summarized below. These patients were allowed to enter study either in error or were given waivers; of these patients, most (9) had a DBP >90 mm Hg and none had a DBP <88 mm Hg.

	Placebo BID	Eplerenone QD			Eplerenone BID			Spirono-lactone BID
	N=53	N=54	N=49	N=56	N=55	N=54	N=48	N=48
		50 mg	100 mg	400 mg	25 mg	50 mg	200 mg	50 mg
No. patients	0	3	1	4	1	1	1	3

Figure 59: Sponsor's Patients Retained Despite Low Screening Blood Pressures

Three patients were terminated because of pre-existing protocol violations: one eplerenone 50 mg QD patient had an ABPM equal to 78 mm Hg, one eplerenone 200 mg BID patient had a creatinine clearance that did not meet the entry criteria, and one spironolactone 50 mg BID patient received testosterone injections once every third week throughout the study period.

Seventeen patients were terminated because of protocol noncompliance as summarized below. The one patient noncompliant in the eplerenone 200 mg BID group was from site US0003.

Reasons included withdrawal of consent, out of assessment window, lack of compliance, and ABPM below the inclusion criteria (85 mm Hg).

	Placebo BID	Eplerenone QD			Eplerenone BID			Spirono-lactone BID
	N=53	N=54	N=49	N=56	N=55	N=54	N=48	N=48
		50 mg	100 mg	400 mg	25 mg	50 mg	200 mg	50 mg
No. patients	1	2	1	1	3	4	1	4

Figure 60: Sponsor's Patients Terminated Because of Protocol Noncompliance

B.1.4.1.3.3 Dosing

All dosing was blinded fixed dose without adjustment. Patient compliance was measured by counting the study medication returned to the study site at the patient visits.

B.1.4.1.3.4 Blinding

Patients were assigned, in the order in which they were enrolled into the study, to receive their allocated treatment according to a sponsor-prepared computer-generated randomization schedule. Investigational drug supplies were provided by Searle, Skokie, Illinois, and consisted of capsules (eplerenone) or tablets (spironolactone) and placebo capsules or tablets identical in size and appearance to a corresponding active drug dosage level. This study used a double-dummy technique. Study drugs were dispensed in six vials labeled A through F. Patients were instructed to take medications daily from each vial as described under the Dosage and Administration section above.

Reviewer's comment: The blinding scheme appears adequate. No blinding violations were reported.

B.1.4.2 Efficacy

B.1.4.2.1 Blood Pressure Endpoints

B.1.4.2.1.1 Sponsor's Presentation of Blood Pressure Endpoints

The sponsor's description of the blood pressure analyses is the following:

"The primary measure of efficacy was the change from Baseline in cuff DBP measured at trough plasma levels after 8 weeks of double-blind treatment. The primary comparison was between total daily dose of eplerenone 50, 100, and 400 mg and placebo. For each patient, the change from Baseline in cuff DBP measured at Week 8 (or Early Termination for those prematurely withdrawn) was used as the dependent variable in an analysis of covariance (ANCOVA) model. The model included factors for treatment and center along with Baseline measurement as the covariate. The adjusted means obtained from this model will be reported in the statistical analyses. Primary treatment comparisons were based on least squares means obtained via a SAS Type III analysis with Baseline value, treatment and center in the linear model. This Type III analysis assigns equal weight to each center, with small centers pooled as described under Pre-Specified Analyses above."

"The secondary measures of efficacy after 8 weeks of double-blind treatment were the change from Baseline in trough cuff SBP, the change from Baseline in 24-hour mean DBP and SBP, and the change from Baseline in trough (the last 4 hour segment of the 24 hours of the 24-hour ABPM measurement) DBP and SBP using the ABPM device. The above analysis for the primary efficacy variable was repeated for these secondary efficacy variables. Response to the eplerenone BID dosing regimen was also evaluated using the sequential testing procedure described above. In addition, for the secondary efficacy variable, the following additional comparisons were performed: (1) BID versus QD dosage regimens at each eplerenone total daily dose level (50, 100 and 400 mg) and (2) placebo versus spironolactone 50 mg BID. These specific comparisons were made using contrast-based t-tests within the linear model described above, with per comparison two tailed α=0.05."

The sponsor's summary of the blood pressure endpoint results is the following:

"In general, reductions in both mean trough seated DBP and SBP were observed for all dose levels of eplerenone compared to placebo. Generally, there was a greater reduction in DBP and SBP with increasing dose levels of eplerenone. Greater decreases in sitting and standing DBP were seen in the 50 mg BID eplerenone group as compared to the 100 mg QD eplerenone group and greater decreases in DBP and SBP trough ambulatory BP were observed in the 200 mg BID eplerenone group as compared to the 400 mg QD eplerenone group."

MEAN CHANGE IN BLOOD PRESSURE (mm Hg) FROM BASELINE AT FINAL VISIT								
	Placebo	Eplerenone QD			Eplerenone BID			Spironolactone
	BID	50 mg	100 mg	400 mg	25 mg	50 mg	200 mg	50 mg BID
Parameter								
Sitting DBP	-1.0	-4.4	-4.5	-8.9	-4.5	-7.8	-9.4	-9.5
Sitting SBP	2.0	-4.6	-8.0	-14.1	-8.9	-11.8	-15.8	-17.6
Standing DBP	-0.7	-3.6	-4.2	-8.1	-4.0	-8.2	-8.0	-9.3
Standing SBP	2.8	-4.3	-8.2	-13.9	-7.6	-12.1	-13.8	-16.1
24-hour ABPM DBP	0.6	-4.8	-6.1	-7.6	-3.9	-7.2	-9.3	-8.9
24-hour ABPM SBP	0.0	-7.1	-9.7	-13.0	-7.4	-12.6	-15.9	-15.7
Trough 24 Hour ABPM DBP	-0.9	-3.9	-6.4	-8.1	-4.8	-7.3	-12.4	-9.7
Trough 24 Hour ABPM SBP	-1.6	-6.5	-10.2	-13.2	-8.7	-12.0	-20.5	-17.3

Figure 61: Sponsor's Tabulation of Mean Blood Pressure Changes

"Based on statistical analyses, the reductions in mean sitting and standing DBP and SBP observed in the eplerenone treatment groups were statistically significantly different ($p<=0.041$) compared to placebo for all dose levels except for mean standing DBP in the 100 mg QD eplerenone dose group ($p=0.058$). Over the range of eplerenone doses, adjusted mean decrease in Baseline BP at Final Visit varied from -4.4 mm Hg to -8.9 mm Hg for cuff sitting DBP and -4.4 mm Hg to -15.0 mm Hg for cuff sitting SBP. The range of adjusted mean decrease in Baseline standing DBP and SBP at Final Visit varied from -3.7 mm Hg to -8.0 mm Hg for DBP and from -3.6 mm Hg to -14.5 mm Hg for SBP. With the exception of the greater reduction in sitting and standing DBP in the 50 mg BID treatment group compared to the 100 mg QD treatment group ($p=0.036$ sitting, $p=0.012$ standing), there were no statistically significant differences between QD and BID dosing regimens ($p>=0.114$) (Tables 8.1-8.2). Analyses of 24-hour and trough ambulatory mean reductions in DBP and SBP were statistically significant across all dose levels ($p<=0.011$) as compared to placebo except for the trough ambulatory DBP and SBP in the 50 mg QD dose level, and trough ambulatory DBP in the 25 mg BID dose level ($p>=0.051$). Adjusted mean decrease in Baseline BP at Final Visit as measured during 24-hour ABPM ranged from -4.1 mm Hg to -9.0 mm Hg for DBP and from -6.2 mm Hg to -16.1 mm Hg for SBP in eplerenone treated patients. The range of adjusted mean change in Baseline trough ambulatory DBP and SBP at Final Visit varied from -4.1 mm Hg to -12.1 mm Hg for DBP and from –5.2 mm Hg to -20.4 mm Hg for SBP. There were no statistically significant differences in the reduction of trough ambulatory SBP and DBP between QD and BID dosing regimens ($p>0.128$) except in the 200 mg BID treatment group compared to the 400 mg QD treatment group ($p<=0.033$), (Tables 8.3 and 8.4).

"Spironolactone 50 mg BID was associated with clinically significant reductions in DBP and SBP from Baseline at Weeks 2, 4, and 8, and these reductions were statistically significant as

compared to placebo at Week 8 (Final Visit.) In general, eplerenone at doses of 400 mg QD and 200 mg BID was associated with decreases in mean DBP and SBP equivalent to those observed in the spironolactone group (Tables 6, 7, and 8)."

B.1.4.2.1.1 Reviewer's Analysis of Blood Pressure Endpoints

The reviewer analyzed the data sets included in the NDA for the endpoints of changes in cuff blood pressures. The reviewer's results for the unadjusted mean changes in cuff blood pressures for the 392 cases in the "ITT" analysis set (randomized and receiving treatment and having at least one post-treatment evaluation and not excluded) are listed in the table below.

Table 3: Reviewer's Analysis of Unadjusted Mean Changes in Cuff Blood Pressures, 392 "ITT" Cases

Treatment	N	Seated		Standing	
		SBP	DBP	SBP	DBP
PLACEBO	50	2.4	-1.0	3.3	-0.8
EPLERENONE 50 MG QD	52	-4.0	-3.8	-3.5	-3.1
EPLERENONE 25 MG BID	51	-8.8	-4.2	-7.4	-3.7
EPLERENONE 100 MG QD	46	-7.6	-4.1	-7.8	-3.9
EPLERENONE 50 MG BID	50	-11.2	-7.1	-11.3	-7.5
EPLERENONE 400 MG QD	53	-14.1	-8.7	-13.9	-7.9
EPLERENONE 200 MG BID	45	-16.3	-9.5	-14.2	-8.0
SPIRONOLACTONE 50 MG BID	45	-17.8	-9.4	-16.2	-9.3

The reviewer's results in the table above are unadjusted means. Because the sponsor states that the NDA analyses are adjusted means from an ANCOVA, the reviewer performed the ANCOVA pre-specified in the protocol for the primary endpoint of change in seated DBP. The reviewer performed the ANCOVA using SAS JMP software with model effects of baseline DBP, treatment group, site, and treatment*site. The results for the adjusted means for this analysis are identical to those in the sponsor's table when performed on the 409 "ITT" cases including center US0003. The statistical results are consistent with the sponsor's remarks about statistical significance of findings. The results change minimally when the 392 "ITT" cases excluding center US0003 are used.

The reviewer also repeated the above analyses using the "as randomized" set (397 cases), i.e., the true intention-to-treat set, rather than the "ITT" analysis set of 392 cases. The results differ minimally and the interpretations of the results do not change if the "as randomized" set is used.

Note that in Table 3 the treatment effects for the eplerenone BID groups appear to be consistently higher than the corresponding QD group. However, BID dosing was not a statistically significant factor in the ANCOVA analyses. The relative efficacy of QD vs. BID dosing is explored in more depth below with regard to the ABPM data. Gender and race (white vs. nonwhite) are also not statistically significant covariates in the ANCOVAs. Interestingly, age

is a significantly significant covariate for both eplerenone and spironolactone, with treatment effect increasing slightly with age.

The reviewer analyzed the ambulatory blood pressure monitoring (ABPM) data as follows: First the reviewer scanned the ABPM data set provided. The sponsor provided ABPM data for "DAY0" and "FINAL" (three patients also had data for a "VISIT6.1"). For the 392 randomized and treated patients with at least one post-treatment evaluation, 392 patients had 43,726 readings recorded on DAY0 and 359 patients had 40,260 readings recorded for FINAL. These 359 patients had 39,988 readings recorded for DAY0. The sponsor also included in the data set a field named "OTHDESC" with comments about suspicious data. The readings flagged as bad appeared to be completely erroneous data, i.e., heart rate and BP of 0. The reviewer rejected the data flagged by the sponsor as bad. The resulting "cleaned" data had 31,694 recordings for DAY0 and 31,124 for FINAL. When summarized by hour, a mean of 353 patients had recordings for both time periods for a given hour, with a range from 345 to 358. The bad recordings appeared to be evenly distributed by treatment group. The reviewer used these "cleaned" data for the analyses presented below.

Next the reviewer examined time plots of the data. The ABPM data showed the expected diurnal variation. The diurnal patterns for all groups and time periods appeared similar. The pattern for DBP in the placebo group at baseline is shown in the figure below. A smooth curve has been fitted to the points using the lowess method in Stata version 4.0.

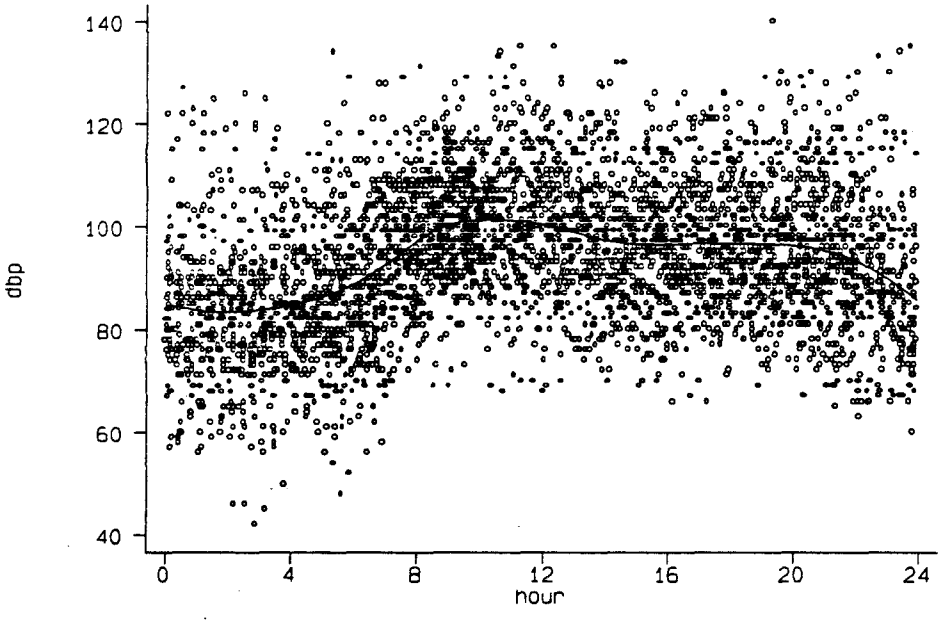


Figure 62: Reviewer's Diurnal Variation in DBP for Placebo Group at Baseline

To make the data more manageable, the reviewer averaged all readings for each hour and then subtracted for each patient the average value for the hour at baseline from the value for the corresponding hour for the final day. A plot of the results for the changes in DBP from baseline to final is shown for the placebo, eplerenone 50 mg BID, and eplerenone 100 mg QD groups below, followed by a figure combining the curves from these three plots. Similar plots for the other eplerenone dosage levels and for combined QD and BID dosages follow. The discussion continues after the figures.

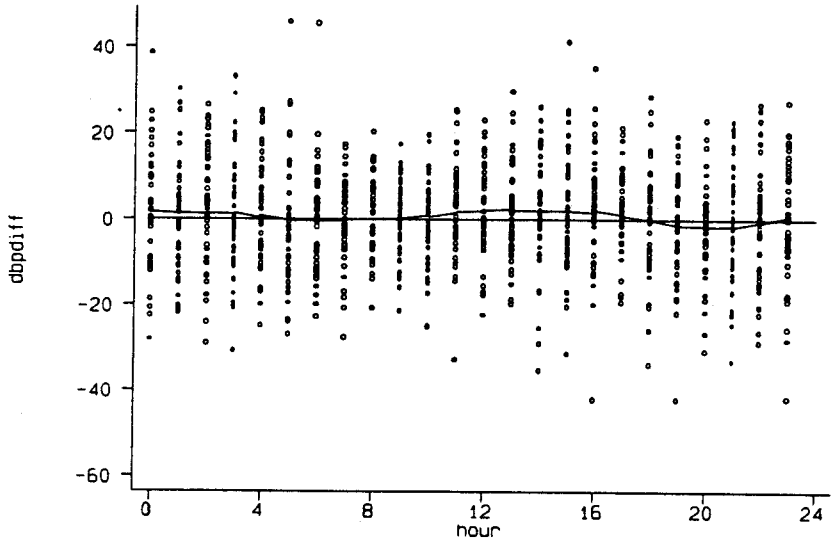


Figure 63: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo Group

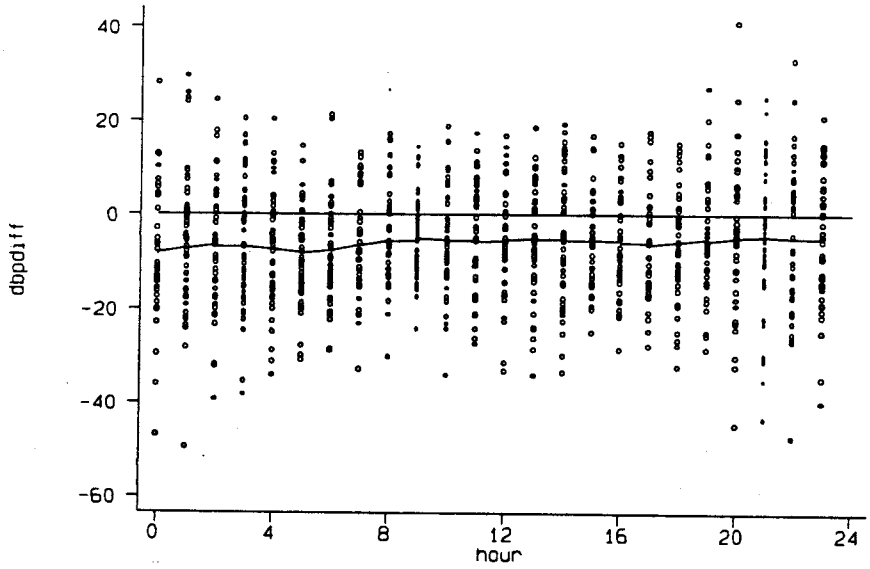


Figure 64: Reviewer's Diurnal Variation in DBP Change from Baseline for 100 mg QD Group

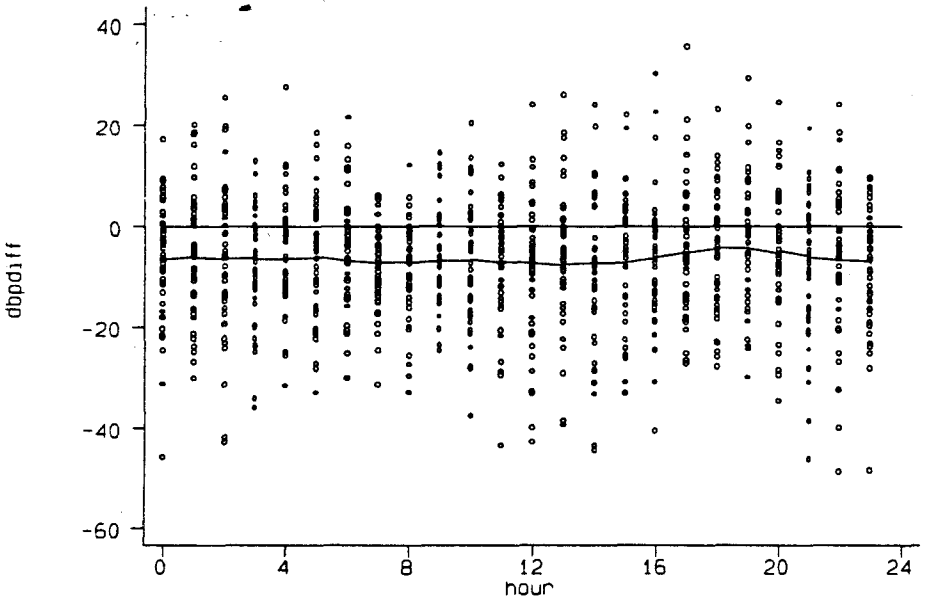


Figure 65: Reviewer's Diurnal Variation in DBP Change from Baseline for 50 mg BID Group

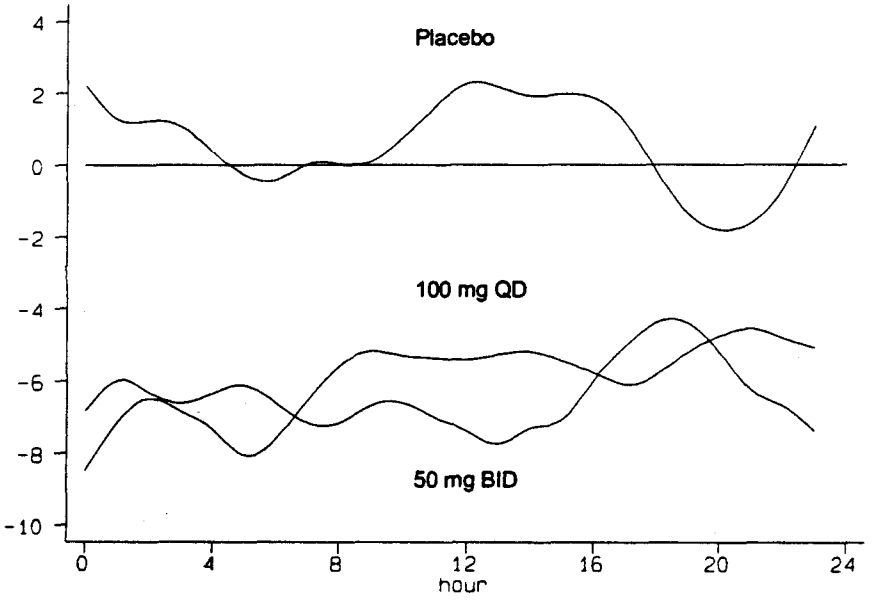


Figure 66: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Eplerenone 100 mg Dosages

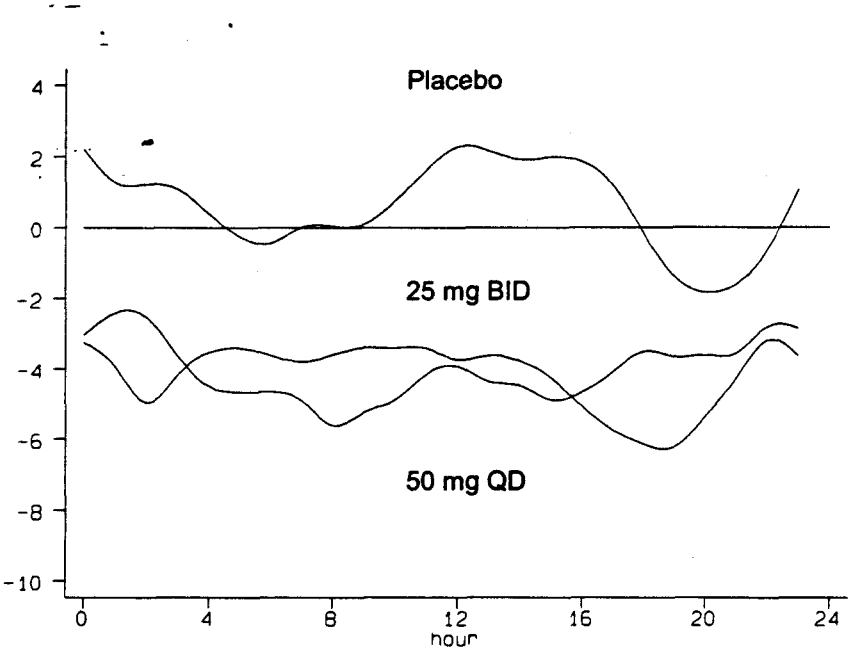


Figure 67: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Eplerenone 50 mg Dosages

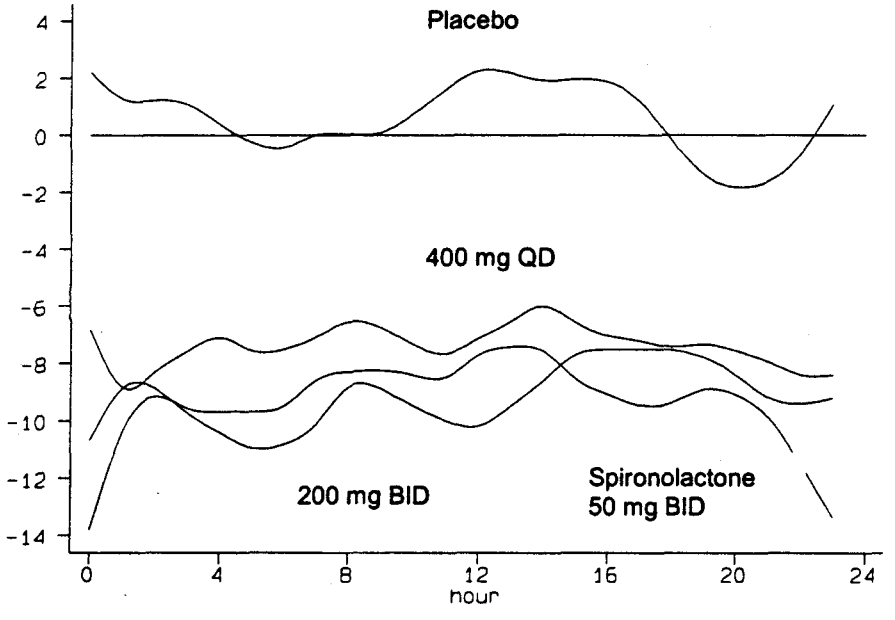


Figure 68: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Eplerenone 400 mg Dosages and Spironolactone 50 mg BID

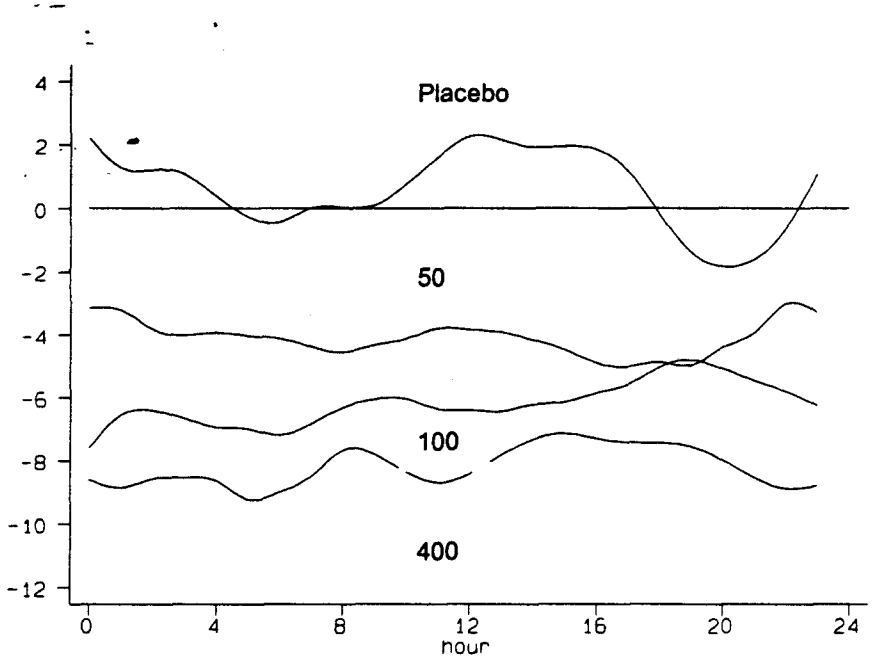


Figure 69: Reviewer's Diurnal Variation in DBP Change from Baseline for Placebo vs. Combined BID and QD Eplerenone Dosages

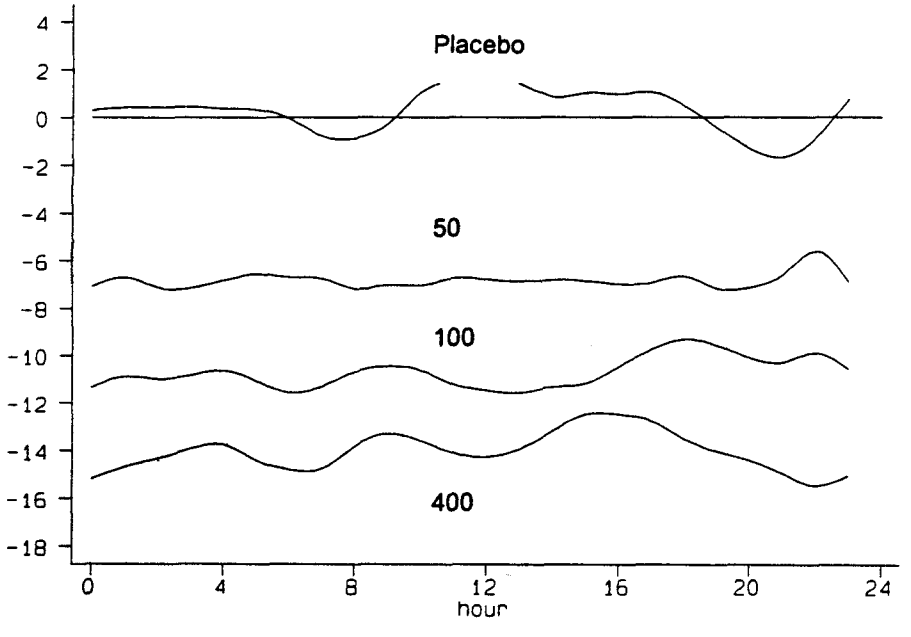


Figure 70: Reviewer's Diurnal Variation in SBP Change from Baseline for Placebo vs. Combined BID and QD Eplerenone Dosages

The preceding graphical displays of the ABPM data confirm the statistical analyses of the cuff BP data and the sponsor's interpretations of the ABPM data. Eplerenone has a dose-response effect for reducing diastolic and systolic blood pressure, shown best by the plot of diurnal variation in SBP change from baseline for placebo vs. combined BID and QD eplerenone groups. There does not appear to be a consistent difference between the QD and BID dosing regimens. Although not shown except in the last figure, eplerenone effects upon SBP are similar to those shown upon DBP with a slighter larger treatment effect upon SBP than DBP.

All of the above ABPM analyses were performed on the "per protocol" set of 375 patients with ABPM readings for both time periods. As a final test of the robustness of the data, the reviewer generated dummy data with BP differences of zero for all hours for the 42 patients missing the ABPM data. The treatment effects shown by this ITT approach are slightly less but still substantial. An example of the results for SBP dose response is shown in the figure below.

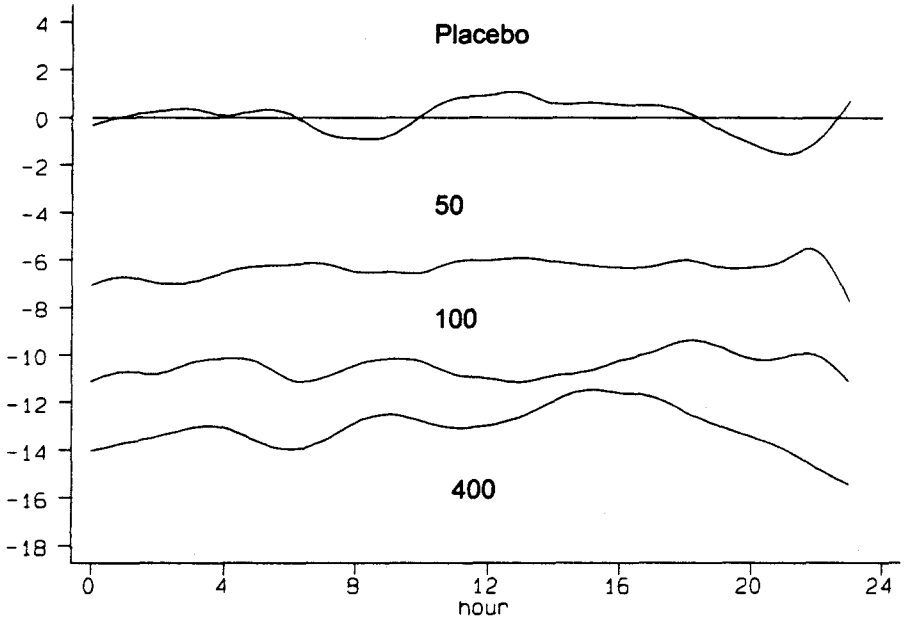


Figure 71: Reviewer's Diurnal Variation in SBP Change from Baseline for Placebo vs. Combined BID and QD Eplerenone Dosages for All Randomized Patients

The reviewer interprets these results as demonstrating that eplerenone has a definite, statistically significant antihypertensive effect. There appears to be a dose-response, with point estimates of reductions in seated DBP ranging from –4.2 for 50 mg QD to –9.4 for 200 mg BID. The reviewer agrees with the sponsor's conclusion that, with regard to the BP endpoints, spironolactone 50 mg BID is roughly equipotent with eplerenone 400 mg per day.

The time course to BP reduction is also clinically relevant. The changes in BP at 2, 4, and 8 weeks are shown in the table below.

Table 64: Sponsor's Mean Change from Baseline in BP at Each Visit

	Placebo	Eplerenone QD			Eplerenone BID			SL
		50	100	400	25	50	200	
SBP:								
Week 2	-5.5	-7.1	-6.9	-10.7	-11.6	-10.8	-17.3	-14.2
Week 4	-3.2	-8	-11.3	-12.5	-12.6	-11.7	-18.1	-18.4
Week 8	1.4	-5	-8.2	-14.1	-8.9	-11.8	-15.9	-17.6
DBP:								
Week 2	-4.9	-4.5	-4.5	-5.8	-5.5	-7.5	-8.4	-6.9
Week 4	-3.9	-5.7	-6.4	-8.3	-6.3	-7.5	-9.8	-8.9
Week 8	-1.3	-4.4	-4.8	-8.9	-4.9	-7.8	-9.5	-9.5

SL = spironolactone (From Tables 7.1 and 7.2)

The reductions in BP with eplerenone are almost fully developed at the week 2 visit. Note that the reductions are slightly higher typically at the week 4 visit than at the week 8 visit.

B.1.4.2.2 Secondary Neurohormonal Endpoints

The sponsor's description of the secondary neurohormonal endpoint analyses is the following:

"Changes from Baseline in neurohormone data (i.e., plasma renin (total and active) and serum aldosterone) were analyzed using ANCOVA methods similar to those described above for the evaluation of BP data. However, the pairwise comparisons based on the linear trend-testing approach were replaced with conventional pairwise comparisons since it could not be assumed that changes from Baseline in neurohormonal profiles would exhibit a monotonic dose-response relationship. Placebo versus eplerenone dose group comparisons were performed using Dunnett's test (two-tailed α=0.05). The other pairwise comparisons were performed using contrast-based t-tests, with per comparison two-tailed α=0.05. Since the difference between Baseline and Final Visit for plasma renin-total and plasma renin-active was found to be heavily skewed to the right (increasing), analyses were done on the log-transformed values."

"Treatment with eplerenone showed a dose-related increase in both total and active plasma renin at Week 8 or Final Visit (Table 11.1). The adjusted mean changes in total plasma renin are shown in Table 12.1, which also show a dose dependency. When these changes were analyzed following log transformation, there were statistically significant differences ($p<=0.05$) between Baseline and Final Visit for all doses of eplerenone treatment groups when compared to placebo (Table 12.1). The adjusted mean changes in active renin levels between Baseline and Final Visit are shown in table 12.1 and were statistically significant ($p<=0.05$) following log transformation, when compared to placebo for the 400 mg QD, 50 mg BID, and 200 mg BID eplerenone treatment groups (Table 12.1). There was a statistically significant difference in the adjusted mean change following log-transformation, in total plasma renin levels between the eplerenone 100 mg QD and 50 mg BID, and the eplerenone 400 mg QD and 200 mg BID treatment groups

(p<=0.025). There were no statistically significant differences in active plasma renin levels between the QD and BID dose regimens (p>=0.051) (Table 12.1).

"At Week 8 or Final Visit, there were increases in both total and active plasma renin in the spironolactone 50 mg BID group compared to Baseline (Table 11.1). The adjusted mean changes in total plasma renin (p<0.001), and active plasma renin (p<0.001) were statistically significant in the spironolactone 50 mg BID group when compared to the placebo group (Table 12.1)."

"There was a dose-related increase in serum aldosterone levels in all the eplerenone treatment groups between Baseline and Week 8 or Final Visit (Table 11.2). Compared to placebo, the increases in serum aldosterone levels at Final Visit were statistically significant (p£0.05) in the eplerenone 100 mg QD, 400 mg QD, 50 mg BID and 200 mg BID groups (Table 12.2). The only statistically significant difference between corresponding eplerenone QD and BID dose levels was the increase in aldosterone observed in the 200 mg BID group compared to that observed in the eplerenone 400 mg QD treatment group (p<0.001).

"Aldosterone levels in the spironolactone 50 mg BID treatment group also increased between Baseline and Week 8 or Final Visit (Table 11.2). Compared to placebo, the increase in serum aldosterone between Baseline and Week 8 or Final Visit seen in the spironolactone group was statistically significant (p<0.001) (Table 12.2)."

The reviewer's analyses confirmed the sponsor's findings above. In addition, the reviewer's analyses suggest that there may be a differential effect of eplerenone upon serum aldosterone and direct renin by gender and race. The results of the reviewer's ANOVAs, performed using Stata version 4.0, are listed in the tables below. No comparable differential is seen for spironolactone.

Table 65: ANOVA of Log Change in Serum Aldosterone for Eplerenone Groups

Source	Partial SS	df	MS	F	Prob > F
Model	99.0072752	4	24.7518188	27.80	0.0000
dose	79.6856818	1	79.6856818	89.50	0.0000
gender	3.34362419	1	3.34362419	3.76	0.0537
white	7.48648708	1	7.48648708	8.41	0.0041
baseval	7.83360331	1	7.83360331	8.80	0.0033
Residual	228.808244	257	.89030445		
Total	327.815519	261	1.25599816		

Table 66: ANOVA of Log Change in Direct Renin for Eplerenone Groups

```
                  Number of obs =      251     R-squared     =  0.1166
                  Root MSE      =  1.12366     Adj R-squared =  0.1022

      Source |  Partial SS    df       MS          F     Prob > F
-------------+------------------------------------------------------
       Model |  40.9847629     4  10.2461907       8.12     0.0000
             |
        dose |  27.5273974     1  27.5273974      21.80     0.0000
      gender |  8.17982945     1  8.17982945       6.48     0.0115
       white |  .259959552     1  .259959552       0.21     0.6504
     baseval |  4.03772837     1  4.03772837       3.20     0.0750
             |
    Residual |   310.59992   246   1.2626013
-------------+------------------------------------------------------
       Total |  351.584683   250  1.40633873
```

Table 67: ANOVA of Log Change in Total Renin for Eplerenone Groups

```
                  Number of obs =      253     R-squared     =  0.1315
                  Root MSE      =  1.11706     Adj R-squared =  0.1175

      Source |  Partial SS    df       MS          F     Prob > F
-------------+------------------------------------------------------
       Model |  46.8665577     4  11.7166394       9.39     0.0000
             |
        dose |  39.8193655     1  39.8193655      31.91     0.0000
      gender |  2.61747618     1  2.61747618       2.10     0.1488
       white |  3.15696638     1  3.15696638       2.53     0.1130
     baseval |  .459793293     1  .459793293       0.37     0.5444
             |
    Residual |  309.459559   248  1.2478208
-------------+------------------------------------------------------
       Total |  356.326116   252  1.41399253
```

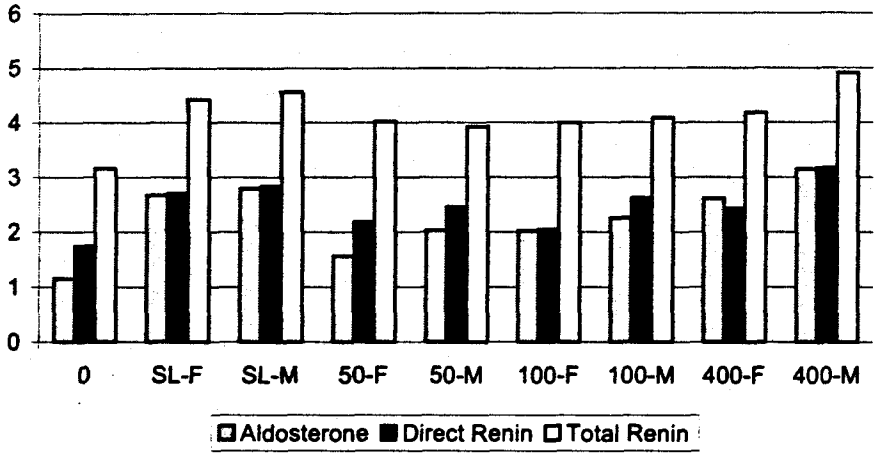


Figure 72: Log Changes in Neurohormones by Group and Gender

Reviewer's comment: Increases in all neurohormones show a dose-response relationship for eplerenone. The magnitudes of the spironolactone 50 mg BID increases are intermediate between the eplerenone 100 mg and eplerenone 400 mg daily dosages. There may be a gender difference for eplerenone for aldosterone and direct renin, with males showing a greater effect. However, because whites predominate in the males, it is not possible to differentiate clearly between a gender effect and a race effect in this study. Differential race and gender effects of eplerenone should be examined in other studies and in the combined data sets.

B.1.4.3 Safety

B.1.4.3.1 Exposure

A total of 417 patients received at least one dose of treatment drug if center US0003 is included; 370 patients completed the study. If center US0003 is excluded, 397 patients received at least one dose of treatment drug and 354 patients completed the study. The distributions of treated and completed patients by treatment groups are shown in the table Reviewer's Summary of Disposition of Cases in Section B.1.4.1.1. Adverse events from center US0003 are included in the analyses of adverse events.

B.1.4.3.2 Serious Adverse Events

Serious adverse events (SAEs) were reported in four patients: 2 (4 percent) eplerenone 50 mg QD, 1 (2 percent) eplerenone 400 mg QD, and 1 (2 percent) spironolactone 50 mg BID patients.

B.1.4.3.2.1 Deaths

There were no deaths reported.

B.1.4.3.2.2 Hospitalizations

The SAEs for which hospitalizations occurred were the following: chest pain in one eplerenone 50 mg QD patient, cellulitis in one eplerenone 50 mg QD patient, accidental injury (spider bite) in one eplerenone 400 mg QD patient, and syncope in one spironolactone 50 mg BID patient.

The investigators judged the cellulitis and the spider bit not to be related to the study drug; both resolved and the study drugs were continued.

The sponsor's description of the chest pain in one eplerenone 50 mg QD patient is as follows: "The patient, a 51 year old female, was randomized to receive eplerenone 50 mg QD. After two days of treatment, the patient was hospitalized because of cardiovascular pain. Evaluation was

unrevealing. An iron deficiency anemia was found which was thought to be related to heavy menses. An adenosine nuclear test three days later was non-diagnostic due to the presence of congenital ISVD. Ventilation/Perfusion Lung scan indicated a low probability of pulmonary embolus, similarly adenosine thallium scan showed no definite evidence of left ventricular ischemia. ECG indicated sinus tachycardia, AV conduction was within normal limits, and mild left axis moderately advanced or moderately severe left bundle branch block (LBBB). Follow-up ECG a day later indicated a slower rate but otherwise was unchanged. The patient was discharged three days after admission for follow-up on an out-patient basis. The Investigator considered that the event was of probable relationship to study drug."

Reviewer's comment: This isolated event is difficult to interpret as drug-related.

The other SAE, syncope in a patient on spironolactone, lead to discontinuation of the study drug, although the investigator judged the event to be of uncertain relationship to the study drug.

B.1.4.3.2.3 Other serious adverse events

There were no SAEs reported other than the four leading to hospitalization described above.

B.1.4.3.3 Events Leading to Discontinuation

The sponsor's summary of events leading to discontinuation is shown in the figure below:

	PLACEBO (N= 53)	EPLERENONE 50MG QD (N= 54)	EPLERENONE 100MG QD (N= 49)	EPLERENONE 400MG QD (N= 56)
ADVERSE EVENT				
CHEST PAIN	1 (2%)	1 (2%)	0 (0%)	0 (0%)
HEADACHE	0 (0%)	0 (0%)	1 (2%)	0 (0%)
HEPATIC FUNCTION ABNORMAL	0 (0%)	1 (2%)	0 (0%)	0 (0%)
AMNESIA	0 (0%)	1 (2%)	0 (0%)	0 (0%)
BACK PAIN	0 (0%)	1 (2%)	0 (0%)	0 (0%)
DIZZINESS	0 (0%)	1 (2%)	0 (0%)	0 (0%)
HYPERCHOLESTEROLEMIA	0 (0%)	1 (2%)	0 (0%)	0 (0%)
HYPERLIPEMIA	0 (0%)	1 (2%)	0 (0%)	0 (0%)
INFLUENZA LIKE SYMPTOMS	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SGPT INCREASED	0 (0%)	1 (2%)	0 (0%)	0 (0%)
SYNCOPE	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	EPLERENONE 25MG BID (N= 55)	EPLERENONE 50MG BID (N= 54)	EPLERENONE 200MG BID (N= 48)	SPIRONOLACTONE 50MG BID (N= 48)
ADVERSE EVENT				
CHEST PAIN	0 (0%)	0 (0%)	1 (2%)	0 (0%)
HEADACHE	0 (0%)	1 (2%)	0 (0%)	0 (0%)
HEPATIC FUNCTION ABNORMAL	1 (2%)	0 (0%)	0 (0%)	0 (0%)
AMNESIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BACK PAIN	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DIZZINESS	0 (0%)	0 (0%)	0 (0%)	0 (0%)
HYPERCHOLESTEROLEMIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
HYPERLIPEMIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
INFLUENZA LIKE SYMPTOMS	0 (0%)	0 (0%)	0 (0%)	1 (2%)
SGPT INCREASED	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SYNCOPE	0 (0%)	0 (0%)	0 (0%)	1 (2%)

Figure 73: Sponsor's Summary of Adverse Events Leading to Withdrawal

Reviewer's comment: Note that "hepatic function abnormal" led to withdrawal in one patient in each of the eplerenone 50 mg QD and 25mg BID groups. The adverse events related to hepatic dysfunction are examined further under events of special interest below. Otherwise the events leading to withdrawal are uncommon and similar between placebo and eplerenone groups.

B.1.4.3.4 Events of Special Interest

Hypotension

Two patients, 1 (2 percent) in the eplerenone 50 mg BID group at the Week 8 visit, and 1 (2 percent) in the eplerenone 200 mg BID group at the Week 2 and Week 4 visits exhibited DBP of ≤ 70 mm Hg. Neither of these events was reported as an adverse event nor did either of these patients exhibit any associated symptomatic hypotensive adverse events.

Hyperkalemia

Seventeen patients (11 male and 6 female) reported increases in serum potassium (defined as ≥ 5.4 mmol/L) at varying visits between baseline and final Visit. The sponsor's summary of these events is shown in the figure below:

Regimen	Age/Gender	Baseline	2 Weeks	4 Weeks	Final Visit
Placebo BID	54/F	WNL	6.1	5.7	WNL
Eplerenone 100 mg QD	44/F	WNL	7.2	WNL	WNL
Eplerenone 400 mg QD	55/M	WNL	WNL	WNL	5.9
	65/M	WNL	5.7	WNL	5.6
	52/F	WNL	5.6	WNL	5.4
	63/M	WNL	5.5	5.5	5.6
	51/M	WNL	WNL	WNL	5.7
	52/M	WNL	5.4	WNL	WNL
	55/M	WNL	WNL	WNL	5.5
Eplerenone 50 mg BID	63/F	WNL	WNL	5.6	WNL
Eplerenone 200 mg BID	77/M	WNL	5.5	WNL	WNL
	55/M	WNL	5.6	WNL	6.8
	60/M	WNL	5.6	5.6	WNL
	57/M	WNL	5.4	WNL	WNL
	50/F	WNL	5.9	WNL	WNL
Spironolactone 50 mg BID	54/M	WNL	5.4	WNL	WNL
	66/F	WNL	5.7	5.4	WNL

Figure 74: Sponsor's Summary of Hyperkalemic Events

Reviewer's comment: Note that hyperkalemia was common only in the eplerenone 400 mg daily (QD or BID) groups. Because of this rate of hyperkalemia, e.g., about 12 percent of patients at 400 mg daily experienced hyperkalemia at some time, the sponsor abandoned the 400 mg daily dose level.

Sex Hormone-Related Events

Sex hormone-related events were infrequent. Four cases of impotence were reported, one considered unrelated to study drug in the placebo group and three considered probably related in the eplerenone groups. Breast pain was reported in one male on placebo, one female on placebo, and one female on spironolactone. One female on spironolactone reported intermenstrual pain and bleeding. No cases of gynecomastia were reported. Responses on a Sexual Dysfunctional Questionnaire showed negligible change.

The sex hormones estradiol, total and free testosterone, dihydrotesterone, FSH, and LH were measured at baseline and final visits in this study. The reviewer analyzed changes in these hormones by ANOVA, with the baseline value and the eplerenone dose as continuous covariates. The reviewer used a LOCF approach for the final values. The results with possible statistical significance for dihydrostestosterone, FSH, and LH are shown in the following tables. The changes from baseline are unadjusted means. There did not appear to be any significant differences between eplerenone and placebo for estradiol or total and free testosterone. The reviewer also did not find any significant differences in these sex hormones by race.

Table 68: Reviewer's Mean Changes in LH Levels from Baseline to Final

Group	Male		Female	
	Change	P	Change	P
0	0.2	0.08	-1.0	0.08
50	0.1		0.6	
100	0.3		2.3	
400	0.6		2.7	
SL	1.1	0.009	-0.1	0.66

SL = spironolactone; P by ANOVA

Table 69: Reviewer's Mean Changes in FSH Levels from Baseline to Final

Group	Male		Female	
	Change	P	Change	P
0	0.2	0.006	0.6	0.02
50	0.001		-0.4	
100	-0.2		0.2	
400	-0.4		4.6	
SL	-0.3	0.045	-3.1	0.43

SL = spironolactone; P by ANOVA

Table 70: Reviewer's Mean Changes in Dihydrotestosterone Levels from Baseline to Final

Group	Male		Female	
	Change	P	Change	P
0	-1.6	0.04	0.6	0.12
50	-2.5		0.2	
100	1.7		1.6	
400	3.1		-4.2	
SL	-3.2	0.43	-1.5	0.17

SL = spironolactone; P by ANOVA

Reviewer's comment: An eight-week study period is too short to be reassuring about the potential for inducing gynecomastia. The sex hormone results are suggestive that eplerenone has a small effect upon pituitary sex hormones. In males the effects are a small increase in LH, a small decrease in FSH, and possibly a small increase in dihydrotestosterone levels. The effects in females are less clear because of the smaller numbers, particularly for spironolactone. The clinical significance of any of these small changes depends upon whether any important side effects, such as impotence, gynecomastia, breast pain, or menstrual disorders, result.

Hepatic Dysfunction

Two patients were withdrawn because of elevated liver function tests. One patient, a 51-year-old white male randomized to 25 mg BID, had completely normal liver function tests at baseline. His liver enzymes peaked at AST of 43, ALT of 88, and GGT of 203 before discontinuation. A second patient, a 43 year old white male randomized to 50 QD, had borderline high liver function tests at baseline, e.g., ALT of 48. His ALTs on treatment ranged from 49 to 59.

Eplerenone appears to have a slight, dose-related effect upon liver enzymes. The mean changes from baseline to final values by treatment group are listed in the table below.

Table 71: Reviewer's Mean Changes in Liver Enzymes from Baseline to Final

Dose	ALT	AST	GGT
0	1	-0.4	5.4
50	1	-0.6	5.5
100	2.4	1	4.9
400	4.7	1.9	11.1
P*	0.003	0.03	0.02

*P by ANOVA

These mean changes were also associated with modest enzyme elevations in a few patients. Two patients in the 400 mg QD and one patient in the 200 mg BID groups had elevations of ALT (100, 101, and 118) greater than two times the upper limit of normal and accompanied by increases in AST and GGT. Modest elevations in GGT (two to three times the upper limit of normal) alone were seen occasionally in all groups, including during the screening period. Other measures of liver function (bilirubin, alkaline phosphatase, prothrombin time) did not vary by treatment group.

Spironolactone did not appear to have a similar effect upon liver enzymes, although the single dose level of spironolactone used in this study may not permit detection of a similar effect.

Renal Dysfunction

No meaningful adverse events related to renal function were reported other than the cases with hyperkalemia described above. Eplerenone produced a slight, dose-related, statistically

significant increase in BUN (mean increase 2.1 at 400 mg, P = 0.001 by ANOVA). Creatinine also increased slightly but insignificantly. In addition to the hyperkalemia, eplerenone also produced a slight decrease in serum sodium (-1.7 at 400 mg) and slight increases in serum calcium (0.2 at 400 mg) and serum uric acid (0.4 at 400 mg). Changes in urinalysis tests such as urine blood and urine protein were erratic and infrequent and did not appear to follow any pattern.

Thyroid Dysfunction

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

Table 72: Reviewer's Mean Changes in TSH Levels from Baseline to Final

Group	Male		Female	
	Change	P	Change	P
0	-0.02	0.02	0.3	0.83
50	0.09		-0.6	
100	0.03		-0.2	
400	0.36		0.2	
SL	-0.16	0.57	0.41	0.23

SL = spironolactone; P by ANOVA

Serum thyroxine levels did not differ significantly among the eplerenone and placebo groups. While this change in TSH levels for males may be a random variation (the p values are not corrected for multiple comparisons), please see the similar results for Study 049 in Appendix B.2 and a complete discussion of the implications in the reviewer's Integrated Summary of Safety.

B.1.4.3.5 Overall Adverse Events

Overall adverse events were not statistically significantly different between placebo and the eplerenone groups. The most common events reported, headache in 8 to 17 percent (highest in placebo) and upper respiratory infections in 2 to 6 percent are typical of double blind trials. Pertinent events have been described in the preceding sections.

B.1.4.3.6 Overdose

No overdoses were reported.

B.1.5 Summary

B.1.5.1 Efficacy Summary

Eplerenone at dosages of 50 to 400 mg daily was effective in reducing seated cuff trough DBP and SBP at 8 weeks. The reduction was almost full at 2 weeks and maximal at 4 weeks. There were no significant differences between the QD and BID dosing regimens except possibly greater reduction in BP in the 50 mg BID group compared to the 100 mg QD group. Graphs of the ABPM data also do not suggest any consistent difference between the QD and BID dosing regimens. There is evidence of a dose response throughout the dosage range of 50 to 400 mg daily. (See the FDA statistical review for a more complete discussion of dose-response.) Eplerenone 400 mg appears to be roughly comparable in BP reduction to spironolactone 50 mg BID.

Eplerenone increases serum aldosterone and total and active plasma renin. All increases in neurohormones show a dose-response relationship for eplerenone. Spironolactone 50 mg BID produces similar increases with magnitudes between the eplerenone 100 mg and 400 mg daily dosages. There may be a gender difference for eplerenone for aldosterone and direct renin, with males showing a greater effect.

B.1.5.2 Safety Summary

Eplerenone was tolerated reasonably well in this study with the exception of a high rate of hyperkalemia (12 percent) in the 400 mg daily groups. Eplerenone appears to cause a slight, dose-related increase in hepatic enzymes but did not lead to high enzyme elevations or overt hepatic disease in this study. Eplerenone may have a small effect upon sex hormones, with a small increase in LH, a small decrease in FSH, and a small increase in dihydrotestosterone levels in males. However, sex-hormone related events were infrequent in all groups in this study. The short study duration (8 weeks) precludes drawing any conclusions regarding these AEs. Eplerenone may also increase TSH levels slightly, with the effect again only evident in males in this study.

B.1.5.3 Reviewer's Conclusions

Eplerenone at dosages of 50-400 mg appears to be an effective anti-hypertensive. The one limiting side effect, hyperkalemia, was limiting only at the highest dosage of 400 mg daily that has now been abandoned by the sponsor because of this side effect. The clinical significance of the statistically significant changes in renin and aldosterone is not clear. Also, the changes in other lab values (sex hormones, TSH) are suggestive but far from conclusive. Their significance depends upon whether clinical events are produced.

B.2 Trial 049, Eplerenone Dose Ranging in Essential Hypertension

Study 049 is entitled "A Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Efficacy and Safety of Ranging Doses of Eplerenone for the Treatment of Mild to Moderate Hypertension." The title aptly describes the nature of this trial. Additional pertinent points are that the dosages tested were 25, 50, 100, and 200 mg once daily and the treatment period was 12 weeks. The primary endpoint was reduction in seated cuff DBP, but ABPM was also done. It is one of the two pivotal studies for establishing the anti-hypertensive efficacy of eplerenone.

B.2.1 Sites and Investigators

53 Investigators enrolled patients at 47 study sites in the U.S. and Brazil. Six investigators participated in the study but did not enroll any patients. The numbers of patients randomized at a site ranged from 1 to 39, with a median of 8 and a mean of 8.5. 38 U.S. investigators enrolled 331 patients and 9 Brazilian investigators enrolled 69 patients.

B.2.2 Background

B.2.2.1 Initial Protocol

This study was conducted in accordance with protocol IE3-00-12-049, "Clinical Protocol for a Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Efficacy and Safety of Ranging Doses of Eplerenone for the Treatment of Mild to Moderate Hypertension, IND [redacted] dated 31 October 2000; the original protocol number was IE3-00-02-049," dated 28 April 2000.

B.2.2.2 Protocol Amendments

The original protocol was amended twice and had two administrative changes during the study.

- Administrative Change 1, dated 5 May 2000, corrected references, removed extraneous wording, removed duplicated wording, and added referenced text to the introduction.

- Amendment 1, dated 28 June 2000, added thyroid testing (TSH, T3, and T4) at Week 0 and Week 8 (or at the Final Visit in case of early withdrawal) and collection and storage of a two-mL aliquot of the laboratory samples collected at Weeks 2, 4, and 12 for TSH, T3, and T4 batch testing at the end of the study, as necessary. Additionally, an eplerenone 200 mg QD treatment arm was added with a total of 50 patients being randomized to this arm.

- Amendment 2, dated 7 September 2000, increased patient enrollment to 405 with patient allocation as follows: placebo [n = 90], 25 mg eplerenone [n = 45], 50 mg eplerenone [n = 90], 100mg eplerenone [n = 90], 200 mg eplerenone [n = 90]. Clarified inclusion/exclusion

so as to remain consistent with ongoing eplerenone trials. Appendix 6.3.B.2 instruction was amended to allow upper seDBP limit to be < 110 mmHg. Clarified that pregnancy and thyroid testing would not be performed at Visit 9.

- Administrative Change 2, dated 8 September 2000, corrected the time of ABPM application to between 6:30 a.m. and 9:30 a.m., and corrected inclusion criteria statements on CRFs 2, 3, and 9 due to Amendment 2.

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

B.2.2.3 Study Dates

The study was conducted between 3 October 2000 and 2 August 2001. Patients were randomized into double-blind treatment between 15 November 2000 and 4 May 2001.

B.2.3 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study consisted of a two-week pretreatment screening period followed by a four-week single-blind, placebo run-in period, prior to randomization to a 12-week double-blind, randomized treatment period. Patients were randomized in a 2:1:2:2:2 ratio to receive either placebo or eplerenone 25 mg, 50 mg, 100 mg, or 200 mg once daily. If at any time during the study, a patient experienced a DBP ≥110 mmHg or SBP ≥180 mmHg on two consecutive occasions, one to three days apart, the patient was to be withdrawn. The study design is diagrammed below:

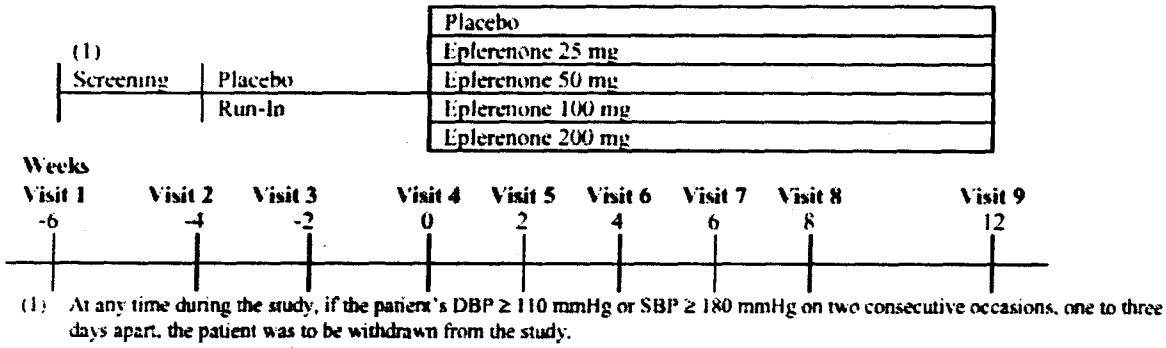


Figure 75: Sponsor's Study 049 Design

B.2.3.1 Objectives :

The primary objective of this study was to evaluate the efficacy of eplerenone as compared to placebo by measuring the mean change from baseline in seated trough cuff diastolic BP at week 12.

The secondary objectives of this study were:

- To evaluate the mean change from baseline in seated systolic BP.
- To evaluate the mean change from baseline in 24-hour DBP and SBP assessed by ambulatory BP monitoring (ABPM).
- To evaluate the mean change from baseline in total and active plasma renin and serum aldosterone levels.

B.2.3.2 Number of Subjects and Randomization

The study was designed to include 405 randomized patients. 400 patients were actually randomized: 90 placebo, 45 eplerenone 25 mg, 87 eplerenone 50 mg, 90 eplerenone 100 mg, and 88 eplerenone 200 mg. The sponsor statistician generated the patient randomization schedule using the sponsor's standard randomization program. The schedule was provided to the 24-hour Interactive Voice Response System (IVRS) center ——— and a designated drug packaging and shipping contractor who generated a list of specific patient randomization codes that were allocated and shipped to each investigator/site. This list was provided to the IVRS center used to assign patient numbers and blinded study drug. The site called the IVRS center to enroll each patient. The investigator provided the IVRS center with various identifiers for each patient and confirmed that all inclusion/exclusion criteria were met. The IVRS center assigned the patient to a treatment according to the patient randomization schedule described above.

Reviewer's comment: The randomization method appears to be excellent for concealing allocation.

B.2.3.3 Inclusion and Exclusion Criteria

The criteria for inclusion to the pretreatment screening period were:

1. The patient was a male or nonpregnant/non-lactating female ≥18 years of age.
2. If the patient was a female, she was post-menopausal, or if of childbearing potential, she was using adequate contraception (e.g., oral contraceptives, hormonal implants, barrier method, etc.), or was surgically sterile. Abstinence was not an acceptable form of contraception.
3. The patient had a history of mild to moderate hypertension or newly diagnosed hypertension (defined as seDBP ≥95 mmHg and < 110 mmHg and seSBP < 180 mmHg).

4. The patient provided written informed consent prior to any test or procedure being performed or medication being changed for this study.

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

1. The patient did not exhibit orthostatic hypotension as determined by the investigator.
2. The patient's previous antihypertensive therapy, if any, had been withdrawn. The patient may have remained on his/her pre-study antihypertensive treatment up to and including the day before Week -4.
3. The patient had no clinically significant abnormal clinical laboratory values, which in the investigator's opinion precluded the patient from safely participating in the study.
4. The patient must be stable and in predominately sinus rhythm and not have any arrhythmia requiring chronic treatment or likely to interfere with ABPM.
5. The patient had a serum potassium level >=3.5 mmol/L and <=5.0 mmol/L.

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

1. The patient had mild to moderate hypertension defined as untreated mean seDBP ≥95 mmHg and < 110 mmHg and untreated mean seSBP < 180 mmHg.
2. The patient had a validated 24-hour ABPM recording with 24-hour mean DBP of > 85 mmHg.
3. The patient's compliance with medication dosing instructions during the single-blind, placebo run-in period was between 80% and 120%, as measured by pill count.
4. If the patient was a female of childbearing potential, she had a negative urine pregnancy test and a negative serum pregnancy test within 72 hours prior to the first scheduled dose of study drug.

The exclusion criteria were the following:

1. The patient was known to have secondary hypertension (e.g., renal, renovascular or adrenocortical disease, pheochromocytoma, Cushing's syndrome, primary aldosteronism, iatrogenic), severe hypertension, or malignant hypertension.
2. The patient could not withdraw from antihypertensives by any route including diuretics, α -blockers, β -blockers, calcium channel blockers, ACE-inhibitors, or A-II antagonists. Patients who had stable angina and had not had their nitrate dosage changed within the past three months (i.e., on a stable maintenance dose) were eligible for this study. Viagra (sildenafil citrate), theophylline, or papaverine were not to have been taken within 24 hours prior to a clinic visit.
3. The patient regularly used glucocorticoids (including cortisone, hydrocortisone).
4. The patient had a history of class II-IV congestive heart failure (New York Heart Association), myocardial infarction or coronary angioplasty revascularization within the past six months, or currently had unstable angina pectoris.
5. The patient presently had a cardiac arrhythmia requiring chronic treatment or likely to interfere with ABPM.

6. The patient had a history of stroke or transient ischemic attack within the past six months, or known presence of hemodynamically relevant stenosis of the arteries perfusing the brain.
7. The patient had type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus defined as an HbA1c ≥10%.
8. The patient had acute or chronic hepatic disease, defined as SGPT/ALT and/or SGOT/AST > two times the upper limit of the normal range, and/or γ -GT > three times the upper limit of the normal range, and/or serum bilirubin > 1.8 mg/dL, and/or serum albumin < 2.5 g/dL.
9. The patient had a serum creatinine level > 1.5 mg/dL for males and > 1.3 mg/dL for females.
10. The patient had current evidence of alcohol or drug abuse problems, which in the investigator's opinion precluded the patient from participating in this study.
11. The patient had any condition, which in the investigator's opinion made participation in this study not in the best interest of the patient.
12. The patient had known hypersensitivity to spironolactone.
13. The patient had received spironolactone, guanethidine, or reserpine within 30 days of entry into the double-blind treatment period.
14. The patient had a severe organic disorder or has had surgery or disease of the gastrointestinal tract, which in the Investigator's opinion may have interfered with the absorption, pharmacokinetics, or elimination of the study medication.
15. The patient had chronic psychoses or behavioral conditions that would have limited the ability of the patient to comply with the requirements of this study.
16. The patient had a comorbid condition that would be expected to result in death during the 18-week trial period (e.g., terminal cancer, AIDS, etc.).
17. The patient had received any investigational medication within 30 days prior to the first dose of study medication or was scheduled to receive an investigational drug other than eplerenone during the course of this study.
18. The patient had been previously admitted to this study.
19. The patient had an arm circumference > 42 cm or < 24 cm for ABPM monitoring.

B.2.3.4 Dosage and Administration

Eplerenone or placebo was to be taken at the same time of day (in the morning) with or without food. Patients were instructed to take all four tablets for each study day. If the morning dosing time was missed, a dose could have been taken in the afternoon. At no time was a patient to take a double dose of study medication to compensate for missing a dose. If the morning dosing time was missed on the day before a scheduled clinic visit, the patient was to call the study site to reschedule the office visit to ensure trough BP measurements were obtained. Patients were instructed to take study medication 24 hours ± 1 hour before the clinic appointment time, and not to take the study medication dose on the day of the visit. The dose was administered at the clinic when all study visit procedures were completed. The sponsor's summary of the dosages is shown in the following figure.

Dose	Randomized Study Medication		Number of Tablets Eplerenone/Placebo
	Eplerenone (Tablets)	Placebo (Tablets)	
Placebo Run-In Period	Placebo	Placebo	0/4
Eplerenone 25 mg	25 mg	25 mg	1/3
Eplerenone 50 mg	50 mg	50 mg	1/3
Eplerenone 100 mg	100 mg	100 mg	1/3
Eplerenone 200 mg	100 mg	100 mg	2/2
Placebo	Placebo	Placebo	0/4

Figure 76: Sponsor's Summary of Dosages

B.2.3.5 Duration and Adjustment of Therapy

No adjustments were specified for study medications. However, patients could be discontinued for the following protocol-specified reasons:

1. Inability to tolerate study medication.
2. Symptomatic hypotension (i.e., dizziness, lightheadedness, or syncope with associated low BP).
3. If the DBP ≥110 mmHg or SBP ≥180 mmHg, at two consecutive occasions, one to three days apart (categorized as treatment failure).
4. Serum potassium level at two consecutive occasions, one to three days apart, > 5.5 mmol/L.
5. Need to prescribe other antihypertensive medications (categorized as treatment failure).
6. Intervening non-study medication related adverse events or intercurrent illness which made study participation impossible.
7. Patient developed an arrhythmia requiring chronic treatment and likely to interfere with ABPM.
8. Positive serum pregnancy test for a female of childbearing potential at any time (such patients were to be withdrawn immediately from study participation).
9. Administrative reasons.
10. To protect the patient's best interest, in the investigator's opinion.
11. Request of the patient to withdraw.
12. Lack of compliance (e.g., not taking medication consistently, failure to follow instructions).
13. Lost to follow-up.
14. Sponsor canceled (or discontinued) the trial.

B.2.3.6 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 12 weeks of double-blind treatment. Trough systolic and diastolic values are the average of the corresponding two values recorded at each visit.

The pre-specified secondary endpoints were the following:

1. Mean change from baseline in seSBP;
2. Mean change from baseline in 24-hour DBP and SBP assessed by ABPM;
3. Mean change from baseline in neurohormones (total and active plasma renin and serum aldosterone) levels.

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

	Screen	Single-Blind (Placebo Run-In)		Double-Blind Treatment					
Week (± 3 days)	-6	-4	-2	0	2	4	6	8	12
Visits	1	2	3	4[1]	5	6	7	8	9
Observations/Procedures [2]									
Medical History	X								
Physical Examination	X								X
ECG 12-Lead	X								X
Heart Rate and Blood Pressure (trough readings)[3]	X	X	X	X[4]	X	X	X	X	X
Assess BP Control[5]		X	X	X	X	X	X	X	X
ABPM Measurement				X					X
Fasted Clinical Safety Labs	X			X	X[6,7]	X[7]		X	X[7]
RAAS Hormone Profile[8]				X					X
Thyroid Tests				X[9]				X[9]	
Dispense Drug		X		X[10]		X		X	
Medication Compliance			X	X	X	X	X	X	X
Adverse Events/Concurrent Medications	X	X	X	X	X	X	X	X	X

1. Randomization to double-blind study number occurred at Week 0 (Day 1), i.e., end of placebo run-in.
2. Written informed consent was obtained prior to any test or procedure or change in medication was made for this trial.
3. Pretreatment (Screening Exam) recordings included measurements on both arms, and a single standing measurement. All other visits required seated, trough measurements only.
4. Final eligibility was determined at Week 0 (Day 1 [before randomization]) based upon inclusion and exclusion criteria.
5. If at any time, a patient experienced a DBP ≤ 110 mmHg or SBP ≥ 180 mmHg on two consecutive occasions, one to three days apart, the patient was to be withdrawn.
6. Potassium level only.
7. A two-mL aliquot of the patient's laboratory sample was stored by ——— for TSH, T3 uptake and T4 (total) batch testing at the end of study as necessary.
8. RAAS hormone profile (total and active plasma renin and serum aldosterone). These samples were drawn at trough, i.e., prior to dosing, and while the patient was seated and at rest at least 30 minutes prior to 10 a.m.
9. TSH, T3 uptake and T4 (total) laboratory tests (if patient withdrew early prior to week 8, these tests were to be performed at Final Visit).
10. Week 0 was to begin at least one day prior to the first dose administration; first dose administration was Day 1 of the Double-Blind Period.

Figure 77: Sponsor's Schedule of Observations and Procedures

B.2.3.7.1 Sample Size Calculations

Enough patients were be enrolled during the single-blind placebo run-in period to ensure that at least a total of 405 patients are randomized to the 5 treatment groups with the following allocation: placebo group [n = 90]; 25 mg group [n = 45]; 50 mg group [n = 90]; 100 mg group [n = 90]; 200 mg group [n = 90]. Assuming two-sided testing at 0.05 level; linear trend contrasts; common standard deviation to be 8 mmHg; group means of seDBP to be 1.1, 2.775, 4.45, 6.1, and 7.45 for the placebo, 25 mg, 50 mg, 100 mg, and 200 mg, respectively (based on study 010), the protocol claimed the following power:

"There will be 100% power to test a difference in adjusted mean change from baseline in seDBP between the placebo and the eplerenone 200 mg group; 99.1% power to test a difference in adjusted mean change from baseline in seDBP between the placebo and the eplerenone 100 mg group; 79.7% power to test a difference in adjusted mean change from baseline in seDBP between the placebo and the eplerenone 50 mg group; and a 19.4% power to test a difference in adjusted mean change from baseline in seDBP between the placebo and the eplerenone 25 mg group."

Reviewer's comment: Ultimately 400 patients were randomized. There is no explanation given regarding why the sample size for the eplerenone 25 mg group was specified as half the size of the other groups.

B.2.3.7.2 Analysis Cohorts

The protocol states that "All randomized patients with at least one post-baseline assessment will be included in the primary efficacy analysis (intent-to-treat population). In each analysis, missing values will be imputed using the last observation carried forward (LOCF) method. The analysis of safety will focus on all randomized patients who took at least one dose of study medication."

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

B.2.3.7.3 Pre-specified Analyses

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

"Blood pressure evaluations will be analyzed at each visit using two-way analysis of covariance (ANCOVA) with the baseline measurement as the covariate and treatment and center as factors. The response variable will be the change from baseline. Before implementing the final ANCOVA model, the assumption of homogeneity of treatment covariate slopes will be tested with an ANCOVA model that includes effects for baseline, treatment, and treatment-by-baseline interaction.

"To prevent artifactual effects of severe imbalances in patient counts among centers, small centers will be pooled prior to analysis. The following algorithm will be used for pooling. Small centers will be defined as those in which total enrollment was less than ½ that of the largest center. Within this group, centers will be pooled from largest to smallest, until the number of patients in the pooled center is larger than ½ of the number of patients in the largest center. Any left over centers from this procedure without a sufficient number of patients to form a pooled center will be pooled with the largest center.

"Treatment comparisons will be based on least squares means obtained via a SAS type III analysis with baseline value, treatment and center in the model. Note that the type III analysis assigns equal weight to each center, with small centers pooled as described above. A preliminary test of treatment by center interaction will be performed to evaluate the consistency of treatment effects across centers. If the p-value for interaction is 0.10 or less, differences between treatments 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, (57, 58) based on the assumption that an increase in the Eplerenone QD dose will lead to an as good or better anti-hypertensive effect. First, the placebo group will be compared to the Eplerenone 200 mg QD group using a linear trend contrast. If not significant at the 5% level, we stop further testing. In that case, all Eplerenone doses will be declared not significantly different from placebo. If significant, however, the 200 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 200 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 Eplerenone QD doses have been declared significantly different from placebo. For completeness, contrast coefficients for the planned sequence of "pairwise" comparisons are provided below:

Comparison	Contrast coefficients
Placebo versus 200 mg QD	-2 -1 0 1 2
Placebo versus 100 mg QD	-3 -1 1 3 0
Placebo versus 50 mg QD	-1 0 1 0 0
Placebo versus 25 mg QD	-1 1 0 0 0

B.2.4 Results

B.2.4.1 Study Implementation

B.2.4.1.1 Disposition of Subjects

The disposition of the cases is shown below in the table.

Table 73: Reviewer's Summary of Disposition of Cases

Stage	0	25	50	100	200	Total
Screened	NA	NA	NA	NA	NA	740
Randomized	90	45	87	90	88	400
Treated at least once	90	45	87	90	88	400
"ITT" - valid BP reading	87	45	83	88	87	390
Treatment failure	11	4	6	1	5	27
Pre-existing violation	3	0	4	3	1	11
Lost	2	3	2	1	0	8
Adverse event	2	3	1	1	3	10
Other	2	1	3	3	3	12
Noncompliance	0	0	1	1	0	2
Pre-existing AE	0	1	1	0	0	2
Total withdrawn	20	12	18	10	12	72
Completed	70	33	69	80	76	328

Reviewer's comment: The number of cases lost for potentially avoidable reasons (no post-treatment BP reading 10, pre-existing violation 11, lost 8, pre-existing AE 2, and 1 of the other reasons, for a total of 32 or 8 percent) is somewhat high but does not invalidate the study. Of these, only the 10 cases without post-treatment blood pressure readings are not included in the "ITT" analysis.

B.2.4.1.2 Subject Demographics and Baseline Characteristics

The mean age was 53 and the median 52.5 with a range from 19 to 78 for the 400 cases. 104 eplerenone cases were age 65 or older. The age distribution is shown in the figure below. Race and gender were fairly evenly distributed and diverse, with white males (excluding Hispanics) comprising 34 percent of the cases.

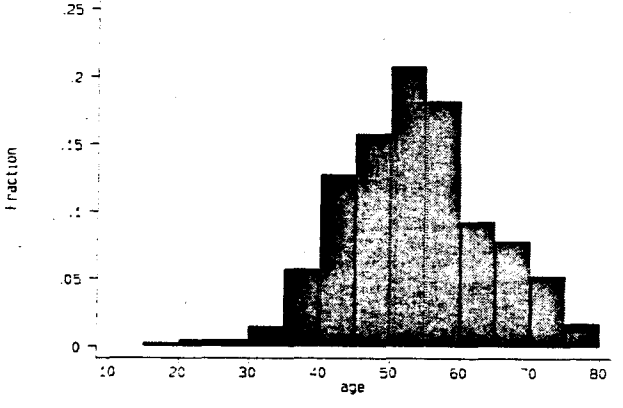


Figure 78: Reviewer's Age Distribution

The sponsor's summary of demographics and baseline characteristics, confirmed by the reviewer, is shown in the figure below.

Demographic Characteristic	Placebo (N=90)	Eplerenone 25 mg QD (N=45)	Eplerenone 50 mg QD (N=87)	Eplerenone 100 mg QD (N=90)	Eplerenone 200 mg QD (N=88)
Gender					
Female	36 (40.0%)	18 (40.0%)	39 (44.8%)	43 (47.8%)	40 (45.5%)
Male	54 (60.0%)	27 (60.0%)	48 (55.2%)	47 (52.2%)	48 (54.5%)
Age (years)					
< 35	3 (3.3%)	2 (4.4%)	1 (1.1%)	4 (4.4%)	1 (1.1%)
35-44	13 (14.4%)	11 (24.4%)	16 (18.4%)	14 (15.6%)	20 (22.7%)
45-54	35 (38.9%)	13 (28.9%)	32 (36.8%)	36 (40.0%)	30 (34.1%)
55-64	19 (21.1%)	15 (33.3%)	29 (33.3%)	28 (31.1%)	19 (21.6%)
> 64	20 (22.2%)	4 (8.9%)	9 (10.3%)	8 (8.9%)	18 (20.5%)
Mean (SD)	54.3 (11.08)	51.2 (11.25)	53.5 (9.09)	52.3 (9.81)	53.0 (10.60)
Range	22 - 78	27 - 73	27 - 77	19 - 78	23 - 74
Ethnicity					
Asian	3 (3.3%)	0 (0.0%)	1 (1.1%)	2 (2.2%)	5 (5.7%)
Black	20 (22.2%)	11 (24.4%)	18 (20.7%)	17 (18.9%)	19 (21.6%)
Caucasian	52 (57.8%)	23 (51.1%)	50 (57.5%)	52 (57.8%)	43 (48.9%)
Hispanic/Latin American	14 (15.6%)	9 (20.0%)	14 (16.1%)	17 (18.9%)	16 (18.2%)
Other	1 (1.1%)	2 (4.4%)	4 (4.6%)	2 (2.2%)	5 (5.7%)
Weight (kg)					
Female					
Mean (SD)	77.3 (15.33)	83.0 (14.34)	77.3 (19.69)	73.9 (15.24)	77.3 (11.83)
Range	47.7 – 126.8	61.3 – 110.4	50.7 – 139.4	40.6 – 116.0	51.0 – 93.3
Male					
Mean (SD)	88.7 (15.92)	88.6 (14.03)	94.4 (19.64)	91.4 (15.93)	87.9 (19.56)
Range	60.9 – 128.8	61.2 – 119.5	67.7 – 143.9	61.8 – 148.9	55.6 – 142.7
Height (cm)					
Female					
Mean (SD)	161.0 (8.03)	160.9 (8.67)	158.9 (8.77)	158.9 (7.39)	161.7 (7.43)
Range	138.0 - 174.0	148.0 – 175.3	134.6 – 182.5	145.0 – 180.0	149.0 – 180.3
Male					
Mean (SD)	175.1 (9.08)	175.4 (7.92)	176.6 (8.13)	175.4 (7.03)	173.1 (9.04)
Range	154.0 – 210.3	156.0 – 193.0	160.0 – 203.2	157.0 – 189.5	152.4 – 195.6
Body Mass Index					
Female					
Mean (SD)	29.7 (4.6)	32.0 (4.9)	30.4 (6.1)	29.1 (4.9)	29.6 (4.3)
Range					
Male					
Mean (SD)	28.8 (4.0)	28.7 (3.7)	30.2 (5.7)	29.7 (4.6)	29.2 (5.6)
Range					
Blood Pressure (mmHg)[1]	(N=87)	(N=45)	(N=83)	(N=88)	(N=87)
Mean seSBP (SD)	151.3 (10.90)	151.2 (13.44)	153.7 (12.36)	154.0 (13.59)	154.8 (12.48)
Mean seDBP (SD)	99.6 (4.33)	99.5 (3.95)	100.8 (4.73)	100.4 (5.06)	100.3 (3.96)

[1]ITT population.

Figure 79: Sponsor's Summary of Baseline Characteristics

In addition to confirming the above results, the reviewer also checked the statistical significance of the baseline characteristic variations using one-way ANOVA for continuous variables and chi-square tests for categorical variables. The reviewer's results are shown in the table below.

Table 74: Reviewer's Summary of Baseline Characteristics

Factor	Value	0	25	50	100	200	Total	P*
Age	mean	54.3	51.2	53.5	52.3	53.0	53.0	0.50
Age	median	53	52	53	52	51.5	52.5	
Male	%	60%	60%	55%	52%	55%	56%	0.83
White	%	73%	71%	74%	77%	67%	73%	0.70
Black	%	22%	24%	21%	19%	21%	21%	0.83
BMI	mean	29.2	30.0	30.3	29.4	29.4	29.6	0.55
SBP	mean	151	151	153	154	155	153	0.28
DBP	mean	99	100	101	100	100	100	0.26
Aldosterone	mean	88.7	94.1	93.2	92.0	93.0	92.0	0.97
Creatinine	mean	0.9	0.9	0.9	0.8	0.9	0.9	0.47
Direct renin	mean	14.6	13.9	13.5	16.9	14.7	14.8	0.36
Potassium	mean	4.3	4.3	4.2	4.3	4.3	4.3	0.86
Total renin	mean	147	139	139	165	133	145	0.40

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

The reviewer also examined baseline characteristic differences between the 9 Brazilian centers (about 15 percent of the cases) and the 28 U.S. centers (about 85 percent of the cases.) The Brazilian patients included more females (74 vs. 38 percent) and fewer whites (38 vs. 59 percent) and were older (mean age 57 vs. 52) and had higher baseline sitting SBP (160 vs. 151) and DBP (102 vs. 100).

Reviewer's comment: The groups appear to be well-matched for baseline characteristics. Any effects of the baseline differences in the U.S. vs. Brazilian patients are explored further below.

B.2.4.1.3 Conduct

B.2.4.1.3.1 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: "Data were entered on the CRFs at the site. Although it was the Investigator's responsibility to ensure accuracy and authenticity of all data entered on the CRFs, the Clinical Monitor also conducted a source verification review of 100% of the CRFs at the site. Data from the CRFs were entered into the — Recorder Clinical Data Management System at — and were verified electronically for consistency and accuracy by Pharmacia. Queries were reviewed with the Clinical Monitor (and in some cases with the Pharmacia Medical Monitor), in conjunction with the Investigator and his staff for resolution.

"The information included on CRFs was entered into the Clinical Data Management System via double-key verification. Data were checked using a computerized edit system. All values that were outside of specified ranges, invalid, or inconsistent with other data were queried by Pharmacia designated staff as noted above. One hundred percent (100%) of the CRFs for 20% of the patients were audited against the database. In addition, 100% of the CRFs containing key efficacy and safety data for 100% of the patient population were audited against the database at

B.2.4.1.3.2 Protocol Violations

Nineteen randomized patients violated the study inclusion or exclusion criteria, as presented in the figure below. Sixteen of these patients failed to meet BP entry criteria..

	Placebo	Eplerenone 25 mg QD	Eplerenone 50 mg QD	Eplerenone 100 mg QD	Eplerenone 200 mg QD
Study Inclusion Criteria Violation					
Single-Blind Placebo Run-In Period					
Serum potassium level was < 3.5 mmol/L			US4937-05942340		US4937-05932334 US4937-05952335
Double-Blind, Randomized Treatment Period					
Untreated mean seDBP was not ≥ 95 mmHg and < 110 mmHg and/or seSBP > 180 mmHg	BR4972-08052452	US4908-01362541	US4908-01392077 US4921-03222181 US4928-04352244	BR4972-08062453 US4908-01332081 US4916-02442141	US4937-05932334
ABPM < 85 mmHga		BR4972-08052452 US4908-01422544	BR4973-08192462 BR4979-08812498 US4900-00162007b US4937-05942340	BR4972-08062453 US4914-09202519	US4906-01002056
Not having a negative urine and serum pregnancy test within 72 hours prior to the first scheduled dose of study drug				US4923-03572199	

a Patients were withdrawn prior to Week 12 when ABPM criteria noted as exclusionary.
b Patient granted an exemption from wearing ABPM due to cuff intolerance.

Figure 80: Sponsor's Violations of Study Inclusion/Exclusion Criteria

Note that no patient was excluded from the ITT efficacy analyses due to violations of inclusion/exclusion criteria. No patient who received at least one dose of study medication was excluded from the safety analyses.

B.2.4.1.3.3 Dosing

All dosing was blinded fixed dose without adjustment. Patient compliance was measured by pill counts. During the 12-week treatment period, the percentage of patients between 80 percent and 120 percent compliant with their study medication was 93 percent in the placebo group and ranged from 87 percent to 98 percent in the eplerenone treatment groups.

B.2.4.1.3.4 Blinding

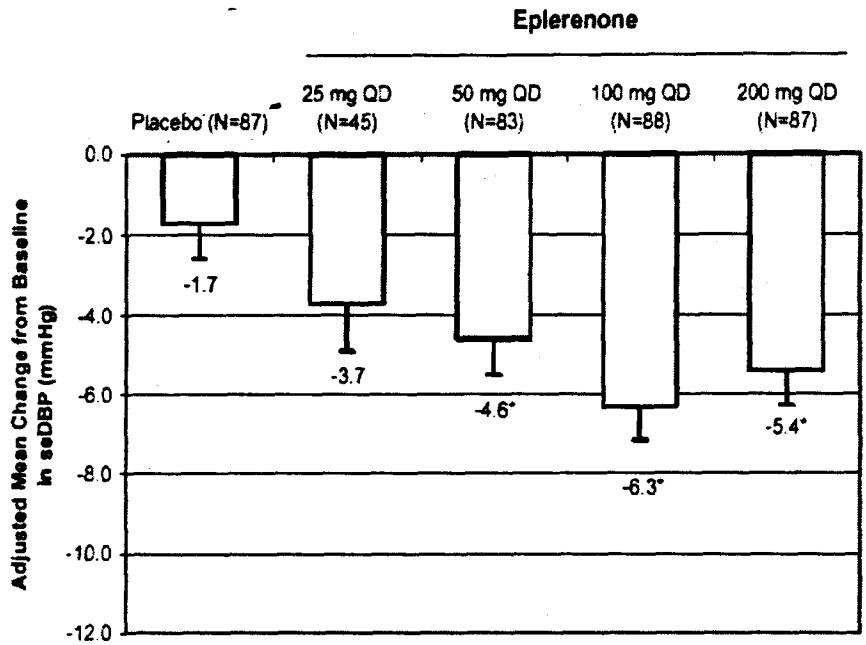
Patients were assigned, in the order in which they were enrolled into the study, to receive their allocated treatment according to a sponsor-prepared computer-generated randomization schedule. Investigational drug supplies were provided by Searle and consisted of 7-day blister packs of four tablets per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

B.2.4.2 Efficacy

B.2.4.2.1 Blood Pressure Endpoints

B.2.4.2.1.1 Sponsor's Presentation of Blood Pressure Endpoints

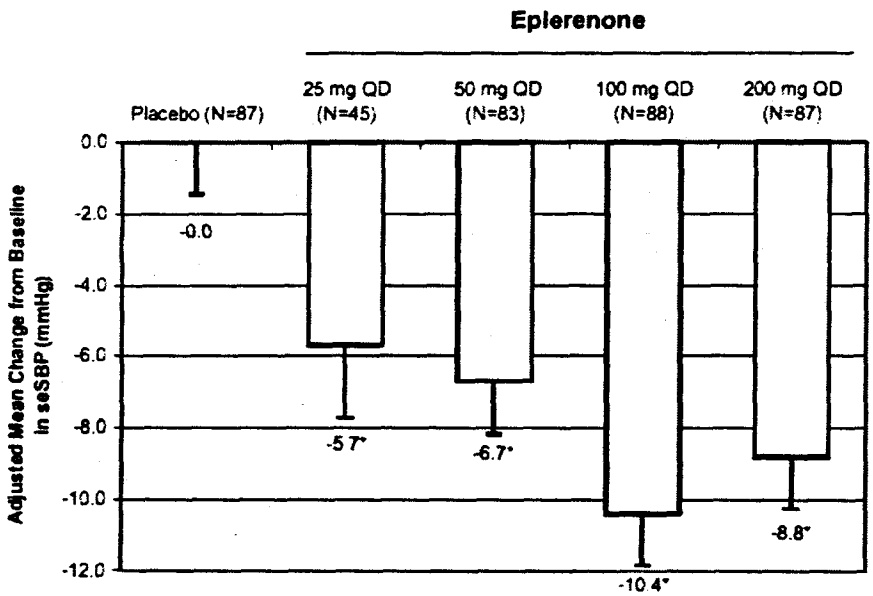
The sponsor summarized well the blood pressure endpoint results in the following series of graphs:



(Figure 9.a)

*Statistically significantly different from placebo ($p \leq 0.0108$).

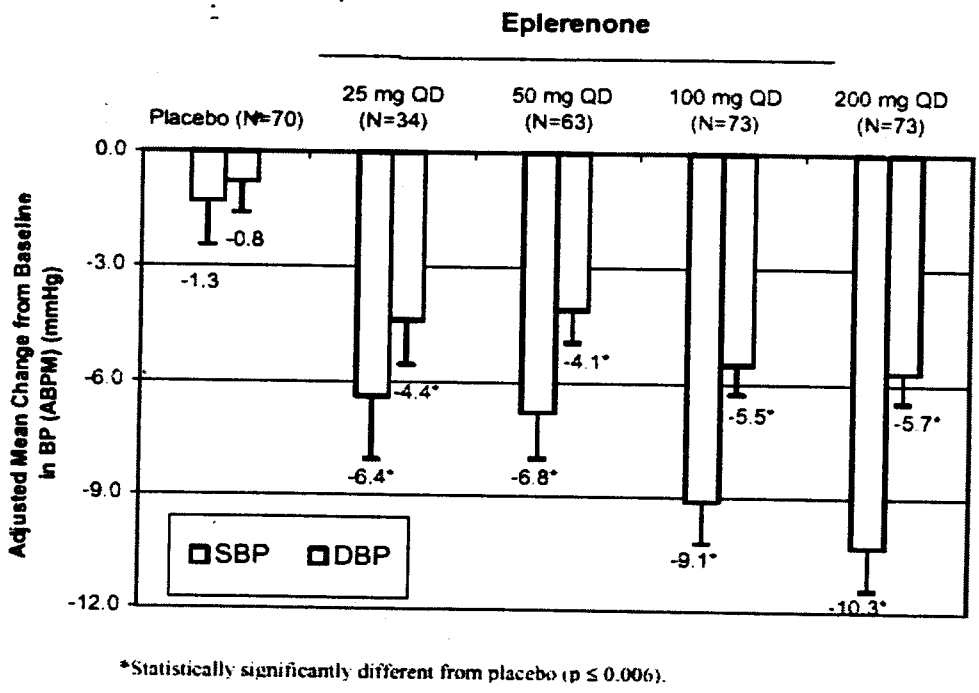
Figure 81: Sponsor's Graph of Change in Seated DBP at Week 12



(Figure 9.b)

*Statistically significantly different from placebo ($p \leq 0.0112$).

Figure 82: Sponsor's Graph of Change in Seated SBP at Week 12



(Figure 9.c)

Figure 83: Sponsor's Graph of Change in Mean 24-hour BP by ABPM at Week 12

Note that one minor change in the statistical plan was made, described by the sponsor as follows: "Centers were pooled according to the Statistical Analysis Plan with the following exception: if the total number of patients in the leftover centers was exactly equal to half the size of the largest center, then the leftover centers were grouped to become a new pooled center, rather than being pooled with the largest center. This implementation of the algorithm was made before the study was unblinded."

B.2.4.2.1.1 Reviewer's Analysis of Blood Pressure Endpoints

The reviewer confirmed that the sponsor's analyses presented above are an accurate representation of the data provided by the sponsor. The reviewer also replicated the ANCOVA pre-specified in the analysis plan with the following variation on pooling of centers: The reviewer pooled U.S. and Brazilian sites separately and grouped the leftover centers as new pooled centers having slightly less than half the patients in the largest center. The results of the ANCOVAs for sitting cuff DBP and SBP are shown in the tables below.

Table 75: Reviewer's ANCOVA for Change in DBP from Baseline to Week 12

```
                Number of obs =     394         R-squared =  0.1264
                Root MSE      = 7.83288     Adj R-squared =  0.0869

    Source |  Partial SS    df       MS           F     Prob > F
-----------+----------------------------------------------------
     Model |  3336.58312    17  196.269595        3.20     0.0000
           |
  base dbp |  380.162755     1  380.162755        6.20     0.0132
      dose |    637.9158     1    637.9158       10.40     0.0014
    center |  2295.60631    15   153.04042        2.49     0.0016
           |
  Residual |  23069.1008   376  61.3539916
-----------+----------------------------------------------------
     Total |   26405.684   393  67.1900355
```

Table 76: Reviewer's ANCOVA for Change in SBP from Baseline to Week 12

```
                Number of obs =     394     R-squared      =  0.1980
                Root MSE      = 12.7328     Adj R-squared =  0.1617

    Source |  Partial SS    df       MS           F     Prob > F
-----------+----------------------------------------------------
     Model |  15045.4804    17  885.028256        5.46     0.0000
           |
  base sbp |  6734.76079     1  6734.76079       41.54     0.0000
      dose |  3093.25786     1  3093.25786       19.08     0.0000
    center |  2732.18802    15  182.145868        1.12     0.3329
           |
  Residual |  60958.8258   376  162.124537
-----------+----------------------------------------------------
     Total |  76004.3062   393  193.395181
```

Note that pooled center is a significant factor in the ANCOVA for change in DBP but not for SDP. U.S. vs. Brazilian site was not a significant factor in similar ANCOVAs. While treatment effect for DBP varied by site, even the sites with the least treatment effects showed reductions in DBP for the higher eplerenone doses. The reviewer's tabulations of mean reductions in sitting cuff SBP and DBP by dosage level are shown in the table below. Note the weak dose-response with virtually not difference between the 100 and 200 mg groups.

Table 77: Reviewer's Unadjusted Mean Change in Sitting Cuff BP from Baseline to Week 12

Dose:	0	25	50	100	200
SBP	0.2	-6.8	-7.1	-10.0	-10.4
DBP	-2.2	-4.3	-5.7	-6.2	-6.2

The reviewer also examined the ABPM data with graphical representations. The reviewer graphed the hourly changes in DBP and SBP smoothed by a lowess smoothing algorithm from Stata version 4.0. The 24 hour changes are shown in the figures below:

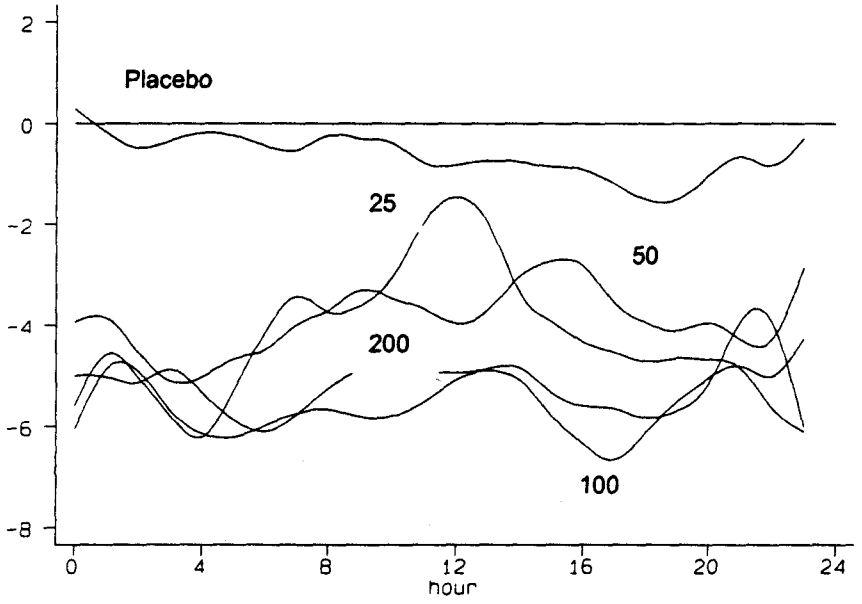


Figure 84: Reviewer's Hourly Change in DBP from ABPM Data

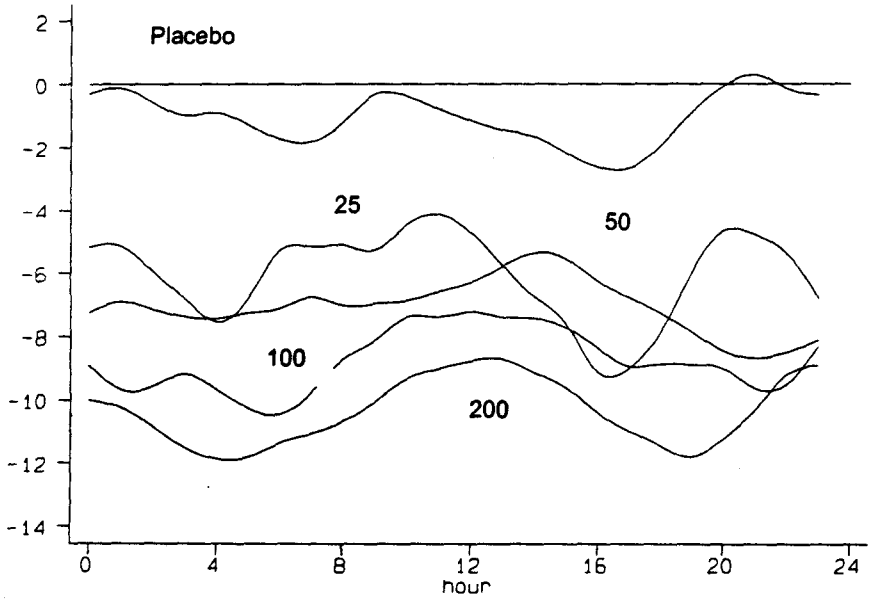


Figure 85: Reviewer's Hourly Change in SBP from ABPM Data