30 Oct 2000 (Day 109). He developed SGOT increased, SGPT increased, and increased GGT on 24 Aug 2000 (Day 42) and nausea on 16 Oct 2000 (Day 95), each of which caused withdrawal from the study. SGOT values were 29 U/L on 14 Jul 2000 (Baseline), 39 U/L on 24 Aug 2000 (Day 42), and 42 U/L on 09 Nov 2000 (Day 119), 10 days after the last dose of study medication. SGPT values were 35 U/L on 14 Jul 2000 (Baseline), 49 U/L on 24 Aug 2000 (Day 42), and 39 U/L on 09 Nov 2000 (Day 119), 10 days after the last dose of study medication. GGT values were 128 U/L on 14 Jul 2000 (Baseline), 164 U/L on 24 Aug 2000 (Day 42), and 197 U/L on 09 Nov 2000 (Day 119), 10 days after the last dose of study medication. The upper limits of normal for SGOT, SGPT, and GGT were 36 U/L, 43 U/L, and 50 U/L, respectively. The SGOT increased, SGPT increased, and increased GGT were continuing as of 30 Oct 2000 (Day 109). The nausea lasted 25 days and resolved on 09 Nov 2000 (Day 119), ten days after the last dose of study medication. Concomitant medications included Viagra, allopurinol, metformin, and tramadol. Each of the events was considered by the Investigator to be severe and to have a probable relationship to study medication."

The sponsor's summary of hepatic adverse events leading to withdrawal is shown in the figure below. The one event that appeared to be symptomatic was in the patient described above.

Adverse Event	Placebo	Eplerenone Monotherapy	Eplerenone Coadministration Therapy	Active Comparators
No. treated	375	1748	772	1422
Increased GGT	1 (0.3)	6 (0.3)	0 (0.0)	3 (0.2)
SGOT increased	1 (0.3)	3 (0.2)	0 (0.0)	2 (0.1)
SGPT increased	1 (0.3)	4 (0.2)	0 (0.0)	2 (0.1)

Source: Table T8.1.1.
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 54: Sponsor's Hepatic AEs Leading to Withdrawal

Gastrointestinal distress

The rates of gastrointestinal distress, including nausea, vomiting, dyspepsia, reflux, abdominal pain or diarrhea, were highest in the spironolactone and open label groups. They were intermediate in the eplerenone monotherapy, coadministration, and active control groups and lowest in the placebo groups. The rates of gastrointestinal distress are shown in the table below.

Table 49: Reviewer's Rates of Gastrointestinal Distress

Group	%	/100 PEY
Active	9%	28
Coadmin	9%	47
Monotherapy	9%	31
Open label	16%	36
Placebo	5%	23
Spironolactone	13%	55

PEY = Patient exposure year

Other Gastrointestinal

Other gastrointestinal adverse effects did not vary significantly by treatment group.

2.3. Hemic and Lymphatic

Hematologic adverse events were rare and seemingly random among eplerenone and control groups. There were no adverse events related to the lymphatic system. The analyses of hematologic laboratory values suggest only one possible association: a higher, but still very low, frequency of drops in hemoglobin for the eplerenone, active control, and particularly the coadministration groups compared to placebo (0.21 to 0.58 percent drops greater than 3.0 gm/dL compared to 0 percent).

An unexpected SAE of disseminated intravascular coagulation (DIC) and renal failure was reported in May 2002 in one patient on a non-IND eplerenone protocol of dose-ranging in symptomatic heart failure. The DIC case was associated with moderate to severe thrombocytopenia (lowest value 23,000). No cases of DIC have been reported in the hypertension studies. Note that mean platelet counts in the eplerenone groups were slightly higher than baseline, although they were also higher in the active control groups. Extreme values of platelet counts, either low (<100,000, <50,000) or high (>450,000, >600,000) were infrequent and evenly distributed among all treatment groups. An AE of thrombocytopenia was reported in three patients, two in Study 025 and one eplerenone-treated patient in Study 022. The patient in Study 022 had an associated petechial rash on the ankles and one of the patients in Study 025 had Graves disease, but there were no associated thrombotic findings in any patient. The minimum platelet counts recorded for these patients were 63,000; 113,000; and 182,000.

2.4. Metabolic and Endocrine

Sex Hormones

Note that two male patients on eplerenone monotherapy and one patient on spironolactone withdrew because of gynecomastia. No patients treated with other drugs

or placebo developed this AE. All patients experiencing male breast AEs for all studies are shown in the table below.

Table 50: Reviewer's Males with Breast AEs

Arm	Drug	Demo	Symptom	Day On-Study		
				Pain	Mass	End
1703	E + enalapril	65WM	GYNECOMASTIA		43	
1901	E + HCTZ	56WM	GYNECOMASTIA/(R) BREAST PAIN	84	84	
1901	E + HCTZ	71WM	TENDERNESS OF (L) NIPPLE	96		
1801	E 100-300 QD	56WM	BREAST DISCOMFORT	77		
1801	E 100-300 QD	56WM	TENDERNESS/ENLARGEMENT	-18	11	
1601	E 25-200 QD	51WM	PAIN OF NIPPLE	188		336
1601	E 25-200 QD	55WM	TENDERNESS/ENLARGEMENT*	183	183	
1701	E 50-200 QD	77WM	SWELLING/INVERSION*		124	189
2101	E 50-200 QD	60WM	PAIN RIGHT BREAST	201		
2201	E 50-200 QD	65WM	PAIN UNDER LEFT NIPPLE	144		177
2601	E 50-200 QD	69WM	SWOLLEN BREAST		35	
2501	E open label	66WM	2 CM (R) AREOLAR MASS		143	169
2501	E open label	71BM	BREAST PAIN/LUMP	146	252	
2501	E open label	72WM	MODERATE GYNECOMASTIA		174	
1008	Spironolactone	44WM	BREAST TENDERNESS	65		
1802	Spironolactone	63WM	BREAST PAIN	78		
1802	Spironolactone	69WM	BREAST PAIN	97		
1802	Spironolactone	49WM	GYNECOMASTIA		72	
1802	Spironolactone	58WM	GYNECOMASTIA*	67	67	
1802	Spironolactone	59WM	INCREASED BREAST SIZE		108	
1802	Spironolactone	59WM	INCREASED SENSITIVITY/SIZE	74	74	
1802	Spironolactone	61WM	MASTODYNIA	34		
1802	Spironolactone	53WM	MASTODYNIA L>R	68		
1802	Spironolactone	57WM	MASTODYNIE (LEFT)*	37		55
1802	Spironolactone	61WM	SORE NIPPLES	114		134
1802	Spironolactone	54WM	TENDERNESS BOTH NIPPLES	61		

E = eplerenone; *caused withdrawal

Note that eplerenone and spironolactone cause two related male breast AEs: pain, tenderness, or increased sensitivity (mastodynia) and enlargement (gynecomastia). In the table above the day on-study when the AE (listed separately for mastodynia and gynecomastia) developed is shown as well as the day the AE ended (if applicable). Mastodynia typically was noted prior to or concurrent with the development of gynecomastia. The time course to the development of gynecomastia was usually delayed, e.g., 4-5 months. Study 018 may be an exception. Study 018 was conducted in patients with hyperaldosteronism who may be expected to have prior treatment with spironolactone. The one eplerenone patient in Study 018 with the early development of gynecomastia on day 11 had prior treatment with spironolactone.

The incidence rates for these male breast AEs were substantially higher in the spironolactone groups than in the eplerenone groups. The incidence rates for the other male sex hormone-related AE, impotence, were also higher in the spironolactone groups than in all other groups. The incidence rates for sex-hormone related AEs is shown in the table below.

Table 51: Reviewer's Rates of Sex Hormone-Related AEs in Males

Group	Any Breast	Gynecomastia	Mastodynia	Impotence
Active control				1.20%
Coadmin	0.24%	0.24%		0.98%
Monotherapy	1.05%	0.52%	0.84%	0.94%
Open label	1.00%	1.00%	0.33%	2.98%
Placebo				1.52%
Spironolactone	13.64%	4.55%	11.36%	3.41%

Note, however, that the dosages of spironolactone used were more efficacious than the dosages of eplerenone used.

Spironolactone also produced more female sex-hormone related AEs. The incidence rates for sex-hormone related AEs in females is shown in the table below.

Table 52: Reviewer's Rates of Sex Hormone-Related AEs in Females

Group	Any Breast	Mass	Breast Pain	Any Menstrual	Dysmenorrhea	Bleeding	Menopausal
Active control	0.16%		0.16%	1.26%	0.31%	0.79%	0.16%
Coadmin							
Monotherapy	0.63%	0.63%	0.13%	1.13%	0.50%	0.63%	
Open label	1.41%	0.70%	0.70%	2.82%		2.11%	0.70%
Placebo	0.56%		0.56%	0.56%	0.56%		
Spironolactone	19.35%	3.23%	16.13%	9.68%		9.68%	

The rates of sex hormone-related AEs in females for eplerenone groups were similar to active controls other than spironolactone and to placebo except possibly for menstrual bleeding in the open label study and breast masses. The breast-related AEs in females are listed in the table below. Note that the one breast "mass" in a spironolactone patient was a report of "swollen breast" that resolved in one day and that several of the breast masses in eplerenone patients were reported earlier than one could expect a biologic effect from eplerenone or any other drug.

Table 53: Reviewer's Females with Breast AEs

Arm	Drug	Demo	Symptom	Day On-Study		
				Pain	Mass	End
1801	E 100-300 QD	73BF	ABNORMAL (R) MAMMOGRAM		81	
1006	E 200 BID	59WF	BREAST CYST		22	
1601	E 25-200 QD	69WF	BREAST CANCER*		146	
2002	E 50-200 QD	54BF	LUMP (R) MAMMOGRAM		1	
2201	E 50-200 QD	55HF	BREAST ABCESS	80	80	89
2501	E open label	69WF	MASS REMOVAL (R) BREAST		196	196
2501	E open label	52WF	(L) BREAST MASS		194	194
2501	E open label	59WF	BREAST TENDERNESS	81		113
2501	E open label	48WF	TENDERNESS IN NIPPLES	3		7
1602	Enalapril 5-40 QD	58BF	RIGHT BREAST TENDERNESS	67		74
1001	Placebo	41WF	BILAT BREAST PAIN	23		31
1008	Spironolactone	48WF	SWOLLEN BREAST		20	21
1008	Spironolactone	39AF	BILATERAL BREAST PAIN	23		42
1802	Spironolactone	43BF	BREAT PAIN	1		8
1802	Spironolactone	51WF	BREAST DISCOMFORT	28		42
1802	Spironolactone	52WF	BREAST TENDERNESS	22		73
1802	Spironolactone	42WF	MASTALGIA	33		59

E = eplerenone; *caused withdrawal

The changes in sex hormone levels can be argued to be supportive of the AE findings. The changes in sex hormone levels are detailed in the laboratory data section above. In summary, eplerenone appear to have a small effect upon pituitary sex hormones not unlike spironolactone. In males the effects are a small increase in LH, a small decrease in FSH, and a small increase in dihydrotestosterone levels. The effects in females are less clear because of the smaller numbers, particularly for spironolactone. The increases in LH and dihydrotestosterone are consistent with an inhibitory effect of eplerenone at the androgen receptor.

Reviewer's comment: Eplerenone appears to cause a slight increase in gynecomastia and mastodynia in males and possibly vaginal bleeding in females. The rates are low, e.g., about one percent, and substantially less than the rates seen with spironolactone, at least at the dosages used in the clinical studies and being proposed for labeling. There does not appear to be any difference between eplerenone and placebo for impotence in males or breast pain in females. However, long-term exposure to eplerenone in the hypertension clinical studies is relatively low, i.e., 106 exposed for more than 360 days. How troublesome gynecomastia or menstrual bleeding will be with eplerenone will depend upon more experience with long-term treatment

Thyroid

Please see the Laboratory Values section above for a discussion possible effects of eplerenone upon TSH values. The mean changes in TSH values suggest that eplerenone

may increase TSH levels slightly, particularly in males. Eplerenone dose not appear to have an effect upon thyroxin levels nor does it cause a change in outlier TSH values, at least during short term treatment. All patients with thyroid AEs are listed in the following table.

Table 54: Reviewer's Patients with Thyroid AEs

Arm	Drug	Demo	Symptom	Begin
1602	Enalapril 5-40 QD	55HM	THYROID GOITER	181
1702	Enalapril 10-40 QD	49WM	HYPERTHYROIDISM SUSPECTED	267
2103	E + enalapril	53BF	ENLARGED THYROID	176
2302	ARB	54WM	HYPOTHYROIDISM	22
2501	E open label	58WM	30 GRAM THYROID	169
2501	E open label	44BF	25 GRAM GOITER, FIRM	171
2501	E open label	61WM	THYROID NODULE	114
2501	E open label	53WF	GRAVES DISEASE	94
2501	E open label	48WF	EXACERBATION HYPOTHYROIDISM	281
2501	E open label	56WF	GOITRE	141
2501	E open label	76WF	COMPENSATED HYPOTHYROIDISM	141
4901	Placebo	67HF	HYPERTHYRODISM	129

E = eplerenone

Note that the most events were reported in the open label study, females predominate, and about half of the events are goiters, one quarter are hypothyroidism, and one quarter are hyperthyroidism. The event rate for the open label study is 1.2 percent or 2.7 per 100 PEY. The event rates for the controlled trials and the open label follow-on study (Study 025) are shown in the table below.

Table 55: Reviewer's Thyroid AE Rates

Group	Any Thyroid		Goiter		Hyper		Hypo	
	%	/100 PEY	%	/100 PEY	%	/100 PEY	%	/100 PEY
Active	0.2%	0.7	0.1%	0.2	0.1%	0.2	0.1%	0.2
Coadmin	0.1%	0.7	0.1%	0.7				
Monotherapy								
Open label	1.2%	2.7	0.7%	1.5	0.2%	0.4	0.3%	0.8
Placebo	0.3%	1.3			0.3%	1.3		
Spironolactone								

PEY = patient exposure years

Reviewer's comment: The small changes in TSH levels and the possible greater rates of thyroid AEs in the open label study do not permit a firm conclusion that eplerenone has no significant effect upon thyroid function. Greater exposure for longer terms is needed.

Other Hormones

Changes from baseline in cortisol levels were minimal for the eplerenone, placebo, and active control groups other than spironolactone. Spironolactone, in the one Study 018 in hyperaldosteronism that included spironolactone and measured cortisol, produced a significant increase (about 15 percent above baseline) in cortisol.

Renin-angiotensin system hormones are discussed in the secondary efficacy sections. No hormones other than those discussed above were monitored.

Glucose

Three patients in the eplerenone monotherapy groups and two patients with eplerenone coadministration with enalapril has SAEs of hyperglycemia or aggravated diabetes reported. Rates of all reported AEs of hyperglycemia or diabetes were similar in the active treatment groups and are shown in the table below.

Table 56: Reviewer's Rates of Hyperglycemic or Diabetes AEs

Group	%	/100 PEY
Active control	1.8%	5.6
Coadmin	1.6%	8.0
Monotherapy	1.5%	5.0
Open label	3.4%	7.7
Placebo	0.5%	2.5
Spironolactone	0.8%	3.6

PEY = patient exposure years

Regarding lab measurements of blood glucose, the effects of eplerenone on mean changes from baseline to final visit, while positive, where less than the changes seen with hydrochlorothiazide. The rates of high outlier values were slightly higher with eplerenone monotherapy and coadministration than placebo but higher than with active controls

Lipids

The one lipid laboratory value that increased slightly but significantly with eplerenone treatment was triglycerides. Mean changes from baseline were similar for epelerenone and hydrochlorothiazide. However, AEs of hypertriglyceridemia were most frequent in the spironolactone group. Rates of hypertriglyceridemia AEs are shown in the table below.

Table 57: Reviewer's Rates of Hypertrigylceridemia AEs

Group	%	/100 PEY
Active control	0.6%	2.0
Coadmin	1.2%	6.0
Monotherapy	1.4%	4.7
Open label	1.4%	3.1
Placebo		
Spironolactone	2.5%	10.9

PEY = patient exposure years

2.5. Musculoskeletal

AEs specific to the musculoskeletal system were rare in all treatment groups. Rates of general symptomatic AEs such as fatigue, back pain, and influenza-like symptoms were higher in the eplerenone monotherapy groups than with placebo but not significantly different from the active control groups. Please see the incidence table section above for the rates.

2.6. Nervous

Please see the Cardiovascular section above for a discussion of cerebrovascular events. The most common nervous system AEs were headaches and dizziness. The rates of headache with eplerenone were nominally less than with placebo. The rates of dizziness with eplerenone were nominally higher than with placebo but comparable to active control. Please see the incidence table section above for the rates. Other AEs specific to the nervous system were rare in all treatment groups.

2.7. Respiratory

Rates of general respiratory AEs such as upper respiratory tract infections, bronchitis, and sinusitis were similar in the eplerenone monotherapy and placebo groups. Rates of cough were slightly higher with eplerenone but not significantly different from the active control groups. Please see the incidence table section above for the rates.

2.8. Dermatological

Rates of skin rashes, urticaria, or pruritus were nominally higher in the eplerenone monotherapy groups but not different than active controls. The rates are shown in the table below.

Table 58: Reviewer's Rates of Rashes, Urticaria, and Pruritus AEs

Group	%	/100 PEY
Active	4.1%	12.9
Coadmin	1.0%	5.3
Monotherapy	2.9%	9.9
Open label	5.1%	11.6
Placebo	1.9%	8.9
Spironolactone	3.4%	14.6

PEY = patient exposure years

2.9. Special Senses

AEs involving special senses were rare in all groups. Visual disturbances were the most frequent but still rare and not significantly different among the groups. The rates of visual disturbances are shown in the table below.

Table 59: Reviewer's Rates of Visual Disturbance AEs

Group	%	/100 PEY
Active	0.3%	1.0
Coadmin	0.1%	0.7
Monotherapy	0.5%	1.7
Open label		
Placebo	0.3%	1.3
Spironolactone		

PEY = patient exposure years

2.10. Genitourinary

Rates of renal AEs were similar between eplerenone and active controls and generally were similar to placebo rates as well. The rates for renal AEs are shown in the table below. Polyuria includes nocturia AEs and "stone" includes both renal calculi and renal colic AEs.

Table 60: Reviewer's Rates of Renal AEs

Group	Proteinuria		Polyuria		Insufficiency		Hematuria		Stone	
	%	/PEY	%	/PEY	%	/PEY	%	/PEY	%	/PEY
Active control	0.7%	2.2	1.0%	3.2	0.2%	0.7	0.3%	1.0	0.2%	0.7
Coadmin	0.4%	2.0	1.0%	5.3	0.0%	0.0	0.0%	0.0	0.1%	0.7
Monotherapy	0.7%	2.3	0.3%	1.2	0.3%	1.0	0.5%	1.7	0.3%	1.0
Open label	0.5%	1.2	0.9%	1.9	0.2%	0.4	0.5%	1.2	0.2%	0.4
Placebo	0.5%	2.5	0.5%	2.5	0.0%	0.0	0.0%	0.0	0.0%	0.0
Spironolactone	0.0%	0.0	0.0%	0.0	0.0%	0.0	0.8%	3.6	0.0%	0.0

/PEY = per 100 patient exposure years

2.11. Miscellaneous

All SAEs and AEs with incidence rates greater than placebo have been discussed in the previous sections.

D. Adequacy of Safety Testing

The sponsor targeted special studies to address particular problems, such as interactions with CYP3A4 inhibitors and QTc prolongation, that are known to be safety issues. The exposure rates and extent of testing in the clinical studies also appear to be excellent for capturing not rare AEs occurring with exposure durations of six months or less. The ability to detect rare events or events requiring longer durations of exposure is less certain. This limitation is not unusual for new NDA submissions. Overall the adequacy of safety testing appears to be excellent.

E. Summary of Critical Safety Findings and Limitations of Data

- Overall eplerenone appears to be well-tolerated. The overall rates of AEs in the placebo-controlled studies are similar for eplerenone and placebo. The rates of AEs with eplerenone are higher in many of the non-placebo controlled studies, but the patient entry criteria for these latter studies selected for sicker patients, e.g., diabetics in one study and older patients in another. AE rates for eplerenone in all studies appears to be comparable to the controls, active or placebo, with the exception of spironolactone. AE rates were substantially higher with spironolactone but, in one study the efficacy of the dosage of spironolactone used was comparable only to the highest dosage eplerenone arm and in the other study that used spironolactone it was more effective than eplerenone.

- Eplerenone has been safely coadministered with hydrochlorothiazide, ACE inhibitors, angiotensin receptor blockers, beta blockers, and calcium channel blockers. Coadministrations were tolerated well without evidence of side effects different than with the drugs used alone. Mean potassium levels were slightly greater with the coadministration of eplerenone and ARBs but clinical events of hyperkalemia remained low. With eplerenone and hydrochlorothiazide coadministration, potassium levels were intermediate between the increases seen with eplerenone and the decreases seen with hydrochlorothiazide.

There is one eplerenone toxicity that is dose limiting, another set of toxicities that, while not life threatening, could limit usefulness, and some unanswered issues. There are no serious safety issues that are identified with enough certainty to warrant disapproval.

- The dose limiting toxicity is hyperkalemia. This toxicity is analyzed extensively by the sponsor in the NDA and addressed appropriately in the labeling. If hyperkalemia

is defined as a maximum potassium value greater than 5.5 meq/L, then for all patients treated with eplerenone 400 mg the rate was about 7.8 percent while for lower dosages it was 1 percent or less. The sponsor has stated that hyperkalemia was the reason for abandoning the 400 mg dosage. For patients with mild renal insufficiency, defined as a baseline creatinine greater than 106 umol/L or 1.2 mg/dL, the rate is 37 percent with combined therapy, 27 percent with an ACE inhibitor alone, and 8 percent with eplerenone alone. However, in diabetics with microalbuminuria, the rate was 33 percent with eplerenone alone, 29 percent even with normal creatinine.

- The set of toxicities that could limit usefulness long term are the sex hormone related AEs. The sponsor minimizes the potential of eplerenone for causing these side effects in the NDA and does not mention them in the proposed labeling. Eplerenone does appear to cause gynecomastia in males and it may also cause vaginal bleeding in females. The rates at which it does so appear to be lower than those with spironolactone, but the extent of the difference is unclear because spironolactone was given at more effective dosages in the two studies in which it was used and compared to eplerenone. Furthermore, gynecomastia is an AE that would be expected to manifest itself only with longer durations of exposure, i.e., six months or more. The durations of exposure in the trials, 283 patients for 180 days or more and 106 patients for more than 360 days, is not adequate to estimate precisely the incidence rates for gynecomastia with extended eplerenone exposure.

- There are two incompletely addressed issues:

  - Eplerenone appears to affect TSH levels. The sponsor concludes in the NDA that eplerenone does not affect TSH. The data from the three studies in which TSH levels were measured are consistent but difficult to interpret: TSH levels rose in eplerenone-treated males and in placebo or enalapril-treated females. Whether these are post-hoc, subgroup spurious results or real differences is not clear. Thyroid AE rates were higher in the open-label eplerenone group but not in the monotherapy groups. Because there is an animal model for thyroid dysfunction and because thyroid clinical effects could be delayed, it would be worthwhile to have TSH measurements and thyroid event follow-up in a larger, long term eplerenone treatment cohort.

  - Whether eplerenone causes any increase in cerebrovascular or peripheral vascular thrombotic AEs is not clear. The absolute rates are low, e.g., 0.2 to 0.7 percent, but they nominally higher than in the placebo controls. The sponsor does not comment on differences in these rates possibly because the sponsor's analyses focus on rates greater than 1 percent or differences that are statistically significance. However, even a low but real increase in these rates could negate the beneficial effects of lowering blood pressure. There is a potential mechanism, increase in PAI-1 levels, that provide a biological basis for increased thrombotic rates. Higher exposure rates are necessary to provide more precise estimates of the effects upon cerebrovascular and cardiovascular event rates.

VIII. Dosing, Regimen, and Administration Issues

Most issues regarding dosing, intervals, time to effect, maintenance, and withdrawal are discussed in detail in Section VI.6. The following is a quick summary of the conclusions there: Eplerenone shows a dose-response relationship between 25 and 400 mg daily. The limitation on the use of the highest dose tested in clinical studies, 400 mg, is the risk of hyperkalemia rather than efficacy, although the precise nature of the dose-response relationship at dosages above 200 mg is not well established. Eplerenone is effective in controlling BP throughout the day with a once in the morning dosage as demonstrated by ABPM data. Eplerenone shows a substantial effect within two weeks and maximal or near maximal effect by four weeks of repeated daily dosing. The BP effects appear to be maintained at least for one year and there do not appear to be adverse withdrawal effects. All of these conclusion are supported well by the data.

One dosing issue not addressed in Section VI.6. is the effect of feeding. Two studies addressed this issue:

In Study 005 twelve healthy, normal subjects were administered a single, oral 100 mg dose of eplerenone under both fed and fasted conditions, the following was concluded: For eplerenone, the high-fat meal led to a statistically significant reduction in the rate of eplerenone absorption, but had no effect on the extent of absorption. Average bioequivalence between the meal treatments was concluded for AUC_{0-96} and $T_{1/2}$. Eplerenone was well tolerated under both fed and fasted conditions. From these results the sponsor concluded that dosing of eplerenone may be made without regard for meal time, as food effect is not clinically significant.

Study 030 was an open-label, randomized, single-dose, four-period, four-sequence, four-treatment crossover design study in 16 healthy subjects with test periods of a high fat meal, antacid, and double-strength grapefruit juice. Administration of eplerenone 100 mg with a high-fat meal did not have a statistically significant effect on eplerenone pharmacokinetics compared to fasting conditions. Administration of eplerenone 100 mg with antacid resulted in an insignificant increase in eplerenone C_{max} (11%), but did not have a statistically significant effect overall eplerenone exposure (as measured by AUC) compared to fasting conditions. Coadministration of eplerenone 100 mg with 250 mL double-strength grapefruit juice resulted in statistically significant increases in eplerenone overall exposure (20% increase in AUC) and maximum plasma concentrations (29% increase in C_{max}) compared to fasting conditions. The sponsor concluded that, due to eplerenone's wide therapeutic index dosage, adjustment is not considered necessary when eplerenone and grapefruit juice are coadministered. Because eplerenone will typically be titrated over a four-fold dose range and because its action is not immediate, the sponsor's conclusion is reasonable.

The grapefruit juice interaction is obviously related to eplerenone's metabolism by CYP3A4. Coadministration with potent inhibitors of CYP3A4 such as ketoconazole

result in markedly increased AUC, e.g., 441 percent with ketoconazole. The sponsor has proposed a labeling precaution regarding this interaction, which is highly advisable.

Results of studies in patients with hepatic or renal impairment are summarized in Section IX.D below. Eplerenone is primarily metabolized in the liver and patients with moderate hepatic impairment have a 42 percent increase in AUC. The sponsor has recommended the usual starting dose of 50 mg in these patients. This recommendation is acceptable. Eplerenone pharmacokinetics are not altered substantially with renal impairment, but the rates of one adverse event are. Hyperkalemia is more frequent with creatinine clearances of < 100 ml/min in type 2 diabetics with microalbuminuria and < 70 ml/min in other patients with essential hypertension. The sponsor has recommended avoiding doses greater than 100 mg in these patients and monitoring potassium levels regularly. This recommendation appears reasonable.

APPEARS THIS WAY
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IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor investigated gender effects both in its PK/PD studies and in its clinical trials. The following PK/PD studies are most relevant to gender effects:

- Study 028, an open-label, randomized, parallel-group design, evaluated the single-dose and steady-state pharmacokinetics of eplerenone in healthy young (18 to 45 years) and healthy elderly (≥ 65 years) subjects. It examined gender effects and found that elderly females had 3 percent higher eplerenone steady-state weight-adjusted CL/F and higher drug exposure (3 percent and 8 percent higher steady-state AUC_{0-24} and C_{max}, respectively) compared to elderly males. However, these differences were not significant. The sponsor does not recommend any dosage adjustment by gender.

- Study 044 was a single-blind, multiple-dose, two-period study conducted in 24 nonsmoking, non-pregnant female subjects taking an oral contraceptive, norethindrone/ ethinyl estradiol. Coadministration of eplerenone resulted in a statistically and clinically insignificant decreases in mean ethinyl estradiol AUC_{0-24} (-0.6%) and C_{max} (-2.4%). It resulted in statistically significant increases in norethindrone AUC_{0-24} (16.7%), C_{max} (19.8%) and C_{min} (21.4%) that the sponsor considered clinically insignificant by protocol prespecified limits. AEs were mild and similar between the eplerenone and control periods. No pregnancies occurred.

For efficacy in the clinical studies, a variety of subgroup analyses were performed including gender. In the ISE the sponsor specifically examined gender effects statistically in Studies 010 and 049 (the placebo-controlled studies) and 023 and 024 (the coadministration with other antihypertensives studies). There were no statistically significant differences in BP reduction by gender in these studies. The sponsor also tabulated blood pressure changes by trial and gender for eplerenone-treated patients in all trials. There is no consistent differential in BP reduction by gender in all trials.

For safety in the clinical studies, subgroup analyses were performed on adverse event and mid-range laboratory value incidence rates to determine whether certain demographic factors affect the difference in the risk of an event or laboratory abnormality between eplerenone monotherapy and placebo, eplerenone monotherapy and active comparators, eplerenone coadministration therapy and active comparators, and eplerenone monotherapy and coadministration. The sponsor used a statistical analytic approach for detecting differing AE rates. For the subgroup comparisons, the analysis provided the risk difference (e.g., eplerenone minus placebo) for each subgroup, the difference between these subgroup risk differences (RDs), and the treatment-by-subgroup interaction p-value based on the Breslow-Day statistic.

In the analysis of adverse events by gender, a significant difference in risk differences was observed between the eplerenone monotherapy and placebo groups for the overall incidence of adverse events. Among males, a higher overall incidence of adverse events was observed for the eplerenone monotherapy group (47.7 percent) compared to the placebo group (37.4 percent; RD = 10.3). Among females, a higher overall incidence of adverse events was observed for the placebo group (52.5 percent) compared with the eplerenone group (46.4 percent; RD = -6.2).

Using the statistical approach the sponsor detected several varied AEs that differed significantly by gender (without performing any multiple comparisons corrections.) Many appear to be random variations in gender differences not unique to eplerenone, e.g., "Among males, the incidence of high mid-range urine WBCs was similar in the eplerenone (1.0 percent) and placebo (2.7 percent; RD = -1.7) groups. Among females, the incidence of high mid-range urine WBCs was higher in the eplerenone group (8.5 percent) compared to the placebo group (3.5 percent; RD = 5.0)." And, "Among males, the incidence of chest pain non-cardiac was higher in the active comparators group compared to the eplerenone monotherapy group, and the incidence of increased GGT was higher in the eplerenone monotherapy group compared to the active comparators group. Among females, the incidence of chest pain non-cardiac was higher in the eplerenone group compared to the active comparators group, while the incidence of increased GGT was similar in the eplerenone and active comparators groups. The magnitude of the RDs was small (-1.3 to 1.5)." None of the differences in AEs appear to be clinically significant.

The sponsor's summary of differences in AEs by gender is the following: "As indicated by the small RDs and the low numbers of adverse events and mid-range laboratory values for which there were significant differences between males and females, gender has no effect on the tolerability or safety of eplerenone."

Reviewer' comment: Overall the sponsor's approach for detecting gender differences in efficacy and safety is adequate. The sponsor's efficacy evaluation concentrated on the two pivotal studies and the two coadministration trials. Potential gender differences in the other trials are relevant, and the reviewer found the suggestive but not conclusive differences summarized below. The sponsor's safety evaluation by gender described above is a generic screen for unexpected problems. It did not identify any. The sponsor also targeted appropriately sex-hormone related AEs as AEs of special interest. The sponsor's analyzed these AEs correctly by gender. The sponsor did not analyze sex hormone levels by gender . The reviewer did.

The reviewer did not find any differences in BP reduction by gender. Eplerenone may have a differential impact upon other measures: renin and aldosterone; liver enzymes; and sex hormones.

- Baseline renin and aldosterone levels varied by race and gender. 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. Eplerenone appears to produce a dose-related increase in renin and aldosterone levels. There appears to be a differential effect of eplerenone by race and gender, with blacks and females showing reduced effect.

- Eplerenone appears to produce slight, statistically-significant, dose-related increases in ALT and GGT and has no detectable effect upon other measures of liver function. The increases in males are slightly greater than the increases in females. Note that the GGT increase in males was also picked up in the sponsor's statistical screen.

- Eplerenone appears to have a small effect upon pituitary sex hormones. In males the effects are a small decrease in FSH, a small increase in dihydrotestosterone, and possibly a small increase in LH. The effects in females are less clear because of the smaller numbers.

- Eplerenone appears to produce slight increases in TSH levels. Whether these increases are limited to or greater in males is suggested but not clearly established by the available data.

None of these effects is large. It is noteworthy that all of differences are greater effects in males. The clinical significance of them depends upon whether any clinical events result, and in this NDA's database there are suggestive but not conclusive event rates. The changes in renin and angiotensin don't appear to be associated with differential changes in BP. The clinical event rates for overt liver AEs or thyroid AEs or too low to detect a gender difference. The sex hormone related AEs, of course, are differentiated by gender. Sex hormone related AEs in males treated with eplerenone appear to exceed rates in placebo and active controls other than spironolactone while sex hormone related AEs in females treated with eplerenone don't.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor investigated age and ethnicity effects in both in its PK/PD studies and in its clinical trials. The following are the most pertinent PK/PD studies to this section:

- Study 028 was an open-label, randomized, parallel-group design that evaluated the single-dose and steady-state pharmacokinetics of eplerenone in 24 healthy young (18 to 45 years) and 24 healthy elderly (≥ 65 years) subjects, equally distributed by gender in each age category. On day 1 and days 3 through 14, subjects took a single 100 mg dose of eplerenone. Plasma clearance (CL/F and CL/F/WT) of eplerenone was statistically significantly decreased in elderly subjects following both single dosing (26.5% decrease on day 1) and multiple dosing (29-31% decreases on days 7 and 14), resulting in statistically significant increases in overall plasma exposure

(36% increase in AUC following single dosing and a 41-45% increase in AUC following multiple dosing). Peak plasma exposure had statistically significantly increased in elderly subjects following both single dosing (14% increase) and multiple dosing on Day 14 (22% increase), but had not statistically significantly increased following multiple dosing on Day 7.

- Study 046 was a double-blind, randomized, multiple-dose, parallel-group study. 24 black and 25 white 55-80 year old subjects were enrolled, with even numbers of males and females and those < 65 and older. Four black and four white subjects were randomized to placebo, while the remaining subjects were randomized to eplerenone 100 mg QD on days 1 and 4-10. Race effect was tested with an analysis of covariance (ANCOVA) model with race as the only factor and body weight as a covariate. The results for the parent drug eplerenone (SC-66110) are shown in the figure below.

Pharmacokinetic Parameter	Least Squares Means[a] Blacks SC-66110 100 mg QD (Test)	Least Squares Means[a] Caucasians SC-66110 100 mg QD (Reference)	Ratio of Means (Test/Ref)	90% CI for Ratio of Means	p-Value[b]
Single-Dose:					
$AUC_{(0-\infty)}$ (hr*ng/mL)	10513.79	12190.45	0.862	(0.689, 1.079)	0.273
$AUC_{(0-tf)}$ (hr*ng/mL)	10851.55	12345.83	0.879	(0.699, 1.105)	0.348
C_{max} (ng/mL)	1666.94	1868.73	0.892	(0.755, 1.054)	0.256
CL/F (L/hr)	9.22	8.10	1.138	(0.905, 1.430)	0.348
CL/F/WT (L/hr/70kg)	8.59	7.53	1.141	(0.907, 1.436)	0.338
T_{max} (hr)	1.80	1.62	--	--	0.530
$T_{1/2}$ (hr)	4.37	4.04	--	--	0.514
$XU_{(0-48)}$ (ug)	964.72	1576.52	0.612	(0.450, 0.832)	0.010
Multiple-Dose:					
$AUC_{(0-\tau)}$ (hr*ng/mL)	10056.14	13599.26	0.739	(0.561, 0.975)	0.073
C_{min} (ng/mL)	73.44	82.07	0.895	(0.485, 1.651)	0.761
C_{max} (ng/mL)	1547.23	1919.68	0.806	(0.641, 1.014)	0.122
CL/F (L/hr)	9.94	7.35	1.352	(1.026, 1.782)	0.073
CL/F/WT (L/hr/70kg)	9.31	6.86	1.357	(1.030, 1.786)	0.070
T_{max} (hr)	1.87	1.95	--	--	0.800
$T_{1/2}$ (hr)	5.03	5.96	--	--	0.230
$XU_{(0-48)}$ (ug)	921.74	1544.50	0.597	(0.388, 0.918)	0.051

(a) Based on an analysis of covariance (ANCOVA) model with race as the only factor and body weight as a covariate. AUC, C_{max}, C_{min}, CL/F, CL/F/WT and $XU_{(0-48)}$ values were natural log-transformed prior to the ANCOVA. Values shown have been back-transformed to the original scale.

(b) F-test p-value based on the ANCOVA model for the race group comparison

Source: Table T9.1

Figure 55: Sponsor's Pharmacokinetic Parameters for Eplerenone (SC-66110) by Race from Study 046

While all but one of the comparisons lacks statistical significance by ANCOVA, note that the point estimates suggest a higher clearance and lower AUC of eplerenone in blacks. This study was sized to detect a 50 percent difference in AUC with 90 percent power. Gender effects were not presented in the study report.

AEs were mild and probably not drug related with two exceptions: One white male on eplerenone had mild ALT elevation. One black patient on eplerenone had a potassium recording of 7.2 on day 10, normal baseline, normal day 11, but 5.5 on day 12.

For efficacy in the clinical studies, a variety of subgroup analyses were performed including age and race. In the ISE the sponsor specifically examined age and ethnicity effects statistically in Studies 010 and 049 (the placebo-controlled studies) and 023 and 024 (the coadministration with other antihypertensives studies). Age was examined in separate analyses with cutpoints of 65 and 75. Ethnicity was categorized as Caucasian, Black, and Non-Caucasian excluding Black. There were no significant interactions between these definitions of age and ethnicity and DBP or SBP in any of these studies.

The sponsor also examined race effects in Study 020. The sponsor concluded that "There was no significant or clinically meaningful interaction in change from Baseline in trough cuff seDBP between treatment (eplerenone vs. placebo) and race." The reviewer's analyses confirmed the sponsor's observation for this study. However, the reviewer also examined Study 019 in low renin hypertension, the other study with substantial black representation, for differential effects by race. In that study blacks showed a reduced BP effect with both eplerenone and losartan alone. The reviewer re-examined the Study 020 data by race and baseline renin level. There appears to be a small decrease in BP response in blacks compared to whites as well as a greater response in patients with lower baseline renin levels in Study 020. The sponsor's and reviewer's analyses for these studies are summarized in Section VI.D.7, Angiotensin Receptor Blockers.

The reviewer also examined differential effects of eplerenone on renin and aldosterone levels by race. The analyses are summarized in Section VI.D.8, Renin-Angiotensin-Aldosterone System. There appears to be a differential effect of eplerenone by race and gender, with blacks and females showing reduced effect.

For subgroup analyses of safety the sponsor used a statistical approach described in Section IX.A above. The results by age and race are similar to those described for gender above. The events with differential rates by age and race for eplerenone do not appear to be clinically significant. The sponsor concluded "As indicated by the small RDs and the low numbers of adverse events and mid-range laboratory values for which there were significant differences between age groups (< 65, ≥ 65, < 75, and ≥ 75 years of age), age has no effect on the tolerability or safety of eplerenone" and "As indicated by the small RDs and the low numbers of adverse events and mid-range laboratory values for which there were significant differences between Caucasians and Blacks, Caucasians and Asians, and Caucasians and Hispanics, race has no effect on the tolerability or safety of eplerenone." The reviewer agrees.

Reviewer's comment: There do not appear to be differential safety concerns by age or ethnicity. However, there are incompletely answered questions regarding whether eplerenone shows reduced efficacy in BP reduction in blacks and reduced effect upon renin and aldosterone levels in blacks. While the evidence is not convincing enough to

conclude that efficacy is reduced in blacks, neither is there sufficient evidence to justify a conclusion that efficacy is equivalent in black and whites.

C. [redacted]

(b)(5)

Reviewer's comment:

D. Comments on Data Available or Needed in Other Populations

The sponsor studied eplerenone pharmacokinetics in patients with mild hepatic impairment and with mild renal impairment in two separate studies:

- Study 012 was an open-label, multiple dose study conducted in 17 normal healthy subjects and 18 subjects with moderate hepatic impairment. The degree of the subject's impairment was Class B (with ascites), based on the Child-Pugh Classification System. These hepatically-impaired individuals were matched with normal healthy volunteers based on sex, age, weight, and smoking status. All study participants received a 400 mg dose of eplerenone in the morning on days 1 and 3-7. Compared to normal control subjects, there was a significant 29 percent reduction ($p = 0.005$) in mean apparent oral clearance of eplerenone at steady state in patients with moderate hepatic impairment, which resulted in a significant 42 percent increase ($p = 0.005$) in mean eplerenone AUC_{0-24} after QD dosing. No significant differences were found in mean steady-state C_{max} and T_{max} of eplerenone between moderately impaired patients and normal control subjects. Steady-state terminal $T_{1/2}$ of eplerenone was 8.1 hours for moderate hepatic impaired patients and 7.6 hours for normal control subjects. Based on this study the sponsor recommends that dosing be initiated at 50 mg QD for patients with mild hepatic impairment.

- Study 034 was an open-label, multiple-dose, parallel-groups study in 23 healthy subjects and 29 subjects with renal impairment. Subjects were stratified into one of the following groups based upon 24-hour creatinine clearances: A – Normal renal function (> 80 mL/min) 23 controls matched by age and weight; B – Mild renal impairment (50-80 mL/min) 7; C – Moderate renal impairment (30- 49 mL/min) 7; D – Severe renal impairment (<30 mL/min) 7; and E – Hemodialysis 8. A single 100mg tablet was given on the mornings of days 1 and 4-8. There were no statistically significant differences between the mildly impaired group and the

corresponding matched group of normal subjects for any of the pharmacokinetic parameters following both single and multiple-dose administration. Similar conclusion was reached for the moderately impaired group. The urinary excretion for the moderate group of subjects was significantly lower, 54 percent and 50 percent respectively, following single and multiple-dose administration. For the severely impaired subjects, C_{max} was about 25 percent higher following single-dose administration. The subjects on hemodialysis did not reveal any statistically significant differences in any of the PK parameters (except T_{max}) following single-dose administration. T_{max} was shorter by about 56 minutes as compared to the normal subjects. Following multiple-dose administration, AUC was decreased slightly followed by an increase in C_{max} and with an earlier onset of T_{max}. Hemodialysis removed only about 10 percent of the administered eplerenone dose from the systemic circulation of the eight dialysis patients.

While eplerenone pharmacokinetics are not substantially different in patients with mild to moderate renal impairment, one eplerenone AE is. The sponsor correlated baseline creatinine clearances with the occurrences of hyperkalemia in all studies. Baseline creatinine clearance levels < 70 mL/min in eplerenone- treated patients were associated with an increased incidence of elevated potassium levels (3.9 percent $\geq$ 6.0 mmol/L) The relationship of baseline creatinine clearance levels < 70 mL/min to increased potassium was observed in coadministration, active control, and placebo groups, although rates were lower for active control and placebo groups. The main exception was Study 021, which only enrolled hypertensive, type 2 diabetics with microalbuminuria. These patients showed a higher incidence of elevated potassium $\geq$ 6.0 mmol/L with creatinine clearance < 100 mL/min, as opposed to < 70 mL/min observed in the general population. The sponsor recommends avoiding doses greater than 100 mg in these patients and monitoring potassium levels regularly.

Use in pregnancy was not studied. One women in Study 019 with low renin hypertension became pregnant while receiving eplerenone and was discontinued. During her pregnancy she was hospitalized twice, once for fluid retention and once for pre-eclampsia. She eventually delivered a healthy infant at 37 weeks gestation.

Exposure in the special populations of prime interest, blacks and both genders, was good in the this development program. The major limitation of the hypertension database is the limited long term, i.e., greater than one year, exposure, e.g., 106 patients at one year. The longer exposure is particularly critical for estimating the risk of significant sex-hormone related AEs such as gynecomastia in males. From the extensive spironolactone experience and also from the limited experience with eplerenone, gynecomastia is an AE with increasing incidence after 6 months or more of exposure. Longer exposure would also help to elucidate whether other laboratory findings, such as the suggestion that TSH levels increase, produce real clinical problems.

X. Conclusions and Recommendations

A. 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, 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.

The sponsor claims that eplerenone is an effective antihypertensive agent regardless of age, gender, body mass index, or race. One study in low renin hypertension showed reduced antihypertensive efficacy in blacks. No studies were powered to show non-inferiority of blood pressure reduction among subgroups.

Eplerenone was well tolerated with overall rates of adverse events comparable to other approved anti-hypertensive medications. The dose-limiting toxicity of eplerenone is hyperkalemia and the reason for the recommendation to limit the maximum dosage to 200 mg daily. Eplerenone, like the related drug spironolactone, causes sex-hormone related side effects such as gynecomastia in males. The rates in the eplerenone trials were low, i.e., overall about one percent for any breast related adverse event in males. However, more long term exposure is need to delineate fully the cumulative frequency of this delayed side effect. More long term exposure would also be helpful in confirming that eplerenone produces no other chronic serious adverse events.

B. Recommendations

The reviewer recommends approval of eplerenone for the treatment of hypertension. One additional recommendation is that the sponsor report promptly to the Division the safety results from its Study 035. The reviewer's recommendations regarding the proposed labeling are given below.

In the sponsor's proposed labeling text below, the reviewer's suggested deletions are indicated with strikethroughs and additions are underlined. Reviewer's comments and explanations are enclosed in square brackets and highlighted in gray. Please see also the FDA biopharmaceutist's recommendations regarding labeling changes.

[

Draft

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

XI. Appendix

A. Other Relevant Materials

References

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B. Individual More Detailed Study Reviews

B.1 Trial 010, Eplerenone Dose Ranging, Including QD vs BID and Spironolactone Active Control, in Essential Hypertension

Study 010 is entitled "Efficacy and Safety Evaluation of a Range of Doses of SC-66110 in the Treatment of Mild to Moderate Hypertension." This multicenter, randomized, double blind, placebo lead-in, parallel group study compared the safety and efficacy of a range of doses of eplerenone (SC-66110) to placebo and to spironolactone. It is one of the two pivotal studies for establishing the anti-hypertensive efficacy of eplerenone.

B.1.1 Sites and Investigators

54 investigators in the U.S conducted the study. 48 investigators enrolled at least one patient in the double-blind portion of the study. The numbers of patients randomized at a site ranged from 1 to 26, with a median of 7 and a mean of 9.

One of the sites selected for audit was US0003 that contributed 20 patients to this study. The Division of Scientific Investigations' field inspector was unable to verify the data at site US0003 because allegedly the data were lost in a flood. The data from this site are excluded from the final efficacy analyses.

Reviewer's comment: No site appears to dominate the study or a group. The results at site US0003 and the impacts of excluding it are examined in the analyses in this report.

B.1.2 Background

B.1.2.1 Initial Protocol

The original protocol EE3-96-02-010 entitled, "Clinical Protocol for Efficacy and Safety Evaluation of a Range of Doses of SC-66110 in the Treatment of Mild to Moderate Hypertension" dated 18 October 1996 was revised prior to the start of this study. This study was conducted in compliance with Protocol EE3-96-12-010 entitled "Revised Clinical Protocol for Efficacy and Safety Evaluation of a Range of Doses of SC-66110 in the Treatment of Mild to Moderate Hypertension," dated 7 November 1996.

B.1.2.2 Protocol Amendments

There were three amendments and two administrative changes made to the initial protocol:

- Administrative Change No. 1, dated 7 November 1996, corrected grammatical errors and typographical errors in the protocol.

• Amendment No. 1, dated 18 December 1996, revised dose regimens and study objectives to compare twice a day (BID) dosing to once a day (QD) dosing.

• Administrative Change No. 2, dated 31 January 1997, deleted estrone from the list of analytes in the steroid profile and clarified the concomitant medications that were not allowed during the study. It also corrected typographical errors in the protocol and revised the statistical analysis section based on Amendment No. 1 dosage changes.

• Amendment No. 2, dated 16 April 1997, revised the inclusion/exclusion criteria to allow women of childbearing potential to enter the study, provided they were using a barrier method of contraception (hormonal contraception was not permitted). In addition, both coronary artery disease and history of cerebrovascular disease were removed as criteria for exclusion.

• Amendment No. 3, dated 21 May 1997, added a Sexual Dysfunction Questionnaire to evaluate the impact of eplerenone on sexual function compared to placebo.

Reviewer's comment: None of the amendments appears to impact adversely the scientific validity of the study.

B.1.2.3 Study Dates

The study was conducted between January 24, 1997, and January 30, 1998. Patients were randomized into double-blind treatment between March 7, 1997, and December 6, 1997.

B.1.3 Study Design

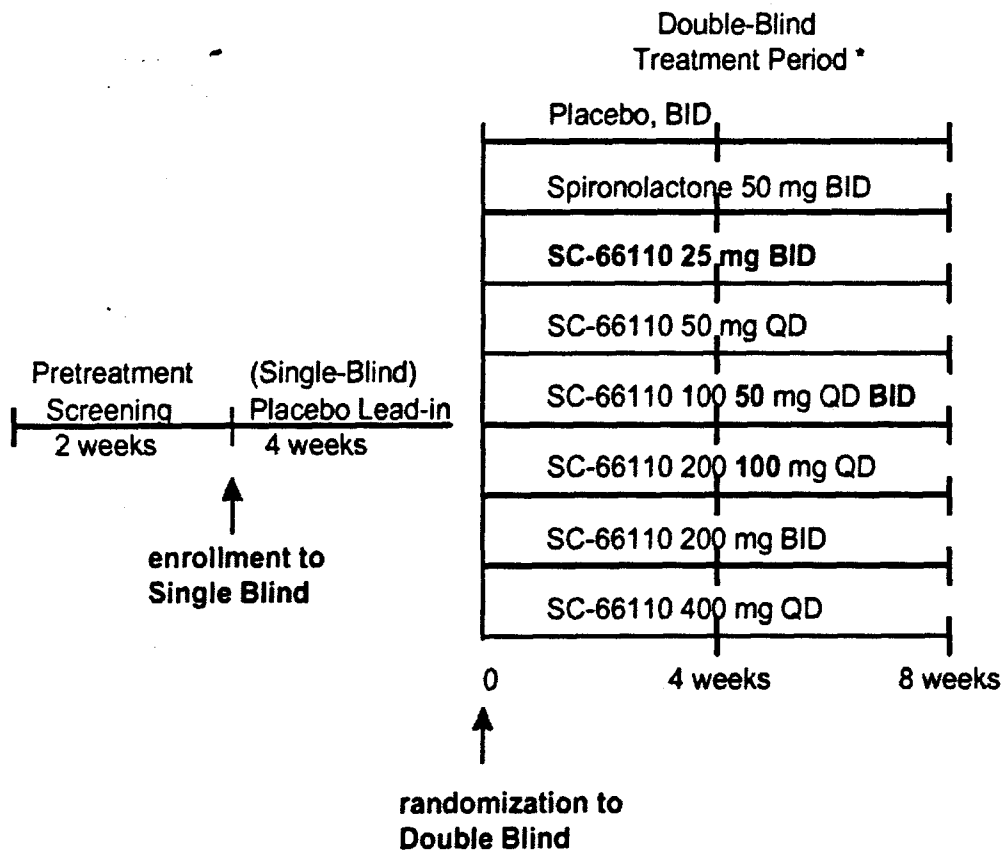
This was a randomized, double-blind, multicenter, placebo-controlled, parallel-group comparison of the efficacy and safety of QD and BID doses of eplerenone to placebo in patients with mild to moderate hypertension. Spironolactone was included as an aldosterone antagonist reference drug. An 8-week double blind treatment period was preceded by a 2-week pretreatment screening period and a 4-week single blind placebo lead-in period. The study is diagramed below.

B.1.3.1 Objectives

The primary objectives of this study were:

- Evaluate the antihypertensive effect of eplerenone at daily doses of 50, 100, and 400 mg as compared to placebo, when administered once daily or in divided doses for 8 weeks to patients with mild to moderate hypertension using change from Baseline in trough seated cuff DBP measurements;

- To establish the safe and effective dose-range of eplerenone for antihypertensive treatment.



* Medications will be packaged in double-dummy fashion with active medications administered in the morning of the QD treatments.

Figure 56: Sponsor's Diagram of Study 010 Design

The secondary objectives of this study were:

- To determine the 24-hour antihypertensive effect of SC-66110 relative to placebo after eight weeks treatment using Ambulatory Blood Pressure Monitoring (ABPM).
- To evaluate changes in trough cuff systolic blood pressure as compared to placebo.
- Compare the antihypertensive effect of eplerenone 50, 100, and 400 mg administered daily as a once a day (QD) dose or in divided doses twice a day (BID);
- To compare the antihypertensive effect of 100 mg spironolactone administered in divided doses (50 mg each) with placebo.

- To evaluate changes in plasma renin and serum aldosterone levels after eight weeks of treatment with SC-66110, relative to placebo.

- Evaluate the effect of eplerenone on sexual function as compared to placebo.

Reviewer's comment: Note that the objectives do not include comparing eplerenone to spironolactone. This latter comparison is of great clinical interest. The last secondary objective, evaluating the effect of eplerenone on sexual function, is not achievable with this study design. Some of the sexual side effects of spironolactone and presumably eplerenone, e.g., gynecomastia, are delayed and may not manifest themselves during an 8-week treatment period.

B.1.3.2 Number of Subjects and Randomization

The protocol originally specified that a sufficient number of subjects will be enrolled to ensure that a total of 350 patients are randomized to the double-blind treatment period; i.e., 50 patients to each of the seven groups. This sample size provides 80% power to detect a true mean difference of 4.5 mmHg for change from baseline in trough cuff diastolic blood pressure between placebo and each SC-66110 QD dose group. Randomization was by computer-generated randomization schedule, stratified by center, prepared by the sponsor prior to the start of the study.

B.1.3.3 Inclusion and Exclusion Criteria

The criteria for inclusion to the screening period were:

1. Male and female patients aged 21-80 inclusive. Female patients must have been post-menopausal, surgically sterile, or practicing barrier contraception.

2. History of mild to moderate hypertension currently controlled with medication, or, if untreated, mild to moderate hypertension defined as seated diastolic blood pressure (seDBP) of >95 mmHg and <115 mmHg.

3. Documented informed consent must have been obtained prior to admission.

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

1. Mild to moderate hypertension defined as untreated seated diastolic blood pressure (seDBP) of >95 and <115 mmHg.

2. A mean 24-hour DBP of >85 mmHg as assessed by ambulatory blood pressure monitoring at the end of the placebo phase.

3. Patients demonstrated better than 80% compliance with dosage instructions (measured by pill counting) during the single-blind placebo run-in period.

The exclusion criteria were the following:

1. Secondary hypertension, severe hypertension, malignant hypertension with or without hypertensive retinopathy.

2. Regular use of any systemic medication that might affect blood pressure e.g., anti-depressants, other antihypertensives, other steroids, cough and cold medications, etc.

Reviewer's comment: While the protocol defines "regular use of ... other antihypertensives" as an exclusion criteria, it later discusses discontinuing antihypertensives during the run-in period. .

3. Regular use of NSAIDs.

4. Myocardial infarction, PTCA, CABG, angina pectoris, or intermittent claudication within the past six months.

5. Severe aortic or mitral valvular disease with cardiac arrhythmia requiring medical treatment or causing hemodynamically relevant disturbances.

6. Hypertrophic cardiomyopathy or history of congestive heart failure, NYHA classification II-IV, requiring digoxin or diuretic therapy.

7. Stroke or transient ischemic attack within the past six months or any clinically significant cerebrovascular disease that may interfere with the conduct of the study.

8. Insulin or oral antidiabetic agent dependent diabetes mellitus or fasting blood sugar >200 mg/dL.

9. Acute or chronic hepatic disease i.e., liver enzymes above 1.5 times the upper limit of normal or serum bilirubin greater than the upper limit of normal or serum albumin lower than 3.0 g/dL.

10. Serum creatinine greater than 1.5 mg/dL or serum potassium greater than 5.0 mEq/L; or acute renal insufficiency or significant impairment of renal function (calculate creatinine clearance using the Cockcroft and Gault formula, and exclude anyone with a clearance less than 50 ml/min).

11. Abnormal clinical laboratories which in the investigator's opinion precludes the patient from safely participating in this study.

12. History of alcohol or drug abuse or current diagnosis of an abuse problem.

13. Any condition which in the investigators opinion makes participation in this study not in the best interest of the patient.

14. Known hypersensitivity to spironolactone, steroids such as cortisone, estrogens, progesterones, etc.

15. Use of any investigational medication other than the study medication 30 days prior to and during study participation.

16. Previous admission to this study.

17. Workers on night shift.

18. Excessive obesity i.e., upper arm circumference greater that 42 cm.

B.1.3.4 Dosage and Administration

This study used a double-dummy technique. The patients were instructed to take two capsules (one each from Bottles A and B) and two tablets (both from Bottle C) in the morning upon arising, and take two capsules (one each from Bottles D and E) and two tablets (both from Bottle F) 12 hours later in the evening. Study medication could be taken without regard to mealtimes. The morning dose was to be taken between 6:00 and 10:00 a.m. in the morning, upon arising. The evening dose was to be taken 12 hours later. For the once daily arms the active drug was included in the morning dose.

B.1.3.5 Duration and Adjustment of Therapy

The double-blind treatment period was eight weeks and the dosages were fixed. However, a patient could be discontinued for a variety of reasons: inability to tolerate study medication, treatment failure and need to prescribe other antihypertensive medications, intervening non-study medication related adverse events or intercurrent illness which makes study participation impossible, inclusion/exclusion violations discovered during the course of the study, administrative reasons, or any other reason which in the opinion of the investigator was to protect the best interest of the patient.

B.1.3.6 Safety and Efficacy Endpoints

The primary efficacy endpoint was change from baseline in seated cuff diastolic blood pressure measured at trough (24 hours postdose) after eight weeks of double-blind treatment. Trough systolic and diastolic values are the average of the corresponding two values recorded at each visit.

Secondary blood pressure efficacy endpoints are listed in the Pre-Specified Analyses section below. The protocol also discusses examining changes in neurohormonal profiles, i.e., plasma renin and serum aldosterone levels.

The protocol briefly discusses adverse event reporting. It describes monitoring vital signs and clinical laboratory tests. The sponsor's schedule of observations and procedures is shown in the figure below.

	Pretreatment (Screening Exam)	Single-Blind Treatment (Placebo Lead-In)			Double-Blind Treatment		
WEEK	-6 to -4	-4	-[redacted]	0	2	4	8 or Final Visit
Visits	1	2	3	4[f]	5	6	7
Observations/Procedures[a]							
Medical History	x						
Physical Examination	x						x
ECG 12-Lead	x			x			x
Heart Rate and Blood Pressure (trough readings)[b]	x	x	x	x[g]	x	x	x
Fasted Clinical Safety Lab	x			x	x	x	x
ABPM				x[g]			x
Steroid Profile[c]				x		x	x
Neurohormone Profile[d]				x		x	x
Dispense Drug		x[e]		x	x	x	
Medication Compliance			x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x
Concurrent Medications		x	x	x	x	x	x
Sexual Dysfunction Questionnaire		x		x			x

a. Informed consent was obtained prior to any test, procedure, or change in medication.
b. Cuff BP was measured sitting and standing.
c. Blood sample for steroid profile
d. Blood sample for neurohormone profile.
e. Drug dispensed was placebo.
f Randomization to double-blind study number occurred at Visit 4, Day 1, (i.e., end of Placebo Lead-In).
g. Final eligibility was determined on Visit 4, Day 1 (before randomization) based upon inclusion criteria.

Figure 57: Sponsor's Schedule of Observations and Procedures

B.1.3.7 Statistical Considerations

B.1.3.7.1 Sample Size Calculations

Enough patients were to be enrolled during the placebo run-in period to ensure that at least 50 patients were randomized to each of the eight treatment groups. This sample size gives at least

80% power to detect a true mean difference of 4.5 mmHg between placebo and each SC-66110 QD dose group. This is based on the following assumptions: (i) the standard deviation for change from baseline in cuff diastolic blood pressure at trough plasma levels is approximately 8 mmHg, (10) and (ii) each SC-66110 dose group are compared to placebo using a sequential testing strategy described below.

Reviewer's comment: Ultimately 409 patients were randomized and received at least one study drug dose and post-treatment evaluation, yielding about the targeted 50 patients per treatment group. Note, however, that the primary efficacy analysis pools the QD and BID eplerenone groups for the same total daily dose to double the group sizes for the eplerenone groups.

B.1.3.7.2 Analysis Cohorts

The protocol states that "All analyses will be on an "intention-to-treat" basis, i.e., data from all randomized patients will be used in the analyses. In each analysis, missing values will be imputed using the last-observation-carried-forward (LOCF) method." However, the Integrated Clinical and Statistical Report for the study states that "The ITT Cohort included all randomized patients who took at least one dose of study medication and who completed at least one post Baseline efficacy evaluation."

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

The safety analysis was to include all subjects randomized to the study and have taken at least one dose of double-blind treatment.

B.1.3.7.3 Pre-specified Analyses

The protocol (with amendments) has the following description of the primary efficacy analysis:

"For each patient, the change from baseline in cuff diastolic blood pressure measured at trough plasma levels after eight weeks of double-blind treatment will be computed. Using this as the dependent variable, an analysis of variance (ANOVA) will be performed with treatment and center and treatment by center interaction terms in the linear model and the baseline value serving as a covariate. To prevent artifactual effects of severe imbalances among centers with respect to patient numbers, small centers will be pooled prior to analysis. The pooling algorithm will be such that, after pooling, the ratio of the largest to smallest center size will be at most two.

"Treatment comparisons will be based on least squares means obtained via a SAS type III analysis with baseline value, treatment, center and the treatment by center interaction being the terms in the linear model. Note that this type III analysis assigns equal weight to each center. Small centers will be pooled prior to analysis, as described earlier.

"If the p-value associated with the treatment by center interaction term is 0.10 or less, differences between treatment within centers will be examined to determine the source of the interaction.

"To ensure that the overall false positive rate is at most 5% (two-tailed) for the primary family of comparisons, the following sequential testing strategy will be used, (11,12) based on the assumption that an increase in the SC-66110 QD dose will lead to an as good or better anti-hypertensive effect. First, the placebo group will be compared to the SC-66110 400 mg QD group using a linear trend contrast. If not significant at the 5% level, we stop further testing. In that case, all SC-66110 doses will be declared not significantly different from placebo. If significant, however, the 400 mg QD group will be declared significantly different from placebo and the 100 mg QD group will then be compared to the placebo group using a linear trend contrast. If this test is not significant at the 5% level, we stop further testing. In this case, only the 400 mg QD dose will be declared significantly different from placebo. If significant, however, 100 mg QD will also be declared significantly different from placebo and the 50 mg QD group will then be compared to placebo using a linear trend contrast. This sequential testing will continue until a statistically insignificant result is reached at the 5% level or until all SC-66110 QD doses have been declared significantly different from placebo. For completeness, contrast coefficients for the planned sequence of "pairwise" comparisons are provided below (assuming that the groups are ordered as placebo first followed by the SC-66110 QD increasing dose groups).

Comparison	Contrast coefficients
placebo versus 400 mg QD	-11 -7 -3 21
placebo versus 100 mg QD	-1 0 1 0
placebo versus 50 mg QD	-1 1 0 0

"The above analysis will be repeated for the secondary efficacy variables indicated below.

- change in trough cuff systolic blood pressure.
- change in 24 hour mean diastolic blood pressure.
- change in 24 hour mean systolic blood pressure.

"Response to the SC-66110 BID dose will also be evaluated using the above sequential testing procedure applied to both primary and secondary efficacy variables.

"In addition, for the primary as well as the secondary efficacy variables, the following additional comparisons will be performed: (i) BID versus QD dosage regimens at each SC-66110 total daily dose level (50, 100, and 400 mg); and (ii) placebo versus spironolactone 50 mg BID. These specific comparisons will be made using contrast-based t-tests within the ANOVA described earlier, with per comparison two-tailed α=0.05."

B.1.4 Results

B.1.4.1 Study Implementation

B.1.4.1.1 Disposition of Subjects

The disposition of the cases, excluding center US0003, is shown below in the table.

Table 61: Reviewer's Summary of Disposition of Cases

Stage	0	025 BID	050	050 BID	100	200 BID	400	SL	Total
Screened	NA	NA	NA	NA	NA	NA	NA	NA	720
Randomized	53	55	54	54	49	48	56	48	417
Excluded (Center US0003)	3	3	2	3	2	3	2	2	20
Treated at least once	50	52	52	51	47	45	54	46	397
Evaluated at least once	50	51	52	50	46	45	53	45	392
Adverse event	1	1	4	1	1	1	0	2	11
Failed	2	2	0	0	2	0	0	1	7
Lost	0	0	2	0	0	0	0	0	2
Noncompliant	1	4	2	5	2	0	2	4	20
Violation	0	0	1	0	0	1	0	1	3
Completed	46	45	43	45	42	43	52	38	354

For comparison the disposition of cases for the excluded site US0003 is shown in the following table:

Table 62: Reviewer's Summary of Disposition of Cases for Excluded Site US0003

Stage	0	025 BID	050	050 BID	100	200 BID	400	SL	Total
Randomized	3	3	2	3	2	3	2	2	20
Treated at least once	2	2	2	3	2	3	1	2	17
Evaluated at least once	2	2	2	3	2	3	1	2	17
Lost	1	1	0	0	0	0	1	0	3
Noncompliant	0	0	0	0	0	1	0	0	1
Completed	2	2	2	3	2	2	1	2	16

Reviewer's comment: Site US0003 cases were distributed quite evenly among the treatment groups. The completion rate for that site (80 percent) was slightly lower than that for the study as a whole (89 percent) but otherwise the disposition of cases for that site don't suggest any special problems with it. The completion rate for the study and the small number of cases lost or with violations are acceptable.

B.1.4.1.2 Subject Demographics and Baseline Characteristics

The distribution of various baseline characteristics among the treatment groups is shown in the table below.

Table 63: Reviewer's Selected Baseline Characteristics by Treatment Group

Factor	N	Value	0	025 BID	050	050 BID	100	200 BID	400	SL	P*
Age	397	mean	53.8	55.2	54.5	52.7	52.0	53.4	52.8	53.0	0.72
Age	397	median	54	56	55.5	53	52	54	52	49.5	0.76
Male	277	%	60%	77%	73%	73%	60%	73%	65%	78%	0.27
White	311	%	74%	83%	81%	78%	77%	84%	72%	78%	0.83
Black	80	%	26%	15%	19%	20%	23%	13%	24%	20%	0.83
BMI	397	mean	29.7	30.7	29.9	31.1	30.1	29.1	29.7	30.0	0.66
SBP	397	mean	153	156	155	153	153	155	152	154	0.91
DBP	397	mean	404	404	404	404	404	402	402	404	0.81
Aldosterone	384	mean	10.5	11.3	10.6	9.9	9.5	10.0	9.5	9.3	0.83
Creatinine	397	mean	1.0	1.1	1.1	1.0	1.0	1.1	1.1	1.0	0.23
Direct renin	381	mean	20.6	34.9	35.1	23.3	22.2	18.4	20.3	26.5	0.08
Potassium	397	mean	4.3	4.2	4.2	4.2	4.2	4.2	4.2	4.2	0.97
Total renin	380	mean	114.8	150.0	142.0	136.0	130.0	127.5	136.9	106.3	0.31

*P by ANOVA for continuous, Chi square for categorical variables

The mean age was 53.4 and the median 54 with a range from 31 to 77 for the 397 randomized and not excluded cases. 53 cases were age 65 or older. The age distribution is shown in the figure below:

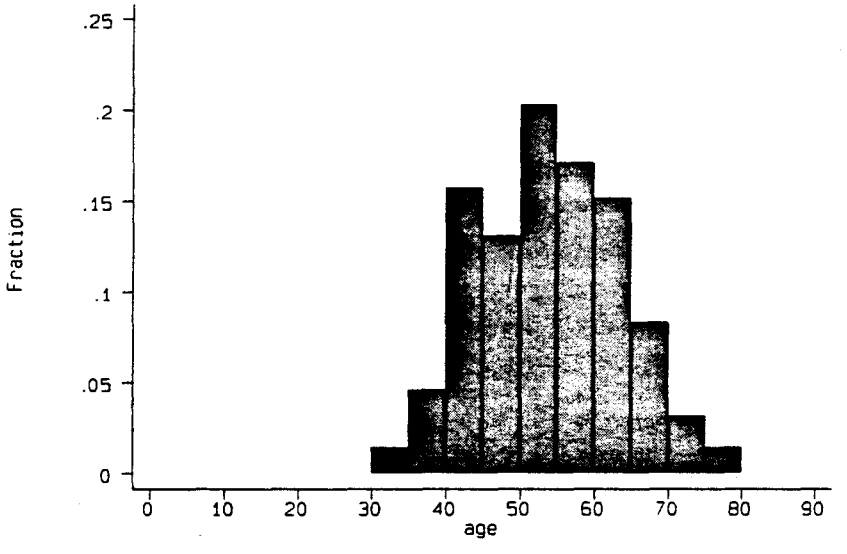


Figure 58: Reviewer's Study Patient Age Distribution

The cross-tabulation of cases by race and gender is shown in the following table:

Table 3: Reviewer's Study Cases by Race and Gender

Race	Female	Male	Col Totals
Asian	2	3	5
Black	37	43	80
White	70	212	282
Hispanic	11	18	29
Other	0	1	1
Row Totals	120	277	397

Reviewer's comment: The baseline characteristics, both those noted in the table above and others, appear to be balanced among the treatment groups. There do not appear to be any baseline characteristic maldistributions such that interpretation is confounded or adjustment is necessary. There are a reasonable number of elderly included in the study (53 cases 65 years old or older) but no pediatric patients. The gender distribution is fairly even by race with one major exception: For whites, males dominate. White males comprise a small majority (53 percent) of all cases.

B.1.4.1.3 Conduct

B.1.4.1.3.1 Monitoring

Sponsor monitors were to make site visits, but the frequencies or details of the visits are not specified. A separate DSMB is not described. The sponsor monitor adjudicated the importance of adverse events and protocol violations and reviewed the data quality.

The sponsor describes its data quality assurance as follow: "All CRF entries relating to safety or efficacy were verified against the source documentation at each study site. The information on the CRFs was entered into the _____ via double key verification. Data were checked using a computerized consistency report. All missing values, and values that were outside of specified ranges, invalid, or inconsistent with other data were queried. The database was audited against the CRFs."

The sponsor noted verbally that no problems were noted during the study with site US0003 but details of site visits or audits are not provided in the NDA.

B.1.4.1.3.2 Protocol Violations

Seven patients had ABPM values below the 85 mm Hg required for entry into the double-blind segment: one eplerenone 50 mg QD, one eplerenone 100 mg QD, one eplerenone 25 mg BID, two eplerenone 50 mg BID, and two spironolactone 50 mg BID. Fourteen patients had DBP values below the 95 mm Hg required for entry into the Double-Dose Assessment Period as