However, PAI-1 also increased (6 percent) with amlodipine therapy. The differences in PAI-1 levels between eplerenone and amlodipine were not statistically significant.

B.6.5. Conclusions

Eplerenone was significantly less efficacious in reducing DBP than amlodipine evaluated either by ABPM or cuff seated trough DBP. Eplerenone reduced SBP less than amlodipine, although the differences in SBP were not statistically significant.

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B.7 Trial 016, Titrated Eplerenone vs. Enalapril

B.7.1 Background

Study 016 is entitled "A Double-Blind, Randomized Titration-to-Effect Study of the Antihypertensive Effect of Eplerenone Versus Enalapril in Patients with Essential Hypertension." The objectives of this study were to compare the long-term safety and antihypertensive effect of eplerenone with enalapril using doses titrated to antihypertensive effect, and to compare the maintenance of the effect after down-titration. This study had two arms (eplerenone 50-200 mg and enalapril 10-40 mg) and included an initial 24-week up-titration and then a forced one-level down-titration at 24 weeks followed by 6-months follow-up with one up-titration allowed. Note that the primary endpoint for this trial was changed from superiority to non-inferiority after trial completion.

B.7.2 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 eplerenone 50 mg or enalapril 10 mg QD. If at week 4, 8, 12, or any subsequent visit up to week 24, DBP was uncontrolled (DBP ≥90 mmHg), the dose was up-titrated by one dose level to level 2 (eplerenone 100 mg QD or enalapril 20 mg QD) or level 3 (eplerenone 200 mg QD or enalapril 40 mg.) After 24 weeks of double-blind treatment, all patients were down titrated by one dose level (to eplerenone 25 mg or enalapril 5 mg QD for patients at level 1) and followed monthly for six months. After week 24, study medication was up-titrated by one dose level once for patients whose BP was uncontrolled. The primary endpoint was mean change from baseline in trough cuff seated DBP at week 24.

38 Investigators randomized 499 patients (253 eplerenone and 246 enalapril) at 38 study sites in the United States, Canada, Poland, Germany, and Spain. 16 percent of the patients were from the U.S. and 39 percent were from Germany. The study was conducted from May 27, 1999, through November 24, 2000. There were no significant differences between the eplerenone and enalapril groups with respect to mean age, ethnicity, gender, weight, height, or body mass index. Mean baseline BP was similar in the eplerenone and enalapril groups.

64 percent of eplerenone patients and 63 percent of enalapril patients were continuing in the study at the week 24 primary endpoint. The most common reasons for premature withdrawal in each group were treatment failure (23 percent eplerenone and 23 percent enalapril) and adverse event (8 percent eplerenone and 9 percent enalapril). Three eplerenone and two enalapril randomized patients were excluded from the primary efficacy analysis. 314 (161 eplerenone, 153 enalapril) patients had controlled BP at the week 24 primary endpoint and were included in the efficacy analyses for the six-month period after forced down titration. 140 eplerenone (55 percent of randomized) and 131 enalapril (53 percent of randomized) completed the 12 month study.

B.7.3 Efficacy Summary

The original protocol was dated November 19, 1998. A revised protocol dated February 16, 1999, incorporated changes from an investigator's meeting including modification of some entry criteria, clarification of some laboratory tests, and clarification of blood pressure measurement requirements. The revised protocol has this description of the sample size calculations:

"The sample size was calculated to assure that adequate numbers of patients enter the down-titration phase to address secondary objectives of the trial. Approximately 180 patients in each group must complete the initial 24-week treatment period and be down-titrated in order to detect a 15% difference in the overall percentage of patients requiring re-up-titration due to rebound hypertension during the subsequent six-month period (80% power, two-tailed alpha=0.05). It is assumed for this calculation that 50% of patients down-titrated in the enalapril group will require re-up-titration for uncontrolled BP, as compared to 35% of patients on eplerenone. Assuming that 20% of patients drop out during the initial 24-week up-titration period, a total of 450 patients should be randomized. With 225 patients evaluated in each group during the initial up-titration phase, the study has over 90% power to detect a treatment difference of at least 2.5 mmHg in mean change from baseline seDBP after six months of treatment (two-tailed 5% significance level, SD=8.0 mmHg)." Note the two-tailed difference of 2.5 mm Hg. The protocol also states that "Treatment comparisons will be based on least squares means obtained via a SAS type III analysis with baseline value, treatment and center in the model."

An administrative change dated February 6, 2001, changed the primary endpoint analysis to the following: "With 123 patients evaluated in each group during the initial up-titration phase, the study has over 90% power for treatment comparison (non-inferiority) of at least 3.0 mmHg in mean change from baseline seDBP after six months of treatment (one-tailed 5% significance level, SD = 8.0 mmHg)." Note the change from a superiority to a non-inferiority hypothesis after trial completion.

Clearly the study does not demonstrate that eplerenone is superior to enalapril (or the reverse.) The unadjusted mean changes from baseline in DBP were virtually identical for the two groups: -11.7 mm Hg for eplerenone and –11.3 for enalapril (p = 0.52 by the protocol-specified ANCOVA.) In the protocol-specified analysis pooled center is a significant factor. The data show substantial differences in the results by country, shown in the table below.

Table 80: Reviewer's Mean Changes in DBP from Baseline by Country

Country	Eplerenone	Enalapril	Both
Canada	-8.4	-9.4	-8.8
Germany	-13.3	-12.4	-12.8
Poland	-15.6	-18.3	-17.0
Spain	-14.0	-10.3	-12.1
U.S.	-5.3	-5.9	-5.6
Total	-11.7	-11.3	-11.5

The results varied by country but are reasonably consistent between eplerenone and enalapril for most countries. (A center*treatment or country*treatment interaction term is not a significant factor in the ANOVA.) The effects were smallest in the U.S. Changes in SBP were similar. There is no obvious explanation of the inter-country variations nor any indication that eplerenone and enalapril differ in antihypertensive efficacy.

The sponsor's adjusted mean changes in DBP from baseline are –11.2 for eplerenone and –11.3 for enalapril with $p < 0.001$ for non-inferiority. For SBP the reductions were –14.5 and –12.7 respectively. At the month 12 endpoint, the adjusted mean decreases from baseline in DBP were -13.3 mm Hg in the eplerenone group (N=161) and -14.1 mm Hg in the enalapril group (N=153). These adjusted mean reductions were not significantly different from each other. At the month 12 endpoint, the adjusted mean decreases from Baseline in seSBP were -16.5 mm Hg in the eplerenone group (N=161) and -14.8 mm Hg in the enalapril group (N=153). These adjusted mean reductions were not significantly different from each other. By month 11, 54 percent of the eplerenone group and 48 percent of the enalapril group had required re-up-titration. By log-rank test, there was no significant difference between the eplerenone and enalapril groups in the percentage of patients who required re-up-titration after forced down-titration.

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

"In the eplerenone and enalapril groups, there were increases from Baseline in total and active plasma renin at the Week 24 primary endpoint that were sustained at the Month 12 endpoint. The adjusted mean percent change in active renin was significantly greater in the enalapril group compared to the eplerenone group. In the eplerenone group, there was an increase from Baseline in the geometric mean for serum aldosterone at the Week 24 primary endpoint that was sustained at the Month 12 endpoint. No clinically significant changes in serum aldosterone occurred in the enalapril group at either the Week 24 primary endpoint or at the Month 12 endpoint.

"A significantly greater adjusted mean percent increase in PAI-1 was observed in the eplerenone group (16.0%) compared to the enalapril group (0.7%) at the Week 24 endpoint. No other significant difference between groups was observed at either the Week 24 or Month 12 endpoint for adjusted mean percent changes in PIIINP or PAI-1.

"In all patients, adjusted mean percent change from Baseline to the Week 24 endpoint in urinary albumin:creatinine ratio (UACR) was -21.2% in the eplerenone group and -12.0% in the enalapril group. There was no further change during the subsequent six months for either the eplerenone or enalapril group. No significant differences were observed between groups."

Reviewer's comment: One notable finding is the increase in PAI-1 (plasminogen activator inhibitor) in the eplerenone group. PAI-1 values were variable, with the standard deviation approximating the mean values at baseline that were very near the reported upper limit of normal (14.99). About 4 percent of patients in both groups had PAI-1 values exceeding twice the upper limit of normal; for the 24 week values about 10 percent of eplerenone and 6.5 percent of enalapril patients had values exceeding twice normal. The effects of eplerenone upon PAI and upon thrombotic AEs are explored in the reviewer's Integrated Summary of Safety.

B.7.4 Safety Summary

All 499 randomized patients received at least one dose of study drug. Approximately two-thirds of patients in each group received double-blind study medication for at least 24 weeks and slightly more than half of patients in each group received double-blind study medication for at least 12 months.

One patient on enalapril died of a suspected myocardial infarction (MI). Fifteen patients (seven eplerenone, eight enalapril) experienced serious adverse events during the study. Of these, six (a TIA and "ischemic spinal stenosis" in eplerenone patients, and a suspected MI, "coronary heart disease", a TIA, and a right carotid occlusion in enalapril patients) were possible thrombotic cardiovascular events. An eplerenone patient also experienced thrombophlebitis not classified as serious. Of these seven patients, PAI-1 levels were normal at baseline but elevated (23.1) at final visit in the patient with "ischemic spinal stenosis" and elevated both at baseline (27.5) and at final (17) in the patient with the suspected MI. PAI-1 values were within normal limits in the other patients. Blood pressure was poorly controlled in the 69 year-old white male eplerenone patient who experienced the TIA (baseline 182/100, final 176/102).

A total of 58 patients (26 eplerenone, 32 enalapril) were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. The most common treatment-emergent adverse events leading to premature withdrawal in the eplerenone group were hypotension (four patients), headache (four patients), nausea (four patients), and liver enzyme elevation (three patients). The most common treatment-emergent adverse events leading to premature withdrawal in the enalapril group were headache (five patients), coughing (five patients), nausea (five patients), peripheral pain (three patients), and abdominal pain (three patients). One eplerenone patient was dropped due to breast cancer and another was dropped due to prostatic cancer.

Eleven patients (6 eplerenone and 5 enalapril) experienced AEs of elevated liver enzymes. Three eplerenone and two enalapril patients group were withdrawn because of the elevations. Most of the elevations were mild to moderate, e.g., < 3 times upper limit of normal). In one eplerenone patient the elevations were more severe and associated with elevated bilirubin. For this 45 year old white male one eplerenone 200 mg the maximum ALT was 472 (>10X), AST 232 (>5X), GGT 739 (>10X), alkaline phosphatase 271 (2.5X) and bilirubin 50 (2.5X) on day 85 with completely normal baseline values. The CRF only records the elevated enzyme and bilirubin values as AEs. The lab values document continued elevation of alkaline phosphatase, ALT, and GGT on day 99 and normal values except for a slightly elevated GGT (108) on day 113. The sponsor's narrative on this patient from the ISS is the following:

"Study 016: Patient # US1001-20840026, was a 45-year-old Caucasian male with a history of arthroscopy, psoriasis, and PPD skin test. He received his first dose of eplerenone 50 mg QD on 27 Jul 1999 (Baseline). His dose was increased to eplerenone 100 mg QD on 25 Aug 1999 (Day 30) and increased to 200 mg QD on 21 Sep 1999 (Day 57); his last dose of eplerenone 200 mg

QD was on 20 Oct 1999 (Day 86). He entered the study with normal values for ALT, AST, alkaline phosphatase, and total bilirubin. By Day 85, the patient had developed elevations in ALT, AST, alkaline phosphatase, and total bilirubin values. The abnormalities had begun to resolve by Day 99, 13 days after the last dose of study medication. Concomitant medications included acetaminophen taken for three days, two weeks prior to the elevation."

The sponsor's summary regarding safety includes the following:

"There were no significant differences between the eplerenone and enalapril groups in the overall incidence of treatment-emergent adverse events. Significantly greater proportions of enalapril patients experienced hyperglycemia (2.8% vs. 0.0%), coughing (6.5% vs. 2.4%), and urinary tract infection (2.8% vs. 0.4%) compared to eplerenone patients. Eplerenone patients did not experience any adverse events in greater proportions than enalapril.

"Four patients (two eplerenone and two enalapril) experienced hyperkalemia. One of the eplerenone patients and one enalapril patient who experienced hyperkalemia also had a potassium level that met laboratory criteria for an event of special interest. Six patients (four eplerenone and two enalapril) experienced hypotension, three patients (one eplerenone and two enalapril) experienced impotence, two eplerenone patients experienced gynecomastia, and six patients (two eplerenone and four enalapril) experienced mild hyperuricemia. One eplerenone patient and one enalapril patient experienced menstrual disorder and one enalapril patient experienced female breast pain."

B.7.5 Conclusions

This study failed to demonstrate that eplerenone was superior to enalapril in antihypertensive effect. The data suggest that eplerenone at dosages of 25 to 200 mg has a similar antihypertensive effect to enalapril at dosages of 5 to 40 mg.

The significance of the changes in PAI is unclear. Numerically thrombotic cardiovascular events were more frequent in the enalapril group, although the difference is not statistically significant. PAI changes are examined further in the reviewer's ISS.

The two cases of gynecomastia are noteworthy in that they occurred only in the eplerenone cases and with timing (183 and 188 days) also typical of spironolactone-induced gynecomastia. The one case of elevated liver enzymes and hyperbilirubinemia without any other explanation in an eplerenone patient is also worrisome. Liver enzyme elevations are also examined further in the reviewer's ISS.

B.8 Trial 018, Eplerenone vs. Spironolactone in Primary Aldosteronism

B.8.1 Background

Study 018 is entitled "A Double-Blind, Controlled, Randomized Comparison Study of the Antihypertensive Effect of Eplerenone and Spironolactone in Patients with Hypertension Secondary to Primary Aldosteronism". Note that this study was in patients with primary hyperaldosteronism. The dosages were titrated and ranged from 100 to 300 mg for eplerenone and 75 to 225 mg QD for spironolactone. The primary endpoint was DBP at 16 weeks with a noninferiority margin of 4 mm Hg.

B.8.2 Design and Conduct

This trial enrolled adult patients (age > 18) with a history of primary aldosteronism secondary to either adenoma or idiopathic forms and documented by elevated aldosterone or renin levels or radiographic evidence of adrenal hyperplasia or adenoma. After a two to three-week placebo run-in, the patients with mild to moderately severe hypertension (DBP 95-119, SBP < 200) were randomized to eplerenone 100 mg or spironolactone 75 mg QD. If BP was uncontrolled (DBP ≥ 90 mmHg) at weeks 4, 8, or 12, the dose of study medication was increased by one dose level to eplerenone 200 or 300 mg QD or spironolactone 150 or 225 mg QD. Endpoint evaluations were at week 16.

23 Investigators randomized 141 (70 eplerenone, 71 spironolactone) patients at 23 sites in the U.S., France, Spain, and the United Kingdom. 30 percent of the patients were from the U.S. and 38 percent were from Spain. The study was conducted from August 5, 1999, to March 20, 2001. There were no significant differences between the eplerenone and spironolactone groups with respect to mean age, ethnicity, gender, or height. The majority (63 percent for eplerenone and 73 percent for spironolactone) of patients in each group were male. Significant differences ($p \leq 0.047$) between the eplerenone and spironolactone groups were observed for female weight (11 kg mean difference) and body mass index. The sponsor considered these differences not important for the results of the study and the reviewer agrees. Mean BP at baseline was similar in the eplerenone and spironolactone groups.

19 of the eplerenone and 16 of the spironolactone patients were taking spironolactone at screening. One eplerenone and two spironolactone patients had protocol violations of taking a dose of spironolactone within 30 days prior to the first dose of study medication.

37 percent of eplerenone patients and 20 percent of spironolactone patients withdrew before study completion. The most common reasons for premature withdrawal in the eplerenone group were treatment failure (20 percent) and adverse event (11 percent). The most common reason for withdrawal in the spironolactone group was adverse event (11 percent). Four patients (two eplerenone and two spironolactone) were excluded from the efficacy analyses because they lacked appropriate post-baseline measurements.

B.8.3 Efficacy Summary

The mean decrease from baseline to week 16 in mean trough cuff seated DBP was –5.6 for eplerenone and –12.5 for spironolactone. Non-inferiority of eplerenone was not established. The 95% confidence interval for the treatment difference in mean change from baseline to the week 16 endpoint in seDBP (-10.6, -3.3) showed that there was a significant difference between the groups ($p < 0.001$). The mean decrease from baseline to week 16 in mean trough cuff seated SDP was –9.9 for eplerenone and –27.0 for spironolactone. This difference was also highly statistically significant ($p < 0.001$).

There was substantial variation in the BP changes by country, although in all four countries the spironolactone decreases exceeded the eplerenone decreases. The decreases were the least in the U.S., particularly for eplerenone. The mean decreases in the U.S. were –5.3/-2.1 for eplerenone and –21.1/-12.2 for spironolactone. The U.S. decreases are similar in magnitude to the decreases seen with placebo in other studies.

Geometric mean total plasma renin increased 64 percent and active plasma renin increased 86 percent in the eplerenone group; the corresponding changes were increases of 171 and 215 percent in the spironolactone group. The differences between the groups were highly statistically significant ($p < 0.001$). Serum aldosterone increased 73 percent in the eplerenone group compared to 112 percent in the spironolactone group ($p = 0.023$). Plasma cortisol changed minimally (- 0.4 percent) in the eplerenone group and increased 13 percent in the spironolactone group ($p = 0.017$).

B.8.4 Safety Summary

All 141 randomized patients received at least one dose of study drug. 61 percent of eplerenone and 78 percent of spironolactone patients had exposures of 15 weeks or more.

No patients died during the study. Five eplerenone and two spironolactone patients experienced SAEs. The eplerenone SAEs included coronary artery disease with ischemia, deep vein thrombosis, and one patient with aortic dissection, stroke, and renal failure starting on day 7. 17 patients (seven eplerenone, 10 spironolactone) were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. Reasons for eplerenone withdrawals were diverse and included headache in two patients and the SAEs of ischemia and aortic dissection. Spironolactone withdrawals included two cases each of hyperkalemia, impotence, heavy menstruation, and gynecomastia.

Two eplerenone and 11 spironolactone male patients reported breast-related AEs. For eplerenone there were one each breast discomfort and breast enlargement AEs. For spironolactone there were seven reports of breast pain or soreness, three reports of breast enlargement or gynecomastia, and one report of both. In addition to the two withdrawals for heavy menstruation four female spironolactone patients experienced breast pain AEs.

One eplerenone and seven spironolactone patients had hyperkalemia AEs reported. Of these one eplerenone and four spironolactone patients met the sponsor's laboratory criteria for hyperkalemia (two consecutive levels > 5.5 mmol/L or one value ≥ 6.0 mmol/L).

B.8.5 Conclusions

In this study in patients with primary aldosteronism spironolactone 75-225 mg QD was clearly more efficacious in controlling blood pressure than eplerenone 100-300 mg. Spironolactone also had evidence of greater activity in changes in renin and aldosterone. However, spironolactone at these dosages also produced more hyperkalemia and sex-hormone related AEs.

B.9 Trial 019, Eplerenone vs. Losartan in Low Renin Hypertension

B.9.1 Background

Study 019 is entitled "A Double-Blind, Randomized Comparison of Eplerenone and Losartan in Patients with Low Renin Hypertension." Low renin was defined as morning plasma renin activity ≤ 1.0 ng/mL/h after having been seated for 30 minutes and off β-blockers and clonidine for ≥ 2 weeks or an active renin value ≤ 25 pg/mL. Eplerenone was titrated from 100 to 200 mg QD and then hydrochlorothiazide 12.5 and 25 mg could be added; losartan was titrated from 50 to 100 mg QD before adding hydrochlorothiazide. Endpoints were evaluated at both week 8 (before the addition of hydrochlorothiazide) and week 16. The pre-specified non-inferiority margin was 3.5 mm Hg.

B.9.2 Design and Conduct

The low renin criterion was originally specified as an active renin value ≤ 15 pg/mL. The threshold for active renin was changed to 25 pg/ml in an amendment dated June 29, 2000. The justification was to allow correlation between the plasma renin activity and active renin results.

After a two to three-week placebo run-in, the patients with mild to moderate hypertension (DBP 90-114, SBP < 200) were randomized to eplerenone 100 mg or losartan 50 mg QD. If, after four weeks of treatment or at following visits, BP was uncontrolled (DBP ≥ 90 mm Hg), the dose of study medication was up-titrated to eplerenone 200 mg or losartan 100 mg. If after eight weeks or at any subsequent visit up to and at week 14, the patient's BP remained uncontrolled on eplerenone 200 mg or losartan 100 mg, HCTZ 12.5 mg was added. If BP remained uncontrolled at subsequent visits after the addition of HCTZ 12.5 mg, the dose of HCTZ was increased to 25 mg. Endpoint evaluations were at week 16.

26 investigators randomized 168 (86 eplerenone and 82 losartan) patients at 26 sites in the U.S., France, Spain, and the United Kingdom. 66 percent of the patients were from the U.S. The study was conducted from November 22, 1999, to April 2, 2001. There were no significant differences between the eplerenone and losartan groups with respect to mean age, ethnicity, gender, weight, height, or body mass index. Mean BP at baseline was similar in the eplerenone and losartan groups. 33 percent of the patients were black. Patients were fairly evenly distributed by race between the two groups, with 30 percent of eplerenone and 35 percent of losartan patients black. Only three patients were Hispanic and one was Asian, so these patients and patients listed as white were reclassified as non-black for the analyses below. Blacks were slightly younger than non-blacks (mean age 52.0 vs. 55.1) but did not have significantly different baseline BP.

Geometric mean baseline values for total (87 vs 103 mU/L) and direct renin (9.4 vs 13.8 mU/L), but not serum aldosterone, differed significantly between blacks and non-blacks. Baseline values for potassium (mean 4.06 vs 4.24 mmol/L) and total protein (mean 74.0 vs. 70.3) also differed significantly between blacks and non-blacks. Baseline values for total, but not direct, renin

differed significantly between males and females, with males having higher values than females (geometric mean 144 vs 101 mU/L).

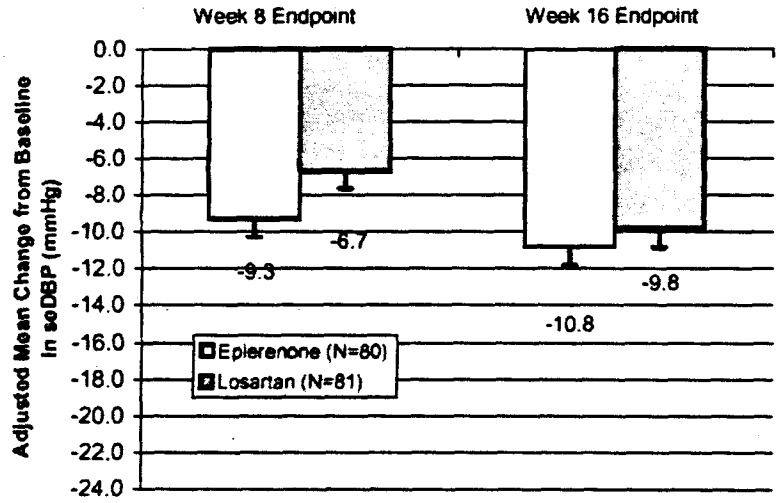
Plasma renin levels in blacks, but not whites, were unevenly distributed between the two groups. Geometric mean direct (8.9 vs 12.7 mU/L) and total (111 vs 129 mU/L) renin levels were lower in the eplerenone arm for blacks.

Considering the baseline direct renin levels, 2 percent of blacks and 19 percent of whites do not meet the original inclusion criterion that the active renin be less than ≤ 15 pg/mL (25 mU/L). The geometric mean baseline direct renin levels by race (black 9.4 vs white 13.8 mU/L) are not substantially different from the levels recorded for Study 020 (black 10.3 vs white 14.1 mU/L) that oversampled blacks 2:1 but did not select upon renin levels.

23 percent of the eplerenone patients and 21 percent of the losartan patients withdrew before study completion. The most common reasons for withdrawal in the eplerenone and losartan groups were adverse events (5.8 percent and 8.5 percent, respectively) and treatment failure (7.0 percent and 7.3 percent, respectively). Seven patients (six eplerenone and one losartan) did not meet the sponsor's intent-to-treat criteria and were excluded from all efficacy analyses because their post-baseline data failed to have a post-baseline BP taken within the dosing period plus one day.

B.9.3 Efficacy Summary

The primary endpoint was change in trough cuff seated DBP. The results are shown graphically in the sponsor's figure below.



Note: Non-inferiority of eplerenone was established at both timepoints ($p \leq 0.001$).

(Figure 9.a)

Figure 100: Sponsor's Adjusted Mean Change From Baseline in seDBP at the Week 8 and Week 16 Endpoints (LOCF)

Eplerenone was non-inferior to losartan at both 8 and 16 weeks. It was superior to losartan in lowering DBP at 8 weeks. The results for SBP were similar. The adjusted mean changes from baseline in SBP at the week 8 and week 16 endpoints were –15.8 and –18.3 mmHg, respectively, in the eplerenone group and –10.1 and –15.0 mmHg, respectively, in the losartan group.

Eplerenone also was superior to losartan with regard to the need for HCTZ for BP control. At week 8, 22.5% of eplerenone patients and 42.0% of losartan patients required the addition of HCTZ. By week 14 (the last visit at which HCTZ could be added), the proportion of patients requiring HCTZ as additional therapy increased to 32.5% and 55.6% in the eplerenone and losartan groups, respectively.

There appeared to be a differential effect by race. 55 of the patients (33 percent) were black. The BP changes by race are shown in the table below.

Table 81: Reviewer's Mean BP Changes by Race

		Week 8		Week 16	
Drug	Race	SBP	DBP	SBP	DBP
Eplerenone	Black	-12.4	-7.1	-12.8	-8.3
	Non-black	-19.3	-12.0	-21.2	-12.5
Losartan	Black	-8.7	-5.7	-19.3	-10.4
	Non-black	-12.6	-7.4	-13.4	-8.9
p race*		0.021	0.014	0.46	0.18
p drug*		0.008	0.011	0.16	0.24

*p by ANCOVA with baseline BP covariate, drug and race as factors

Blacks showed a reduced effect with both eplerenone and losartan alone. Hydrochlorothiazide (HCTZ) was added more frequently in blacks on losartan (79 percent) than non-blacks on losartan (42 percent) or patients on eplerenone (about 30-31 percent for each racial group). Patients on HCTZ had greater reductions in BP regardless of treatment group or race, and HCTZ use was the most significant factor in ANCOVAs of change in SBP or DBP at final visit with base BP as a covariate and arm, HCTZ use, and race as factors. Whether the reduced efficacy of eplerenone in blacks with low renin hypertension is a real effect or a random variation seemingly significant in subgroup analyses is explored in other studies and summarized in the reviewer's ISE.

Changes in RAAS hormones did not vary by race with one exception: Total renin was virtually unchanged at week 8 in blacks on losartan while it increased similarly (mean change 51-70) in the other groups. At week 16 all changes in total renin were similar.

B.9.4 Safety Summary

All 168 randomized patients received at least one dose of study drug. 78 percent of eplerenone patients and 82 percent of losartan patients were exposed for longer than 90 days.

No patients died during the study. Three eplerenone and one losartan patient experienced SAEs. The eplerenone SAEs were hyperparathyroidism, angina pectoris, and cognitive dysfunction. Five eplerenone and seven losartan patients withdrew because of AEs. Besides the angina and cognitive function SAEs, one patient withdrew because of "coronary artery blockages".

Overall treatment-emergent adverse events were reported by 63 percent of eplerenone patients and by 72 percent of losartan patients. The most common AEs in each group were headache, upper respiratory infections, and dizziness. No patients experienced hyperkalemia. Two male eplerenone patients experienced gynecomastia after 84 and 96 days of treatment. One male eplerenone and one male losartan patient experienced impotence. No female eplerenone patients experienced menstrual disorders or breast pain, although one losartan experienced a menstrual disorder AE.

B.9.5 Conclusions

In this study eplerenone 100-200 mg QD was more efficacious than losartan 50-100 mg QD in reducing blood pressure in patients with low renin hypertension. Blood pressure reduction was less in blacks for both eplerenone and losartan. The rates of adverse events were similar with the two drugs, although note that gynecomastia occurred only with eplerenone.

B.10 Trial 023, Eplerenone, ACE Inhibitors and Angiotensin Receptor Blockers

B.10.1 Background

Study 023 is entitled "A Double-Blind, Randomized, Placebo-Controlled Comparison Study of the Safety and Antihypertensive Effect of Eplerenone versus Placebo when Co-Administered with an Angiotensin-Converting Enzyme Inhibitor or an Angiotensin II Antagonist in Patients with Mild to Moderate Hypertension," which aptly describes the study. The specific ACEIs and ARBs used or dosages were not dictated. The dosage of eplerenone was 50-100 mg QD titrated.

B.10.2 Design and Conduct

Eligible patients were adults 18 to 85 receiving a fixed dose of an ACEI or ARB with other antihypertensive medication and a history of hypertension or mild to moderate hypertension on exam. After a two- to four-week single-blind, placebo run-in period continuing on the fixed dose ACEI or ARB, patients with mild to moderate hypertension (DBP 95-109, SBP < 180) were randomized, stratified by ACEI/ARB, to placebo or eplerenone 50 mg. If BP was uncontrolled (DBP ≥90 mmHg) at week 2, the dose of study medication was to be increased to eplerenone 100 mg QD or placebo. If BP was uncontrolled at weeks 4 or 6, and the dose of study medication had not already been increased, the dose was to be increased to eplerenone 100 mg QD or placebo. The dose was to be increased only once during the study. The primary endpoint was mean change in trough cuff seated DBP at 8 weeks.

47 Investigators randomized 341 patients (177 ACEI, 164 ARB) at 47 study sites in the U.S., Argentina, Australia, Brazil, Canada, Mexico, and New Zealand. 24 percent of the patients were from the U.S. and 27 percent were from Argentina. The study was conducted from February 1 to October 30, 2000. Among the 177 patients in the ACE-I cohort, 90 were randomized to receive placebo and 87 were randomized to receive eplerenone. Among the 164 patients in the ARB cohort, 81 were randomized to receive placebo and 83 were randomized to receive eplerenone. (The sample size estimates were based on 60 patients per group.) Within the ACEI and ARB cohorts, there were no statistically significant differences between the placebo and eplerenone groups with respect to mean age, ethnicity, gender, weight, or body mass. In the ARB cohort, a statistically significant difference between the placebo and eplerenone groups was observed for female height, a statistical difference not relevant to the results. Mean BP at baseline was similar in the placebo and eplerenone groups in each cohort.

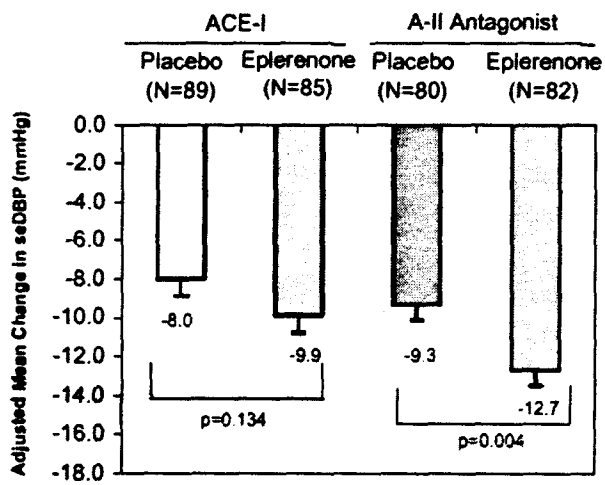
Among patients in the ACEI cohort, the most common ACE inhibitors used in both groups were enalapril (33 percent placebo and 36 percent eplerenone), lisinopril (17 percent placebo and 21 percent eplerenone), ramipril (12 percent placebo and 10 percent eplerenone), and quinapril (17 percent placebo and 7 percent eplerenone). The most commonly prescribed dosages were 10 mg QD for enalapril, 20 mg QD for lisinopril, 5 mg QD for ramipril, and 20 mg QD for quinapril. Among patients in the ARB cohort, the most common ARBs used in both groups were losartan (31 percent placebo and 28 percent eplerenone) and irbesartan (27 percent placebo and 22

percent eplerenone). The most commonly prescribed dosages were 50 mg QD for losartan and 150 mg QD for irbesartan.

59 patients (33 percent) in the ACEI cohort and 37 patients (23 percent) in the ARB cohort were withdrawn from the study prior to completion. Within the ACEI cohort, the rate of withdrawal was similar between the placebo and eplerenone groups (36 percent and 31 percent, respectively). Within the ARB cohort, the rate of withdrawal was similar in the placebo and eplerenone groups (23 percent and 22 percent, respectively). The most common reason for withdrawal in each group was treatment failure. More placebo patients withdrew due to treatment failure compared to eplerenone patients, regardless of whether they were receiving an ACEI (29 percent vs. 17 percent) or an ARB (21 percent vs. 10 percent). Five patients (two in the ACEI-eplerenone group, one each in the other groups) were excluded from the efficacy analyses because they lacked a post-baseline evaluation.

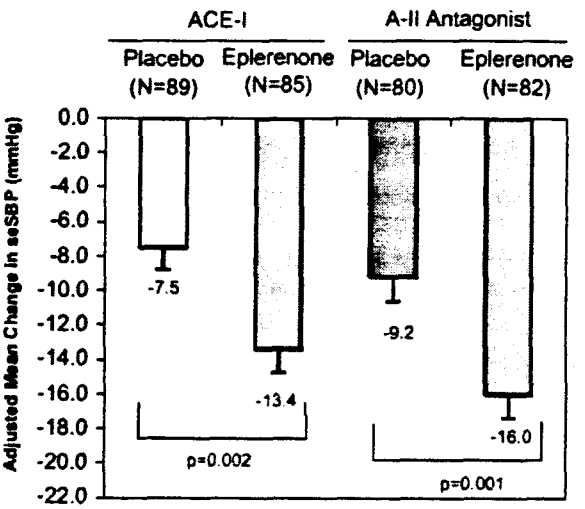
B.10.3 Efficacy Summary

The results for the primary endpoint are shown in the figure below.



(Figure 10.a)

Figure 101: Sponsor's Adjusted Mean Change from Baseline in seDBP at Week 8 (LOCF)



(Figure 10.b)

Figure 102: Sponsor's Adjusted Mean Change from Baseline in seSBP at Week 8 (LOCF)

Note that while the eplerenone effects with ARBs were statistically significant, they were not with ACEIs. Both effects were statistically significant with regard to SBP as shown in the figure above.

The sponsor summarized the secondary neurohormonal endpoint changes as follows: "In both cohorts, there were decreases in the geometric means for total plasma renin and serum aldosterone in the placebo groups and increases in the eplerenone groups; the differences in mean percent change between the placebo and eplerenone groups were statistically significant ($p < 0.001$) for total plasma renin and serum aldosterone. In each cohort, there were increases in the geometric means for active plasma renin in the placebo and eplerenone groups; the differences in mean percent change in active plasma renin between the placebo and eplerenone groups were statistically significant ($p < 0.001$). In both cohorts, there were no clinically important changes in plasma cortisol."

B.10.4 Safety Summary

All 341 randomized patients received at least one dose of study drug. The percentage of patients exposed to treatment for seven weeks or more (up to 10 weeks) ranged from 64.4% to 81.9% across the groups in both cohorts.

One patient died in this study. After one day of treatment, a 69-year-old eplerenone patient in the ACEI cohort experienced a fatal myocardial infarction. This patient had a history of diabetes mellitus type 2, chronic obstructive pulmonary disease, an ejection fraction of 50 percent, and a

complete left bundle branch block with a normal PR interval without signs of ischemia. There were three other SAEs: syncope in an ACEI-placebo patient, and aggravated hypertension and a hernia in ACEI-eplerenone patients. Five patients, two ACEI-placebo, two ACEI-eplerenone, and one ARB-eplerenone, withdrew because of AEs. The ACEI-placebo patients had the SAEs of MI and aggravated hypertension; the ARB-eplerenone patient had orchitis and a severe headache.

The most common treatment-emergent AEs in the ACEI cohort were headache (13 percent placebo, 16 percent eplerenone) and dizziness (1.1 percent placebo, 5.7 percent eplerenone). The most common AEs in the ARB cohort were headache (20 percent placebo, 23 percent eplerenone), nausea (4.9 percent placebo, 9.6 percent eplerenone), polyuria (6.2 percent placebo, 4.8 percent eplerenone), and asthenia (11 percent placebo, 2.4 percent eplerenone).

No patient had a SAE or was prematurely discontinued from the study due to an AE of hyperkalemia. Only one patient (eplerenone-ACEI) experienced an AE of mild hyperkalemia (5.5 mmol/L) after 17 days of treatment; however, the potassium level returned to normal (4.9 mmol/L) by the end of the study. While the one AE of hyperkalemia was observed in the eplerenone-ACEI group, the one group that experienced a statistically significant (p 0.0083 by ANOVA) mean increase in serum potassium from baseline to final was the eplerenone-ARB group. The mean increase was 0.13 meq/L compared to 0.03 in the ARB group, 0.07 in the ACEI group, and 0.09 in the eplerenone-ACEI group.

There were no reports of gynecomastia or menstrual abnormalities in either cohort.

B.10.5 Conclusions

Adding eplerenone to usual dosages of an ARB was efficacious in reducing both DBP and SDP while adding eplerenone to usual dosages of an ACEI was efficacious only in reducing SBP in this study. The study has the limitation that the ACEI and ARB dosages were usual dosages and no attempt was made to optimize them.

The combination of eplerenone with ACEIs and ARBs was well tolerated in this study. Hyperkalemia was minimal in these patients with normal renal function. No other adverse events were increased in the combined therapy groups. Note that two cases of gynecomastia with eplerenone were reported in this study.

B.11 Trial 024, Eplerenone and Calcium Channel and β Blockers

B.11.1. Background

Study 024 is entitled "A Double-Blind, Randomized, Placebo-Controlled Comparison Study of the Safety and Antihypertensive Effect of Eplerenone Versus Placebo When Co-Administered With a Calcium- Channel Blocker or a B-Blocker in Patients With Mild to Moderate Hypertension" which aptly describes the study. The specific calcium channel blockers (CCBs) and β blockers (BBs) used or dosages were not dictated. The dosages of eplerenone were 50-100 mg QD titrated.

B.11.2. Design and Conduct

Eligible patients were adults 18 to 85 receiving a fixed dose of a BB or CCB with other antihypertensive medication and a history of hypertension or mild to moderate hypertension on exam. After a two- to four-week single-blind, placebo run-in period continuing on the fixed dose BB or CCB, patients with mild to moderate hypertension (DBP 95-109, SBP < 180) were randomized, stratified by BB/CCB, to placebo or eplerenone 50 mg. If BP was uncontrolled (DBP ≥90 mmHg) at week 2, the dose of study medication was to be increased to eplerenone 100 mg QD or placebo. If BP was uncontrolled at weeks 4 or 6, and the dose of study medication had not already been increased, the dose was to be increased to eplerenone 100 mg QD or placebo. The dose was to be increased only once during the study. The primary endpoint was mean change in trough cuff seated DBP at 8 weeks.

28 Investigators randomized 272 (135 BB, 137 CCB) patients at 27 study sites in Belgium, Germany, Slovakia, Sweden, and the United Kingdom. 31 percent of the patients were from Germany and 32 percent were from Slovakia. The study was conducted from January 31, 2000, to February 7, 2001. In the CCB cohort 67 patients were randomize to placebo and 70 to eplerenone; in the BB cohort 66 patients were randomized to placebo and 69 to eplerenone. Within the CCB and BB cohorts, there were no significant differences between the placebo and eplerenone groups with respect to mean age, ethnicity, gender or height. In the BB cohort, a significant difference between the placebo and eplerenone groups was observed for female weight and body mass index, but this was not observed in the CCB cohort. The sponsor did not consider these differences to be important to the results of the study and the reviewer agrees. Mean BP at baseline was similar in the placebo and eplerenone groups in each cohort.

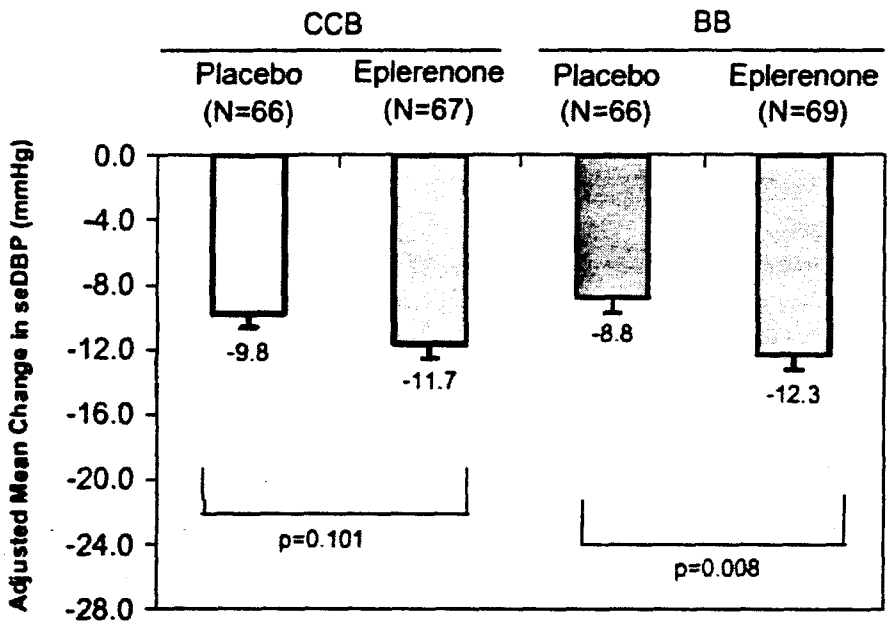
Among patients in the CCB cohort, the most common CCBs used in both groups were amlodipine (41.8 percent placebo and 37.1 percent eplerenone), felodipine (16.4 percent placebo and 20.0 percent eplerenone), diltiazem (16.4 percent placebo and 11.4 percent eplerenone), and isradipine (10.4 percent placebo and 10.0 percent eplerenone). The most commonly prescribed dosages were 5 mg QD for amlodipine, 5 mg QD for felodipine, 120 mg QD for diltiazem, and 5 mg QD for isradipine. Among patients in the BB cohort, the most common BBs used in both groups were bisoprolol (34.8 percent placebo and 36.2 percent eplerenone), atenolol (27.3 percent placebo and 29.0 percent eplerenone) and metoprolol (27.3 percent placebo and 24.6

percent eplerenone). The most commonly prescribed dosages were 5 mg QD for bisoprolol, 50 mg QD atenolol, and 100 mg QD for metoprolol.

A total of 35 (25.5 percent) patients in the CCB cohort and 31 (23.0 percent) patients in the BB cohort were withdrawn from the study prior to completion. Within the CCB cohort, the incidence of withdrawal was similar between the placebo (26.9 percent) and eplerenone (24.3 percent) groups. Within the BB cohort, the incidence of withdrawal was higher in the placebo group compared to the eplerenone group (31.8 percent versus 14.5 percent). The most common reason for withdrawal in each group was treatment failure. A greater number of placebo patients withdrew due to treatment failure compared to eplerenone patients, regardless of whether they were receiving a CCB (20.9 percent versus 12.9 percent) or a BB (28.8 percent versus 10.1 percent). Four patients in the CCB cohort (three eplerenone and one placebo) did not have adequate post-baseline evaluations and were excluded from all efficacy analyses.

B.11.3. Efficacy Summary

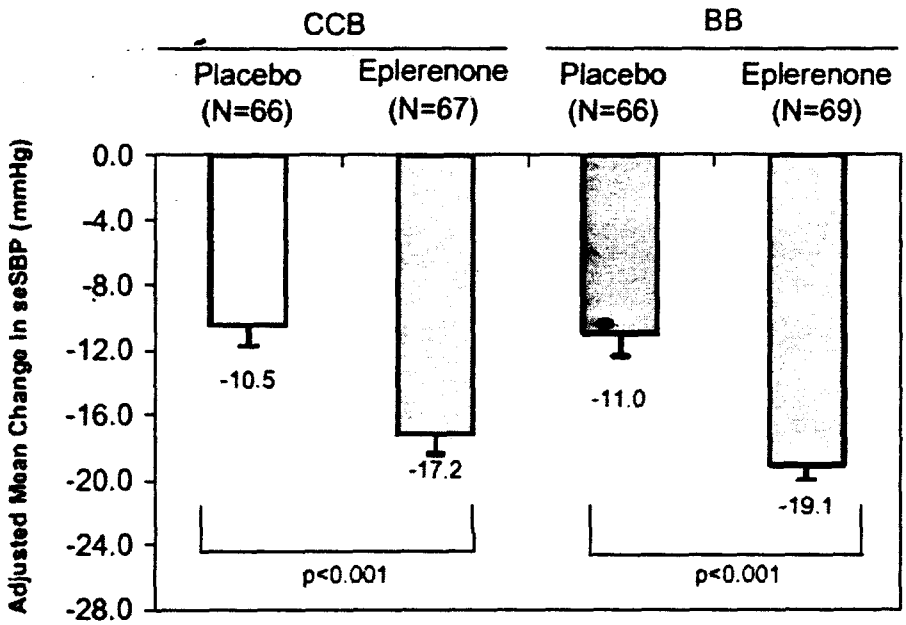
The results for the primary endpoint are shown in the figure below.



(Figure 9.a)

Figure 103: Sponsor's Adjusted Mean Change from Baseline in seDBP at Week 8 (LOCF)

Note that while the eplerenone effects with BBs were statistically significant, they were not with CCBs. Both effects were statistically significant with regard to SBP as shown in the figure below.



(Figure 9.b)

Figure 104: Sponsor's Adjusted Mean Change From Baseline in seSBP at Week 8 (LOCF)

The sponsor summarized the secondary neurohormonal endpoint changes as follows: "In the CCB and BB cohorts, the increases from Baseline to the Week 8 endpoint in total and active plasma renin in the eplerenone groups was significantly different than the decreases observed in the placebo groups. In the CCB and BB cohorts, the increase in serum aldosterone in the eplerenone groups was significantly greater than that in the placebo groups. In the CCB and BB cohorts, there were no clinically significant changes in plasma cortisol."

11.4. Safety Summary

All 272 randomized patients received at least one dose of study drug. 71 to 84 percent of patients in each group had exposures exceeding 49 days.

No patients died during the study. One SAE was reported, a PTCA on day 28, in a CCB patient on placebo. In the CCB cohort, four (5.7%) eplerenone patients were prematurely withdrawn from the study due to at least one treatment-emergent adverse event. The AEs were varied (aortic aneurysm, heart failure, scotoma, fatigue/dizziness). In the BB cohort, one eplerenone patient was prematurely withdrawn due to hyperkalemia. No placebo patients withdrew due to an adverse event.

Overall in the CCB cohort, treatment-emergent adverse events were reported by 22.4 percent of placebo patients and 27.1 percent of eplerenone patients. In the BB cohort, treatment-emergent AEs were reported by 25.8 percent of placebo patients and 26.1 percent of eplerenone patients. The most common AEs in the CCB cohort were headache (3.0 percent placebo, 7.1 percent eplerenone) and nausea (0 percent placebo, 5.7 percent eplerenone). The most common AEs in the BB cohort were headache (7.6 percent placebo, 2.9 percent eplerenone), influenza-like symptoms (6.1 percent placebo, 0.0 percent eplerenone), and hyperkalemia (0 percent placebo, 5.8 percent eplerenone).

One eplerenone patient was prematurely discontinued from the study due to an adverse event of hyperkalemia (5.7 mmol/L) that occurred after 17 days of treatment. Three other eplerenone patients in the BB cohort also experienced hyperkalemia (5.6 or 5.7 mmol/L) but not patients in the CCB cohort. There were not sex-hormone related AEs reported in this study.

B.11.5. Conclusions

Adding eplerenone to usual dosages of an BB was efficacious in reducing both DBP and SDP while adding eplerenone to usual dosages of an CCB was efficacious only in reducing SBP in this study. The study has the limitation that the BB and CCB dosages were usual dosages and no attempt was made to optimize them. The combination of eplerenone with BBs and CCBs was well tolerated.

APPEARS THIS WAY
ON ORIGINAL

B.12 Trial 017, Eplerenone and Enalapril for LVH

B.12.1 Background

Study 017 is entitled "A Double-Blind, Controlled, Randomized, Comparison Study of the Efficacy and Safety of Eplerenone and Enalapril Alone and in Combination with Each Other in Patients with Left Ventricular Hypertrophy and Essential Hypertension". Patients had to have left ventricular hypertrophy (LVH) by ECG or echo criteria. Eplerenone was forced titrated from 50 to 200 mg and enalapril from 10 to 40 mg QD. In the combination group eplerenone was forced titrated from 50 to 200 mg but enalapril was kept constant at 10 mg. Hydrochlorothiazide 12.5-25 mg and then amlodipine 10 mg were added to control BP if needed. The primary endpoint was change in left ventricular mass (LVM) at month 9 measured by MRI. Note that the primary analysis was changed from a superiority hypothesis to a non-inferiority hypothesis on December 3, 2000, eleven months after study initiation.

B.12.2 Design and Conduct

Eligible patients were adults (≥ 18) having a history of mild to moderate essential hypertension and LVH on ECG (Sokolow Lyon voltage criteria ≥ 35 mm) or echocardiogram (Devereux criteria LVMI ≥ 134 g/m^2 for males and ≥ 110 g/m^2 for females). After a two-week placebo run-in period patients with mild to moderate hypertension (DBP 90-114, SBP 141-200) were randomized to receive eplerenone 50 mg QD plus placebo, enalapril 10 mg QD plus placebo, or eplerenone 50 mg QD/enalapril 10 mg QD. The dose of study medication was up-titrated for all patients at week 2 regardless of whether DBP < 90 mmHg (to eplerenone 100 mg plus placebo, enalapril 20 mg plus placebo, or eplerenone 100 mg plus enalapril 10 mg), and at week 4 regardless of whether DBP < 90 mmHg (to eplerenone 200 mg plus placebo, enalapril 40 mg plus placebo, or eplerenone 200 mg plus enalapril 10 mg). If BP was uncontrolled (DBP ≥ 90 mmHg or SBP > 180 mmHg) at week 8, hydrochlorothiazide (HCTZ) 12.5 mg was added. If BP was uncontrolled at week 10, the HCTZ dose was increased to 25 mg or HCTZ 12.5 mg was added if not previously done so at week 8. If BP was uncontrolled at week 12, HCTZ 12.5 mg was added if not previously done so at weeks 8 or 10; or the HCTZ dose was increased to 25 mg if not done so at week 10; or amlodipine 10 mg was added if the patient was receiving HCTZ 25 mg.

35 Investigators randomized 202 (64 eplerenone, 71 enalapril, 67 both) patients at 35 sites in France, Germany, the Netherlands, Poland, Spain, Switzerland, and the United States. 10 percent of the patients were from the U.S., 35 percent from Spain, and 29 percent from Germany. 64 percent were male and 91 percent were white. The study was conducted from December 28, 1999 to June 18, 2001. There were no significant differences among the three groups with respect to mean age, race, gender, weight, or body mass index. A significant difference was observed among the treatment groups with respect to female height. The sponsor considered this difference not important to the results of the study and the reviewer agrees. Mean LV mass and mean BP at baseline were similar in the three groups.

Similar proportions of patients who received eplerenone (22 percent), enalapril (20 percent), and eplerenone/enalapril (16 percent) were prematurely withdrawn from the study. The most common reason for premature withdrawal in each treatment group was adverse event (6.3 percent eplerenone, 7.0 percent enalapril, and 6.0 percent eplerenone/enalapril).

49 (14 eplerenone, 17 enalapril, and 18 eplerenone/enalapril) patients were excluded from the primary efficacy analysis. 39 (14 eplerenone, 11 enalapril, and 14 eplerenone/enalapril) patients did not have an endpoint MRI. Two (one enalapril and one eplerenone/enalapril) patients did not have a baseline MRI within 21 days of the first dose of study medication. Five (three enalapril and two eplerenone/enalapril) patients had a baseline MRI that was not acceptable to the core laboratory. Three (two enalapril and one eplerenone/enalapril) patients did not have a final MRI within 21 days of the last dose of study medication.

B.12.3 Efficacy Summary

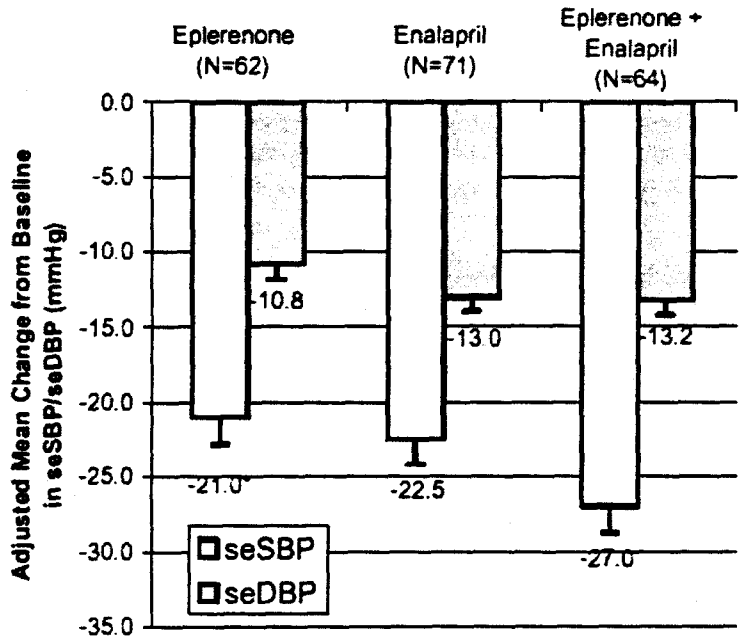
The revised protocol dated December 3, 1999, has this description of the statistical analysis: "Assuming a standard deviation of 24 g in change from baseline values of LVM, a sample size of 55 patients per group provides 90% power to detect an average reduction in LVM that is 15 g greater in the eplerenone group as compared to patients receiving enalapril alone (two-tailed alpha = 0.05). For BP evaluations, the study has 80% power to detect a 4.4 mmHg difference between treatments in change from baseline seated DBP, using a two-sided test at the 5% significance level, and assuming a standard deviation of 8.0 mmHg...The primary efficacy hypothesis to be established is that the reduction from baseline in LVM in the eplerenone group is greater than that in the enalapril group."

An amendment dated December 12, 2000, changed the primary analysis to a non-inferiority hypothesis: "Assuming a standard deviation of 24 g in change from baseline values of LVM, a sample size of 55 patients per group provides 94% power to detect an average reduction in LVM that is 15 g greater between the eplerenone and enalapril groups (one-tailed alpha = 0.05)... The primary efficacy hypothesis to be established is that the reduction from baseline in LVM in the eplerenone group is similar (non-inferior) to the enalapril group."

The following is the sponsor's summary of the primary endpoint: "The change from Baseline to the Month 9 endpoint in LVM was -14.5 g in the eplerenone treatment group and -19.7 g in the enalapril treatment group (Table T5.1.1). Since the one-sided LCL was -12.8 g, non-inferiority of eplerenone was established (p = 0.018). The 95% confidence interval for the treatment difference (-14.3, 3.9) showed no significant differences between the treatment groups in mean change from Baseline to the Month 9 endpoint in LVM." The sponsor also makes the following observations about the secondary endpoint of comparing LVM in all three groups: "Treatment with enalapril or eplerenone/enalapril caused similar reductions from Baseline in LVM at the Month 9 endpoint. A significantly greater reduction from Baseline was observed in the eplerenone/ enalapril treatment group [-27.2 g] compared to the eplerenone treatment group in LVM at the Month 9 endpoint (p = 0.007)."

Reviewer's comment: The original hypothesis was superiority of eplerenone over enalapril in reducing LVM. These data fail to document superiority of eplerenone.

The changes in the secondary BP endpoints are shown in the figure below:



(Figure 9.b)

* Statistically significant difference between the eplerenone and eplerenone/enalapril treatment groups (p = 0.017).

Figure 105: Sponsor's Adjusted Mean Change From Baseline in BP at the Month 9 Endpoint (LOCF)

Note that HCTZ and amlodipine could be added. The following figure shows their use.

Final Dose Level	Eplerenone 50 → 200 mg QD (N=60)[a]	Enalapril 10 → 40 mg QD (N=70)[a]	Eplerenone 50 → 200 mg QD/ Enalapril 10 mg QD (N=62)[a]
No Addition	42	33	47
One Addition Required[b]	13	24	11
Two Additions Required[c]	5	13	4

a Only patients who had usable BP data while receiving their final dose level were included.
b HCTZ or amlodipine
c HCTZ and amlodipine

Figure 106: Sponsor's Number of Patients by Requirement for Additional Antihypertensive Medication at the Month 9 Endpoint

Use of HCTZ and amlodipine was similar in the eplerenone and eplerenone/ enalapril groups and higher in the enalapril group. These data at the month 9 endpoint suggest that the combination is more effective than enalapril alone. Because they are confounded by the use of HCTZ and amlodipine, it is also worthwhile to examine the changes at week 8, after the forced up-titration and prior to the use of other drugs. The mean BP changes at week 8 are shown in the table below.

Table 82: Reviewer's Mean Changes in BP at Week 8

	Eplerenone	Enalapril	Both
SBP	-19.4	-12.4	-25.5
DBP	-10.1	-8.5	-12.8

These data also suggest that eplerenone is more efficacious at these dosages than enalapril alone and that the combination produces greater reductions in BP.

The sponsor's summary of other secondary endpoints is the following: "Increases from Baseline at the Month 9 endpoint in t-PA were observed in the eplerenone (16.1%), enalapril (2.9%), and eplerenone/enalapril (13.9%) treatment groups. These increases were significant within the eplerenone There were no significant differences between any of the treatment groups in change from Baseline at the Month 9 endpoint in any of the aortic compliance and ventricular filling parameters (end-diastolic volume, end-systolic volume, ejection fraction, peak filling rate, and systolic compliance index). No significant differences within or between treatment were observed for percent change from Baseline in PIIINP or PAI-1. Significant decreases from Baseline at the Month 9 endpoint in 24-hour UACR were observed within the eplerenone (-28.7%), enalapril (-39.1%), and eplerenone/enalapril (-50.7%) treatment groups. The difference between the eplerenone and eplerenone/ enalapril treatment groups was significant. Increases from Baseline at the Month 9 endpoint in t-PA were observed in the eplerenone (16.1%), enalapril (2.9%), and eplerenone/enalapril (13.9%) treatment groups. These increases were significant within the eplerenone and eplerenone/enalapril treatment groups. The increase in the eplerenone treatment group was significantly greater than that in the enalapril treatment group."

B.12.4 Safety Summary

All 202 randomized patients received at least one dose of study drug. Exposure for more than 240 days was 78 to 85 percent if all groups. No patients died during the study. Seven eplerenone, five enalapril, and nine eplerenone/ enalapril patients experienced SAEs. The eplerenone SAEs include two myocardial infarctions (MI), one angina, one peripheral vascular disease, and one hyperkalemia; the enalapril SAEs included one MI and one peripheral vascular disease; the eplerenone/enalapril SAEs included one MI, one coronary artery disorder, and one cerebrovascular disorder. Eight eplerenone, six enalapril, and six eplerenone/ enalapril patients withdrew because of AEs. The AEs causing withdrawal overlapped with the SAEs but also included one gynecomastia in an eplerenone patient and two coughs in enalapril patients.

Overall treatment-emergent AEs were reported by 66 percent of patients in the eplerenone treatment group, 70 percent of patients in the enalapril treatment group, and 55 percent of patients in the eplerenone/enalapril treatment group. Event rates were similar except coughing was experienced by a significantly greater proportion of patients in the enalapril treatment group compared to the eplerenone treatment group. All of this AE information is incorporated into the ISS.

B.12.5 Conclusions

This study failed to show superiority of eplerenone over enalapril in reducing left ventricular mass. Eplerenone appeared to show considerable efficacy in reducing BP both alone and in combination with enalapril. However, in the absence of a placebo group, the absolute reductions or their significance are difficult to appreciate. Eplerenone and eplerenone in combination with enalapril was reasonably well tolerated in this study, although the suggestion of more cardiovascular thrombotic events in eplerenone groups is of concern.

APPEARS THIS WAY
ON ORIGINAL

B.13 Trial 021, Eplerenone vs. Enalapril in Diabetics with Proteinuria

B.13.1 Background

Study 021 is entitled "A Double-Blind, Randomized, Active-Controlled Comparison Study of the Antihypertensive, Renal, and Metabolic Effects of Eplerenone Versus Enalapril in Patients with Type 2 Diabetes Mellitus, Albuminuria, and Hypertension." Patient had to have type 2 diabetes with a urine albumin:creatinine ratio (UACR) ≥ 100 mg/g by first morning voided spot urine. Patients with mild renal dysfunction (creatinine to 1.7 mg/dl) were allowed to be enrolled. Eplerenone was forced titrated from 50 to 200 mg and enalapril from 10 to 40 mg QD. In the combination group eplerenone was forced titrated from 50 to 200 mg but enalapril was kept constant at 10 mg. Hydrochlorothiazide 12.5-25 mg and then amlodipine 10 mg were added to control BP if needed. The primary endpoint was change in UACR at 24 weeks, with a noninferiority hypothesis that the ratio (eplerenone to enalapril) of the ratios (week 24 to baseline) was < 2.

B.13.2 Design and Conduct

After a two-week placebo run-in period patients with mild to moderate hypertension (DBP 90-114, SBP 141-200) were randomized to receive eplerenone 50 mg QD plus placebo, enalapril 10 mg QD plus placebo, or eplerenone 50 mg QD/enalapril 10 mg QD. The dose of study medication was up-titrated for all patients at week 2 regardless of whether DBP < 90 mmHg (to eplerenone 100 mg plus placebo, enalapril 20 mg plus placebo, or eplerenone 100 mg plus enalapril 10 mg), and at week 4 regardless of whether DBP < 90 mmHg (to eplerenone 200 mg plus placebo, enalapril 40 mg plus placebo, or eplerenone 200 mg plus enalapril 10 mg). If BP was uncontrolled (DBP ≥ 90 mmHg or SBP > 180 mmHg) at week 8, hydrochlorothiazide (HCTZ) 12.5 mg was added. If BP was uncontrolled at week 10, the HCTZ dose was increased to 25 mg or HCTZ 12.5 mg was added if not previously done so at week 8. If BP was uncontrolled at week 12, HCTZ 12.5 mg was added if not previously done so at weeks 8 or 10; or the HCTZ dose was increased to 25 mg if not done so at week 10; or amlodipine 10 mg was added if the patient was receiving HCTZ 25 mg.

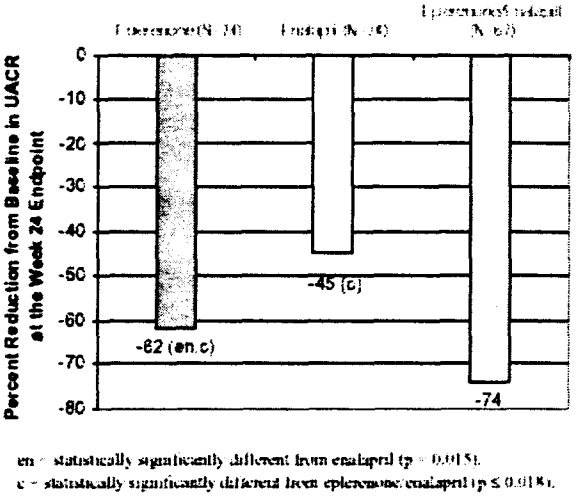
59 Investigators randomized 266 (93 eplerenone, 84 enalapril, 89 both) patients at 60 study sites in Argentina, Australia, Brazil, Canada, Germany, Italy, Mexico, New Zealand, Poland, Spain, U.K., and the United States. 11 percent of the patients were from the U.S., 21 percent from Argentina, and 18 percent from Spain. 58 percent were male. 74 percent were white, 18 percent Hispanic, and 7 percent black. The mean age was 61 and 40 percent were 65 or older. The study was conducted from February 17, 2000, to June 28, 2001. There were no significant differences among the eplerenone, enalapril, and eplerenone/enalapril treatment groups with respect to mean age, race, gender, weight, body mass index, baseline BP, or baseline UACR.

Two patients in the eplerenone/enalapril group did not receive any study medication and were excluded from all analyses. Similar proportions of patients who received eplerenone (32 percent) and eplerenone/enalapril (36 percent) were prematurely withdrawn from the study. A lesser proportion of enalapril patients (17 percent) were prematurely withdrawn from the study.

The most common reason for premature withdrawal in the eplerenone and enalapril treatment groups was adverse event (8.6 percent and 6.0 percent, respectively). The most common reason for premature withdrawal in the eplerenone/enalapril treatment group was increased potassium level (15.7 percent). Forty-nine (19 eplerenone, 10 enalapril, and 20 eplerenone/enalapril) patients did not have appropriate post-treatment UACR measurements and were excluded from the efficacy analyses.

B.13.3 Efficacy Summary

The change in the primary endpoint, UACR, is shown in the following figure.

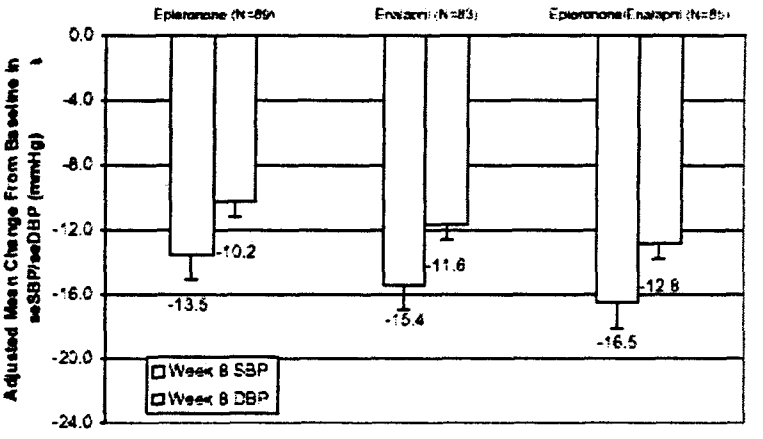


(Figure 9.a)

Figure 107: Sponsor's Adjusted Mean Ratio in UACR at the Week 24 Endpoint (LOCF)

The reduction in UACR was significantly greater in the eplerenone treatment group compared to the enalapril treatment group ($p = 0.015$). Treatment with eplerenone/enalapril resulted in significantly greater UACR reductions compared to eplerenone or enalapril ($p \leq 0.018$).

Changes in the secondary BP endpoints at week 8 is shown in the figure below.



(Figure 9.b)

Figure 108: Sponsor's Adjusted Mean Change From Baseline in seSBP/seDBP at the Week 8 Endpoint (LOCF)

There were no significant differences in BP at week 8, the end of the forced titration period before HCTZ or amlodipine were added. At the week 24 endpoint, the reduction in DBP in the eplerenone/enalapril group (-16.2) was significantly greater than that in the eplerenone group (-13.2).

The sponsor's summary of other secondary endpoint is the following: "No significant differences between the treatment groups were noted for adjusted mean change from Baseline at the Week 24 endpoint in collagen, fibrinolytic markers, or metabolic effects, triglycerides, or total cholesterol. None of the changes were considered clinically significant."

B.13.4 Safety Summary

264 randomized patients received at least one dose of study drug. 65 percent of eplerenone, 82 percent of enalapril, and 66 percent of eplerenone/enalapril patients were exposed to study medication for 23 weeks or more. Two patients died during this study. A 70-year old white female on eplerenone suffered a hemorrhagic stroke on day 133 and died on day 137. A 64-year old white male on eplerenone/enalapril had emergency surgery for a bleeding ulcer on day 164, arrested post-op, and died from "anoxic encephalopathy" on day 179.

Nine eplerenone, five enalapril, and eight eplerenone/enalapril patients experienced SAEs. They included two strokes in the eplerenone group and one "hemiparesis", one "worsening of dysarthria", and one hypertensive encephalopathy in the eplerenone/enalapril group, and two myocardial infarctions in the enalapril group. A hyperkalemia SAE was reported in two eplerenone and in one each enalapril and enalapril/eplerenone patients.

39 patients (14 eplerenone, seven enalapril, and 18 eplerenone/enalapril) were prematurely withdrawn from the study due to AEs. The most common treatment-emergent adverse event leading to premature withdrawal was hyperkalemia (six patients in the eplerenone treatment group, two patients in the enalapril treatment group, and 13 patients in the eplerenone/enalapril treatment group).

Overall AEs were reported by 65 percent of patients in the eplerenone treatment group, 66 percent of patients in the enalapril treatment group, and 71 percent of patients in the eplerenone/enalapril treatment group. Types of events were similar between the groups except a significantly greater percentage of eplerenone patients experienced hyperkalemia compared to enalapril patients (16 percent vs. 6 percent). Hyperkalemia was also common in the eplerenone/enalapril group (24 percent). The sponsor also noted the following: "In an additional exploratory analysis, a slight association between Baseline creatinine clearance (calculated) and the maximum serum potassium level was observed in that lower creatinine clearance was associated with more hyperkalemia."

B.13.5 Conclusions

In this study eplerenone reduced microalbuminuria more than enalapril and the combination of eplerenone and enalapril produced additional reduction in microalbuminuria. Eplerenone led to reductions in blood pressure that are comparable to those produced with enalapril at the dosages (eplerenone 200 mg, enalapril 40 mg QD) used in this study. The combination was not clearly superior at the 8 week endpoint (the end of the forced titration.) The superiority in DBP reduction at 24 weeks is confounded slightly by the addition of HCTZ and amlodipine, although note that HCTZ and amlodipine use was lower in the combined treatment group.

The rates of hyperkalemia were substantial in this study. The high rates are probably related to the inclusion of patients with mild renal dysfunction in this study. The renal dysfunction may be manifested in diabetics by the microalbuminuria alone, since rates of hyperkalemia in this study were high even with normal baseline creatinine. Hence the sponsor has recommended a labeling caution regarding hyperkalemia for both impaired renal function and type 2 diabetes with microalbuminuria.

B.14 Trial 025, Eplerenone Open Label, Long Term Use

B.14.1 Background

Study 025 is entitled "A Long Term, Open Label Study of the Safety and Efficacy of Eplerenone." This study enrolled patients from Study 015, the hydrochlorothiazide factorial study, or adult patients with mild hypertension who had not participated in the eplerenone trials. Eplerenone was titrated to effect from 50 to 200 mg. If BP remained uncontrolled, other antihypertensives were added.

B.14.2 Design and Conduct

The study consisted of a one-week screening/washout period, a 10-week open-label, dose-titration period, and up to a 14-month open-label maintenance period. Patients received eplerenone 50 mg QD for the first two weeks of the dose-titration period. If BP was uncontrolled (DBP $\geq$ 90 mmHg or SBP $\geq$ 140 mm Hg) at week 2 or week 4, the dose was increased by one dose level to eplerenone 100 mg QD (week 2) or to 100 mg QD or 200 mg QD (week 4). If BP was uncontrolled at any time from week 6 up to and including the month 3 visit, a second antihypertensive medication of the investigator's choice could have been added to eplerenone 200 mg QD, or the eplerenone dose was increased by one dose level, if not done so at a previous visit. The dose of the second antihypertensive medication could have been adjusted or the agent changed at any time up to and including the month 3 visit.

77 investigators enrolled 586 patients at 77 sites in the United States, Argentina, Brazil, Canada, Spain, the Netherlands, and Belgium. 61 percent of the patients were from the U.S. and 16 percent were from Canada. 52 percent were male, 80 percent were white, and 11 percent were black. Mean age was 55 and 22 percent were age 65 or older. The study was conducted from September 7, 1999, to November 18, 2000. The case report forms for this study have check boxes for indicating that patients were previously enrolled in four studies: 015, 020, 021, and 022. However, the ENRHIST file included as part of the case tabulations only lists patients from Study 015, the factorial study with hydrochlorothiazide, and patients without previous eplerenone trial exposure. 41 percent of the patients were from Study 015 and the rest were de novo.

385 patients (66 percent) completed the study (i.e., had received open-label treatment for a minimum of six months) and 201 (34 percent) were withdrawn from the study prior to completion. The most common reason for withdrawal was treatment failure (17 percent).

The most common add-on antihypertensive medications were ACE-inhibitors (e.g., lisinopril; 13 percent), CCBs (e.g, amlodipine; 11 percent), and hydrochlorothiazide (7 percent).

B.14.3 Efficacy Summary

This was not a double-blind randomized controlled trial, so the sponsor summarized the efficacy with withdrawal rates: "Over the course of the study, 98 (16.8%) of the 582 patients in the intent-to-treat population withdrew due to uncontrolled BP. During the first four months, 70 (12.0%) patients withdrew due to treatment failure." Note also that 238 patients (41 percent) required the addition of an additional antihypertensive medication. 219 patients (37 percent) completed the study on eplerenone alone.

This was the longest study in the eplerenone development program, so maintenance of BP reduction is of particular interest. The following figure shows the BP changes by time in this study.

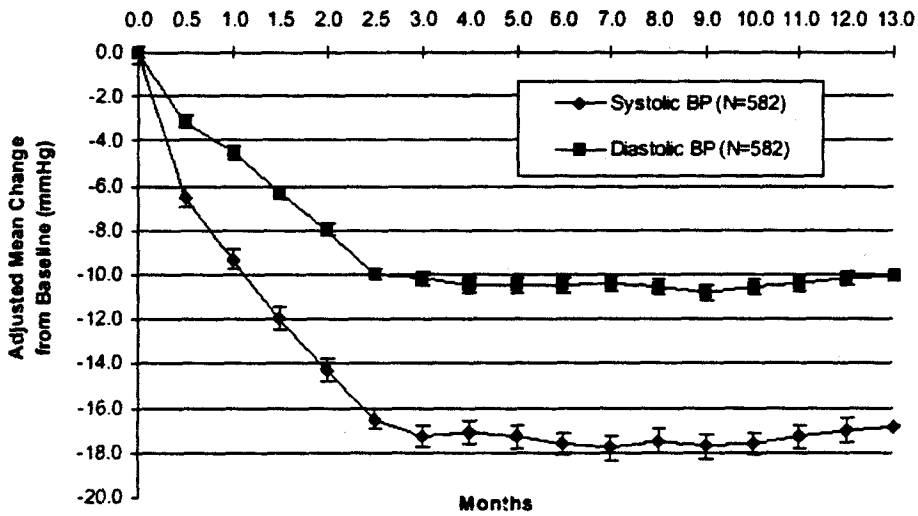


Figure 109: Sponsor's Adjusted Mean Change from Baseline by Month (LOCF)

There appears to be a slight trend towards decreasing BP control after nine months. Given the uncontrolled nature of this study, the interpretation of this trend is difficult. There is no hard evidence that eplerenone loses effectiveness with time.

B.14.4 Safety Summary

All 586 patients received at least one dose of study medication. The majority of patients (70 percent) received open-label study medication for at least six months. Ninety-eight patients (17 percent) were treated for at least 12 months.

One patient died in this study. A 64 year-old white male died of ventricular tachycardia associated with an automobile accident on day 212. He was taking eplerenone 200 mg and lisinopril 20 mg.

35 patients (6 percent) experienced SAEs, 41 patients (7 percent) were withdrawn because of AEs, and 403 patients (67 percent) reported as least one AE. SAEs and dropouts are included in the reviewer's ISS. The most common AEs were upper respiratory tract infection (19 percent), headache (13 percent), influenza-like symptoms (7.3 percent), accidental injury (7.0 percent), nausea (6.8 percent), dizziness (6.7 percent), dyspepsia (5.5 percent), diarrhea (5.1 percent) and sinusitis (5.1 percent).

14 (2.4 percent) patients had hyperkalemia problems by one or more of the following criteria: experienced an AE of hyperkalemia, had a laboratory values of > 5.5 mmol/L on two consecutive occasions or ≥6.0 mmol/L on any occasion, or were withdrawn due to an increased potassium level. 10 of these patients (2.6 percent of 378) were taking eplerenone 200 mg while 4 (1.9 percent of 208) were taking lower doses.

Nine patients experienced impotence, two male patients experienced gynecomastia, seven female patients experienced menstrual abnormalities, and two female patients experienced female breast pain during the study.

B.14.5 Conclusions

In this longer-term study eplerenone showed reasonable efficacy in controlling blood pressure. It also shows minor, but not ignorable, side effects: hyperkalemia in 2.4 percent of patients and an assortment of sex-hormone related side effects (impotence, gynecomastia, menstrual abnormalities, and female breast pain.) The value of this study would have been enhanced if patients from a wider range of trials had been included and if the more patients were exposed to longer durations of treatment, i.e., more than one year.

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/s/

Thomas Marciniak
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MEDICAL OFFICER

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW
120-Day Safety Update

NDA: 21-437

Name of Drug: eplerenone
Trade Name: (not assigned)
Drug Class: diuretic
Formulation: oral tablets
Related Application: IND [redacted]

Proposed Indication: hypertension
Sponsor: Pharmacia Corporation

Date of Submission: 04/05/02
Date Received by FDA: 04/08/02
Date Assigned: 04/10/02
Date Review Completed: 04/17/02
Reviewer: Thomas A. Marciniak, M.D.

Background:

Eplerenone is an aldosterone receptor competitive antagonist similar to the approved drug spironolactone. An NDA for the indication of the treatment of hypertension was submitted on November 29, 2001. This submission is the 120-day safety update.

Safety Update:

This report summarizes the safety information obtained after the cutoff date of October 2001 for the Integrated Summary of Safety through February 1, 2002. During the update period seven trials were ongoing, two in patients with hypertension, two in patients with heart failure, and three pharmacology trials. The two hypertension trials, a dose-ranging trial with 193 patients randomized and an open-label follow-on with 105 patients, are in Japanese patients; no patients have experienced serious adverse events (SAEs). The large 035 trial in heart failure has randomized 6,642 patients; 766 patients have died and 2,955 have experienced at least one SAE, but the details are not given. In a second dose-ranging study in heart failure 120 patients have enrolled and eight patients have experienced SAEs including stroke, nausea, vomiting, stress, ventricular

fibrillation, respiratory distress, asthma, and worsening failure. No SAEs have been experienced in the pharmacology trials.

Study 063 was a rechallenge, crossover study in a Japanese subject who had experienced liver enzyme elevations during eplerenone treatment with a high-calorie diet in a pharmacokinetic study. In the rechallenge liver enzyme elevations occurred with placebo and high-calorie diet during period 1 and not with eplerenone and maintenance diet during period 2.

Comments:

No new safety issues are raised. The results of the rechallenge study do resolve one existing safety question.

Recommendations:

The results of this safety update will be incorporated into the NDA review.

/S/
Thomas A. Marciniak, M.D.

cc:

ORIG: NDA 21-437
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Thomas Marciniak
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