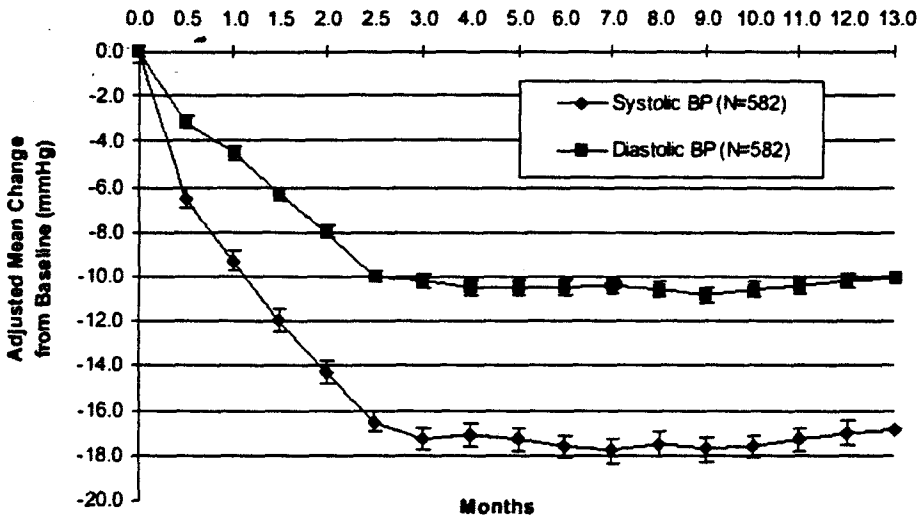


Figure 21: Sponsor's Adjusted Mean Change in BP from Baseline by Month (LOCF) for Study 025

Reviewer's comment: The BP changes over time for Study 025 appear to show a slight loss in BP control after nine months. However, given the uncontrolled nature of that study, such a detailed interpretation is not justifiable. Overall there is no strong evidence that eplerenone loses efficacy over time. This conclusion would be strengthened if data showing stable dosages over time were available.

6. Withdrawal

Studies 020, 021, 022, 023, 024, and 026 had a scheduled safety visit one week after the final treatment visit. The sponsor summarized BP changes as follows: "The incidence of patients who exhibited a 15 mmHg drop from Baseline to the final visit in SBP that subsequently increased 5 mmHg above the original Baseline value at the safety visit was similar between the placebo (2.3%), eplerenone monotherapy (2.3%), eplerenone coadministration therapy (2.7%), and active comparator (2.2%) treatment groups. ... Similar results were observed for DBP. Among these patients, the mean change from the final visit to the safety visit in SBP was 3.3 mmHg in the placebo treatment group, 6.5 mmHg in the eplerenone monotherapy group, 6.2 mmHg in the eplerenone coadministration therapy group, and 5.2 mmHg in the active comparator group. ... In the analyses of DBP, the mean increases in BP between the final visit and safety visit were slightly lower for the eplerenone monotherapy (3.1 mmHg), eplerenone coadministration therapy (4.0 mmHg) and active comparators (2.9 mmHg) treatment groups." Rebound effects are discussed in the ISS.

7. Use Compared to or With Other Antihypertensives

Beyond the pivotal Studies 010 and 049, the other studies in the development program addressed use compared to and with other antihypertensives, sometimes in disease subsets and sometimes with other primary endpoints. This section summarizes the use compared to or with other antihypertensives for BP endpoints.

Hydrochlorothiazide (HCTZ)

Study 015, a dose ranging factorial study of eplerenone and hydrochlorothiazide, is the only study with defined hydrochlorothiazide arms. Hydrochlorothiazide add-on to control BP was specified in three trials (019, 017, and 021) and permitted in Study 025. The relatively negative results of Study 015, presumably due to a large placebo effect, have already been discussed under 1. above. There was evidence of additive efficacy but only the eplerenone 200/HCTZ 25 combination reduced DBP statistically significantly more than the corresponding monotherapies. The monotherapies produced similar reductions in DBP with a slight dose trend, but no monotherapy group was significantly different than placebo. Eplerenone 200 mg and HCTZ 25 mg did produce comparable to each other and significant reductions in SBP compared to placebo. The details are in Appendix B.3. The combination was well tolerated. No patients experienced clinical hyperkalemia in this study, but the combinations produced small decreases in mean potassium levels as opposed to the increases seen with eplerenone monotherapy.

β Blockers (BBs)

Eplerenone titrated 50-100 mg was added to a BB in 135 patients not completely controlled on their usual dosages of unspecified BBs in Study 024. The primary endpoint was change in seated trough cuff DBP at eight weeks. Eplerenone produced significant additional reductions in DBP (-12.3 vs. –8.8) and SBP and SBP (-19.1 vs –11.0). The BB dosage was not optimized, limiting the interpretation of these results. The combination was very well tolerated with similar AE rates between the two arm, although hyperkalemia occurred only in the eplerenone add-on arm.

Calcium Channel Blockers (CCBs)

Eplerenone titrated 50-100 mg was also added to a CCB in 137 patients not completely controlled on their usual dosages of unspecified CCBs in Study 024. The primary endpoint was change in seated trough cuff DBP at eight weeks. Eplerenone failed to produce a significant reduction in DBP (-11.7 vs. –9.8, p=0.10) but did for SBP (-17.2 vs. –10.5). The interpretation of these results is further limited by the fact that CCB dosage was not optimized. The combination was very well tolerated.

Eplerenone was directly compared to the CCB amlodipine in two trials, Trial 026 in patients with essential hypertension and Trial 022 in patients with systolic hypertension.

Trial 026 randomized 179 adults with mild to moderate hypertension to titrated eplerenone 50-200 mg or amlodipine 2.5-10 mg QD for 16 weeks. The primary endpoint was change in mean DBP by ABPM with a non-inferiority margin of 4 mm Hg. 18 patients in each group were excluded because of invalid ABPM measurements. Eplerenone was inferior to amlodipine in reducing mean DBP by ABPM. The mean change in DBP by ABPM was –7.5 in the eplerenone group and -10.2 mm Hg in the amlodipine group. There was no significant difference in reductions in SBP by ABPM (eplerenone –14.0, amlodipine –16.1). The changes in cuff BP were similar with the same statistical significance. 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.)

Trial 022 randomized 269 patients with systolic hypertension to titrated eplerenone 50-200 mg or amlodipine 2.5-10 mg QD for 24 weeks. Elevated SBP was defined as either SBP $\geq$150 and < 165 mmHg, and pulse pressure $\geq$ 70 mm Hg, or SBP $\geq$ 165 and < 200 mmHg and DBP < 95 mmHg. Age was restricted to $\geq$ 50. The primary endpoint was change in seated trough cuff SBP. The original protocol specified a superiority hypothesis. An amendment one month before study completion changed the primary analysis to a non-inferiority comparison with a margin of 6 mm Hg. The adjusted mean change in the primary endpoint, adjusted mean seated trough cuff SBP, was –20.5 for eplerenone and –20.1 for amlodipine. This result showed no significant difference by the original protocol primary analysis and non-inferiority by the amended analysis. Amlodipine was again superior to eplerenone in reducing DBP (-6.9 vs –4.5 mm Hg, p = 0.014).

In this population of older patients 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.

Amlodipine was specified as an add-on drug to control BP in the two trials with non-BP primary endpoints, Study 017 in hypertensive patients with left ventricular hypertrophy and Study 021 in hypertensive diabetics with albuminuria. Both studies included three arms: eplerenone, enalapril, and combined. Amlodipine was added after HCTZ to 25 mg was added first. The exposure in these trials was about 25 patients, so little information is provided about amlodipine co-administration.

Reviewer's comment: Studies 022 and 026 consistently showed that amlodipine is superior to eplerenone in reducing DBP while the effects upon SBP are similar.

ACE Inhibitors (ACEIs)

Eplerenone titrated 50-100 mg was added to an ACEI in 177 patients not completely controlled on their usual dosages of unspecified ACEIs in Study 023. The primary endpoint was change in seated trough cuff DBP at eight weeks. Eplerenone failed to produce a statistically significant reduction in DBP vs. placebo (-9.9 vs –8.0 mm Hg, p=0.134) but did for SBP (-13.4 vs. –7.5, p=0.002). The ACEI dosage was not optimized, limiting the interpretation of these results. The combination arm was well-tolerated with AE rates similar to the ACEI-placebo arm with more dizziness in the eplerenone-ACEI arm (5.7 vs. 1.0 percent). One patient in the eplerenone-ACEI arm had a mild (5.5 meq/L) hyperkalemia AE that returned to normal by the end of the study. Mean change in potassium levels did not differ between the two groups.

Eplerenone was directly compared to the ACEI enalapril in Study 016. That study randomized 499 patients with mild to moderate essential hypertension to eplerenone titrated 50-200 mg or enalapril titrated 10-40 mg for 24 weeks. It also included a forced down-titration at 24 weeks with an additional 6 months follow-up that is described in the Maintenance section. The primary endpoint at 24 weeks was change in seated trough cuff DBP. The endpoint analysis was changed from a superiority hypothesis to a non-inferiority one with a margin of 3 mm Hg after trial completion. At 24 weeks eplerenone and enalapril produced similar mean reductions in BP, -11.2 and –11.3 respectively for DBP and –14.5 and –12.7 for SBP.

Enalapril was compared to and combined with the ACEI enalapril in two studies with non-BP primary endpoints: Study 017 in hypertensive patients with left ventricular hypertrophy and a primary endpoint of change in left ventricular mass and Study 021 in hypertensive diabetics with albuminuria and a primary endpoint of change in albuminuria. In both studies patients were randomized to eplerenone forced-titrated 50-200 mg QD over four weeks, enalapril forced-titrated 10 to 40 mg QD, or eplerenone forced-titrated over four weeks plus fixed enalapril 10 mg QD. HCTZ 12.5-25 mg and then amlodipine 10 mg could be added after eight weeks to control BP if necessary. Study 017 randomized 202 patients and Study 021 randomized 266 patients. The blood pressure changes at eight weeks are shown in the table and figure below:

Table 7: Reviewer's Mean Changes in BP at Week 8 in Study 017

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

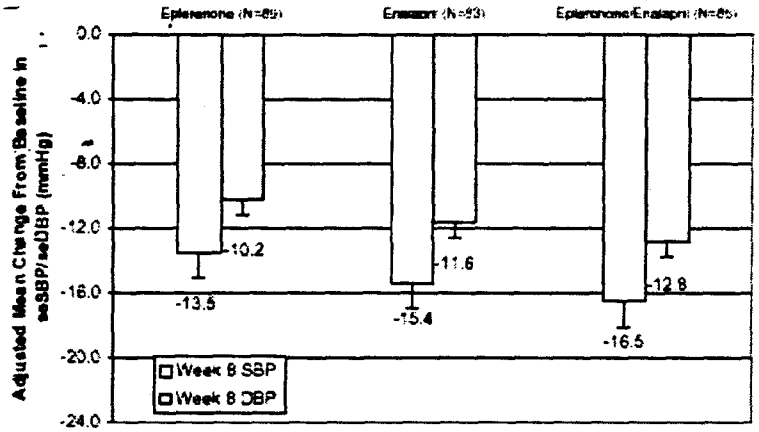


Figure 22: Sponsor's Adjusted Mean Change From Baseline in BP at Week 8 in Study 021

In Study 017 the BP reductions at 8 weeks were greater for eplerenone while in Study 021 they were slightly less. In both studies the addition of enalapril 10 mg produced slightly greater BP lowering than eplerenone 200 mg or enalapril 40 mg alone.

The primary endpoint evaluation for Study 017 was at 36 weeks and for Study 021 at 24 weeks. While BP reductions for these endpoints are confounded by the use of HCTZ and amlodipine they are consistent with the week 8 results. For Study 017 the reductions in DBP and SBP were similar for the eplerenone and enalapril groups (very slightly higher for enalapril) and the reductions in the combined group virtually identical to the enalapril group for DBP and statistically significantly higher than the eplerenone group for SBP. The results for Study 021 were a slight variation, with the reductions in DBP and SBP again similar for the eplerenone and enalapril groups (very slightly higher for enalapril) but for Study 017 the DBP reduction in the combined group was significantly higher than for the eplerenone group.

Study 021 is notable because of the high rates of hyperkalemia: 16 percent in the eplerenone arm and 24 percent in the combined arm vs. 6 percent in the enalapril arm. Six eplerenone and 13 combined vs. 2 enalapril patients were withdrawn because of hyperkalemia. This study permitted the enrollment of patients with mild renal dysfunction (creatinine to 1.7 mg/dL). The sponsor noted an association between lower creatinine clearance and more hyperkalemia.

Reviewer's comment: Eplerenone 50-200 mg QD appears to be comparable to enalapril 10-40 mg QD in antihypertensive efficacy. Eplerenone produces some additional BP reduction when added to an ACEI but it is not clearly established from these studies that the additional reduction is significant.

Angiotensin Receptor Blockers (ARBs)

Eplerenone titrated 50-100 mg was added to an ARB in 164 patients not completely controlled on their usual dosages of unspecified ACEIs in Study 023. The primary endpoint was change in seated trough cuff DBP at eight weeks. Eplerenone produced statistically significant reductions compared to placebo in both DBP (-12.7 vs –9.3 mm Hg, p = 0.004) and SBP (-16.0 vs –9.2, p = 0.001). The ARB dosage was not optimized, limiting the interpretation of these results. The combination arm was well-tolerated with AE rates similar to the ARB-placebo arm with more nausea in the eplerenone-ARB arm (9.6 vs. 4.9 percent) and more asthenia in the placebo-ARB arm (11 vs 2.4 percent). No patients had hyperkalemia AEs. The eplerenone-ARB group did have a statistically significant increase in mean potassium levels (0.13 vs 0.03 meq/L, p = 0.0083).

Eplerenone was compared to the ARB losartan and placebo in Study 020. Randomization was stratified by race in a 2:1 ratio of black patients to white. 551 patients were randomized to eplerenone titrated 50-200 mg QD, losartan titrated 50-100 mg QD, or placebo for 16 weeks. The primary endpoint was seated trough cuff DBP. 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. The reductions in BP for blacks and whites were very similar with eplerenone, although the reductions tended to be slightly less for blacks for all groups with the exception of SBP reduction in blacks on eplerenone.

Eplerenone was compared to losartan in patients with low-renin essential hypertension in Study 019. 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. 168 patients were randomized to eplerenone titrated 100-200 mg QD or losartan titrated 50-100 mg QD. HCTZ 12.5-25 mg could be added to control BP. Endpoints were evaluated at both week 8 (before the addition of HCTZ) and week 16. The pre-specified non-inferiority margin was 3.5 mm Hg difference in trough cuff seated DBP. Eplerenone was non-inferior to losartan in DBP reduction at both 8 weeks (-9.3 vs –6.7 mm Hg) and 16 weeks (-10.8 vs. –9.8 mm Hg). It was superior to losartan in lowering DBP at 8 weeks. The results for SBP were similar.

There appeared to be a differential effect by race in Study 019. 55 of the patients (33 percent) were black. The BP changes by race are shown in the table below.

Table 8: Reviewer's Mean BP Changes by Race in Study 019

Drug	Race	Week 8 SBP	Week 8 DBP	Week 16 SBP	Week 16 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

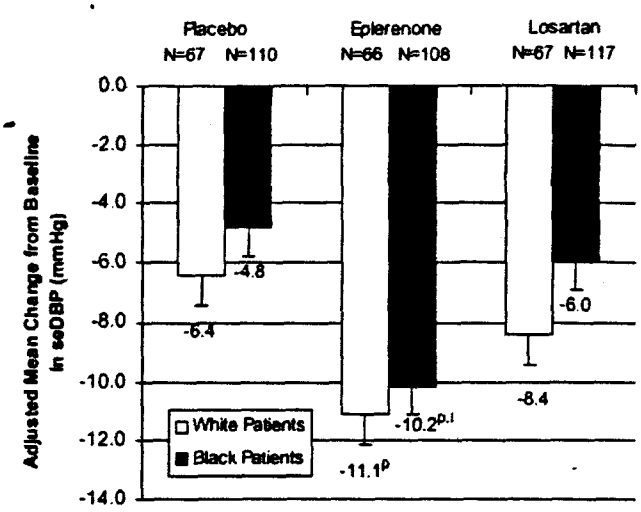
Blacks showed a reduced effect with both eplerenone and losartan alone. Hydrochlorothiazide (HCTZ) was added more frequently in blacks on losartan (79 percent) than non-blacks on losartan (42 percent) or patients on eplerenone (about 30-31 percent for each racial group). Patients on HCTZ had greater 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.

Because of this striking difference in response by race in Study 019, the other study with substantial black representation, Study 020, was re-examined for differences by race and renin levels. Baseline direct renin levels were actually similar in the two studies despite the selection for low renin levels in Study 019. In Study 019, mean baseline levels were 10.9 mU/L (median 10.5) for blacks and 17.5 mU/L (median 12.6) for whites. In Study 020, mean levels were 12.4 mU/L (median 9.1) for blacks and 17.6 mU/L (median 13.2) for whites. 67 percent of the patients had baseline levels < 15 mU/L. Study 020 did not show a differential effect of eplerenone on BP reduction by race either for all patients or for the subset with lower renin levels. Mean DBP changes in the eplerenone arm are shown by baseline renin level and race in the table below and the changes in DBP by arm are shown in the figure that follows.

Table 9: DBP Reductions by Race and Baseline Direct Renin for Eplerenone Patients in Study 020

Race	Baseline Direct Renin ≥ 15 mU/L	Baseline Direct Renin < 15 mU/L
Blacks	-7.3	-10.9
Whites	-8.6	-12.4

There appears to be a small decrease in response in blacks compared to whites. There also appears to be a greater response in patients with lower baseline renin levels with the small black/white differential preserved by renin level.



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

Figure 23: Sponsor's Adjusted Mean Change From Baseline in seDBP at Week 16 in Study 020

Study 020 shows a slight, but not statistically significant, reduced efficacy of eplerenone in blacks. The Study 020 race differential is much less than that in Study 019. Study 019 has at least one other probably random variation: Plasma renin levels in blacks were not evenly distributed between the two groups. 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.

Reviewer's comment: While the data suggest that eplerenone is slightly less effective in blacks, the evidence is not convincing enough to conclude that eplerenone is less effective in that subgroup. One can also not conclude that eplerenone is as effective in blacks as in whites because none of the trials was powered as a non-inferiority trial to establish that eplerenone is equally effective in blacks.

8. Disease Subsets

Eplerenone use for systolic hypertension in Study 022 and low-renin hypertension in Study 019 is discussed in the previous section. Eplerenone effect on non-BP endpoints in hypertensive patients with left ventricular hypertrophy and in hypertensive diabetics with albuminuria is discussed in the next section. The other study that addressed a hypertensive disease subset is Study 018.

Study 018 randomized 141 adults with primary aldosteronism and mild to moderately severe hypertension to eplerenone titrated 100-300 mg QD or spironolactone titrated 75-225 mg QD for 16 weeks. Primary aldosteronism was determined by 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. The primary endpoint was trough cuff seated DBP at 16 weeks with a noninferiority margin of 4 mm Hg.

The mean decrease from baseline to week 16 in mean 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 ($p < 0.001$). Renin and aldosterone levels increased significantly more in the spironolactone group.

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.

Reviewer's comment: 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 QD. Spironolactone also produced greater increases in renin and aldosterone. However, spironolactone at these dosages also led to more hyperkalemia and sex-hormone related AEs. The other study comparing eplerenone and spironolactone, Study 010, showed that eplerenone 400 mg daily was roughly equal to spironolactone 100 mg daily in reducing BP in essential hypertension. These two studies are consistent in that they suggest that eplerenone is substantially less potent than spironolactone in controlling BP.

9. Other Endpoints

All studies evaluated a range of secondary non-BP endpoints such as renin and aldosterone. Two studies, 017 and 021, specifically targeted non-BP primary endpoints and are discussed first.

Left Ventricular Mass

Study 017 randomized 202 hypertensive adults with left ventricular hypertrophy (LVH) to eplerenone forced-titrated 50-200 mg QD over four weeks, enalapril forced-titrated 10 to 40 mg QD, or eplerenone forced-titrated over four weeks plus fixed enalapril 10 mg QD. HCTZ 12.5-25 mg and then amlodipine 10 mg could be added after eight weeks to control BP if necessary. LVH was defined by ECG or echo criteria. The primary

endpoint was change in left ventricular mass (LVM) at month 9 measured by MRI. The primary analysis was changed from a superiority hypothesis to a non-inferiority hypothesis eleven months after study initiation. Mean change from baseline in LVM was –14.5 for the eplerenone arm, -19.7 for the enalapril arm, and -27.2 for the combined arm. Only the difference between the eplerenone arm and the combined arm is statistically significant. While the sponsor claims that this study documents non-inferiority of eplerenone to enalapril in reducing LVM, by the original hypothesis superiority of eplerenone is not established. BP reductions were similarly ordered, i.e., least with eplerenone, slightly higher with enalapril, and greatest with the combination.

Albuminuria

Study 021 randomized 266 hypertensive adult type 2 diabetics with albuminuria to eplerenone forced-titrated 50-200 mg QD over four weeks, enalapril forced-titrated 10 to 40 mg QD, or eplerenone forced-titrated over four weeks plus fixed enalapril 10 mg QD. HCTZ 12.5-25 mg and then amlodipine 10 mg could be added after eight weeks to control BP if necessary. Albuminuria was defined as a urine albumin:creatinine ratio (UACR) $\geq$ 100 mg/g by first morning voided spot urine. 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. UACR was reduced by 62 percent in the eplerenone arm, 45 percent in the enalapril arm, and 74 percent in the combined arm compared to baseline. The reduction in UACR was significantly greater in the eplerenone are compared to the enalapril arm ($p = 0.015$) and in the combined arm compared to eplerenone or enalapril ($p \leq 0.018$). BP decreases increased slightly from eplerenone to enalapril to the combined arm, with only the difference between DBP in the eplerenone and combined arms being statistically significant.

Changes in UACR were evaluated as secondary endpoints in Studies 016, 020, and 022. Significant decreases (12-27 percent) from baseline in UACR were observed in the eplerenone, losartan, and enalapril treatment groups in these studies after 16 or 24 weeks of treatment. No significant change from baseline in UACR was noted in the amlodipine treatment group in Study 022 or in the placebo treatment group in Study 020. The decreases in UACR were significantly greater in the eplerenone treatment group compared to the placebo treatment group in Study 020 and compared to the amlodipine treatment group in Study 022. The sponsor also noted that in Study 022, trough cuff SBP reduction at the week 24 endpoint was comparable between eplerenone and amlodipine, but amlodipine treatment resulted in a greater reduction in DBP. Hence UACR reduction is not strictly related to BP reduction.

Renin-Angiotensin-Aldosterone System

Renin and aldosterone levels were measured in all studies except Studies 022 and 025 at baseline and final visit to assess the activity of the renin-angiotensin-aldosterone system (RAAS). Increases in total and direct (active) renin and aldosterone levels were noted in all studies with eplerenone treatment and were typically highly statistically significant.

The changes by study are summarized well in the NDA. The more refined questions of interest are the following: (1) What is the dose-response for changes in RAAS levels? (2) How do the changes seen with eplerenone compare to those with other antihypertensives? (3) Are there variations by race or gender?

Three studies, 010, 015,and 049, had fixed eplerenone dose and placebo arms. The mean and median changes in RAAS hormones by eplerenone dose are shown in the following three tables.

Table 10: Reviewer's Changes from Baseline In Direct Renin Levels in Fixed Dose Studies

	010		015		049	
Dose	Mean	Median	Mean	Median	Mean	Median
0	2.2	2.5	13.3	1.4	-0.2	-0.8
25			0.0	4.3	5.2	0.1
50	2.0	6.0	7.3	4.1	3.5	1.8
100	14.4	9.0			4.6	2.4
200			7.3	7.1	9.7	3.4
400	25.7	15.0				

Table 11: Reviewer's Changes from Baseline In Total Renin Levels in Fixed Dose Studies

	010		015		049	
Dose	Mean	Median	Mean	Median	Mean	Median
0	-0.6	-4	45.7	-1.7	12.3	-0.3
25			51.2	19.4	60.4	26.0
50	54.1	36	32.9	19.2	47.1	26.0
100	70.9	51			66.0	48.8
200			64.3	57.8	86.9	47.0
400	123	98				

Table 12: Reviewer's Changes from Baseline In Serum Aldosterone Levels in Fixed Dose Studies

	010		015		049	
Dose	Mean	Median	Mean	Median	Mean	Median
0	1.0	1.0	1.2	1.0	0.7	0.0
25			5.9	5.0	3.3	2.4
50	6.6	4.0	5.6	4.0	5.8	4.7
100	10.2	7.0			6.5	5.2
200			12.2	10.5	9.7	8.5
400	24.8	16.0				

The RAAS levels show considerable variability with distributions skewed towards high values. The sponsor typically applied a log transformation to the values and displayed geometric means. The reviewer displays median values in this section.

The changes in each study appear to be reasonably consistent with the changes in BP: Study 010 shows a consistent, not quite linear increase with dose. Study 015 shows more erratic change, particularly with means. There are increases in the placebo group in mean renin levels (recall the large placebo effect in this study), but the median changes are small. Study 049 shows lower increases in RAAS levels relative to 010 with less differentiation between the 100 and 200 mg doses, similar to the BP changes.

The reviewer performed ANCOVA of the differences in the values with the base values and eplerenone doses as continuous factors. The eplerenone dose factors for all three RAAS hormone changes are highly statistically significant (p 0.0001 or less). There appears to be a dose-response relationship between increasing eplerenone dosage and increasing changes in RAAS level. At the low end the 25 mg dose shows activity particularly regarding changes in aldosterone levels. At the high end the 400 mg dose is again differentiated from lower doses in Study 010.

Hydrochlorothiazide (HCTZ) also shows a dose-response relationship in Study 015. The mean and median changes in RAAS levels by HCTZ dose are shown in the table below.

Table 13: Reviewer's Changes from Baseline In RAAS Levels by Hydrochlorothiazide Dose in Study 015

	Direct Renin		Total Renin		Aldosterone	
Dose	Mean	Median	Mean	Median	Mean	Median
0	13.3	1.4	45.7	-1.7	1.2	1.0
12.5	7.0	6.1	51.9	51.6	3.5	3.0
25	23.8	7.5	110.0	78.0	4.9	4.0

Compared to eplerenone the increases are comparable to the lower eplerenone doses and the higher HCTZ dose produces less than proportional increases in RAAS levels. The reviewer performed ANCOVA of the differences in the values for Study 015 with the base values and eplerenone and HCTZ doses as continuous factors. Both dose factors for all three RAAS hormone changes are highly statistically significant ($p < 0.0001$ except for eplerenone dose with direct renin $p = 0.001$).

Eplerenone can be compared to spironolactone 50 mg BID in Study 010. With spironolactone the mean increase in direct renin was 13.3 and the median was 12.5 and in aldosterone the mean increase was 19.2 and the median increase was 14. These median values are 13-17 percent lower than the increases produced by the eplerenone 400 mg dosages. In Study 018, titrated eplerenone 100-300 mg and spironolactone 75-225 mg in primary aldosteronism, the median increases with spironolactone substantially exceeded (0.8 to 2.8 fold) the increases with eplerenone.

The two other drugs that directly affect the RAAS and that were compared to eplerenone are losartan and enalapril. In Study 020, titrated eplerenone 50-200 mg vs losartan 50-100 mg, losartan produced a small decrease in aldosterone levels and increases in direct and total renin levels that were 62 and 26 percent less than those with eplerenone. In Study 016, titrated eplerenone 25-200 mg vs enalapril 5-40 mg, enalapril also produced a small decrease in aldosterone levels but increases in direct and total renin levels that were 65 and 14 percent more than those with eplerenone.

Eplerenone can also be compared to amlodipine, another drug that does not directly affect the RAAS. In Study 026, titrated eplerenone 50-200 mg vs amlodipine 2.5-10 mg, amlodipine produced increases in direct and total renin and aldosterone levels that were 53, 63, and 75 percent less than those with eplerenone.

In the eplerenone studies baseline RAAS levels varied by race and gender but not by age. White females had about 25 percent lower direct renin levels than white males but similar aldosterone levels. Levels in blacks were not differentiated by gender but direct renin levels were about 45 percent lower than those in white males and aldosterone levels were about 20 percent lower.

In the fixed dose eplerenone studies, race and gender are significant factors for direct and total renin and aldosterone except for race and total renin in ANCOVAs of changes from baseline with base value, dose, race, and gender as factors. If all eplerenone only arms are lumped together, there appears to be a gradient of absolute increases in RAAS levels by race and gender, with white males > white females > black males > black females. However, the relative increases from baseline are similar for whites of both genders and black males, with black females showing a diminished relative response.

If one considers only Study 020, the study that oversampled blacks, then the pattern of changes with eplerenone is similar to that just described with some variations: Both genders are similar regarding a lesser aldosterone increase and only black females have a reduced total renin increase. Losartan does not appear to produce a differential response by gender but it does by race, with blacks having decreased response in renin levels.

Study 019 in patients with low renin hypertension measured RAAS levels at 8 weeks prior to the addition of HCTZ. If the 8 week RAAS levels are analyzed by race and gender, the numbers are small and the results are too erratic to suggest any patterns. If the 8 week data from Study 019 are combined with the data from Study 020, the results are still varied. Black females show the lowest increases for renin levels with both eplerenone and losartan. Increases in whites average greater than those in blacks. In an ANCOVA of the changes with base value, treatment (eplerenone, losartan, or placebo), gender, and race as factors, base value, treatment, and race are significant factors but gender is not. If an interaction term for race and gender is included, then gender and the interaction term just achieve significance for aldosterone changes.

Reviewer's comment: Eplerenone appears to produce a dose-related increase in renin and aldosterone levels. These dose effects are evident for the entire range of dosages tested, 25 through 400 mg. The 400 mg daily dosage appears slightly more effective in increasing RAAS levels than spironolactone 50 mg BID. The eplerenone increases exceed those produced by drugs with similar antihypertensive efficacy that do not act directly on the RAAS, such as hydrochlorothiazide and amlodipine. There appears to be a differential effect of eplerenone by race and gender, with blacks and females showing reduced effect.

D. Efficacy Conclusions

- Two adequate and well controlled studies, Studies 010 and 049, demonstrated that eplerenone in dosages ranging from 50 to 400 mg daily significantly reduces diastolic and systolic blood pressure in patients with essential hypertension. Ten other randomized trials, one with both active and placebo control arms and the others only with active controls, support the antihypertensive efficacy of eplerenone.

- One trial, Study 015 that was a factorial study with hydrochlorothiazide, showed more limited efficacy of eplerenone compared to placebo. However, that trial also showed limited efficacy of hydrochlorothiazide relative to placebo and a large placebo response, so its results are more suspect than the two pivotal trial results.

- Eplerenone shows a dose-response relationship for the entire range of doses tested, from 25 mg to 400 mg daily. The precise shape of the dose-response relationship is not clearly defined by the data. There is inconsistent data regarding whether there is tapering of the response in the 200-400 mg range.

- Ambulatory blood pressure monitoring demonstrated that once a day administration was effective in controlling blood pressure throughout the day.

- Blood pressure reductions with eplerenone were substantial at two weeks after initiating therapy and near maximal at four weeks.

- Blood pressure control was maintained for at least one year.

- No rebound or withdrawal effects were observed.

- Compared to other antihypertensives:

    - Spironolactone 50 mg BID and eplerenone 400 mg daily showed comparable efficacy in essential hypertension. Spironolactone titrated 75-225 mg QD was significantly more effective than eplerenone 100-300 mg QD in controlling BP in primary aldosteronism

- Hydrochlorothiazide 25 mg and eplerenone 200 mg produced comparable and significant reductions in SBP compared to placebo.

- Amlodipine 2.5-10 mg QD was superior to eplerenone 50-200 mg QD in reducing DBP in essential hypertension in one study. In another study amlodipine 2.5-10 mg QD was comparable to eplerenone 50-200 mg QD in reducing SBP in systolic hypertension but amlodipine was again superior in reducing DBP

- Enalapril 10-40 mg QD was comparable to eplerenone 50-200 mg QD in reducing DBP and SBP.

- Losartan 50-100 mg QD was less effective than eplerenone 50-200 mg QD in reducing DBP both in blacks and in whites. In low renin hypertension the effects of the two drugs were comparable.

- Eplerenone was added to ACE inhibitors, angiotensin receptor blockers, beta blockers, and calcium channel blockers in patients not controlled on their usual dosages of one of these drugs. Eplerenone produced additional decreases in DBP and SBP with BBs and ARBs but only in SBP for ACEI and CCBs. These results are limited by the failure to optimize use of the usual drug. The coadministrations were tolerated well.

- In one study in low-renin hypertension, eplerenone was less effective in reducing blood pressure in blacks compared to whites. In a larger study, eplerenone efficacy was similar in blacks and whites, although there is evidence in this study for a slightly smaller effect in blacks. The evidence is inconclusive regarding whether eplerenone is equally effective in blacks and whites.

- Eplerenone appears to reduce left ventricular mass and reduce albuminuria in diabetics. The clinical relevance of these changes is not fully established.

- Eplerenone appears to produce a dose-related increase in renin and aldosterone levels. These dose effects are evident for the entire range of dosages tested, 25 through 400 mg. The 400 mg daily dosage appears slightly more effective in increasing RAAS levels than spironolactone 50 mg BID. The eplerenone increases exceed those produced by drugs with similar antihypertensive efficacy that do not act directly on the RAAS, such as hydrochlorothiazide and amlodipine. There appears to be a differential effect of eplerenone by race and gender, with blacks and females showing reduced effect.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Eplerenone appears to be a relatively safe, well-tolerated drug comparable to other first-line antihypertensives. The incidence rates of minor side effects are comparable to placebo rates and those with active controls. Because the active controls included in the eplerenone trials were major first-line drugs including hydrochlorothiazide, amlodipine, and enalapril, the comparability to active controls is reassuring. Eplerenone was also compared to spironolactone and appears to have fewer side effects. However, because spironolactone was more effective, the risk/benefit ratio of eplerenone to spironolactone is not adequately defined.

Eplerenone does appear to have two side effects that may be limiting:

(1) Hyperkalemia was particularly troublesome with the highest dosage (400 mg daily) tested in one trial but dropped from further study and not recommended for clinical practice. However, hyperkalemia was also problematic for patients with mild renal insufficiency and when eplerenone was combined with an ACE inhibitor.

(2) Eplerenone can cause gynecomastia in males and vaginal bleeding in females. The rates appear lower with eplerenone than with spironolactone but the comparison is confounded by the differences in efficacy at the dosages used. Also, gynecomastia is a delayed effect and its incidence may not be defined fully by the short study durations used in the hypertension trials.

B. Description of Patient Exposure

1. Exposure

The sponsor's summary of the patient exposure, including center US0003 from study 010, is the following:

"• Of the 3106 patients who received at least one dose of eplerenone with or without other active medication in any eplerenone trial, 2853 (91.9%) were exposed for more than 30 days, 1366 (44.0%) were exposed for more than 90 days, 690 (22.2%) were exposed for more than 180 days, 213 were exposed for more than 336 days (48 weeks; 6.8%), and 106 (3.4%) were exposed for more than 360 days.

"• Of the 2520 patients who received at least one dose of eplerenone with or without other antihypertensive medication in the combined controlled trials, 2302 (91.3%) were exposed for more than 30 days, 889 (35.3%) were exposed for more than 90 days, and 283 (11.2%) were exposed for more than 180 days.

"• Of the 586 patients who received at least one dose of eplerenone with or without other active medication in the long-term safety trial, 407 (69.4%) were exposed to eplerenone for more than 180 days, 133 (22.7%) were exposed for more than 336 days, and 98 (16.7%) were exposed for more than 360 days.

"• Exposure to any dose of eplerenone with or without other active medication totals over 1081 patient-years. Exposure to the eplerenone 50 mg dose totals over 286 patient-years, the 100 mg dose totals over 246 patient-years, and the 200 mg dose totals over 475 patient-years."

The sponsor's summary of total exposure by dose in the 14 studies is shown in the figure below:

	Eplerenone						
Exposure (Days)	**25 mg**	**50 mg**	**100 mg**	**200 mg**	**300 mg**	**400 mg**	**Overall***
Eplerenone Only							
1-15	5	684	504	198	1	4	107
16-30	14	358	339	230	4	0	78
31-60	52	238	228	166	19	78	713
61-90	41	131	149	148	4	22	459
91-120	3	62	81	64	0	0	324
121-150	2	11	26	87	0	0	46
151-180	26	68	23	15	0	0	157
181-270	15	35	47	112	0	0	92
271-336	0	40	46	45	0	0	194
337-360	0	4	10	11	0	0	95
> 360	0	14	0	1	0	0	69
No. Treated	158	1645	1453	1077	28	104	2334
Eplerenone Plus Other Active Medication (Coadministration Background, or Additional Antihypertensive)							
1-15	13	939	640	58	1	4	146
16-30	18	419	409	122	4	0	107
31-60	127	461	305	271	19	78	954
61-90	57	158	146	180	4	22	533
91-120	3	62	91	82	0	0	361
121-150	2	11	26	183	0	0	63
151-180	26	68	23	42	0	0	252
181-270	15	35	47	235	0	0	189
271-336	0	40	46	104	0	0	288
337-360	0	4	10	41	0	0	107
> 360	0	14	0	1	0	0	106
No. Treated	261	2211	1743	1319	28	104	3106

Source: Table T3.8.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 026, and 049.
* Represents patients irrespective of dose and is not necessarily the sum of individual eplerenone columns.

Figure 24: Sponsor's Duration of Eplerenone Exposure by Dose

The sponsor's summary of the person-year exposure by dose is shown in the figure below.

	Eplerenone						
	25 mg	50 mg	100 mg	200 mg	300 mg	400 mg	Overall
Eplerenone Only							
Combined Controlled Trials	38.9	154.3	142.7	160.1	3.6	16.1	515.8
Uncontrolled, Long-Term Safety Trial (Study 025)	N/A	81.0	83.3	95.1	N/A	N/A	259.4
Long-Term Trials	22.6	162.9	147.3	202.3	N/A	N/A	535.1
Overall Exposure[a]	38.9	235.3	225.9	255.2	3.6	16.1	775.2
Eplerenone Plus Other Active Medication (Coadministration Background, or Additional Antihypertensive)							
Combined Controlled Trials	53.7	205.1	163.5	257.1	3.6	16.1	699.2
Uncontrolled, Long-Term Safety Trial (Study 025)	N/A	81.0	83.3	217.9	N/A	N/A	382.2
Long-Term Trials	22.6	168.8	152.9	405.3	N/A	N/A	749.6
Overall Exposure[a]	53.7	286.1	246.7	475.0	3.6	16.1	1081.3

Source. Tables T4.4, T4.5, T4.6, and T4.7
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 026, and 049.
N/A=not applicable
a Overall exposure represents exposure to eplerenone and each individual dose for all controlled and uncontrolled trials.

Figure 25: Sponsor's Patient-Years of Exposure to Eplerenone by Dose

Reviewer's comment: The raw exposure statistics--3102 patients exposed to eplerenone in the trials, 1081 person-years of total exposure—are reasonably robust for detecting short-term (less than six months) safety problems with eplerenone. The database is less robust for detecting long term side effects such as gynecomastia: In the controlled trials 283 patients were exposed for 180 days or more. Only 106 patients were exposed for more than 360 days and these longer exposure times were in the open-label follow-on study. These limitations are discussed further below with regard to the analysis of sex hormone-related side effects.

2. Demographics

The sponsor's summary of the geographic representation in the trials is shown in the figure below followed by a figure with the sponsor's summary of the demographics. Note that the U.S. and Canada are well represented in the trial data. Men and women are almost equally represented, although there is a slightly majority of men. Exposure in blacks is reasonable (377 exposed) and also in the elderly (588 age >= 65). Children were excluded from these trials.

Region	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
Combined Controlled Trials								
No. treated	375		1748		772		1422	
Africa	37	(9.9)	37	(2.1)	0	(0.0)	41	(2.9)
Europe	11	(2.9)	461	(26.4)	286	(37.0)	590	(41.5)
North America	312	(83.2)	1135	(64.9)	343	(44.4)	637	(44.8)
Pacific Rim	0	(0.0)	20	(1.1)	13	(1.7)	20	(1.4)
Latin America	15	(4.0)	95	(5.4)	130	(16.8)	134	(9.4)
Uncontrolled, Long-Term Safety Trial (Study 025)								
No. treated	-		586		-		-	
Europe	-	-	68	(11.6)	-	-	-	-
North America	-	-	448	(76.5)	-	-	-	-
Latin America	-	-	70	(11.9)	-	-	-	-

Source: Tables T2.11.1 and T2.11.2.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 025, 026, and 049.
Data are expressed as N (% of patients).
Africa: South Africa.
Europe: Belgium, France, Germany, Italy, Netherlands, Poland, Slovakia, Spain, Sweden, Switzerland, and United Kingdom.
North America: Canada and United States.
Pacific Rim: Australia and New Zealand.
Latin America: Argentina, Brazil and Mexico.

Figure 26: Sponsor's Number of Treated Patients by Region

Characteristic	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
No. treated	375		1748		772		1422	
Age (years)								
< 35	13	(3.5)	60	(3.4)	32	(4.1)	40	(2.8)
35-44	59	(15.7)	270	(15.4)	96	(12.4)	170	(12.0)
45-54	151	(40.3)	515	(29.5)	238	(30.8)	380	(26.7)
55-64	95	(25.3)	533	(30.5)	218	(28.2)	451	(31.7)
65-74	45	(12.0)	305	(17.4)	155	(20.1)	303	(21.3)
> 74	12	(3.2)	65	(3.7)	33	(4.3)	78	(5.5)
Mean		53.2		55.1		55.6		56.8
Range		20-80		19-89		19-89		19-91
Ethnicity								
Asian	4	(1.1)	19	(1.1)	11	(1.4)	13	(0.9)
Black	152	(40.5)	309	(17.7)	58	(7.5)	209	(14.7)
Caucasian	192	(51.2)	1263	(72.3)	597	(77.3)	1082	(76.1)
Hispanic	26	(6.9)	136	(7.8)	102	(13.2)	112	(7.9)
Other	1	(0.3)	21	(1.2)	4	(0.5)	6	(0.4)
Gender								
Female	177	(47.2)	794	(45.4)	363	(47.0)	666	(46.8)
Male	198	(52.8)	954	(54.6)	409	(53.0)	756	(53.2)

Figure 27: Sponsor's Demographics for the Combined Clinical Trials

C. Methods and Specific Findings of Safety Review

1. Background and Methodology for Safety Review

1.1. Deaths

Five patients died during the trials, four treated with eplerenone:

In Study 016, a 57-year-old male patient died after 321 days of treatment with enalapril due to a suspected myocardial infarction that was considered by the investigator to have no relationship to study medication.

In Study 021, two patients died. Fourteen days after the last dose of eplerenone (123 days of treatment), a 70-year-old female patient experienced a hemorrhagic stroke considered by the investigator to be of uncertain relationship to study medication. A 64-year-old male patient was treated for 163 days. On day 164 he was hospitalized for abdominal pain. On day 168 an operation was performed and a bleeding duodenal ulcer was diagnosed. Post-op he suffered respiratory arrest and was transferred to the ICU. He was diagnosed as postanoxic encephalopathy on day 172 and died on day 179.

In Study 023, after one day of treatment, a 69-year-old female eplerenone patient in the ACEI cohort experienced a sudden cardiac death that was considered by the investigator to be unrelated to study medication. This patient had a history of diabetes mellitus type 2, chronic obstructive pulmonary disease, an ejection fraction of 50%, and a complete left bundle branch block with a normal PR interval without signs of ischemia.

In Study 025, the uncontrolled follow-on study, one 64-year-old male patient died. This patient was treated in the study for 212 days. Seven days after the last dose of eplerenone (200 mg), the patient had an automobile accident. The patient was found at the scene to be in ventricular tachycardia with no pulses and did not respond to cardioversion en route to the hospital. The impression was that the patient had a myocardial infarction prior to the accident. This patient was also taking lisinopril 20 mg. The patient's last potassium value taken 7 days prior to the accident was within normal limits. These events were considered by the investigator to be of uncertain relationship to study drug.

The mortality rates by treatment group are shown in the table below.

Table 14: Reviewer's Mortality Rates by Treatment Groups, All Trials

Group	N	PEY*	Deaths	D/100.000	D/100 PEY
Eplerenone	3106	1081	4	129	0.37
Active control	1422	473	1	70	0.21
Placebo	375	79	0	0	0.00

*PEY = Patient Exposure Years

Reviewer's comment: There were no deaths probably related to eplerenone use. There is no pattern of deaths suggestive of a problem with eplerenone.

1.2. Other Serious Adverse Events

1.2.1. Reviewer's Analysis of Serious Adverse Events

The sponsor's Integrated Summary of Safety includes an Appendix 2.3 that lists all serious adverse events (SAEs). That appendix lists 239 serious adverse events in 163 patients. Of these 163 serious adverse events were reported in 116 patients treated with eplerenone.

The vast majority of multiple SAEs occurring in the same patient were temporally and probably causally related, e.g., abdominal pain and intestinal obstruction or myocardial infarction and abnormal ECG. To eliminate this redundant reporting the reviewer classified the multiple SAEs in the same patient into non-redundant groups, e.g., the reviewer classified intestinal obstruction and myocardial infarction from the previous examples as non-duplicates and abdominal pain and abnormal ECG as duplicates. The reviewer classified 50 SAEs as duplicative. For this analysis the reviewer also classified the SAEs into classes relevant to eplerenone toxicities. Finally, for this analysis the reviewer calculated the rates of these SAE classes per 100 patient exposure years (PEYs) for the combined treatment groups from the 13 controlled trials of placebo, active control, eplerenone alone, and eplerenone coadministered with another antihypertensive and any eplerenone use (alone or coadministered) vs. no eplerenone use (placebo or active control). The results of this analysis are shown in the table below:

Table 15: Reviewer's Rates of SAEs by Combined Treatment Group for Controlled Trials

	Active	Coadmin	Mono	Placebo	Any E	No E
N:	1422	772	1748	375	2520	1797
PEY:	437.6	168.9	496.9	78.9	665.8	516.5
AE Class	**SAEs per 100 PEYs**					
Accident	0.2	0.6	0.4		0.5	0.2
Neoplasm	0.5		1.0	1.3	0.8	0.6
Cerebrovascular	0.9	1.2	1.8		1.7	0.8
Other neurologic	0.5	1.2	0.2		0.5	0.4
Cardiovascular	4.1	3.6	3.0	1.3	3.2	3.7
Endocrine		1.8	0.6		0.9	
Gastrointestinal	1.4	5.3	1.6	3.8	2.6	1.7
Hematologic			0.6		0.5	
Hypertension		1.8	0.2		0.6	
Infection	0.9		1.0		0.8	0.8
Hyperkalemia	0.2	0.6	0.6		0.6	0.2

	Active	Coadmin	Mono	Placebo	Any E	No E
Hepatic			0.2		0.2	
Other	0.2	0.6			0.2	0.2
Pain		1.8	0.4	1.3	0.8	0.2
Renal	0.9		0.6		0.5	0.8
Sex hormonal	0.2	0.6	0.4		0.5	0.2

What stands out in the table of SAEs above is that, for many classes of SAEs, the eplerenone rates are higher than placebo but comparable to the rates in the active controls. However, the comparison in the table above may not be the optimal one because not all trials had placebo arms. If SAEs only in trials with placebo arms are considered, the SAE rates are as in the following table.

Table 16: Reviewer's Rates of SAEs by Combined Treatment Group for Placebo-Controlled Trials

Group	Active	Coadmin	Mono	Placebo	Any E	No E
N:	339	309	961	376	1270	715
PEY:	69.6	44.9	182.5	78.9	227.4	148.5
AE Class	**SAEs per 100 PEYs**					
Accident			0.5		0.4	
Neoplasm			1.6	1.3	1.3	0.7
Cerebrovascular	1.4	2.2	1.1		1.3	0.7
Other neurologic	1.4		0.5		0.4	0.7
Cardiovascular	4.3	2.2	1.6	1.3	1.8	2.7
Gastrointestinal	1.4	6.7	1.6	3.8	2.6	2.7
Infectious	1.4		1.6		1.3	0.7
Other	1.4					0.7
Pain		2.2		1.3	0.4	0.7
Renal	1.4		0.5		0.4	0.7

There still appear to be differences in the rates between eplerenone and placebo. The differences are explored by class below. The following tables include the SAEs from the open label, uncontrolled study 025.

Accident

Seven patients experienced accidents, such as traumatic fractures and a spider bite, that appear unrelated to drug use.

Neoplasms

Included in this class are two pituitary macroadenomas, one in a placebo-treated patient and another in an eplerenone-treated patient. Of the other eight neoplasms reported, two breast cancers in eplerenone monotherapy patients occurred too early (days 1 and 23) to

have any presumed relationship to eplerenone. The other cancers in eplerenone-treated patients were one each prostate cancer, breast cancer, renal cell carcinoma, and hepatic metastasis. There is no clear pattern, but the exposure is too short to rule out a carcinogenic effect.

Cerebrovascular

Eighteen patients experienced cerebrovascular SAEs. The types of events are listed in the table below.

Table 17: Reviewer's Cerebrovascular SAEs

Demo	Study	Group	Drug	Onset	Description
63F	2003	Active	Losartan 50-100 QD	56	CEREBRAL ANEURYSM
55M	1602	Active	Enalapril 5-40 QD	221	TRANSIENT ISCHEMIC ATTACK
69M	1602	Active	Enalapril 5-40 QD	101	CAROTID STENOSIS
73M	1602	Active	Enalapril 5-40 QD	36	AMNESIA
50M	1512	Coadmin	E 200 + HCTZ 25 QD	54	SUBARACHNOID HEMORRHAGE
68M	1703	Coadmin	E 50-200 + enalapril 10-40 QD	2	TRANSIENT ISCHEMIC ATTACK
71M	2501	Coadmin	E 50-200 QD + antihypertensive	281	STROKE
56F	2501	Coadmin	E 50-200 QD + antihypertensive	124	STROKE
63M	2501	Coadmin	E 50-200 QD + antihypertensive	66	AMAUROSIS FUGAX
77M	2101	Mono	E 50-200 QD	109	STROKE
61F	2002	Mono	E 50-200 QD	72	STROKE
54M	2601	Mono	E 50-200 QD	2	STROKE
70F	2101	Mono	E 50-200 QD	133	STROKE
58F	1504	Mono	E 200 QD	61	CEREBRAL HEMORRHAGE
84F	2201	Mono	E 50-200 QD	17	STROKE
65M	1601	Mono	E 25-200 QD	109	ISCHEMIC SPINAL STENOSIS
69M	1601	Mono	E 25-200 QD	14	TRANSIENT ISCHEMIC ATTACK
74M	1801	Mono	E 100-300 QD	7	STROKE

E = Eplerenone

While the rates in eplerenone-treated patients are numerically the highest, they are not significantly different from the active controls.

Other Neurologic

Six patients had other neurologic SAEs including anxiety, depression, altered sensorium, cognitive dysfunction, right vestibulopathy, and acute vertigo. The rates with and without eplerenone are similar.

Cardiovascular

Forty-seven patients experienced the cardiovascular SAEs shown in the table below.

Table 18: Reviewer's Cardiovascular SAEs

Demo	Study	Group	Drug	Onset	Description
77F	2202	Active	Amlodipine 2.5 QD	128	TACHYCARDIA VENTRICULAR
57M	1602	Active	Enalapril 5-40 QD	321	MYOCARDIAL INFARCTION
60M	1602	Active	Enalapril 5-40 QD	253	CORONARY ARTERY DISORDER
56M	1702	Active	Enalapril 10-40 QD	140	PERIPHERAL VASCULAR DISEASE
57M	1702	Active	Enalapril 10-40 QD	32	MYOCARDIAL INFARCTION
51M	1702	Active	Enalapril 10-40 QD	25	FIBRILLATION ATRIAL
83M	1802	Active	Spironolactone 75-225 QD	6	FIBRILLATION ATRIAL
56M	2003	Active	Losartan 50-100 QD	40	CARDIAC FAILURE
46F	2003	Active	Losartan 50-100 QD	21	CORONARY ARTERY DISORDER
70M	1008	Active	Spironolactone 50 BID	5	SYNCOPE
68M	2102	Active	Enalapril 10-40 QD	195	MYOCARDIAL INFARCTION
73M	2202	Active	Amlodipine 2.5 QD	144	MYOCARDIAL INFARCTION
81M	2202	Active	Amlodipine 2.5 QD	114	UNSTABLE ANGINA
86M	2202	Active	Amlodipine 2.5 QD	113	CARDIAC FAILURE
72F	2301	Active	ACEI	59	VASOVAGAL SYNCOPE
63F	2602	Active	Amlodipine 2.5-10 QD	3	CARDIAC FAILURE
57F	2401	Active	CCB	28	ELECTIVE REVASCULARIZATION
69M	2102	Active	Enalapril 10-40 QD	162	MYOCARDIAL INFARCTION
63M	1901	Coadmin	E 100-200 + HCTZ 12.5-25 QD	74	ANGINA PECTORIS
51F	1511	Coadmin	E 200 + HCTZ 12.5 QD	60	EDEMA PERIPHERAL
47F	1703	Coadmin	E 50-200 + enalapril 10-40 QD	20	MYOCARDIAL INFARCTION
56M	2501	Coadmin	E 50-200 QD + antihypertensive	344	FIBRILLATION ATRIAL
45F	2501	Coadmin	E 50-200 QD + antihypertensive	143	FIBRILLATION ATRIAL
66F	1703	Coadmin	E 50-200 + enalapril 10-40 QD	219	CORONARY ARTERY DISORDER
51M	2501	Coadmin	E 50-200 QD + antihypertensive	166	MYOCARDIAL INFARCTION
52M	2501	Coadmin	E 50-200 QD + antihypertensive	41	CORONARY ARTERY DISORDER
62F	2501	Coadmin	E 50-200 QD + antihypertensive	340	MYOCARDIAL ISCHEMIA
64M	2501	Coadmin	E 50-200 QD + antihypertensive	212	TACHYCARDIA VENTRICULAR
71M	2501	Coadmin	E 50-200 QD + antihypertensive	82	THROMBOSIS ARTERIAL LEG
69F	2303	Coadmin	E 50-100 QD + ACEI	1	MYOCARDIAL INFARCTION
72F	2103	Coadmin	E 50-200 + enalapril 10-40 QD	73	SINUS TACHYCARDIA
84F	2201	Mono	E 50-200 QD	20	FIBRILLATION ATRIAL
51F	1003	Mono	E 50 QD	15	ANGINA PECTORIS
78F	2201	Mono	E 50-200 QD	110	MYOCARDIAL INFARCTION
57M	4905	Mono	E 200 QD	66	MYOCARDIAL INFARCTION
73M	4902	Mono	E 25 QD	4	MYOCARDIAL INFARCTION
56M	1701	Mono	E 50-200 QD	51	ANGINA PECTORIS

Demo	Study	Group	Drug	Onset	Description
47F	1701	Mono	E 50-200 QD	70	MYOCARDIAL INFARCTION
56M	1701	Mono	E 50-200 QD	233	PERIPHERAL VASCULAR DISEASE
66M	1801	Mono	E 100-300 QD	45	CORONARY ARTERY DISORDER
84F	2201	Mono	E 50-200 QD	57	ANGINA PECTORIS
51F	1701	Mono	E 50-200 QD	11	MYOCARDIAL INFARCTION
74M	1801	Mono	E 100-300 QD	7	AORTIC DISSECTION
73M	2201	Mono	E 50-200 QD	6	UNSTABLE ANGINA
74M	2101	Mono	E 50-200 QD	98	CARDIAC FAILURE
63M	2201	Mono	E 50-200 QD	93	ANGINA PECTORIS
59M	4901	Placebo	Placebo	3	UNSTABLE ANGINA

E = Eplerenone

Note in the table above that the eight of the nine occurrences of arrhythmias occurred in the active control or coadministration groups; only one occurred in the eplerenone monotherapy group The non-arrhythmia CV SAEs were evenly distributed among the eplerenone, active control, and coadministration groups.

Endocrine

In addition to the sex hormone-related SAEs described below, nine patients experienced endocrine-related SAEs listed in the table below.

Table 19: Reviewer's Endocrine SAEs

Demo	Study	Group	Drug	Onset	Description
69F	2501	Coadmin	E 50-200 QD + antihypertensive	357	HYPERPARATHYROIDISM
56F	2501	Coadmin	E 50-200 QD + antihypertensive	141	GOITRE
71M	2501	Coadmin	E 50-200 QD + antihypertensive	70	PARATHYROID DISORDER
53M	2103	Coadmin	E 50-200 + enalapril 10-40 QD	58	HYPERGLYCEMIA
54F	1901	Coadmin	E 100-200 + HCTZ 12.5-25 QD	66	HYPERPARATHYROIDISM
68M	1703	Coadmin	E 50-200 + enalapril 10-40 QD	17	HYPERGLYCEMIA
57F	2101	Mono	E 50-200 QD	187	DIABETES MELLITUS AGGRAVATED
73F	2101	Mono	E 50-200 QD	39	HYPERGLYCEMIA
55F	1701	Mono	E 50-200 QD	224	DIABETES MELLITUS

The results in the table above suggest that eplerenone effects upon blood glucose and calcium should be scrutinized, which is done in the lab value section below.

Gastrointestinal

Thirty-five patients experienced gastrointestinal SAEs listed in the table below.

Table 20: Reviewer's Gastrointestinal SAEs

Demo	Study	Group	Drug	Onset	Description
44M	2602	Active	Amlodipine 2.5-10 QD	62	HERNIA
76F	1505	Active	HCTZ 12.5 QD	39	ESOPHAGITIS
67M	1802	Active	Spironolactone 75-225 QD	95	PEPTIC ULCER HEMORRHAGIC
64M	1902	Active	Losartan 50-100 + HCTZ 12.5-25 QD	46	CHEST PAIN NON-CARDIAC
70M	2202	Active	Amlodipine 2.5 QD	91	INTESTINAL PERFORATION
74F	2202	Active	Amlodipine 2.5 QD	102	ABDOMINAL PAIN
64M	2103	Coadmin	E 50-200 + enalapril 10-40 QD	164	ABDOMINAL PAIN
62M	1508	Coadmin	E 25 + HCTZ 25 QD	56	HIATAL HERNIA
70F	1512	Coadmin	E 200 + HCTZ 25 QD	5	GASTROESOPHAGEAL REFLUX
57M	1511	Coadmin	E 200 + HCTZ 12.5 QD	18	DIVERTICULITIS
67F	1703	Coadmin	E 50-200 + enalapril 10-40 QD	211	DIARRHEA
60M	2103	Coadmin	E 50-200 + enalapril 10-40 QD	143	HERNIA
72F	2103	Coadmin	E 50-200 + enalapril 10-40 QD	78	DIARRHEA
54F	2501	Coadmin	E 50-200 QD + antihypertensive	59	GASTRIC ULCER HEMORRHAGIC
60F	2501	Coadmin	E 50-200 QD + antihypertensive	346	CHOLECYSTITIS
68F	2501	Coadmin	E 50-200 QD + antihypertensive	106	CHEST PAIN NON-CARDIAC
61M	2501	Coadmin	E 50-200 QD + antihypertensive	151	INTESTINAL OBSTRUCTION
72F	2103	Coadmin	E 50-200 + enalapril 10-40 QD	72	VOMITING
75F	2501	Coadmin	E 50-200 QD + antihypertensive	101	DIARRHEA
64M	2303	Coadmin	E 50-100 QD + ACEI	7	HERNIA
67F	2501	Coadmin	E 50-200 QD + antihypertensive	33	VOMITING
50F	2501	Coadmin	E 50-200 QD + antihypertensive	8	APPENDICITIS
67M	2501	Coadmin	E 50-200 QD + antihypertensive	149	HERNIA
57F	2501	Coadmin	E 50-200 QD + antihypertensive	334	POST-OP VOMITING
80M	2002	Mono	E 50-200 QD	23	DIVERTICULITIS
73F	2101	Mono	E 50-200 QD	43	DIVERTICULITIS
69M	1502	Mono	E 25 QD	1	VOMITING
52F	4903	Mono	E 50 QD	80	ESOPHAGITIS
70F	2201	Mono	E 50-200 QD	80	GI HEMORRHAGE
49M	1701	Mono	E 50-200 QD	153	GASTRITIS
60M	1601	Mono	E 25-200 QD	229	HERNIA
74F	2201	Mono	E 50-200 QD	44	PREVIOUSLY SCHEDULED SURGERY
77M	2001	Placebo	Placebo	84	HEMORRHAGE RECTUM
47M	2001	Placebo	Placebo	25	CHEST PAIN NON-CARDIAC
61F	2001	Placebo	Placebo	68	GASTROENTERITIS

E = Eplerenone

The coadministration group had the highest GI SAE rate. The events are fairly diverse, and there is no clear pattern to their occurrence.

Hematologic

Hematologic complications were rare and diverse (anemia, polycythemia, incisional bleeding, and thromboplebitis).

Hypertension

Three patients in the coadministration group and one in the eplerenone monotherapy experienced aggravated hypertension.

Infection

Eleven patients experienced infection-related SAEs shown in the table below.

Table 21: Reviewer's Infection-Related SAEs

Demo	Study	Group	Drug	Onset	Description
73M	2202	Active	Amlodipine 2.5 QD	33	PNEUMONIA
45F	2003	Active	Losartan 50-100 QD	34	SEPSIS
60M	1602	Active	Enalapril 5-40 QD	80	PERITONSILLAR ABSCESS
62M	1602	Active	Enalapril 5-40 QD	289	PNEUMONIA
42M	2501	Coadmin	E 50-200 QD + antihypertensive	168	ARTHRITIS
63M	2501	Coadmin	E 50-200 QD + antihypertensive	59	PNEUMONIA
61F	2002	Mono	E 50-200 QD	71	SINUSITIS
53M	1801	Mono	E 100-300 QD	20	CELLULITIS
51F	1601	Mono	E 25-200 QD	5	SINUSITIS
69M	1502	Mono	E 25 QD	2	SEPSIS
41M	1003	Mono	E 50 QD	12	CELLULITIS

E = Eplerenone

The rates are similar with and without eplerenone.

Hyperkalemia

Six patients, one in an enalapril group, three in eplerenone monotherapy, and two in coadministration group, experienced a hyperkalemia SAE. Potassium values for these patients ranged from 5.7 to 6.6. No associated arrhythmias were described in the case summaries. The dosage for the eplerenone cases was 100 mg QD in one case and 200 mg QD in the rest. For serious and AEs leading to withdrawal the coadministration cases included three with enalapril as well as one each with hydrochlorothiazide and verapamil. Hyperkalemia is also discussed in the laboratory findings section below.

Hepatic

One person in the eplerenone monotherapy group experienced an SAE related to liver enzyme elevations. This SAE and liver enzyme elevations are discussed further in the laboratory findings section below.

Pain

The eleven pain-related SAEs were diverse (arthritis, non-cardiac chest pain, back pain, etc.) and not prominent in the eplerenone monotherapy group.

Renal

Eight renal SAEs were reported as shown in the table below.

Table 22: Reviewer's Renal SAEs

Demo	Study	Group	Drug	Onset	Description
73M	2202	Active	Amlodipine 2.5 QD	148	HEMATURIA
73M	2202	Active	Amlodipine 2.5 QD	26	ROUTINE CYSTOSCOPY
45F	2003	Active	Losartan 50-100 QD	27	RENAL CALCULUS
49M	1702	Active	Enalapril 10-40 QD	118	RENAL CALCULUS
50M	2501	Coadmin	E 50-200 QD + antihypertensive	108	RENAL PAIN
73F	2101	Mono	E 50-200 QD	39	URINARY TRACT INFECTION
80M	2002	Mono	E 50-200 QD	23	RENAL CALCULUS
74M	1801	Mono	E 100-300 QD	7	RENAL FAILURE ACUTE

E = Eplerenone

Renal SAEs were not increased in the eplerenone groups compared to the active controls.

Sex Hormonal

Five sex hormone related SAEs were reported as listed in the table below.

Table 23: Reviewer's Sex Hormone Related SAEs

Demo	Study	Group	Drug	Onset	Description
65M	2102	Active	Enalapril 10-40 QD	130	BENIGN PROSTATIC HYPERPLASIA
44F	2501	Coadmin	E 50-200 QD + antihypertensive	192	MENSTRUAL DISORDER
69M	2103	Coadmin	E 50-200 + enalapril 10-40 QD	78	BENIGN PROSTATIC HYPERPLASIA
72M	2201	Mono	E 50-200 QD	4	BENIGN PROSTATIC HYPERPLASIA
57M	1601	Mono	E 25-200 QD	7	BENIGN PROSTATIC HYPERPLASIA

The cases of benign prostatic hyperplasia in eplerenone-treated patients at days 4 and 7 are difficult to relate to drug use. The one SAE that may be related to eplerenone is the case of menorrhagia. Regardless, the incidence of sex hormone related SAEs with eplerenone appears to be very low.

Other

Other SAEs reported were one case of elevated CPK in an active control (hydrochlorothiazide) patient and one case of respite care in a coadministration patient.

1.2.2. Sponsor's Summary of Serious Adverse Events

The sponsor's summary of SAEs is the following:

"• The overall incidence of serious adverse events in the combined controlled trials was similar among patients who received eplerenone monotherapy, eplerenone coadministration therapy, and active comparators, and greater than placebo.

"• Patients who received eplerenone/enalapril had a significantly higher incidence of serious adverse events compared to patients who received enalapril alone."

The sponsor did not find any significant differences between the enalapril and eplerenone/enalapril treatment groups for the incidence of any specific serious adverse event. The sponsor's Table 8.22 summarizing the SAEs with enalapril and eplerenone is shown below.

Adverse Event	Eplerenone Monotherapy	Enalapril	Eplerenone/Enalapril Coadministration Therapy
No. treated	157	155	154
Any event	13 (8.3)	5 (3.2)*	14 (9.1)
Gastrointestinal Disorders			
Abdominal pain	0 (0.0)	0 (0.0)	2 (1.3)
Diarrhea	0 (0.0)	0 (0.0)	2 (1.3)
Metabolic and Nutritional Disorders			
Hyperglycemia	1 (0.6)	0 (0.0)	2 (1.3)
Hyperkalemia	2 (1.3)	0 (0.0)	1 (0.6)

Source: Table T9.9.
Includes Studies 017 and 021; no additional antihypertensive medication data included.
Data are expressed as N (% of patients) except for No. treated, and include any serious adverse events in ≥ 2 patients in either group or with a significant difference between eplerenone monotherapy versus eplerenone/enalapril and enalapril versus eplerenone/enalapril ($p \leq 0.05$).
* Significant difference versus eplerenone/enalapril.

Figure 28: Sponsor's Summary of SAEs with Eplerenone and Enalapril

1.2.3. Reviewer's Summary of Serious Adverse Events

While the SAE rate appears higher with eplerenone and enalapril, there is no clear pattern to the SAEs with this combination. The sponsor's general conclusion that SAEs were comparable among the active treatment groups and higher than placebo appears accurate as demonstrated by the reviewer's analyses.

1.3. Dropouts

1.3.1. Reviewer's Analysis of Adverse Events Causing Dropouts

The sponsor's Integrated Summary of Safety includes an Appendix 2.4 that lists all adverse events causing withdrawal. That appendix lists 440 adverse events in 300 patients. Of these 282 serious adverse events were reported in 188 patients treated with eplerenone.

The reviewer analyzed the AEs causing dropouts similarly to the analyses of SAEs. To eliminate redundant reporting the reviewer classified the multiple AEs in the same patient into non-redundant groups. The reviewer classified 112 AEs as duplicative. For this analysis the reviewer also classified the AEs into classes relevant to eplerenone toxicities. Finally, for this analysis the reviewer calculated the rates of these AE classes per 100 patient exposure years (PEYs) for the combined treatment groups from the 13 controlled trials of placebo, active control, eplerenone alone, and eplerenone coadministered with another antihypertensive and any eplerenone use (alone or coadministered) vs. no eplerenone use (placebo or active control). The results of this analysis are shown in the table below:

Table 24: Reviewer's Rates of AEs Causing Dropout

Group	Active	Coadmin	Mono	Placebo	Any E	No E
N:	1422	772	1748	375	2520	1797
PEY:	437.6	168.9	496.9	78.9	665.8	516.5
AE Class	**AEs Causing Dropout per 100 PEYs**					
Accident	0.2		0.2		0.2	0.2
Cerebrovascular	0.9	1.2	1.6		1.5	0.8
Other neurologic	0.9	1.2	1.2	1.3	1.2	1.0
Cough	1.8		0.2		0.2	1.5
Arrhythmia	0.9	0.6	0.6		0.6	0.8
Edema	2.1	0.6	0.2	5.1	0.3	2.5
Hypertension		1.8	0.2		0.6	
Hypotension	0.9	1.2	1.6		1.5	0.8
Other cardiovascular	2.3	3.6	2.2	1.3	2.6	2.1
Dizziness		1.2	0.2		0.5	
Endocrine		0.6	0.2		0.3	
General	0.7	1.2	0.2		0.5	0.6
Gastrointestinal	3.0	3.6	1.6	1.3	2.1	2.7
Hematologic	0.5		0.2		0.2	0.4
Infection	0.7		0.2		0.2	0.6
Hyperkalemia	1.1	8.3	3.0	1.3	4.4	1.2
Hepatic	0.9		1.4	1.3	1.1	1.0
Neoplasm	0.2		0.8		0.6	0.2
Pulmonary			1.2		0.9	

Group	Active	Coadmin	Mono	Placebo	Any E	No E
Other	0.5		0.4		0.3	0.4
Pain	3.7	2.4	3.8	1.3	3.5	3.3
Renal	0.9	1.2		1.3	0.3	1.0
Sex hormonal	1.4	0.6	0.4		0.5	1.2
Skin	1.1	0.6	0.4	1.3	0.5	1.2

Many of the classes show no excesses of AEs in the eplerenone groups, i.e., accidents, other neurologic, general, gastrointestinal, hematologic, infection, hepatic, other, pain, renal, and skin. Other classes show not unexpected differences, e.g., more edema in placebo patients, more hypotension in active treatment, and more cough in active (ACE inhibitor) controls. The discussion below concentrates on the unexplained differences and two expected differences of particular interest, hyperkalemia and sex hormone related AEs.

Cerebrovascular

The cerebrovascular AEs causing dropout are listed in the table below.

Table 25: Reviewer's Cerebrovascular AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
55M	1602	Active	Enalapril 5-40 QD	221	TRANSIENT ISCHEMIC ATTACK
69M	1602	Active	Enalapril 5-40 QD	101	CAROTID STENOSIS
63F	2003	Active	Losartan 50-100 QD	51	CEREBRAL ANEURYSM
56F	2501	Coadmin	E 50-200 QD + antihypertensive	124	STROKE
71M	2501	Coadmin	E 50-200 QD + antihypertensive	281	STROKE
50M	1512	Coadmin	E 200 + HCTZ 25 QD	54	SUBARACHNOID HEMORRHAGE
68M	1703	Coadmin	E 50-200 + enalapril 10-40 QD	2	TRANSIENT ISCHEMIC ATTACK
70F	2101	Mono	E 50-200 QD	133	STROKE
77M	2101	Mono	E 50-200 QD	109	STROKE
61F	2002	Mono	E 50-200 QD	72	STROKE
54M	2601	Mono	E 50-200 QD	2	STROKE
59M	1003	Mono	E 50 QD	6	AMNESIA
69M	1601	Mono	E 25-200 QD	14	TRANSIENT ISCHEMIC ATTACK
65M	1601	Mono	E 25-200 QD	109	ISCHEMIC SPINAL STENOSIS
58F	1504	Mono	E 200 QD	61	CEREBRAL HEMORRHAGE

The rates of cerebrovascular events in the eplerenone-treated patients are higher but not statistically significant. There does not appear to be a temporal pattern to the events with regard to duration of therapy. The diurnal patterns of blood pressure control in the studies using ABPM do not suggest a problem with rebound hypertension or excessive hypotension.

Arrhythmia

Eleven patients dropped out because of the arrhythmia AEs shown in the table below.

Table 26: Reviewer's Arrhythmia AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
56M	1802	Active	Spironolactone 75-225 QD	19	PALPITATION
83M	1802	Active	Spironolactone 75-225 QD	6	FIBRILLATION ATRIAL
39F	1602	Active	Enalapril 5-40 QD	60	PALPITATION
70M	1008	Active	Spironolactone 50 BID	5	SYNCOPE
64M	2501	Coadmin	E 50-200 QD + antihypertensive	212	TACHYCARDIA VENTRICULAR
72F	2501	Coadmin	E 50-200 QD + antihypertensive	16	PALPITATION
75M	2501	Coadmin	E 50-200 QD + antihypertensive	139	SYNCOPE
69F	2303	Coadmin	E 50-100 QD + ACEI	1	SUDDEN DEATH
60M	2601	Mono	E 50-200 QD	15	PALPITATION
68M	2101	Mono	E 50-200 QD	2	PALPITATION
51F	2002	Mono	E 50-200 QD	9	TACHYCARDIA

Arrhythmia events were similar in the any eplerenone and no eplerenone groups. ECG effects of eplerenone are examined in the ECG section below.

Hypertension

Four patients dropped out because of the hypertensive AEs shown in the table below.

Table 27: Reviewer's Hypertensive AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
55F	2303	Coadmin	E 50-100 QD + ACEI	28	HYPERTENSION AGGRAVATED
71M	2103	Coadmin	E 50-200 + enalapril 10-40 QD	38	ENCEPHALOPATHY HYPERTENSIVE
62F	1703	Coadmin	E 50-200 + enalapril 10-40 QD	4	HYPERTENSION AGGRAVATED
50F	1801	Mono	E 100-300 QD	27	HYPERTENSION AGGRAVATED

Note that the hypertensive AEs occurred early, e.g., within about a month, suggesting a failure to respond. Note that cerebrovascular AEs are also more frequent in the eplerenone groups.

Other Cardiovascular

Thirty patients dropped out because of the other cardiovascular AEs shown in the table below.

Table 28: Reviewer's Other Cardiovascular AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
56M	2003	Active	Losartan 50-100 QD	40	CARDIAC FAILURE
57M	1602	Active	Enalapril 5-40 QD	321	MYOCARDIAL INFARCTION
70M	1602	Active	Enalapril 5-40 QD	75	ECG ABNORMAL SPECIFIC

Demo	Study	Group	Drug	Onset	Description
63F	2602	Active	Amlodipine 2.5-10 QD	3	CARDIAC FAILURE
60M	1602	Active	Enalapril 5-40 QD	253	CORONARY ARTERY DISORDER
57M	1702	Active	Enalapril 10-40 QD	32	MYOCARDIAL INFARCTION
81M	2202	Active	Amlodipine 2.5 QD	114	UNSTABLE ANGINA
73M	2202	Active	Amlodipine 2.5 QD	144	MYOCARDIAL INFARCTION
46F	2003	Active	Losartan 50-100 QD	21	CORONARY ARTERY DISORDER
69M	2102	Active	Enalapril 10-40 QD	42	ANGINA PECTORIS
47F	1703	Coadmin	E 50-200 + enalapril 10-40 QD	20	MYOCARDIAL INFARCTION
66F	1703	Coadmin	E 50-200 + enalapril 10-40 QD	219	CORONARY ARTERY DISORDER
65M	1901	Coadmin	E 100-200 + HCTZ 12.5-25 QD	8	CORONARY ARTERY DISORDER
54M	2403	Coadmin	E 50-100 QD + CCB	15	CARDIAC FAILURE
52M	2501	Coadmin	E 50-200 QD + antihypertensive	41	CORONARY ARTERY DISORDER
63M	1901	Coadmin	E 100-200 + HCTZ 12.5-25 QD	74	ANGINA PECTORIS
51M	2501	Coadmin	E 50-200 QD + antihypertensive	166	MYOCARDIAL INFARCTION
70M	2403	Coadmin	E 50-100 QD + CCB	26	AORTIC ANEURYSM
66M	1801	Mono	E 100-300 QD	45	CORONARY ARTERY DISORDER
74M	1801	Mono	E 100-300 QD	7	AORTIC DISSECTION
63M	2201	Mono	E 50-200 QD	93	ANGINA PECTORIS
51F	1003	Mono	E 50 QD	15	ANGINA PECTORIS
78F	2201	Mono	E 50-200 QD	75	ANGINA PECTORIS
56M	1701	Mono	E 50-200 QD	51	ANGINA PECTORIS
47F	1701	Mono	E 50-200 QD	70	MYOCARDIAL INFARCTION
57M	4905	Mono	E 200 QD	66	MYOCARDIAL INFARCTION
73M	4902	Mono	E 25 QD	4	MYOCARDIAL INFARCTION
58F	1006	Mono	E 200 BID	1	ANGINA PECTORIS
51F	1701	Mono	E 50-200 QD	11	MYOCARDIAL INFARCTION
59M	4901	Placebo	Placebo	3	UNSTABLE ANGINA

The majority of the other cardiovascular AEs were clearly related to coronary artery disease, e.g., angina and myocardial infarction. The rates were similar in the any eplerenone and no eplerenone groups.

Dizziness

Three patients, two coadministrations and one eplerenone monotherapy, dropped out because of "dizziness". The case report forms for these patients did not provide additional information to differentiate the etiologies, e.g., lightheadedness due to hypotension or arrhythmia or vertigo due to neurologic causes.

Endocrine

Five patients dropped out because of the endocrine AEs shown in the table below.

Table 29: Reviewer's Endocrine AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
69F	2501	Coadmin	E 50-200 QD + antihypertensive	357	HYPERPARATHYROIDISM
51M	2501	Coadmin	E 50-200 QD + antihypertensive	32	HYPERTRIGLYCERIDEMIA
51M	2501	Coadmin	E 50-200 QD + antihypertensive	32	HYPERCHOLESTEROLEMIA
53M	2103	Coadmin	E 50-200 + enalapril 10-40 QD	58	HYPERGLYCEMIA
43M	1003	Mono	E 50 QD	20	HYPERCHOLESTEROLEMIA

Only one of the endocrine AEs causing dropout occurred in the eplerenone monotherapy group. There is no clear pattern to the endocrine AEs. However, see the summaries of lipids and glucose in the laboratory findings section.

Hyperkalemia

Hyperkalemia led to the withdrawal of 36 patients: 1 placebo; 5 active controls (2 enalapril, 2 spironolactone, and 1 amlodipine); 15 coadministrations (1 with a beta blocker and 1 in the follow-on study and the rest with enalapril); and 15 eplerenone monotherapy. Hyperkalemia is discussed in more detail in the laboratory findings section.

Neoplasm

Six patients dropped out because of the neoplastic AEs shown in the table below.

Table 30: Reviewer's Neoplastic AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
49F	1702	Active	Enalapril 10-40 QD	138	GI NEOPLASM BENIGN
75F	2501	Coadmin	E 50-200 QD + antihypertensive	113	RENAL CARCINOMA
61M	2002	Mono	E 50-200 QD	10	PITUITARY MACROADENOMA
40F	1801	Mono	E 100-300 QD	30	MELANOMA MALIGNANT
69F	1601	Mono	E 25-200 QD	146	BREAST CANCER
54M	1601	Mono	E 25-200 QD	210	CARCINOMA OF THE PROSTATE

While the rate of neoplastic events is nominally higher in the eplerenone groups, there is no pattern to the neoplasms and two occurred too early to be attributed to treatment.

Sex Hormonal

Nine patients dropped out because of sex hormonal AEs shown in the table below.

Table 31: Reviewer's Sex Hormonal AEs Causing Dropout

Demo	Study	Group	Drug	Onset	Description
51F	1802	Active	Spironolactone 75-225 QD	47	MENSTRUAL DISORDER

Demo	Study	Group	Drug	Onset	Description
57M	1802	Active	Spironolactone 75-225 QD	37	MASTODYNIA
69M	1802	Active	Spironolactone 75-225 QD	57	IMPOTENCE
58M	1802	Active	Spironolactone 75-225 QD	67	GYNECOMASTIA
58M	1802	Active	Spironolactone 75-225 QD	67	IMPOTENCE
59F	1506	Active	HCTZ 25 QD	31	MENSTRUAL DISORDER
64M	2501	Coadmin	E 50-200 QD + antihypertensive	75	IMPOTENCE
58M	2304	Coadmin	E 50-100 QD + ARB	49	ORCHITIS
77M	1701	Mono	E 50-200 QD	124	GYNECOMASTIA
55M	1601	Mono	E 25-200 QD	183	GYNECOMASTIA

It is notable that two male patients on eplerenone alone developed gynecomastia. The timing of the development of gynecomastia was comparable to that reported for spironolactone, i.e., gynecomastia develops after a treatment duration of 3-6 months. The dosage for the patient in Study 017 was 200 mg QD and for the patient in Study 016 was 50 mg QD.

1.3.2. Sponsor's Summary of Adverse Events Causing Dropouts

The sponsor's summary of adverse events (AEs) causing dropouts is the following:

"• The overall incidence of withdrawals due to adverse events in the combined controlled trials was similar between the eplerenone monotherapy and coadministration groups and the active comparator groups.

"• In the combined controlled trials, the most common adverse events leading to withdrawal in the eplerenone monotherapy group were headache and hyperkalemia and the most common adverse event leading to withdrawal in the eplerenone coadministration therapy group was hyperkalemia.

"• No dose-dependent increase in the incidence of any specific adverse event leading to withdrawal was observed in eplerenone patients treated in placebo-controlled, fixed-dose monotherapy trials.

"• Spironolactone-treated patients had a significantly higher incidence of withdrawal due to adverse events compared to eplerenone-treated patients.

"• Eplerenone-treated patients had a significantly higher incidence of withdrawal due to adverse events of hyperkalemia compared to enalapril-treated patients.

"• Amlodipine-treated patients had a significantly higher incidence of withdrawals due to adverse events of edema peripheral compared to eplerenone-treated patients.

"• In the eplerenone monotherapy versus active comparators trials, the overall incidence of withdrawal due to adverse events and the incidence of any specific adverse event leading to withdrawal were similar between eplerenone and the HCTZ and the losartan treatment groups.

"• Patients who received eplerenone/enalapril had a significantly higher incidence of withdrawal due to adverse events compared to patients who received enalapril alone.

"• The overall incidence of withdrawal due to adverse events for patients who received long-term administration of eplerenone monotherapy was similar to that observed for eplerenone-treated patients in studies of shorter durations."

1.3.3. Reviewer's Summary of Adverse Events Causing Dropouts

The sponsor's summary statements appear to be accurate. Overall the patterns of AEs causing dropout do not suggest serious problems with eplerenone. The dropouts due to hyperkalemia are not unexpected and would not appear to be troublesome at the dosages recommended for marketing. The occurrences of gynecomastia, although uncommon with the durations of therapy in the trials, could be problematic with long term therapy. One question not fully answered is whether there is an increased incidence of cerebrovascular events with eplerenone. This question is examined further in the review of systems.

1.4. Other Search Strategies

No special search strategies were used in this review.

1.5. Adverse Event Incidence Tables

The sponsor's tabulation of adverse events with incidence $\geq 2\%$ in any treatment group in the combined controlled trials is shown below.

Adverse Event	Placebo		Eplerenone Monotherapy		Eplerenone Coadministration Therapy		Active Comparators	
No. treated	375		1748		772		1422	
Any event	167	(44.5)	919	(52.6)	330	(42.7)	698	(49.1)
Body as a Whole - General Disorders								
Fatigue	5	(1.3)	40	(2.3)	21	(2.7)	36	(2.5)
Back pain	4	(1.1)	42	(2.4)	16	(2.1)	27	(1.9)
Injury accidental	12	(3.2)	29	(1.7)	12	(1.6)	27	(1.9)
Edema peripheral	11	(2.9)	30	(1.7)	7	(0.9)	61	(4.3)
Influenza-like symptoms	4	(1.1)	45	(2.6)	6	(0.8)	42	(3.0)
Peripheral pain	6	(1.6)	30	(1.7)	6	(0.8)	28	(2.0)
Central and Peripheral Nervous System Disorders								
Headache	53	(14.1)	224	(12.8)	62	(8.0)	168	(11.8)
Dizziness	8	(2.1)	57	(3.3)	35	(4.5)	46	(3.2)
Gastrointestinal System Disorders								
Nausea	6	(1.6)	48	(2.7)	37	(4.8)	35	(2.5)
Diarrhea	4	(1.1)	37	(2.1)	14	(1.8)	44	(3.1)
Dyspepsia	5	(1.3)	36	(2.1)	10	(1.3)	25	(1.8)
Abdominal pain	2	(0.5)	27	(1.5)	10	(1.3)	29	(2.0)
Metabolic and Nutritional Disorders								
Hyperkalemia	3	(0.8)	28	(1.6)	24	(3.1)	16	(1.1)
Respiratory System Disorders								
Upper respiratory tract infection	19	(5.1)	115	(6.6)	19	(2.5)	77	(5.4)
Coughing	3	(0.8)	34	(1.9)	14	(1.8)	38	(2.7)
Bronchitis	6	(1.6)	34	(1.9)	9	(1.2)	28	(2.0)
Sinusitis	10	(2.7)	43	(2.5)	8	(1.0)	19	(1.3)

Source: Table T7.1.1.
Includes Studies 010, 015, 016, 017, 018, 019, 020, 021, 022, 023, 024, 026, and 049, no additional antihypertensive medication data included.
Data are expressed as N (% of patients) except for No. treated.

Figure 29: Sponsor's Adverse Events With Incidence ≥2% in Any Treatment Group: Combined Controlled Trials

The above table is a reasonable summary of the symptom-related AEs that are not rare with eplerenone. In addition to hyperkalemia the symptoms that appear to be more frequent with eplerenone therapy than placebo are fatigue, back pain, influenza-like symptoms, gastrointestinal distress, dizziness, and coughing. The one symptom-related event of importance that did not produce an incidence rate exceeding two percent is gynecomastia in males. This table also does not include asymptomatic AEs based on laboratory findings. The sponsor's table from the proposed labeling that includes laboratory value AEs is shown below.

	<TRADEMARK> (n=960)	Placebo (n=375)
Metabolic		
Hypercholesterolemia	1.1	0.3
Hypertriglyceridemia	1.1	0.0
Digestive		
Nausea	2.4	1.6
Diarrhea	1.6	1.1
Dyspepsia	1.4	1.3
Abdominal pain	1.1	0.5
Musculoskeletal		
Arthralgia	1.4	1.1
Urinary		
Albuminuria	1.0	0.5
Respiratory		
Upper respiratory infection	6.7	5.1
Sinusitis	3.0	2.7
Coughing	1.5	0.8
Rhinitis	1.0	0.0
Central/Peripheral Nervous System		
Dizziness	3.2	2.1
Body as a Whole		
Fatigue	2.0	1.3
Back Pain	1.4	1.1
Influenza-like Symptoms	1.8	1.1
Abnormal Laboratory Test	1.0	0.5
Liver/Biliary System		
Increased GGT	1.1	0.5
Increased SGPT	1.1	0.8

Figure 30: Sponsor's Incidence (%) of Adverse Events Occurring in ≥1% of Patients Treated with Eplerenone (25 to 400 mg) and at a More Frequent Rate than in Placebo-Treated Patients