CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-437

Statistical Review(s)

Statistical Review and Evaluation

Review of Carcinogenicity Studies (Step Sections of Rat Kidneys)

NDA#:	**21-437**
(IND#:	[redacted]
APPLICANT:	**Pharmacia**
NAME OF DRUG:	**Eplerenone (SC-66110)**
INDICATION:	**Hypertension**
STUDIES REVIEWED:	**Step-Sections of Kidneys of Ad-libitum Feed and Diet Restricted Two-Year Carcinogenicity Studies in Rats, 05/17/02**

PHARMACOLOGY REVIEWER: Elizabeth Hausner, D.V.M. (HFD-110)

STATISTICAL REVIEWER: Roswitha Kelly, M.S. (HFD-710)

/S/

Roswitha E. Kelly, M.S.
Pre-clinical Coordinator, DB1

/S/

George Chi, Ph.D.
Director, Division of Biometrics 1

CC: Archival NDA 21-437
HFD-110/Dr. Hausner
HFD-110/Dr. DeFelice
HFD-110/Mr. Allis
HFD-710/Dr. Chi
HFD-710/Dr. Hung
HFD-710/Ms. Kelly
HFD-700/Dr. Anello
This review consists of 8 pages of text and a two-page appendix. MS Word: eplerone_2.doc. 07/10/02

Table of Contents

Table of Tables

I. Introduction

In the two-year ad libitum feed study an apparent increase in renal tumors among female rats had raised concerns. In response, the medical division requested the sponsor to re-evaluate the standard sections and to perform and evaluate step sections of the kidney of all animals. This review addresses the findings of the combined standard and step sections of the ad-libitum feed carcinogenicity study as well as the results of a previously not-reviewed diet restricted study, both submitted by the sponsor 05/17/02.

II. Ad Libitum Feed Rat Study

II.1 Study Design

A total of 85 ——— CD [Crl: CD(SD)BR] rats per gender were assigned to treatment with eplerenone via gavage at dose levels of 0 (vehicle), 20, 75, or 250 mg/kg/day. The first ten animals of each group (by identification numbers) were designated to be used for hormone and clinical pathology assessment. Of these ten animals per group, those surviving one year were sacrificed at week 53. However, all animals were fully necropsied and all tissues were microscopically examined regardless of their time of natural death or sacrifice. Therefore, all 85 animals per group were part of the carcinogenicity assessment.

At the request of the reviewing Division (HFD-110), the sponsor performed additional 10 step-sections per kidney and evaluated these in a blinded and randomized manner. Proliferative changes were peer reviewed.

II.2 Sponsor's Findings

The sponsor provided a table with the incidence of renal tumors per time interval (Table 5, Appendix) at the request of this reviewer. The sponsor submitted the results of the re-evaluation of the standard sections and the step-section analysis in electronic format as well. For the male rats, the p-values for the combined standard and re-sections for adenomas, carcinomas, and adenomas and carcinomas combined were 0.80, 1.00 and 0.89 respectively. For the female rats, the corresponding p-values were $\leq$0.01, 0.21, and $\leq$ 0.01 for adenomas, carcinomas, and adenomas and carcinomas combined. The sponsor also presented results when taking chronic progressive nephropathy findings and their grading into account.

II.3 Reviewer's Findings

The sponsor's statistical methodology depended on the number of tumors observed and over how many time intervals they were distributed. The methods, such as logistic regression, etc., are appropriate, but are not those routinely applied to carcinogenicity data by the Center. Therefore, differences in p-values can be expected, though overall conclusions should be similar.

There are three sets of renal tumor data: (1) the standard sections from the original electronic submission; (2) the 'standard sections only' which were submitted 05/17/02 by the sponsor after re-evaluation (lower half of Table 5 in Appendix); and (3) the combined standard and step sections (upper half of Table 5 in Appendix). The re-reading of the standard sections resulted in some changes in the number of adenomas and carcinomas (Table 1). In particular for males, renal tubular adenomas changed from an original total of zero to a total of 4. This review addresses only the data from the combined (re-read) standard and step sections.

Table 1: Number of Renal Tumors, Standard Sections only, from Original Submission and after Re-reading

Sex	Renal Tumor	Incidence, Original	Incidence Re-read
Male	Adenoma	0, 0, 0, 0	2, 0, 1, 1
	Carcinoma	2, 0, 0, 0	1, 0, 0, 0
Female	Adenoma	1, 0, 0, 1	1, 0, 0, 2
	Carcinoma	0, 0, 0, 2	0, 0, 0, 1

This reviewer found that the number of tumors based on the electronic data set submitted May 17, 2002, are identical to those reported in the sponsor's hard copy (cf. Appendix). However, there are minor differences in the denominators per time intervals reported by the sponsor and by this reviewer, as was the case in the original review. These differences may be due to differences in converting days to weeks, or considering an animal a natural death versus a sacrifice, but should not affect any conclusions. Tables 6 (Appendix) gives the number of animals dying per time interval (this reviewer's tabulation is based on the sponsor's electronic data set) to demonstrate the differences with the denominators of the sponsor's table (Table 5).

Table 2 below gives the tumor incidences and p-values for the exact permutation trend test for the renal tubular tumors, standard and step-sections combined. There are no statistically significant increases with dose in tubular adenomas or carcinomas, or their combination, among the male rats. All seven (7) hyperplasias were observed among the treated males, however not in a dose related fashion. Therefore, the trend test did not reach statistical significance. Among the female rats, the increase in tubular adenomas of the kidneys reached statistical significance for common tumors ($p=0.0017$ vs. $\alpha=0.005$). The single tubular carcinoma did not reach statistical significance and occurred in an animal that also had an adenoma. Therefore, for the female rats, the test results for the

combined adenomas and carcinomas are identical to the findings of the adenomas alone. Similarly to the males, all nine (9) hyperplasias occurred among the treated females, but not in a dose response manner and did not reach statistical significance. Though the p-values differ between this reviewer and the sponsor, the findings are consistent.

Table 2: Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Code	Organ Name	Tumor Code	Tumor Name	CTRL	LOW	MED	HIGH	pValue (Exact)	pValue (Asymp)	Natural Tumor # in control group	Natural Rate (in ctrl group)	Tumor type
20	KIDNEY (S)	1	#B - TUBULAR ADENOMA	4	1	2	2	0.6741	0.6794	4	5%	IN
20	KIDNEY (S)	2	#M - TUBULAR CARCINOMA	1	0	0	0	1.0000	0.8389	1	1%	IN
20	KIDNEY (S)	4	TUBULAR ADENOMA +CARCINOMA	5	1	2	2	0.7754	Not done	5	6%	IN
20	KIDNEY (S)	3	HYPERPLASIA	0	3	2	2	0.3747	0.3972	0	.0%	IN

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
KIDNEY(S)	20	#B - TUBULAR ADENOMA	1	3%	2	2	0	8	IN	0.0017	0.0008
KIDNEY(S)	20	#M - TUBULAR CARCINOMA	2	.0%	0	0	0	1	IN	0.2083	0.0316
KIDNEY(S)	20	TUB. ADENOMA +CARCINOMA	4	3%	2	2	0	8*	IN	0.0017	0.0008
KIDNEY(S)	20	HYPERPLASIA	3	.0%	0	4	0	5	IN	0.0349	0.0261

*One animal had both an adenoma and a carcinoma

III. Diet Restricted Rat Study

III.1 Study Design

This study was not previously reviewed. The study lasted two years and consisted of 85 control and high-dose male and female rats. The high dose was identical to the one in the ad-libitum feed study (250 mg/kg/day). Only kidney tissues were analyzed by histopathology. This reviewer used the sponsor's hard copy data (below) in her analysis.

III.2 Sponsor's Findings

The sponsor provided the following table (retyped by reviewer) (Table 3). They noted that there were no proliferative lesions in the standard sections and no carcinomas in the study. Their statistical methods were similar to those used for the ad lib study. For the male rats, the p-value was 0.75 to compare the incidence of adenomas between the control and high dose. For the females, the corresponding p-value was 0.14.

Table 3: Rat Renal Tubular Tumors (Adenoma*), Combined Standard and Step Sections

Sex	Time (weeks)	Control	High Dose
Male	0-52	0/7	0/10
	Interim Sac.	0/10	0/8
	53-78	0/2	0/4
	79-91	0/7	0/5
	92-104	0/6	0/6
	Terminal Sac.	1/53	1/52
Female	0-52	0/3	0/1
	Interim Sac.	0/10	0/10
	53-78	0/8	0/6
	79-91	0/9	0/8
	92/104	0/14	1/13
	Terminal Sac.	0/41	2/47

*There were no carcinomas or proliferative lesions in this study.

III.3 Reviewer's Findings

When all cells of a time interval have zero incidence, the interval does not contribute to the statistic. Therefore, for the male rats, only the data observed during Terminal Sacrifice affect the p-value, which is not close to statistical significance

(p(exact)=0.7476, p(asymptotic)=0.4946). For the female rats, the last two intervals contribute to the statistical test, which also does not reach statistical significance with the usual exact permutation test (p(exact)=0.1360, p(asymptotic)=0.0461). Both tests are one-sided pair-wise comparisons. The results are identical to those reported by the sponsor.

As this is a diet-restricted study, it is not clear what the proper α-levels for statistical significance should be. As fewer tumors are expected in a 'diet optimized' study than in an ad-libitum feed study, it stands to reason to have less restrictive levels of statistical significance for a diet-restricted study. However, the exact α-levels have not been established. It is therefore possible that the results for the female rats approach statistical significance.

IV. Summary

The sponsor was requested to re-evaluate the standard sections and do step sections of the rat kidney. Ten additional (to the two standard) step sections were taken and randomly and blindly reviewed. Those identified as having proliferative changes were peer-reviewed. The sponsor reported a 99% concordance rate with the primary evaluator.

For the ad libitum feed study, there are three sets of kidney tumor data: those from the original IND submission, the re-evaluated standard sections, and the combined (re-evaluated) standard and step sections (submitted in hard copy as well as an electronic file, May 17, 2002). It is noted that the numbers of adenomas and carcinomas changed between the original standard sections and their re-evaluation, in particular the number of adenomas for the male rats (see Table 2 above). There is no standard to assess whether the degree of change was unusual.

The number of tubular adenomas and carcinomas from the original standard sections and from the combined (re-read) standard and step-sections and the corresponding p-values for trend tests are summarized below to ease the comparison (Table 4). As can be seen, the step sections resulted in a major increase in adenomas, which reached statistical significance for the females. The combination of tubular adenomas and carcinomas resulted in the same level of significance since one female had both an adenoma and a carcinoma. In addition, hyperplasia (7 among males, 9 among females) was observed only among the treated animals but not to a statistically significant degree, as there was no dose response. These findings are consistent with the sponsor's.

Table 4: Comparison of Original Standard and Combined Re-read Standard and Step Section Findings of Rat Renal Tubular Tumors

Sex	Kidney Tumor	Incidence of Standard Sections	p-value (Trend, Exact Test)	Incidence of Standard and Step Sections	p-value (Trend, Exact Test)
Male	Adenoma	No tumors	N/A	4, 1, 1, 2	0.6741
	Carcinoma	2, 0, 0, 0	1.000	1, 0, 0, 0	1.000
Female	Adenoma	1, 0, 0, 1	0.3750	2, 2, 0, 8	0.0017
	Carcinoma	0, 0, 0, 2	0.0430*	0, 0, 0, 1	0.2083

*Tumors were both incidental and fatal, therefore p-value may not be exact.

The sponsor also submitted results of a restricted diet study with only control and high dose (same as in ad lib feed study) animals. No carcinomas or hyperplasia of the kidney were observed. Among the males there was basically an equal incidence in the two groups. Among the females, the three observed adenomas all occurred in high dose animals. The finding did not appear to reach statistical significance with the exact permutation test (p=0.1360), but the alpha level appropriate for a diet restricted pair-wise comparison has not been established. The sponsor's and this reviewer's p-values were identical for these tests.

In summary, the re-reading of the original standard sections and the step-sectioning of kidneys increased the number of adenomas and the level of statistical significance over the earlier findings in female rats. Tubular adenomas and adenomas and carcinomas combined reached statistical significance (p=0.0017) based on an exact permutation trend test.

Table 5: Number of Renal Tumors per Time Interval, Sponsor's Table *

97129/SA4663 Ad Libitum Feeding Study Rat Renal Tubular Tumors

Section Type	Sex	Time (weeks)	Adenoma				Carcinoma				Adenoma + Carcinc		
			C	L	M	H	C	L	M	H	C	L	M
Combined standard and step sections	M	0-52	0/8	0/10	0/11	0/8	0/8	0/10	0/11	0/8	0/8	0/10	0/11
		Interim sac	0/8	0/9	0/9	0/10	0/8	0/9	0/9	0/10	0/8	0/9	0/9
		53-78	0/20	0/18	1/15	0/13	0/20	0/18	0/15	0/13	0/20	0/18	1/15
		79-91	1/14	0/19	0/18	0/15	0/14	0/19	0/18	0/15	1/14	0/19	0/18
		92-104	0/13	0/9	1/14	0/15	1/13	0/9	0/14	0/15	1/13	0/9	1/14
		Final sac	3/22	1/20	0/18	2/24	0/22	0/20	0/18	0/24	3/22	1/20	0/18
	F	0-52	0/1	0/0	0/4	0/4	0/1	0/0	0/4	0/4	0/1	0/0	0/4
		Interim sac	0/11	0/10	0/10	0/9	0/11	0/10	0/10	0/9	0/11	0/10	0/10
		53-78	0/16	0/17	0/15	0/21	0/16	0/17	0/15	0/21	0/16	0/17	0/15
		79-91	0/11	1/15	0/20	4/20	0/11	0/15	0/20	0/20	0/11	1/15	0/20
		92-104	1/20	1/17	0/13	1/11	0/20	0/17	0/13	0/11	1/20	1/17	0/13
		Final sac	1/26	0/26	0/23	3/20	0/26	0/26	0/23	1/20	1/26	0/26	0/23
Standard sections only	M	0-52	0/8	0/10	0/11	0/8	0/8	0/10	0/11	0/8	0/8	0/10	0/11
		Interim sac	0/8	0/9	0/9	0/10	0/8	0/9	0/9	0/10	0/8	0/9	0/9
		53-78	0/20	0/18	1/15	0/13	0/20	0/18	0/15	0/13	0/20	0/18	1/15
		79-91	0/14	0/19	0/18	0/15	0/14	0/19	0/18	0/15	0/14	0/19	0/18
		92-104	0/13	0/9	0/14	0/15	1/13	0/9	0/14	0/15	1/13	0/9	0/14
		Final sac	2/22	0/20	0/18	1/24	0/22	0/20	0/18	0/24	2/22	0/20	0/18
	F	0-52	0/1	0/0	0/4	0/4	0/1	0/0	0/4	0/4	0/1	0/0	0/4
		Interim sac	0/11	0/10	0/10	0/9	0/11	0/10	0/10	0/9	0/11	0/10	0/10
		53-78	0/16	0/17	0/15	0/21	0/16	0/17	0/15	0/21	0/16	0/17	0/15
		79-91	0/11	0/15	0/20	1/20	0/11	0/15	0/20	0/20	0/11	0/15	0/20
		92-104	0/20	0/17	0/13	0/11	0/20	0/17	0/13	0/11	0/20	0/17	0/13
		Final sac	1/26	0/26	0/23	1/20	0/26	0/26	0/23	1/20	1/26	0/26	0/23

* 05/17/02 Submission

APPEARS THIS WAY
ON ORIGINAL

Table 6: Number of Deaths per Time Interval

Male Rats

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week 0-52	8	10	12	9	39
53-78	21	18	16	14	69
79-91	14	20	17	14	65
92-103	12	8	14	15	49
104-104	22	20	18	24	84
INTERIM	8	9	8	9	34
Total	85	85	85	85	340

Female Rats

	Treatment Group				Total
	CTRL	LOW	MED	HIGH	
	N	N	N	N	N
Week 0-52	2		4	4	10
53-78	17	18	16	22	73
79-91	12	15	19	19	65
92-103	17	16	13	11	57
104-104	27	26	23	20	96
INTERIM	10	10	10	9	39
Total	85	85	85	85	340

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Roswitha Kelly
7/12/02 10:18:56 AM
BIOMETRICS

George Chi
7/15/02 12:45:25 PM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION

STATISTICAL KEY WORDS: Dose response, multiple comparisons, sequential testing.

NDA NUMBER:	21-437
SERIAL NUMBER:	N000
DATE RECEIVED BY CENTER:	November 28, 2001
DRUG NAME:	Eplerenone tablets
INDICATION:	Hypertension
SPONSOR:	G. D. Searle LLC/ Pharmacia Corporation
DOCUMENTS REVIEWED:	Electronic submission and data sets
STATISTICAL REVIEWER:	John Lawrence, Ph.D. (HFD-710)
STATISTICAL TEAM LEADER:	Jim Hung, Ph.D. (HFD-710)
BIOMETRICS DIVISION DIRECTOR:	George Chi, Ph.D. (HFD-710)
CLINICAL REVIEWER:	Thomas Marciniak, M.D. (HFD-110)
PROJECT MANAGER:	Daryl Allis (HFD-110)

1 Executive Summary of Statistical Findings

1.1 Overview of Clinical Program and Studies Reviewed

The development program includes the results from 13 controlled clinical studies. Ten of these studied patients with essential hypertension. The remaining three studies included patients with left ventricular hypertrophy (LVH) and essential hypertension; patients with type 2 diabetes mellitus, albuminuria, and hypertension; and patients with secondary hypertension due to hyperaldosteronism.

Of the ten studies in patients with essential hypertension, one is a placebo-controlled, fixed-dose monotherapy studies (Study 049). Seven are active-controlled, three of which also included a placebo arm (Studies 010, 015, 016, 019, 020, 022, and 026). Two studies (023 and 024) investigated coadministration of eplerenone compared to placebo when there was incomplete response to another antihypertensive.

This review will only discuss the findings from the two pivotal studies (Studies 010 and 049).

1.2 Principal Findings

Fixed total daily doses of eplerenone (EP) between 50 mg and 400 mg taken either once daily or twice daily appear to be significantly better than placebo at reducing trough cuff diastolic blood pressure. The doses studied appear to be safe and well-tolerated.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction and Background

The pivotal studies for the treatment of essential hypertension are Studies 010 and 049. Both of these studies compared fixed doses of eplerenone to placebo. There were no forced-titration studies in the development program, although several of the other studies were titration-to-effect. Unless otherwise noted, the summaries in this review are based upon the sponsor's analysis. I confirmed the sponsor's results only in the two pivotal studies (Studies 010 and 049).

2.2 Data Analyzed and Sources

2.2.1 Study 010

This was an eight-arm study (placebo, EP 50 mg QD, EP 100 mg QD, EP 400 mg QD, EP 25 mg BID, EP 50 mg BID, EP 200 mg BID, spironolactone 50 mg BID). Male or female patients between 21 and 80 years of age with a history of hypertension were admitted to the study. The demographic characteristics of the patients by treatment group are summarized in Table 1. For continuous variables, the sample mean ± the standard deviation appears in the table.

There were no significant imbalances between the groups with respect to these demographic variables.

Table 1 Patient Disposition and Baseline Demographics *[Source: pages 33 and 34 of Study Report]*

Variable	Treatment group							
	Placebo	EP QD (mg)			EP BID (mg)			spirono-lactone 50 mg BID
		50	100	400	25	50	200	
N	53	54	49	56	55	54	48	48
Age	54 ± 8	55 ± 12	53 ± 10	53 ± 9	55 ± 10	53 ± 9	53 ± 10	53 ± 10
Caucasian	31	36	33	37	41	38	35	31
Black	13	10	12	14	8	10	7	10
Other	9	8	4	5	6	6	6	7
Male	31	38	30	36	40	38	33	36
Female	22	16	19	20	15	16	15	12
SeDBP	101 ± 5	101 ± 5	101 ± 4	102 ± 6	101 ± 5	101 ± 5	102 ± 5	101 ± 5
SeSBP	154±15	156±18	153±15	152±14	156±13	154±16	155±15	154 ± 14

There was a screening period, followed by a four-week placebo run-in period and an eight-week double-blind treatment period. The primary endpoint in the study was change in trough seated diastolic blood pressure (SeDBP). Trough cuff BP measurements were defined as those recorded approximately 24 hours after study drug administration, immediately before the next study drug dose. Twenty-four hour ambulatory blood pressure monitoring (ABPM) was performed before the beginning of the double-blind, randomized treatment period and was repeated at the final visit.

The primary analysis was on the subgroup of patients who took at least one dose of study medication and had at least one post-baseline measurement. This definition was used to define the ITT population in the Study Report. The last observation was carried forward to week 8 for patients with missing values. The majority of patients in each treatment group completed the study as shown in Table 2.

Table 2 Reasons for termination *[Source: p. 31 of Study Report]*

Variable	Treatment group							
	Placebo	EP QD (mg)			EP BID (mg)			spironolactone 50 mg BID
		50	100	400	25	50	200	
N	53	54	49	56	55	54	48	48
Completed study	48	45	44	53	47	48	45	40
Treatment failure	2	0	2	0	2	0	0	1
Lost to follow-up	1	2	0	1	1	0	0	0
Pre-existing violation	0	1	0	0	0	0	1	1
Protocol noncompliance	1	2	2	2	4	5	1	4
Adverse sign or symptom	1	4	1	0	1	1	1	2

2.2.2 Study 049–

This was a five-arm study (placebo, EP 25 mg QD, EP 50 mg QD, EP 100 mg QD, EP 200 mg QD). Male or female patients at least eighteen years of age with a history of hypertension were admitted to the study. There was a screening period, followed by a four-week placebo run-in period and a twelve-week double-blind treatment period. The primary endpoint in the study was change in trough seated diastolic blood pressure (SeDBP). Trough cuff BP measurements were defined as those recorded approximately 24 hours after study drug administration, immediately before the next study drug dose. Twenty-four hour ABPM was performed before the beginning of the double-blind, randomized treatment period and was repeated at the final visit.

The demographic characteristics of the patients by treatment group are summarized in Table 3. For continuous variables, the sample mean ± the standard deviation appears in the table. There were no significant imbalances between the groups with respect to these demographic variables.

Table 3 Patient Disposition and Baseline Demographics [*Source: page 49 of Study Report*]

Variable	Treatment group (placebo or daily eplerenone dose)				
	Placebo	25 mg	50 mg	100 mg	200 mg
N	90	45	87	90	88
Age	54 ± 11	51 ± 11	54 ± 9	52 ± 10	53 ± 11
Caucasian	52	23	50	52	43
Black	20	11	18	17	19
Other	18	1	19	21	26
Male	54	27	48	47	48
Female	36	18	39	43	40
SeDBP	100 ± 4	100 ± 4	101 ± 5	100 ± 5	100 ± 4
SeSBP	151 ± 11	151 ± 13	154 ± 12	154 ± 14	155 ± 12

The primary analysis was on the subgroup of patients who took at least one dose of study medication and had at least one post-baseline measurement. This definition was used to define the ITT population in the Study Report. The last observation was carried forward to week 12 for patients with missing values. The majority of patients in each treatment group completed the study as shown in Table 4.

APPEARS THIS WAY
ON ORIGINAL

Table 4 Reasons for termination *[Source: p. 46 of Study Report]*

Variable	Treatment group (placebo or daily eplerenone dose)				
	Placebo	25 mg	50 mg	100 mg	200 mg
N	90	45	87	90	88
Completed study	70	33	69	80	76
Treatment failure	11	4	6	1	45
Lost to follow-up	2	3	2	1	0
Pre-existing violation	3	0	4	1	1
Protocol noncompliance	0	0	1	1	0
Adverse sign or symptom	2	3	1	1	3

2.3 Statistical Evaluation of Evidence on Efficacy/ Safety

2.3.1 Sponsor's Results and Conclusions- Study 010

The primary efficacy variable was the change in SeDBP from baseline to week 8. The primary analysis was on the ITT population (defined in Section 2.2.1) using a linear model that included terms for baseline, treatment group, and center. Small centers were pooled together using a pre-specified algorithm. Within each treatment regimen (once daily or twice daily), an overall two-sided alpha of 0.05 was maintained using a sequential testing strategy. Contrasts in the least squares estimates of the treatment effects from the linear models were used in each test. First, the highest dose was declared to be significantly better than placebo if the linear contrast with coefficients (-11, -7, -3, 21) was significantly greater than 0 at level alpha = 0.05. If the high dose was significant, the middle dose was tested using the contrast (-1, 0, 1, 0). Finally, the low dose was tested using the contrast (-1, 1, 0, 0) if both higher doses were found to be better than placebo. As a secondary analysis, the procedure was repeated for SeSBP.

The mean baseline BP and final BP (including LOCF measurements for missing data) appear in Table 5. The mean change and standard error within each group also appears in this table. The observed mean changes are the simple arithmetic averages of the observed changes while the adjusted mean changes adjust for both center and baseline using the linear model from the primary analysis. These observed mean changes differ slightly from the least square estimates used in the efficacy analysis because no adjustments are made for any covariates. The p-values in the table represent the nominal p-values using the contrasts described above in the primary efficacy analysis.

Table 5 Observed mean change and adjusted mean change in BP from baseline by treatment group *[Source: pp. 46, 47, and 53 of Study Report, results for SeDBP confirmed by reviewer. Adjusted means per FDA analysis using model in primary analysis]*

Variable	Treatment group							
	Placebo	EP QD (mg)			EP BID (mg)			spirono-lactone 50 mg BID
		50	100	400	25	50	200	
N	52	54	48	54	53	53	48	47
SeDBP								
Baseline	101	101	101	102	101	101	102	101
Final	100	96	96	93	97	94	93	91
Obs. Mean Change	-1	-4.4	-4.5	-8.9	-4.5	-7.8	-9.4	-9.5
SE	1.0	1.0	1.2	1.1	1.2	1.2	1.1	1.5
Adj. Mean Change	-1.1	-4.5	-4.4	-8.7	-4.4	-7.8	-8.9	-9.5
SE	1.1	1.1	1.2	1.1	1.1	1.1	1.2	1.2
P-value		0.027	0.036	<0.001	0.031	<0.001	<0.001	
SeSBP								
Baseline	153.6	155.6	153.5	151.8	155.8	153.8	155.4	155.1
Final	155.6	150.9	145.5	137.7	146.9	142.0	139.6	137.5
Obs. Mean Change	2.0	-4.6	-8.0	-14.1	-8.9	-11.8	-15.8	-17.6
SE	1.8	2.0	2.1	2.0	1.9	2.3	2.2	2.1
Adj. Mean Change	1.6	-4.4	-7.9	-15.0	-8.0	-11.7	-14.8	-16.7
SE	1.8	1.8	1.9	1.8	1.8	1.8	1.9	1.9
P-value		0.022	<0.001	<0.001	<0.001	<0.001	<0.001	

nominal p-values using the contrasts described in text

2.3.2 Statistical Reviewer's Findings- Study 010

The reviewer confirmed the results for the primary analysis in Table 5. There is a suggestion of an increasing effect with increasing dose and to further quantify this relationship, a model was fit using the same model as in the primary analysis, but with a quadratic term for dose. Separate models were fit for the QD regimens and the BID regimens. The coefficient of the quadratic term in the regression model for the QD regimens was not significant ($p = 0.21$). This suggests that the doses for the QD regimens are in the part of the dose response curve where increasing the dose can still gain a proportional increase in response. However, when the model was fit to the BID regimens, a significant quadratic term was found ($p=0.0008$). Since the estimate of this coefficient is positive, this suggests that there may be less additional effect on the response with incremental changes in the dose in the dose range studied.

2.3.3 Sponsor's Results and Conclusions- Study 049

The primary efficacy variable was the change in SeDBP from baseline to week 12. The primary analysis was on the ITT population using a linear model that included terms for baseline, treatment group, and center. Small centers were pooled together using a pre-specified algorithm. An overall two-sided alpha of 0.05 was maintained using a sequential testing strategy. Contrasts in the least squares estimates of the treatment effects from the linear models were used in each test. First, the highest dose (200 mg QD) was declared to be significantly better than placebo if the linear contrast with coefficients (-2, -1, 0 , 1, 2) was significantly greater than 0 at level alpha = 0.05. If the high dose was significant, the 100 mg QD dose was tested using the contrast (-3, -1, 1, 3, 0). If this was significant, the 50 mg QD dose was tested using the contrast (-1, 0, 1, 0, 0). Finally, the 25 mg QD dose was tested using the contrast (-1, 1, 0, 0, 0) if all higher doses were found to be better than placebo. As a secondary analysis, the procedure was repeated for SeSBP.

The mean baseline BP and final BP (including LOCF measurements for missing data) appear in Table 6. The adjusted mean change and standard error within each group also appears in this table. These adjusted mean changes are estimates from the linear model used in the primary analysis, i.e. adjusting for baseline and center. The p-values in the table represent the nominal p-values using the contrasts described above in the primary efficacy analysis. The 1-sided p-values are from the Study Report while the 2-sided p-values are from the FDA analysis.

Table 6 Adjusted mean change in BP from baseline by treatment group [*Source: p. 103 of Study Report, results for SeDBP confirmed by reviewer*]

Variable	Treatment group (placebo or daily eplerenone dose)				
	Placebo	25 mg	50 mg	100 mg	200 mg
N	87	45	83	88	87
SeDBP					
Change	-1.7	-3.7	-4.6	-6.3	-5.4
SE	0.9	1.2	0.9	0.9	0.9
1-sided P-value		0.098	0.011	<0.0005	<0.0005
2-sided P-value		0.198	0.022	0.0002	0.0006
SeSBP					
Change	0.0	-5.7	-6.7	-10.4	-8.8
SE	1.4	2.0	1.5	1.4	1.4
1-sided P-value		0.011	0.0007	<0.0005	<0.0005

p-values represent nominal significance of linear trend test described in text above

2.3.4 Statistical Reviewer's Findings- Study 049

The reviewer confirmed the results for the primary analysis in Table 6. There is a suggestion of an increasing effect with increasing dose and to further quantify this relationship, a model was fit using the same model as in the primary analysis, but with a quadratic term for dose. A significant quadratic term was found (p=0.006). Since the estimate of this coefficient is positive, this suggests that there may be less additional effect on the response with incremental changes in the dose in the dose range studied. This is contrary to what was found in Study 010 for the once daily regimens studied at doses of 50 mg, 100 mg, and 400 mg.

2.4 Findings in Special/Subgroups Populations

2.4.1 Study 010

The results for the primary efficacy analysis by subgroup are presented in Table 7. There do not appear to be any significant differences in the effects across subgroups. Moreover, there did not appear to be a significant treatment by center interaction when this interaction term was added to the model used in the primary analysis (p = 0.15).

Table 7 Change in SeDBP from baseline in special subgroups [*Source: FDA analysis*]

	Treatment group						
		EP QD (mg)			EP BID (mg)		
Variable	Placebo	50	100	400	25	50	200
Age ≥ 60	-2 ± 6	-6 ± 8	-8 ±7	-11 ± 9	-6 ± 7	-8 ± 8	-11 ± 9
Caucasian	-1 ± 7	-6 ± 7	-4 ± 8	-9 ± 7	-4 ± 8	-7 ± 8	-10 ± 7
Black	-1 ± 9	-2 ± 4	-4 ± 10	-8 ± 9	2 ± 5	-9 ± 10	-8 ± 13
Other	-3 ± 6	-3 ± 11	-6 ± 8	-13 ± 18	-14 ± 5	-11 ± 9	-10 ± 9
Male	0 ± 8	-5 ± 8	-5 ± 8	-8 ± 7	-5 ± 9	-7 ± 8	-9 ± 8
Female	-2 ± 6	-4 ± 8	-4 ± 9	-10 ± 9	-3 ± 7	-10 ± 10	-11 ± 8

2.4.2 Study 049

The results for the primary efficacy analysis by subgroup are presented in Table 8. There do not appear to be any significant differences in the effects across subgroups. Moreover, there did not appear to be a significant treatment by center interaction when this interaction term was added to the model used in the primary analysis (p = 0.82).

Table 8 Change in SeDBP from baseline in special subgroups [*Source: FDA analysis*]

	Treatment group (placebo or daily eplerenone dose)				
Variable	Placebo	25 mg	50 mg	100 mg	200 mg
Age ≥ 60	-3 ± 8	-5 ± 10	-5 ± 9	-4 ± 8	-6 ± 7
Caucasian	-2 ± 8	-4 ± 10	-3 ± 10	-8 ± 8	-6 ± 9
Black	-3 ± 8	-4 ± 8	-7 ± 7	-5 ± 11	-7 ± 7
Other	-2 ± 7	-5 ± 7	-7 ± 7	-4 ± 8	-5 ± 5
Male	-2 ± 8	-4 ± 9	-4 ± 9	-9 ± 8	-6 ± 8
Female	-2 ± 8	-4 ± 9	-6 ± 9	-4 ± 9	-5 ± 7

2.5 Statistical and Technical Issues

In study 010, there was no adjustment for multiple comparisons made in the analysis for testing two different regimens. In other words, the BID regimens and the QD regimens were each tested using a two-sided alpha of 0.05. This adjustment should have been done. However, the conclusions would not likely change for this data.

In study 049, the p-values reported in the Study Report were one-sided and the nominal p-values were appropriately compared to 0.025. There is nothing scientifically wrong with this approach. However, confusion is avoided if two-sided p-values are consistently reported.

2.6 Statistical Evaluation of Collective Evidence

In each of the two pivotal studies in hypertensive patients, once daily doses of 50 mg and 100 mg of eplerenone were shown to be effective at reducing SeDBP relative to placebo. Eplerenone 400 mg QD was shown to be effective in one study, while eplerenone 200 mg QD was shown to be effective in the other study. Eplerenone 25 mg QD was evaluated in only one study and was not significantly different from placebo.

Twice daily doses of eplerenone were evaluated in only one study. All three doses studied (25 mg, 50 mg, and 200 mg BID) were nominally better than placebo.

In all regimens studied, there were no apparent adverse events related to treatment or dose. The most common adverse event reported was headache. Among all adverse events, there was no significant difference in the incidence between any active treatment group and placebo nor a suggestion of a trend with increasing dose.

2.7 Conclusions and Recommendations

From the evidence in the two pivotal studies, it appears that eplerenone 50 mg QD or higher are effective at reducing SeDBP. It is unclear whether a plateau in response is reached in the range of doses studied (up to 400 mg QD). Twice-daily regimens were evaluated in only one

study. From the evidence, including ABPM measurements, there are no apparent differences between QD doses and twice daily doses with the same total daily dose.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Lawrence
4/24/02 04:21:09 PM
BIOMETRICS

James Hung
4/24/02 04:27:57 PM
BIOMETRICS

George Chi
4/25/02 11:36:59 AM
BIOMETRICS

Demographic Worksheet

Application Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-437 Submission Type: N/A (pilot) Serial Number: N/A (pilot)

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	1665	All Females	1441	Females >50	964
Age:	0-≤1 Mo.	0	>1 Mo.-≤2Year	0	>2-≤12	0
	12-16	0	17-64	2421	≥65	685
Race:	White	2331	Black	429	Asian	44
	Other	302				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was gender-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

Age-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was age-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below		Was race-based analysis included in labeling? Yes	No
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent	☒	☐

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☒Sponsor ☒FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment: