DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21437 / S_005
Drug Name:	INSPRA® (eplerenone) Tablets
Indication(s):	Treatment of Hypertension in Pediatrics
Applicant:	Pfizer Inc.
Date(s):	Date of Document: July, 31 2007 Completion Date: November 14, 2007
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardio-Renal Drug Products, HFD-110
Clinical Team:	Thomas Marciniak, M.D. Norman Stockbridge, M.D., Ph.D.
Project Manager:	John David, PharmD
Keywords:	Eplerenone, Hypertension, Pediatrics

Table of Contents

List of Tables

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study fails to show a dose-response relationship in the 6-week randomized double-blind phase. The efficacy of eplerenone in reducing sitting systolic blood pressure is demonstrated only in the high dose in the 4-week randomized placebo-withdrawal phase. The study is considered interpretable according to the written request (WR) issued by FDA. However, the efficacy of eplerenone should not be granted since the dose response is not interpretable.

1.2 Brief Overview of Clinical Study

This sNDA consists of pediatric studies in complete response to a Written Request (WR) for Pediatric Studies issued by FDA on June 7, 2006. This review pertains only to the dose-response trial with a placebo-withdrawal phase (A6141001) in hypertensive pediatric patients.

The primary objective of the dose- response trial was to evaluate the efficacy and safety of eplerenone in children ages 6 to 16 years with hypertension. The study consisted of a 6-week randomized double-blind phase (Phase A) followed by 4-week randomized placebo-withdrawal phase (Phase B). In Phase A, subjects were randomized to receive 1 of 3 doses of eplerenone (25 mg once daily [QD], 25 mg twice daily [BID], or 50 mg BID) and in Phase B, subjects were to undergo a placebo-controlled randomized withdrawal phase (half continued active treatment vs half who received placebo). The primary efficacy variable of the study was the change in the sitting systolic blood pressure (SBP) from baseline of phase B to the end of the study.

1.3 Statistical Issues and Findings

It is noticed that there seems to be some discrepancy in powering the study between the WR issued by FDA and the criteria used by the sponsor. In the WR issued by FDA, a 3-mmHg reduction on blood pressure is defined as clinically meaningful treatment benefit and should be used for powering the study; however, a 5-mmHg reduction was used by the sponsor. The treatment effect detected in the study was -2.76 mmHg with a standard deviation of 10.14 mmHg. If the true treatment effect is -2.76 mm Hg, then the sample size planned for the study would not have enough power (only 49%) to detect such effect. This may partially explain why the study fails to demonstrate a dose-response relationship.

2. INTRODUCTION

2.1 Overview

Eplerenone is a steroid nucleus-based antimineralocorticoid that acts as a competitive and selective blocker of aldosterone at mineralocorticoid receptor sites in various tissues throughout the body. It is a selective aldosterone blocker (SAB). Adult subjects treated with oral eplerenone 50 to 200 mg daily, experienced significant decreases in sitting systolic and diastolic blood pressure (BP) at trough, with differences from placebo of 6 to 13 mmHg for systolic and 3 to 7 mmHg for diastolic. The FDA issued a Written Request first on August 17, 2000, and reissued on July 2, 2002, March 21, 2003, and October 1, 2004 and last on June 7, 2006.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\NONECTD\N21437\N_000\2007-07-31 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

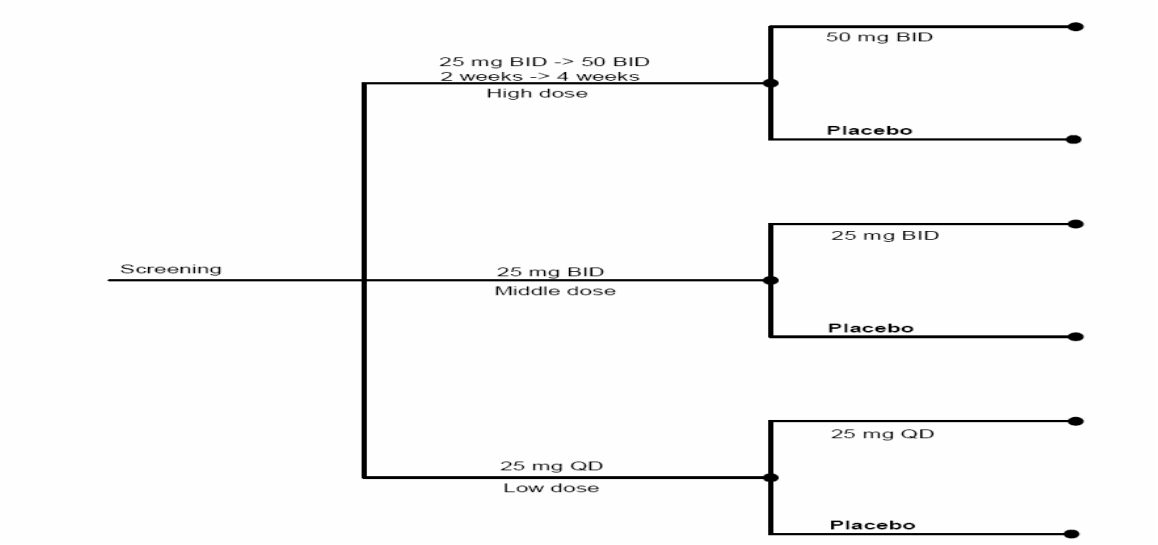
3.1.1 STUDY A6141001

3.1.1.1 Study Objectives

The primary objective of the study was to evaluate the efficacy of eplerenone in children ages 6 to 16 years with hypertension.

3.1.1.2 Study Design

This study was randomized, double-blind, placebo-controlled, dose-response study with a placebo-withdrawal phase. The study consisted of a 6-week randomized double-blind phase (Phase A) followed by 4-week randomized placebo-withdrawal phase (Phase B) described as the followings:



3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary efficacy endpoint was change in SBP from baseline of Phase B to the End-of-Study visit.

(2) Secondary Efficacy Endpoints

- Change in Diastolic Blood Pressure
- Dose Response for Change in Systolic and Diastolic Blood Pressure
- Change in Systolic Blood Pressure During Phase B for Subjects Defined as Phase A responders
- Change in Systolic and Diastolic Blood Pressure During Phase B Using mg Eplerenone/kg Body Weight

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Tables 1 and 2 summarize patient disposition, demographic and baseline characteristics. Subjects ranged in age from 4 to 16 years (mean age ranged from 12-13 years across treatment groups). A total of 52.6% of the subjects were ≤12 years of age and 47.4% were 13 to 16 years of age. The majority of the subjects were white (57%), followed by black (35%), and Asian (8%). A total of 191 subjects (63%) were male and 113 (37%) were females. About half of the female population was menarchal (47%) and half were premenarchal (53%).

Table 1 Subject Disposition

	Number (%) of Subjects								
	High-Dose Eplerenone, mg			Mid-Dose Eplerenone, mg			Low-Dose Eplerenone, mg		
	Phase A 25-50 BID	Phase B 50 BID	Phase B Placebo	Phase A 25 BID	Phase B 25 BID	Phase B Placebo	Phase A 25 QD	Phase B 25 QD	Phase B Placebo
Screened, N=393									
Assigned to study treatment, N=304									
Treated	184	86	84	62	28	27	58	26	26
Completed	170 (92.4)	85 (98.8)	79 (94.0)	55 (88.7)	27 (96.4)	27 (100)	52 (89.7)	26 (100)	26 (100)

(Source: Sponsor's Table 13.1.1)

Table 2 Demographic and Baseline Characteristics

	25BID-50BID/50BID						25BID-50BID/Placebo					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	57		43		100		56		28		84	
Age (years):												
<= 12	26	(45.6)	26	(60.5)	52	(52.0)	26	(46.4)	19	(67.9)	45	(53.6)
13 - 16	31	(54.4)	17	(39.5)	48	(48.0)	30	(53.6)	9	(32.1)	39	(46.4)
Mean	12.8		11.6		12.3		13.0		11.8		12.6	
SD	2.6		2.4		2.6		2.7		2.0		2.5	
Range	5-16		6-16		5-16		6-16		7-15		6-16	
Race:												
WHITE	36	(63.2)	23	(53.5)	59	(59.0)	39	(69.6)	12	(42.9)	51	(60.7)
BLACK	17	(29.8)	20	(46.5)	37	(37.0)	12	(21.4)	16	(57.1)	28	(33.3)
ASIAN	4	(7.0)	0		4	(4.0)	5	(8.9)	0		5	(6.0)
Ethnicity:*												
HISPANIC/LATINO	4	(7.0)	7	(16.3)	11	(11.0)	9	(16.1)	3	(10.7)	12	(14.3)
NOT HISPANIC/LATINO	53	(93.0)	36	(83.7)	89	(89.0)	47	(83.9)	25	(89.3)	72	(85.7)
Weight (kg):												
Mean	74.1		70.9		72.7		76.7		71.5		75.0	
SD	34.3		32.8		33.5		31.0		34.0		31.9	
Range	20.0-162.3		20.5-200.0		20.0-200.0		20.0-159.0		31.0-147.0		20.0-159.0	
N	57	(100.0)	43	(100.0)	100	(100.0)	56	(100.0)	28	(100.0)	84	(100.0)
Height (cm):												
Mean	162.2		153.1		158.3		162.7		155.4		160.3	
SD	19.5		15.8		18.5		18.3		10.0		16.3	
Range	108.0-193.5		112.0-174.0		108.0-193.5		107.0-188.0		137.0-173.0		107.0-188.0	
N	57	(100.0)	43	(100.0)	100	(100.0)	56	(100.0)	28	(100.0)	84	(100.0)
Hormonal Status:												
Menarchal			16	(37.2)	16	(16.0)			15	(53.6)	15	(17.9)
Premenarchal			27	(62.8)	27	(27.0)			13	(46.4)	13	(15.5)

	25BID/25BID						25BID/Placebo					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	24		11		35		15		12		27	
Age (years):												
<= 12	14	(58.3)	5	(45.5)	19	(54.3)	8	(53.3)	6	(50.0)	14	(51.9)
13 - 16	10	(41.7)	6	(54.5)	16	(45.7)	7	(46.7)	6	(50.0)	13	(48.1)
Mean	11.4		12.4		11.7		12.8		12.9		12.9	
SD	3.7		3.1		3.5		2.6		2.2		2.3	
Range	4-16		6-16		4-16		8-16		9-16		8-16	
Race:												
WHITE	12	(50.0)	6	(54.5)	18	(51.4)	9	(60.0)	4	(33.3)	13	(48.1)
BLACK	9	(37.5)	4	(36.4)	13	(37.1)	3	(20.0)	6	(50.0)	9	(33.3)
ASIAN	3	(12.5)	1	(9.1)	4	(11.4)	3	(20.0)	2	(16.7)	5	(18.5)
Ethnicity:*												
HISPANIC/LATINO	1	(4.2)	1	(9.1)	2	(5.7)	0		1	(8.3)	1	(3.7)
NOT HISPANIC/LATINO	23	(95.8)	10	(90.9)	33	(94.3)	15	(100.0)	11	(91.7)	26	(96.3)
Weight (kg):												
Mean	58.4		65.3		60.5		71.2		69.8		70.5	
SD	32.3		32.3		32.0		31.9		36.3		33.2	
Range	20.0-151.4		20.0-120.0		20.0-151.4		24.0-149.8		24.0-159.2		24.0-159.2	
N	24	(100.0)	11	(100.0)	35	(100.0)	15	(100.0)	12	(100.0)	27	(100.0)
Height (cm):												
Mean	152.2		154.9		153.0		160.8		155.3		158.3	
SD	25.7		19.7		23.7		15.8		15.6		15.6	
Range	105.5-186.0		108.0-180.0		105.5-186.0		137.0-183.0		130.0-178.0		130.0-183.0	
N	24	(100.0)	11	(100.0)	35	(100.0)	15	(100.0)	12	(100.0)	27	(100.0)
Hormonal Status:												
Menarchal			7	(63.6)	7	(20.0)			7	(58.3)	7	(25.9)
Premenarchal			4	(36.4)	4	(11.4)			5	(41.7)	5	(18.5)

	25QD/25QD						25QD/Placebo					
	MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
Number (%) of Subjects	23		9		32		16		10		26	
Age (years):												
<= 12	11	(47.8)	5	(55.6)	16	(50.0)	6	(37.5)	8	(80.0)	14	(53.8)
13 - 16	12	(52.2)	4	(44.4)	16	(50.0)	10	(62.5)	2	(20.0)	12	(46.2)
Mean	12.0		11.0		11.7		12.8		11.4		12.3	
SD	3.0		3.0		3.0		3.1		2.0		2.8	
Range	6-16		5-14		5-16		6-16		9-15		6-16	
Race:												
WHITE	14	(60.9)	5	(55.6)	19	(59.4)	9	(56.3)	5	(50.0)	14	(53.8)
BLACK	7	(30.4)	3	(33.3)	10	(31.3)	7	(43.8)	2	(20.0)	9	(34.6)
ASIAN	2	(8.7)	1	(11.1)	3	(9.4)	0		3	(30.0)	3	(11.5)
Ethnicity:*												
HISPANIC/LATINO	3	(13.0)	1	(11.1)	4	(12.5)	2	(12.5)	0		2	(7.7)
NOT HISPANIC/LATINO	20	(87.0)	8	(88.9)	28	(87.5)	14	(87.5)	10	(100.0)	24	(92.3)
Weight (kg):												
Mean	69.5		62.0		67.4		78.3		56.6		69.9	
SD	28.7		24.8		27.5		20.9		24.3		24.3	
Range	19.0-130.6		22.0-112.7		19.0-130.6		46.0-127.0		20.0-94.5		20.0-127.0	
N	23	(100.0)	9	(100.0)	32	(100.0)	16	(100.0)	10	(100.0)	26	(100.0)
Height (cm):												
Mean	156.1		153.0		155.2		161.8		145.3		155.5	
SD	19.3		20.7		19.4		14.3		13.8		16.1	
Range	115.5-180.3		109.0-172.0		109.0-180.3		133.3-182.0		123.0-167.0		123.0-182.0	
N	23	(100.0)	9	(100.0)	32	(100.0)	16	(100.0)	10	(100.0)	26	(100.0)
Hormonal Status:												
Menarchal			6	(66.7)	6	(18.8)			2	(20.0)	2	(7.7)
Premenarchal			3	(33.3)	3	(9.4)			8	(80.0)	8	(30.8)

(Source: Sponsor's Table 13.2.1)

3.1.1.5 Sponsor's Primary Efficacy Results

The slope of the dose-response was zero (p=0.8084) in the randomized phase (Phase A). During the randomized placebo withdrawal phase (Phase B), there was no difference in mean change from baseline in SBP between placebo and the low-dose (-2.61 mmHg), the medium-dose (2.32), only the high dose is statistically significantly different from

placebo (-2.76). Table 3 summarizes the analysis results. The nominal p-values for the pairwise comparison of each dose versus placebo are 0.0484, 0.3498, and 0.3006 in the order of decreasing dose.

Table 3 Summary of SBP During the Randomized and Placebo Withdrawal Phases by Dose Group (ITT)

		High-Dose Eplerenone		Mid-Dose Eplerenone		Low-Dose Eplerenone	
		50 mg BID	Placebo	25 mg BID	Placebo	25 mg QD	Placebo
Change in SBP	N	85	84	27	27	26	26
	Mean (SE)	-1.76 (1.1)	1.00 (1.1)	-0.04 (1.8)	-2.36 (1.8)	-1.49 (1.9)	1.12 (1.8)
	Difference	-2.76		2.32		-2.61	
	P-value	0.0484		0.3498		0.3006	
Dose-Response Slope (SE)	Mean (SE)	32.4 (9.3)					
	P-value	0.8084					

(Source: Sponsor's Tables 8 and 13.4.3.1)

3.1.1.6 Sponsor's Secondary Efficacy Results

The secondary efficacy analysis results are presented in section 7.3, Tables 9, 10, and 11, respectively.

3.1.1.7 Reviewer's Results

It is noticed that there seems to be some discrepancy in powering the study between the WR issued by FDA and the criteria used by the sponsor. In the WR issued by FDA, a 3-mmHg reduction on blood pressure is defined as clinically meaningful treatment benefit and should be used for powering the study; however, a 5-mmHg reduction was used by the sponsor. The treatment effect detected in the study was -2.76 mmHg with a standard deviation of 10.14 mmHg. If the true treatment effect is -2.76 mm Hg, then the sample size planned for the study would not have enough power (only 49%) to detect such effect. This may partially explain why the study fails to demonstrate a dose-response relationship.

The reviewer verified the sponsor's results and confirmed the conclusions that a statistically significant reduction in systolic blood pressure is shown comparing the high dose of eplerenone to placebo and a dose-response relationship is not demonstrated.

3.1.1.8 Conclusions

The study fails to demonstrate a dose-response relationship in children. The efficacy of eplerenone in reducing sitting systolic blood pressure is demonstrated only in the high dose, but not in the low and middle doses. The study is considered interpretable according to the WR, however, the efficacy of eplerenone should not be granted since the dose response is not interpretable.

3.2 Conclusions and Recommendations

The study fails to demonstrate a dose-response relationship in children. The efficacy of eplerenone in reducing sitting systolic blood pressure is demonstrated only in the high dose, but not in the low and middle doses. The study is considered interpretable according to the WR, however, the efficacy of eplerenone should not be granted since the dose response is not interpretable.

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

/s/

Ququan Liu
12/3/2007 10:01:30 AM
BIOMETRICS

James Hung
12/5/2007 03:07:56 PM
BIOMETRICS