%)	44 (59.5)	52 (72.2)	47 (64.4)	41 (56.2)	36 (50.0)	220 (60.4)
# <65 years (%)	46 (62.2)	54 (75.0)	52 (71.2)	55 (75.3)	55 (76.4)	262 (72.0)

Efficacy

The primary efficacy parameter was defined as the mean change from baseline sitting diastolic blood pressure at trough. Baseline was defined as the mean of the last two qualifying visits during the placebo run-in period, and the endpoint used to determine change was the last available record during the double blind treatment period. Summary of the mean change in primary efficacy analysis is presented in Table 49.3 below. The results showed that eprosartan 600 mg and the 1200 mg doses produced a statistically significant decrease in sitting diastolic blood pressure over the placebo effect.

Table 49.3 Mean (±SEM) Trough Sitting Diastolic Blood Pressure at Baseline and Study Endpoint for All Randomized Patients

	MEDICATION REGIMEN				
		Eprosartan			
Sitting DBP	Placebo (N = 72)	400 mg (N = 70)	600 mg (n = 73)	800 mg (n = 72)	1200 mg (n = 71)
Baseline*	100.6 ± 0.5	102.0 ± 0.6	101.5 ± 0.6	100.7 ± 0.5	100.6 ± 0.6
Study Endpoint**	97.3 ± 1.1	96.9 ± 1.1	95.3 ± 1.0	94.8 ± 0.9	93.0 ± 1.1
Change from Baseline	-3.3 ± 1.0	-5.1 ± 0.9	-6.2 ± 0.9	-5.9 ± 0.8	-7.6 ± 0.9
Difference from Placebo		-1.8	-2.9	-2.6	-4.3
P-value†		0.121	0.0274	0.0934	0.0298

N = the number of patients with a Baseline value and study Endpoint value
* = Baseline sitting DBP was the mean of last 2 clinic visits during the placebo run-in period
** = Study Endpoint sitting DBP was recorded at the last clinic visit during double-blind period.
† = P-value resulted from a multiple comparison analysis using the modified Bonferroni procedure

Secondary Efficacy Parameters

Results of the secondary efficacy parameters are summarized in Table 49.4.

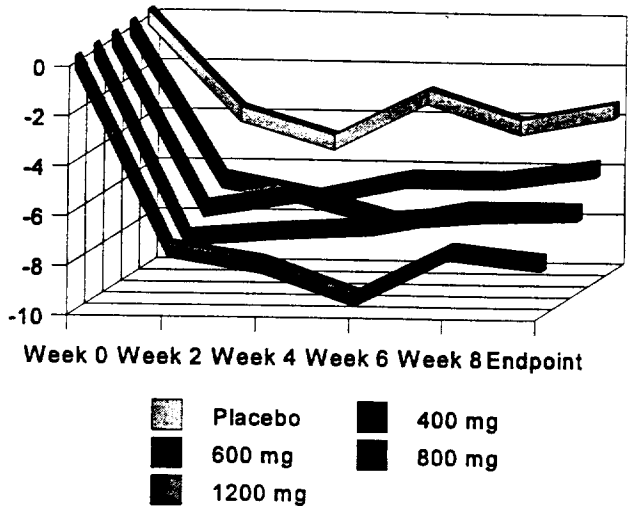
Table 49.4 Mean (±SEM) Trough Secondary Efficacy Parameters at Baseline and Study Endpoint

	MEDICATION REGIMEN				
		Eprosartan			
Vital Sign Measures	Placebo	400 mg	600 mg	800 mg	1200 mg
Sitting SBP (mm Hg)	(n = 72)	(n = 70)	(n = 73)	(n = 72)	(n = 71)
Baseline	154.5±1.8	153.3±1.6	154.1±1.8	151.9±1.6	154.6±1.7
Study Endpoint	153.3±2.3	148.5±2.1	145.9±2.2	146.3±1.9	144.6±2.0
Change from Baseline	-0.8±1.5	-4.8±1.5	-8.2±1.4	-5.6±1.5	-10.0±1.4
Sitting Heart Rate (bpm)	(n = 72)	(n = 70)	(n = 73)	(n = 72)	(n = 71)
Baseline	72.9±0.9	72.9±0.9	72.8±0.9	73.2±1.0	73.1±0.9
Study Endpoint	72.6±1.0	72.5±1.1	72.8±0.9	72.7±1.1	71.4±0.8
Change from Baseline	-0.3±0.9	-0.4±0.7	0.0±0.7	-0.5±1.0	-1.7±0.8
Standing DBP (mm Hg)	(n = 72)	(n = 70)	(n = 73)	(n = 72)	(n = 71)
Baseline	101.7±0.6	102.0±0.8	102.0±0.7	101.0±0.6	101.2±0.8
Study Endpoint	99.4±1.1	97.8±1.2	96.9±1.1	96.8±0.9	95.1±1.1
Change from Baseline	-2.3±0.9	-4.2±0.9	-5.1±0.9	-4.2±0.8	-6.1±0.8
Standing SBP (mm Hg)	(n = 72)	(n = 70)	(n = 73)	(n = 72)	(n = 71)
Baseline	153.7±1.9	152.4±1.8	152.5±1.8	150.3±1.5	153.5±1.6
Study Endpoint	152.5±2.3	146.0±2.0	146.8±2.2	145.2±1.9	145.2±2.1
Change from Baseline	-1.2±1.5	-6.4±1.4	-5.7±1.3	-5.1±1.6	-8.3±1.5
Standing Heart Rate (bpm)	(n = 72)	(n = 70)	(n = 73)	(n = 72)	(n = 71)
Baseline	76.1±0.9	75.3±1.0	75.4±1.0	75.8±1.1	76.2±0.8
Study Endpoint	75.1±1.1	75.3±1.0	75.8±1.0	76.0±1.1	74.4±0.9
Change from Baseline	-1.0±0.9	-0.0±0.8	0.4±0.9	0.2±0.8	-1.8±0.7

n = the number of patients with a baseline value and study endpoint value.

Development of Blood Pressure Effect Over Time

Figure 49.2 Diastolic BP Effect Over Time



The effect of eprosartan on sitting diastolic blood pressure is presented in Figure 49.2. The Least square means with modified Bonferroni procedure showed that at 2 weeks there was statistical significant difference from placebo with the 600 mg, 800 mg and 1200 mg doses. This differences persisted throughout the study period.

Subgroup Efficacy Analysis

Results of subgroup analysis are provided below.

Age:

The change in sitting diastolic blood pressure (the primary endpoint) by age-group (< 65 years and≥ 65 years) showed that 600 mg and 1200 mg doses of eprosartan produced statistically significant decrease in DBP from baseline. The observed differences for the other doses of eprosartan were about the same, however, they did not reach statistical significance probably because of decrease in statistical power. The results are summarized in Table 49.5

Table 49.5 DBP change from baseline by Age group - Least Squares Means

	< 65 Years			≥ 65 years		
Tx. Group	n	Change in DBP	Difference from Placebo	n	Change in DBP	Difference from Placebo
Placebo	46	-3.2±1.3	–	26	-3.3±1.4	–
400 mg	54	-5.4±1.0	-2.2	18	-4.2±1.8	-0.9
600 mg	52	-5.8±1.1	-2.7**	21	-7.2±1.6	-3.9*
800 mg	55	-5.8±1.0	-2.7**	17	-6.2±1.6	-2.9
1200 mg	54	-7.8±1.1	-3.6†	17	-7.2±1.1	-3.9††

change in DBP is presented as mean±SEM
P values presented below resulted from multiple comparison analysis using the modified Bonferroni procedure.
* = P < 0.0287 † = P < 0.0071
** = P < 0.0401 †† = P < 0.0322

Gender:

Comparison of sitting diastolic blood pressure (the primary endpoint) by gender showed that the 600 mg and 1200 mg doses significantly decreased DBP among male subjects. The data obtained from females at the end of study showed a statistically significant medication by center interaction. Results of the analysis of variance are summarized in Table 49.6.

Table 49.6 DBP change from baseline by Gender

	Female			Male		
Tx. Group	n	Change in DBP	Change from Placebo	n	Change in DBP	Change from Placebo
Placebo	30	-3.3±*	–	44	-3.2±1.2	–
400 mg	20	-6.5±*	-3.2	52	-4.5±1.1	-1.3
600 mg	26	-6.8±*	-3.5	46	-5.9±1.1	-2.7**
800 mg	32	-8.0±*	-4.7	41	-4.2±1.2	-1.0
1200 mg	36	-8.7±*	-5.4	36	-6.5±1.3	-3.3**

Data source Table 14.1.3
change in DBP is presented as mean±SEM (raw means)
* = Due to significant medication-center interaction, variability was unavailable
** = Statistically significant difference from placebo at $\alpha = 0.05$, with modified Bonferroni procedure

Race:

Comparison of sitting diastolic blood pressure (the primary endpoint) by race showed that among black subjects there was no statistically significant decrease in DBP. The lack of statistically significant difference among the black subjects may be related to lack of statistical power. Among caucasians, the 600 mg ,800 mg and 1200 mg doses significantly decreased DBP. The data is summarized in Table 49.7 below.

Table 49.7 DBP change from baseline by Race - Least Squares Means

	Non-Black			Black		
Tx. Group	n	Change in DBP	Change from Placebo	n	Change in DBP	Change from Placebo
Placebo	56	-3.4±1.1	–	16	-2.6±1.9	–
400 mg	55	-5.5±1.1	-2.1	17	-3.6±1.8	-1.0
600 mg	56	-6.3±1.1	-2.9	17	-5.9±1.7	-3.3
800 mg	60	-6.5±1.1	-3.1	12	-2.7±2.0	-0.1
1200 mg	56	-7.8±1.1	-4.4	15	-7.1±1.8	-4.5

change in DBP is presented as mean±SEM
Data Source Table 14.1.4

Effect on Lipid profile, Glucose, and Electrolytes

There were no clinically significant effect of any dose of eprosartan on lipid profile, glucose, and electrolytes [1].

Trough-Peak Differences

The trough-peak differences in sitting diastolic blood pressure is presented in Tables 49.8.
The placebo subtracted trough-peak ratio is defined as:

$$PlaceboSubtractedTrough-PeakRatio=\frac{(Trough_{Epro.Fixed}-Trough_{Epro.B})-(Trough_{PlaceboFixed}-Trough_{PlaceboB})}{(Peak_{Epro.Fixed}-Peak_{Epro.B})-(Peak_{PlaceboFixed}-Peak_{PlaceboB})}$$

Where Trough values are group means and Peak values are also group means.

Table 49.8 Placebo Subtracted Trough-Peak Ratios in Sitting Diastolic Blood Pressures at Week 4 of Double-blind Treatment Period

Tx. Group	n	1-hour post dose	2-hour post dose	3-hour post dose
Placebo	63			
400 mg	66	0.47	0.56	0.34
600 mg	65	0.22	0.24	0.20
800 mg	64	0.61	0.46	0.66
1200 mg	65	0.82	0.52	0.59

Data Source 14.23.1

During the 2-hour post-dose observation period, which represents the greatest blood pressure reduction for most regimen, the trough-to-peak ratio was 0.56 for eprosartan 400 mg, 0.24 for eprosartan 600 mg, 0.46 for eprosartan 800 mg, and 0.52 for eprosartan 1200 mg. These are placebo corrected ratios.

Conclusion:

Based on the review of this study, it was concluded that eprosartan was effective in significantly reducing both systolic and diastolic blood pressure, without any statistically significant change in heart rate. Subgroup analyses showed that eprosartan was effective in subjects less than 65 years and above 65 years. Due to medication-center interaction, the comparison by gender was inconclusive. Comparison by race was also inconclusive due to small number of black subjects. However, eprosartan was effective in the caucasian group. The effect of eprosartan could be observed two weeks after initiation of medication.

There are some inconsistencies noted - the 800 mg dose did not produce statistically significant decrease in blood pressure. Also the trough/peak ratios are low for the 400 mg and 600 mg doses.

Active Controlled Trials

Introduction:

There were four active controlled trials included in this NDA submission. Two of these active control trials (protocols 014 and 053) were designed primarily to evaluate the incidence of cough between eprosartan and enalapril. The other two studies (protocols 041 and 047) were designed to compare the antihypertensive efficacy of eprosartan against Procardia XL and enalapril respectively. The two studies designed to compare the incidence of cough between eprosartan and enalapril have been thoroughly reviewed in the safety section by Dr Gordon, but will be independently reviewed on its efficacy results only in this section, just for completeness.

Protocol 014. A 26-Week, Double-blind, Parallel, Multi center, Multi country Comparison Study of the Effect of Eprosartan and Enalapril on Cough and Blood Pressure in Patients with Essential Hypertension (Diastolic Blood Pressure ≥95 mm Hg and ≤114 mm Hg)

Protocol

Design & Objective

This was a Phase III, multi center, double-blind, double-dummy, parallel-group study in patients with essential hypertension. Patients were randomized to eprosartan or enalapril, the active control. The study consisted of four periods: Screening, Placebo Run-in, Double-blind Treatment, and Follow-up. The primary objective of this study was to compare the incidence of persistent, nonproductive (dry) cough associated with study medication in patients treated with eprosartan and enalapril. The secondary objectives of the study were:

- To compare the incidence of probable cough, possible cough, and tickle in throat in patients treated with eprosartan and enalapril.
- **To compare the antihypertensive efficacy of eprosartan at doses of 200 mg and 300 mg twice daily (titrated to effect) and enalapril at doses of 5 mg to 20 mg once daily (titrated to effect) in patients with essential hypertension (average SitDBP ≥95 mm Hg and ≤ 114 mm Hg, Korotkoff V).**
- To compare the effects of treatment with eprosartan to enalapril on health-related quality of life.
- To compare the effects of eprosartan and enalapril on fasting serum concentrations of lipids, glucose, and electrolytes.
- To compare the safety of eprosartan and enalapril with regard to adverse experiences (in addition to cough), laboratory abnormalities, and changes in ECGs.

Eligibility criteria

Inclusion criteria

Men or women at least 18 years old were eligible. Women were required to be postmenopausal, ie, 6 months without menses, surgically sterile, or using hormonal or barrier contraceptives or intrauterine contraceptive devices. Patients were required to have essential hypertension with an average SitDBP of ≥95 mm Hg and ≤114 mm Hg at three consecutive weekly visits before the end of the Placebo Run-in Period. The difference between the highest and lowest SitDBP values for the three visits could not exceed 12 mm Hg, and the difference between the averages at the last two visits could not exceed 8 mm Hg. Also eligible were patients with newly diagnosed essential hypertension and those previously treated patients whose antihypertensive therapy could be safely withdrawn for the duration of the Placebo Run-in Period. All eligible patients were required to read and write the language of the available QOL questionnaire, and all were required to give written informed consent.

Exclusion Criteria

Patients were to be excluded if any of the following conditions were present:

1. Pregnancy or lactation.
2. Secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, or pheochromocytoma.
3. Advanced hypertensive retinopathy (ie, Keith-Wagener Grade III or IV).
4. Average SitSBP >200 mm Hg.

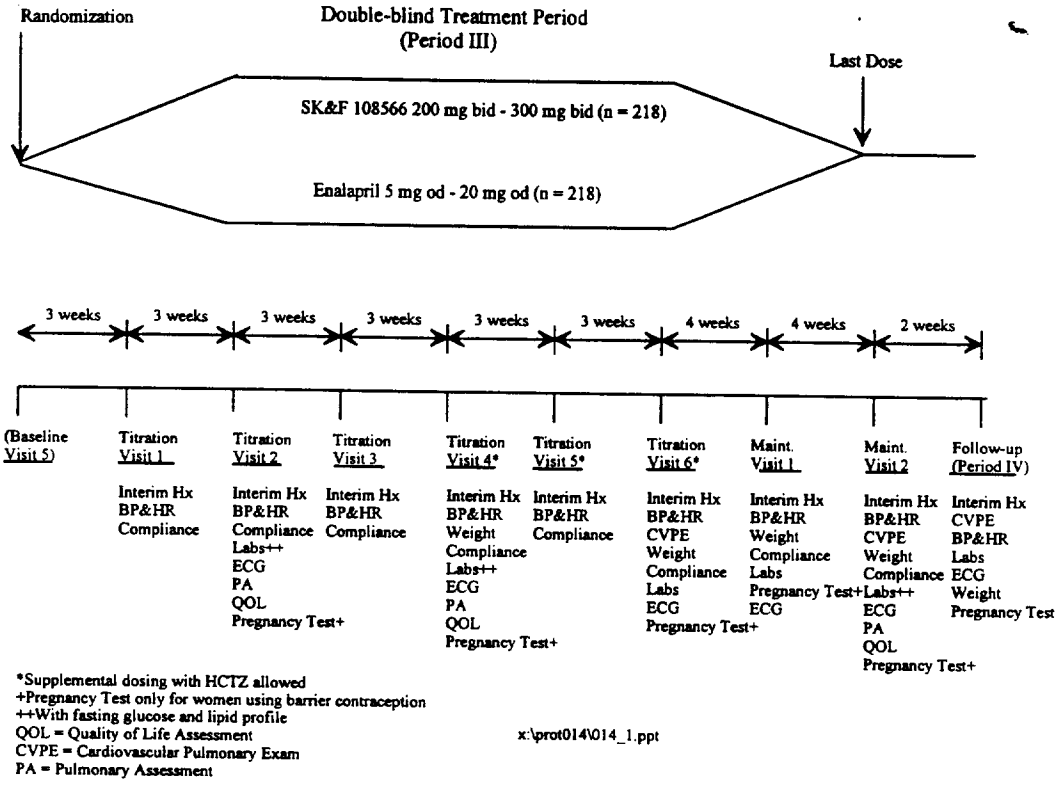
5. Advanced atrioventricular conduction defects (ie, second- or third-degree heart block) unless a pacemaker is in place.
6. Significant ventricular tachyarrhythmias requiring therapy.
7. Bradycardia (resting SitHR <50 beats/minute) after withdrawal of previous antihypertensive medications.
8. Signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days.
9. Congestive heart failure (CHF) on treatment with ACE-Is or diuretics (patients with untreated reduced ejection fraction were eligible).
10. Angina pectoris treated with regular doses of nitrates, b-blockers, or calcium channel blockers.
11. Emphysema or chronic bronchitis with daily cough and sputum production; asthma with a dry cough.
12. Upper respiratory infection (URI) with symptoms within 2 weeks of screening. (Patients who have had a recent acute URI but have been symptom-free for 2 weeks before screening may be included. Patients must also be free of URI by the end of the Placebo Run-in Period.)
13. Diabetes mellitus that is unstable (repeated episodes of ketoacidosis, hyperglycemic coma, or hypoglycemic shock) despite treatment with insulin or oral hypoglycemic agents
14. Presence of clinically significant renal or hepatic disease: serum creatinine >2.5 mg/dL (220 micromol/L); ALAT, ASAT, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range.
15. Leukocyte count <3000/mm3 or platelet count <100,000/mm3.
16. Other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality that, in the opinion of the investigator, could preclude participation or survival.
17. Active alcohol or drug abuse.
18. Use of warfarin or other oral anticoagulants within 30 days prior to screening.
19. Use of an investigational drug within 30 days of enrollment into this study or within five half-lives of the investigational drug (the longer period will apply).
20. Concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazine derivatives.
21. Concomitant administration of any medication known to affect blood pressure.
22. Concomitant administration of any medication known to influence cough (e.g., codeine or other morphine derivatives).
23. Concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDS (except low-dose aspirin, up to 325 mg per day): patients must have discontinued such drugs for at least 1 week prior to the Screening Visit.

Description of Phases

The study consisted of four periods: Screening, Placebo Run-in, Double-blind Treatment, and Follow-up. After Screening, patients entered the 3- to 5-week, single-blind, Placebo Run-in Period to establish baseline parameters. When subjects qualified for inclusion they were randomized (1:1) into treatment with eprosartan, 200 mg twice daily, or enalapril 5 mg once daily. Placebo forms of each drug (double-dummy) were dispensed together with active forms to maintain the blind. The double-blind treatment period consisted of 18 weeks of dose titration and 8 weeks of dose maintenance. If the patient's DBP was <90 mm Hg at Titration Visit 1, dosage continued at Level I: eprosartan 200 mg twice daily or enalapril 5 mg once daily. However, if the patient's DBP was ≥ 90 mm Hg, the patient's dose was advanced to Level II: 200 mg eprosartan twice daily (unchanged from Level I)) or 10 mg enalapril once daily (increased from Level I). At Titration Visit 2, If the patient's DBP was <90 mm Hg, dosage continued at the current level. If the patient's DBP was ≥ 90 mm Hg, the dosage was increased to Level III: (300 mg eprosartan twice daily or 20 mg enalapril once daily). If the patient's DBP was <90 mm Hg at Titration Visit 3, dosage continued at the current level: Level I, Level II, or Level III. If the patient's DBP was ≥ 90 mm Hg and the maximum dosage had not been reached, the dosage was increased to the next higher level: Level II or Level III. If the patient's DBP

was ≥ 90 mm Hg and the patient had reached the maximum dosage (Level III: eprosartan 300 mg twice daily or enalapril 20 mg once daily), he or she continued at that level. Patients who did not enter the long term open label extension study returned within 7 to 14 days for a follow-up visit. The study design after randomization is presented in Figure 14.1.

Figure 14.1 Study Design: Double-Blind Treatment Period



Hypertension Efficacy Assessment

The mercury column sphygmomanometer was used to measure blood pressure throughout the study. All measurements were made using the same cuff size and the same equipment on the same arm, which was supported at heart level. If the patient's arm circumference was >32 cm, a large blood pressure cuff was used. Diastolic blood pressure was measured at the disappearance of Korotkoff sounds - phase V. If possible, measurements were taken by the same staff member at each visit. After the patient sat quietly for at least 5 minutes, blood pressure and heart rate were measured three times at approximately 2-minute intervals. The three measurements were recorded and averaged to obtain the mean SitSBP and SitDBP. After the patient stood for 3 minutes, blood pressure and heart rate were measured three times at approximately 2-minute intervals. The three measurements were recorded and averaged to obtain the mean StaSBP and StaDBP.

Statistical Methods

The primary clinical parameter was the incidence of persistent, nonproductive (dry) cough associated with treatment and not due to upper respiratory infection (definite cough of interest). The secondary parameters are the following:

- Maximum cough, including definite cough, probable and possible cough (below) and tickle in throat.
- Probable cough of interest
- Possible cough of interest
- Tickle in throat
- **Mean change from baseline in sitting DBP at trough**
- **Mean change from baseline in sitting SBP at trough**
- **Mean change from baseline in sitting heart rate at trough**
- Mean change from baseline in standing DBP at trough
- Mean change from baseline in standing SBP at trough
- Mean change from baseline in standing heart rate at trough
- Proportion of responders in each treatment group; that is, the percent of patients whose sitting DBP is <90 mm Hg, or ≥100 mm Hg and decreased from baseline by at least 10 mm Hg
- Mean change from baseline in lipid values (total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride) and serum glucose
- Effects of treatment on quality of life.

For cough incidence and response rate, the two medication regimens were compared using a Cochran-Mantel-Haenszel (CMH) statistic adjusting for center interaction with regimen, which was assessed with the Breslow-Day test (PROC FREQ in SAS). **For vital signs, lipids, and serum glucose, an analysis of variance (PROC GLM in SAS) was used.** The model included medication regimen, center, and regimen-by-center interaction. If the interaction was not significant (P>.10), comparisons of the regimens were reported along with confidence intervals. For some subgroup analyses, numbers may have been insufficient; analyses were done where possible.

Results

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 14.1

Table 14.1 Patient Disposition

No of patients:	Enalapril	Eprosartan	Total
Screened			675
Entered run-in			645
Randomized	264	264	528
Completed treatment	217	230	447

Data Source: Tables 13.1, 13.2

Eighty-One subjects did not complete the study, the reasons for early termination are summarized in Table 14.2

Table 14.2 The Number and Percentage of Randomized Patients Who Completed the Study or Were Withdrawn by the Reason for Study Withdrawal

Study Conclusion Reason	Eprosartan (n=264)	Enalapril (n=264)	Total (n=528)
Completed Study*	230(87.1)	217(82.2)	447(84.7)
Early Termination	34(12.9)	47(17.8)	81(15.3)
Withdrawal Reason			
Adverse Experiences**	14(5.3)	23(8.7)	37(7.0)
Lack of Efficacy	13(4.9)	12(4.5)	25(4.7)
Lost to Follow-up	2(0.8)	3(1.1)	5(0.9)
Other Reasons+	2(0.8)	9(3.4)	11(2.1)
Protocol Violation/Noncompliance	2(0.8)	0(0.0)	2(0.4)
Termination by Sponsor	1(0.4)	0(0.0)	1(0.2)

* Patients are considered to have completed the study if they completed all 26 weeks of double-blind treatment. Double-blind Treatment Period with or without the Follow-up Visit.

** Including death, if on- or 1 day post-therapy.

\+ Includes lost to follow-up, non-compliance, and non-study-related personal reasons. Also includes one patient randomized to eprosartan (014.200.01854) who was withdrawn following the hypertriglyceridemia; see Sections 6.9 and 11.0.

Data Source: Table 13.4.

Demographic Characteristics

The study was conducted in nine countries including the United States of America. The mean age was 52.9±1.9 (range: 36-73) for subjects that were screened only but did not proceed to the placebo run-in phase. The mean age for subjects who participated in the placebo run-in phase but did not meet eligibility criteria for randomization was 53.9±1.0, with a range of 21 to 78 years. The subjects who were randomized to enalapril had a mean age of 56.0±0.7 with a range 24 to 84 years, and the mean age for subjects randomized into the eprosartan treatment had a mean age of 55.6±0.7 with a range of 23 to 84 years. Patient demographic information are summarized in Table 14.2.

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Table 14.2 Patient Demographic Characteristics

		Nonrandomized		Randomized	
Characteristics		Screened Only	Run-in Only	Enalapril	Eprosartan
Sample Size		n = 30	n = 117	n = 264	n = 264
Age (years)		52.9±1.9	53.9±1.0	56.0±0.7	55.6±0.7
Age Range (years)		36 - 73	21 - 78	24 - 84	23 - 84
Race	Black	6(20.0)	18(15.4)	19(7.2)	21(8.0)
	Caucasian	18(60.0)	7(8.6)	231(87.5)	225(85.2)
	Oriental	2(6.7)	2(1.7)	4(1.5)	2(0.8)
	Others	4(13.3)	5(4.3)	10(3.8)	16(6.1)
Sex	Female	13(43.3)	54(46.2)	117(44.3)	114(43.2)
	Male	17(56.7)	63(53.8)	147(55.7)	150(56.8)

Data Source: Tables 13.10, 13.11, 13.14, and 13.15

Incidence of Definite Cough

This study was to detect a difference in the incidence of cough, and the results of the analysis showed that there was significantly less cough in the eprosartan group, compared to the enalapril group. A summary of the results of the Cochran-Mantel-Haenszel analysis is provided in Table 14.3.

Table 14.3 Difference Between Treatments - Results of the Cochran-Mantel-Haenszel Analysis of the Incidence of Definite Cough (Investigator's Assessment), Controlling for Centers

Incidence of Cough	Eprosartan	Enalapril	Relative Risk (95% CI)	P-Values
Titration Week 6 Definite Cough No Definite Cough	2/255 (0.8%) 253/255 (99.2%)	4/253 (1.6%) 249/253 (98.4%)	2.03 (0.41, 10.2)	0.432
Titration Week 12 Definite Cough No Definite Cough	2/248 (0.8%) 246/248 (99.2%)	7/237 (3.0%) 230/237 (97.0%)	4.03 (0.98, 16.7)	0.057
Cough Endpoint* Definite Cough No Definite Cough	4/259 (1.5%) 255/259 (98.5%)	14/261 (5.4%) 247/261 (94.6%)	3.42 (1.26, 9.35)	0.017**
Cough at Any Time Prior to HCTZ+ Definite Cough No Definite Cough	4/259 (1.5%) 255/259 (98.5%)	14/261 (5.4%) 247/261 (94.6%)	3.45 (1.26, 10.0)	0.018**
Entire Treatment Period++ Definite Cough No Definite Cough	4/259 (1.5%) 255/259 (98.5%)	16/261 (6.1%) 245/261 (93.9%)	3.85 (1.48, 10.3)	0.007**

* Refers to the number and percentage of patients with cough at the last available visit during titration phase, prior to allowing the addition of HCTZ.

** Statistically significant at the 0.05 level using Cochran-Mantel-Haenszel methodology controlling for center effect.

\+ Visit at which cough first occurred, but prior to the addition of HCTZ. If no cough occurred, cough endpoint is the last visit prior to the addition of HCTZ. This is the

primary time point of interest.
++ Refers to the incidence of cough at any point during the double-blind treatment period
Data Source: Table 14.1.1

Efficacy Results

The only secondary objectives that will be considered here will be the sitting vital signs obtained at trough. This is because, the sitting diastolic blood pressure is the standard for evaluating the efficacy of new drug entities. Table 14.4 presents a summary of the analysis of sitting vital signs at trough. This analysis was to test the hypothesis that there were no difference between the blood pressure effects of eprosartan and enalapril. The ANOVA test failed to reject the null hypothesis that there is no statistically significant difference in the blood pressure lowering effect of eprosartan and enalapril.

Table 14.4 Mean ± SEM Sitting Vital Signs at Baseline and Titration Endpoint

Sitting DBP	Enalapril (n = 264)	Eprosartan (n = 264)	p-value
Baseline	101.2±0.3	100.7±0.3	
End of Titration	87.2±0.5	86.2±0.5	
Change from Baseline	-14.0±0.4	-14.5±0.4	0.120
Sitting SBP			
Baseline	156.3±0.9	156.3±0.9	
End of Titration	139.7±1.0	138.9±0.9	
Change from Baseline	-16.6±0.8	-17.5±0.8	0.498
Sitting Heart Rate			
Baseline	74.1±0.6	73.1±0.5	
End of Titration	72.5±0.6	72.8±0.5	
Change from Baseline	-1.6	-0.4±0.5	0.514

Data Source: Tables 14.2 - 14.7

Conclusion

Based on the review of this study, it was concluded that there were statistically significant less cough among the eprosartan group compared to the enalapril group. There were no statistically significant difference in the blood pressure lowering effects of eprosartan and enalapril. The absolute magnitude of the blood pressure lowering effects of the two drugs were significantly different from zero. However, we must remember that included in the absolute magnitude of effect is the placebo effect which has not been corrected for in these numbers.

Reviewer's Comments

The intended implication and logic of these results are that eprosartan reduces blood pressure just as well as enalapril. Enalapril is an approved drug for the control of hypertension, therefore eprosartan must be approved for the control of hypertension. This logic seems fine on its face value, however in order to propound this logic there are certain assumption that must be met. First is that enalapril must be the most effective drug in its class. Secondly, the point estimate of the effect of eprosartan must not be less than 50% of the point estimate of the most effective drug. Thirdly, both drugs must have demonstrated superior efficacy against placebo, (ie, both would have beaten placebo, had placebo been present). So the question that has not been addressed is, "is enalapril the most effective drug in the class?" and Why and how was enalapril selected for the study?

Another important consideration is the fact that this study design does not lend itself to the comparison of the efficacy of two different drugs. In order to compare two different drugs, at least 3 different doses of each drug must be studied to generate dose response curves with each drug. It is the dose response curves that can be compared to evaluate efficacy.

There is no doubt in this reviewers mind, after the review of all the placebo controlled studies, that eprosartan reduces blood pressure, the question this reviewer possess is what is the minimum effective dose of eprosartan, and what is the dosing frequency? The sponsor proposes in the labeling, a once daily dosing of eprosartan, but choose to compare its effectiveness to enalapril (a once daily medication) by using twice daily dosing. The observation, which permeates the whole NDA data is that it takes twice daily dosing of eprosartan to achieve the same effectiveness of once daily enalapril.

Protocol 041. A 12-Week , Double-Blind, Parallel, Multi center Trial to Compare Regimens of Eprosartan and Procardia XL, Given Alone and Combined, in Patients with Essential Hypertension (DBP ≥100 and ≤114 mm Hg)

Protocol

Design & Objective

This was Phase III, multi center, double-blind, double-dummy, parallel group study, patients were randomized to eprosartan or Procardia XL. The study consisted of a Screening Visit and three periods: Placebo Run-in, Double-blind Treatment, and Follow-up. The primary Objective of this study was to compare the antihypertensive effect of eprosartan 200 mg or 300 mg twice daily to Procardia XL 60 or 90 mg once daily, both titrated to effect, in patients with essential hypertension having an average sitting diastolic blood pressure (SitDBP) ≥100 and ≤114 mm Hg. The secondary objectives were:

- To assess the safety of eprosartan through observation of adverse experiences, laboratory abnormalities, and electrocardiograms (ECGs).
- To compare the efficacy and safety of combined regimes of eprosartan and Procardia XL®.
- To compare the effects on fasting serum concentration of lipids, glucose, and electrolytes of combined regimens of eprosartan and Procardia XL®.

Eligibility Criteria

Inclusion Criteria

1. Men or women over 18 years of age with SitDBP ≥100 and ≤114 mm Hg. Women of childbearing potential (ie, premenopausal and not surgically sterile) must have used some form of contraception, e.g., hormonal (oral or parenteral), intrauterine device, or barrier (condoms or diaphragms).
2. Patients with newly diagnosed essential hypertension, or previously treated patients from whom antihypertensive therapy could be safely withdrawn for the duration of the Placebo Run-in Period.

Exclusion Criteria

Patients were to be excluded if any of the following conditions were present:

1. Pregnancy or lactation.
2. Secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, or pheochromocytoma.
3. Hypertension due to current use of hormonal contraceptive agents.
4. Advanced hypertensive retinopathy (ie, Keith-Wagener Grade III or IV).
5. Average SitSBP > 200 mm Hg.
6. Advanced atrioventricular conduction defects (ie, second- or third-degree heart block) unless a pacemaker is in place.
7. Significant ventricular tachyarrhythmias requiring therapy.
8. Bradycardia (resting SitHR < 50 beats/minute) after withdrawal of previous antihypertensive medications.
9. Signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days.

10. Congestive heart failure (CHF) on treatment with ACE-Is or diuretics. Patients with untreated reduced ejection fraction were eligible.
11. Angina pectoris treated with regular doses of nitrates, beta blockers, or calcium channel blockers.
12. Diabetes mellitus that was unstable (repeated episodes of ketoacidosis, hyperglycemic coma, or hypoglycemic shock) despite treatment with insulin or oral hypoglycemic agents.
13. Presence of clinically significant renal or hepatic disease: serum creatinine >2.5 mg/dL (220 micromol/L); ALAT, ASAT, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range.
14. Leukocyte count < 3000/mm3 or platelet count < 100,000/mm3.
15. Other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality which, in the opinion of the investigator, could preclude participation or survival.
16. Active alcohol or drug abuse.
17. Use of warfarin or other oral anticoagulants within 30 days prior to the Screening Visit.
18. Use of an investigational drug within 30 days of enrollment into this study or within five half-lives of the investigational drug (the longer period applied).
19. Concomitant administration of any medication known to affect blood pressure.
20. Concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low-dose aspirin up to 325 mg daily). Patients must have been off such drugs for at least 1 week prior to the Screening Visit.
21. Concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, and phenothiazine derivatives.
22. Sensitivity to eprosartan or other drugs in its class or to Procardia XL® or other drugs in its class.
23. Treatment with randomized medication in a previous trial of eprosartan.

Description of Phases

This study consisted of four periods: Screening, Placebo run-in, Double-blind treatment, and follow-up. After screening, patients entered the 3 to 5 weeks, single blind placebo run-in period to establish baseline parameters. When subjects qualified for inclusion they were randomized to receive orally (level 1 dosage) either: eprosartan 200 mg tablets twice daily and procardia XL placebo capsule once daily, or eprosartan placebo twice daily and procardia XL 60 mg once daily for three weeks. After the three weeks on level 1 dosage, if patients blood pressure was not controlled, then the drugs were titrated to effect by titrating up to level 2 dosage (eprosartan 300 mg twice daily and procardia XL placebo once daily, or eprosartan placebo twice daily and procardia XL 90 mg once daily) for three weeks. After treatment at level 2 dosage for three weeks patients were up titrated to level 3 dosage (eprosartan 300 mg twice daily plus procardia XL 30 mg once daily or eprosartan 100 mg twice daily plus procardia XL 90 mg once daily) three weeks. Then the subjects were up titrated to level 4 dosage (eprosartan 300 mg bid plus procardia XL 60 mg qd or eprosartan 200 mg bid plus procardia 90 mg qd) for three more weeks. The double-blind treatment period ended at week 6 for patients who (regardless of sitDBP) received Level 1 dosage for 6 weeks, at week 6 for patients who received Level 2 dosage and had a sitDBP <90 mm Hg at Week 9 for patients who received Level 3 dosage and had a sitDBP <90 mm Hg, and at Week 12 for all other patients. Patients who did not enter the long term study extension returned 7 to 14 days after the last day of study medication for follow-up assessment.

Patients completed if:

- Patients who remained on the starting dosages (Level I: eprosartan 200 mg twice daily or Procardia XL 60 mg once daily) throughout the 6-week period completed the trial regardless of DBP and were eligible to enter an open-label extension study or proceed to Follow-up.
- Patients who had their dosage increased at Level 2 (eprosartan 300 mg twice daily or Procardia XL 90 mg once daily) and whose SitDBP was <90 mm Hg completed the trial and were eligible to enter an open-label extension study or proceed to Follow-up.

Patients continued if:

- Patients receiving the Level 2 dosage and whose SitDBP was ≥90 mm Hg were continued at the same dosage with the combination of the other study medication as follows:

- Patients receiving eprosartan 300 mg twice daily continued on that dosage plus Procardia XL 30 mg once daily.
- Patients receiving Procardia XL 90 mg once daily continued on that dosage plus eprosartan 100 mg twice daily.

After three weeks (Treatment Visit 3) of combination treatment, SitDBP was evaluated. Patients whose SitDBP was <90 mm Hg completed the study and were eligible for the extension study or follow-up. Patients whose sitting DBP was ≥90 mm Hg, had their dosage increased as follows:

- For patients who had been receiving eprosartan 300 mg twice daily plus Procardia XL 30 mg once daily, the Procardia XL dose was increased to 60 mg once daily for an additional three weeks.
- For patients who had been receiving Procardia XL 90 mg once daily plus eprosartan 100 mg twice daily, the eprosartan dose was increased to 200 mg twice daily for an additional three weeks.

Primary & Secondary Endpoints

Primary efficacy criterion was the difference between eprosartan and Procardia XL in regard to SitDBP from baseline to study endpoint measured at the end of the administration interval. Secondary efficacy criteria were as follows:

- Mean change from baseline for SitSBP
- Mean change from baseline for SitHR
- Mean change from baseline for StaDBP
- Mean change from baseline for StaSBP
- Mean change from baseline for StaHR
- Response rate determined as the percentage of patients whose SitDBP was either < 90 mm Hg or < 100 mm Hg and decreased from baseline by at least 10 mm Hg
- Mean change from baseline for glucose, lipids (total cholesterol, HDL, LDL, and triglycerides), and electrolytes

Committees

There were no steering, safety, events or executive committees involved in this study.

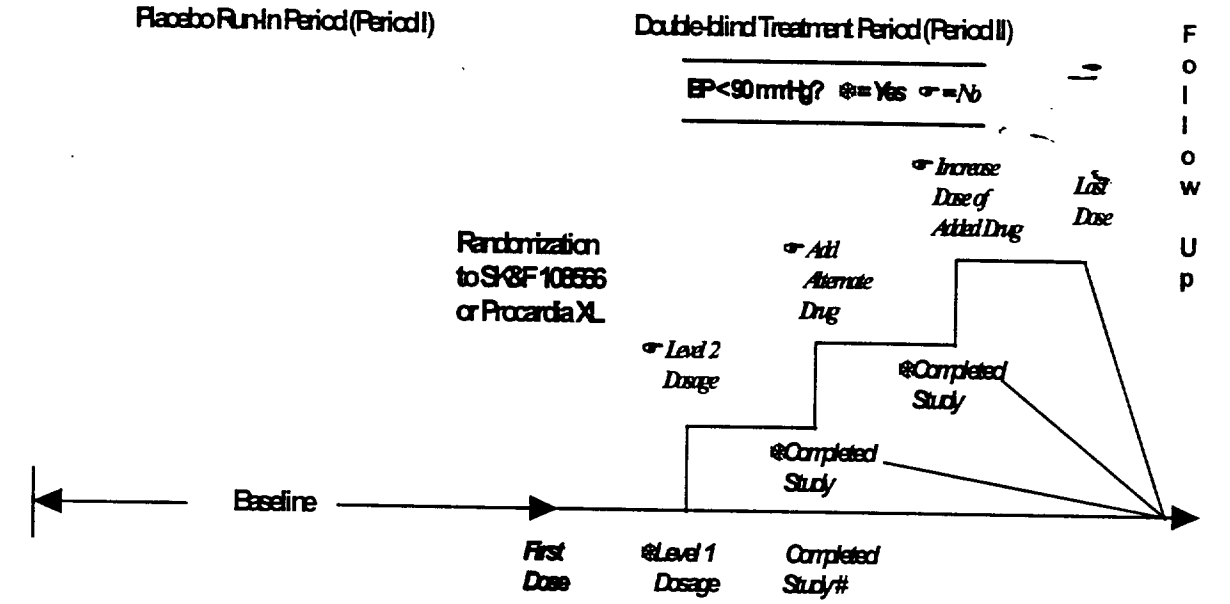
Interim Analysis

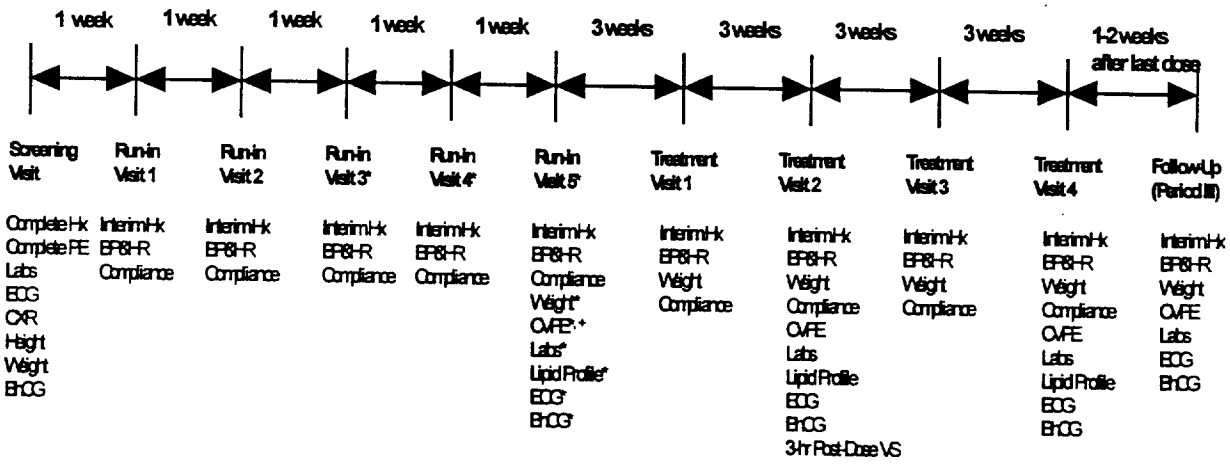
No interim analysis was planned or carried out for this study.

Statistical Methods

The primary time point of interest was monotherapy endpoint. Comparisons were also done for Week 3 and Week 6, and for combination therapy (Weeks 9, 12 and combination therapy endpoint). For the continuous variables, expressed as differences from baseline, an analysis of variance (PROC GLM in SAS) was used. The model included medication regimen, center and regimen-by-center interaction. Where regimen-by-center interaction was not significant (P>.10), it was removed from the model. The differences between the two regimens were assessed using the reduced model. For the categorical variable, response rate, each pair of regimens were assessed using a Cochran-Mantel-Haenszel statistic adjusting for center or subgroup interaction with regimen, which was assessed with the Breslow-Day test (PROC FREQ in SAS). If the interaction was not significant (P>.10), comparisons of the regimens were reported along with 95% confidence intervals of the relative risk. For some subgroup analyses, numbers may have been insufficient to assess regimen-by-subgroup interaction; it was assessed where possible. The sample size of 55 evaluable patients per group was estimated to provide 90% power to detect a 5 mm Hg difference in change from baseline between any two treatment groups at Treatment Visit 2 (end of monotherapy treatment). This assumed a standard deviation of 8.0 mm Hg and used 0.05 level of significance and two-sided testing. A minimum of 145 patients were to be enrolled.

Figure 41.1 Study Design





The two randomized treatment regimens are:

Weeks 1-3: SK&F 108666 200 mg twice daily or Procardia XL 60 mg once daily.

Weeks 4-6: SK&F 108666 200 or 300 mg twice daily or Procardia XL 60 or 90 mg once daily.

Weeks 7-9: SK&F 108666 300 mg twice daily + Procardia XL 30 mg once daily or Procardia XL 90 mg once daily + SK&F 108666 100 mg twice daily.

Weeks 10-12: SK&F 108666 300 mg twice daily + Procardia XL 60 mg once daily or Procardia XL 90 mg once daily + SK&F 108666 200 mg twice daily.

* Fasting labs with lipid profile, ECG, CVPE, weight, & pregnancy test will be performed at either Run-In Visit 3, 4 or 5, whenever the patient qualifies for randomization.

\+ CVPE = Cardiovascular pulmonary exam

Patients who continued to receive Level 1 dosage will complete the study at Treatment Visit 2, regardless of blood pressure response at that visit.

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protocol 041

Results

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 41.1. Thirty (30) patients, 14.6% withdrew prior to completing the study. Adverse experiences accounted for the largest number (15/30, 50%) of the withdrawals. There were slightly less withdrawals in the eprosartan group (n=13) than in the Procardia XL group (n=17). A similar pattern was found for the number of patients who were withdrawn due to adverse experience, eprosartan 6, Procardia XL 9. The number of withdrawals between the two eprosartan dose groups was similar (4 Vs 5) while there was considerably more withdrawals from the Procardia XL 60 mg dose (10) than from the 90 mg dose (4).

Table 41.1 Patient Disposition

No of patients:	Eprosartan 200 mg BID	Procardia 60 mg QD	Total
Screened			313
Entered run-in			282
Randomized	103	102	205
Completed treatment	90	85	175

Data Source: Table 13.3, 13.5, 15.19.

Demographic Characteristics

The study was conducted by 20 investigators at 20 centers in the United States. A summary of patients

Table 41.2 Demographic Characteristics of Non-randomized, and Evaluable Patients

		Nonrandomized		Randomized	
Characteristic		Screened Only	Run-in Only	Eprosartan	Procardia XL
Sample Size		(n=31)	(n=77)	(n=101)	(n= 97)
Age (years) (mean±SEM)		58.8±2.4	55.1±1.4	55.5±1.0	53.4±1.1
Age Range (years)		33-82	18-78	31-79	31-74
Race	Black	7(22.6)	10(13.0)	15(14.9)	22(22.7)
	Caucasian	22(71.0)	62(80.5)	76(75.2)	71(73.2)
	Other	2(6.5)	5(6.5)	10(9.9)	4(4.1)
Sex	Male	22(71.0)	47(61.0)	63(62.4)	58(59.8)
	Female	9(29.0)	30(39.0)	38(37.6)	39(40.2)

Data Source: Tables 13.10, 13.12, 13.14, 13.15

Efficacy Results

Clinically significant reductions in sitting diastolic blood pressure from baseline values were observed after treatment with eprosartan (10.9 mm Hg) or Procardia XL (14.7 mm Hg) as monotherapy. However, the decrease from baseline in sitting DBP was greater for Procardia XL than for eprosartan at monotherapy endpoint. This difference (3.8 mm Hg) was statistically significant. Patients who reached combination therapy had higher mean sitting and standing BP at monotherapy endpoint than the patient population as a whole. The eprosartan group experienced greater mean decreases from monotherapy endpoint to combination therapy endpoint when compared to the Procardia XL group for sitting and standing DBP, as well as sitting and standing SBP. Thus at combination

therapy endpoint, the mean values were similar between the two regimens.

Table 41.4 Mean ±SEM Trough Sitting Diastolic Blood Pressure at Baseline and Week 3

Sitting DBP	Eprosartan 200 mg BID	Procardia 60 mg QD
Sample Size	101	97
Baseline	103.7±0.3	103.6±0.3
Week 3	94.4±0.7	91.1±0.8
Change from Baseline	-9.3	-12.5
Difference		-3.2*

* Indicates significance at 0.0003 using modified Bonferroni procedure
Data Source Tables 14.1.1-14.4

Secondary endpoints

The least squares mean difference between the two medications in sitting systolic blood pressure was -3.3 ($p<0.103$). However the differences in standing blood pressures were statistically significant between the two medication groups. Least squares mean difference in standing diastolic blood pressure was -4.7 ($p<0.0001$), and systolic blood pressure was -5.3 ($p<0.009$).

Conclusion

Based on the review of this study, it was concluded that eprosartan 200 mg given twice daily decreases blood pressure but not to the extend that is achieved by procardia XL given once daily.

Reviewer's Comments

Again this reviewer notes that for a drug that is intended for once daily dosing, it is interesting that when the sponsor wishes to compare its efficacy with "other" once daily antihypertensive medications, that the sponsor uses twice daily dosing of eprosartan. In this case, the 200 mg twice daily did not achieve the same efficacy results as the 60 mg of procardia. To note, the 60 mg dose of procardia is not the starting dose of procardia XL.

Protocol 047. A 10-Week, Double-Blind, Parallel, Multi center Comparison of Oral Eprosartan and Enalapril in Patients with Severe Hypertension (DBP ≥ 115 and ≤ 125 mm Hg).

Protocol

Design & Objective

This was a double-blind, double-dummy, active (Enalapril) controlled, randomized, multi center, parallel group study in patients with severe hypertension. The primary objective of the study was to compare the antihypertensive efficacy of eprosartan in titrated doses of 200 to 400 mg twice daily and enalapril in titrated doses of 10 to 40 mg once daily in patients with severe hypertension (sitting DBP ≥ 115 and ≤ 125 mm Hg).

The secondary objectives of this study were to compare the safety of eprosartan and enalapril with regard to adverse experiences, laboratory abnormalities, and changes in ECGs and to compare the need for additional diuretic (hydrochlorothiazide (HCTZ)) therapy in the two medication regimens.

Eligibility criteria

Inclusion criteria

1. Men, or women without child-bearing potential (postmenopausal, i.e., > 6 months without a

menstrual period; surgically sterile; or using hormonal or barrier contraceptives or an intrauterine contraceptive device), who were at least 18 years of age and had given written informed consent to participate.

2. Patients with severe established essential hypertension defined as an average sitting DBP of > 115 and < 125 mm Hg (Korotkoff Phase V). These patients may have been newly diagnosed, or may have received anti-hypertensive treatment previously provided that they have been off such treatment (other than thiazide diuretics) for at least 7 days prior to the day of entry into the study, or currently treated with a thiazide diuretic (stable dose for at least 7 days) which may have been continued.

Exclusion Criteria

A patient was excluded from the study if any one of the following criteria applied to that patient:

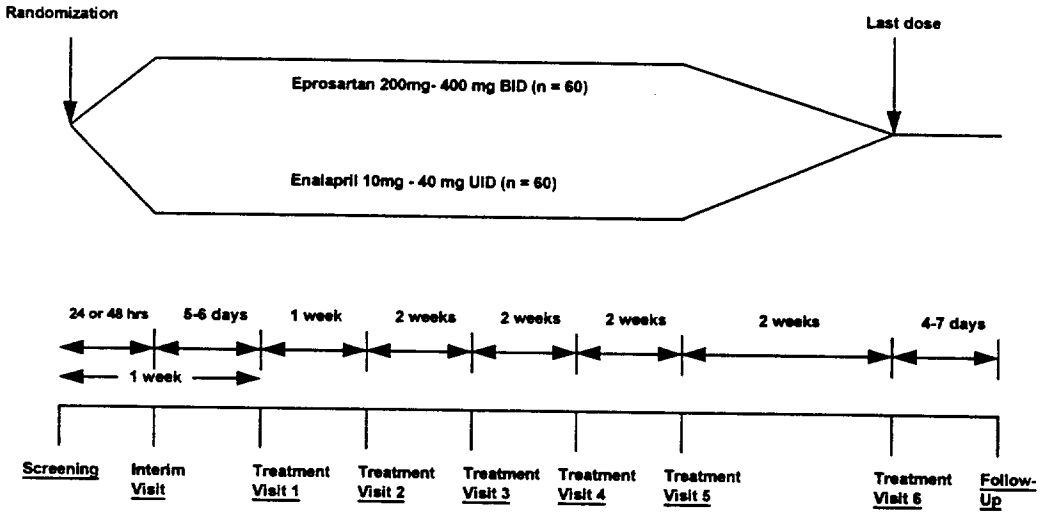
1. Pregnancy or lactation.
2. Malignant (accelerated) hypertension (evidence of encephalopathy, retinal hemorrhage) or history of malignant hypertension, or secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, pheo-chromocytoma, or due to current use of hormonal contraceptive agents.
3. Advanced hypertensive retinopathy (Keith-Wagener Grade IV).
4. Average sitting SBP > 240 mm Hg.
5. Advanced atrioventricular conduction defects (i.e., second or third degree heart block).
6. Significant ventricular tachyarrhythmias requiring therapy.
7. Bradycardia (resting sitting heart rate < 50 beats/minute) after withdrawal of previous antihypertensive medications.
8. Signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the previous 90 days, or ECG evidence of ischaemia.
9. Congestive heart failure (CHF) on treatment with ACE-I or diuretics, or CHF NYHA Class > II.
10. Angina pectoris treated with regular doses of nitrates, beta blockers, or calcium channel blockers.
11. Diabetes mellitus, that was unstable (repeated episodes of ketoacidosis, hyperglycemic coma, or hypoglycemic shock) despite treatment with insulin or oral hypoglycemic agents.
12. Presence of clinically significant renal or hepatic disease: serum creatinine > 2.05 mg/dL (180 micromol/L); proteinuria > ++ on dip stick, confirmed > ++ at treatment visit 1; ALT, AST, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range.
13. Leukocyte count < 3000/mm3 or platelet count < 100,000/mm3.
14. Other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality which, in the opinion of the investigator, could have precluded participation or survival.
15. Active alcohol or drug abuse.
16. Use of warfarin or other oral anticoagulants within 30 days prior to screening.
17. Use of an investigational drug within 30 days of enrollment into the study or within 5 half-lives of the investigational drug (the longer period applied).
18. Concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, or phenothiazine derivatives.
19. Concomitant administration of any medication known to affect blood pressure, except a thiazide diuretic.
20. Concomitant chronic treatment (i.e. longer than 7 days) with sympathomimetic amines (e.g., phenylephrine or pseudoephedrine) or NSAIDS (except low-dose aspirin up to 325 mg per day). Patients must have been off such drugs for at least 1 week prior to the screening visit.
21. Patients sensitive to eprosartan or other drugs in its class, or thiazide diuretics or any drugs in its class.
22. Patients with documented allergic responses to enalapril or other drugs in its class.

23. Patients who had received randomized medication in a previous trial of eprosartan.

Description of Phases

The study consisted of three periods, namely screening, double-blind treatment and follow-up. Patients qualified for enrolment in the study if at the screening visit measurement of two mean sDBP values was ≥115 and ≤ 125 mm Hg two hours apart. Eligible patients then entered the titration phase of the double-blind treatment period and were randomized to a medication regimen with either eprosartan 200 mg twice daily or enalapril 10 mg once daily (Level 1). Randomization was stratified for current use of thiazide diuretic. Visits were scheduled for 24 or 48 hours and one week after starting Level I study medication. Patients were seen at weeks 2, 4 and 6 for titration, if necessary, to 20 mg and then to 40 mg enalapril (maximum) once daily or to 300 mg and then to 400 mg eprosartan (maximum) twice daily (Level III) after week 2. At week 6, patients who were receiving dose Level III, who were not already receiving a thiazide diuretic and whose blood pressure had not been controlled (DBP ≤ 90 mm Hg), had HCTZ 25 mg once daily added to their double-blind medication. Patients entered a 2-week maintenance phase at week 8 at the dosage level selected by titration. The study design is schematically presented in Figure 47.1.

Figure 47.1 Study Design



Primary & Secondary Endpoints

The primary comparison of the antihypertensive efficacy of eprosartan in titrated doses of 200 to 400 mg twice daily and enalapril in titrated doses of 10 to 40 mg once daily in patients with severe hypertension (sitting DBP > 115 and ≤ 125 mm Hg). The Secondary comparisons were to compare: the safety of eprosartan and enalapril with regard to adverse experiences, laboratory abnormalities, and changes in ECGs; the need for additional diuretic (HCTZ) therapy in the two medication regimens.

Statistical Methods

The medication regimens were compared at baseline with respect to categorical demographic and clinical characteristics using the Chi-Square test adjusting for differences between centers and the severity of hypertension. For continuous variables, baseline differences were assessed by an analysis of variance (PROC GLM in SAS]) which included the terms for center, treatment, current use of thiazide diuretic at entry and interactions with center. Comparisons were made at the end of the titration phase, at the end of the maintenance phase and at the study endpoint. For the continuous variables, expressed as differences from baseline, an analysis of variance (PROC GLM in SAS) was used. The model includes medication regimen, center and regimen-by-center interaction. Where regimen-by-center interaction was not significant (P>.10), it was removed from the model. The difference in medication regimens was calculated, along with a confidence interval, based on the reduced model. The full and reduced models were also fit using as a covariable the baseline value of the continuous variable.
For the categorical variables, responder rate and "need for addition of diuretic therapy" rate, assessments were made using a Cochran-Mantel-Haenszel statistic adjusting for center or subgroup (see the section entitled "Subgroup analyses" below) interaction with regimen, which were assessed with the Breslow-Day test (PROC FREQ in SAS). If the interaction is not significant (P>.10), the comparison of the medication regimens were reported along with a confidence interval of the relative risk ratio. For some subgroup analyses, numbers were insufficient to assess regimen-by-subgroup interaction; it was assessed where possible.

Results

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 47.1

Table 47.1 Patient Disposition

No of patients:	Eprosartan	Enalapril	Total
Screened			123
Randomized	59	59	118
Completed treatment	59	59	118

Data Source: Table 13.3, 13.10.

Demographic Characteristics

The study was conducted in 7 countries, mostly in Europe, plus South Africa. A summary of patients demographic characteristics are presented in Table 47.2

Table 47.2 Demographic characteristics of all randomized patients

		Randomized		
Characteristic		Eprosartan	Enalapril	TOTAL
Sample Size		(n=59)	(n=59)	(n=118)
Age (years)	<65	46 (78.0%)	46 (78.0%)	92 (78.0%)
	>65	13 (22.0%)	13 (22.0%)	26 (22.0%)
Race	Black	7 (11.9%)	2 (3.4%)	9 (7.6%)
	Caucasian	47 (79.7%)	52 (88.1%)	99 (83.9%)
	Other	5 (8.5%)	5 (8.5%)	10 (8.5%)
Sex	Male	29 (49.2 %)	28 (47.5%)	57 (48.3%)
	Female	30 (50.8%)	31 (52.5%)	61 (51.7%)
Use of Thiazide	No	39 (66.1%)	35 (59.3%)	74 (62.7%)
	Yes	20 (33.9%)	24 (40.7%)	44 (37.3%)

Data Source: Tables 13.10

Efficacy Results

The primary objective of this study was to compare the anti-hypertensive efficacy of eprosartan in titrated doses of 200 to 400 mg twice daily and enalapril in titrated doses of 10 to 40 mg once daily in patients with severe hypertension (sitting DBP ≥115 and ≤125 mm Hg). Tables 47.3 and 47.4 present summary of the analyses of sitting vital signs at trough.

Table 47.3 Mean ± SEM Sitting Vital Signs at Baseline and Titration Endpoint

Sitting DBP	Eprosartan (n = 59)	Enalapril (n = 59)	p-value
Baseline	116.6±0.5	116.6±0.5	
End of Titration	95.7±2.0	99.1±1.8	
Change from Baseline	-20.9±1.9	-17.9±1.8	0.148
Sitting SBP			
Baseline	179.9±2.4	178.4±2.1	
End of Titration	153.1±3.2	158.3±2.8	
Change from Baseline	-26.8±2.7	-20.1±2.5	0.014
Sitting Heart Rate			
Baseline	74.1±1.3	74.3±1.2	
End of Titration	74.5±1.1	74.1±1.5	
Change from Baseline	0.4±1.4	0.2±1.2	0.082

Data Source: Tables 14.2 - 14.7

Table 47.4 Mean ± SEM Sitting Vital Signs at Baseline and Study Endpoint

Sitting DBP	Eprosartan (n = 59)	Enalapril (n = 59)	p-value
Baseline	116.6±0.5	116.6±0.5	
Study Endpoint	96.0±2.1	99.7±1.8	
Change from Baseline	-20.6	-17.2	0.136
Sitting SBP			
Baseline	179.9±2.4	178.4±2.1	
Study Endpoint	153.2±3.4	158.0±2.9	
Change from Baseline	-26.7±2.9	-20.4±2.7	0.025
Sitting Heart Rate			
Baseline	74.1±1.3	74.3±1.2	
Study Endpoint	75.4±1.3	73.9±1.5	
Change from Baseline	1.3±1.2	0.4±1.1	0.0845

Data Source: Tables 14.1.1, 14.15.1

Conclusion

Based on the review of this study, it was concluded that there were no statistically significant difference in sitting diastolic blood pressure between eprosartan and enalapril. Sitting diastolic blood pressure was defined as the primary endpoint of the study, and the analysis failed to show any difference. Therefore, the testing of secondary endpoints are not allowed based on statistical principles.

Protocol 053. A six-week, double-blind, double-dummy, parallel, placebo-controlled, multi center comparison of eprosartan and enalapril on cough in patients with angiotensin-converting enzyme inhibitor(ACE-I)-induced cough and essential hypertension (DBP ≥ 95 and ≤ 114 mm Hg).

Protocol

Design & Objective

The study was a multi center, randomized, double-blind, double-dummy, parallel group comparison of twice-daily doses of eprosartan 300 mg, a once-daily dose of enalapril 20 mg, and placebo in patients with essential hypertension (DBP ≥ 95 and ≤114 mm Hg) and a history of ACE-I-induced cough who developed cough during Enalapril Challenge. The study consisted of a screening visit and five periods: Placebo Run-in, Enalapril Challenge, Placebo Washout, Double-Blind Treatment, and Follow-up. The primary objective of the study was to compare the incidence of persistent, nonproductive (dry) cough during treatment with eprosartan, enalapril, or placebo in patients with essential hypertension (DBP ≥ 95 and ≤114 mm Hg) and a history of ACE-I-induced cough who developed cough during Enalapril Challenge. The secondary objectives of the study were: to compare the antihypertensive efficacy of eprosartan 300 mg twice daily and enalapril 20 mg once daily; to compare the effects of eprosartan to enalapril on health-related quality of life; to compare the safety of eprosartan and enalapril with regard to adverse experiences (in addition to cough), laboratory test abnormalities, and changes in ECGs.

Eligibility criteria

Inclusion criteria

1. Men or women who were at least 18 years of age. Women were to be postmenopausal (ie, at least 6 months without menstrual period), surgically sterile, or using hormonal or barrier contraceptives or

intrauterine contraceptive devices.

2. History of cough induced by treatment with ACE-Is and development of cough during Enalapril Challenge.
3. Essential hypertension (DBP ≥95 and ≤114 mm Hg) from whom antihypertensive therapy could be safely withdrawn during the 4- or 5-week Placebo Run-in Period and the 8- to 10-week period including the Placebo Washout and Double-Blind Treatment.

Exclusion Criteria

1. Pregnancy or lactation.
2. Secondary forms of hypertension including, but not limited to, coarctation of the aorta, primary aldosteronism, or pheochromocytoma.
3. Advanced hypertensive retinopathy (ie, Keith-Wagener Grade III or IV).
4. Average sitting systolic BP (SitSBP) >200 mm Hg.
5. Advanced atrioventricular conduction defects (ie, second or third degree heart block) unless a pacemaker is in place.
6. Significant ventricular tachyarrhythmias requiring therapy.
7. Bradycardia (resting sitting heart rate <50 beats/minute) after withdrawal of previous antihypertensive medications.
8. Signs, symptoms, or history of myocardial infarction or a cerebrovascular accident within the past 90 days.
9. Congestive heart failure (CHF) on treatment with ACE-Is or diuretics. Patients with untreated reduced ejection fraction could be included.
10. Angina pectoris treated with regular doses of nitrates, beta blockers, or calcium channel blockers.
11. Emphysema or chronic bronchitis with daily cough and sputum production; asthma with a dry cough.
12. Upper respiratory infection (URI) with symptoms within two weeks of screening. Patients who had recent acute URI but were symptom-free for two weeks before screening could be included. Patients were also required to be free of URI by the end of the Placebo Run-in Period.
13. Unstable diabetes mellitus (repeated episodes of ketoacidosis, hyperglycemic coma, or hypoglycemic shock) despite treatment with insulin or oral hypoglycemic agents.
14. Presence of clinically significant renal or hepatic disease: serum creatinine >2.5 mg/dL (220 micromol/L); ALAT, ASAT, total bilirubin, or alkaline phosphatase more than 2.5 times the upper limit of the laboratory reference range.
15. Leukocyte count <3000/mm3 or platelet count <100,000/mm3.
16. Other concurrent severe disease, e.g., neoplasm or other disease indicated by significant laboratory abnormality that, in the opinion of the investigator, could preclude participation or survival.
17. Active alcohol or drug abuse.
18. Use of warfarin or other oral anticoagulants within 30 days prior to screening.
19. Use of an investigational drug within 30 days of enrollment into this study or within five half-lives of the investigational drug, whichever was longer.
20. Concomitant treatment with monoamine oxidase inhibitors, tricyclic antidepressants, and phenothiazine derivatives.
21. Concomitant administration of any medication known to affect blood pressure.
22. Concomitant administration of any medication known to influence cough (e.g., codeine and other morphine derivatives).
23. Concomitant chronic treatment (ie, longer than 7 days) with sympathomimetic amines, e.g., phenylephrine or pseudoephedrine, or NSAIDs (except low-dose aspirin up to 325 mg per day). Patients must have been off such drugs for at least one week prior to the screening visit.
24. Hypertension due to current use of hormonal contraceptive agents.
25. Sensitivity to, or intolerance of, eprosartan or other drugs in its class.
26. Documented allergic responses to enalapril or other drugs in its class.

27. Treatment with randomized medication in a previous trial of eprosartan.

Description of Phases

The study consisted of a screening visit and five periods: Placebo Run-in, Enalapril Challenge, Placebo Washout, Double-Blind Treatment, and Follow-up (Figure 53.1). After the initial screening visit subjects entered a 4- to 5-week, single-blind, Placebo Run-in Period (I). Patients with qualifying blood pressure measurements then entered the 3-to-4-week, single-blind Enalapril Challenge Period (II), during which they received enalapril 20 mg capsules (10 mg for the initial 3 days) and eprosartan placebo. Patients who developed a persistent nonproductive cough then entered a 2-to 4-week Placebo Washout Period (III) for coughing to clear. At the final washout visit, eligible patients entered the 6-week Double-blind Treatment Period (IV) and were randomized (1:1:1) to treatment with either eprosartan 300 mg twice-daily (200 mg for the initial 3 days), enalapril 20 mg once-daily (10 mg for the initial 3 days), or placebo. Patients who completed the Double-blind Treatment Phase returned for a Follow-up visit (V). The Follow-up visit was also required for all patients who withdrew from the study, who did not develop coughing during the Enalapril Challenge, or who did not enter the long-term extension study from Period IV. Patients who completed the Double-blind Treatment Period could enter an extension study (Study 039) at their option.

Statistical Methods

The sample size of 49 patients per medication regimen is based on an estimated 35% difference in cough incidence between the eprosartan group (33% incidence) and the enalapril group (68% incidence) at the 0.05 level of significance with 90% power, two-sided testing, for two comparisons of interest (enalapril versus eprosartan and placebo versus eprosartan). Estimations of cough incidence were derived from an earlier study on a renin inhibitor. Placebo patients in the present study are expected to have a cough incidence lower than those previously reported, because the study design hinders their identification of treatment period changes. Since the sample size was powered only for assessing differences between regimens with regard to cough, it is inadequate to assess differences with regard to blood pressure. The codes for randomization were generated by the SmithKline Beecham automated random code generating system (Coding Memo System, Version 2.0). The patient-assessed cough and the change from baseline in quality of life parameters (scores of the Psychological General Well-Being) were analyzed by Dr. Fletcher. For the investigator-assessed cough, ie, the categorical variables definite cough and maximum cough experienced, and also the response rates, analysis was done applying a Cochran-Mantel-Haenszel statistic pairwise for the two comparisons of interest, adjusting for center or subgroup (see "subgroup comparisons" below) interaction with regimen, which was assessed with the Breslow-Day test (PROC FREQ in SAS). If the interaction was not significant ($P>0.10$), comparisons of the regimens were reported along with confidence intervals of the relative risk ratios. Significance of the two comparisons of interest were determined using the modified Bonferroni procedure due to Hochberg. Under the Hochberg procedure, the larger p-value is compared to 0.05. If it is less than or equal to 0.05, then both p-values are statistically significant. If not, the next larger p-value is compared to 0.025 (0.05/2). If it is less than or equal to 0.025, then it is significant at the 0.05 level.
It is noted here that the study was powered to detect differences in the investigator-assessed cough. Thus the p-values reported for the response rate analysis should be considered as exploratory data analysis.

Results

Patient Disposition

The disposition of patients who participated in this protocol is summarized in Table 47.1

Table 53.1 Patient Disposition

No of patients:	Eprosartan	Enalapril	Placebo	Total
Screened				231
Single-blind Placebo				226
Enalapril Challenge Period				158
Placebo Washout Period				140
Randomized	46	45	45	136
Completed treatment	39	35	34	108

Data Source: Table 13.3, 13.10.

Twenty-Eight subjects did not complete the study, the reasons for early termination are summarized in Table 14.2

Table 53.2 The Number and Percentage of Randomized Patients Who Completed the Study or Were Withdrawn by the Reason for Study Withdrawal

Study Conclusion Reason	Placebo (n=45)	Eprosartan (n=46)	Enalapril (n=45)	Total (n=136)
Completed Study	34	39	35	108
Early Termination	11	7	10	28
Withdrawal Reason				
Adverse Experiences	2	1	4	7
Lack of Efficacy	2	1	1	4
Other Reasons+	4	3	2	9
Protocol Violation/Noncompliance	4	0	0	1
Termination by Sponsor	2	2	3	7

Data Source: Table 13.3

Demographic Characteristics

A summary of patients demographic characteristics are presented in Table 53.2

Table 53.2 Demographic characteristics of all randomized patients

		Randomized			
Characteristic		Placebo	Eprosartan	Enalapril	TOTAL
Sample Size		(n=45)	(n=46)	(n=45)	(N=136)
Age (years)	<65	36 (80.0)	33 (71.7)	32 (71.1)	101 (74.3)
	≥65	9 (20.0)	13 (28.3)	13 (28.9)	35 (25.7)
Race	Black	1 (2.2)	2 (4.3)	5 (11.1)	8 (5.9)
	Caucasian	30 (66.7)	33 (71.7)	28 (62.2)	91 (66.9)
	Other	14 (31.1)	11 (23.9)	12 (26.6)	37 (27.2)
Sex	Female	24 (53.3)	19 (41.3)	22 (48.9)	65 (47.8)
	Male	21 (46.7)	27 (58.7)	23 (51.1)	71 (52.2

Data Source: Tables 13.9

Incidence of Definite Cough

This study was to detect a difference in the incidence of cough, and the results of the analysis showed that there was significantly less cough in the eprosartan group, compared to the enalapril group. A summary of the results of the Cochran-Mantel-Haenszel analysis is provided in Table 53.3.

Table 53.3 Incidence of Investigator-assessed Definite Cough at Weeks 2, 4, and 6, at Study Endpoint, and Entire Double-Blind Period

Incidence of Cough	Placebo	Eprosartan 300 mg BID	Enalapril 20 mg QD
Titration Week 2 Definite Cough No Definite Cough Relative Risk (95% CI) P-Values	0/44 (0)) 44/44 (100.0)	1/46 (2.2) 45/46 (97.8) + (+,+) +	5/42 (11.9) 37/42 (88.1) 0.23(0.03,1.92) 0.121
Week 4 Definite Cough No Definite Cough Relative Risk (95% CI) P-Values	1/40 (2.5) 39/40 (97.5)	1/41 (2.4) 40/41 (97.6) 1.07 (0.05,22.9) 0.871	7/47 (14.9) 40/47 (85.1) 0.13(0.02,0.94) 0.020*
Week 6 Definite Cough No Definite Cough Relative Risk (95% CI) P-Values	1/34 (2.9) 33/34 (97.1)	1/38 (2.6) 37/38 (97.4) 0.67(0.02,28.3) 0.779	3/36 (8.3) 33/36 (91.7) # (#,#) #
Study Endpoint** Definite Cough No Definite Cough Relative Risk (95% CI) P-Values	1/45 (2.2) 44/45 (97.8)	1/46 (2.2) 45/46 (97.8) 0.67(0.02,28.3) 0.779	3/44 (6.8) 41/44 (93.2) # (#,#) #
Entire Double-blind Period Definite Cough No Definite Cough Relative Risk (95% CI) P-Values	2/45 (4.4) 43/45 (95.6)	1/46 (2.2) 45/46 (97.8) 1.67(0.09,30.87) 0.652	9/44 (20.5) 35/44 (79.5) 0.12(0.02,0.726) 0.008

Data Source: Table 14.1.1.

* Indicates statistical significance at 0.05 level using modified Bonferroni procedure.

** Last on-therapy assessment.

\+ Data are too sparse to allow testing for regimen-by-center interaction; the p-value is not interpretable

\# Significant ($p<0.1$) regimen-by-center interaction exists; the p-value is not interpretable.

Efficacy Results

The only secondary objectives that will be considered here will be the sitting vital signs obtained at trough. This is because, the sitting diastolic blood pressure is the standard for evaluating the efficacy of new drug entities. Table 53.4 presents a summary of the analysis of sitting vital signs at trough. It must be noted that this study was not powered to detect statistical differences in antihypertensive effects of the two drugs. This analysis was to test the hypothesis that there were no difference between the blood pressure effects of eprosartan and enalapril. The ANOVA test failed to reject the null hypothesis that there is no statistically significant difference in the blood pressure lowering effect of eprosartan and enalapril.

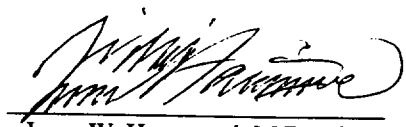
Table 53.4 Mean ± SEM Sitting Vital Signs at Baseline and Study Endpoint

Sitting DBP	Placebo (N = 44)	Eprosartan 300 mg BID (n = 46)	Enalapril 20 mg QD (n = 44)	p-value
Baseline	99.9±0.6	101.5±0.6	100.7±0.7	
End of Titration	95.5±1.1	92.7±1.3	92.8±1.3	
Change from Baseline	-4.4±1.0	-8.7±1.1	-7.9±1.1	
Sitting SBP				
Baseline	154.0±2.2	153.1±2.2	154.4±2.1	
End of Titration	148.3±2.3	142.6±2.6	143.4±2.4	
Change from Baseline	-5.7±2.2	-10.5±2.3	-11.1±2.4	
Sitting Heart Rate				
Baseline	74.4±1.2	75.9±1.1	74.7±1.5	
End of Titration	74.7±1.3	74.4±1.4	76.2±1.4	
Change from Baseline	0.2±1.1	-1.5±1.0	1.5±1.3	

Note: n = The number of patients with a baseline value and a study endpoint value.
Data Source: Tables 14.4.1, 14.5-14.6.

Conclusion

Based on the review of this study, it was concluded that there were statistically significant more cough among the enalapril group compared to the enalapril and placebo group at week 4. However, the difference was not sustained. By study endpoint there were no differences in the incidence of cough among the 3 groups. Eprosartan 300 mg twice daily effectively lowered blood pressure (diastolic and systolic) compared to placebo and was comparable to enalapril 20 mg once daily.



Isaac W. Hammond, M.D., Ph.D.

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HFD-344/L. O Martynec

APPENDIX

Table A.1 contains a list of drugs and lot numbers used in the different studies.

Study #	Treatment Dose Units/Strength	Lot #
010	Eprosartan 50 Placebo	U-93080 U-930880
011	Eprosartan 25 mg Eprosartan 100 mg Placebo	U-94090 U-93235 U-94031
013	Eprosartan 100 mg Eprosartan 200 mg Placebo 100 mg Placebo 200 mg	U-94191 U-94190 U-94189 M-94209
014	Eprosartan 100 mg (Tablet) Eprosartan Placebo (Tablet) Enalapril 5 mg (Overencapsulated) Enalapril 5 mg (Tablet) Enalapril 10 mg (Overencapsulated) Enalapril 10 mg (Tablet) Enalapril 20 mg (Overencapsulated) Enalapril 20 mg (Tablet) Enalapril Placebo (Overencapsulated Enalapril Placebo (Tablet) HCTZ (Tablet)	U-94068 U-94044 U-94206 X-94155, X94108 U-94207 U-94109, X-94156 U-94157 U-94208, X-94157, X-94206 U-94158 X-94133, X94165
016	Eprosartan 50 mg Eprosartan 100 mg Eprosartan Placebo HCTZ 25 mg	U-93225 U-93235 U-94031 X-94101
017	Eprosartan 100 mg Eprosartan Placebo	U-94068 U-94111
041	Eprosartan 100 mg Eprosartan Placebo Procardia XL Procardia XL Placebo	U-94191 U-94189 U-95019 U-95034
045	Eprosartan 200 mg Placebo	U-93175 U-93217
047	Eprosartan 100 mg (Tablets) Eprosartan Placebo (Tablets) Enalapril 10 mg (Overencapsulated Tablet) Enalapril 20 mg (Overencapsulated Tablet) Enalapril Placebo (Overencapsulated Tablet) HCTZ 25 mg (Tablets)	U-94191 U-94189 U-94207 U-94208 X94158 A-6874
049	Eprosartan 200 mg Placebo	U-94190 U-94210
053	Eprosartan 100 mg (Tablets) Eprosartan Placebo (Tablets) Enalapril 10 mg (Capsules) Enalapril 20 mg (Capsules) Enalapril Placebo (Capsules)	U-94068 U-94044 U-94207 U-94208 U-94158

D. Willard

JUL 30 1997

SAFETY REVIEW AND EVALUATION

NDA # 20,738 October 11, 1996

Applicant: SmithKline Beecham

Drug Name: eprosartan mesylate (Teveten®)

Indication: hypertension

Reviewer: Maryann Gordon, M.D. Maryann Gordon MD

Date of Review: July 30, 1997

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REVIEW OF SAFETY
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Eprosartan is an angiotensin II receptor blocker seeking an indication for the treatment of essential hypertension. This drug is poorly absorbed from the gastrointestinal tract, there are no active metabolites, and most of the drug is eliminated in the urine. This agent does not interact with cytochrome P450 enzymes.

The primary safety of eprosartan was determined from 15 Phase II/III hypertension studies. Of these, 11 were short term and controlled (6 placebo controlled, 1 background HCTZ, 4 active controlled) and 4 were long term and uncontrolled (and still ongoing). Doses of eprosartan tested in these studies ranged from 50 mg twice daily to 1200 once daily. The majority of the studies utilized a twice daily dosing regimen. The total number of patients who received eprosartan in 1 of the 15 studies was 2334. There were 1202 patients (51% of total) who received eprosartan and 352 patients who received placebo in the 6 placebo controlled trials. There were 635 subjects who received eprosartan in 1 of 29 clinical pharmacology studies. The safety update added only 33 new eprosartan patients to the total number of patients.

The patients enrolled into the Phase II/III hypertension studies had a mean age of 57 years, with 29% at least 65 and 5% at least 75 years of age. About 40% were female and most were white (82%). Patients with concurrent disease other than hypertension were not studied with the exception of those with diabetes, liver disease or renal disease. Mean duration on drug for all eprosartan patients was 145 days. The majority of patients received a total daily dose of 400 mg.

In the placebo controlled trials, the placebo subtracted rate for reporting at least 1 event was 1.6%. The events with a placebo subtracted reporting rate of >1% were upper respiratory tract infection (2.5%), injury (1.3%), hypertriglyceridemia (1.2%), rhinitis (1.2%), and pharyngitis (1.1%). None of the events showed a dose response and there were no safety concerns with the once daily versus twice daily dosing regimens. The overall reporting of cough by patients on eprosartan was half the rate reported by patients on enalapril. There were more enalapril patients who dropped out for cough compared to eprosartan patients, but the differences were small. The combination with HCTZ did not affect the safety profile of eprosartan, however, it would be worth exploring the use of higher doses of eprosartan (>100 mg bid) with lower doses of HCTZ (<25 mg qd).

Less than 1% of patients died during or shortly after eprosartan therapy. The majority (11/16) died during a long term study and the etiology of most of the deaths was cardiovascular. No death could be linked to eprosartan use. The withdrawal rate for adverse events in the placebo controlled trials was 4.2% for eprosartan patients and 6.5% for placebo patients. The adverse event resulting in the most drop outs in the eprosartan treated patients was headache (3.4%).

There was no evidence that eprosartan had a deleterious impact on laboratory values. Overall, there were minor decreases in hemoglobin (expected in these agents) and minor increases in BUN. There were few drop outs for laboratory abnormalities.

Eprosartan did not change heart rate or other ECG intervals including PR, QRS and QT. Patients receiving eprosartan and reporting ECG abnormalities were rare and only palpitations were reported by at least 1% of the patients. There were 4 patients who died suddenly but no link with eprosartan use

could be established.

There is no evidence that the safety of eprosartan is influenced by age, gender, or race. The clearance of eprosartan was reduced in patients with renal impairment, and the AUC and median Tmax were increased in patients with liver impairment. While there was no evidence that a dose reduction in these patients is necessary, it would be prudent to consider it. Eprosartan is not removed during dialysis.

Since eprosartan is not metabolized, no drug interactions are expected and none were found. There is no evidence that the long term exposure to or abrupt withdrawal from eprosartan has a deleterious effect on patient safety.

Overall, there are no safety issues for eprosartan that have been realized in the testing of approximately 3000 subjects.

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1.0 Introduction

The US IND for oral eprosartan (IND) was submitted in May, 1992, the US NDA for oral eprosartan in essential hypertension was submitted October 11, 1996, and the 120-day safety update was submitted February 10, 1997.

The sponsor is seeking the approval of eprosartan, an angiotensin II receptor blocker, for the treatment of essential hypertension. The majority of this safety review focuses upon those patients who took part in 1 of the 15 Phase II/III hypertension studies. The safety, both routine and serious safety, for eprosartan was determined by these studies. Patients and subjects who participated in the Phase I studies are discussed separately.

Numerous volumes from the NDA 20,738 as well as the Safety Update were examined during the safety review. The sources of tables, figures and appendices from the NDA used to create tables in this review are identified. Optical images or the paper copy of the case report forms for all deaths were examined by this reviewer.

1.1 Mechanism of action

This section is taken from the sponsor's nonclinical pharmacology summary.

Eprosartan mesylate (referred to in this document as eprosartan) is a non-biphenyl tetrazole angiotensin II receptor (AT1) antagonist. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g., vascular smooth muscle, adrenal gland). Eprosartan does not exhibit any partial agonist activity at the AT1 receptor.

The affinity of eprosartan for the AT1 receptor is 1,000 times greater than for the angiotensin II receptor (AT2). *In vitro* binding studies indicate that eprosartan is a reversible, competitive inhibitor of the AT1 receptor. Eprosartan does not inhibit kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin. Neither does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

1.2 Related agents

Two oral agents of the same class of drugs as eprosartan were recently approved. The general opinion about these agents is that they are safe and effective antihypertensive agents.

1.3 Foreign marketing history

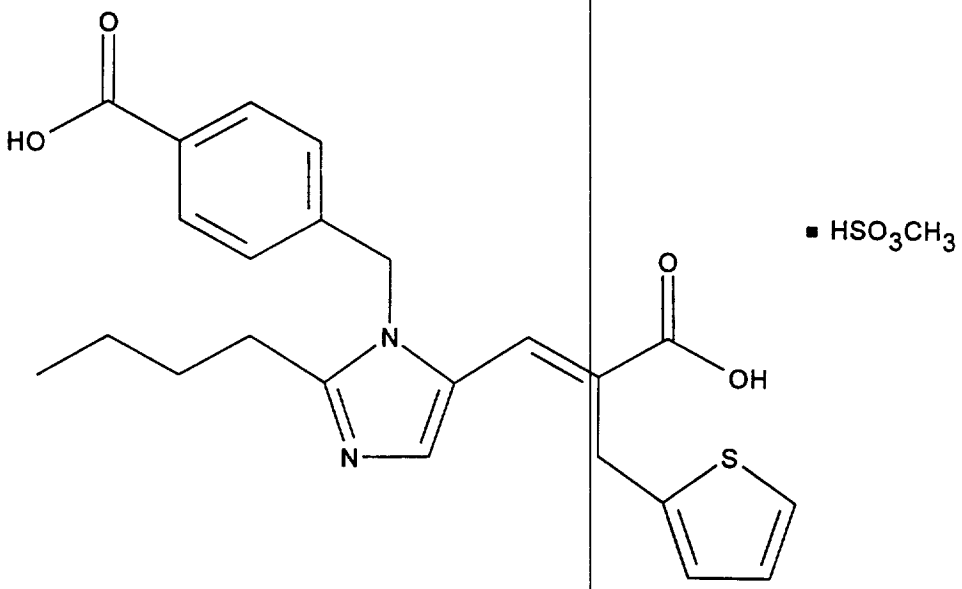
Eprosartan is not presently commercially available in any part of the world.

1.4 Chemistry

Chemical Abstracts Name

(E)-a-[[2-Butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl] methylene]-2-thiophenepropanoic acid monomethanesulfonate (CA Vol. 118)

The chemical structure is shown below:



from item 2: annotated package label

1.5 Human pharmacokinetics summary

This section is taken from the sponsor's human pharmacology summary.

Absorption and Bioavailability: Absolute bioavailability (300 mg oral dose of eprosartan) is about 13%, due to poor oral absorption. Maximal plasma concentrations of eprosartan were typically observed within 1 to 2 hours following a single 300 mg oral dose of the commercial tablet formulation of eprosartan in the fasted state. After attaining Cmax, eprosartan concentrations declined over time in a mono- or bi-exponential fashion with a mean terminal elimination half-life of approximately 4.5 hours (range 1.5 to 12.3 hours). The mean terminal elimination half-life of eprosartan after intravenous administration was approximately 2 hours. The terminal elimination half-life of eprosartan following oral administration is approximately 5 to 9 hours. Administration of the commercial formulation of eprosartan with a high fat meal results in minor changes (<25%) in Cmax and AUC. Plasma concentrations of eprosartan increase in a slightly less than dose proportional manner.

Distribution: Plasma protein binding of eprosartan is high (approximately 98%) and constant over the concentration range achieved with therapeutic doses. Following a single 20 mg intravenous dose of

eprosartan, the steady-state volume of distribution of eprosartan was about 13 liters which approximates total extracellular water.

Metabolism and Elimination: There are no active metabolites following oral and intravenous dosing with [14C] eprosartan in human subjects. Approximately 20% of the radioactivity excreted in the urine is an acyl glucuronide of eprosartan (corresponding to about 7% of the intravenous dose and about 2% of the oral dose) with the remaining 80% being unchanged eprosartan. Oral clearance was shown to be a linear function of age with CL/F decreasing 0.62 L/h for every year increase. Eprosartan does not inhibit human cytochrome P450 enzymes CYP1A, 2A6, 2C9/8, 2C19, 2D6, 2E and 3A *in vitro*.

2.0 Overview of clinical program

This large program consists of 29 clinical pharmacology studies, 15 Phase II/III hypertension trials, and 5 additional studies: 090 in diabetics, 094 and 095 drug interaction studies, 076 examining uric acid section, and 091 examining protein excretion. The core of the Integrated Safety Summary is based on the 15 hypertension studies with safety for the clinical pharmacology discussed separately.

Eprosartan was given in single or multiple doses to a total of 2969 subjects: 635 subjects/patients enrolled into the Phase I studies and 2334[1] hypertension patients enrolled into the Phase II/III hypertension trials. The patient number 2969 does not include patients enrolled into studies 090, 094, 095, 076, and 091 (fax dated 5-8-97). The Safety Update includes data on 33 new and 78 ongoing patients. For the NDA, routine safety including nonserious adverse events and laboratory, serious safety, and withdrawals resulting from adverse events relied upon data from the 2334 patients. Safety from phase I studies was discussed separately and not integrated with the other studies. Deaths were reported for all studies.

Hypertension (appendix 1)

Appendix 1 shows completed and ongoing Phase II/III hypertension studies by study type. The Phase II/III hypertension program consists of 15 studies in total (11 controlled and 4 uncontrolled): 6 placebo controlled, 2 enalapril controlled (014 to assess cough and 047 in severe hypertension), 1 both enalapril and placebo controlled (053 to assess cough), 1 placebo controlled with HCTZ as background therapy, 1 nifedipine controlled, and 4 open label, uncontrolled extension studies.

Protocol numbers included in NDA

controlled trials				uncontrolled extension trials
placebo		active		
monotherapy	plus HCTZ	enalapril	nifedipine	
010, 011, 013, 017, 045, 049	016	014, 047, 053*	041	039, 040, 050, 052

*also had a placebo group

All controlled trials were double blind, randomized, with parallel treatment groups. Of the 11 trials, 8 used twice daily dosing, 2 had once daily dosing, and 1 used both regimens. The total daily dose ranged from 50 mg (25 mg bid) to 1200 mg, the duration of double blind treatment period ranged from 4 to 26 weeks, and sample sizes ranged from 61 to 538 patients. Studies were conducted in approximately equal numbers in the US and abroad. The 15 studies are described in the tables below.

[1]Dr. Fiddes enrolled 48 patients into 3 hypertension trials (011, 050, 053)

Placebo controlled trials

protocol no.	duration of double blind (weeks)	no. of patients enrolled: epro/placebo	doses (mg)/dosing regimen
010*	4	96 / 22	50, 100, 150, 200/bid
011	8	445/ 93	25,100,200, 300, 400/bid
013	13	157/86	400-800/bid, 200-400 qd^
017+	9	183/47	100, 200, 300/bid^
045*	4	31/30	400/qd
049	8	290/74	400, 600, 800, 1200/qd
Total		1202/352	

*enrolled only male patients
+enrolled only patients ≥63 years of age
^dose was titrated to blood pressure effect
table 8.D.2 vol 1.079

The placebo controlled trial (016) that evaluated the combination of eprosartan and HCTZ 25 mg with placebo and HCTZ 25 mg was not included in the sponsor's analysis of placebo controlled trials, but was examined separately.

HCTZ controlled trial

protocol no.	duration of double blind (weeks)	no. of patients enrolled: epro/placebo	doses (mg)/dosing regimen
016	4	104/52	50,100 bid

The active controlled trials include 2 enalapril controlled, 1 enalapril and placebo controlled, and 1 nifedipine controlled trials. The design for all studies was double blind, randomized and parallel group. The objective of 2 controlled trials with enalapril with and without a placebo arm (014 and 053) was to compare the cough rates of the treatment groups; the objective of the other enalapril trial (047) was blood pressure control in moderately severe hypertension. The nifedipine trial (041) was a standard positive controlled trial evaluating blood pressure effect. Patients received the 2 drugs in combination for the final 6 weeks of the trial if they remained hypertensive.

Positive control trials

protocol no./active control	duration of double blind (weeks)	no. of patients enrolled: epro/active	doses (mg)/dosing regimen	
			epro	active
014/enalapril	26	264/264	200,300/bid^	5,10,20/qd^
047#/enalapril+	10	59/59	200-400+/bid^	10-40/ qd^
053*/enalapril	6	46/45/45 placebo	300 bid	20 qd
041/nifedipine extended release	12 (6 with monotherapy/ 6 with combination allowed)	103/102	200-300/bid^	60-90 qd^
Total		472/470		

*only patients with enalapril induced cough were enrolled
patients with DBP115-125 mmHg were enrolled
^dose was titrated to blood pressure effect
+HCTZ was allowed as add on

Of the 4 open label, uncontrolled extension trials, 2 used twice daily dosing. The total daily doses ranged from 200 mg (100 mg bid) to 800 mg, treatment duration was 1 year, and half were conducted in the US and Canada. All studies allowed HCTZ to be added if needed for blood pressure control and all enrolled patients from the controlled trials, regardless of the medication received in the trial, as well as *de novo* patients.

These 4 trials are still ongoing with interim reports for the NDA.

Uncontrolled trials

protocol no./base studies	total no. of patients enrolled	total no. of *de novo* patients enrolled	doses (mg)/ dosing regimen
039+/014, 016, 041, 053	140	174	100, 200, 300 bid
040+/014, 017, 051, 047	253	128	100, 200, 300 bid
050*/011,049	336	213	400-800^ qd
052#/013	75	41	400-800^ qd
Total	804	556	

+safety data cut off 1-96
*safety data cut off 12-95
#safety data cut off 2-96
^dose was titrated to blood pressure effect
vol 079 table 8.E.2 and fax dated 11-14-96

Phase I (appendix 2)

There 635 subjects who received eprosartan in 29 clinical pharmacology studies: 26 studies (see

appendix 2) used only the oral formulation, 2 studies used both oral and intravenous formulations and 1 study used only intravenous formulation (study 004 with 12 subjects is not included below).

Single dose

A total of 407 subjects (399 healthy volunteers and 8 patients with hepatic impairment) received a single oral dose of eprosartan on one or more occasions in 16 studies.

Multiple dose

A total of 216 subjects (80 healthy volunteers, 68 hypertensive patients, 53 patients with renal impairment, and 15 patients with diabetes) received multiple oral doses of eprosartan up to 28 days of consecutive dosing in 10 studies.

Complete/Ongoing Misc. Studies (appendix 1)

The completed/ongoing studies not part of the hypertension program include a placebo controlled trial evaluating cerebral blood flow (037), an enalapril controlled trial evaluating left ventricular hypertrophy (051), a placebo controlled trial with HCTZ background therapy (061), a losartan controlled trial evaluating the uricosuric effect (076), 2 placebo controlled trials evaluating proteinuria (090 described in section 3.4 and 091 still ongoing), an open label long term trial evaluating proteinuria (110), an open label long term trial with HCTZ combination (105), and 2 trials in congestive heart failure (054 and 055). There was 1 recently completed study (099), a single dose pharmacokinetic study in 10 patients with end stage renal disease and 10 normal volunteers (not shown in appendix 1).

Safety Update

The Safety Update was submitted 19 February, 1997 and added 33 new patients as well as 78 patients who had been in previous studies and were rolled over into ongoing open label extension trials (039, 040, 050, and 052). Therefore, the Safety Update includes a total of 2367 unique Phase II/III hypertension patients and reflects any additional deaths, serious safety, and withdrawals for adverse events (and any new information about previously reported deaths, serious safety, and withdrawals for adverse events) reported between 31 May 1996, the cut off date for the NDA, and 31 October, 1996, the cut off date for the Safety Update. These sections of the safety review have been revised to reflect the additional data. Routine adverse events and laboratory safety were not updated and, therefore, reflect data submitted in the original NDA.

2.1 Phase II/II Hypertension

2.1.1 All trials

Number of patients

There were 2334 patients who received eprosartan in the 15 Phase II/III trials:

- 1778 were studied under controlled trials:
  1202 in 6 placebo controlled trials,

576 in 5 active controlled trials,
- 556 in 4 open label, uncontrolled trials.

The 6 placebo controlled trials (protocols 010, 011, 013, 017, 045, and 049) were combined by the sponsor for subset analyses with a total of 1202 eprosartan and 352 placebo patients. Of the 5 active controlled trials, 3 trials (014, 047, 053) were combined for subset analyses (looking primarily at cough rates) with a total of 369 eprosartan and 368 enalapril patients.

Patient characteristics

Study patients could be of either sex (with the exception of studies 010 and 045 that enrolled only males), at least 18 years of age, and had to have either newly diagnosed essential hypertension or be receiving treatment for hypertension.

Patients were generally excluded from the trials if they had:

·secondary forms of hypertension; advanced hypertensive retinopathy; average SitSBP > 200 mmHg;
·advanced atrioventricular conduction defects unless a pacemaker was in place; significant ventricular tachyarrhythmias requiring therapy; bradycardia (<50 beats/minute);
·myocardial infarction or a cerebrovascular accident within the past 90 days; treated CHF; treated angina;
·unstable diabetes mellitus; clinically significant renal or hepatic disease; leukocyte count <3000/mm^3 or platelet count <100,000/mm^3; other concurrent severe disease;
·active alcohol or drug abuse;
·use of warfarin or other anticoagulants within 30 days prior to screening;
·use of an investigational drug within 30 days;
·concomitant administration of any medication known to affect blood pressure.

The demographics for the eprosartan patients are shown below.

	eprosartan N=2334^
mean age	56.8 years
age range	20-93 years
≥ 65 years	29.2 %
≥75 years	5.3 %
males/females	60.5/39.5 %
white/black/other	81.6/10.9/7.5 %
mean duration on drug	145.0 days

^includes 609 patients who received eprosartan in combination with HCTZ for all or part of the study
table 4.1 vol 405; appendix 4.1.1

Mean age of these patients was about 57 years with 29% being at least 65 and 5% being at least 75. The majority of patients were male and nearly 82% of patients were white. Mean duration on eprosartan was 145 days.

Duration of exposure

The duration of exposure, regardless of dose, for the eprosartan patients is shown below.

	eprosartan N=2334
	n (%)
less than 29 days	231 (9.9)
29 to 90 days	871 (37.3)
91 to 180 days	494 (21.2)
181 to 360 days	572 (24.5)
> 361 days	166 (7.1)

Appendix 3.1.1.A

The majority of patients were treated for at least 3 months with 7% treated for a year or more.

The duration of exposure by dose and dosing regimen for all eprosartan patients receiving a total daily dose of at least 200 mg is shown below. Patients appear more than once if they received more than 1 dose.

Number of patients

		Duration of Exposure			
dose and dosing regimen	N	> 28 days	> 3 months	> 6 months	> 1 year
once daily					
400 mg qd	834	290	121	69	20
600 mg qd	629	378	206	148	42
800 mg qd	345	282	135	74	0
1200 mg qd	72	70	0	0	0
twice daily					
100 mg bid	858	406	162	56	3
200 mg bid	1046	618	205	125	2
300 mg bid	673	444	206	3	17
400 mg bid	165	132	0	0	0

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The number of patients receiving eprosartan total daily dose 200 to 1200 mg for more than 6 months is 475. Exposure to the highest dose, 1200 mg, was given to few patients and for no longer than 3 months.

2.1.2 Controlled trials

There were 1778 patients who received eprosartan in the 11 controlled Phase II/III trials: 1202 patients in 6 placebo controlled trials and 576 in 5 active controlled trials. Approximately half of the studies had a fixed dose scheme, the others allowed the dose to be titrated to achieve a desired blood pressure effect.

The number of patients exposed to eprosartan by total daily dose is shown below. Patients appear only once.

Number of patients (controlled trials only)

protocol/ dosing regimen/ duration (wks)		eprosartan total daily dose (mg)								
	placebo/ active	50	100	150	200	300	400	600	800	1200
Placebo studies										
010/ bid/4	22		26		26	22	22			
011/bid/8	93	91			87		90	86	91	
045/qd/4	30						31			
049/qd/8	74						72	73	73	72
013^/ bid,qd/13	86						157			
017^/bid/9	47				92		91			
sub total	352	91	26	0	205	22	463	159	164	72
Other controlled studies										
014^/bid/26	264 enalapril						264			
047^/bid/10	59 enalapril						59			
053/bid/6	45/45 enalapril							46		
041^/bid/12	102 nifedipine						103			
016+/bid/4	52	53	51							
total	919	144	77	0	205	22	889	205	164	72

^titration study: patients' randomized dose
+background HCTZ

The majority (74.8%, 1330/1778) of patients received a total daily dose of 400 mg or more. Very few (4.0%, 72/1778), however, received the highest dose.