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APPLICATION NUMBER
21-268

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

NDA #:	21-268
Applicant:	Unimed Pharmaceuticals, Inc.
Name of Drug:	Teveten® (eprosartan mesylate/hydrochlorothiazide)
Indication:	Replacement therapy for hypertensive patients taking the free combination
Document reviewed:	Volumes 1.1, 1.147-1.261 A-H, 1.262
Date of submission:	August 30, 2000
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Medical Reviewer:	Norman Stockbridge, M.D. (HFD–110)

1. Introduction

Eprosartan mesylate, or eprosartan, is an angiotensin-II receptor antagonist that is approved by the agency for the treatment of hypertension. SmithKline Beecham markets it under the trade name Teveten®. Hydrochlorothiazide (HCTZ) is a diuretic and antihypertensive agent that has been marketed in the U.S. since 1959. According to the sponsor, the combination of eprosartan and HCTZ has been shown to be effective among hypertensive patients who do not respond to eprosartan alone. The increased efficacy of the combination is due to the different mechanisms of action. The sponsor is requesting marketing approval for two tablet strengths of the combination product: eprosartan 600 mg/HCTZ 12.5 mg and eprosartan 600 mg/HCTZ 25 mg. There were eight Phase III trials conducted to support the safety and efficacy of the combination.

This review contains the study designs and summaries of the sponsor's analyses of the primary and secondary efficacy variables as well as safety data and subgroup analyses for the eight Phase III trials. In addition, the FDA analysis of the pivotal efficacy trial, Study 148 is included.

2. Study Designs

The safety and efficacy of the product was studied in eight Phase III trials. Four of the studies (Studies 016, 061, 088, and 148) support the labeling objective for a fixed dose combination of eprosartan 600 mg/HCTZ 12.5 mg. The remaining four studies (Studies 014, 047, 120, and 145) support the addition of HCTZ to monotherapy nonresponders. Table 2.1 summarizes the designs of these eight trials and a more detailed description of each trial follows this table.

Table 2.1 Summary of the designs of the eight Phase III trials. EP = eprosartan

Study	Treatment arms				# of Patients Randomized	Primary Objective
014	Titrated EP 200 mg or 300 mg bid		Titrated enalapril 5 mg to 20 mg		528	Compare incidence of cough
016	Placebo + HCTZ 25 mg	EP 50 mg bid + HCTZ 25 mg	EP 100 mg bid + HCTZ 25 mg		156	Compare reduction in SiDBP among two EP arms
047	Titrated EP 200 mg to 400 mg bid		Titrated enalapril 10 to 40 mg once daily		118	Compare reduction in SiDBP
061	Placebo	EP 400 mg + HCTZ 12.5 mg	EP 400 mg + HCTZ 25 mg		380	Compare reduction in SiDBP among active treatments
088	EP 600 mg alone		EP 600 mg + HCTZ 12.5 mg		309	Compare reduction in SiDBP
120	Titrated doses of EP at 600, 800, and 1200 mg		Titrated doses of enalapril at 10, 20, and 40 mg		360	Compare reduction in SiSBP in patients with severe systolic hypertension
145	Placebo		Titrated dose of EP 600 mg or 1200 mg		283	Compare reduction in SiSBP in patients with isolated systolic hypertension
148	Placebo	EP 600 mg once daily	HCTZ 12.5 mg	EP 600 mg + HCTZ 12.5 mg	473	Evaluate efficacy of combination

2.1 Study 014

675 patients were screened and entered the study and 645 entered the 3-5 week double-blind placebo run-in period. Patients were required to have essential hypertension (SiDBP between 95 and 114 mmHg inclusive) at three consecutive weekly visits. 528 entered the double-blind treatment period (eprosartan 200 mg bid or enalapril 5 mg once daily). During the first 18 weeks (the titration period), visits occurred every 3 weeks. The dose was titrated upward during the titration period (eprosartan 300 mg bid or enalapril 10 mg or 20 mg once daily) if the patients DBP was not controlled. If the patient's DBP was not controlled and they were at the highest dose, then HCTZ 12.5 mg was added. Patients whose blood pressure was not controlled after the 18 week titration period were withdrawn from the study for lack of efficacy. The remaining patients continued for an 8 week maintenance period and had visits every 4 weeks.

Of the 528 patients that that were randomized, 297 were male and 231 were female, 456 were Caucasian and 40 were Black. The mean age was 56, the mean weight was 83.4 kg, and the mean baseline SiDBP was 100.9. 264 patients were randomized to eprosartan (21 Blacks); 264 patients were randomized to enalapril (19 Blacks). There were no significant differences in age, weight, or baseline SiDBP among the patients in the two treatment arms.

2.2 Study 016

259 patients were initially treated in an open-label HCTZ run-in period (including twice-daily single-blind placebo) for four to five weeks. Patients were eligible to continue to the double-blind treatment phase if their SiDBP was between 95 mmHg and 114 mmHg inclusive at the end of the run-in period. 156 patients were randomized to placebo, eprosartan 50 mg, or eprosartan 100 mg, administered twice daily with HCTZ 25 mg once daily for four weeks. BP and HR measurements and other measurements were taken once each week during scheduled office visits during the entire study period.

Of the 156 patients that that were randomized, 112 were male and 44 were female, 109 were Caucasian and 33 were Black. The mean age was 53.4, the mean weight was 90.7 kg, and the mean baseline SiDBP was 100.5. 52 patients were randomized to placebo (13 Blacks); 53 patients were randomized to eprosartan 50 mg (12 Blacks); 51 patients were randomized to eprosartan 100 mg (8 Blacks). There were no significant differences in age, weight, or baseline SiDBP among the patients in the three treatment arms.

2.3 Study 047

Patients qualified for enrollment in the study if at the screening visit measurement of two mean sDBP values was between 115 mmHg and 125 mmHg. 118 patients were randomized to eprosartan 100 mg bid or enalapril 10 mg administered once daily. Randomization was stratified by current use of thiazide diuretic. Visits were scheduled for 24 hours, 48 hours, and one week after starting medication. Patients were seen at weeks 2, 4, and 6 for titration, if necessary, to 300 mg and then to 400 mg eprosartan bid or to 20 mg and then 40 mg enalapril once daily after week 2. At week 6, patients who were already receiveing the maximum dose and were not taking a thiazide diuretic had HCTZ 25 mg once daily added to their double-blind medication if their DBP was at least 90 mmHg. Patients entereed a 2-week maintenance phase at week 8 at the dosage level selected by titration.

Of the 118 patients that were randomized, 57 were male and 61 were female, 99 were Caucasian and 9 were Black. Three-fourths were under 65 years old, the mean weight was 79 kg, and the mean baseline SiDBP was 117. 59 patients were randomized to eprosartan (7 Blacks) and 59 patients were randomized to enalapril (2 Blacks). There were no significant differences in age, weight, or baseline SiDBP among the patients in the two treatment arms.

2.4 Study 061

506 patients enrolled in the study and received placebo run-in medication for three to five weeks. Patients were eligible to continue to the double-blind treatment phase if their SiDBP was between 95 mmHg and 114 mmHg inclusive at the end of the run-in period. 380 patients were randomized to placebo, eprosartan 400 mg + HCTZ 12.5 mg,

or eprosartan 400 mg + HCTZ 25 mg administered once daily for eight weeks. BP and HR measurements and other measurements were taken once each week during scheduled office visits during the run-in period and every other week during the 8 week double-blind treatment phase.

Of the 380 patients that were randomized, 214 were male and 166 were female, 318 were Caucasian and 39 were Black. The mean age was 54.6, the mean weight was 85.7 kg, and the mean baseline SiDBP was 100.7. 124 patients were randomized to placebo (15 Blacks); 128 patients were randomized to the low dose (12 Blacks); 128 patients were randomized to the high dose (12 Blacks). There were no significant differences in age, weight, or baseline SiDBP among the patients in the three treatment arms.

2.5 Study 088

494 patients with SiDBP between 98 mmHg and 114 mmHg were initially treated in an open-label eprosartan 600 mg run-in period (including twice-daily single-blind placebo) for four to five weeks. Patients were eligible to continue to the double-blind treatment phase if they did not respond to monotherapy (response defined by SiDBP< 90 mmHg or a decrease of at least 10 mmHg from baseline at the end of the run-in period). 309 patients were randomized to eprosartan 600 mg alone or eprosartan 600 mg + HCTZ 12.5 mg administered in the form of two tablets (monotherapy and combination tablets were indistinguishable) once daily for eight weeks. BP and HR measurements and other measurements were taken once each week during scheduled office visits during the entire study period.

Of the 309 patients that were randomized, 52.4% were male and 47.6% were female, 97.4% were Caucasian and 1.6% were Black. The mean age was 56.1 years, the mean weight was 81.9 kg, and the mean baseline SiDBP was 99.4. 157 patients were randomized to monotherapy (3 Blacks); 152 patients were randomized to combination therapy (2 Blacks). There were no significant differences in age, weight, or baseline SiDBP among the patients in the two treatment arms.

2.6 Study 120

412 patients were screened. Patients were eligible to continue to the double-blind treatment phase and were immediately randomized if they had severe systolic hypertension. The definition was based on the average of two measurements taken 1 hour apart and was defined as: 240>SiSBP≥180 mmHg untreated or ≥160 treated and 125≥SiDBP≥90. 360 patients were randomized and received at least one dose of the study medication in the double-blind treatment phase. At least one measurement on-therapy was obtained on 353 patients. The double-blind phase was 12 weeks and visits were scheduled after 1 week, 2 weeks, and every 2 weeks thereafter. During the first 2 weeks, all patients were randomized to Teveten 600 mg once daily or enalapril 10 mg once daily. There were three monotherapy dose levels for each drug: Teveten 600, 800,

1200 mg once daily and enalapril 10, 20, 40 mg once daily. A fourth level of medication consisted of the level three dose with HCTZ 25 mg once daily on top of the double-blind treatment. At the end of Week 2, the patient was titrated upward one level if SiSBP≥140 or SiDBP≥90. At the end of Week 4, the patient was titrated upward one level if SiSBP≥140 or SiDBP≥90. At this time, if a patient was already at the highest dose of monotherapy and was not responding (SiSBP≥140 or SiDBP≥90) and was not receiving HCTZ at baseline, then HCTZ 25 mg once daily was added in addition to their double-blind treatment. Patients who were already receiving HCTZ at baseline were discontinued from the study.

Of the 360 patients that were randomized and received at least one dose of medication, 47% were female and 53% were male, 59% were Caucasian and 24% were Black. The mean age was 56 years, the mean weight was 89 kg, and the mean baseline SiSBP was 177. 180 patients were randomized to Teveten (40 Blacks); 180 patients were randomized to enalapril (48 Blacks). There were no significant differences in age, weight, or baseline SiSBP among the patients in the two treatment arms.

2.7 Study 145

437 patients entered the 5-week placebo run-in period. Patients were eligible to continue to the double-blind treatment phase if they had isolated systolic hypertension defined as SiSBP> 160 mmHg and SiDBP<90 at three consecutive visits (visits were scheduled weekly). 283 patients were randomized and received at least one dose of the study medication in the double-blind treatment phase. The double-blind phase was 13 weeks and visits were scheduled after 3 weeks, 6 weeks, 9 weeks, and 13 weeks. During the first 9 weeks, all patients were randomized to Teveten 600 mg once daily or a matched placebo. A response was defined as a decrease in SiSBP of at least 15 mmHg for a patient with baseline value between 160 and 175 or a measurement below 160 for a patient with a baseline value above 175. Patients who did not respond were increased to Teveten 1200 mg once daily or matched placebo. At week 9, patients whose SiSBP was at least 145 mmHg and SiDBP was at least 75 mm Hg entered a 4-week treatment period during which single-blind HCTZ 12.5 mg once daily was added to their double-blind medication regimen.

Of the 283 patients that were randomized and received at least one dose of medication, 55% were female and 45% were male, 67% were Caucasian and 10% were Black. The mean age was 70 years, the mean weight was 77 kg, and the mean baseline SiSBP was 170. 135 patients were randomized to placebo (13 Blacks); 148 patients were randomized to Teveten (14 Blacks). There were no significant differences in age, weight, or baseline SiSBP among the patients in the two treatment arms.

2.8 Study 148

609 patients were screened and entered a 3 to 5 week placebo run-in phase. Patients qualified to continue to the double-blind treatment phase if their average SiDBP was between 95 mmHg and 114 mmHg inclusive at three consecutive visits during the run-in period. 473 patients were randomized to placebo, eprosartan 600 mg, HCTZ 12.5 mg, or eprosartan 600 mg + HCTZ 12.5 mg administered once daily for eight weeks. BP and HR measurements and other measurements were taken once each week during scheduled office visits during the run-in period and at Weeks 2, 4, and 8 during the 8 week double-blind treatment phase.

Of the 473 patients that were randomized, 223 were male and 250 were female, 416 were Caucasian. The mean age was 58.5, the mean weight was 81 kg, and the mean baseline SiDBP was 102. 122 patients were randomized to placebo; 118 patients were randomized to eprosartan monotherapy; 117 patients were randomized to HCTZ montherapy, and 116 were randomized to combination therapy. There were no significant differences in age, weight, or baseline SiDBP among the patients in the four treatment arms.

3. Primary Efficacy Variables and Planned Statistical Analyses

3.1 Study 014

The primary efficacy variable was the incidence of definite cough defined as persistent, non-productive cough associated with treatment and not due to upper respiratory infection, as judged by the investigator. The cough must have been present for at least 2 weeks unless the patient voluntarily discontinued because of coughing before completing 2 weeks of treatment after the cough began. The primary comparison is the rate of incidence during the 12 week titration phase. The two groups were compared using a Cochran-Mantel-Haenszel statistic adjusting for center interaction.

3.2 Study 016

The primary efficacy variable was the mean change in SiDBP from baseline to study endpoint. Baseline was defined as the average of the last two qualifying visits of the run-in period. Endpoint was defined as the last available observation on each patient that was randomized and received at least one dose of study medication during the double-blind period and had at least one efficacy measurement in that period.

There were three comparisons of interest consisting of all of the pairwise comparisons between the three treatment groups. The modified Bonferroni procedure due to Hochberg was used to adjust for multiple comparisons. The largest of the p-values from the pairwise comparisons was compared to 0.05. If it was less than 0.05, then all p-values were declared statistically significant. If not, then the next largest p-value was compared to 0.05/2. If this was less than 0.05/2, then it and the smallest p-value were

both declared significant. If not, the third largest p-value was compared to 0.05/3 to determine the significance of this smallest p-value.

Analysis of variance was applied to the intent-to-treat population using a model that included medication regimen, center, and regimen-by-center interaction. If the interaction term was not significant (p>0.1), then the interaction term would be removed.

3.3 Study 047

The primary efficacy parameter was the mean change from baseline in SiDBP at study endpoint. Baseline is defined as the value at screening and endpoint is defined as the last available record of patients who received at least one dose of study medication. Analysis of variance with terms for treatment, center and treatment by center interaction was used to model the primary efficacy variable. If the interaction term was not significant (p>0.1), then it was dropped from the model.

3.4 Study 061

The primary efficacy variable was the mean change in SiDBP from baseline to study endpoint. Baseline was defined as the average of the last two qualifying visits of the run-in period. Endpoint was defined as the last available observation on each patient that was randomized and received at least one dose of study medication during the double-blind period and had at least one efficacy measurement in that period.

There were three comparisons of interest consisting of all of the pairwise comparisons between the three treatment groups. The modified Bonferroni procedure due to Hochberg was used to adjust for multiple comparisons. The largest of the p-values from the pairwise comparisons was compared to 0.05. If it was less than 0.05, then all p-values were declared statistically significant. If not, then the next largest p-value was compared to 0.05/2. If this was less than 0.05/2, then it and the smallest p-value were both declared significant. If not, the third largest p-value was compared to 0.05/3 to determine the significance of this smallest p-value.

Analysis of variance was applied to the intent-to-treat population using a model that included medication regimen, center, and regimen-by-center interaction. If the interaction term was not significant (p>0.1), then the interaction term would be removed.

3.5 Study 088

Volume 151, p. 57 of the submission states that the primary efficacy parameter was "sitDBP at study endpoint", but p. 62 states that the primary efficacy variable was "mean change from baseline in trough sitDBP at study endpoint". The reviewer could not find the definition of baseline (beginning of run-in period or beginning of double-blind

treatment period). Endpoint was defined as the last available observation on each patient that was randomized and received at least one dose of study medication during the double-blind period and had at least one efficacy measurement in that period. In the results section, the primary efficacy variable was the mean change in SiDBP from baseline to study endpoint.

Analysis of variance was applied to the intent-to-treat population using a model that included medication regimen, center, and regimen-by-center interaction. If the interaction term was not significant ($p>0.1$), then the interaction term would be removed.

3.6 Study 120

The primary efficacy variable was the mean change in SiSBP from baseline to monotherapy endpoint. Baseline was defined as the average of all observations prior to randomization. Generally, this was the average of the two observations taken 1 hour apart at the screening visit, but two optional repeat visits prior to randomization were allowed. Endpoint was defined as the last available on-therapy observation on each patient who received at least one dose of randomized medication during the double-blind period.

The primary comparison was the difference between the two treatment groups in efficacy achieved at endpoint. Analysis of variance was applied to the intent-to-treat population using a model that included medication regimen, center, and regimen-by-center interaction. If the interaction term was not significant ($p>0.1$), then the interaction term would be removed.

3.7 Study 145

The primary efficacy variable was the mean change in SiSBP from baseline to monotherapy endpoint. Baseline was defined as the average of the last two qualifying visits prior to randomization. Endpoint was defined as the last available on-therapy observation on each patient who received at least one dose of randomized medication during the double-blind period prior to the addition of HCTZ.

The primary comparison was the difference between the Teveten treatment group and placebo in efficacy achieved at monotherapy endpoint. Analysis of variance was applied to the intent-to-treat population using a model that included medication regimen, center, and regimen-by-center interaction. If the interaction term was not significant ($p>0.1$), then the interaction term would be removed.

3.8 Study 148

The primary efficacy parameter was the mean change from baseline in trough SiDBP at study endpoint. Baseline was defined as the average of the last two measurements which qualified the patient to enter the double-blind phase. Endpoint was defined as the last available observation of patients who were randomized and received at

least one dose of medication. The primary hypothesis was that the combination provides a greater reduction in blood pressure than both of the components and eprosartan monotherapy provides a greater reduction in blood pressure than placebo. Analysis of variance with terms for treatment, center, and the interaction betwen treatment and center was specified as the model that would be used. However, the exact way that the hypothesis would be tested was not specified.

4. Sponsor's Analysis of Primary Efficacy Variables

4.1 Study 014

15% of the patients did not complete the study: 37 for adverse experiences (14 on Eprosartan vs. 23 on Enalapril), 25 for lack of efficacy (13 vs. 12), 5 lost to follow-up, 2 protocol violations, 12 for other reasons). Both the number and the reasons for dropout in the two groups were comparable [*Source: Vol 253, Table 13*].

The enalapril group had a significantly higher incidence of definite cough (5.4% of the patients in the enalapril group and 1.5% of the patients in the eprosartan group). The relative risk controlling for center effect was 3.45, i.e. patients in the enalapril group were 3.45 times as likely to experience definite cough. A 95% confidence interval for the relative risk is (1.26, 10.0) and the p-value associated with the relative risk from the CMH test is 0.018.

4.2 Study 016

A total of 7 patients did not complete the study (2 for adverse experiences, 1 for lack of efficacy, 1 lost to follow-up, 1 protocol violation, 2 for other reasons).

The mean change in SiDBP for the placebo group was -4.9 mmHg. The mean change for the 50 mg dose was -7.9 mmHg and the mean change for the 100 mg dose was -7.7 mmHg. The point estimates and 95% Bonferroni confidence intervals for the differences in adjusted mean changes between treatment groups appear in Table 4.2.1. The p-values in this table are not adjusted for multiple comparisons. There was no statistically significant difference between the treatment groups using the protocol specified adjustment for multiple comparisons [*Source: Study Report Vol. 149, Table 14*].

Table 4.2.1 Point estimates, 95% Bonferroni confidence intervals and unadjusted p-values for differences between treatment groups in adjusted mean change in SiDBP from baseline.

Treatment Groups	Point Estimate	95% CI	P-value
50 mg vs. Placebo	-3.0	(-6.1, 0.2)	0.026
100 mg vs. Placebo	-2.8	(-6.0, 0.4)	0.038
100 mg vs. 50 mg	0.2	(-3.0, 3.4)	0.894

4.3 Study 047

All patients in the eprosartan group completed the titration phase with roughly equal numbers in each dose level (15 at 200 mg, 10 at 300 mg, 14 at 400 mg, 20 at 400 mg + HCTZ). Forty-three patients went on to complete the maintenance phase with the following number of patients in each dose level: 10, 6, 7, 20.

57/59 patients in the enalapril group completed the titration phase (6 at 10 mg, 12 at 20 mg, 19 at 40 mg, 20 at 40 mg + HCTZ). Forty-six completed the mainenance phase with 4, 8, 13, and 21 patients in each dose level.

Overall, 5 patients withdrew because of adverse experiences, 17 for lack of efficacy, 1 lost to follow-up, 1 for protocol violations, and 1 for other reasons.

The adjusted mean change in SiDBP (primary efficacy variable) from baseline in the eprosartan group was -20.1 mmHg and the adjusted mean change in the enalapril group was -16.2 mmHg. The difference in the mean change from baseline between the two groups was 3.9 mmHg. This difference was not statistically significant (p=0.136) [*Source: Vol 254, Table 19*].

4.4 Study 061

A total of 28 patients did not complete the study, with similar numbers in the three arms (10 for adverse experiences, 9 for lack of efficacy, 2 lost to follow-up, 4 protocol violation, 3 for other reasons).

The mean change in SiDBP for the placebo group was -5.4 mmHg. The mean change for the low dose was -9.8 mmHg and the mean change for the high dose was -12.2 mmHg. The point estimates and 95% Bonferroni confidence intervals for the differences in adjusted mean changes between treatment groups appear in Table 4.4.1. Each pairwise comparison was statistically significant using the protocol specified adjustment for multiple comparisons [*Source: Study Report Vol. 150, Table 15*]

Table 4.4.1 Point estimates, Bonferroni confidence intervals and p-values for differences between treatment groups in adjusted mean change in SiDBP from baseline.

Treatment Groups	Point Estimate	95% CI	P-value
Low dose vs. Placebo	-4.4	(-6.7, -2.1)	<0.0001
High dose vs. Placebo	-6.9	(-9.1, -4.6)	<0.0001
High dose vs. Low dose	-2.5	(-4.7, -0.2)	0.0095

Low dose = EP 400 mg + HCTZ 12.5 mg, High dose = EP 400 mg + HCTZ 25 mg

4.5 Study 088

A total of 19 patients did not complete the study (11 for adverse experiences, 2 for lack of efficacy, 1 lost to follow-up, 2 protocol violation, 3 for other reasons).

The treatment by center interaction term was dropped from the model because it was not significant. Using the reduced model, the adjusted mean change in SiDBP for the monotherapy group was -7.9 mmHg. The adjusted mean change for the combination group was -10.7 mmHg. The confidence interval for the differences in adjusted mean changes between treatment groups is (-4.4, -1.1). This difference was statistically significant with a p-value of 0.001 [*Source: Study Report Vol. 151, Table 12*].

4.6 Study 120

A total of 148 patients who were randomized did not complete the study, with similar numbers in the two arms with similar numbers in each arm (24 for adverse experiences, 85 for lack of efficacy, 11 lost to follow-up, 17 protocol violation, 11 for other reasons).

The treatment by center interaction term was dropped from the model because it was not significant. The adjusted mean change in SiSBP for the Teveten group was -25.7 mmHg and the adjusted mean change for the enalapril group was -24.6 mmHg. The confidence interval for the difference in adjusted mean changes between treatment groups is (-3.0, 5.2) and this difference was not significant (p=0.59) [*Source: Table 15, Study Report Vol. 259*].

4.7 Study 145

A total of 33 patients who were randomized did not complete the study, with similar numbers and reasons in the two arms (11 for adverse experiences, 6 for lack of efficacy, 2 lost to follow-up, 5 protocol violation, 9 for other reasons).

The treatment by center interaction term was dropped from the model because it was not significant. The mean change in SiSBP for the placebo group was -9.6 mmHg and the mean change for the Teveten group was -18.0 mmHg. The confidence interval for the difference in adjusted mean changes between treatment groups is (-10.9, -4.5) and the difference was significant at p<0.0001 [*Source: Table 12, Study Report Vol. 174*].

4.8 Study 148

60 patients that were randomized withdrew from the study early with similar distributions and numbers in each arm: 16 for adverse experiences (4 on placebo, 2 on eprosartan, 7 on HCTZ, 3 on combination), 8 for lack of efficacy (4, 2, 2, 0), 4 lost to follow-up (0, 1, 3, 0), 19 for protocol violations (8, 3, 4, 4), 13 for other reasons (3, 2, 2, 6) [*Source: Vol. 207, Table 7*].

Since the treatment by center interaction term was not significant, it was removed from the model. The adjusted mean change in SiDBP in the 4 groups using the reduced linear model are in Table 4.8.1. In addition, the estimated differences in the mean change from baseline between groups appears in this table together with the associated p-values from nominal pairwise comparisons, i.e. not adjusted for multiplicity.

Table 4.8.1 Point estimates for adjusted mean change in SiDBP (mmHg) from baseline among the four treatment groups and differences between groups.

Placebo -6.5	EP 400 mg Monotherapy -8.3	EP vs. Placebo -1.8 (p=0.08)
HCTZ 12.5 mg Monotherapy -8.0	Combination 400/12.5 mg -11.0	Combination vs. HCTZ -2.9 (p=0.01)
HCTZ vs. Placebo -1.5 (p>0.1)	Combination vs. EP -2.6 (p=0.01)	

Source: Vol. 207 Table 14 except for the comparison of HCTZ vs. Placebo

The FDA attempted to confirm the results in Table 4.8.1 from the raw data submitted with the application. The FDA results differ numerically, but not materially, from the results in the Study Report. Recall that changes in trough SiDBP were to be measured at Weeks 2, 4, and 8. The reasons for the differences between the FDA analysis and the sponsor's are as follows:

Patient 148.002.52421: Was randomized on July 3, 1998 and had a Week 8 observation of -10 (change in mmHg from baseline) on August 21 (49 days after randomization). A subsequent observation of -5 was measured on September 8 (67 days after randomization). This patient was on study medication for 68 days. The FDA analysis uses -10 and the sponsor's analysis uses -5.

Patient 148.002.52422: Was randomized on June 9, 1998 and had a Week 8 observation of -5 on July 31 (52 days after randomization). Subsequent observations of -8 (off-trough) on August 21 (73 days after randomization) at 7:00 pm and -3 on September 1 (84 days after randomization) at 8:10 am were measured. This patient was on study medication for 74 days. The FDA analysis uses -5 and the sponsor's analysis uses -8.

Patient 148.002.52438: Was randomized on June 28, 1998 and had no Week 8 observation. The Week 4 observation of -10 was measured on July 26 (28 days after randomization). Subsequent off-trough observations of 12 on August 7 (40 days after randomization) at 7:30 pm and -2 on August 18 (51 days after randomization) at 3:20 pm were measured. This patient was on study medication for 41 days. The FDA analysis uses -10 and the sponsor's analysis uses 12.

Patient 148.003.52028: Was randomized on May 5, 1998 and had no Week 8 observation. The Week 4 observation of 20 was measured on June 1 (27 days after randomization). Subsequent observations of 3 on June 13 (39 days after randomization) and 2 on June 22 (48 days after randomization) were measured. This patient was on study medication for 39 days. The FDA analysis uses 20 and the sponsor's analysis uses 3.

Patient 148.003.52033: Was randomized on April 29, 1998 had no Week 8 observation. The Week 4 observation of -4 was measured on May 23 (24 days after randomization). A subsequent observation of -9 was measured on June 6 (38 days after randomization). This patient was on study medication for 38 days. The FDA analysis uses -4 and the sponsor's analysis uses -9.

Patient: 148.003.52118: Was randomized on April 23, 1998 had no Week 8 observation. The Week 4 observation of 2 was measured on May 15 (22 days after randomization). A subsequent observation of 11 was measured on May 29 (36 days after randomization). This patient was on study medication for 36 days. The FDA analysis uses 2 and the sponsor's analysis uses 11.

Patient 148.007.52074: Was randomized on June 4, 1998 and had no Week 8 observation. The Week 4 observation of -7 was measured on June 29 (25 days after randomization). Subsequent observations of -10 on July 13 (30 days after randomization) and -8 on July 27 (44 days after randomization) were measured. This patient was on study medication for 39 days. The FDA analysis uses -7 and the sponsor's analysis uses -10.

Patient 148.302.51807: Was randomized on June 17, 1998 and had no Week 8 observation. The Week 4 observation of 4 was measured on July 15 (28 days after randomization). Subsequent measurements of 1 on July 22 (35 days after randomization) and -7 on July 29 (42 days after randomization) were measured. This patient was on study medication for 35 days. The FDA analysis uses 4 and the sponsor's analysis uses 1.

Patient 148.302.52464: Was randomized on June 18, 1998 and had no Week 8 observation. The Week 4 observation of -1 was measured on July 16 (28 days after randomization). Subsequent observations of 12 on July 20 (32 days after randomization) and -3 on August 24 (65 days after randomization) were measured. This patient was on study medication for 32 days. The FDA analysis uses -1 and the sponsor's analysis uses 12.

Patient 148.302.52594: Was randomized on June 29, 1998 and had no Week 8 observation. The Week 4 observation of -5 was measured on July 28 (29 days after randomization). Subsequent observations of -4 on August 3 (35 days after randomization) and -13 on September 7 (70 days after randomization) were measured. This patient was on study medication for 35 days. The FDA analysis uses -5 and the sponsor's analysis uses -4.

Patient 148.302.52623: Was randomized on August 7, 1998 and had no Week 8 observation. The Week 4 observation of -4 was measured on August 28 (21 days after randomization). Subsequent observations of -2 on September 16 (40 days after randomization) and -15 on October 22 (76 days after randomization) were measured. This patient was on study medication for 71 days. The FDA analysis uses -4 and the sponsor's analysis uses -2.

Patient 148.304.51844: Was randomized on June 4, 1998 and had no Week 8 observation. The Week 4 observation of 11 was measured on July 2 (28 days after randomization). Subsequent observations of -1 on July 9 (35 days after randomization) and -8 on July 16 (42 days after randomization) were measured. This patient was on study medication for 35 days. The FDA analysis uses 11 and the sponsor's analysis uses -1.

Note that there are other cases where both the FDA and the sponsor's analysis use values that were not taken at trough. In particular, there are three cases where the last available observation was taken after 4:00 pm. The results from the FDA analysis appear in Table 4.8.2.

Table 4.8.2 Point estimates for adjusted mean change in SiDBP (mmHg) from baseline among the four treatment groups and differences between groups.

Placebo -6.4	EP 400 mg Monotherapy -8.4	Eprosartan vs. Placebo -1.9 (p=0.062)
HCTZ 12.5 mg Monotherapy -8.0	Combination 400/12.5 mg -11.0	Combination vs. HCTZ -3.0 (p=0.005)
HCTZ vs. Placebo -1.5 (p>0.1)	Combination vs. EP -2.6 (p=0.015)	

Source: FDA analysis.

The conclusions that can be drawn from either Table 4.8.1 or Table 4.8.2 are that the combination therapy was significantly better than either monotherapy in this study. However, neither monotherapy was significantly better than placebo. The usual criteria for approval of a combination product is that at least one of the components must be significantly better than placebo and the combination must be significantly better than each component. In this particular case, the study report indicates that no difference was expected between HCTZ and placebo, so the objective was to show that eprosartan monotherapy beat placebo and the combination beat both components. When this study is

evaluated on its own, the results do not meet the usual criteria for approval of a combination product. There may be some concern that although the efficacy of each monotherapy has been shown elsewhere, they did not work very well in this study and this made it easier for the combination to beat each component in this study. The combination therapy was significantly better than placebo ($p<0.001$).

5. Sponsor's Analyses of Secondary Efficacy Variables and Exploratory Subgroup Analyses

This section shows the results concerning the secondary variables and analysis of the primary efficacy variables in subgroups for those studies where the primary objective was reached.

5.1 Study 014

The difference in incidence of cough was not significant at Week 6 or Week 12 of the titration phase. There appeared to be a significant difference in the incidence of cough at the last available visit. There were no apparent differences between the eprosartan and the enalapril group in changes from baseline in SiDBP (-14.5 vs. -14.0 mmHg) or SiSBP (-17.5 vs. -16.6 mmHg). Comparisons of the primary efficacy variable were conducted on subgroups according to age, gender, race, and severity of hypertension. The incidence of definite cough among the subgroups was similar to that observed in the overall population [*Source: Vol. 253 Sec. 5.4*].

5.2 Study 061

The mean changes from baseline in SiSBP were -5.5, -14.0, and -16.3 for the placebo group, low dose, and high dose, respectively. Comparisons in the treatment groups among various subgroups appear in Table 5.2.1 [*Source: Sponsor's Data Source Tables 14.1.2, 14.1.3, and 14.1.4*]. Both active treatments appeared to be more effective than placebo in all subgroups except Blacks. There did not appear to be any difference between the low and high dose in any subgroup.

Table 5.2.1 Confidence intervals and point estimates for differences between treatment groups in adjusted mean change in SiDBP from baseline among various subgroups.

Subgroup	Treatment Groups	Point Estimate (mmHg)	95% CI

<65 yrs. old (n=306)	Low dose vs. Placebo	-4.6	(-7.1, -2.1)
	High dose vs. Placebo	-6.8	(-9.3, -4.2)
	High dose vs. Low dose	-2.2	(-4.7, 0.2)
≥65 yrs. old (n=70)	Low dose vs. Placebo	-3.6	(-10.1, 3.0)
	High dose vs. Placebo	-6.3	(-12.3, -0.3)
	High dose vs. Low dose	-2.7	(-9.8, 4.4)
Male (n=212)	Low dose vs. Placebo	-3.4	(-6.5, -0.3)
	High dose vs. Placebo	-6.5	(-9.6, -3.5)
	High dose vs. Low dose	-3.1	(-6.3, 0.1)
Female (n=164)	Low dose vs. Placebo	-5	(-8.8, -1.2)
	High dose vs. Placebo	-6.5	(-10.4, -2.7)
	High dose vs. Low dose	-1.6	(-5.1, 2.0)
Black (n=38)	Low dose vs. Placebo	-3.6	(-14.7, 7.4)
	High dose vs. Placebo	-12.3	(-22.8, -1.7)
	High dose vs. Low dose	-8.6	(-19.6, 2.4)
Caucasian (n=315)	Low dose vs. Placebo	-4.5	(-6.9, -2.1)
	High dose vs. Placebo	-6.3	(-8.8, -3.9)
	High dose vs. Low dose	-1.8	(-4.2, 0.5)

5.3 Study 088

The mean changes from baseline in SiSBP for the monotherapy group was -5.8 and was -9.2 for the combination. Changes in SiDBP among various subgroups appear in Table 5.3.1 [*Source: Vol. 151, Table 18*]. The combination appeared to be more effective in all the subgroups except for those patients 65 or older.

Table 5.3.1 Point estimates (± standard error of mean) for adjusted mean change in SiDBP from baseline among various subgroups.

		Treatment group		Combination -
Subgroup	n	Monotherapy	Combination	Monotherapy
<65 yrs. old	226	-7.6 ± 0.7	-11.6 ± 0.8	-4.0 ± 1.1
≥65 yrs. old	79	-11.2 ± 1.3	-11.4 ± 1.0	-0.2 ± 1.6
Male	161	-8.2 ± 0.9	-12.7 ± 0.9	-4.5 ± 1.3
Female	144	-9.0 ± 0.9	-10.3 ± 1.0	-1.3 ± 1.3
Black	5	-5.0 ± 8.4	-17.5 ± 4.5	-12.5 ± 9.5
Caucasian	297	-8.6 ± 0.7	-11.4 ± 0.7	-2.8 ± 1.0

5.4 Study 145

87 patients in the placebo group and 81 patients in the Teveten group had a combination therapy measurement. The mean changes from baseline (same definition as

for monotherapy baseline) in trough SiSBP at combination endpoint (last on therapy value after the addition of HCTZ at Week 9) were -15.5 mmHg in the placebo group and -21.9 mmHg for the Teveten group. The confidence interval for the difference in adjusted mean change from baseline is (-12.0, -2.8).

Both placebo and Teveten grouped showed significant reduction in trough SiSBP from monotherapy endpoint to combination endpoint. The reductions were 8.9 mmHg for the placebo group and 9.4 mmHg for the Teveten group. However, the between-group mean differences were not significantly different. A confidence interval for the between-group difference in adjusted mean change is (-5.1, 4.1). In other words, it appears that adding HCTZ on top of Teveten has roughly the same effect as adding HCTZ on top of placebo.

Comparisons in the treatment groups among various subgroups appear in Table 5.4.1 [*Source: Vol. 174, Table 19*]. Teveten appeared to be more effective in all the subgroups.

Table 5.4.1 Point estimates (± standard error of mean) for adjusted mean change in SiDBP from baseline among various subgroups.

		Treatment group		Combination -
Subgroup	n	Placebo	Teveten	Monotherapy
<75 yrs. old	200	-7.7 ± 1.5	-17.1 ± 1.2	-9.4 ± 1.9
≥75 yrs. old	78	-14.7 ± 2.8	-20.3 ± 2.1	-5.6 ± 3.5
Male	125	-9.5 ± 2.2	-18.2 ± 1.5	-8.7 ± 2.7
Female	153	-9.7 ± 1.8	-17.9 ± 1.5	-8.2 ± 2.3
Black	27	-9.6 ± 5.3	-14.1 ± 4.4	-4.5 ± 6.9
Caucasian	186	-10.0 ± 1.7	-18.9 ± 1.3	-8.9 ± 2.1

5.5 Study 148

Although one can argue about whether the primary objective was reached in this study, it is the only study in the submission with a factorial design. Because of the importance of this study in this submission, the secondary variables and analyses of the primary effeicacy variable by subgroup appear below. The mean changes from baseline in trough SiSBP appear in Table 5.5.1.

Table 5.5.1 Point estimates for adjusted mean change in SiSBP (mmHg) from baseline among the four treatment groups and differences between groups.

Placebo	Eprosartan Montherapy	Eprosartan vs. Placebo
-7.1	-10.6	-3.5 (p=0.056)
HCTZ Montherapy	Combination	Combination vs. HCTZ

-12.6	-16.4	-3.8 (p=0.04)
HCTZ vs. Placebo -5.5 (p <0.01)	Combination vs. Eprosartan -5.9 (p=0.002)	

Source: Vol. 207 Table 16 except for the comparison of HCTZ vs. Placebo

Comparisons in the treatment groups among various subgroups appear in Table 5.5.2 [*Source: Vol. 207, Table 20*]. The only subgroup where the combination appeared to be significantly better than both monotherapy groups is Males. However, among males, neither monotherapy appeared to work significantly better than placebo.

Table 5.5.2 Estimates of adjusted mean change in SiDBP (mmHg) from baseline to study endpoint among various subgroups. Within each subgroup, the point estimates in each treatment group appear in the first row and the point estimates (± standard error of mean) for the difference between the combination and each monotherapy are in the second row.

Subgroup	n	Treatment group			
		Placebo	Eprosartan	HCTZ	Combination
<65 yrs. old	310	-5.7	-9.3	-8.1	-11.5
≥65 yrs. old	154	-9.7	-8.3	-10.3	-12.5
Male	217	-7.2	-8.2	-7.8	-12.1
Female	247	-6.8	-9.9	-9.7	-11.7
Baseline SiDBP <105 mmHg	355	-6.9	-8.5	-9.3	-11.5
Baseline SiDBP ≥105 mmHg	109	-7.0	-11.0	-7.5	-12.8

6. Adverse events

6.1 Study 014

76% of the patients in the eprosartan group and 81% of the patients in the enalapril group experienced at least one adverse event during the double-blind treatment phase. Pharyngitis was the most common adverse experience in both groups (17% vs. 24% respectively). Coughing was the second most frequently reported adverse

experience overall (13% vs. 22%). No adverse experience appeared to be reported significantly more often in the eprosartan group.

Among those adverse experiences that were judged by the investigator to be related or possibly related to study medication, the only specific experiences where there was an apparent difference in rate were coughing, pharyngitis, and rhinitis. The rates of these adverse experiences were all favorable for the eprosartan group: 6.8% vs. 14.0%, 4.5% vs. 9.1%, and 0.4% vs. 2.3% respectively [*Source: Vol. 253 Table 41*].

6.2 Study 016

21 of 52 patients in the placebo group, 27/53 patients in the 50 mg group, and 22/51 patients in the 100 mg group reported one or more adverse experiences during the double-blind period. No specific adverse experience was reported significantly more often in the active treatment groups. In addition, there were no specific adverse experiences that were considered by the investigator to be "related or possibly related" to study medication that appeared to be reported more often in the active treatment groups.

6.3 Study 047

59% of the patients in the eprosartan group and 61% of the patients in the enalapril group reported at least one adverse experience. Headache was the most commonly reported experience. Headache was also the most commonly reported adverse expereicen that was judged by the investigator to be related or possibly related to the study medication (5 patients in the eprosartan group vs. 12 patients in the enalapril group).

6.4 Study 061

54.8% of the patients in the placebo group, 58.6% of the patients in the low dose, and 62.5% of the patients in the high dose reported one or more adverse experiences during the double blind treatment period. The most common adverse experience was headache (reported by 13.7%, 7.8%, 11.7% of patients respectively). There seemed to be an increase in the incidence of dizziness with increased dose. Dizziness was reported by 1.6%, 3.1%, and 8.6% of patients respectively. Moreover, the number of patients who reported dizziness that was judged by the investigator to be related or possibly related to medication was 2/124 in the placebo group , 4/128 in the low dose group, and 10/128 in the high dose group. This was the only specific adverse experience judged by the investigator to be related or possibly related to medication where there was an apparent increase in incidence with increase in dose.

6.5 Study 088

39.5% of patients in the monotherapy group and 45.4% of the patients in the combination group reported one or more adverse experiences during the double-blind period. The most common adverse experience was headache (4.5% in monotherapy and 5.3% in combination). No specific adverse experience was reported significantly more often in the combination group. In addition, dizziness was the only specific adverse experience that was considered by the investigator to be "related or possibly related" to study medication that appeared to be reported more often in the combination group (5/152 in combination and 1/157 in monotherapy). The sponsor prudently observed that since all randomized patients had to have tolerated the monotherapy run-in period, the adverse event profile must be viewed in consideration of the fact that some patients who were unable to tolerate eprosartan have been selected out prior to randomization.

6.6 Study 120

111 patients receiving Teveten and 113 patients receiving enalapril reported one or more adverse experiences on-therapy. Headache was the most commonly reported adverse experience (Teveten 17.2% and enalapril 12.2%). 17.2% of the Teveten group and 18.3% of the enalapril group had adverse experiences that were considered by the investigator to be of probable or suspected relationship to the medication. However, there was no specific adverse experience that was considered by the investigator to be related to study medication that appeared to be reported more often in either group.

6.7 Study 145

48.9% of patients in the placebo group and 41.2% of the patients in the Teveten group reported one or more adverse experiences during the double-blind period. The most common adverse experience was headache (10.4% placebo and 8.1% in Teveten). Urinary tract infection was the only specific adverse experience was reported significantly more often in the Teveten group (5/148 patients versus 0/135 patients). In addition, there was no specific adverse experience that was considered by the investigator to be "related or possibly related" to study medication that appeared to be reported more often in the Teveten group.

6.8 Study 148

43% of patients in the placebo group, 40% in the eprosartan group, 37% in the HCTZ, and 38% of the patients in the combination group reported one or more adverse experiences during the double-blind period. The most common adverse experience was headache (9%, 8.5%, 6%, 1.7% of the patients in each group). In addition, there was no specific adverse experience that was considered by the investigator to be "related or

possibly related" to study medication that appeared to be reported more often in either monotherapy group or the combination group.

7. Conclusions

Table 7.1 summarizes the conclusions from the primary analysis from each of the eight trials.

Table 7.1 Summary of the results of the Phase III trials (see Section 4 for more detail). EP = eprosartan

Study	Treatment arms				Conclusion
014	Titrated EP 200 mg or 300 mg bid		Titrated enalapril 5 mg to 20 mg		Definite cough occurs less often in EP (p=0.018, see Section 4.1)
016	Placebo + HCTZ 25 mg	EP 50 mg bid + HCTZ 25 mg	EP 100 mg bid + HCTZ 25 mg		No difference among two EP arms
047	Titrated EP 200 mg to 400 mg bid		Titrated enalapril 10 to 40 mg once daily		No difference
061	Placebo	EP 400 mg + HCTZ 12.5 mg	EP 400 mg + HCTZ 25 mg		EP+ HCTZ 25 mg is superior to EP + HCTZ 12.5 mg and is superior to placebo (p=0.01 and p<0.0001, see Table 4.4.1)
088	EP 600 mg alone		EP 600 mg + HCTZ 12.5 mg		Significant difference in reduction in SiDBP; combination is superior (p=0.001, see Sec. 4.5)
120	Titrated doses of EP at 600, 800, and 1200 mg		Titrated doses of enalapril at 10, 20, and 40 mg		No difference
145	Placebo		Titrated dose of EP 600 mg or 1200 mg		EP superior to placebo (p<0.0001, see Section 4.7)
148	Placebo	EP 600 mg once daily	HCTZ 12.5 mg	EP 600 mg + HCTZ 12.5 mg	Combination moderately better than either monotherapy (p=0.01). Neither EP nor HCTZ monotherapy was significantly better than placebo (p=0.08 and p>0.1, see Section 4.8)

We may draw the following conclusions relevant to the efficacy of a fixed combination:

i) Adding HCTZ 12.5 mg to eprosartan 600 mg increases the efficacy (from Study 088 and Study 148). Adding eprosartan 600 mg to HCTZ 12.5 mg increases efficacy (Study 148). However, in Study 148, the efficacy of either eprosartan 600 monotherapy or HCTZ 12.5 mg monotherapy was not established.

ii) It was not proven that eprosartan 600 mg is better than placebo in Study 148, but in Study 145, it was proven that if the patients are titrated up to 1200 mg, then this regimen is better than placebo.

iii) adding HCTZ 25 mg to eprosartan 400 mg seems to increase the efficacy more than the addition of HCTZ 12.5 mg (Study 061). However, no study in the submission indicates that there is any benifit to adding HCTZ 25 mg to eprosartan 600 mg. So, there does not seem to be any confirmation that a second fixed dose combination (600 mg/25 mg instead of 600 mg/12.5 mg) serves any purpose.

At the doses studied, there appear to be very mild side effects, so the drugs alone or in combination appear to be well tolerated at these doses.

11/21/01

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This review consists of 22 pages of text, tables, and figures.

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