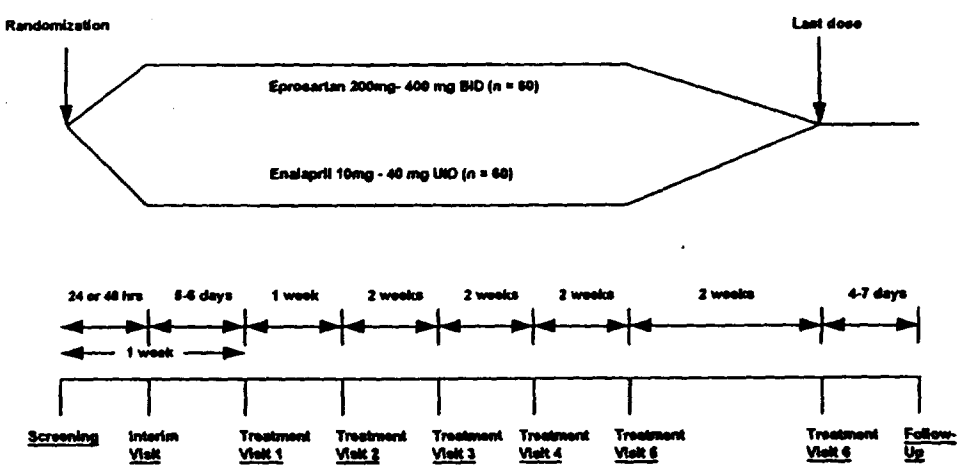
NDA 20-738

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 I). 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.

NDA 20-738

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 interactions. 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

NDA 20-738

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

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 EOG 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

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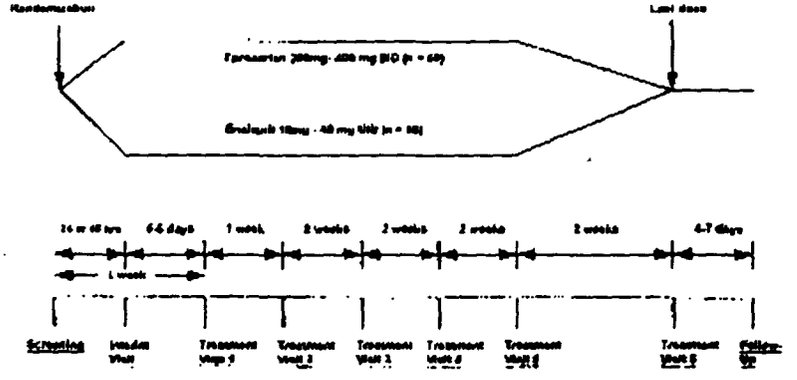
.5 Patients who had received randomized medication in a previous trial of eprosartan.

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 I). 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.

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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 interactions. 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	56	59	115

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

NDA 20-738

Table 3.2 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	38 (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	93.7±2.0	99.1±1.8	
Change from Baseline	-20.9±1.9	-17.5±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	74.0±1.3	74.3±1.2	
End of Titration	74.5±1.8	74.1±1.5	
Change from Baseline	0.4±1.4	0.2±1.2	0.882

Data Source: Tables 14.2 - 14.7

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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.

A.6 Study 050: A long-term (two-year), open-label, multicenter study of once daily oral SK&F 108566-J (eprosartan mesylate) in patients with essential hypertension.

A.6.1 Source documents

This review is based upon the final study report dated 8 December 1998 (NDA volume 1.132).

A.6.2 Investigators

The study was conducted at 55 centers in US and 3 centers in Canada.

A.6.3 Study dates

The study was conducted between 21 November 1994 and 16 February 1998.

A.6.4 Study design

The objective was to establish long-term safety of eprosartan 400 to 800 mg qd, and 400 mg in combination with HCTZ.

This was an open-label follow-on to Study 011[32], 014[33], 037[34], and 049[35]. Subjects could also be enrolled without a previous trial.

Subjects entered into a 3- to 12-week titration period with visits at 3-week intervals, starting at eprosartan 400 mg qd, increasing to 600 and 800 mg qd as needed to achieve sitting DBP <90 mmHg. Subjects not controlled on eprosartan 800 mg qd also received HCTZ 12.5 and then 25 mg qd. With blood pressure control for at least 3 weeks, subjects entered into a maintenance phase lasting for up to 24 months with visits at 3-month intervals. Subjects were instructed to take study drug with meals. Conventional safety data were collected. The final follow-up visit was 7 to 14 days after the last dose.

Lots used for the study were U94040, U94068, U93235, and U94191-S1 (all eprosartan 100 mg), U94190, U5018-S1, U95118, and U95240 (eprosartan 200 mg) and X94219 and X95133 (HCTZ).

There were no significant amendments to the protocol.

A.6.5 Results

A.6.5.1 Conduct

A total of 706 subjects were enrolled, of whom 128 had no prior study participation, 83% completed one year in study, and 44% completed 2 years of study. Individual sites enrolled 1 to 47 subjects.

Reasons for withdrawal were adverse events (14%), lack of effectiveness (15%), loss to follow-up (5%), protocol violations (2%), and other reasons (7%).

Of enrolled subjects, 61% were male, 77% were Caucasian, and the mean age was 55 years.

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[32] *Study 011 was a randomized, double-blind, parallel, placebo-controlled, fixed-dose, dose-ranging trial (eprosartan bid only) conducted in subjects with mild to moderate hypertension. It is reviewed on page 21 of the primary medical review of effectiveness for NDA 20-738.*

[33] *See page 40 for a description of inclusion and exclusion criteria for Study 014.*

[34] *Study 037 was a randomized, double-blind, parallel, placebo-controlled, dose-titration study conducted in elderly subjects. It is was reviewed on page 45 of the primary medical review of effectiveness for NDA 20-738.*

[35] *Study 049 was a randomized, double-blind, parallel, placebo-controlled, fixed-dose, dose-ranging trial (eprosartan qd only) conducted in subjects with mild to moderate hypertension. It is reviewed on page 55 of the primary medical review of effectiveness for NDA 20-738.*

Exposure by treatment is summarized in Table 16.

Table 16. Exposure to study drug (Study 050).

	Eprosartan			Eprosartan/HCTZ			
	400	600	800	600/12.5	600/25	800/12.5	800/25
N	171	140	60	48	64	71	152
Mean	299	360	383	349	357	411	437
Subject-years	140	138	63	46	63	80	182

A.6.5.2 Effectiveness

Population mean blood pressure remained stable throughout study, around 138/88 mmHg, but this has more to do with the study design than any indication of effectiveness.

A.6.5.3 Safety

Safety is reviewed in context of the full development program.

A.6.6 Summary

A substantial fraction of subjects remained on study drug for at least 1 year. Over the course of 2 years, there was no evident upward creep in dose. A more useful demonstration of sustained effectiveness would have been obtained with a randomized withdrawal phase.

APPEARS THIS WAY
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A.7 Study 052: A long-term, open-label, multi-centre, multi-country extension study of once daily oral SK&F 108566 (eprosartan) in patients with essential hypertension who have completed a clinical trial with eprosartan.

A.7.1 Source documents

This review is based upon the final study report dated 8 February 1999 (NDA volume 1.133).

A.7.2 Investigators

The study was conducted at 21 centers in Europe (Germany, UK, Belgium, Netherlands, Italy, Sweden).

A.7.3 Study dates

The study was conducted between 24 June 1995 and 17 April 1998.

A.7.4 Study design

The objective was to establish long-term safety of eprosartan 400 to 800 mg qd, alone or in combination with HCTZ.

This was an open-label follow-on to Study 013 [36].

Subjects entered into a 3- to 12-week titration period with visits at 3-week intervals, starting at eprosartan 400 mg qd, increasing to 600 and 800 mg qd as needed to achieve sitting DBP <90 mmHg. Subjects not controlled on eprosartan 800 mg qd also received HCTZ 12.5 and then 25 mg qd. With blood pressure control for at least 3 weeks, subjects entered into a maintenance phase lasting for up to 24 months with visits at 3-month intervals. Subjects were instructed to take study drug with meals. Conventional safety data were collected. The final follow-up visit was 7 to 14 days after the last dose.

Lots used for the study were U5018, U95118, and U95240 (eprosartan 200 mg) and X95032 (HCTZ).

There were no significant amendments to the protocol.

A.7.5 Results

A.7.5.1 Conduct

A total of 136 subjects were enrolled, of whom 32% had been on placebo in Study 013, 97 completed one year in study, and 49 completed 2 years of study. Individual sites enrolled 1 to 19 subjects.

Reasons for withdrawal were adverse events (13%), lack of effectiveness (15%), loss to follow-up (4%), protocol violations (2%), and other reasons (10%).

Of enrolled subjects, 43% were male, 91% were Caucasian, and the mean age was 58 years.

Exposure by treatment is summarized in Table 16.

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[36] *Study 013 was a randomized, double-blind, parallel, placebo-controlled, dose-titration trial (eprosartan qd versus bid only) conducted in subjects with mild to moderate hypertension. It is reviewed on page 29 of the primary medical review of effectiveness for NDA 20-738.*

Table 17. Exposure to study drug (Study 052).

	Eprosartan			Eprosartan/HCTZ	
	400	600	800	800/12.5	800/25
N	135	108	80	61	47
Mean	120	110	109	98	257
Subject-years	44	33	24	16	33

A.7.5.2 Effectiveness

Population mean blood pressure remained stable throughout study, around 143/87 mmHg, but this has more to do with the study design than any indication of effectiveness.

A.7.5.3 Safety

Safety is reviewed in context of the full development program.

A.7.6 Summary

A substantial fraction of subjects remained on study drug for at least 1 year. Over the course of 2 years, there was no evident upward creep in dose. A more useful demonstration of sustained effectiveness would have been obtained with a randomized withdrawal phase.

APPEARS THIS WAY
ON ORIGINAL

A.8 Study 061: An 8-week, double-blind, double-dummy, placebo-controlled, parallel group, multicenter comparison of regimens of oral SK&F 108566 and hydrochlorothiazide in combination in patients with mild to moderate essential hypertension (DBP >95 and <114 mmHg).

AUG 8 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER REVIEW

NDA #:	20-738	NDA Volume:	1.1091-6
DRUG NAME:	Teveten™ (Eprosartan) Tablets	Doc ID	BM (M19.1 - M19.6)
SPONSOR:	SmithKline Beecham Pharmaceuticals		
TYPE OF DOCUMENT:	New NDA (Clinical Pharmacology Review)		
DATE OF CORRESPONDENCE:	*03-Jul-1997*	DATE ASSIGNED:	*08-Jul-1997*
DATE RECEIVED:	*07-Jul-1997*	DATE COMPLETED	*10-Jul-1997*
MEDICAL OFFICER:	Khin Maung U, M.D.		

1. STUDY PROTOCOL

1.1 Title

Protocol 061: ***An 8-week, double-blind, double-dummy, placebo-controlled, parallel group, multicenter comparison of regimens of oral SK&F 108566 and hydrochlorothiazide given in combination in patients with mild to moderate essential hypertension (DBP ≥ 95 & ≤ 114 mmHg)***

1.2 Rationale

A-II receptor antagonists affect the conversion of angiotensinogen to A-I, and potentially offer therapeutic advantages (absence of side effects such as non-productive cough and angioedema) over ACE-inhibitors. Hydrochlorothiazide (HCTZ) is a diuretic used as a standard therapy for hypertension, and is often used in combination with other antihypertensive agents. This study evaluates the efficacy and safety of adding eprosartan to HCTZ therapy in those patients whose blood pressure is not controlled with HCTZ alone.

1.3 Objectives

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

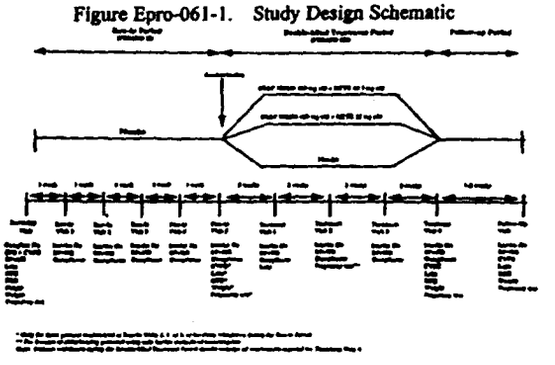
1.4 Study design

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

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

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

Figure Epro-061-1. Study Design Schematic



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

1.5 **Protocol Amendments**

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

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

1.6 **Population enrolled/analyzed**

519 patients with newly diagnosed mild to moderate hypertension (average sitting diastolic blood pressure ≥ 95 and ≤ 114 mmHg) including women without child bearing potential or using hormonal or barrier contraceptives or IUCDs, at least 18 years of age without secondary hypertension, arrhythmias, clinical evidence of congestive heart failure, myocardial infarction or a cerebrovascular accident, angina pectoris, unstable diabetes mellitus, clinically significant renal or hepatic disease, alcohol or drug abuse, or chronic/concomitant treatment with drugs known to affect blood pressure, were enrolled.

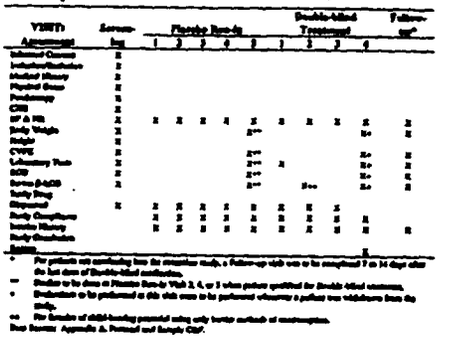
Compliance: This was determined by the number of tablets dispensed at each visit and subtracting the returned number of tablets.

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

1.7 **Study procedures**

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

Table Epro-061-1. Schedule of study assessments



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

1.8 **Efficacy assessments:**

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

The secondary efficacy criteria were as follows:

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

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

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

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

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

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

2. STUDY POPULATION

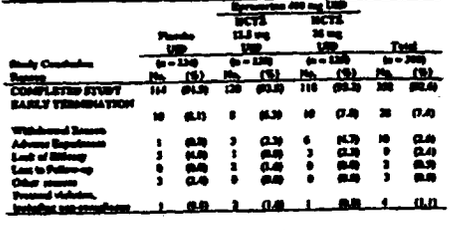
2.1 **Subject disposition:**
519 patients were screened. 13 (2.5%) withdrew prior to receiving single-blind placebo run-in medication (2=protocol violation, 1= lost to follow-up, 10 = "other reasons"). 126 (24.9%) were not randomized (21=withdrawn due to adverse experiences, 21=protocol violations, 6=lack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

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

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

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

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



2.3 **Protocol violations:**

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

Table Epro-061-3

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

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

Note: A patient may have had more than one violation and may be counted twice.
**The number of patients include the 60 patients listed in Section 11.A [illegible]. These patients may or may not have other violations and therefore are not subtracted from the total

2.4 **Demography**

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

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

Parameter	Screening Only	Run-in Only	Placebo UID	Eprosartan 400 mg UID HCTZ 12.5 mg UID	Eprosartan 400 mg UID HCTZ 25 mg UID	Total
Age (years)						
<65 years	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
≥65 years	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mean ± SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Range	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Sex						
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Race						
Black	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Caucasian	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Oriental	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Other**	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Weight (kg)						
Mean ± SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Range	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Height (cm)						
Mean ± SD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Range	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

* [illegible]
** [illegible]
\# [illegible]

2.5 **Baseline characteristics**

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

3 SAFETY RESULTS

3.1 **Deaths:** There were no deaths during the study or for 30 days following each patient's completion of the clinical trial.

3.2 **Withdrawals:** A total of 10 patients were withdrawn due to adverse experiences. Of these, 3 patients had serious, on-therapy adverse experiences which led to withdrawal (1 patient (#061.052.00257) for attempted suicide (randomized to placebo), 1 patient (#061.052.00217) for sarcoidosis, and 1 patient (#061.272.00273) for dizziness, anemia and adenocarcinoma of the esophagus, the latter two being randomized to eprosartan 400 mg/HCTZ 25 mg treatment group. 7 more patients with non-serious adverse experiences were also withdrawn. 4 had severe adverse experiences: 2 patients on eprosartan 400 mg/HCTZ 12.5 mg reported headache (#061.001.00052) and dyspepsia (#061.004.00071), 2 patients on eprosartan 400 mg/HCTZ 25 mg reported headache (#061.005.00033) and pharyngitis (061.004.00102). 2 other patients on eprosartan 400 mg/HCTZ 25 mg reported non-severe adverse experiences of nausea (#061.274.00277) and myalgia (061.573.00457), and 1 patient on eprosartan 400 mg/HCTZ 12.5 mg reported moderate abdominal pain (#061.007.00123). The details are shown in Table Epro-061-5.

Table Epro-061-5

Listing of Patients Withdrawn From the Study Due to On-therapy Adverse Experiences

Identification Patient Number	Age (years)	Sex (M/F)	Days on Double-blind	Reason for Withdrawal (Adverse Experience)	Days on Study at Onset	Duration	Intensity	Relationship
Placebo UID								
061.052.00257*	41	F	35	Suicide Attempt	35	1 days	Severe	Not Related
Eprosartan 400 mg/HCTZ 12.5 mg UID								
061.001.00052	62	F	31	Headache	31	2 days	Severe	Poss. Related
061.004.00071	41	M	14	Dyspepsia	1	Ongoing	Severe	Poss. Related
061.007.00123	64	M	31	Abdominal Pain	31	4 days	Moderate	Not Related
Eprosartan 400 mg/HCTZ 25 mg UID								
061.052.00217*,**	60	F	3	Sarcoidosis	1	Ongoing	Severe	Not Related
061.004.00102	30	F	18	Pharyngitis	15(1)	4 days	Severe	Poss. Related
061.005.00033	47	F	42	Headache	16	Ongoing	Severe	Poss. Related
061.272.00273*,+	60	M	22	Dizziness	22	Ongoing	Severe	Not Related
061.274.00277	51	F	12	Nausea	2	11 days	Moderate	Poss. Related
061.573.00457	32	M	4	Myalgia	3	4 days	Mild	Poss. Related

* Adverse experiences classified as serious (see Section 4.4).

** Although patient 061.052.00217 was withdrawn for adverse experience, the conclusion reason is listed as "protocol violation" in Data Sources: Table 12.3, Appendix B, Listing 4, Appendix I, Listing 1. This patient did not have a screening sheet x-ray (protocol violation) until the first day of double-blind medication. When the results came back on Day 3 indicating sarcoidosis, the patient was withdrawn.

\+ Patient 061.272.00273 had other adverse experiences (esophageal carcinoma and anemia) that met the definition of serious.

3.3 **Serious, Non-fatal Adverse Events:** There were 8 patients with serious, on-therapy adverse experiences, 3 of which led to withdrawal (1 patient (#061.052.00257) for attempted suicide (randomized to placebo), 1 patient (#061.052.00217) for sarcoidosis, and 1 patient (#061.272.00273) for dizziness, anemia and adenocarcinoma of the esophagus, the latter two being randomized to eprosartan 400 mg/HCTZ 25 mg treatment group. Of the other 5 serious adverse experiences, 3 patients (#061.002.00157, #061.006.00046 (who had transient aphasia) , and #061.010.00017 who had atrial fibrillation) received placebo, 1 patient (#061.472.00401) received eprosartan 400 mg/HCTZ 12.5 mg and 1 patient (#061.052.00218) received eprosartan 400 mg/HCTZ 25 mg. Details are shown in Table Epro-061-6.

Table Epro-061-6

Listing of Randomized Patients With Serious On-therapy Adverse Experiences That Did Not Lead to Withdrawal From the Study

Identification Patient Number	Age (years)	Sex (M/F)	Days on Double-blind	Adverse Experience	Days on Study at Onset	Duration	Intensity	Relationship
Placebo UID								
061.002.00157	54	M	60	Melanoma	60	1 day	Mild	Not Related
061.006.00046	75	F	31	Transient Aphasia	31	1 day	Moderate	Possibly Related
061.010.00017	66	M	35	Atrial Fibrillation	34(1)	3 days	Moderate	Not Related
Eprosartan 400 mg/HCTZ 12.5 mg UID								
061.472.00401	50	F	36	Left Hip Prosthesis due to Worsening of Arthritis	16	14 days	Mild	Not Related
Eprosartan 400 mg/HCTZ 25 mg UID								
061.052.00218	35	M	36	Gastroenteritis from strychnine smoking in 24 hr hospital stay	12	2 days	Severe	Not Related

3.4 **Adverse Events:**

Headache was the most common adverse experience during the placebo run-in period, occurring in 71 of 380 (18.7%) patients (22 of 124 (17.7%) patients on placebo, 28 of 128 (21.9%) patients receiving eprosartan 400 mg/HCTZ 12.5 mg and 21 of 128 (16.4%) patients receiving eprosartan 400 mg/HCTZ 25 mg).

During the double-blind study period, the most common adverse experience was headache reported by 42 of 380 (11.1%) patients, with 17 of 124 (13.7%) patients receiving placebo, 15 of 128 (11.7%) of patients receiving

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

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

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

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

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

ECG Abnormality	Placebo QD (n=380) No.	(%)	Eprosartan 400 mg QD HCTZ 12.5 mg QD (n=380) No.	(%)	HCTZ 25 mg QD (n=128) No.	(%)
Conduction						
First degree AV block	0	(0.0)	1	(0.3)	1	(0.7)
Left bundle branch block NOS	1	(0.7)	0	(0.0)	0	(0.0)
Left ventricular hypertrophy	1	(1.3)	1	(0.3)	1	(0.7)
Morphology						
ECG finding of ischemia	0	(0.0)	1	(0.3)	0	(0.0)
Myocardial infarction old	0	(0.0)	1	(0.3)	0	(0.0)
Rhythm						
Sinus bradycardia	1	(0.7)	3	(1.1)	1	(0.7)
Sinus tachycardia	0	(0.0)	0	(0.0)	2	(1.5)
Atrial fibrillation	1	(1.3)	0	(0.0)	0	(0.0)
Total with at least one new onset ECG abnormality	7		7		5	

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

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

Patient Identification Number	Sex	Age (years)	Days on Double-Blind	Adverse Experience (Preferred Term)	Days on Study Drug at Onset	Duration	Severity	Relationship	Action
Placebo QD									
061.003.00010	Female	51	10	Palpitation	10	1 day	mild	Possibly related	Dose unchanged
					37	1 day	mild	Possibly related	None
061.005.00016	Female	75	14	ECG abnormal	14 (12)*		mild	Unrelated	None
061.005.00017	Male	68	28	Fibrillation atrial**	28 (12)*	1 day	Moderate	Unrelated	None
061.021.00028	Female	58	28	Palpitation	28	1 day	Severe	Unrelated	None
061.472.00002	Female	68	28	Fibrillation atrial	28 (12)*		mild	Unrelated	None
061.274.00020	Male	59	28	ECG abnormal, specific	28 (12)*		mild	Unrelated	None
Eprosartan 400 mg/HCTZ 12.5 mg QD									
061.005.00008	Female	58	28	Palpitation	28	30 days	mild	Unrelated	None
061.472.00005	Female	59	28	Tachycardia	28	1 day	mild	Possibly related	None
061.274.00005	Female	68	28	ECG abnormal, specific	28 (12)*		mild	Unrelated	None
Eprosartan 400 mg/HCTZ 25 mg QD									
061.005.00030	Male	54	28	Palpitation	28	7 days	mild	Possibly related	None
061.005.00035	Female	68	28	Palpitation	3	25 days	mild	Unrelated	None
061.204.00005	Male	58	28	Palpitation	28	28 days	mild	Possibly related	None
061.472.00030	Male	58	28	Dyspepsia	28		Moderate	Possibly related	None

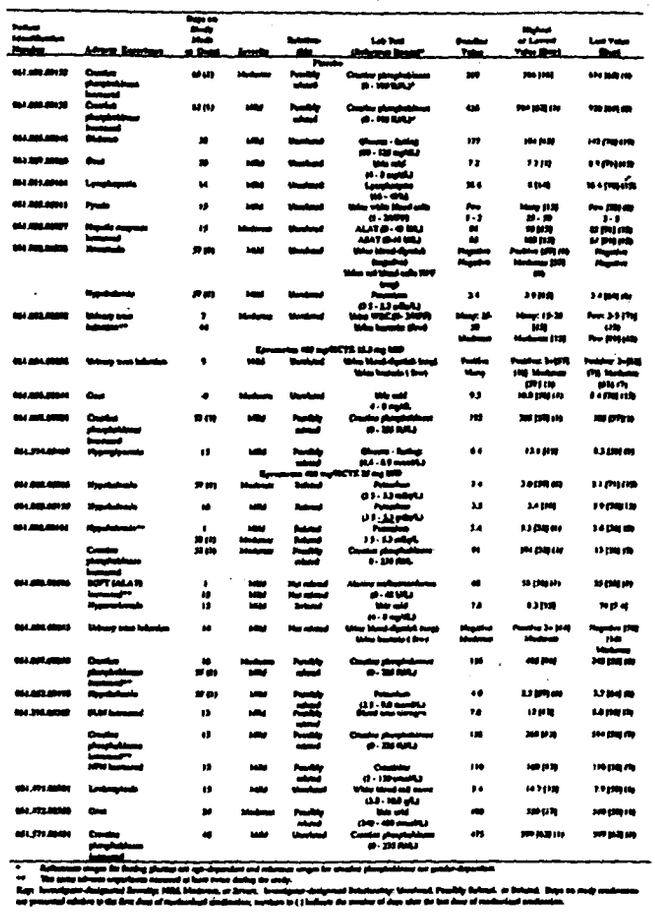
* ( ) Indicates the number of days after the last dose of randomized medication.
** This adverse experience was considered by the investigator to be serious.

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

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

Table Epro-061-9

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



EFFICACY RESULTS

.1 Statistical considerations

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

.2 Primary Efficacy Parameter

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

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

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

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

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

4.3 Secondary Efficacy Parameters

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

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

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

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

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

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

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

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

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

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

5. **CONCLUSION**

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

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

/S/
8/8/97
Khin Maung U, MBBS, MMedSc, MD(NSW), MD, FACP

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HFD-110 / CSO / A. Karkowsky / K.M.U

A.9 Study 077: A study to evaluate the relative bioavailability and the effect of food on the pharmacokinetics of eprosartan/hydrochlorothiazide (HCTZ) combination in healthy adult volunteers.

A.9.1 Source documents

This review is based upon the final study report dated 22 October 1997 (NDA volume 1.139).

A.9.2 Investigators

The study was conducted at 1 center in US.

A.9.3 Study dates

The study was conducted between 17 February 1997 and 24 April 1997.

A.9.4 Study design

The objective was to examine, in normal subjects, the effect of food on the pharmacokinetics of eprosartan and HCTZ in targeted commercial formulation.

Subjects were normal, 18 to 60 years old, males or females of low childbearing potential.

This was a randomized, open-label, four-period crossover design study. Study periods consisted of a single dose and 48 hours of PK data collection, with >7 days between periods. Treatments were eprosartan 800 mg plus HCTZ 25 mg (2 x 400/12.5) fed and fasted, eprosartan 800 mg (2 x 400) fasted, and HCTZ 25 mg (2 x 12.5) fasted.

The meal was a standard high-fat (1020 calories, 58-75 g fat) breakfast consumed immediately before study drug administration. Plasma samples were collected pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, 24, 32, and 48 hours. HPLC assay had a lower limit of quantitation for eprosartan of 10 ng/mL and for HCTZ 2 ng/mL. Pharmacokinetic parameters were estimated through noncompartmental modeling.

The sponsor's power calculation suggested that 16 subjects gave 90% power to detect a 30% between-group difference in AUC or C_{max} for eprosartan or HCTZ.

Lots used for the study were U96214 (eprosartan 400 mg, HCTZ 12.5), and U96215 (eprosartan 400 mg).

Other than the change in the eprosartan dose range, there were no substantive amendments to the protocol.

A.9.5 Results

A.9.5.1 Conduct

A total of 16 subjects were enrolled (out of 31 screened), of whom all completed study.

Subjects were 18 to 54 years old, and all but 3 were males.

Only minor protocol violations were reported.

A.9.5.2 Pharmacokinetics

The mean plasma levels of eprosartan and HCTZ are shown in Figure 1.

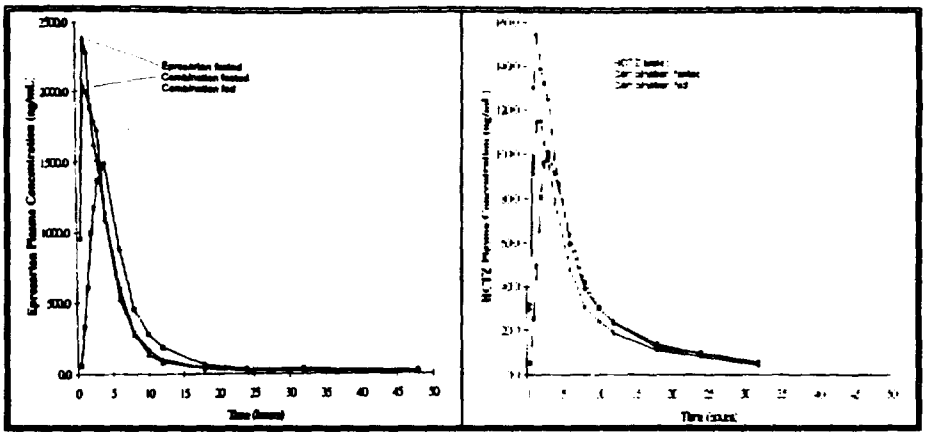

Figure 1. Mean plasma levels of eprosartan and HCTZ (Study 077).

Population mean plasma levels of eprosartan (left) and HCTZ (right) following single doses of monotherapy reference formulation (fasted) and the combination formulation (fasted and fed).

The principal pharmacokinetic parameters are shown in Table 18.

Table 18. Pharmacokinetic parameters (Study 077).

	Eprosartan			HCTZ		
	Fasted		Fed	Fasted		Fed
	Mono	Combo	Combo	Mono	Combo	Combo
AUC_{0-t} (μg.h/mL)	10.0±3.1	10.5±3.8	9.7±2.6	1.1±0.2	0.8±0.2	0.9±0.2
C_{max} (μg/mL)	2.8±1.2	2.7±1.1	1.8±0.6	0.17±0.05	0.13±0.03	0.12±0.02
T_{max} (h)	1.3 (1.0-3.0)	1.3 (0.5-3.0)	4.0 (1.5-6.0)	1.7 (1.0-4.0)	2.0 (1.0-4.0)	3.0 (1.5-6.0)

The C_{max} from eprosartan was increased in the fasted state, whether or not combined with HCTZ. The t_{max} for eprosartan was decreased in the fasted state, whether or not combined with HCTZ. The net effect was negligible for AUC. This is probably a reasonable description for HCTZ as well.

A.9.5.3 Safety

Safety is reviewed in context of the full development program.

A.9.6 Summary

Under fasted conditions, plasma levels of eprosartan and HCTZ obtained with the combination product were somewhat smaller than with the reference monotherapy formulations, but the time course was otherwise quite similar. A high fat meal consumed just before administration of the combination formulation delayed and reduced peak plasma levels of both eprosartan and HCTZ, but the total AUC was similar to the fasted condition.

A.10 Study 078: A study to determine the bioequivalence of the proposed commercial combination formulation of eprosartan plus hydrochlorothiazide (600/12.5 mg) relative to the clinical trials combination formulation of eprosartan plus hydrochlorothiazide (2 x 300/6.25 mg) in healthy volunteers.

A.10.1 Source documents

This review is based upon the final study report dated 9 September 1999 (NDA volumes 1.140-1.141).

A.10.2 Investigators

The study was conducted at 1 center in US.

A.10.3 Study dates

The study was conducted between 11 March 1999 and 30 March 1999.

A.10.4 Study design

The objective was to compare, in normal subjects, the bioavailability of eprosartan and HCTZ in the principal study and targeted commercial formulations.

Subjects were normal, 18 to 55 years old, males or females of low childbearing potential.

Subjects received, in random order, the proposed commercial formulation of eprosartan/HCTZ 600/12.5 mg and the previously studied formulation of (2 x) 300/6.25 mg. The single dose was administered after overnight fast and plasma samples were collected over the next 32 hours. The limit of quantitation for the assay was [redacted] ng/mL for eprosartan and [redacted] g/mL for HCTZ. A minimum of 7 days elapsed between treatments.

Lots used for the study were U98200 (eprosartan/HCTZ 600/12.5 mg), and U99250 (eprosartan/HCTZ 300/6.25 mg).

The trial was designed with an interim analysis after 72 subjects were enrolled. Another 60 subjects were to be enrolled "if necessary".

A.10.5 Results

A.10.5.1 Conduct

A total of 72 subjects were enrolled (out of 75 screened), of whom all completed study. The second cohort of subjects was never entered.

Subjects were 20 to 55 years old, and all were males.

No protocol violations were reported.

A.10.5.2 Pharmacokinetics

The mean plasma levels of eprosartan and HCTZ are shown in Figure 1.

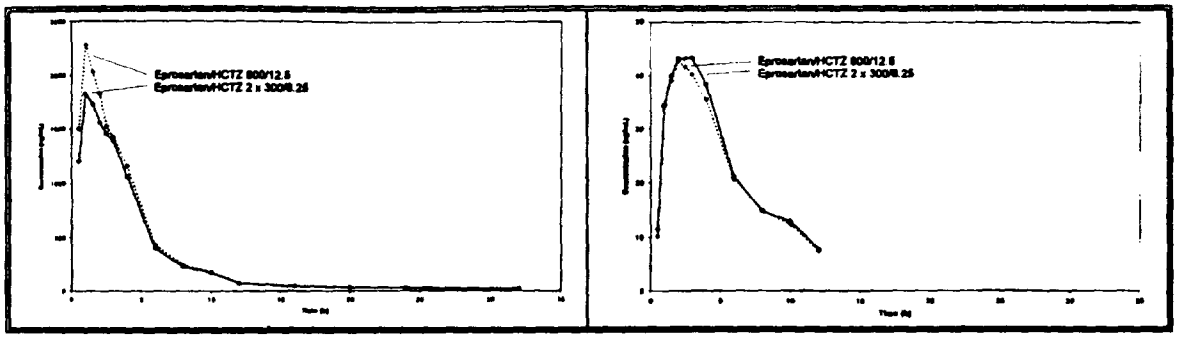

Figure 2. Mean plasma levels of eprosartan and HCTZ (Study 078).

Population mean plasma levels of eprosartan (left) and HCTZ (right) following single doses of the 600/12.5-mg combination and 2 x 300/6.25 mg.

The principal pharmacokinetic parameters are shown in Table 19.

Table 19. Pharmacokinetic parameters (Study 078)

	Eprosartan		HCTZ	
	2x300/6.26 (trial)	**600/12.5 (commercial)**	**2x300/6.26 (trial)**	**600/12.5 (commercial)**
AUC_{0-t} (µg.h/mL)	**8.6±4.3**	**9.6±4.7**	0.29±0.08	0.28±0.09
C_{max} (µg/mL)	2.4±1.2	2.8±1.4	0.05±0.01	0.05±0.01
T_{max} (h)	1.0 (0.5-4.0)	1.0 (0.5-4.0)	2.25 (1.0-4.0)	2.0 (1.0-4.0)

The largest discrepancy in pharmacokinetic parameters between the two formulations was in C_{max} for eprosartan. These values differed by about 15%.

A.10.5.3 Safety

Safety is reviewed in context of the full development program.

A.10.6 Summary

Plasma levels of eprosartan and HCTZ were similar following administration of either the formulation used in the clinical trials or the to-be-marketed formulation. The largest discrepancy was a 15% higher maximum eprosartan concentration following administration of the to-be-marketed formulation. This difference is not likely to have clinical significance.

APPEARS THIS WAY
ON ORIGINAL

A.11 Study 079: A study to examine the pharmacokinetics of eprosartan and hydrochlorothiazide (HCTZ) when administered alone or in combination in healthy adult volunteers.

A.11.1 Source documents

This review is based upon the final study report dated 21 October 1997 (NDA volume 1.142).

A.11.2 Investigators

The study was conducted at 1 center in US.

A.11.3 Study dates

The study was conducted between 10 February 1997 and 6 April 1997.

A.11.4 Study design

The objective was to compare, in normal subjects, the pharmacokinetics of eprosartan and HCTZ alone and in combination.

Subjects were normal, 18 to 60 years old, males or females of low childbearing potential.

Subjects received, in random order, single oral doses of eprosartan (2 x 400 mg), HCTZ (2 x 12.5 mg), and the to-be-marketed formulation of (2 x) 400/12.5 mg. The single dose was administered after overnight fast and plasma samples were collected over the next 48 hours. The first meal was at 5 hours after dosing. The limit of quantitation for the [redacted] was [redacted] ng/mL for eprosartan and [redacted] ng/mL for HCTZ. A minimum of 7 days elapsed between treatments.

Lots used for the study was U96205 (eprosartan 400 mg); the lot for the combination is not described in the study report.

The trial was designed with an interim analysis after 72 subjects were enrolled. Another 60 subjects were to be enrolled "if necessary".

A.11.5 Results

A.11.5.1 Conduct

A total of 18 subjects were enrolled (out of 33 screened), of whom all completed study.

Subjects were 19 to 53 years old, and all but 3 were males. Nine were Caucasian and 8 were Black.

No protocol violations were reported.

A.11.5.2 Pharmacokinetics

The mean plasma levels of eprosartan and HCTZ are shown in Figure 3.

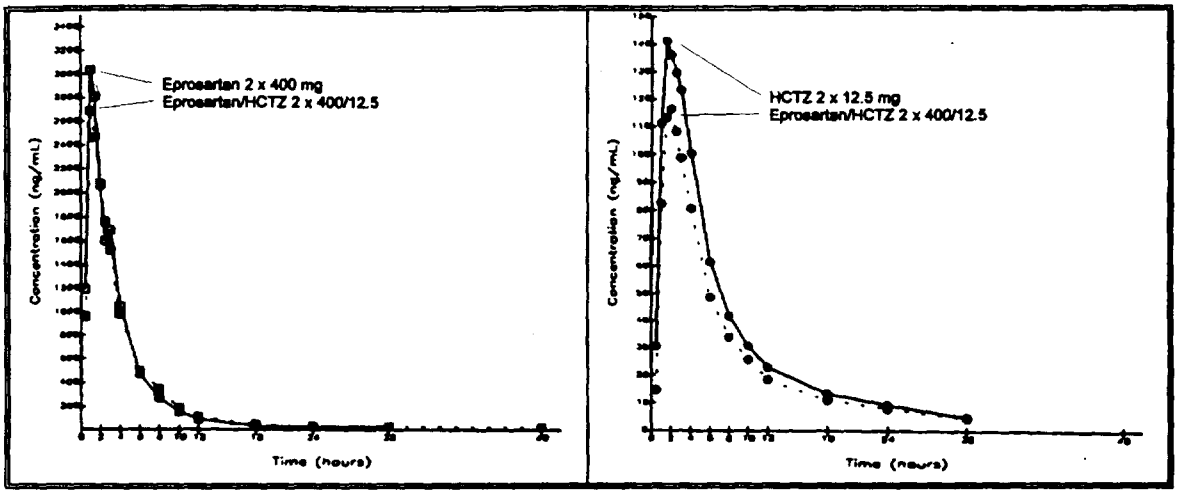

Figure 3. Mean plasma levels of eprosartan and HCTZ (Study 079).

Population mean plasma levels of eprosartan (left) and HCTZ (right) following single doses of eprosartan 2 x 400 mg, HCTZ 2 x 12.5-mg, or the combination.

The principal pharmacokinetic parameters are shown in Table 20.

Table 20. Pharmacokinetic parameters (Study 078)

	Eprosartan		HCTZ	
	2 x 400	**2 x 400/12.5**	**2 x 12.5**	**2 x 400/12.5**
AUC_{0-t} (μg.h/mL)	**10.6±4.6**	**10.6±4.9**	1.05±0.25	0.85±0.23
C_{max} (μg/mL)	3.3±1.9	3.0±1.4	0.16±0.05	0.13±0.05
T_{max} (h)	1.0 (1.0-3.0)	1.0 (1.0-3.0)	1.5 (1.0-3.0)	2.0 (1.0-3.0)

The largest discrepancy in pharmacokinetic parameters between the two formulations was in C_{max} for HCTZ. These values differed by about 20%.

A.11.5.3 Safety

Safety is reviewed in context of the full development program.

A.11.6 Summary

Plasma levels of eprosartan and HCTZ were similar following administration of either the formulation used in the clinical trials or the to-be-marketed formulation. The largest discrepancy was a 20% lower maximum HCTZ concentration following administration of the combination formulation. This difference is not likely to have clinical significance.

APPEARS THIS WAY
ON ORIGINAL

A.12 Study 088: An 8 week, double-blind, parallel group, multi-centre study of oral eprosartan and hydrochlorothiazide given in combination to patients with essential hypertension (DBP >98 and <114 mmHg) not adequately controlled by eprosartan monotherapy (600 mg OD).

A.12.1 Source documents

This review is based upon the amended protocol, dated 5 March 1998, dated amendments, a final study report dated 6 July 2000 (NDA volumes 1.37-1.59), and electronic datasets.

A.12.2 Investigators

The study was conducted at 29 centers in France, Belgium, and Ireland.

A.12.3 Study dates

Enrollment in the double-blind trial was from 25 April 1998 to 6 November 1998.

A.12.4 Study design

The objective was a placebo-vs.-HCTZ comparison of seated diastolic pressure in subjects with mild-to-moderate hypertension treated with eprosartan 600 mg.

Subjects were males or females of non-childbearing potential age 18 or older with seated diastolic pressure 98 to 114 mmHg at the end of the run-in phase. Entry into the double-blind phase required measurements of diastolic pressure to differ by 8 mmHg or less, and good compliance during run-in. Exclusion criteria were (1) pregnancy or lactation, (2) secondary hypertension, (3) advanced retinopathy, (4) sitting SBP>200 mmHg, (5) ventricular tachyarrhythmias requiring therapy, (6) evidence of MI or CVA within 90 days, (7) CHF, (8) treated angina, (9) unstable diabetes mellitus, (10) clinically significant renal or hepatic disease, (11) alcohol or drug abuse, (12) other significant disease, (13) concomitant MAO inhibitors, antidepressants, phenothiazines, medication affecting blood pressure, sympathomimetics, NSAIDs, (13) sensitivity to study drugs, or (14) previous participation in a study of eprosartan.

Upon completion of a 3-week open-label run-in period, during which subjects received eprosartan 600 mg qd, subjects were randomized to placebo or HCTZ 12.5 mg (as combination tablet with eprosartan) for 8 weeks. Study drug was administered once daily in the morning, with no specified relationship to food. This dose was withheld on study days and all blood pressure assessments were to be 24±3 hours from the previous dose. The primary end point was change in seated diastolic pressure (average of 3 readings with a mercury sphygmomanometer) at 8 weeks; at 110 subjects per arm, the trial was sized to detect with 90% power, a 3.5-mmHg treatment difference from placebo. Conventional safety monitoring was employed.

Lots used for the double-blind study were U96307 (eprosartan 300 mg), and U97335 (eprosartan 300 mg + HCTZ 6.25mg).

There were no substantive amendments to the protocol.

A.12.5 Results

A.12.5.1 Conduct

A total of 518 subjects were screened, 494 enrolled and 309 were randomized. Individual sites randomized 3 to 56 subjects. Two hundred ninety subjects completed.

Ten subjects discontinued for adverse events and 4 discontinued for lack of efficacy during run-in. Discontinuations from double-blind treatment are characterized in Table 21.

Table 21. Discontinuations (Study 088).

	Placebo N=157	HCTZ N=152
Adverse event	6	5
Treatment failure	2	0
Protocol violation	2	0
Loss to follow-up	0	1
Other	1	2
Total	11	8

Demographic characteristics of the four treatment groups were similar. Mean ages ranges from 55 to 57, the proportion of males was 49 to 55%, the proportion of non-Caucasians ranged from 2 to 3%.

At baseline, the seated diastolic pressure (means) ranged from 99 to 100 mmHg and seated systolic pressures ranged from 155 to 156 mmHg.

Sixty-six to 73% of subjects had previously been on antihypertensive drug therapy. The most common accompanying medical histories were hypercholesterolemia (18%), and menopause (14%).

A.12.6 Protocol violations

Fifty-six percent of subjects had at least one protocol violation, the most common of which were study drug not taken 22-25 hours prior to end point assessment [37] (42%), and end point assessment between noon and midnight (18%).

A.12.6.1 Effectiveness

Four subjects (3 on combination withdrew after randomization but before the first blood pressure assessment, and are not included in the ITT-LOCF analyses. Results for the LOCF analyses are shown in Table 22.

Table 22. Changes from baseline and placebo in vital signs at trough at week 8 (Study 088)[38].

	Placebo N=156	HCTZ N=149
seDBP	-7.9±0.7	-10.7±0.7
seSBP	-5.8±1.1	-9.2±1.1

The changes in seated diastolic and systolic pressure were both statistically significant.

Comparison of all available data at week 2 and study end point shows that the effects were substantially or fully apparent at this earliest assessment.

The sponsor's analysis of proportion of subjects with normalized diastolic pressure (<90 mmHg) at week 8 was 49% on placebo, and 59% on HCTZ, a difference that was not statistically significant.

The sponsor performed subgroup analyses of seated diastolic and systolic pressure by age and gender. The results were consistent in these subgroups.

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[37] *The nature of these violations could not be further characterized from the electronic data. Obviously the timing matters most for assessments not at end point, and, at end point, a late measurement would be preferable to an early one.*

[38] *Sponsor's analyses of mean effects.*

Study 088

A.12.6.2 Safety

Safety is reviewed in context of the full development program.

A.12.7 Summary

Addition of HCTZ 12.5 mg to the usual starting dose of eprosartan (600 mg) produced statistically significant decreases in seated diastolic and systolic pressure. Two weeks is probably adequate for the effects of adding HCTZ to be manifest.

A.13 Study 105: An open-label, long-term multicenter extension study of the safety of oral eprosartan in combination with hydrochlorothiazide in patients with essential hypertension who have completed study 108566/061.

A.13.1 Source documents

This review is based upon the final study report dated 3 December 1998 (NDA volume 1.134).

A.13.2 Investigators

The study was conducted at 19 centers in US, France, United Kingdom, and Netherlands.

A.13.3 Study dates

The study was conducted between 9 May 1996 and 24 August 1997.

A.13.4 Study design

The objective was to establish long-term safety of eprosartan plus HCTZ..

This was an open-label follow-on to Study 061 [39]. Subjects had to have completed Study 061 to be enrolled.

Subjects were instructed to take study drugs (eprosartan 400 mg and HCTZ 25 mg) once daily in the morning with no specified relationship to meals. Subjects were seen for vital signs at weeks 4, 8, 12, 20, 28, 40, and 52. There was a final follow-up visit 7 to 14 days after the last dose of study drug. Other safety data (not collected at each visit) included ECG and clinical laboratory assessments.

The primary efficacy end point was change from baseline (end of on-treatment period of Study 061) in sitting DBP. There was placebo-controlled withdrawal period.

Lots used for the study were U95113S1 and U96119S1 (eprosartan 400 mg), and U96123 (HCTZ 25 mg).

There were no amendments to the protocol.

A.13.5 Results

A.13.5.1 Conduct

A total of 232 subjects were enrolled (out of 352 completing Study 061), of whom 186 completed study. Of subjects enrolled, 71 were previously receiving placebo, 80 were on eprosartan plus HCTZ 12.5 mg, and 81 were on eprosartan plus HCTZ 25 mg.

Demographic characteristics, past medical history, and baseline characteristics of the four treatment groups were similar.

Reasons for withdrawal were adverse events (11%), lack of effectiveness (3%), loss to follow-up and protocol violations (each <1%), and other reasons (5%).

Eighty-seven percent of subjects had at least one protocol violation, usually vital sign assessment outside the 22- to 24-hour window from the previous dose.

A.13.5.2 Effectiveness

Changes in sitting diastolic pressure are shown in Table 23.

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[39] *See page 71 for description of inclusion and exclusion criteria for Study 061.*

Table 23. Changes in sitting DBP by double-blind treatment (Study 105).

	Treatment group in Study 061		
	Placebo N=70	**Eprosartan + HCTZ 12.5 N=78**	**Eprosartan + HCTZ 25 N=80**
Baseline	94.9±0.9	90.5±0.9	87.4±0.8
End point	88.6±1.1	88.7±0.9	87.5±0.8
Change	-6.3±1.2	-1.9±0.8	0.1±0.7

As expected, the largest change was in the group previously treated with placebo. There was a small blood pressure reduction in the group previously treated with HCTZ 12.5 mg.

A.13.5.3 Safety

Safety is reviewed in context of the full development program.

A.13.6 Summary

The largest changes in sitting diastolic pressure were seen in subjects previously on placebo. There was no placebo withdrawal phase, but such a design would have provided useful confirmation of continued activity.

APPEARS THIS WAY
ON ORIGINAL

A.14 Study 120: A 12-week, multicenter, double-blind, parallel, positive-controlled, dose-titration study of Teveten (eprosartan mesylate, SK&F 108566-J) compared to enalapril in patients with severe systolic hypertension.

A.14.1 Source documents

This review is based upon the final study report dated 8 April 1999 (NDA volume 1.143).

A.14.2 Investigators

The study was conducted at 36 centers in US.

A.14.3 Study dates

The study was conducted between 18 August 1997 and 23 March 1998.

A.14.4 Study design

The objective was to compare the effectiveness of eprosartan (600-1200 mg once daily) and enalapril (10-40 mg once daily), among subjects with severe systolic hypertension (180 to 240 / 90 to 140 mmHg).

Subjects were at least 18 years old, males or females of non-childbearing potential, with blood pressure either >180/90 mmHg untreated or >160/90 mmHg treated. Exclusions were (1) malignant or secondary hypertension, (2) advanced hypertensive retinopathy, (3) symptomatic conduction defects, (4) ventricular tachyarrhythmias requiring treatment, (5) MI or CVA within 90 days or ischemia on ECG, (6) CHF, (7) angina requiring regular treatment, (8) unstable diabetes mellitus, (9) significant renal or hepatic disease, (10) alcohol or drug abuse, (11) need for MAO inhibitors, tricyclic antidepressants, or phenothiazines, (12) use of antihypertensives other than HCTZ, and (13) chronic sympathomimetics or NSAIDs. Subjects could be on stable doses of HCTZ at entry; this was not discontinued.

There was no washout phase. Subjects were randomized to enalapril 10 mg or eprosartan 600 mg, and followed at 1 day, 1 week, and then every 2 weeks for 12 weeks. As needed to control blood pressure <140/90 mmHg, the dose could be uptitrated up to week 8 to (enalapril) 20 or 40 mg or (eprosartan 800 or 1200 mg [40]). Subjects not controlled on monotherapy could have added HCTZ 25 mg. The dose could not be increased during the final 4 weeks of double-blind treatment. Entry into the maintenance phase required sitting blood pressure <140/90 or specified substantive reductions from baseline. There was a final follow-up visit 7 to 14 days after the last dose of study drug.

The primary efficacy end point was change from baseline in sitting systolic pressure. At 174 subjects per arm, the study was sized to detect (90% power, 2-sided α=0.05) an 8-mmHg difference between groups.

Lots used for the study were U96120 and U96306 (eprosartan 300 mg), and U96119 (eprosartan 400 mg).

Other than the change in the eprosartan dose range, there were no substantive amendments to the protocol.

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[40] *The original protocol specified eprosartan doses of 400, 600, and 800 mg.*

A.14.5 Results

A.14.5.1 Conduct

A total of 360 subjects were enrolled (out of 412 screened), of whom 212 completed study. Individual sited enrolled 1 to 21 subjects.

The mean age was 56-57 years. Fifty-three to 54 percent of subjects were male, and 58-61% were Caucasian. The mean blood pressure at study baseline (all on treatment) was about 176/101 mmHg. Eighty-three to 86 percent of subjects were on a previous antihypertensive treatment at baseline.

Overall 41% of subjects withdrew (not different between groups). Reasons for withdrawal were adverse events (7%), lack of effectiveness (24%), loss to follow-up (3%), protocol violations (5%), and other reasons (3%).

Seventy-six percent of subjects had at least one protocol violation, usually vital sign assessment outside the 22- to 24-hour window from the previous dose.

A.14.5.2 Effectiveness

Five subjects had no on-treatment vital signs. Sixty-three to 65 percent of subjects received at least one other antihypertensive treatment during double-blind treatment. The design of the study does not permit assessment of the additive effects of eprosartan and HCTZ.

A.14.5.3 Safety

Safety is reviewed in context of the full development program.

A.14.6 Summary

The study design does not permit interpretation of the effectiveness of eprosartan and HCTZ.

APPEARS THIS WAY
ON ORIGINAL

A.15 Study 137: An open-label, multicenter study of Teveten (eprosartan mesylate, SK&F 108566-J) at doses of 600, 800, and 1200 mg once daily in patients with severe systolic hypertension.

A.15.1 Source documents

This review is based upon the final study report dated 29 September 1999 (NDA volume 1.135).

A.15.2 Investigators

The study was conducted at 24 centers in US.

A.15.3 Study dates

The study was conducted between 20 November 1997 and 12 October 1998.

A.15.4 Study design

The objective was to establish long-term safety of eprosartan, alone and in combination, among subjects with severe systolic hypertension (180 to 240 / 90 to 140 mmHg) previously participating in Study 120[41].

Subjects previously on eprosartan remained on the same dose level (600, 800, or 1200 mg, or 1200 mg plus HCTZ 25 mg). Subjects previously receiving enalapril were switched to a comparable dose level of eprosartan. Study drug was taken once daily in the morning with no specified relationship to meals. Subjects were seen for vital signs and possible dose adjustment at weeks 2, 4, 6, 8, 12, and 26. Subjects not achieving blood pressure control (SBP <140 mmHg) on eprosartan alone had HCTZ 25 mg added, then other antihypertensive agents as needed. There was a final follow-up visit 7 to 14 days after the last dose of study drug. Other safety data (not collected at each visit) included ECG and clinical laboratory assessments.

There was no primary efficacy end point. There was placebo-controlled withdrawal period.

Lots used for the study were U96203 (eprosartan 300 mg), and U97116 (eprosartan 400 mg).

There were no substantive amendments to the protocol.

A.15.5 Results

A.15.5.1 Conduct

A total of 121 subjects were enrolled (out of 212 completing Study 120), plus one subject not previously studied, of whom 103 completed study. Of subjects enrolled, 16% were previously receiving eprosartan alone, 31% were on eprosartan plus HCTZ, 29% were receiving enalapril alone, and 23% were on enalapril plus HCTZ.

The mean age was 59 years. Fifty percent of subjects were male, and 67% were Caucasian. The mean blood pressure at study baseline (all on treatment) was about 140/85 mmHg. Fifty-four percent of subjects were on another antihypertensive at the start of treatment (30% calcium channel blocker, 12% beta-blocker, 7% diuretic); this rose to 67% by the end of study.

Reasons for withdrawal were adverse events (4%), lack of effectiveness (3%), loss to follow-up (<1%), protocol violations (2%), and other reasons (6%).

Ninety-nine percent of subjects had at least one protocol violation, usually vital sign assessment outside the 22- to 24-hour window from the previous dose.

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[41] *See page 91 for a description of inclusion and exclusion criteria for Study 120.*

A.15.5.2 Effectiveness

The trial design precludes assessment of effectiveness.

A.15.5.3 Safety

Safety is reviewed in context of the full development program.

A.15.6 Summary

The study was open-label, and there was no comparison group. Subjects not adequately treated with eprosartan alone usually required more than the addition of HCTZ.

APPEARS THIS WAY
ON ORIGINAL

A.16 Study 145: A 13-week double-blind, placebo-controlled, parallel, multicenter study of Teveten given in titrated doses of 600 mg or 1200 mg once daily in patients with isolated systolic hypertension (SitSBP ≥160 mmHg and sitDBP <90 mmHg).

A.16.1 Source documents

This review is based upon the amended protocol, dated 11 September 1998, dated amendments, a final study report dated 22 February 2000 (NDA volumes 1.60-1.92), and electronic datasets.

A.16.2 Investigators

The study was conducted at 42 centers in US, Mexico, France, and Netherlands.

A.16.3 Study dates

Enrollment in the double-blind trial was from 7 May 1998 to 6 July 1999.

A.16.4 Study design

The objective was a placebo-vs.-titrated eprosartan comparison of seated systolic pressure in subjects with isolated systolic hypertension.

Subjects were males or females of non-childbearing potential age 60 or older with seated systolic pressure >160 mmHg at the end of the run-in phase. Exclusion criteria were (1) malignant hypertension, (2) advanced retinopathy, (3) seSBP > 220 mmHg, (4) ventricular tachyarrhythmia requiring treatment, (5) evidence of MI or CVA within 90 days, (6) CHF requiring treatment, (7) angina requiring treatment, (8) .unstable diabetes mellitus, (9) clinically significant renal or hepatic disease, (10) alcohol or drug abuse, (11) other significant concomitant disease limiting participation, (12) drugs affecting blood pressure, chronic sympathomimetics, NSAIDs, MAO inhibitors, antidepressants, or phenothiazide, or (13) sensitivity to eprosartan or HCTZ.

Upon completion of a 3- to 5-week single-blind, placebo run-in period subjects were randomized to placebo or eprosartan 300 mg for 9 weeks. Study drug was administered once daily in the morning, with no specified relationship to food. This dose was withheld on study days and all blood pressure assessments were to be 22 to 24 hours from the previous dose. Subjects with systolic pressure >160 or <15 mmHg decrease could be titrated to eprosartan 1200 mg. After 9 weeks, subjects meeting blood pressure goals (systolic pressure <145 mmHg) or diastolic pressure <75 mmHg were discontinued. All remaining subjects received HCTZ 12.5 mg qd through week 13. The primary end point was change in seated systolic pressure at 9 weeks; at 124 subjects per arm, the trial was sized to detect with 90% power, a 7-mmHg treatment difference from placebo. Conventional safety monitoring was employed.

Lots used for the double-blind study were U96306 (eprosartan 300 mg), and U97273 (HCTZ).

There were no substantive amendments to the protocol.

A.16.5 Results

A.16.5.1 Conduct

A total of 437 subjects were screened, and 283 were randomized. Individual sites randomized 1 to 22 subjects. Two hundred fifty subjects completed.

Discontinuations from double-blind treatment are characterized in Table 24.

Table 24. Discontinuations (Study 145).

	Started monotherapy		Started HCTZ	
	Placebo N=135	Eprosartan N=148	Placebo N=89	Eprosartan N=83
Adverse event	8	1	1	1
Lack of effectiveness	5	1	0	0
Lost to follow-up	2	0	0	0
Protocol violation	1	3	0	1
Other	4	5	0	0
Total	22	10	1	2

Demographic characteristics of the four treatment groups were similar. Mean ages in both groups were 70, the proportion of males was 44 and 45%, the proportions of non-Caucasians were 32 and 33%.

At baseline, the seated diastolic pressure (means) were both 83 mmHg and seated systolic pressure means were 170 and 171 mmHg.

Two-thirds of subjects had previously been on antihypertensive drug therapy. The most common accompanying medical histories were retinopathy (25%), hyperlipidemia (20%), and osteoarthritis (19%).

A.16.5.2 Protocol violations

Eighty-three percent of randomized subjects had at least one protocol violation. They were vital signs outside 22-25 hours[42] from previous dose (76%), HCTZ use prior to week 9 (26%), antihypertensive drug use during run-in (15%), and use of chronic sympathomimetics or NSAIDs (13%).

A.16.5.3 Effectiveness

Four subjects (3 on combination withdrew after randomization but before the first blood pressure assessment, and are not included in the ITT-LOCF analyses. Results for the sponsor's analyses are shown in Table 25.

Table 25. Changes from baseline and placebo in vital signs at trough (Study 145)[43].

		Monotherapy		+HCTZ	
		Placebo N=130	Epro N=148	Placebo N=87	Epro N=81
Seated	SBP	-9.6±1.4	-18.0±1.1	-15.5±1.5	-21.9±1.8
	DBP	-0.5±0.5	-1.7±0.5	-1.2±0.7	-3.5±0.8
Standing	SBP	-7.8±1.5	-15.5±1.2	-15.8±1.5	-19.3±1.3
	DBP	-0.2±0.6	-2.1±0.6	-0.8±0.7	-3.2±0.9

The change in seated systolic pressure on monotherapy (primary end point) was statistically significant. Addition of HCTZ produced 3 to 4 mmHg decreases in systolic pressure among subjects randomized to eprosartan (and not meeting blood pressure goals on monotherapy).

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[42] Study report uses 22-25 hours. CRF says 22-24 hours. The nature of these violations could not be further characterized from the electronic data. Obviously the timing matters most for assessments not at end point, and, at end point, a late measurement would be preferable to an early one.

[43] Sponsor's analyses of mean effects.

Comparison of all available data at week 3 and study end point shows that the effects were substantially or fully apparent at this earliest assessment.

The sponsor's analysis of proportion of subjects responding systolic pressure <160 mmHg or decrease by 15 mmHg at week 9 on monotherapy was 32% on placebo, and 57% on eprosartan, a difference that was highly statistically significant.

The sponsor performed subgroup analyses of seated diastolic and systolic pressure by age and gender. The results were consistent in these subgroups.

A.16.5.4 Safety

Safety is reviewed in context of the full development program.

A.16.6 Summary

Eprosartan titrated between 600 and 1200 mg was effective at reducing systolic pressure in elderly subjects with isolated systolic hypertension. In subjects not adequately controlled on monotherapy, addition of HCTZ 12.5 mg resulted in further decreases in systolic pressure, more so in the placebo group. A forced titration scheme would have provided a more reliable quantitative estimate of the magnitude of effect produced by addition of HCTZ. The high proportion of protocol violations also makes these data difficult to interpret. The electronic datasets do not contain data characterizing the time of end point assessments relative to the previous dose of study drug.

APPEARS THIS WAY
ON ORIGINAL

A.17 Study 148: An 8-week, multicentre, double-blind, parallel group, placebo-controlled, factorial design study to compare oral eprosartan and hydrochlorothiazide given alone and in combination in patients with essential hypertension (DBP >95 and <114 mmHg).

A.17.1 Source documents

This review is based upon the protocol, dated 5 March 1998, a final study report dated 21 June 2000 (NDA volumes 1.93-1.127), and electronic datasets.

A.17.2 Investigators

The study was conducted at 44 centers in France, Belgium, Germany, and Netherlands.

A.17.3 Study dates

Enrollment in the double-blind trial was from 18 April 1998 to 20 October 1998.

A.17.4 Study design

The objective was to establish the effectiveness of eprosartan plus HCTZ..

Subjects were males or females of non-childbearing potential age 18 or older with seated diastolic pressure ≥95 mmHg and ≤114 mmHg at 3 consecutive run-in phase visits, with the difference between the highest and lowest visits being ≤8 mmHg. Exclusion criteria were (1) malignant hypertension, (2) advanced retinopathy, (3) seSBP > 200 mmHg, (4) ventricular tachyarrhythmia requiring treatment, (5) evidence of MI or CVA within 90 days, (6) CHF requiring treatment, (7) angina requiring treatment, (8) unstable diabetes mellitus, (9) clinically significant renal or hepatic disease, (10) alcohol or drug abuse, (11) other significant concomitant disease limiting participation, (12) drugs affecting blood pressure, chronic sympathomimetics, NSAIDs, MAO inhibitors, antidepressants, or phenothiazide, or (13) sensitivity to eprosartan or HCTZ.

Upon completion of a 3- to 5-week single-blind, placebo run-in period subjects were randomized to placebo, eprosartan 600 mg, HCTZ 12.5 mg, or the combination for 8 weeks, with visits every 2 weeks. Study drug was administered once daily in the morning, with no specified relationship to food. This dose was withheld on study days and all blood pressure assessments were to be 22 to 24 hours from the previous dose. The primary end point was change in seated diastolic pressure at trough at 8 weeks; at 110 subjects per arm, the trial was sized to detect with 90% power, a 3.5-mmHg pairwise treatment difference. Three comparison were planned: eprosartan vs. placebo, and combination vs. each component. Conventional safety monitoring was employed.

Lots used for the double-blind study were U96307 (eprosartan 300 mg), and U97273 (HCTZ 6.25 mg), and the combination (U97335).

There were no amendments to the protocol.

A.17.5 Results

A.17.5.1 Conduct

A total of 609 subjects were screened, and 473 were randomized. Individual sites randomized 1 to 76 subjects. Four hundred thirteen subjects completed.

Discontinuations from double-blind treatment are characterized in Table 26.

Table 26. Discontinuations (Study 148).

	Placebo N=122	HCTZ N=117	Eprosartan N=118	Combin N=116
Adverse event	4	7	2	3
Lack of effectiveness	4	2	2	0
Lost to follow-up	0	1	3	0
Protocol violation	8	4	3	4
Other	3	2	2	6
Total	19	16	12	13

Demographic characteristics of the four treatment groups were similar. Mean ages 58 to 60, the proportion of males was 41 to 53%, the proportion of non-Caucasians was 2 to 3%.

At baseline, the seated diastolic pressure (means) ranged from 101 to 102 mmHg and seated systolic pressure means were 162 to 163 mmHg.

Two-thirds of subjects had previously been on antihypertensive drug therapy. The most common accompanying medical histories were menopause (11%), hyperlipidemia (11%), and diabetes (10%).

A.17.5.2 Protocol violations

Fourteen subjects were mistakenly given randomized treatment during run-in and placebo during the double-blind period. Half of these were in the placebo group, so the violation was of no consequence. These subjects contributed to the analyses according to the actual treatment with which they began the double-blind period (not ITT), but their screening visit blood pressure was used to establish a baseline.

Eighty-four percent of randomized subjects had at least one protocol violation. They were vital signs outside 22-25 hours [44] from previous dose (76%), antihypertensive drug use during run-in (13%), vital signs not taken during morning (11%), and use of chronic sympathomimetics or NSAIDs (9%). The incidence of various protocol violations was similar in the 4 treatment groups.

A.17.5.3 Effectiveness

Nine subjects had no on-treatment assessments. Results for the sponsor's analyses are shown in Table 27.

Table 27. Changes from baseline in vital signs at trough (Study 148)[45].

	Placebo N=119	HCTZ N=116	Eprosartan N=117	Combin N=112
DBP	-6.9±0.8	-8.8±0.8	-9.0±0.9	-11.9±0.8
SBP	-7.4±1.2	-13.0±1.3	-11.0±1.7	-17.4±1.4

Treatment with eprosartan plus HCTZ produced statistically significantly [46] greater reduction in seated diastolic pressure than did either treatment alone (co-primary end

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[44] *Study report uses 22-25 hours. CRF says 22-24 hours. The nature of these violations could not be further characterized from the electronic data. Obviously the timing matters most for assessments not at end point, and, at end point, a late measurement would be preferable to an early one.*

[45] *Sponsor's analyses of mean effects.*

[46] *Sponsor's statistical analysis.*

points). Changes in systolic pressure were also nominally statistically significantly greater on combination treatment.

Comparison of all available data at week 2 and study end point shows that the effects were substantially or fully apparent at this earliest assessment.

The sponsor's analysis of proportion of subjects responding diastolic pressure <90 mmHg or decrease by 10 mmHg at study end point was 41% on placebo, 51% on HCTZ, 52% on eprosartan, and 65% on the combination.

The sponsor performed subgroup analyses of seated diastolic and systolic pressure by age, gender, prior antihypertensive treatment, and baseline diastolic pressure. The results were consistent in subgroups other than age. Subjects under the age of 65 had somewhat larger blood pressure reductions in response to HCTZ, eprosartan, and the combination, compared with subjects over the age of 65.

A.17.5.4 Safety

Safety is reviewed in context of the full development program.

A.17.6 Summary

Combination treatment with eprosartan 600 mg plus HCTZ 12.5 mg produced greater (placebo-subtracted) reductions in diastolic and systolic pressure than did either treatment alone.

A.18 Study 164: ABPM ancillary study of an 8-week, multicentre, double-blind, parallel group, placebo-controlled, factorial design study to compare oral eprosartan and hydrochlorothiazide given alone and in combination in patients with essential hypertension (DBP >95 and <114 mmHg).

A.18.1 Source documents

This review is based upon the protocol, dated 7 May 1998, and a final study report dated 8 August 2000 (NDA volumes 1.128, 1.128A-B).

A.18.2 Investigators

The study was conducted at 6 centers in France.

A.18.3 Study dates

Enrollment in the double-blind trial was from 18 April 1998 to 20 October 1998.

A.18.4 Study design

The objective was to establish, by ABPM, the effectiveness of eprosartan plus HCTZ..

This was a substudy of Study 148. Subjects were males or females of non-childbearing potential age 18 or older with seated diastolic pressure ≥95 mmHg and ≤114 mmHg at 3 consecutive run-in phase visits, with the difference between the highest and lowest visits being ≤8 mmHg. Exclusion criteria were (1) malignant hypertension, (2) advanced retinopathy, (3) seSBP > 200 mmHg, (4) ventricular tachyarrhythmia requiring treatment, (5) evidence of MI or CVA within 90 days, (6) CHF requiring treatment, (7) angina requiring treatment, (8) unstable diabetes mellitus, (9) clinically significant renal or hepatic disease, (10) alcohol or drug abuse, (11) other significant concomitant disease limiting participation, (12) drugs affecting blood pressure, chronic sympathomimetics, NSAIDs, MAO inhibitors, antidepressants, or phenothiazide, or (13) sensitivity to eprosartan or HCTZ.

Subjects underwent a 3- to 5-week single-blind, placebo run-in period with a 25-hour ABPM record collected at the end. Subjects were randomized to placebo, eprosartan 600 mg, HCTZ 12.5 mg, or the combination for 8 weeks, with visits every 2 weeks, with a final ABPM beginning after the last dose of study drug. Study drug was administered once daily in the morning, with no specified relationship to food. This dose was withheld on study days and all blood pressure assessments were to be 22 to 24 hours from the previous dose. The exact primary end point for the ABPM study was not described. Conventional safety monitoring was employed.

ABPM data were collected every 15 minutes between 0700 and 2100 hours, and every 30 minutes from 2200 to 0600 hours. Valid data were limited to 60-250/40-150 (pulse pressure 20-150 mmHg, and heart rate 20 to 200 bpm.

Lots used for the double-blind study were U96307 (eprosartan 300 mg), and U97273 (HCTZ 6.25 mg), and the combination (U97335).

There were no amendments to the protocol.

A.18.5 Results

A.18.5.1 Conduct

A total of 120 subjects were randomized, of whom 107 completed study and 79 had 2 validated ABPMs.

Demographic characteristics, past medical history, and baseline characteristics of the four treatment groups were similar.

A.18.5.2 Effectiveness

Hourly mean effects (group means) on systolic, diastolic, and mean blood pressure are shown in Figure 4 below.

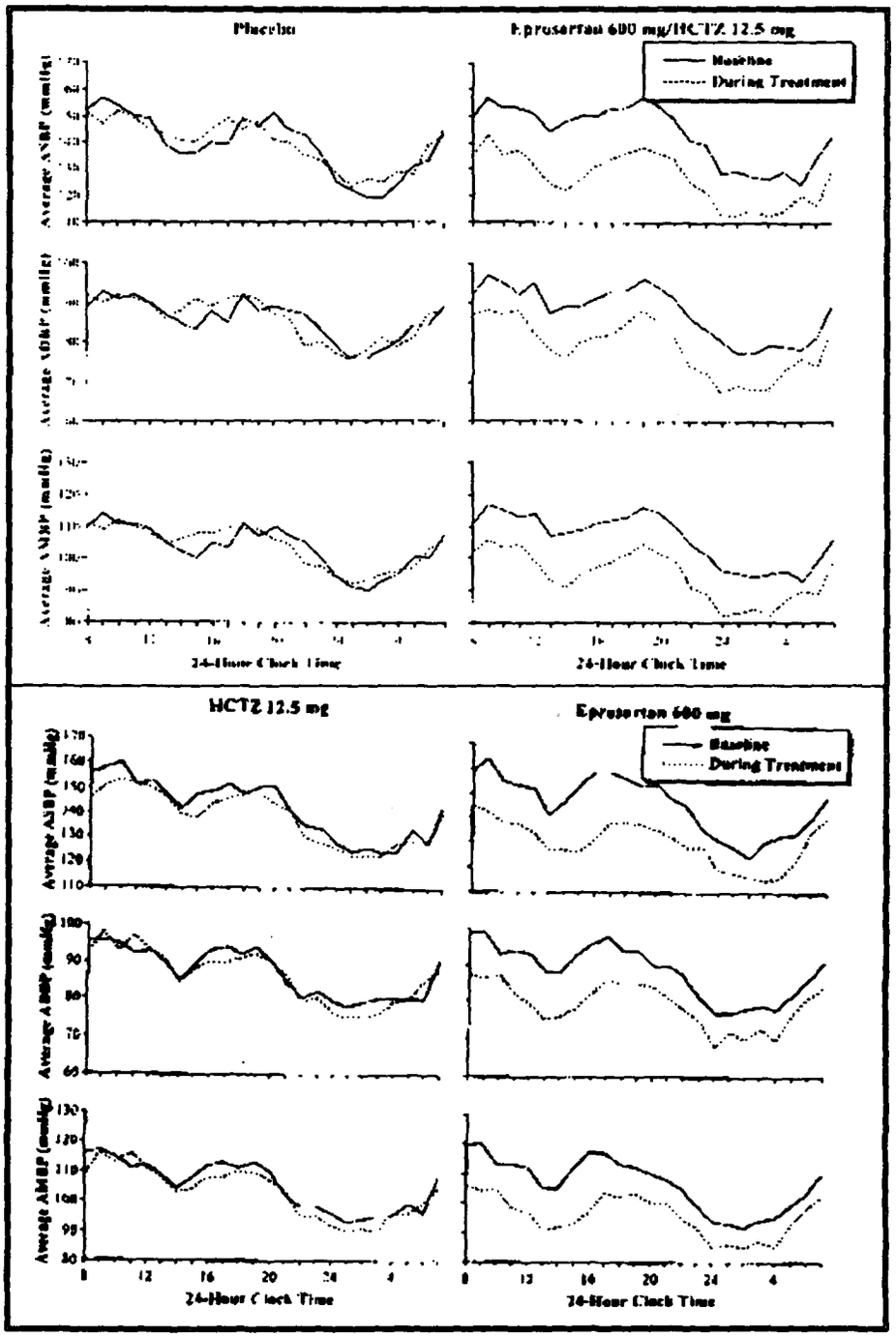

Figure 4. ABPM data for placebo, HCTZ, eprosartan, and combination groups (Study 164).

Figure from sponsor's final study report. Rows are for ambulatory diastolic, systolic, and mean blood pressure. Curves are for baseline and after 8 weeks of treatment.

Since there is no apparent placebo effect, subtraction from the placebo group can only increase the noise. Figure 5 shows the baseline-subtracted data for systolic and diastolic pressure in the three active treatment groups.

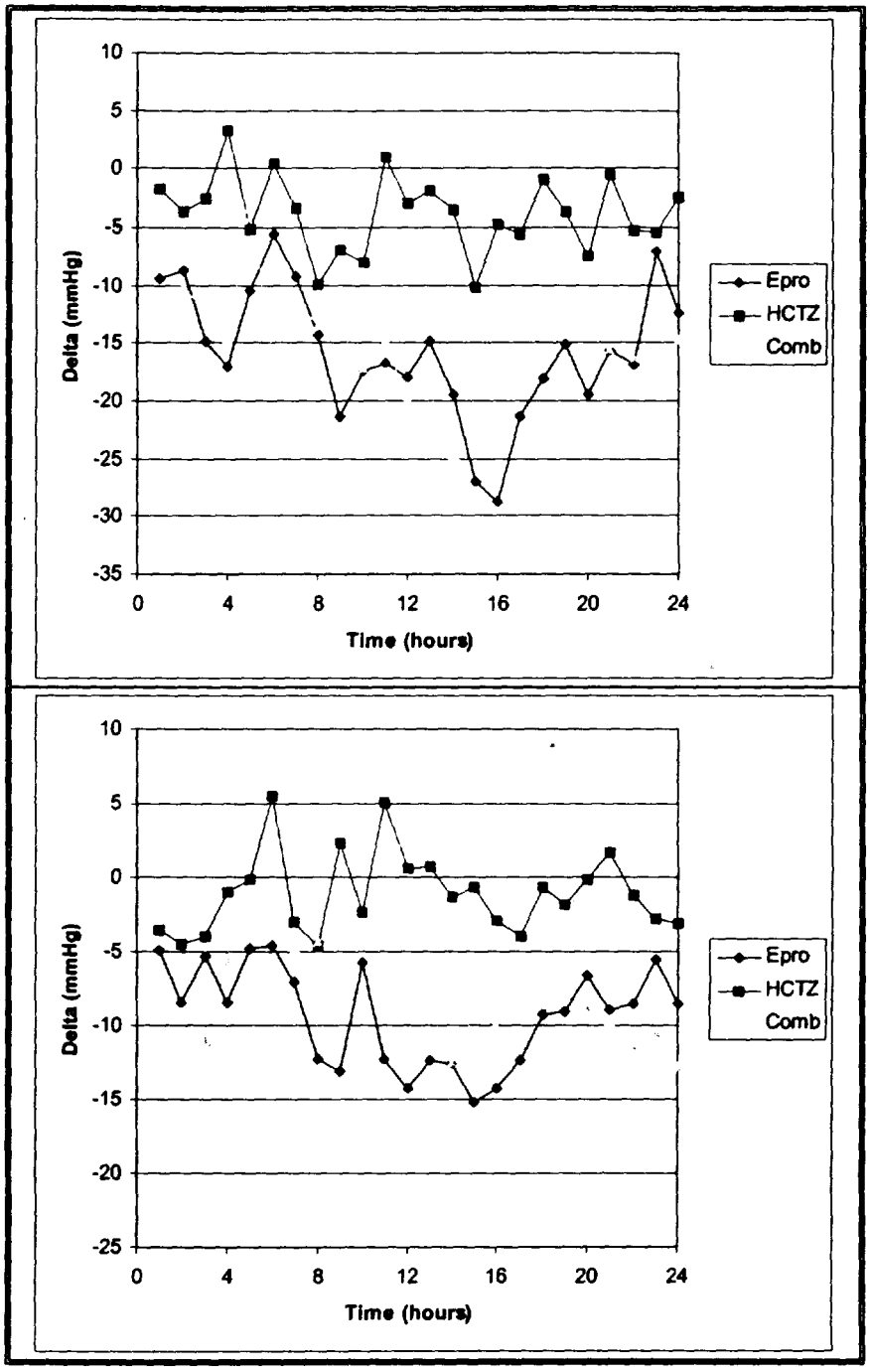

Figure 5. Baseline-subtracted systolic (top) and diastolic (bottom) pressures by time (Study 164).

Data were differences in hourly means between the on-treatment and baseline ABPMs for subjects who had two ABPM sessions. Hourly means for each subject and session were provided by the sponsor. Analysis by reviewer.

There is no detectable placebo effect and no detectable effect of HCTZ alone. Blood pressure decreases similarly following treatment with eprosartan or eprosartan plus HCTZ. The reduction is manifest throughout the inter-dosing interval, but appears to taper off some towards the end of that interval.

A.18.5.3 Safety

Safety is reviewed in context of the full development program.

A.18.6 Summary

Combination treatment with eprosartan 600 mg plus HCTZ 12.5 mg produced greater (placebo-subtracted) reductions in diastolic and systolic pressure than did HCTZ treatment alone, but a difference from eprosartan alone was not shown. ABPM showed that the antihypertensive effect was manifest throughout the interdosing interval, but appeared to taper off towards the end of that interval.

APPEARS THIS WAY
ON ORIGINAL

20 pages redacted from this section of the approval package consisted of draft labeling