CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-268

Medical Review(s)

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Draft Clinical Review

NDA: 21-268

Sponsor: Unimed Pharmaceuticals Inc (Solvay)

Submission: (30 August 2000) Request for marketing approval for a combination of eprosartan and hydrochlorothiazide, for the treatment of essential hypertension.

Review date: June 25, 2001

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Summary: Eprosartan and hydrochlorothiazide (HCTZ) appear to be safe and effective when used together for the treatment of mild to moderate essential hypertension. The proposed formulations adequately cover the useful dose range of each product for once-daily use, but final approval should be withheld until there are scored tablets to permit twice-daily dosing.

Distribution: NDA 21-268
HFD-110/Project Manager
HFD-110/Stockbridge

Table of contents

List of tables

List of figures

1 Materials utilized in the review

1.1 Materials from NDA/ IND

No reference was made to the IND during the course of this review.

Materials from the NDA that were utilized for this review are listed in the table below.

Submission	Vol.	Description
30 August 2000	1.1, 1.32-1.146	Original NDA submission
19 October 2000	2.1	Response to reviewer's request
19 December 2000	2.1	120-day safety update
23 March 2001	2.1	Proposed labeling

In addition to the documents, the electronic data supplied by the sponsor were used in this review.

1.2 Related reviews or consults

Specific reference is made to the clinical reviews for NDA 20-738 (Eprosartan for hypertension). Reviews of individual studies that were reviewed with NDA 20-738 but which are pertinent to eprosartan/HCTZ are reproduced from the earlier NDA.

The Statistical Review of Dr. John Lawrence, dated 21 Nov 2000, was consulted. Its descriptions of the protocols and results of studies 014, 016, 047, 061, 088, 120, 145, and 148 differ in no substantive fashion from what is in this review.

Reference is also made to other primary reviews of NDA 21-268.

1.3 Other resources

Not applicable.

APPEARS THIS WAY
ON ORIGINAL

2 Background

2.1 Indication

The proposed indication for eprosartan/HCTZ is for the treatment of essential hypertension:

> *"TEVETEN [redacted] is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensives such as calcium channel blockers. This fixed dose combination is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION)."*

2.2 Information from pharmacologically related agents

There are three other angiotensin II receptor antagonist-diuretic combinations approved for the treatment of hypertension.

2.3 Administrative history

This development program was managed under IND {redacted} (opened 22 July 1992). The Division last met with the sponsor in February 2000. The development program was uncomplicated.

The combination of eprosartan and HCTZ is not approved for marketing in any country.

The need for pediatric studies has been waived because this is a combination product not thought to be useful in children and because of the difficulties of doing such studies in children.

The sponsor provided financial disclosure information for study 145 only.

2.4 Proposed labeling

Labeling is reviewed fully in section 9 (page 17).

2.5 Other background information

Not applicable.

APPEARS THIS WAY
ON ORIGINAL

3 Chemistry, manufacturing, and controls

3.1 Basis of review

This section is based upon the review by Dr. Ramsharan Mittal, dated 9 April 2001.

3.2 Summary

At the time of this review, the following issues remain open:

- EER for HCTZ
- CMC for the tablet containing eprosartan 600 mg plus HCTZ 25 mg.
- Methods validation for the 600/25 tablet
- Trade name of [redacted] or TEVETEN HCT

CMC labeling comments for the package insert have been included in section 9 of this review.

Various other minor deficiencies and queries of the sponsor are detailed in the CMC review, but support for the 600/25 tablet is the only crucial issue.

APPEARS THIS WAY
ON ORIGINAL

4 Animal pharmacology

4.1 Basis of review

This section is based on the draft review and evaluation of pharmacology and toxicology data by Dr. Proakis, dated 14 March 2001.

4.2 Summary of significant findings

4.2.1 Acute toxicology

Single-dose toxicity was studied in dogs with eprosartan 1000 mg/kg and HCTZ 0.3 to 2 mg/kg, without mortality.

4.2.2 Chronic toxicology

Repeated-dose toxicity was studied in mice over 3 months at eprosartan 300 or 2000 mg/kg/day and HCTZ 9 or 62 mg/kg/day. There was no mortality considered related to treatment and no gross or histological findings (not even juxtaglomerular hyperplasia).

Repeated-dose toxicity was studied in dogs over 1 month at eprosartan 100 or 1000 mg/kg/day and HCTZ 3 and 31 mg/kg/day. Two animals were sacrificed with renal failure at the higher dose combination. Surviving animals had findings of renal tubular degeneration, upper gastrointestinal inflammation, and atrophied thymus.

A three-month toxicity study in dogs was performed with eprosartan 1000 mg/kg/day and HCTZ 0.3 or 1 mg/kg/day. There was no treatment-related mortality. Some animals had small reductions in hematocrit or hemoglobin. There were no gross or histological findings.

4.2.3 Reproductive toxicology

Eprosartan 3 or 10 mg/kg/day and HCTZ 1 or 3 mg/kg/day were administered late in gestation to rabbits. There was no mortality and no evident toxicity. There were more resorptions in the high dose group, but no malformations attributed to drug.

Eprosartan 10 or 30 mg/kg/day and HCTZ 3 or 10 mg/kg/day were administered in mid gestation in rabbits. There was one unexplained death, but no effects on litters.

4.2.4 Genotoxicity

The Ames bacterial mutagenicity test, performed with or without S9, was negative.

A chromosomal aberration test in cultured human lymphocytes was positive at cytotoxic concentrations in the presence of S9, a finding not considered clinically significant.

The mouse micronucleus assay was considered negative.

4.3 Labeling

The pharmacologist considered these studies compatible with approval. Recommended changes to the description of these findings in labeling are incorporated in the review in section 9.

5 Description of clinical data sources

5.1 Primary source data

5.1.1 Study type and design

The eprosartan/HCTZ development program consists of 17 studies, all complete at the time of NDA filing. Basic features of fixed-dose combination studies are shown in Table 1. These studies are adequate to determine if the combination of eprosartan and HCTZ produces greater antihypertensive effects than do the individual components.

Table 1. Fixed-dose combination studies.

Study	Page	Design[1]	N[2]	Dosing[3]	Population	Comment
016	48	DB, ||el, PC	104/156	50/25 qd 100/25 qd	Mild-moderate	Eprosartan produced greater reduction in seated diastolic pressure at 3 weeks than did placebo in subjects hypertensive on HCTZ alone. Doses not distinguishable.
061	71	DB, ||el, PC	256/380	400/12.5 qd 400/25 qd	Mild-moderate	Both active arms produced significant reductions in sitting DBP, with HCTZ 25 > 12.5.
088	86	DB, ||el, PC	152/309	600 qd 600/12.5 qd	Mild-moderate	HCTZ more effective than placebo in reducing DBP in subjects not controlled on eprosartan alone.
164	101	DB, ||el, PC	60/120	600/0 qd 0/12.5 qd 600/12.5 qd	Mild-moderate	ABPM substudy of #148. Combination more effective than placebo in reducing DBP. Effect tapers off at end of daily dosing interval.

Studies of HCTZ added to subjects not adequately treated by eprosartan alone are described in Table 2. These studies are supportive of the effectiveness of the combination over the individual components.

Table 2. Studies of HCTZ added to eprosartan non-responders.

Study	Page	Design[4]	N[5]	Dosing[6]	Population	Comment
014	40	DB, ||el, AC	218/436	200 bid 300 bid 300/? bid	Mild-moderate	Comparison with enalapril for cough. HCTZ allowed last 14 weeks. Useful for safety only.
047	57	DB, ||el, AC	59/118	200 bid 400 bid 400/?	Severe; 115<DBP< 125	Comparison with enalapril. Useful for safety only.
120	91	DB, ||el, AC	180/360	600-1200 qd 1200/25 qd	Severe systolic	Comparison with enalapril. Useful for safety only.
145	95	DB, ||el, PC	83/172	300-1200 qd any/12.5	Systolic	HCTZ more effective than placebo in reducing SBP in subjects not adequately controlled on eprosartan alone.

Open-label studies that allowed treatment with eprosartan and HCTZ are described in Table 3. These studies provide additional safety data. None of these studies has a late phase placebo-controlled withdrawal.

---

[1] *DB=double-blind, ||el=parallel, PC=placebo-controlled, AC=active control, OL=open-label, XO=cross-over*

[2] *number on eprosartan / total*

[3] *dose of eprosartan / dose of HCTZ*

[4] *DB=double-blind, ||el=parallel, PC=placebo-controlled, AC=active control, OL=open-label, XO=cross-over*

[5] *number on eprosartan / total*

[6] *dose of eprosartan / dose of HCTZ*

Table 3. Open-label follow-on studies of eprosartan/HCTZ.

Study	Page	Design[7]	N[8]	Dosing[9]	Population	Comment
039	54	OL	403/403	100 bid 200 bid 300 bid 300/25 bid	Mild-moderate	Only 37% of subjects on combination. Of interest for safety only.
040	56	OL	342/342	100 bid 200 bid 300 bid 300/25 bid	Mild-moderate	Only 17% of subjects on combination. Of interest for safety only.
050	67	OL	706/706	400-800 qd 600/12.5 qd 600/25 qd 800/12.5 qd 800/25 qd	Mild-moderate	Of interest for safety only.
052	69	OL	136/136	400-800 qd 800/12.5 qd 800/25 qd	Mild-moderate	Of interest for safety only.
105	89	OL	232/232	400/25 qd	Mild-moderate	No control. Of interest for safety only.
137	93	OL	121/121	600-1200 qd 1200/25 qd	Severe systolic	Only 31% of subjects on combination. Of interest for safety only.

Studies of the pharmacokinetics of eprosartan and HCTZ in combination are described in Table 4.

Table 4. Studies of pharmacokinetics.

Study	Page	Design[10]	N[11]	Dosing[12]	Population	Comment
077	80	OL, XO	16/16	2 x 400/0 2 x 0/12.5 2 x 400/12.5	Normal	High fat meal reduced peak eprosartan and HCTZ levels, but kept AUC's similar to fasted state.
078	82	OL, XO	72/72	300/6.25 x 2 600/12.5	Normal	Plasma profiles of two formulations were similar.
079	84	OL, XO	18/18	2 x 400/0 2 x 0/12.5 2 x 400/12.5	Normal	Plasma profiles of two formulations were similar.

5.1.2 Financial disclosure

The sponsor provided individual financial disclosure forms for most of the investigators in Study 145. These data do not raise questions about the interpretation of this study.

5.1.3 Subject enumeration and exposure

Exposure in controlled studies of mild-moderate hypertension is summarized in Table 5.

---

[7] DB=double-blind, ||el=parallel, PC=placebo-controlled, AC=active control, OL=open-label, XO=cross-over

[8] number on eprosartan / total

[9] dose of eprosartan / dose of HCTZ

[10] DB=double-blind, ||el=parallel, PC=placebo-controlled, AC=active control, OL=open-label, XO=cross-over

[11] number on eprosartan / total

[12] dose of eprosartan / dose of HCTZ

Table 5. Exposure to eprosartan/HCTZ in controlled studies of mild-moderate hypertension[13].

	<600/12.5	<600/25	600/25
N	128	232	268
Mean (days)	55	43	19
Subject-years	19	27	40

Exposure in supportive studies, in which HCTZ was added to eprosartan, is described in Table 6.

Table 6. Exposure to eprosartan/HCTZ in supportive studies.[14]

	Mild-moderate Study 014		Severe Study 047	Systolic Study 145		Severe systolic Study 120
	600/12.5	600/25	600/25	600/12.5	>600/12.5	>600/25
N	29	46	23	23	60	94
Mean (days)	56	55	15	28	27	24
Subject-years	4	7	<1	2	4	6

Exposure in open-label studies is summarized in Table 7.

Table 7. Exposure to eprosartan/HCTZ in open-label studies of hypertensive subjects.

	600/12.5	>600/12.5	<600/25	600/25	>600/25
N	30	75	232	263	290
Mean (days)	568	579	323	554	459
Subject-years	47	119	205	399	365

Including studies of pharmacokinetics in normal volunteers, the sponsor calculated 422 subjects exposed to eprosartan/HCTZ 600/12.5 mg for a total of 88 subject-years, and 289 subjects exposed to 600/25 mg for a total of 351 subject-years.

The 120-day safety update provided little additional information.

5.1.4 Demographics

Demographic characteristics of the subjects in controlled studies are described in Table 8.

Table 8. Demographics of subjects receiving eprosartan/HCTZ in controlled studies.

	<600/12.5 N=128	<600/25 N=232	600/12.5 N=268
Male (%)	52	63	50
Age >65 (%)	13	15	30
Caucasian	84	79	98
Black	9	14	2

Baseline diastolic pressure was <105 mmHg in 81% of subjects in controlled studies. Twenty-six percent of subjects in these trials were newly treated for hypertension.

---

[13] *Studies 016, 061, 148, and 088. Data from sponsor's Integrated Summary of Safety.*

[14] *Data from sponsor's Integrated Summary of Safety.*

5.2 Secondary source data

5.2.1 Other studies

Some studies of eprosartan and HCTZ were conducted under and reviewed with NDA 20-738. The primary medical review for NDA 20-738 is referenced here. There are no other known studies with eprosartan and HCTZ.

5.2.2 Post-marketing experience

There is no post-marketing experience with eprosartan and HCTZ.

5.2.3 Literature

A MedLine search was performed to look for clinical trials of eprosartan and HCTZ.

These publications all refer to Study 014:

Elliott WJ. 1999. Double-blind comparison of eprosartan and enalapril on cough and blood pressure in unselected hypertensive patients. *J Hum Hypertens* **13(6):**413-417.

Levine B. 1999. Effect of eprosartan and enalapril in the treatment of black hypertensive patients: subgroup analysis of a 26-week, double-blind, multicentre study. *Curr Med Res Opin* **15(1):**25-32.

Gavras I, Gavras H. 1999. Effects of eprosartan versus enalapril in hypertensive patients on the renin-angiotensin-aldosterone system and safety parameters: results from a 26-week, double-blind, multicentre study. *Curr Med Res Opin* **15(1):**15-24.

Argenziano L, Trimarco B. 1999. Effect of eprosartan and enalapril in the treatment of elderly hypertensive patients: subgroup analysis of a 26-week, double-blind, multicentre study. *Curr Med Res Opin* **15(1):**9-14.

This publication refers to Study 047.

Sega R. 1999. Efficacy and safety of eprosartan in severe hypertension. *Blood Press* **8(2):**114-121.

No publications were found that did not correspond with identified studies.

5.3 Adequacy of clinical experience

The clinical experience amounts to about 440 subject-years of experience on the targeted doses (88 on 600/12.5 and 351 on 600/25) plus about 750 subject-years on other dose levels (a substantial fraction of which is >600/25). From the "rule of three", the data from 1200 subject-years of experience gives 95% confidence one has not missed a safety hazard occurring at a rate of 1 event per 400 subject-years. Since the presumed benefit of antihypertensive treatment is about 1 event prevented per 800 patient-years of exposure, these data are not, by themselves, adequate to ensure a net benefit.

It is not unreasonable, however, to 'borrow' enough about what is known of the safety of these drugs by themselves to make up the difference.

5.4 Data quality and completeness

Case report forms were provided for all subjects who died or were withdrawn for medical reasons. A spot-check comparing values in the CRF with the sponsor's electronic data turned up no problems.

6 Clinical pharmacology and biopharmaceutics

This section is based upon the review of clinical pharmacology and biopharmaceutics by Dr. Dorantes, dated 4 June 2001. Three of the studies she reviewed (077, 078, and 079) are described in the appendix to this clinical review. The final study (S1711006; "A randomized two-period, cross-over study to compare the bioavailability of one combination tablet of eprosartan 600 mg / HCTZ 25 mg relative to the combination of one 600-mg eprosartan tablet and one 25-mg HCTZ tablet in healthy male and female volunteers") was only reviewed by Dr. Dorantes.

The following comments are made:

- The to-be-marketed formulations of eprosartan/HCTZ 600/12.5 and 600/25 are not bioequivalent to the individual components, with respect to Cmax (about 15% higher in the 600/12.5 combination and 15% lower in the 600/25 combination). The clinical significance of this observation is minimal.
- The proposed dissolution specifications should be changed to not less than ( )% for eprosartan and HCTZ at 30 minutes. Further dissolution data are requested, and these may lead to changes in the recommendation for dissolution specifications at a later date.

There are no comments on labeling.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

7 Integrated review of effectiveness

7.1 Mild to moderate diastolic hypertension

There were 4 studies whose designs were adequate to assess the effectiveness of eprosartan and HCTZ in combination in the treatment of mild to moderate essential hypertension.

Study 016[15] was a randomized, double-blind, parallel study in which subjects with mild to moderate hypertension who were inadequately controlled on HCTZ 25 mg alone were randomized to placebo, eprosartan 50 mg bid, or eprosartan 100 mg bid (N=51-53 per group) for 4 weeks. Neither active group was distinguishable from placebo (mean reductions in placebo-subtracted diastolic pressure of 3 mmHg in both groups).

Study 061[16] was a randomized, double-blind, parallel study in which subjects with mild to moderate essential hypertension were randomized to placebo, eprosartan 400 mg plus HCTZ 12.5 mg, or eprosartan 400 mg plus HCTZ 25 mg (N=124-128 per group) and followed for 8 weeks. Baseline- and placebo-subtracted blood pressure reductions (all highly statistically significant) were -8.6/-4.4 on 400/12.5 and -10.9/-6.9 on 400/25. However, this trial design does not demonstrate a contribution of eprosartan to the observed antihypertensive effects.

Study 088[17] was a randomized, double-blind, parallel study in which subjects with mild to moderate essential hypertension on eprosartan 600 mg qd were randomized to placebo or HCTZ 12.5 mg (N=149-156 per group) for 8 weeks. The baseline- and placebo-subtracted reduction in blood pressure was -3.4/-2.8 mmHg (highly statistically significant). However, this trial design does not demonstrate a contribution of eprosartan to the observed antihypertensive effects.

Study 148[18] was a randomized, double-blind, parallel study in which subjects with mild to moderate essential hypertension were randomized placebo, eprosartan 600 mg qd, HCTZ 12.5 mg qd, or the combination (N=112-119 per group) with follow-up at 8 weeks. The baseline- and placebo-subtracted reductions in blood pressure are shown in Table 9.

Table 9. Baseline- and placebo-subtracted changes in blood pressure (Study 148).

		Eprosartan	
		0	600
HCTZ	0	—	-3.6/-2.1
	12.5	-5.6/-1.9	-10.0/-5.0

The primary end points in Study 148 were the monotherapy DBP differences from placebo; these were statistically significant. Other differences for systolic pressure and

---

[15] *"Study 016: A 4-week, double-blind, parallel, placebo-controlled, multicenter trial of oral eprosartan added to hydrochlorothiazide therapy in patients with essential hypertension (DBP >95 and <114 mmHg).", described on page 48.*

[16] *"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).", described on page 71.*

[17] *"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).", described on page 86.*

[18] *"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).", described on page 98.*

the combination group's systolic and diastolic pressures were all nominally significantly different from placebo. This was the only study structurally appropriate to demonstrate a contribution of both eprosartan and HCTZ on blood pressure in subjects with mild to moderate diastolic hypertension; both components did appear to contribute.

Study 164[19] was an ABPM substudy of Study 148. One hundred and twenty subjects were randomized to placebo, HCTZ 12.5 mg, eprosartan 600 mg, or the combination of HCTZ and eprosartan and were followed with 24-hour ABPMs at baseline and at 8 weeks. Seventy-nine subjects had both ABPM assessments. Results showed no effect of HCTZ alone and an effect of eprosartan alone that was indistinguishable from the combination of eprosartan and HCTZ. The effects of eprosartan and eprosartan plus HCTZ were diminished toward the end of the interdosing interval.

7.2 Severe diastolic hypertension

There was one controlled study (047[20]) in subjects with severe diastolic hypertension (115 < DBP < 125 mmHg). Study 047 was a randomized, parallel study in which subjects were randomized to eprosartan (titrated 200-400 mg bid) or enalapril (titrated 10 to 40 mg qd) after stratification for baseline use of thiazide. This trial did not demonstrate a statistically significant effect on its primary end point (between group change in DBP), and the thiazide subgroup was not analyzed as part of the review of NDA 20-738.

7.3 Systolic hypertension

There were two controlled studies in subjects with systolic hypertension.

Study 120[21] enrolled subjects with blood pressure >180/90 or >160/90 mmHg treated, and randomized them to enalapril (titrated 10 to 40 mg) or eprosartan (titrated 600 to 1200 mg) for 12 weeks. HCTZ 25 mg could be added as needed. The design does not permit assessment of the additive effects of eprosartan and HCTZ.

Study 145[22] was a randomized, double-blind, parallel study of subjects with BP >160/<90 mmHg, who were randomized to placebo or eprosartan 600-1200 mg qd. After 9 weeks, subjects with SBP <145 or DBP < 75 mmHg were discontinued. The remainder all received HCTZ 12.5 mg. This design does not demonstrate an effect of HCTZ added to eprosartan, because subjects were not randomized to placebo or HCTZ.

7.4 Subgroups

For the three successful studies of mild-to-moderate essential hypertension, the distribution of subjects by age, gender, and race are shown in Table 10.

---

[19] *"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)."*, *described on page 101.*

[20] *"Study 047: A 10-week, double-blind, multicenter, comparison of oral eprosartan and enalapril in patients with severe hypertension (DBP >115 and <125 mmHg)."*, *described on page 57.*

[21] *"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."*, *described on page 91.*

[22] *"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)."*, *described on page 95.*

Table 10. Subgroups in studies 061, 088, and 148.

		Age		Sex		Race		
		<65	>65	M	F	Cauc	Black	Other
N	061	310	70	214	166	318	39	23
	088	228	81	162	147	301	5	3
	148	318	155	223	250	461	8	4
Comparability [23]	061	Similar		Similar		Too few non-Caucasians to assess		
	088	>		>				
	148	>		Similar				

7.5 Summary

Among studies of mild-to-moderate essential hypertension, 2 studies (061, 088) demonstrate that HCTZ 12.5 mg reduces blood pressure when used with a background of eprosartan 400 or 800 mg. A study intended to show that eprosartan works with a background of HCTZ 25 mg failed, but the dose of eprosartan was probably too low (100 or 200 mg/day). There is one 2x2 factorial study (148) demonstrating that the effects of eprosartan plus HCTZ are greater than those of HCTZ 12.5 mg or eprosartan 600 mg alone, and that both monotherapies are better than placebo. Together these studies constitute compelling evidence of the effectiveness of the combination of eprosartan and HCTZ in the treatment of mild-to-moderate essential hypertension. Effects in subgroups are best described as inconclusive.

None of the studies in severe diastolic hypertension or systolic hypertension had designs appropriate to assess the use of the combination of eprosartan and HCTZ.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

[23] *Reviewer's assessment based on the sponsor's analyses of treatment effects (Table 10.1 of Integrated Summary of Efficacy).*

8 Integrated review of safety

8.1 Methodology

8.1.1 Mortality

The sponsor enumerated deaths in all treatment groups of the controlled and long-term, open-label phases of the development program. Case report forms for these subjects were provided and reviewed to assess potential relatedness to study drug.

8.1.2 Withdrawals

Withdrawals for non-fatal and non-serious events were enumerated by study. Reasons for withdrawal were sought in case report forms for subjects who withdrew for medical causes.

8.1.3 Adverse events

Serious adverse events were evaluated for possible relationship to study drug, using case report forms where available.

Common adverse events were compiled across controlled studies and during open-label phases.

Electronic datasets were not provided, so any compilation shown is based upon the sponsor's analyses or the case report forms.

8.1.4 Laboratory findings

The sponsor identified laboratory values of potential clinical concern as shown in Table 11.

Table 11. Criteria for identification of laboratory abnormalities of clinical concern.

		Lower	Upper
Hematology	Hemoglobin	<80% LLN	>120% ULN
	WBC	<3000/mm^3	>20000/mm^3
	Neutrophils	<1500/mm^3	—
	Eosinophils	—	>250% ULN
	Platelets	<100/nL	>750/nL
Chemistry	ASAT	—	>350% ULN
	ALAT	—	>350% ULN
	Alk phosphatase	—	>350% ULN
	Fasting glucose	<60 mg/dL	>130 mg/dL
	Creatinine	—	>250% ULN
	BUN	—	>50 mg/dL
	Potassium	<3 mM	>5.5 mM
	Sodium	<130 mM	>150 mM

8.1.5 ECGs

ECGs were performed at baseline and at the end of treatment in most controlled studies. Follow-up ECGs were performed at investigators' discretion. The sponsor's criteria for identifying abnormalities on ECG parameters were PR interval >200 ms, QRS >110 ms, and QTc >430 ms.

8.1.6 Subgroups

The sponsor performed analyses of adverse events by age, sex, race, and baseline diastolic pressure.

Only 21% of subjects were age >65, only 8% were non-Caucasian, and 19% were 'moderate' hypertension, making these subgroups unlikely to manifest safety signals had one been present. The distribution of subjects by sex were more even (45% female).

8.1.7 Safety update

The sponsor's 120-day safety update mentions 2 ongoing open-label studies. At the time of reporting, Study [redacted] had 768 subjects on eprosartan monotherapy and 268 subjects on eprosartan plus HCTZ, almost all of whom were on eprosartan 1200 mg plus HCTZ 25 mg, a dose for which there are no data supporting effectiveness. Study [redacted] is a still-blinded bioavailability study in normal volunteers; a few non-serious adverse events are reported. Therefore, the results in this review omit the data from the 120-day update.

8.2 Results

8.2.1 Deaths

The sponsor reported no deaths among normal volunteers, subjects in controlled studies of mild-to-moderate hypertension, isolated systolic hypertension, or severe systolic hypertension.

Deaths in the open-label studies are described in Table 12. The sponsor reported several deaths more than 30 days from the last dose of study drug, but these are not described here.

Table 12. Deaths within 30 days of treatment.

Epro/HCTZ	Study	Subject	Description
200/0	040	017.414.00145	88-year old male with history of ischemic cardiomyopathy, atrial fibrillation, and 2 cerebrovascular accidents had sudden death (possible myocardial infarction) after 161 days.
	040	017.414.00198	84-year old female had sudden death after 316 days.
400/0	040	017.414.00149	77-year old female had sudden death after 243 days.
	040	047.433.00551	73-year old female died from cerebrovascular accident after 432 days, 1 day after the last dose.
	050	011.011.00578	45-year old male died from pancytopenia attributed to chemotherapy for acute lymphocytic leukemia after 216 days, 19 days after the last dose. (CRFs contain no clue to support ALL diagnosis or that subject died.)
	050	049.032.03639	43-year old male died from hemorrhagic gastric ulcer after 39 days. (Death not described on CRFs.)
	050	049.067.03682	74-year old female died with myocardial infarction after 23 days, 1 day after last dose. (Death not described on CRFs.)
	050	013.621.00261	70-year old male with history of diabetes and mitral insufficiency died with suspected myocardial infarction after 78 days.
600/0	040	017.311.00079	79-year old female died with cerebrovascular accident after 74 days, 24 days after last dose.
800/0	052	013.527.00253	52-year old male had apparent sudden death after 53 days.
	137	137.032.01932	66-year old male died with cerebrovascular accident on day 193, 26 days after last dose. (CRFs not provided.)
400/25	105	061.571.00463	67-year old male died with lung cancer after 372 days.
600/25	039	016.002.00085	72-year old male died of unknown cause on day 158, 22 days after last dose. Subject had abdominal carcinomatosis.
	050	011.001.00638	36-year old male died with probably pulmonary embolus associated with acute thrombophlebitis, after 190 days, 1 day after the last dose.

None of these events is unusual in the population studied. There is little likelihood that these events were related to eprosartan or to HCTZ.

8.2.2 Withdrawals

Reasons for discontinuation for controlled trials are summarized by dose in Table 13.

Table 13. Causes for withdrawal by dose (Studies 061, 088, 148).

	Eprosartan/HCTZ dose						
	0/0 N=246	0/12.5 N=117	400/0 N=118	400/12.5 N=128	400/25 N=128	600/0 N=157	600/12.5 N=116
Adverse event	5	7	2	3	6	6	3
Lack of efficacy	9	2	2	1	3	2	0
Loss to follow-up	0	1	3	2	0	0	0
Protocol violation	9	4	3	2	1	2	4
Other	6	2	2	0	0	1	6

There does not appear to be a treatment-related pattern to withdrawals.

Fourteen subjects discontinued from eprosartan plus HCTZ in controlled studies of mild-to-moderate hypertension with events that were neither fatal nor serious. The following were reasons for discontinuation that were reported by more than 2 subjects: headache (N=4), nausea (3), and dizziness (3). Headache and dizziness were also among the most common reasons for discontinuing from placebo.

Twenty subjects discontinued for adverse events from open-label studies of mild-to-moderate essential hypertension. No associated adverse event was reported by more than 2 subjects.

8.2.3 Adverse events

8.2.3.1 Serious adverse events

Controlled studies. Eight subjects reported serious adverse events on eprosartan plus HCTZ during placebo-controlled studies of mild-to-moderate hypertension. No event was reported by more than one subject, nor were any events particularly rare.

Open-label studies. The following serious adverse events were reported by more than 2 subjects on eprosartan plus HCTZ in long-term, open-label studies: injury (n=15), arthritis (4), carcinoma (3), cellulitis (3), cerebrovascular disorder (3), and chest pain (3).

8.2.3.2 Common adverse events

Controlled studies. No electronic datasets are available. The sponsor's analysis of common adverse events in the controlled trials did not give the incidence of events in the placebo group.

Of 628 subjects on eprosartan plus HCTZ in controlled trials in mild-to-moderate essential hypertension, 303 (48%) reported at least one adverse event. The most common adverse events (>3%), without regard to attributed causality, were headache (4.5%), dizziness (4.1%), back pain (3.5%), and myalgia (3.2%).

Open-label studies. Of 890 subjects on eprosartan and HCTZ in open-label studies, 687 (77%) reported at least one adverse event; the most common of which were urinary tract infection (13%). Injury (11%), headache (9%), myalgia (7%), sinusitis (7%), cough (7%), arthralgia (7%), back pain (7%), and dizziness (6%).

8.2.4 Laboratory findings

Controlled studies. The sponsor did not tabulate event rates on placebo.

The sponsor identified 9 subjects (1.4%) with potentially clinically significant low neutrophil counts[24], 3 (0.5%) with low WBC, and 1 (<1%) with low hemoglobin (present at baseline).

Three subjects had elevated SGOT or SGPT.

The most common laboratory abnormality was in fasting glucose elevations (13.8%). Three-fourths of these subjects had baseline abnormalities in glucose.

Ten subjects (1.6%) had elevated potassium.

Open-label studies. One hundred eighty-six subjects (24%) had high fasting glucose levels, somewhat higher than the rate in shorted-term studies. Other abnormalities of hematology or clinical chemistry were rare and similar to the rates in controlled studies.

The most common adverse events relating to laboratory abnormalities were hyperglycemia (3%) and anemia (2%).

8.2.5 ECGs

Controlled studies. In controlled studies, the sponsor reports that about 5% of subjects in various combinations of eprosartan and HCTZ had elevated values of PR and QRS intervals, and that 25-30% had QTc >430 ms. Rates on placebo are not described.

There were 16 adverse events related to cardiac dysrhythmias on active treatment, about half of which were palpitations.

Open-label studies. During open-label studies, elevated PR and QRS intervals were reported in 8% of subjects, and QTc >430 ms was reported in 49%.

Nineteen adverse events related to cardiac dysrhythmias were reported for open-label studies.

8.2.6 Subgroups

Headaches were reported more commonly by women than men, by about 6-fold. No other subgroup differences were plausibly demonstrated.

8.3 Summary

Eprosartan is approved for once- or twice-daily dosing at 400 to 800 mg/day, with 600 mg being the usual recommended starting dose. This dose range was adequately studied in the development program for eprosartan plus HCTZ.

The NDA did not include an integrated safety database for review, and the sponsor's presentation of safety information did not include the placebo group for controlled studies. These shortcomings precluded some of the usual aspects of a safety review.

Within those constraints, however, the available safety data suggest the only concerns about the combination of eprosartan 400 to 800 mg plus HCTZ 6.25 to 25 mg are predictable from the individual components.

---

[24] *Five of these subjects had abnormalities at baseline. None of the values were <1000/mm³. All 9 subjects completed the study. Seven of the 9 had neutrophil counts >1500 /nL at the last visit.*

9 Labeling review

The redline version of the label that follows here includes considerations offered by OPDRA, DDMAC (e-mail from Andrew Haffer, dated 20 June 2001), and reviewers of chemistry, biopharmaceutics, and pharmacology.

The Office of Post-marketing Drug Risk Assessment (review dated 28 Nov 2000) recommended the name "Teveten HCT", rather than [redacted] They also make various recommendations regarding packaging to better distinguish the monotherapy and combination products.

DRAFT

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

P. 18 - 36

10 Summary and recommendations

10.1 Chemistry

Various other minor deficiencies and queries of the sponsor are detailed in the CMC review, but stability data for the 600/25 tablet is the only crucial issue. There is no issue pertinent to approvability.

10.2 Pharmacology and toxicology

There are no pharmacology/toxicology issues pertinent to approvability.

10.3 Biopharmaceutics

There are no biopharmaceutics issues pertinent to approvability.

10.4 Effectiveness

Studies 061 and 088 showed that HCTZ 12.5 mg reduced blood pressure in subjects with mild-to-moderate essential hypertension whose blood pressure was inadequately treated with eprosartan 400 or 800 mg. Factorial study 148 showed the combination of eprosartan 600 mg and HCTZ 12.5 mg was superior to either treatment alone. Together these studies constitute compelling evidence of the effectiveness of the combination of eprosartan and HCTZ in the treatment of mild-to-moderate essential hypertension.

Study 164 is pertinent to the proper interdosing interval. As is the case for eprosartan alone, the effect of eprosartan plus HCTZ wanes toward the end of a 24-hour interdosing interval.

Effects in subgroups are best described as inconclusive.

None of the studies in severe diastolic hypertension or systolic hypertension had designs appropriate to assess the use of the combination of eprosartan and HCTZ.

10.5 Safety

The sponsor's development program was conventional in its power to resolve safety problems. The experience did not identify noteworthy problems associated with the use of eprosartan and HCTZ together.

10.6 Recommended regulatory action

Technically, the combinations of eprosartan/HCTZ 600/12.5 and 600/25 do not allow coverage of the acknowledged dose range for eprosartan. However, eprosartan is a little peculiar in having such a narrow range from the usual starting dose (600 mg) to the maximum recommended dose (800 mg). The label for eprosartan monotherapy implies a fairly flat dose-response relationship from 200 to 1200 mg.

Thus, concerns about addition of dose-independent side effects notwithstanding, there appears to be little basis for recommending coverage of eprosartan 800 mg in the combination. One can expect substantially greater effects on blood pressure in going from eprosartan 600 mg to the 600/12.5 mg combination than in going up in dose on eprosartan.

Eprosartan alone is recommended for use once or twice daily. The ABPM study (164) supports such use for eprosartan alone and for the combination of eprosartan plus HCTZ. Divided dosing (300/6.25 or 300/12.5) is not possible using the proposed formulations for marketing.

Eprosartan/HCTZ combination, 600/12.5 and 600/25 mg tablets, could be approved as "replacement therapy" for the treatment of essential hypertension. Such an approval captures the spirit of the principle of not having a combination product influence the practice of medicine with respect to total daily dose, but not with respect to once- or twice-daily dosing. This problem could be addressed with two new dosage strengths or

with scored tablets. One could decide this is not a significant approvability issue, that it should be resolved prior to final approval, or that it should be resolved after approval.

It is the recommendation of this reviewer that the application be considered "approvable", but that final approval be withheld until the scored tablets are made available.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix A Reviews of individual studies.

This section contains reviews of individual studies. Four studies (014, 016, 047, and 061) were formally reviewed under NDA 20-738. The reviews of these 4 studies are reproduced here. Four long-term open-label follow-on studies (039, 040, 050, and 052) were incorporated into the safety review of NDA 20-738. These studies are briefly described here.

A bioavailability study for the 600/25-mg combination is not reviewed here.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

A.1 Study 014: A 26-week, double-blind, parallel, multicenter, multicountry comparison study of SK&F 108566 and enalapril on cough and blood pressure in patients with essential hypertension (DBP >95 and <114 mmHg).

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

Protocol

Design & Objective

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

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

Eligibility criteria

Inclusion criteria

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

Exclusion Criteria

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

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

NDA 20-738

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

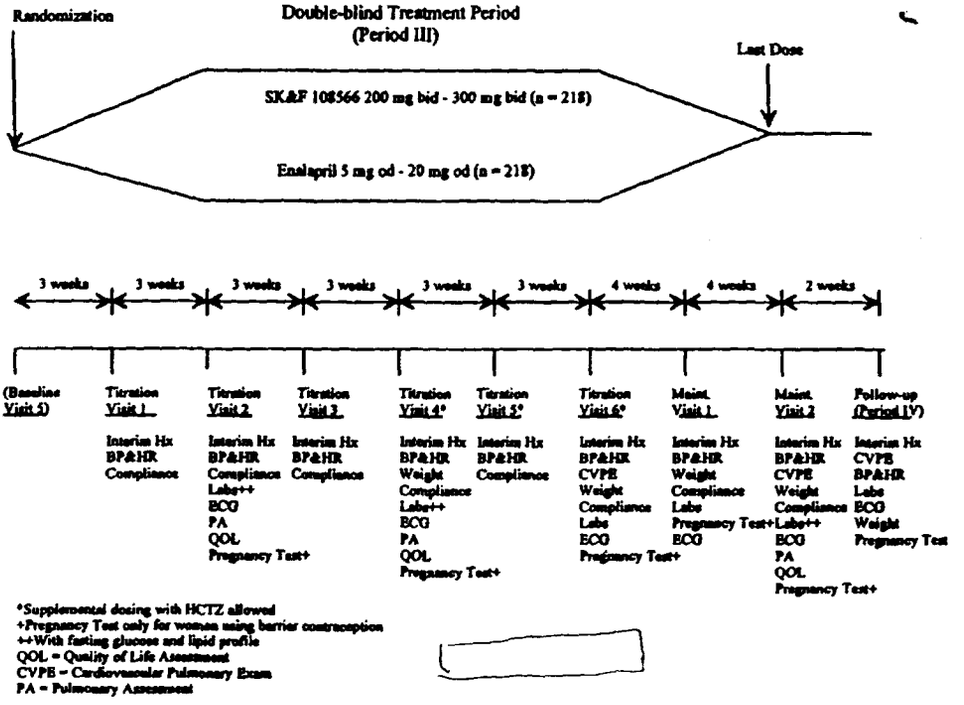
Description of Phases

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

NDA 20-738

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

Figure 14.1 Study Design: Double-Blind Treatment Period



Hypertension Efficacy Assessment

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

NDA 20-738

Statistical Methods

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

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

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

Results

Patient Disposition

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

Table 14.1 Patient Disposition

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

Data Source: Tables 13.1, 13.2

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

NDA 20-738

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

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

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

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

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

Data Source: Table 13.4.

Demographic Characteristics

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

APPEARS THIS WAY
ON ORIGINAL

NDA 20-738

Table 14.2 Patient Demographic Characteristics

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

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

Incidence of Definite Cough

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

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

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

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

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

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

NDA 20-738

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

Efficacy Results

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

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

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

Data Source: Tables 14.2 - 14.7

Conclusion

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

Reviewer's Comments

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

NDA 20-738

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

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

A.2 Study 016: A 4-week, double-blind, parallel, placebo-controlled, multicenter trial of oral eprosartan added to hydrochlorothiazide therapy in patients with essential hypertension (DBP >95 and <114 mmHg).

NDA 20-738

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

Protocol

Design & Objective

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

Eligibility Criteria

Inclusion Criteria

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

Exclusion Criteria

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

laboratory reference range.

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

Description of Phases

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

APPEARS THIS WAY
ON ORIGINAL

NDA 20-738

Table 16.1 Schedule of Assessments for efficacy and safety parameters

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

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

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

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

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

Data Source: Appendix A, Protocol and Sample CRF.

Primary & Secondary Endpoints

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

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

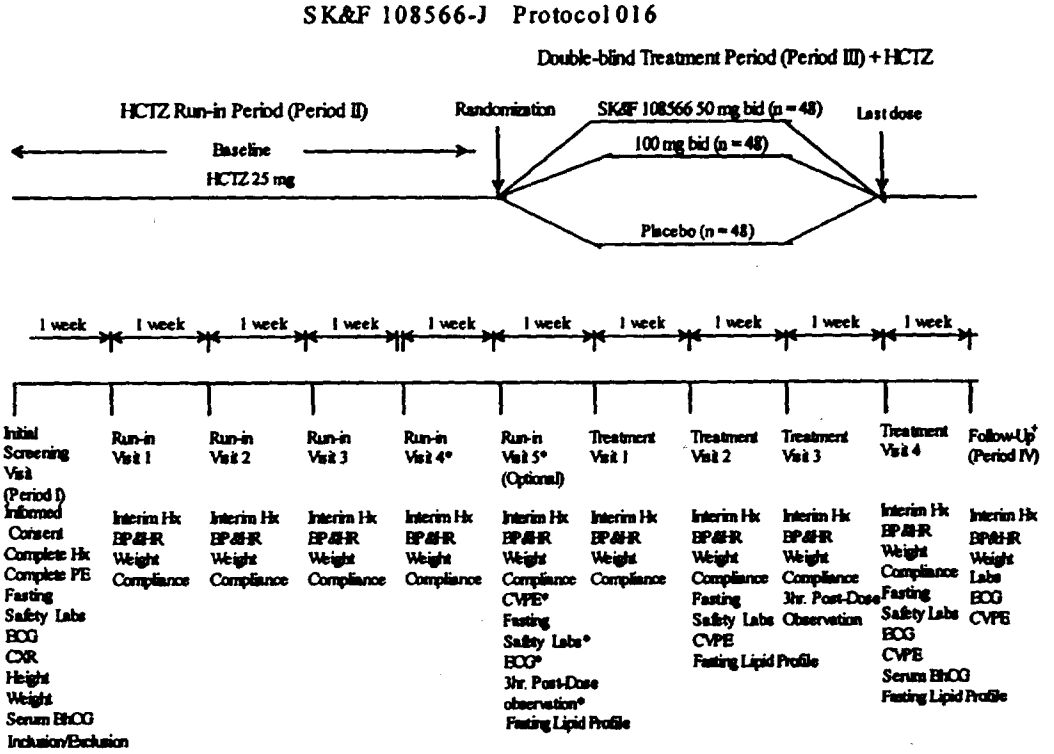
NDA 20-738

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

Committees

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

Figure 16.1 Study Design



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

y:\pro016\csreport\016sch.ppt

Statistical Analysis Plan

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

NDA 20-738

of the primary efficacy parameter: mean change from baseline for SitDBP. Under the Hochberg procedure, the largest p-value is compared to 0.05. If it is less than or equal to 0.05, than all p-values are statistically significant. If not, the next largest p-value is compared to 0.025 (0.05/2). If it is less than or equal to 0.025, then it and all smaller p-values are significant at the 0.05 level. If not, this procedure is continued for the third largest p-value, which must be less than 0.0167 (0.05/3).
There are three comparisons of interest: eprosartan 50 mg vs placebo, eprosartan 100 mg vs placebo, and eprosartan 50 mg vs 100 mg. Multiple comparisons of differences between regimens using the modified Bonferroni procedure were performed, and the Analysis of variance (ANOVA) was applied. The model included medication regimen, center, and regimen-by-center interaction. If there was no significant (P>0.10) regimen-by-center interaction, the interaction term was removed, and the reduced model was used. The analysis was applied to the intent-to-treat population at each visit and at endpoint. However, conclusions are based on the intent-to-treat analysis at endpoint. Patients who took the first dose of double-blind medication and had blood pressure measured only after that dose (peak observation) were not to be included in this analysis. (No patient fit this category.)

Results

Disposition

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

Table 16.2 Patient Disposition

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

Data Source: Tables 13.2,13.5

Demographic

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

APPEARS THIS WAY
ON ORIGINAL

NDA 20-738

Table 16.3 Patient Demography

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

Data Source: Table 13.10, 13.11

Primary Efficacy Evaluation

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

Table 16.4 Mean Change in Sitting Diastolic Blood Pressure

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

Data Source Table 14.1

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

Secondary Efficacy Evaluation

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

Conclusions

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

A.3 Study 039: A long-term (two-year) open-label, multicenter extension study of twice daily oral SK&F 108566-J (eprosartan mesylate) in patients with essential hypertension who have completed a clinical trial with SK&F 108566-J—extension of treatment.

A.3.1 Source documents

This review is based upon the final study report dated 3 November 1998 (NDA volume 1.130).

A.3.2 Investigators

The study was conducted at 48 centers in US.

A.3.3 Study dates

The study was conducted between 5 August 1994 and 16 February 1998.

A.3.4 Study design

The objective was to establish long-term safety of eprosartan 100 to 300 mg bid, and 300 mg in combination with HCTZ.

This was an open-label follow-on to Study 014[25], 016[26], 041[27], and 053[28]. Subjects had to have completed one of these studies to be enrolled.

Subjects entered into a 3- to 12-week titration period with visits at 3-week intervals, starting at eprosartan 100 mg bid, increasing to 200 and 300 mg bid as needed to achieve sitting DBP <90 mmHg. Subjects not controlled on eprosartan 300 mg bid also received HCTZ 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 and with the two doses 12±1.5 hours apart. Conventional safety data were collected. The final follow-up visit was 5 to 7 days after the last dose.

Lots used for the study were U94068, U94132, U95017-S1, U95116-S1, U95104, U95239, and U96025 (all eprosartan 100 mg). Commercial lots of HCTZ were used.

There were numerous amendments to the protocol. Early amendments allowed women practicing barrier contraception and reduced the upper limit for systolic pressure from 210 to 200 mmHg.

A.3.5 Results

A.3.5.1 Conduct

A total of 401 subjects were enrolled, of whom 3 had no post-baseline assessments, 263 completed one year in study, and 129 completed 2 years of study. Individual sites enrolled 1 to 20 subjects.

Reasons for withdrawal were adverse events (12%), lack of effectiveness (18%), loss to follow-up (5%), protocol violations (2%), and other reasons (7%).

Of enrolled subjects, 67% were male, 72% were Caucasian, and the mean age was 55 years.

---

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

[26] *See page 48 for a description of inclusion and exclusion criteria for Study 016.*

[27] *Study 041 was a 12-week, randomized, double-blind, parallel comparison of titrated doses of eprosartan and nifedipine. It is reviewed on page 71 of the primary medical review of effectiveness for NDA 20-738.*

[28] *Study 053 was a 6-week, randomized, double-blind, parallel, placebo- and enalapril-controlled, fixed-dose study. It is reviewed on page 81 of the primary medical review of effectiveness for NDA 20-738.*

Doses at various points in the trial are shown in Table 14. As subjects left the study, the proportion remaining on various doses remained fairly constant.

Table 14. Dose levels (percent of subjects enrolled; Study 039).

	Treatment				
	100 mg bid	**200 mg bid**	**300 mg bid**	**300 + HCTZ**	**Discontinued**
Titration	28	20	14	37	0
1 year	17	16	15	32	20
2 years	7	10	9	17	57

About 5% of subjects took some prohibited drug known to affect blood pressure, at some time during the maintenance phase.

A.3.5.2 Effectiveness

Population mean blood pressure remained stable throughout study, around 135/87 mmHg, but this has more to do with the study design than any indication of effectiveness.

A.3.5.3 Safety

Safety is reviewed in context of the full development program.

A.3.6 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

APPEARS THIS WAY
ON ORIGINAL

A.4 Study 040: A long-term open-label, multi-centre, multi-country extension study of twice daily oral SK&F 108566 (eprosartan) in patients with essential hypertension who have completed a previous clinical trial with eprosartan.

A.4.1 Source documents

This review is based upon the final study report dated 15 April 1999 (NDA volume 1.131).

A.4.2 Investigators

The study was conducted at 38 centers in Europe.

A.4.3 Study dates

The study was conducted between 29 May 1995 and 18 March 1998.

A.4.4 Study design

The objective was to establish long-term safety of eprosartan 100 to 300 mg bid, and 300 mg in combination with HCTZ.

This was an open-label follow-on to Study 014[29], 017[30], and 047[31]. Subjects had to have completed one of these studies to be enrolled.

Subjects entered into a 3- to 12-week titration period with visits at 3-week intervals, starting at eprosartan 100 mg bid, increasing to 200 and 300 mg bid as needed to achieve sitting DBP <90 mmHg. Subjects not controlled on eprosartan 300 mg bid also received HCTZ 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 and with the two doses about 12 hours apart. 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 U94191, U95017, and U95116 (all eprosartan 100 mg) and X95032 (HCTZ).

There were no significant amendments to the protocol.

A.4.5 Results

A.4.5.1 Conduct

A total of 342 subjects were enrolled, of whom 5 had no post-baseline assessments, 300 completed one year in study, and 85 completed 2 years of study. Individual sites enrolled 1 to 55 subjects.

Reasons for withdrawal were adverse events (11%), lack of effectiveness (6%), loss to follow-up (2%), protocol violations (2%), and other reasons (5%).

Of enrolled subjects, 43% were male, 93% were Caucasian, and the mean age was 63 years.

Doses at various points in the trial are shown in Table 14. As subjects left the study, the proportion remaining on various doses remained fairly constant.

---

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

[30] *Study 017 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..*

[31] *See page 57 for a description of inclusion and exclusion criteria for Study 047.*

Table 15. Dose levels (percent of subjects enrolled; Study 040).

	Treatment				
	100 mg bid	**200 mg bid**	**300 mg bid**	**300 + HCTZ**	**Discontinued**
Titration	45	25	12	17	<1
1 year	38	22	11	17	12
2 years	20	8	6	11	54

About 7% of subjects took some prohibited drug known to affect blood pressure, at some time during the maintenance phase.

A.4.5.2 Effectiveness

Population mean blood pressure remained stable throughout study, around 145/86 mHg, but this has more to do with the study design than any indication of effectiveness.

A.4.5.3 Safety

Safety is reviewed in context of the full development program.

A.4.6 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

A.5 Study 047: A 10-week, double-blind, multicenter, comparison of oral eprosartan and enalapril in patients with severe hypertension (DBP >115 and <125 mmHg).

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

Protocol

Design & Objective

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

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

Eligibility criteria

Inclusion criteria

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

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

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

Exclusion Criteria

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

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