The ABPM data show some evidence of a dose-response effect, although with considerable overlap. There does not appear to be a major trough-peak difference such that the once daily dosing appears effective.

As a secondary endpoint the sponsor examined the changes in BP at all timepoints. The changes in BP at all visits are shown in the figures below.

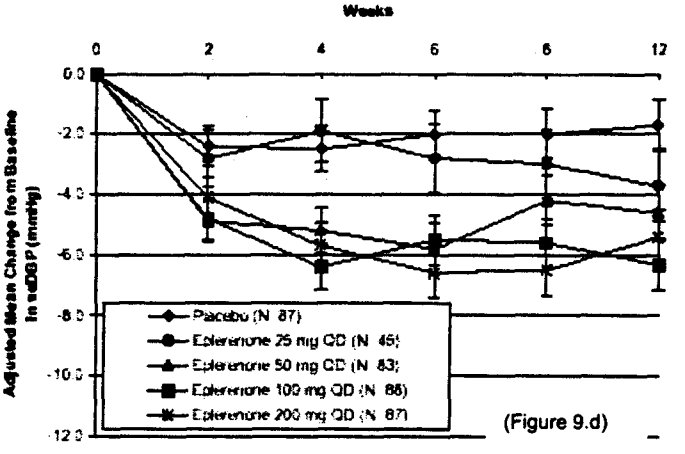


Figure 86: Sponsor's Adjusted Mean Change from Baseline in Cuff seDBP at Each Timepoint (LOCF)

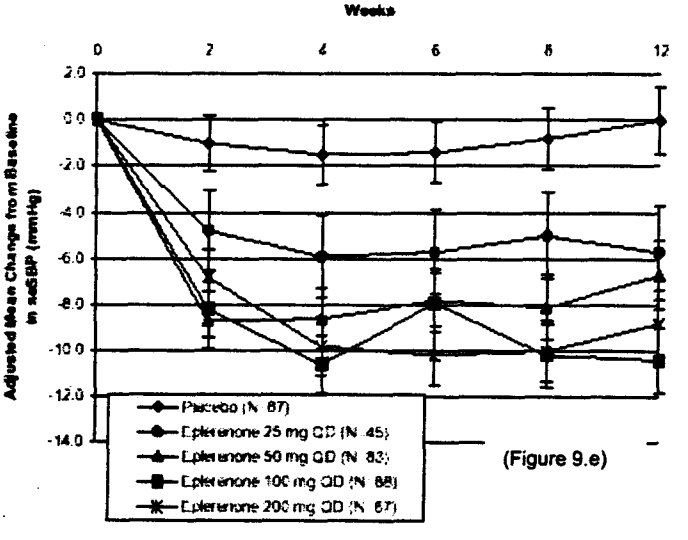


Figure 87: Sponsor's Adjusted Mean Change from Baseline in Cuff seSBP at Each Timepoint (LOCF)

Note that the reductions were near maximal at two weeks and maximal at four weeks. There appears to be some tapering of the reductions at 12 weeks, but the tapering is also evident with placebo.

B.2.4.2.2 Secondary Neurohormonal Endpoints

The sponsor summarized the changes in the secondary neurohormonal endpoints in the following table.

	Placebo	Eplerenone			
		25 mg QD	50 mg QD	100 mg QD	200 mg QD
Total Plasma Renin (mU/L)	(N=78)	(N=39)	(N=74)	(N=79)	(N=79)
Baseline Geometric Mean	127.3	120.9	122.8	128.1	111.2
Geometric Mean at Week 12	126.0	146.5	157.1	181.2	172.0
Mean Percent Change	-0.7	20.8	28.5	43.0	53.1
95% CI (a)	(-8.67, 7.87)	(7.28, 35.93)	(17.91, 40.00)	(31.70, 55.36)	(40.86, 66.30)
p-value vs. placebo (b)		0.0040	< 0.0005	< 0.0005	< 0.0005
Active Plasma Renin (mU/L)	(N=78)	(N=39)	(N=73)	(N=78)	(N=78)
Baseline Geometric Mean	11.7	11.5	11.1	13.5	12.5
Geometric Mean at Week 12	10.4	12.7	14.0	16.9	17.6
Mean Percent Change	-12.5	8.2	23.9	28.1	42.4
95% CI (a)	(-21.60, -2.35)	(-7.37, 26.42)	(10.68, 38.77)	(14.73, 42.98)	(27.59, 58.91)
p-value vs. placebo (b)		0.0141	< 0.0005	< 0.0005	< 0.0005
Serum Aldosterone (ng/dL)	(N=79)	(N=39)	(N=74)	(N=81)	(N=80)
Baseline Geometric Mean	7.3	8.4	7.4	7.8	8.0
Geometric Mean at Week 12	7.7	11.2	12.3	13.5	16.2
Mean Percent Change	3.6	38.9	64.7	72.8	105.6
95% CI (a)	(-6.79, 15.12)	(19.38, 61.54)	(47.72, 83.70)	(55.76, 91.71)	(85.22, 128.31)
p-value vs. placebo (b)		0.0009	< 0.0005	< 0.0005	< 0.0005

CI = confidence interval

(a) Two-sided 95% confidence interval for the within-group mean percent change from Baseline, based on ANCOVA with Baseline value as a covariate and treatment and center as factors.

(b) Comparisons versus placebo are based on a planned sequential testing strategy using linear trend contrasts to identify minimally effective dose. The p-values are adjusted for monotonicity and are assessed at the one-sided 2.5% level. P-values are based on ANCOVA with Baseline value as a covariate and treatment and center as factors.

Figure 88: Sponsor's Summary of Neurohormonal Endpoint Changes (Table 9.c)

The reviewer confirmed the sponsor's results. In addition, the reviewer noted that the changes in neurohormones may be differentiated by race or gender as was noted for the study 010 results. The race/gender effects will be explored in more detail in the reviewer's ISE.

B.2.4.3 Safety

B.2.4.3.1 Exposure

All 400 randomized patients received at least one dose of study drug. Patient exposure to study drug for at least two months in eplerenone 25 mg, 100 mg, and 200 mg QD was 75.6%, 80.5%, 88.9%, and 88.6% respectively. Patient exposure to placebo for at least two months was 77.8%.

B.2.4.3.2 Serious Adverse Events

Serious adverse events (SAEs) were reported in four patients: one incident of unstable angina in a placebo patient, myocardial infarctions in two patients, one each in the eplerenone 25 and 200 mg groups, and esophagitis in one patient in the 50 mg group. These SAEs are described further below.

B.2.4.3.2.1 Deaths

There were no deaths reported.

B.2.4.3.2.2 Hospitalizations

The following are narratives of the two SAEs reported in eplerenone groups requiring hospitalization. (The fourth SAE was unstable angina on day 3 of placebo in a 59-year-old diabetic white male.)

A 73-year-old white male with a history of remote transient ischemic attack and cerebrovascular accident suffered a myocardial infarction (MI). He received his first dose of eplerenone 25 mg QD on 20 Feb 2001 (Day 1); his last dose of eplerenone 25 mg QD was on 23 Feb 2001 (Day 4). He experienced a myocardial infarction on 23 Feb 2001 (Day 4), which caused withdrawal from the study. Concomitant medications included aspirin, isosorbide, diltiazem, and heparin. The events were considered by the investigator to be severe and of no relationship to study medication.

A 57- year-old Hispanic male with a history of ulcers, arm weakness, moderate shoulder joint pain, and active type 2 diabetes also suffered a MI. He received his first dose of eplerenone 200 mg QD on 31 Jan 2001 (Day 1); his last dose of eplerenone 200 mg QD was on 06 Apr 2001 (Day 66). He experienced a MI on 06 Apr 2001 (Day 66), which caused withdrawal from the study. Concomitant medications included glyburide. The event was continuing as of 06 Apr 2001 (Day 66). The event was considered by the investigator to be severe and of no relationship to study medication.

B.2.4.3.2.3 Other Serious Adverse Events

A 52-year-old postmenopausal white female with a history of double vision, migraines, gastric ulcer, gallstones, pyloroplasty/vagotomy for peptic ulcer disease, fundoplication for gastroesophageal reflux disease, and cholecystectomy. She received her first dose of eplerenone 50 mg QD on 14 Mar 2001 (Day 1); her last dose of eplerenone 50 mg QD was on 01 Jun 2001 (Day 80). She developed esophagitis on 01 Jun 2001 (Day 80), which caused withdrawal from the study. Concomitant medications included various estrogens, medroxyprogesterone, morphine, nitroglycerin, ibuprofen and acetaminophen. This event lasted three hours and resolved on 01 Jun 2001 (Day 80). This event was considered by the investigator to be severe and of no relationship to study medication.

B.2.4.3.3 Events Leading to Discontinuation

A total of 10 patients (two placebo, three eplerenone 25 mg QD, one eplerenone 50 mg QD, one eplerenone 100 mg QD, and three eplerenone 200 mg QD) were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. Treatment-emergent adverse events leading to premature withdrawal in more than one patient were headache (one eplerenone 25 mg QD patient and one eplerenone 100 mg QD patient) and myocardial infarction (one eplerenone 25 mg QD patient and one eplerenone 200 mg QD patient). The other AEs leading to withdrawal were dizziness, esophagitis, back pain, and flushing and dyspnea.

Reviewer's comment:

There is no obvious pattern in the events leading to discontinuation suggesting a toxicity problem with eplerenone.

B.2.4.3.4 Events of Special Interest

Hypotension

One eplerenone 200 mg QD patient experienced an adverse event of "hypotension" lasting 45 minutes on day 62. He continued on-study. This event was considered by the investigator to be moderate in severity and to be of probable relationship to study medication.

Hyperkalemia

One eplerenone 200 mg QD patient experienced an adverse event of hyperkalemia (5.8 mmol/L) reported by the investigator. This event was considered by the Investigator to be mild in severity and to be of no relationship to study medication. One placebo patient had an elevated potassium level ≥6.0 mmol/L (6.9 mmol/L) that was not reported as an adverse event and the potassium value was 4.4 mmol/L at the final visit. No other patients had potassium values that met the laboratory criteria for an event of special interest.

Sex Hormone-Related Events

One placebo patient and one eplerenone 100 mg QD patient experienced impotence during the study that the investigator considered to be mild in severity and of probable and uncertain relationship to study medication, respectively. No patients developed gynecomastia, female breast pain, or menstrual irregularities.

Hepatic Dysfunction

One placebo patient, but no eplerenone patient, was withdrawn because of elevated liver enzyme. In contrast to the results for study 010, liver enzyme changes did not show any relationship to eplerenone dosages.

Renal Dysfunction

One placebo patient and one eplerenone 200 mg QD patient experienced hyperuricemia that the investigator considered to be mild in severity and of no relationship to study mediation. One eplerenone 100 mg QD patient had uric acid values that met the laboratory criteria of > 594.8 μmol/L that was not reported as an adverse event.

Mean values for creatinine, BUN, and uric acid were very slightly increased in the eplerenone groups with a slight dose-response effect. However, these slight changes are probably not clinically significant.

Thyroid Dysfunction

While not prespecified as an event of special interest, the reviewer discovered the following results regarding thyroid function changes when reviewing the changes in hormone determinations:

Table 78: Reviewer's Mean Changes in TSH Levels from Baseline to Final

Group	Male		Female	
	Change	P	Change	P
0	0.07		0.36	
25	0.004		-0.48	
50	0.07	0.03	-0.14	0.46
100	0.13		0.06	
200	0.27		0.26	

P by ANOVA

Thyroxine and T3 resin update levels did not differ significantly between the eplerenone and placebo groups. While this change in TSH levels for males may be a random variation (the p values are not corrected for multiple comparisons), please see the similar results for Study 010 in Appendix B.1 and a complete discussion of the implications in the reviewer's Integrated Summary of Safety.

B.2.4.3.5 Overall Adverse Events

AEs other than the ones described above were typical of double-blind trials. The most frequently reported AEs in the eplerenone groups were headache and upper respiratory infections and were comparable to placebo.

B.2.4.3.6 Overdose

No overdoses were reported.

B.2.5 Summary

B.2.5.1 Efficacy Summary

Eplerenone at dosing of 50 to 200 mg QD was effective in reducing seated cuff trough DBP and SBP at 12 weeks. The reductions were almost full at 2 weeks and maximal at 4 weeks. Eplerenone 25 mg QD was effective in reducing seated cuff trough SBP but the reduction in cuff DBP was not statistically significant. Reductions in mean 24-hour DBP and SBP by ABPM were statistically significant for all eplerenone dosages at week 12. The curves of ABPM data by hour suggest some decreased efficacy in reducing DBP at midday for the 25 mg dose and possibly early afternoon for the 50 mg dose. There is a dose-response relationship for this range of doses from 25 to 200 mg. However, for cuff BP the 100 mg dose produces nearly identical reductions to the 200 mg dose, although by ABPM there appears to be slightly greater effect upon SBP with the 200 mg dose.

Eplerenone produced clear dose-dependent increases in renin and aldosterone. The clinical significance of these increases is not known.

B.2.5.2 Safety Summary

Eplerenone was tolerated well in this study. Both hyperkalemia and sex hormone-related AEs were minimal. Liver enzyme increases were not related to dose as in Study 010. However, TSH levels increased slightly with dose in males as in Study 010. These changes are discussed further in the reviewer's ISE.

B.2.5.3 Reviewer's Conclusions

Eplerenone at dosing of 50 to 200 mg QD appears to be effective in reducing BP and well tolerated. Eplerenone at a dosage of 25 mg QD reduces SBP slightly and probably DBP slightly but should not be a recommended dosage for primary treatment of hypertension in adults.

B.3 Trial 015, Eplerenone and Hydrochlorothiazide Factorial

Study 015 is entitled "A Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Safety and Efficacy of Ranging Doses of Eplerenone Relative to Placebo, Hydrochlorothiazide and Daily Dose Combinations of Eplerenone and Hydrochlorothiazide for the Treatment of Mild to Moderate Hypertension." This trial was a factorial study of eplerenone dosages 25, 50, and 200 mg QD with hydrochlorothiazide 12.5 and 25 mg QD. The primary endpoint was reduction in trough cuff seated DBP.

B.3.1 Sites and Investigators

66 Investigators enrolled patients at 66 study sites in six countries: the U.S., Canada, the Netherlands, Poland, Spain, and Belgium. The majority of the patients (73 percent) finishing the trial were from the U.S., 10 percent were Canadian, and the rest were distributed among the four European countries.

B.3.2 Background

B.3.2.1 Initial Protocol

This study was conducted in accordance with protocol IE3-98-02-015, "Revised Clinical Protocol for a Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Safety and Efficacy of Ranging Doses of Eplerenone Relative to Placebo, Hydrochlorothiazide and Daily Dose Combinations of Eplerenone and Hydrochlorothiazide for the Treatment of Mild to Moderate Hypertension," IND [redacted] dated 19 January 1999; the original protocol number was IE3-98-02-015, dated 18 November 1998.

B.3.2.2 Protocol Amendments

The original protocol was amended once: "IE3-99-A1-015, 19 January 1999, details the change in study procedures to exclude special laboratory studies including: androgenic and progestational hormones (total testosterone, total estradiol and luteinizing hormone), plasminogen activator inhibitor (PAI), the aminoterminal propeptide of type III procollagen (PIIINP), and microalbuminuria. The inclusion criteria has therefore been modified to allow for patients receiving estrogen hormone replacement therapy as well as hormonal contraceptives (oral or implanted)."

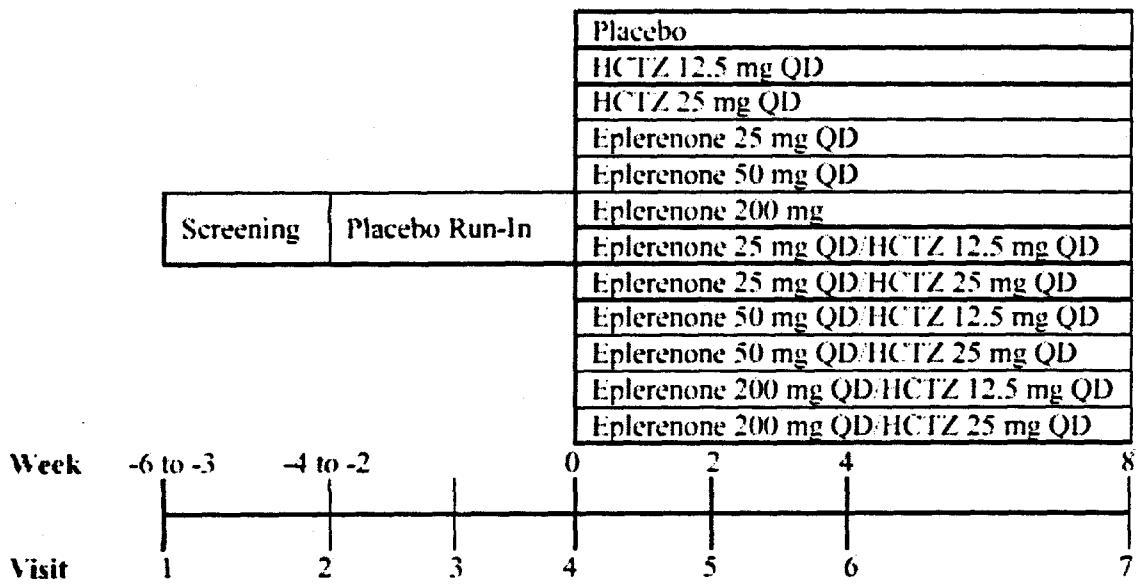
Reviewer's comment: The amendment does not appear to impact adversely the scientific validity of the study.

B.3.2.3 Study Dates

The study was conducted between 29 March 1999 and 15 November 1999.

B.3.3 Study Design

This was a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group, dose-ranging study designed to compare the safety and efficacy of eplerenone and HCTZ given alone or in combination, versus placebo in patients with mild to moderate hypertension. The study consisted of a one- to two-week Pretreatment Screening Period followed by a two- to four-week Single-Blind, Placebo Run-In Period, prior to randomization to an eight-week Double-Blind, Randomized Treatment Period. The study design is diagrammed below:



(Figure 6.a)

Figure 89: Sponsor's Study 015 Design

B.3.3.1 Objectives

The primary objectives of this study were:

1. To evaluate the safety and efficacy of eplerenone versus placebo versus HCTZ by measuring seated cuff trough diastolic blood pressure (seDBP) and by evaluating reported adverse events, clinical safety laboratory results, and vital signs.

2. To evaluate the safety and efficacy of different dose combinations of eplerenone and HCTZ by measuring seDBP and evaluating reported adverse events, clinical safety laboratory results, and vital signs.

The secondary objectives of this study were:

1. To evaluate the efficacy of eplerenone versus placebo versus HCTZ, and combinations of eplerenone and HCTZ by measuring seated cuff trough systolic blood pressure (seSBP).
2. To evaluate the effect of eplerenone on RAAS hormones, plasma renin (total and active) and serum aldosterone levels.
3. To evaluate the effect of eplerenone on serum potassium, sodium, magnesium, bicarbonate, and uric acid levels.

B.3.3.2 Number of Subjects and Randomization

A sample size of 540 completed patients was planned, with 45 patients in each group. A total of 614 patients were randomized into the study by 66 investigators. Three additional patients received randomized study medication in error for a total of 617 patients who received randomized study medication. Each of the 12 groups had between 50 and 52 patients. A randomization schedule was generated by a sponsor statistician and provided to the drug distribution contractor and to an Interactive Voice Response System (IVRS) center. Sites called the IVRS for randomization.

B.3.3.3 Inclusion and Exclusion Criteria

The criteria for inclusion to the pretreatment screening period were:

1. Male or non-pregnant/non-lactating female patients > 18 years of age.
2. If the patient is a female, she is post-menopausal, or if of childbearing potential, she is using adequate contraception (e.g., oral contraceptives, hormonal implants, barrier method, etc.), or is surgically sterile, and is non-lactating. Abstinence is not an acceptable form of contraception.
3. History of mild to moderate hypertension, or newly diagnosed hypertension defined as seDBP of > 90mmHg and <110mmHg.
4. The patient must provide documented, written informed consent prior to any test or procedure is performed, or medication(s) is changed for admission to this study.

The additional criteria for inclusion to the single-blind, placebo run-in period were:

1. Patient does not exhibit orthostatic hypotension as determined by the Investigator.
2. Previous antihypertensive therapy, if any, has been withdrawn.
3. No clinically significant abnormal clinical laboratory values which in the Investigator's opinion precludes the patient from safely participating in this study.

4. Patient has a normal serum potassium level > 3.0mEq/L and < 5.0mEq/L.

The additional criteria for inclusion to the randomized, double blind period were:

1. Untreated mean seated diastolic blood pressure (seDBP) of > 95mmHg and < 110mmHg as measured and described in Appendix 3.1.
2. Untreated mean seated systolic blood pressure (seSBP) <180mmHg as measured and described in Appendix 3.1.
3. Compliance with medication dosing instructions during the Single-Blind Placebo Run-In between 80-120% as determined by pill count.
4. If the patient is a female of child bearing potential, she has had a negative urine pregnancy test within 24 hours prior to the first scheduled dose of study medication, and a negative serum pregnancy test prior to entering the Double-Blind Period.

The exclusion criteria were the following:

1. Secondary hypertension, severe hypertension or malignant hypertension.
2. Current use of any systemic medication that might effect blood pressure, e.g., other anti-hypertensives, ßeta blockers, anti-arrhythmia medications. Other medications that might effect blood pressure include: tricyclic anti-depressants, sympathomimetic decongestants, NSAIDS (except aspirin < 325 mg once daily), weight reduction medications, and inhaled ßeta agonists (bronchodilators).
3. History of myocardial infarction, coronary revascularization, unstable angina pectoris, or cerebrovascular accident within the past six months.
4. Severe aortic or mitral valve disease requiring medical treatment or causing hemodynamically relevant disturbances.
5. History of congestive heart failure (NYHA classification II-IV), requiring medical treatment or causing hemodynamically relevant disturbances, or has pulmonary hypertension.
6. History or evidence of a pacemaker.
7. Uncontrolled diabetes mellitus defined as HbA 1c > 10%.
8. Acute or chronic hepatic disease, i.e., liver enzymes above 2.0 times the upper limit of normal, or serum bilirubin > 2.5 mg/dL or serum albumin < 2.5g/dL.
9. Serum potassium > 5.0mEq/L, serum creatinine > 1.5mg/dL.
10. Abnormal clinical laboratory values which, in the investigator's opinion, precludes the patient from safely participating in this study.
11. Any condition which in the investigator's opinion makes participation in this study not in the best interest of the patient, e.g., cancer therapy within the last 12 months.
12. Current evidence of alcohol or drug abuse or any other condition associated with potentially poor compliance.
13. Surgery or disease of the gastrointestinal tract which in the opinion of the investigator may influence the absorption or elimination of the study medication.
14. Receiving any investigational medication within 30 days prior to the first dose of study medication, or anticipated receiving an investigational drug other than eplerenone during the course of this study.
15. Inability to return for scheduled clinic visits.

16. Known hypersensitivity to eplerenone, hydrochlorothiazide or related compounds.
17. Previous admission to this study.

B.3.3.4 Dosage and Administration

Eplerenone or placebo was to be taken at the same time of day (in the morning upon rising) with or without food. To ensure blinding all arms used blister cards with six tablets for each day. Patients were instructed to take all six tablets from the blister card each day.

B.3.3.5 Duration and Adjustment of Therapy

Duration of treatment during the double-blind period was 8 weeks. No adjustments were specified for study medications. However, patients could be discontinued for the following protocol-specified reasons: If at any time during the Screening, Single-Blind Run-In, or Double-Blind Periods, a patient experienced a DBP > 110 mmHg or SBP > 180 mmHg, the patient was to be withdrawn from the study. A patient was to be discontinued for inability to tolerate study medication, treatment failure and need to prescribe other antihypertensive medications, intervening non-study medication, related adverse events or intercurrent illness which made continued study participation impossible, inclusion/exclusion violations discovered during the course of the study, administrative reasons, or any other reason which in the opinion of the Investigator is to protect the best interest of the patient.

B.3.3.6 Safety and Efficacy Endpoints

The primary efficacy variable was the trough cuff seDBP at Week 8 or at the Final Visit in case of early withdrawal. Secondary efficacy variables were trough cuff seSBP and plasma renin and serum aldosterone at Week 8 or at the Final Visit in case of early withdrawal.

Safety was checked by history, physical exam and vitals signs, and clinical laboratory tests. The sponsor's schedule of observations and procedures is shown in the figure below.

B.3.3.7 Statistical Considerations

B.3.3.7.1 Sample Size Calculations

A sample size of 540 completed patients was planned, with 45 patients in each group. Assuming a standard deviation of 7.5 mm Hg, this sample size was sufficient to detect a 4.5 mm Hg difference between any two groups in mean seDBP change from Baseline with at least 80% power at the 5% significance level using a two-tailed test.

	Pretreatment Screening Period	Single-Blind, Placebo Run-In Period		Double-Blind, Randomized Treatment Period			
Week	**-6 to -4**	**-4**	**-2**	**0**	**2**	**4**	**8 or Final Visit**
Visits	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**
Observations/Procedures[b]							
Medical History	X						
Physical Exam	X						X
12-Lead ECG	X			X			X
Heart Rate	X	X	X	X[c]	X	X	X
Blood Pressure (trough readings)[d]	X	X	X	X[c]	X	X	X
Fasted Clinical Safety Labs	X	X	X	X	X	X	X
RAAS Hormone Profile[e]				X			X
Dispense Drug		X	X	X[f]	X	X	
Medication Compliance			X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concurrent Medications	X	X	X	X	X	X	X

[a] If patient met mild to moderate BP criteria after two weeks of the Single-Blind, Placebo Run-In Period, Week -2 was not applicable and the patient may have entered the Double-Blind, Randomized Treatment Period and Week 0 procedures were to be completed.

[b] Informed consent was obtained prior to any test or procedure or change in medication was made for the purpose of this trial.

[c] Final eligibility was determined at Week -2 or Week 0 (before randomization) based upon inclusion criteria.

[d] Pretreatment recordings included measurements on both arms and a single standing measurement. All other visits required seated, trough measurements only.

[e] RAAS hormone profile included plasma renin (total and active) and serum aldosterone. These samples were drawn at trough, i.e., prior to dosing and while the patient was in the seated position.

[f] Randomization to double-blind study number occurred at Week 0 (Day 1), i.e., end of Single-Blind, Placebo Run-In Period.

(Table 6.b)

Figure 90: Sponsor's Schedule of Study Evaluations

B.3.3.7.2 Analysis Cohorts

Efficacy analyses were based on the intent-to-treat population which included all randomized patients with a baseline BP assessment and at least one post-Baseline assessment during the double-blind dosing period (first dose to last dose plus one day during the eight-week double-blind, randomized treatment period). In each efficacy endpoint analysis, missing values were imputed using the last post-baseline observation carried forward (LOCF) method at all timepoints. The safety analysis included all randomized patients who took at least one dose of study medication (safety population).

Reviewer's comment: Note that the Division agreed to this analysis approach at a meeting with the sponsor on July 19, 2001.

B.3.3.7.3 Pre-specified Analyses

The statistical methods used reflect those outlined in the Statistical Analysis Plan rather than the protocol. The Statistical Analysis Plan was prepared prior to breaking the study blind. Analyses performed after the unblinding are described as post-hoc.

Blood pressure evaluations were analyzed using one-way analysis of covariance (ANCOVA) with the Baseline measurement as the covariate and treatment as factor. The response variable was the change from Baseline. A treatment-by-center interaction term was not included since the number of patients randomized to each group at every center was expected to be few. Before implementing the final ANCOVA model, the assumption of homogeneity of treatment covariate slopes was tested with an ANCOVA model that included effects for Baseline, treatment, and treatment-by-Baseline interaction.

To test effectiveness of eplerenone monotherapy, the 200 mg dose was tested versus placebo at the 0.05 level of significance, and testing continued through the lower doses in sequence until a dose was found not to be significantly different from placebo. Any doses still lower were then declared to be not significantly different from placebo. These tests were performed as one-degree-of-freedom contrasts in the larger ANCOVA model that included all 12 groups.

Pairwise comparisons were conducted between each combination treatment and its components and between each active treatment (i.e., combination treatments and components) and placebo using Fisher's least significant difference (LSD) test, based on adjusted means and the mean square error from the ANCOVA. Individual pairs of treatments were declared significantly different if the overall test of treatment effect in the ANCOVA was significant ($p \leq 0.050$) and the pairwise comparison was also significant ($p \leq 0.050$).

A global test recommended by Hung, et al. was applied to the endpoint reductions in seDBP to test whether at least one dose combination was more effective than each of its components. Response surface analysis methods were used for figures showing the BP and potassium response to the various doses of eplerenone and HCTZ.

B.3.4 Results

B.3.4.1 Study Implementation

B.3.4.1.1 Disposition of Subjects

The majority of patients in each group (80 to 92 percent) completed the study. The most common reasons for premature withdrawal across the groups were treatment failure, adverse

event, and protocol non-compliance. The percentage of patients who were prematurely withdrawn due to treatment failure was highest in the placebo and HCTZ 25 mg QD groups (both about 8 percent). The disposition of the cases is shown below in the table.

		Eplerenone QD		
Disposition	Placebo	25 mg	50 mg	200 mg
All randomized patients				
Placebo	52	52	50	51
HCTZ 12.5 mg QD	52	51	52	51
HCTZ 25.0 mg QD	51	52	51	52
Completed study				
Placebo	43 (82.7%)	48 (92.3%)	40 (80.0%)	46 (90.2%)
HCTZ 12.5 mg QD	45 (86.5%)	44 (86.3%)	48 (92.3%)	46 (90.2%)
HCTZ 25.0 mg QD	44 (86.3%)	45 (86.5%)	45 (88.2%)	46 (88.5%)
Withdrawn				
Placebo	9 (17.3%)	4 (7.7%)	10 (20.0%)	5 (9.8%)
HCTZ 12.5 mg QD	7 (13.5%)	7 (13.7%)	4 (7.7%)	5 (9.8%)
HCTZ 25.0 mg QD	7 (13.7%)	7 (13.5%)	6 (11.8%)	6 (11.5%)
Reason for Withdrawal[a]				
Treatment failure				
Placebo	4 (7.7%)	2 (3.8%)	3 (6.0%)	2 (3.9%)
HCTZ 12.5 mg QD	2 (3.8%)	3 (5.9%)	1 (1.9%)	0 (0.0%)
HCTZ 25.0 mg QD	4 (7.8%)	1 (1.9%)	0 (0.0%)	2 (3.8%)
Lost to Follow-Up				
Placebo	0 (0.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)
HCTZ 12.5 mg QD	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
HCTZ 25.0 mg QD	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (1.9%)
Pre-existing Violation				
Placebo	0 (0.0%)	0 (0.0%)	1 (2.0%)	1 (2.0%)
HCTZ 12.5 mg QD	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)
HCTZ 25.0 mg QD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Compliance				
Placebo	1 (1.9%)	0 (0.0%)	3 (6.0%)	0 (0.0%)
HCTZ 12.5 mg QD	2 (3.8%)	1 (2.0%)	0 (0.0%)	2 (3.9%)
HCTZ 25.0 mg QD	0 (0.0%)	1 (1.9%)	1 (2.0%)	0 (0.0%)
Adverse Event				
Placebo	2 (3.8%)	1 (1.9%)	3 (6.0%)	1 (2.0%)
HCTZ 12.5 mg QD	1 (1.9%)	2 (3.9%)	0 (0.0%)	1 (2.0%)
HCTZ 25.0 mg QD	3 (5.9%)	3 (5.8%)	2 (3.9%)	2 (3.8%)
Pre-Existing Adverse Event				
Placebo	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HCTZ 12.5 mg QD	0 (0.0%)	0 (0.0%)	1 (1.9%)	0 (0.0%)[b]
HCTZ 25.0 mg QD	0 (0.0%)	1 (1.9%)[c]	1 (2.0%)	0 (0.0%)
Adverse Event 7 Days After Last Dose				
Placebo	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.0%)
HCTZ 12.5 mg QD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
HCTZ 25.0 mg QD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

(Table 8.a)

Figure 91: Sponsor's Disposition of Patients

Reviewer's comment: Withdrawals appear to be fairly evenly distributed among the groups with the possible exceptions of withdrawals for treatment failure in the placebo and hydrochlorothiazide 25 mg groups as the sponsor noted.

B.3.4.1.2 Subject Demographics and Baseline Characteristics

617 patients received randomized study medication (including 3 erroneously during the run-in period) as follows: 52 placebo, 52 eplerenone 25 mg QD, 50 eplerenone 50 mg QD, 51 eplerenone 200 mg QD, 52 HCTZ 12.5 mg QD, 51 HCTZ 25 mg QD, 51 eplerenone 25 mg QD/HCTZ 12.5 mg QD, 52 eplerenone 25 mg QD/HCTZ 25 mg QD, 52 eplerenone 50 mg QD/HCTZ 12.5 mg QD, 51 eplerenone 50 mg QD/HCTZ 25 mg QD, 51 eplerenone 200 mg QD/HCTZ 12.5 mg QD, 52 eplerenone 200 mg QD/HCTZ 25 mg QD. The sponsor's tabulation of demographic and baseline characteristics is shown in the figure below.

Reviewer's comment: The sponsor noted that the differences in seated DBP at baseline were statistically significant but were judged not to be clinically significant. The differences are small (maximum 1.4 between lowest and highest groups), usually less than 0.5 mm Hg, and not associated with statistically significant differences in SBP. The reviewer agrees that these differences are probably not clinically significant. The rest of the baseline characteristics appear to be evenly distributed.

Gender was even split, i.e., 51 percent male and 49 percent female. Race was predominately white (78 percent) with the 11 percent black representation solely from the U.S. Eighteen percent were age 65 or older.

Demographic Characteristic		Placebo	Eplerenone (QD) 25 mg	50 mg	200 mg
All Randomized Patients (N)					
	Placebo	52	52	50	51
	HCTZ 12.5 mg QD	52	51	52	51
	HCTZ 25.0 mg QD	51	52	51	52
Age (Years)					
Mean (SD)	Placebo	54.5 (9.9)	53.4 (10.4)	55.5 (11.6)	53.5 (12.2)
	HCTZ 12.5 mg QD	57.2 (13.3)	53.4 (11.9)	51.9 (11.0)	52.6 (10.3)
	HCTZ 25.0 mg QD	54.3 (11.2)	53.1 (11.8)	54.7 (11.5)	51.4 (11.1)
Median	Placebo	53.5	54.5	54.5	52.0
	HCTZ 12.5 mg QD	55.5	55.0	51.0	51.0
	HCTZ 25.0 mg QD	53.0	54.0	52.0	51.5
Range	Placebo	37 - 79	26 - 70	23 - 81	27 - 87
	HCTZ 12.5 mg QD	36 - 91	27 - 82	28 - 84	29 - 74
	HCTZ 25.0 mg QD	19 - 85	29 - 77	29 - 78	21 - 79
Ethnicity N (%)					
Asian	Placebo	1 (1.9%)	1 (1.9%)	0 (0.0%)	2 (3.9%)
	HCTZ 12.5 mg QD	1 (1.9%)	3 (5.9%)	2 (3.8%)	0 (0.0%)
	HCTZ 25.0 mg QD	1 (2.0%)	2 (3.8%)	1 (2.0%)	0 (0.0%)
Black	Placebo	6 (11.5%)	4 (7.7%)	7 (14.0%)	3 (5.9%)
	HCTZ 12.5 mg QD	5 (9.6%)	5 (9.8%)	4 (7.7%)	7 (13.7%)
	HCTZ 25.0 mg QD	7 (13.7%)	6 (11.5%)	7 (13.7%)	7 (13.5%)
Caucasian	Placebo	42 (80.8%)	40 (76.9%)	37 (74.0%)	43 (84.3%)
	HCTZ 12.5 mg QD	44 (84.6%)	40 (78.4%)	41 (78.8%)	40 (78.4%)
	HCTZ 25.0 mg QD	40 (78.4%)	36 (69.2%)	39 (76.5%)	42 (80.8%)
Hispanic/ Latin American	Placebo	3 (5.8%)	7 (13.5%)	5 (10.0%)	1 (2.0%)
	HCTZ 12.5 mg QD	2 (3.8%)	3 (5.9%)	4 (7.7%)	3 (5.9%)
	HCTZ 25.0 mg QD	3 (5.9%)	8 (15.4%)	4 (7.8%)	3 (5.8%)
Other	Placebo	0 (0.0%)	0 (0.0%)	1 (2.0%)	2 (3.9%)
	HCTZ 12.5 mg QD	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (2.0%)
	HCTZ 25.0 mg QD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gender N (%)					
Female	Placebo	23 (44.2%)	24 (46.2%)	32 (64.0%)	26 (51.0%)
	HCTZ 12.5 mg QD	23 (44.2%)	21 (41.2%)	28 (53.8%)	25 (49.0%)
	HCTZ 25.0 mg QD	23 (45.1%)	24 (46.2%)	21 (41.2%)	32 (61.5%)
Male	Placebo	29 (55.8%)	28 (53.8%)	18 (36.0%)	25 (49.0%)
	HCTZ 12.5 mg QD	29 (55.8%)	30 (58.8%)	24 (46.2%)	26 (51.0%)
	HCTZ 25.0 mg QD	28 (54.9%)	28 (53.8%)	30 (58.8%)	20 (38.5%)
Female Weight (kg)					
Mean (SD)	Placebo	78.0 (19.5)	79.5 (19.8)	77.2 (16.1)	79.4 (12.3)
	HCTZ 12.5 mg QD	85.8 (19.8)	78.1 (16.0)	84.2 (20.4)	86.9 (24.9)
	HCTZ 25.0 mg QD	78.3 (12.6)	83.8 (21.7)	84.7 (15.2)	80.2 (25.5)
Median	Placebo	77.0	76.3	76.4	78.6
	HCTZ 12.5 mg QD	84.5	76.5	81.2	83.2
	HCTZ 25.0 mg QD	77.3	74.4	80.0	72.6

Figure 92: Sponsor's Demographics and Baseline Characteristics (Table 9.b)

Demographic Characteristic		Placebo	Eplerenone (QD) 25 mg	50 mg	200 mg
Range	Placebo	50.0 - 124.1	51.3 - 124.7	52.0 - 114.0	55.0 - 102.7
	HCTZ 12.5 mg QD	48.1 - 138.0	49.9 - 111.2	48.0 - 139.0	50.1 - 136.2
	HCTZ 25.0 mg QD	57.5 - 101.6	59.0 - 133.0	51.8 - 114.8	48.0 - 133.9
Male Weight (kg)					
Mean (SD)	Placebo	90.1 (13.2)	96.1(15.8)	93.2(19.5)	95.6(15.3)
	HCTZ 12.5 mg QD	93.6 (13.7)	92.7(17.8)	97.1(22.0)	95.0(15.7)
	HCTZ 25.0 mg QD	91.8 (14.7)	93.7(13.5)	94.7(17.2)	93.2(16.0)
Median	Placebo	90.5	93.6	88.5	93.2
	HCTZ 12.5 mg QD	93.0	91.8	89.5	94.0
	HCTZ 25.0 mg QD	92.1	90.1	91.1	90.4
Range	Placebo	69.1 - 115.3	75.5 - 130.5	67.3 - 143.5	65.0 - 125.0
	HCTZ 12.5 mg QD	69.5 - 121.3	57.0 - 146.3	63.7 - 157.7	69.2 - 145.0
	HCTZ 25.0 mg QD	63.6 - 123.5	64.5 - 134.5	66.1 - 137.0	62.0 - 124.5
Female Height (cm)					
Mean (SD)	Placebo	160.3 (6.9)	162.8 (6.1)	160.1 (5.7)	162.3 (7.5)
	HCTZ 12.5 mg QD	160.8 (4.7)	161.5 (6.9)	163.9 (5.7)	161.9 (6.0)
	HCTZ 25.0 mg QD	161.2 (6.9)	160.5 (10.8)	164.3 (9.0)	161.3 (5.9)
Median	Placebo	160.0	162.6	160.0	162.2
	HCTZ 12.5 mg QD	161.0	161.0	163.3	162.5
	HCTZ 25.0 mg QD	162.6	160.5	163.0	160.0
Range	Placebo	147.3 - 172.7	151.0 - 172.0	149.9 - 175.3	150.0 - 182.9
	HCTZ 12.5 mg QD	152.4 - 170.2	149.9 - 177.8	155.0 - 180.3	150.0 - 174.0
	HCTZ 25.0 mg QD	149.5 - 177.8	121.9- 180.3	147.9 - 190.0	146.0 - 173.0
Male Height (cm)					
Mean (SD)	Placebo	176.3 (8.8)	179.2 (6.7)	176.1 (9.0)	175.9 (5.5)
	HCTZ 12.5 mg QD	178.9 (9.2)	175.1 (8.0)	176.1 (7.9)	177.9 (6.6)
	HCTZ 25.0 mg QD	177.0 (7.1)	174.3 (8.4)	176.5 (9.4)	176.7 (6.9)
Median	Placebo	175.3	178.0	177.8	175.3
	HCTZ 12.5 mg QD	180.0	172.8	177.8	177.9
	HCTZ 25.0 mg QD	178.2	174.0	175.3	177.8
Range	Placebo	153.5 - 193.0	167.6 - 190.5	162.0 - 190.5	162.6 - 185.5
	HCTZ 12.5 mg QD	160.0 - 197.9	162.0 - 193.4	155.0 - 188.6	160.0 - 188.4
	HCTZ 25.0 mg QD	154.6 - 188.0	147.3 - 187.9	165.0 - 205.7	165.0 - 187.7
Female Body Mass Index (kg/cm^2)					
Mean (SD)	Placebo	30.1 (6.8)	29.9 (6.8)	30.1 (6.0)	30.2 (4.5)
	HCTZ 12.5 mg QD	33.4 (8.4)	30.0 (5.8)	31.3 (7.1)	33.0 (8.7)
	HCTZ 25.0 mg QD	30.2 (5.2)	32.6 (8.1)	31.7 (6.7)	30.6 (8.6)
Median	Placebo	28.6	30.1	30.4	30.2
	HCTZ 12.5 mg QD	33.2	30.1	29.9	32.1
	HCTZ 25.0 mg QD	28.1	29.3	30.1	28.3
Range	Placebo				
	HCTZ 12.5 mg QD				
	HCTZ 25.0 mg QD				
Male Body Mass Index (kg/cm^2)					
Mean (SD)	Placebo	29.1 (4.2)	29.9 (4.1)	30.2 (6.3)	30.9 (4.7)
	HCTZ 12.5 mg QD	29.1 (2.9)	30.3 (5.5)	31.1 (5.4)	30.0 (4.5)
	HCTZ 25.0 mg QD	29.4 (5.0)	31.1 (6.0)	30.4 (4.9)	29.8 (4.5)
Median	Placebo	29.2	28.8	29.6	30.5
	HCTZ 12.5 mg QD	28.1	29.2	29.9	29.4
	HCTZ 25.0 mg QD	28.2	30.3	30.1	29.4
Range	Placebo				
	HCTZ 12.5 mg QD				
	HCTZ 25.0 mg QD				

Figure 92: Sponsor's Demographics and Baseline Characteristics (Continued)

Demographic Characteristic		Placebo	Eplerenone (QD) 25 mg	50 mg	200 mg
Mean BP (mmHg) at Baseline					
	Placebo	52	52	50	51
	HCTZ 12.5 mg QD	52	51	52	51
	HCTZ 25.0 mg QD	51	52	51	52
seSBP (OC)					
Mean (SE)	Placebo	151.1 (1.9)	151.5 (1.9)	151.8 (1.9)	152.0 (1.8)
	HCTZ 12.5 mg QD	152.3 (1.8)	149.7 (1.9)	149.6 (2.0)	151.9 (1.5)
	HCTZ 25.0 mg QD	150.9 (2.1)	155.6 (1.9)	151.9 (1.9)	151.4 (2.0)
seDBP[1] (OC)					
Mean (SE)	Placebo	99.3 (0.5)	98.9 (0.5)	98.9 (0.5)	99.4 (0.5)
	HCTZ 12.5 mg QD	100.3 (0.6)	100.1 (0.5)	99.0 (0.5)	99.2 (0.4)
	HCTZ 25.0 mg QD	99.5 (0.5)	99.9 (0.5)	99.9 (0.6)	99.1 (0.5)

OC = observed case
[1]Statistically significant difference among groups (p = 0.003).

Figure 92: Sponsor's Demographics and Baseline Characteristics (Continued)

B.3.4.1.3 Conduct

B.3.4.1.3.1 Monitoring

Sponsor monitors were to make site visits, but the frequencies or details of the visits are not specified. A separate DSMB is not described.

The sponsor describes its data quality assurance as follow: "The study was monitored at the investigational sites by a Pharmacia Clinical Monitor, or Monitors designated by Pharmacia. Data were entered on the CRFs at the site. Although it was the Investigator's responsibility to ensure accuracy and authenticity of all data entered on the CRFs, the Clinical Monitor also conducted a source verification review of 100 percent of the CRFs at the site. Data from the CRFs were entered into the — Recorder Clinical Data Management System at — and were verified electronically for consistency and accuracy by Pharmacia. Queries were reviewed with the Clinical Monitor (and in some cases with the Pharmacia Medical Monitor), in conjunction with the Investigator and his staff for resolution."

B.3.4.1.3.2 Protocol Violations

Five randomized patients violated exclusion criteria by using systemic medication that might affect blood pressure. No patient was excluded from the intent-to-treat efficacy analysis due to violations of inclusion/exclusion criteria or for violation of concomitant medication use as described above. No patients who received at least one dose of study medication during the Double-Blind, Randomized Treatment Period was excluded from the safety analyses. Three patients received double-blind study medication in error during the Single-Blind, Placebo Run-In Period and were not included in any of the efficacy or safety analyses. These patients were included in disposition and demographic analyses. Five patients did not have at least one post-

Baseline assessment and were excluded from the efficacy analyses. This includes the three patients who received Double-Blind study medication in error during the Single-Blind, Placebo Run-In period.

B.3.4.1.3.3 Dosing

All dosing was blinded fixed dose without adjustment. Patient compliance was measured by pill counts. The majority of patients (84.3 percent to 96.2 percent across groups) were between 80 percent and 120 percent compliant with their study medication. There does not appear to be any trend to decreased compliance with higher dosages.

B.3.4.1.3.4 Blinding

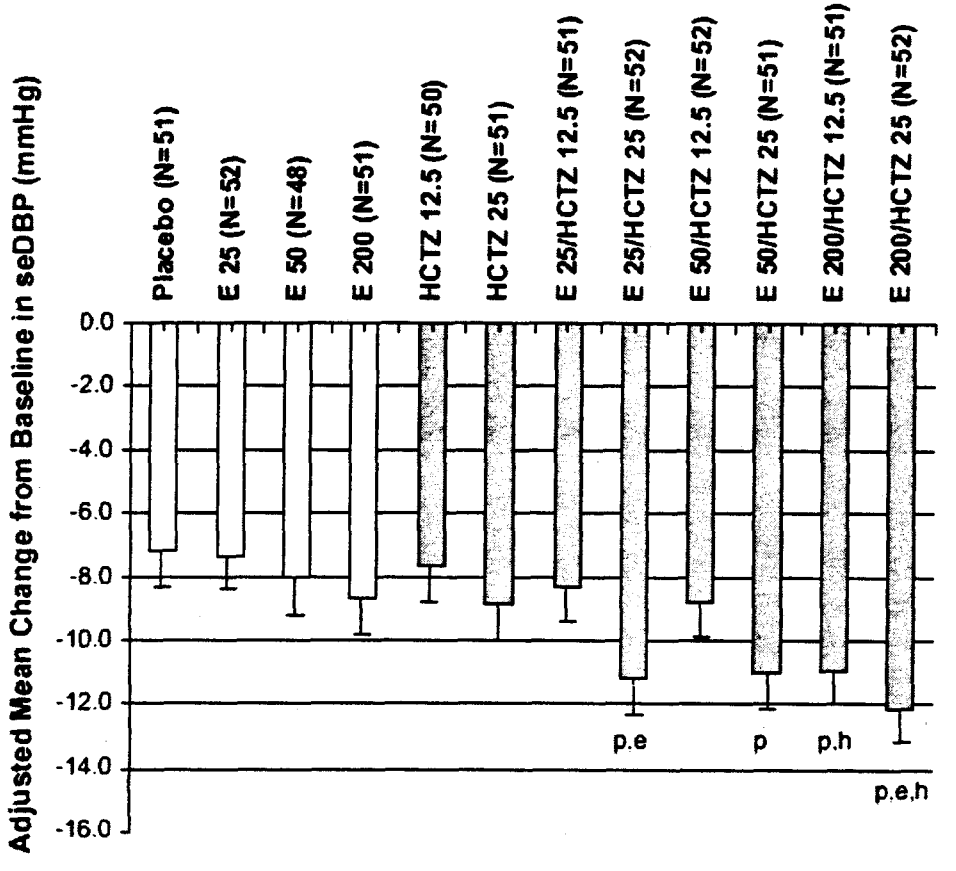
Patients were assigned, in the order in which they were enrolled into the study, to receive their allocated treatment according to a sponsor-prepared computer-generated randomization schedule. Investigational drug supplies consisted of 7-day blister packs of six tablets per day. All patients were instructed to take six tablets in the morning upon rising.

B.3.4.2 Efficacy

B.3.4.2.1 Blood Pressure Endpoints

B.3.4.2.1.1 Sponsor's Presentation of Blood Pressure Endpoints

The sponsor's graphic presentation of the primary endpoint is shown in the figure below:



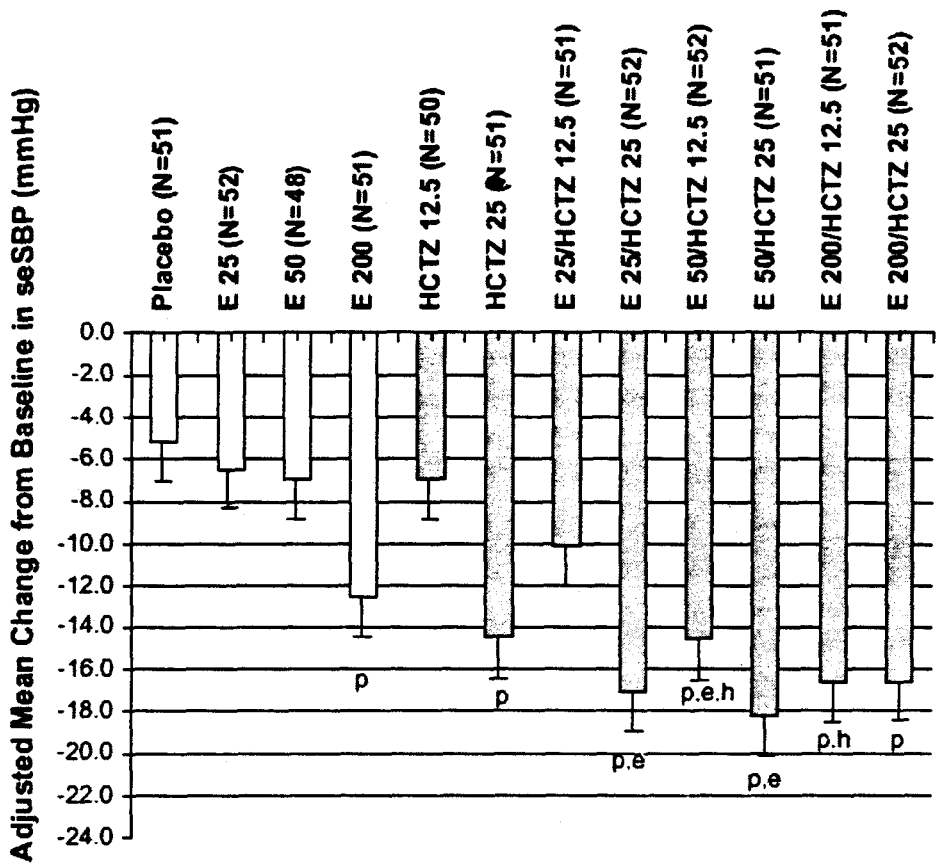
p=statistically significantly different from placebo ($p \leq 0.020$).
e=statistically significantly different from corresponding eplerenone monotherapy ($p \leq 0.030$).
h=statistically significantly different from corresponding HCTZ monotherapy ($p \leq 0.049$).
E=eplerenone, HCTZ=hydrochlorothiazide

Figure 93: Sponsor's Adjusted Mean Change from Baseline to Final Visit (LOCF) in seDBP (Figure 9.a)

Note the substantial placebo effect and the resulting lack of statistical significance of many group change differences compared to placebo. Eplerenone does appear to have an additive effect

upon DBP reduction with hydrochlorothiazide, although the incremental reduction is minimal beyond the combination of eplerenone 50 mg and hydrochlorothiazide 50 mg.

Changes in SDP were similar and are shown in the following figure.



p=statistically significantly different from placebo ($p \leq 0.005$).
e=statistically significantly different from corresponding eplerenone monotherapy ($p \leq 0.004$).
h=statistically significantly different from corresponding HCTZ monotherapy ($p \leq 0.004$).
E=eplerenone, HCTZ=hydrochlorothiazide

(Figure 9.b)

Figure 94: Sponsor's Adjusted Mean Change from Baseline to Final Visit (LOCF) in seSBP

The sponsor's summary of the eplerenone monotherapy results is the following: "However, the primary efficacy hypothesis that eplerenone monotherapy would reduce seDBP compared to placebo was not achieved. The unexpectedly larger placebo effect possibly influenced interpretation of monotherapy results."

The sponsor's summary of the combination therapy results is the following: "Of the six combination doses tested, eplerenone 50 mg QD/HCTZ 12.5 mg QD was significantly superior

with respect to mean change from Baseline in seSBP and eplerenone 200 mg QD/HCTZ 25mg QD was significantly superior with respect to mean change from Baseline in seDBP compared to each component given alone. Using the Hung procedure, only the combination therapy of eplerenone 25 mg QD/HCTZ 25 mg QD resulted in a significantly greater mean decrease from Baseline to the Final Visit in seDBP compared to either of the corresponding monotherapies."

B.3.4.2.1.1 Reviewer's Analysis of Blood Pressure Endpoints

The reviewer examined the mean BP changes from baseline by country to determine whether country variations could explain the high placebo effect. The reviewer's results are shown in the table below.

Table 79: Reviewer's Mean BP Changes from Baseline by Country

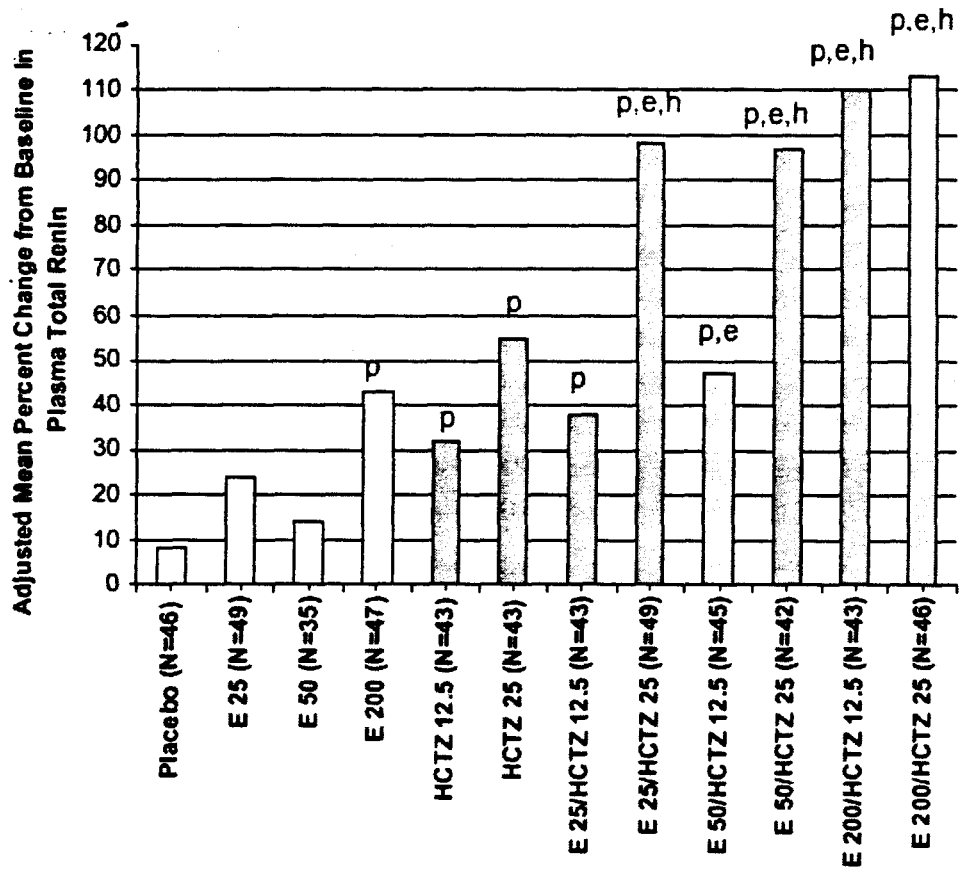
Country	Placebo			Any Treatment		
	N	SBP	DBP	N	SBP	DBP
Belgium	3	-10.0	-4.6	31	-20.9	-13.1
Canada	4	3.3	-4.8	59	-9.0	-6.3
Holland	2	-20.8	-4.0	16	-16.7	-10.7
Poland	3	-10.7	-13.3	24	-10.2	-12.0
Spain	3	4.7	-6.7	23	-14.4	-10.3
Non-U.S.	15	-5.1	-6.7	153	-13.2	-9.6
U.S.	36	-4.8	-7.2	408	-12.9	-9.3
Total	51	-4.9	-7.1	561	-13.0	-9.4

Note that the U.S. numbers are very close to the total averages and not significantly different from the non-U.S. averages. The results for eplerenone and hydrochlorothiazide separately are similar to the above. The numbers for placebo are too small in the non-U.S. countries to draw any conclusions about them. These numbers do not suggest any country variations in the placebo effect. For active treatment effects Belgium appears to be a high outlier and Canada a low outlier. Poland shows extreme changes for diastolic BP in both placebo and active treatment and similar results for both SBP and DBP for placebo and active treatment. However, the close correspondence between the U.S. and non-U.S. averages argues against a major country effect and the other variations are erratic enough so that distinguishing between randomness and systematic bias is impossible.

The reviewer's other analyses were repeats of the sponsor's analyses. The reviewer confirmed the accuracy of the sponsor's results for BP changes.

B.3.4.2.2 Secondary Neurohormonal Endpoints

The sponsor's summary of changes from baseline in total plasma renin is shown in the following figure.

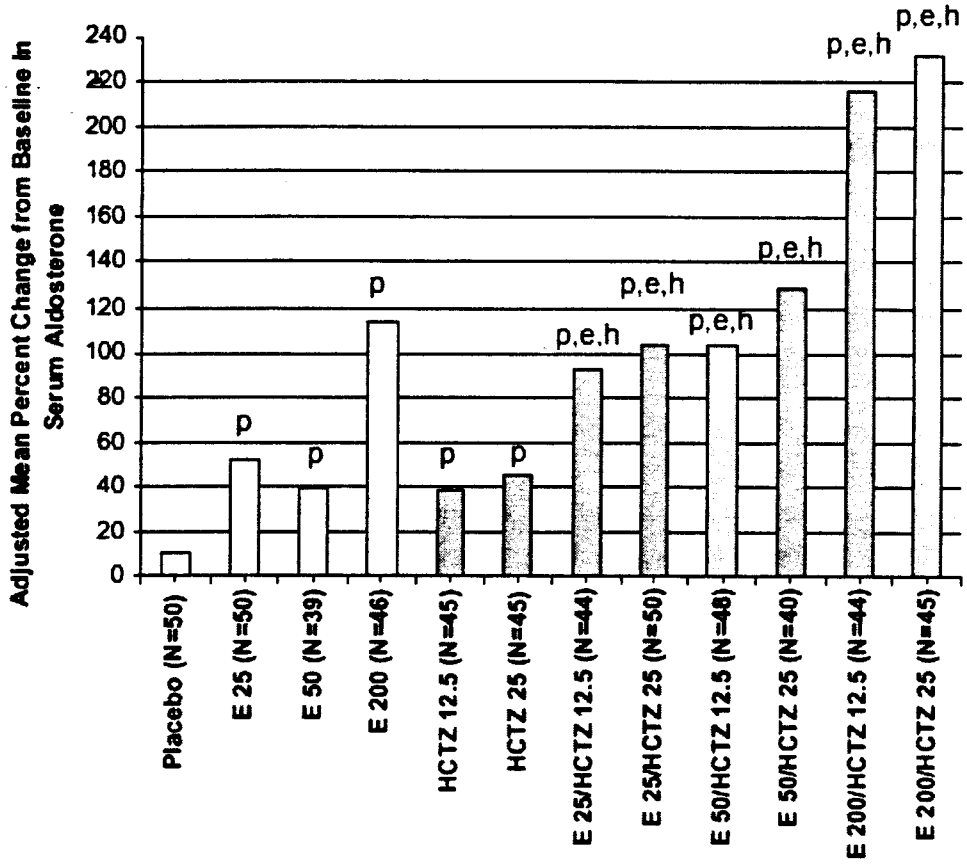


p=statistically significantly different from placebo ($p \leq 0.026$).
e=statistically significantly different from corresponding eplerenone monotherapy ($p \leq 0.007$).
h=statistically significantly different from corresponding HCTZ monotherapy ($p \leq 0.008$).
E=eplerenone, HCTZ=hydrochlorothiazide

(Figure 9.c)

Figure 95: Sponsor's Adjusted Mean Change from Baseline to Final Visit (LOCF) in Plasma Total Renin

The sponsor's summary of changes from baseline in serum aldosterone is shown in the following figure. Note that both eplerenone and hydrochlorothiazide increase plasma total renin and serum aldosterone and their effects appear to be additive.



p significantly different from placebo ($p \leq 0.031$).
e=statistically significantly different from corresponding eplerenone monotherapy ($p \leq 0.019$).
h=statistically significantly different from corresponding HCTZ monotherapy ($p \leq 0.002$).
E=eplerenone, HCTZ=hydrochlorothiazide

(Figure 9.e)

Figure 96: Sponsor's Adjusted Mean Change from Baseline to Final Visit (LOCF) in Serum Aldosterone

The sponsor's summary of the changes in neurohormones is the following:

"Mean percent increases from Baseline in total renin were greater in all 11 active groups compared to the placebo group and in all combination groups compared to the corresponding monotherapy groups. Except for some low dose combinations, significantly greater mean percent increases from Baseline in total renin were observed for combination therapy compared to the corresponding monotherapy. Results for active renin were similar to those observed with total renin. However, of the active monotherapies, only HCTZ 25 mg QD had a significantly greater mean percent increase compared to placebo.

"M ercent increases from Baseline in serum aldosterone were significantly greater in all 11 act oups compared to the placebo group and in all combination treatments compared to the cor nding monotherapy. Decreases in seDBP and seSBP when eplerenone is combined with HC uggest that aldosterone receptor antagonism is an effective means of reducing BP even in the ence of high aldosterone levels.

"Bi ic activity of eplerenone monotherapy as low as 25mg QD was also demonstrated by a sig ant increase in aldosterone versus placebo. All combination treatments demonstrated sig ant increase in serum aldosterone as compared to either corresponding monotherapy."

Rev er's comment: The reviewer did not perform any independent analyses of neurohormones in th tudy. The sponsor's results for eplerenone alone, hydrochlorothiazide alone, and the com ation are useful for contrasting with results from other studies for eplerenone alone.

B.3 Safety

The s ety results from this study are integrated into the Integrated Summary of Safety. The safety results of this study are summarized briefly below both with regard to unusual events in this study and events related to the combination of eplerenone with hydrochlorothiazide.

B.3.4.3.1 Exposure

All 617 randomized patients received at least one dose of study drug. The majority of patients in each group were exposed to study drug for at least six weeks. The sponsor's summary of exposure is shown in the following figure.

	Days of Exposure				
Group	≥1	≥15	≥29	≥43	≥57
Placebo	51	49	45	43	18
Eplerenone 25 mg QD	52	51	48	48	15
Eplerenone 50 mg QD	49	45	42	40	24
Eplerenone 200 mg QD	51	50	47	46	24
HCTZ 12.5 mg QD	51	49	48	46	23
HCTZ 25 mg QD	51	49	48	44	22
Eplerenone 25 mg QD/ HCTZ 12.5 mg QD	51	48	45	44	23
Eplerenone 25 mg QD/ HCTZ 25 mg QD	52	48	46	45	18
Eplerenone 50 mg QD/ HCTZ 12.5 mg QD	52	49	48	47	18
Eplerenone 50 mg QD/ HCTZ 25 mg QD	51	50	49	45	18
Eplerenone 200 mg QD/ HCTZ 12.5 mg QD	51	49	47	45	20
Eplerenone 200 mg QD/ HCTZ 25 mg QD	52	51	48	47	19

Figure 97: Sponsor's Extent of Exposure (Table 10.a)

B.3.4.3.2 Serious Adverse Events

B.3.4.3.2.1 Deaths

There were no deaths reported.

B.3.4.3.2.2 Serious Adverse Events

SAEs occurred in 18 patients. The events were diverse and fairly evenly distributed among the groups. The most noteworthy events were two cerebrovascular hemorrhages. One was a cerebral hemorrhage in a 58-year-old Asian female on day 61 of eplerenone 200 mg monotherapy and the other was a subarachnoid hemorrhage on day 54 in a 50-year-old white male on combination eplerenone 200 mg and hydrochlorothiazide 25 mg. The patient with cerebral hemorrhage had a baseline BP of 165/99 and a last reported BP of 144/100. The patient with subarachnoid hemorrhage had a baseline BP of 138/99 and a last reported BP of 120/92. Recorded blood pressures were similar to the last readings for all visits during the active treatment period.

Reviewer's comment: Reporting of the cerebral hemorrhage in the NDA is problematic. The event is reported as "a serious adverse event of cerebral hemorrhage occurred in a eplerenone 200 mg QD patient 32 days after the last dose of study drug." The patient number 39850795 was last seen on July 28, 1999, and no adverse events were recorded then. The cerebral hemorrhage is recorded as occurring on August 29, 1999. There is no record of termination of the patient on

July 28, 1999, although that is the date recorded for termination in the NDA files. A similar discrepancy, also for a patient with a CVA, is present in the NDA for a patient in Study 021. The sponsor confirmed that the wording in the NDA was misleading for the patient in Study 021.

The data files regarding symptomatic AEs appear to be complete and correspond to the case report forms. The reviewer has used his analyses of the data files rather than relying upon the sponsor's text.

B.3.4.3.3 Events Leading to Discontinuation

A total of 23 patients were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. Nausea (four patients, all in combination treatment groups), dizziness (three patients) and fatigue (three patients) were the most frequently reported adverse events that led to premature withdrawal from the study. Patients withdrawn for AEs were evenly distributed among the treatment groups.

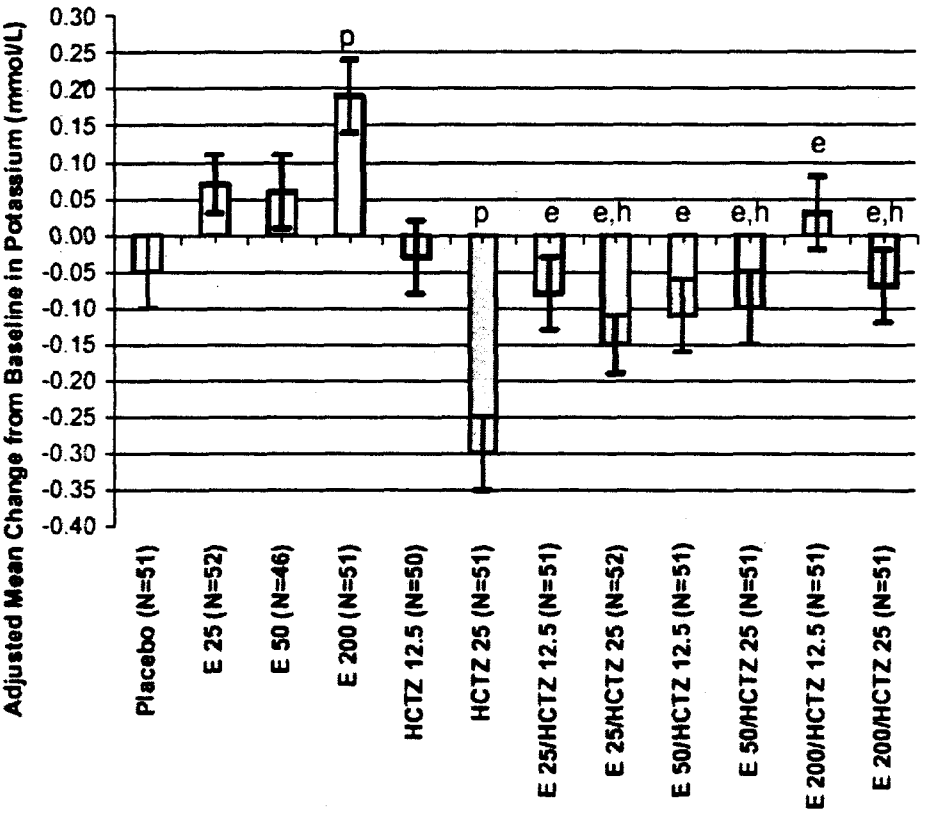
B.3.4.3.4 Events of Special Interest

Hypotension

One eplerenone 25 mg QD/HCTZ 12.5 mg QD patient experienced postural hypotension after the first dose of study medication. This event lasted four days.

Hyperkalemia

No patient experienced a serious adverse event of hyperkalemia. One placebo patient was prematurely withdrawn from the study due to mild hyperkalemia (5.1 mmol/L). Potassium levels had returned to normal (4.3 mmol/L) by the last observation for this patient. No other patients experienced an adverse event of hyperkalemia. The adjusted mean changes from baseline in potassium are shown in the figure below.



p=statistically significantly different from placebo ($p < 0.001$).
e=statistically significantly different from corresponding eplerenone monotherapy ($p \leq 0.019$).
h=statistically significantly different from corresponding HCTZ monotherapy ($p \leq 0.017$).
E=eplerenone, HCTZ=hydrochlorothiazide

(Figure 10.a)

Figure 98: Sponsor's Adjusted Mean Change from Baseline to the Final Visit in Serum Potassium

Sex Hormone-Related Events

Two patients, both on combination therapy, experienced impotence after six and seven days of treatment. No patients experienced gynecomastia. Two patients, one eplerenone monotherapy age 47 and one hydrochlorothiazide monotherapy age 59, experienced vaginal bleeding.

B.3.4.3.5 Overall Adverse Events

The most common (≥ 5 percent of patients in any group) treatment-emergent adverse events were headache, dizziness, upper respiratory tract infection, peripheral edema, hypertriglyceridemia, influenza-like symptoms, and non-cardiac chest pain. There were no statistically significant differences between any of the active groups and the placebo group in the

incidence of any treatment-emergent adverse event. Nausea was evenly distributed among the groups but vomiting occurred only in the eplerenone and combination therapy groups, with two incidents in the eplerenone 200 mg plus hydrochlorothiazide 25 mg group. Dizziness was reported most frequently in the combination therapy groups. Significantly more patients in the eplerenone 200 mg QD group reported treatment-emergent adverse events compared to the placebo group (54.9 vs. 31.4 percent).

B.3.4.3.6 Overdose

No overdoses were reported.

B.3.5 Summary

B.3.5.1 Efficacy Summary

The sponsor's initial summary comments regarding efficacy are the following: "While both eplerenone and HCTZ decreased BP in a dose-dependent manner, none of the monotherapy treatment groups demonstrated significant differences from placebo. The large placebo response (change from baseline in seDBP of –7.2 mmHg) should be noted as one factor in interpreting this lack of significance for both eplerenone and HCTZ. In contrast to the present study, a previous monotherapy study reported a seDBP reduction that was significantly greater with eplerenone 50 mg (-4.5 mmHg) compared to placebo (-1.1 mmHg) (36). When compared to placebo, all combination therapies except eplerenone 25mg/HCTZ 12.5 mg and eplerenone 50 mg/HCTZ12.5 mg significantly reduced seDBP. Significant reductions in seSBP occurred in all combinations except eplerenone 25 mg/ HCTZ 12.5 mg compared to placebo. Difference in Baseline BP, age, gender, and renin status provided no explanation for the large placebo response."

Reviewer's comment: The sponsor's summary is accurate.

B.3.5.2 Safety Summary

The sponsor's initial summary comments regarding efficacy are the following: "Eplerenone as monotherapy or co-administered with HCTZ was safe and well tolerated. There were no significant differences between eplerenone and placebo or HCTZ in the incidence of any treatment-emergent adverse events, the incidence of serious adverse events, or in the incidence of adverse events causing premature withdrawal. Importantly, there was only one report of hypotension. In contrast to what one might anticipate with spironolactone (40), there were no reports of impotence, gynecomastia, or breast pain in eplerenone monotherapy patients. However, the duration of treatment in the study may have been insufficient to observe such side effects."

Reviewer's comment: Both eplerenone and eplerenone in combination with hydrochlorothiazide appear to have been well tolerated. There may be an increased incidence of more severe nausea and vomiting with combination therapy. Conversely, increases in serum potassium associated with eplerenone monotherapy are reduced with combination therapy with hydrochlorothiazide. Whether there is any significance to the two cases of cerebral bleeds associated with eplerenone therapy is examined further in the Integrated Summary of Safety.

B.3.5.3 Reviewer's Conclusions

In thus study eplerenone or hydrochlorothiazide monotherapies did not reduce DBP greater than placebo, possibly because of the large placebo effect. The only combination that significantly reduced DBP greater than placebo and both monotherapies was the combination of the highest dosages, eplerenone 200 mg and hydrochlorothiazide 25 mg.

Eplerenone combined with hydrochlorothiazide was safe and well tolerated. Other than a possible increased incidence of severe nausea and vomiting there do not appear to be any adverse effects that are increased with combination therapy. Serum potassium increases are reduced with combination therapy.

APPEARS THIS WAY
ON ORIGINAL

B.4 Trial 020, Eplerenone and Losartan in Blacks and Whites with Proteinuria

B.4.1 Background

Study 020 is entitled "A Double-Blind, Randomized, Placebo- and Active-Controlled Comparison Study of the Antihypertensive Effect and Safety of Eplerenone Versus Placebo and Versus Losartan in Black and White Hypertensive Patients." The primary objectives of this study were to compare the antihypertensive effect of eplerenone versus placebo in all patients (black and white) with mild to moderate essential hypertension as measured by seated diastolic BP at Week 16 and to evaluate the safety and tolerability of the drug. The secondary objectives were to compare the antihypertensive and other pharmacodynamic actions of eplerenone and losartan in black and white patients. Randomization was stratified by race in a 2:1 ratio of black patients to white. Eplerenone dosages were 50, 100, and 200 mg; losartan dosages were 50 and 100 mg. Both were titrated to effect.

B.4.2 Design and Conduct

After a two to four-week placebo run-in, adult (age > 18) patients with mild to moderate primary hypertension (DBP 95-109, SBP < 180) were randomized to placebo, eplerenone, or losartan. Black patients and white patients were enrolled in approximately a 2:1 ratio, balanced and pre-stratified within each study center. Starting dosages were 50 mg for eplerenone and 50 mg for losartan. Dosages were up-titrated at four and eight weeks if BP exceeded 140/90. Eplerenone had two possible up-titrations (100 mg and 200 mg) while losartan had only one (100 mg).

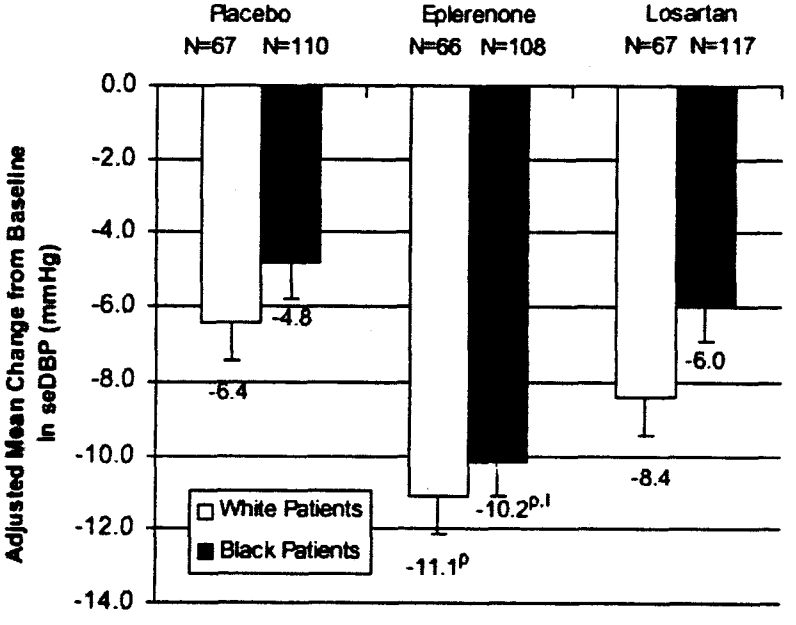
50 Investigators randomized 551 patients at 50 sites in the United States and South Africa. 79 percent of the randomized patients were from the U.S. 181 patients were randomized to placebo, 182 to eplerenone, and 188 to losartan. The study was conducted from January 4, 2000, to January 19, 2001. There were no significant differences among the placebo, eplerenone, and losartan groups with respect to mean age, race, weight, height, or body mass index. Mean baseline BP was similar in the placebo, eplerenone, and losartan groups.

The percentage of patients withdrawn was lowest in the eplerenone group (26 percent). The percentages of patients withdrawn in the placebo and losartan groups were both about 41 percent. The most common reason for premature withdrawal in each group was treatment failure. The percentages of patients who were prematurely withdrawn due to treatment failure in the placebo and losartan groups (25 percent and 23 percent, respectively) were approximately twice that in the eplerenone group (11 percent). Sixteen (four placebo, eight eplerenone, and four losartan) patients did not have a post-baseline assessment and were excluded from all efficacy analyses.

B.4.3 Efficacy Summary

The primary efficacy variable was trough cuff DBP at week 16 or at the final visit in case of early withdrawal. The mean adjusted change was -5.3 for the placebo, –10.3 for the eplerenone, and –6.9 for the losartan group. The differences of eplerenone from placebo and from losartan were highly statistically significant ($p < 0.001$). The mean adjusted change in SBP was –3.4 for the placebo, –12.8 for the eplerenone, and –6.3 for the losartan group, also highly statistically significant differences.

One secondary endpoint was the change in DBP within and between racial groups. The changes by racial group are shown in the figure below. Changes in SBP by race were similar. Eplerenone appears efficacious in both blacks and whites. The reviewer did not find any significant country variations in these results.



p = statistically significantly different from placebo ($p \leq 0.001$).
l = statistically significantly different from losartan ($p = 0.001$). (Figure 9.b)

Figure 99: Sponsor's Adjusted Mean Change From Baseline in seDBP at Week 16

Regarding other secondary endpoints, treatment with eplerenone or losartan reduced urinary albumin/creatinine ration in all patients and white patients compared to placebo, but eplerenone did not produce a statistically significant reduction in black patients. Eplerenone increased active renin and aldosterone levels and losartan increased active renin and decreased aldosterone. No changes were seen with placebo.

B.4.4 Safety Summary

All 551 randomized patients received at least one dose of study drug. The majority of patients in each group were exposed to study drug for at least three months. No deaths were reported. A total of 14 patients (three placebo, six eplerenone, and five losartan) experienced serious adverse events. Among these were two breast neoplasms detected during screening and day 1 and a pituitary adenoma detected day 10 in eplerenone patients. A total of 21 patients (six placebo, seven eplerenone, and eight losartan) were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. One of these was a 61 year old white female with a cerebral infarction on day 72 of eplerenone 50 mg therapy. Her baseline BP was 156/96 and her last recorded BP was 134/83 with pressures as low as 122-166/82-84. She also experienced sinusitis. One losartan patient withdrew because of a cerebral aneurysm.

One placebo and two eplerenone patients had reported AEs of hyperkalemia, which led to withdrawal for one of the eplerenone patients. No patients developed gynecomastia, but one placebo and one losartan patient reported impotence and two eplerenone and one losartan patient experienced abnormal vaginal bleeding.

Overall eplerenone was well-tolerated in this study. No unusual toxicities or patterns were evident in this study. The safety findings from this study are incorporated into the reviewer's ISS.

B.4.5 Conclusions

Eplerenone was an efficacious antihypertensive in both black and white patients in this study. That eplerenone had a greater antihypertensive effect than losartan in blacks is not surprising because losartan is known to be less effective in that racial group. That eplerenone is equally efficacious in blacks and whites is not established by this study. This study was not powered as a noninferiority trial of eplerenone in blacks and whites.

B.5 Trial 022, Eplerenone vs. Amlodipine in Systolic Hypertension

B.5.1 Background

Study 022 is entitled "A Double-Blind, Randomized, Active-Controlled Comparison Study of the Antihypertensive Effect of Eplerenone Versus Amlodipine in Patients with Elevated Systolic Blood Pressure." Elevated SBP was defined as either SBP ≥ 150 and < 165 mmHg, and pulse pressure ≥ 70 mm Hg, or SBP ≥ 165 and < 200 mmHg and DBP < 95 mmHg. Age was restricted to ≥ 50. The original protocol dated August 11, 1999, specified a comparison between the two groups of mean change in seated trough cuff SBP at week 24. An amendment dated January 10, 2001, (about one month before study completion) changed the primary endpoint to a non-inferiority comparison with a margin of 6 mm Hg.

B.5.2 Design and Conduct

Blood pressure and age criteria are listed under Background above. After a two- to four-week single-blind, placebo run-in period patients were randomized in an equal ratio to receive either eplerenone 50 mg QD or amlodipine 2.5 mg QD. If SBP was uncontrolled (SBP ≥ 140 mmHg) after two weeks of treatment, the dose of study medication was up-titrated by one dose level to eplerenone 100 mg QD or amlodipine 5 mg QD. If SBP was uncontrolled at week 6 or thereafter, the dose of study medication was up-titrated by one dose level (to eplerenone 100 mg or 200 mg QD or amlodipine 5 mg QD or 10 mg QD). The primary endpoint was mean change from baseline in seated trough cuff SBP at week 24. ABPM was also done.

43 Investigators randomized 269 patients at 43 study sites in the United States, Australia, Belgium, Canada, and New Zealand. 68 percent of the patients were from the U.S. The study was conducted from January 3, 2000, to February 16, 2001. There were no significant differences between the eplerenone and amlodipine groups with respect to mean age, ethnicity, gender, weight, height, or body mass index. Mean BP at baseline was similar in the eplerenone and amlodipine groups. 53 percent of the patients were female but only 3 percent were black. The mean age was 68. The percentage of patients withdrawn from the study was 23.9 percent in the eplerenone group and 30.4 percent in the amlodipine group. The most common reasons for withdrawal in both groups were treatment-emergent adverse events (7.5 percent eplerenone and 12.6 percent amlodipine) and other reasons (e.g., personal reasons; 7.5 percent eplerenone and 5.9 percent amlodipine). Six eplerenone and three amlodipine patients were excluded from the efficacy because they lacked a post-treatment evaluation.

B.5.3 Efficacy Summary

The adjusted mean change in the primary endpoint, adjusted mean seated trough cuff SBP, was –20.5 for eplerenone and –20.1 for amlodipine. These are obviously not significantly different by the original protocol specified superiority analysis. Per the sponsor non-inferiority is established ($p < 0.001$) for the amended non-inferiority primary analysis.

Adjusted mean decreases from baseline in DBP were significant for both agents, -4.5 mm Hg in the eplerenone group and -6.9 mm Hg in the amlodipine group. Based on 95% confidence intervals (-4.4, -0.5) for the treatment difference, the adjusted mean decrease from baseline in DBP was greater (p = 0.014) in the amlodipine group compared to the eplerenone group. Other secondary cardiovascular endpoints (pulse pressure, ABPM HR, PP, SBP, and DBP, carotid-femoral or carotid-radial pulse wave velocity) were not significantly different between the two groups per the sponsor's analyses.

The sponsor's summary of other secondary endpoints is the following: "The collagen marker PIIINP level was normal at Baseline and no clinically significant change was noted by treatment with either agent. 7SIVC was significantly reduced with eplerenone but not amlodipine treatment; however, no differences in treatment effect were noted. ICTP was not significantly modified by either treatment. Markers of fibrinolytic balance (PAI-1 and t-PA) were in the normal range at Baseline and did not change significantly at the Week 24 endpoint. In patients with pre-existing microalbuminuria (Baseline UACR ≥3393 g/mmol), eplerenone treatment resulted in a significantly greater reduction in microalbuminuria than amlodipine treatment (-52.3% and -10.4%, respectively; p = 0.041). Quality of Life (QoL) assessment showed eplerenone had a significant positive effect in the following five symptoms: swelling of feet and ankles, weight gain, nocturia, increased urination, and shortness of breath." (PIIINP = aminoterminal propeptide of type III procollagen; 7SIVC = 7S domain of type IV collagen; ICTP = type I collagen telopeptide; PAI-1 = plasminogen activator inhibitor-1; t-PA = tissue plasminogen activator; UACR = urinary albumin to creatinine ratio).

Two of the secondary efficacy endpoints deserve further comment: (1) In this study eplerenone did not appear to have any significant effect upon PAI-1 levels as opposed to the increases seen in Study 016. The reviewer confirmed the lack of effect upon PAI-1 levels as noted by the sponsor. (2) Eplerenone statistically significantly decreased microalbuminuria. The change from baseline for the geometric mean of UACR was –27 percent for eplerenone and –3 percent for amlodipine. The reviewer confirmed the p of 0.002 for the significance of this difference by ANCOVA with baseline value as the covariate and treatment as factor.

B.5.4 Safety Summary

All 269 randomized patients received at least one dose of study drug. 76 percent of eplerenone patients and 70 percent of amlodipine patients had exposures exceeding 23 weeks.

No deaths were reported in this study. The rates of SAEs were similar in both groups (8 in each group, or about 6 percent). In the eplerenone group, two patients experienced angina pectoris, one unstable angina, and one a myocardial infarction; one of the patients with angina also had a stroke. In the amlodipine group one patient had a myocardial infarction, one had unstable angina, one had heart failure, and one had torsade de pointes. 27 patients (11 eplerenone, 16 amlodipine) were prematurely withdrawn from the study due to the occurrence of at least one

treatment-emergent adverse event. Six amlodipine patients and no eplerenone patients withdrew because of peripheral edema. Two eplerenone patients withdrew because of hyperkalemia.

The overall AE rate was 64 percent in the eplerenone group and 70 percent in the amlodipine group. The sponsor's summary of other AEs is the following: "The only significant difference for the incidence of adverse events in the study was noted for peripheral edema (25.2% amlodipine vs. 3.7% eplerenone). In addition, a significantly greater proportion of amlodipine patients prematurely withdrew from the study due to peripheral edema than eplerenone patients (4.4% vs. 0.0%). Six patients (four eplerenone and two amlodipine) experienced hyperkalemia. One of the eplerenone patients who experienced hyperkalemia also had a potassium level that met laboratory criteria for an event of special interest. An additional amlodipine patient had potassium values that met the laboratory criteria for an event of special interest (potassium > 5.5 mmol/L on two consecutive occasions or ≥ 6.0 mmol/L on any occasion). One amlodipine patient experienced hypotension, two patients (one eplerenone and one amlodipine) experienced postural hypotension, two eplerenone patients experienced impotence, and one eplerenone patient experienced mild hyperuricemia. There were no reports of gynecomastia, menstrual abnormalities, or female breast pain."

B.5.5 Conclusions

In this study of older patients with systolic hypertension, eplerenone 50-200 mg led to a decrease in SBP virtually identical to that with amlodipine 2.5-10 mg QD. However, eplerenone was inferior to amlodipine in reducing DBP. In this population and study duration the serious AE rate was high (6 percent) but identical for the two drugs. Overall AE rates were similar with small differences in the types of AEs experienced, e.g., more peripheral edema with amlodipine and more hyperkalemia with eplerenone.

B.6 Trial 026, Eplerenone vs. Amlodipine ABPM

B.6.1. Background

Study 026 is entitled "A Double-Blind, Randomized, Active-Controlled Comparison Study of the Antihypertensive Effect of Eplerenone Versus Amlodipine Assessed by Ambulatory Blood Pressure Monitoring in Patients with Mild to Moderate Hypertension." The title aptly describes the purpose of the study. Note that the primary endpoint, change in DBP, was evaluated by ambulatory blood pressure monitoring (ABPM). The dosages were eplerenone 50, 100, and 200 mg and amlodipine 2.5, 5, and 10 mg titrated to effect.

B.6.2. Design and Conduct

After a two to four-week placebo run-in, adult (age > 18) patients with mild to moderate primary hypertension (cuff DBP 95-109, SBP < 180) were randomized to eplerenone 50 mg or amlodipine 2.5 mg. If DBP was uncontrolled (DBP ≥ 90 mmHg) at week2, the dose of study medication was up-titrated by one dose level to eplerenone 100 mg or amlodipine 5 mg. If BP was uncontrolled at weeks 4, 6, 8, or 12, the dose of study medication was up-titrated by one dose level (to eplerenone 100 mg or 200 mg or amlodipine 5 mg or 10 mg). If at these visits, the patient had received eplerenone 200 mg or amlodipine 10 mg for at least 14 days and BP was uncontrolled, the patient was to be withdrawn from the study. If symptomatic hypotension (i.e., lightheadedness, dizziness, or syncope associated with low BP) occurred at weeks 4, 6, 8, or 12 and the patient was on dose level 2 or 3, the dose was decreased one dose level (to dose level 1 or 2). If symptomatic hypotension occurred at week 2 or weeks 4, 6, 8, or 12 and the patient was on the lowest dose level (dose level 1), the patient was to be withdrawn. The priority endpoint was mean change from baseline in mean 24-hour DBP by ABPM at week 16.

26 investigators randomized 179 patients at 26 study sites in Germany, Netherlands, Spain, and the United Kingdom. The study was conducted from April 14, 2000, to January 18, 2001. There were no significant differences between the eplerenone and amlodipine groups with respect to mean age, ethnicity, gender, weight, height, or body mass index. All but one patient were white. Mean 24-hour BP by ABPM and cuff BP at baseline were similar in the eplerenone and amlodipine groups.

Thirty-six patients (18 eplerenone and 18 amlodipine) were excluded from the primary efficacy analysis primarily because the final post-baseline ABPM did not meet validity criteria. Thirty-three patients violated the inclusion and/or exclusion criteria; the majority of these patients did not have BP in the specified range. Patients were not excluded from analyses because of these violations.

54 eplerenone (61 percent) and 74 (81 percent) amlodipine patient completed the study. The major reasons for failure to complete was treatment failure in the eplerenone group, 24 patients or 28 percent, as opposed to 8 patients, or 9 percent, in the amlodipine group.

B.6.3. Efficacy Summary

The protocol pre-specified margin for establishing non-inferiority was 4 mm Hg. The mean change in DBP by ABPM was –7.5 mmHg in the eplerenone group and -10.2 mmHg in the amlodipine group. The 95% confidence interval for the treatment difference (-4.9, -0.6) demonstrated a significant difference between the groups in mean change from baseline to the week 16 endpoint in 24-hour DBP (p= 0.013).

Regarding secondary endpoints, the mean change in SBP by ABPM was -14.0 mmHg in the eplerenone group and -16.1 mmHg in the amlodipine group at the week 16 endpoint. Based on the 95% confidence interval (-5.3, 1.0) for the treatment difference, the adjusted mean decreases from baseline in mean 24-hour SBP were not significantly different between the eplerenone and amlodipine groups. Decrease from baseline in cuff DBP in the eplerenone group (-10.5 mmHg) was significantly less than that for amlodipine group (-13.2 mmHg) (p = 0.020). Decrease from baseline in cuff SBP in the eplerenone group (-15.0 mmHg) was not significantly less than that for amlodipine group (-17.1 mmHg).

Mean daytime DBP by ABPM was greater in the eplerenone group compared to the amlodipine group at baseline and the week 16 endpoint; however, the mean nighttime DBP by ABPM was similar in both groups. Mean daytime SBP by ABPM was lower in the amlodipine group compared to the eplerenone group at the week 16 endpoint; mean nighttime values were similar in each group.

Total and active plasma renin and serum aldosterone demonstrated significantly greater increases from Baseline at the Week 16 endpoint in the eplerenone group compared to the amlodipine group (p =0.012). Plasma cortisol levels did not differ between the two groups.

B.6.4. Safety Summary

All 179 randomized patients received at least one dose of study drug. 61 percent of eplerenone and 81 percent of amlodipine patients were exposed to study drug for at least 15 weeks. No patients died during the study. Three patients, two amlodipine and one eplerenone, had SAEs. The eplerenone SAE was a cerebral infarct. 11 patients (four eplerenone, seven amlodipine) were prematurely withdrawn from the study due to adverse events. The reasons for withdrawal were diverse but included two withdrawals for dyspnea and the cerebral infarct in eplerenone patients. Overall rates of AEs were similar in the two groups except amlodipine patients experienced a greater rate of peripheral edema (12 percent amlodipine vs. 0 percent eplerenone.) No patients experienced a hyperkalemia AE. One 69 year old male eplerenone patient had a "swollen breast" after 35 days of treatment and another experienced impotence. The AEs and other safety information from this study are included in the Integrated Summary of Safety.

Plasminogen activation inhibitor-1 (PAI-1) was measured in this study. The geometric mean increased about 16 percent with eplerenone therapy, significantly greater than baseline.