

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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NDA#	21437
Submission Dates	07/31/2007
Brand Name	INSPRA® (25mg and 50 mg tablet)
Generic Name	Eplerenone
Reviewer	Hao Zhu, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Patrick J Marroum, Ph.D.
OCP Division	DPE I (HFD-110)
OND Division	DCRP (HFD-110)
Sponsor	Pfizer Inc.
Relevant IND	51,780
Submission Type	SE5 (Different/New Population) Labeling Changes Pediatric Exclusivity Determination Requested

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## 1 EXECUTIVE SUMMARY

Inspra (Eplerenone), an aldosterone antagonist, was approved on September 27, 2002 for improving survival of stable patients with left ventricular (LV) systolic dysfunction (ejection fraction  $\leq 40\%$ ) and clinical evidence of congestive heart failure (CHF) after an acute myocardial infarction. Eplerenone is also indicated to be used alone or in combination with other antihypertensive agents for the treatment of hypertension.

The Sponsor submitted this supplemental application (for NDA21-437) to fulfill the requirements listed in FDA's Written Request (WR) issued on June 7, 2006, October 1, 2004, March 21, 2002, July 2, 2000, and August 17, 2000. The Sponsor is seeking pediatric exclusivity and labeling changes.

According to the Pediatric Decision Tree (Section 1.4), the Sponsor needs to conduct both PK studies and safety and efficacy trials because we could not assume that pediatric juvenile hypertensive patients are similar to adult hypertensive patients with regard to disease progression and medicine intervention. Therefore, the Sponsor conducted both PK and safety and efficacy studies. This application consists of two PK studies (One PK study with intensive PK sampling, the other one being part of the long-term safety study with sparse PK sampling), one clinical efficacy/safety study in juvenile hypertensive patients aged 6-16 yrs, and one long-term, open label, safety study. The Sponsor has fulfilled the requirements listed in WR and FDA granted the pediatric exclusivity on Oct 24, 2007.

An adequate link was established between the commercial tablet and the clinical trial tablet. The tablet cores of the clinical and commercial presentations are formulated identically, with the only difference in the finished tablets being the tablet shape, the color, and the composition of the tablet coating. The differences between the clinical tablets and the commercial tablets had no effect on release characteristics of eplerenone drug substance as demonstrated by the similarity in the in vitro dissolution profiles of the 2 tablets. Furthermore, the same clinical tablet formulation has been used previously in the clinical trials in the prior applications of NDA-21437.

Pharmacokinetic properties of eplerenone in pediatric hypertension patients aged 6-16 were characterized in 2 PK studies by using both intensive sampling and sparse sampling. PK parameters from subjects aged 4-6 were also derived from population PK approach. It is to note that 80% of the subjects (4 out of 5 subjects) in this age group likely received different formulations (i.e. crushed tablet together with applesauce rather than tablet). Furthermore, fewer PK samples with shorter sampling duration were taken in this age group. (PK samples were taken at 0.5, 4, 6 hour post-dose for patients aged 4-6, whereas samples were taken at 0.5, 1, 2, 4, 8, 24 hour post-dose for patients aged 6 -16). Then, PK parameters (especially  $K_a$  and  $CL/F$ ) in this age group should not be directly compared to the other age groups, because formulation is a confounding factor with age and clearance can not be reliably estimated due to lack of PK information in elimination phase. The comparison of PK samples in different age groups (6-11, and 12 -16) indicated that subjects aged 12 to 16 had about 2-fold higher of  $V_c/F$  compared to age 6 – 11 yr. Further population pharmacokinetic analysis showed that body weight is a

significant covariate for  $V_c/F$ , but not for  $CL/F$  in pediatric patients. It appears that  $V_c/F$  increases as body weight increases in a nonlinear fashion.

When dose was normalized to 50 mg, no significant different AUCs were observed in the pediatric patients aged 6 -16 compared to adults. However, 27% higher  $C_{max}$ s were shown in the pediatric patients compared to adults. This difference is statistically significant ( $P = 0.03$ ). Compared to the adults, body weight also drives the PK parameter difference observed between pediatric and adult patients. After adjusted by body weight, the ANCOVA analysis indicated that there were no statistical significant differences between the adults and pediatric patients (aged 6-16 years) with regard to  $AUC_{0-24}$ ,  $C_{max}$  or  $T_{max}$ , values for eplerenone and its major metabolites (SC70303 and SC71597) ( $P \geq 0.2607$ ).

### **1.1 Recommendations**

The Sponsor adequately characterized PK in juvenile hypertension patients aged 6 years to 16 years old and evaluated effect of body weight on PK of eplerenone. The Office of Clinical Pharmacology has found this sNDA to be acceptable provided that satisfactory agreement is reached between the Sponsor and the Division regarding the language in the package insert (PI) and patient prescription information (PPI). Recommendations for consideration for the final labeling are included in the Labeling Section (Section 3) of the review.

### **1.2 Phase 4 Commitments**

None. PK has been adequately characterized in the pediatric patients, and no Phase 4 PK study is needed. However, if the sponsor plans to conduct further clinical trials, population PK components may be added to additional clinical safety/efficacy trials to confirm exposure in patients either outside of the age/weight limits (e.g., < 10 kg).

### **1.3 Summary of Important Clinical Pharmacology Findings**

This application consists of two PK studies: one study was conducted in 18 pediatric patients (aged 4 – 14) and 8 adult patients with intensive PK sampling, the other study was part of the long-term safety study with sparse PK samples taken in pediatric patients aged 5-16.

From Clinical Pharmacology point of view, the Pediatric Written Request (PWR) for eplerenone was fulfilled. Per PWR, pharmacokinetic sampling in patients should span the same age range as those studied for effectiveness. Because the effectiveness study was conducted in pediatric patients aged 6 – 16, this requirement was fulfilled. The PWR also required enrolling no less than 25% of black patients in the effectiveness study, because response to some therapies in adult hypertension appears to be different in black and non-black populations. In the two PK studies, totally 40% of the pediatric subjects were black; therefore the PK information in the black subjects was adequately collected. However, PK information was only collected from limited white patients (5 out of 54). To determine the racial difference in pediatric patients might not be feasible due to the imbalanced design of racial effect in the PK studies.

An adequate link was established between the commercial tablet and the clinical trial tablet. The tablet cores of the clinical and commercial presentations are formulated identically, with the only difference in the finished tablets being the tablet shape, the color, and the composition of the tablet coating. The differences between the clinical tablets and the commercial tablets had no effect on release

characteristics of eplerenone drug substance as demonstrated by the similarity in the in vitro dissolution profiles of the 2 tablets. Furthermore, the same clinical tablet formulation has been used previously in the clinical trials in the prior applications of NDA-21437.

Pharmacokinetic properties of eplerenone in pediatric hypertension patients aged 6-16 were characterized in 2 PK studies by using both intensive sampling and sparse sampling (Table 1). PK parameters from subjects aged 4-6 were also derived from population PK approach. It is to note that 80% of the subjects (4 out of 5 subjects) in this age group likely received different formulations (i.e. crushed tablet together with applesauce rather than tablet). Furthermore, fewer PK samples with shorter sampling duration were taken in this age group. (PK samples were taken at 0.5, 4, 6 hour post-dose for patients aged 4-6, whereas samples were taken at 0.5, 1, 2, 4, 8, 24 hour post-dose for patients aged 6 -16). Then, PK parameters (especially Ka and CL/F) in this age group should not be directly compared to the other age groups, because formulation is a confounding factor with this age group and clearance can not be reliably estimated due to lack of PK information in elimination phase. The comparison of PK samples in different age groups (6 – 11 and 12 -16) indicated that subjects aged 12 to 16 had about 2-fold higher of Vc/F compared to age 6 – 11 yr. Further population pharmacokinetic analysis showed that body weight is a significant covariate for Vc/F, but not for CL/F in pediatric patients. The relationship between the interindividual variability of Vc/F and body weight was shown in Figure 1. It appears that Vc/F increases as body weight increases in a nonlinear fashion.

When dose was normalized to 50 mg, no significant different AUCs were observed in the pediatric patients aged 6 -16 compared to adults. However, 27% higher Cmaxs were shown in the pediatric patients in this age group compared to adults. This difference is statistically significant (P = 0.03) (Table 2). Compared to the adult patients, body weight also drives the PK parameter difference observed between pediatric and adult patients. After adjusted by body weight, the ANCOVA analysis indicated that there were no statistical significant differences between the adults and pediatric patients (aged 6-16 years) with regard to AUC<sub>0-24</sub>, C<sub>max</sub> or T<sub>max</sub>, values for eplerenone and its major metabolites (SC70303 and SC71597) (P ≥ 0.2607) (Table 2).

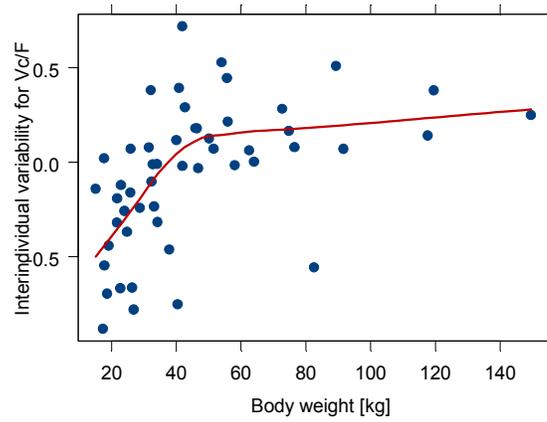
**Table 1 Summary of major PK parameters in pediatric patients aged 6 -16**

PK Parameters	Age		Note
	6 - 11 yr	12 - 16 yr	
Number of observations	15	31	Derived from Population PK Including Study NE3-01-02-055 and Study A6141077
CL/F (L/hr) Geometric Mean (CV %)	4.90 (110.69)	6.69 (75.27)	
Vc/F (L) Geometric Mean (CV %)	18.77 (29.67)	35.75 (39.58)	
Ka (1/hr) Geometric Mean (CV %)	0.92 (87.74)	1.54 (178.55)	

**Table 2 Ratios and 90% Confidence Intervals for SC-66110, SC-70303, and SC-71597 Pharmacokinetic Parameters for Patients  $\leq$  6 Years of Age**

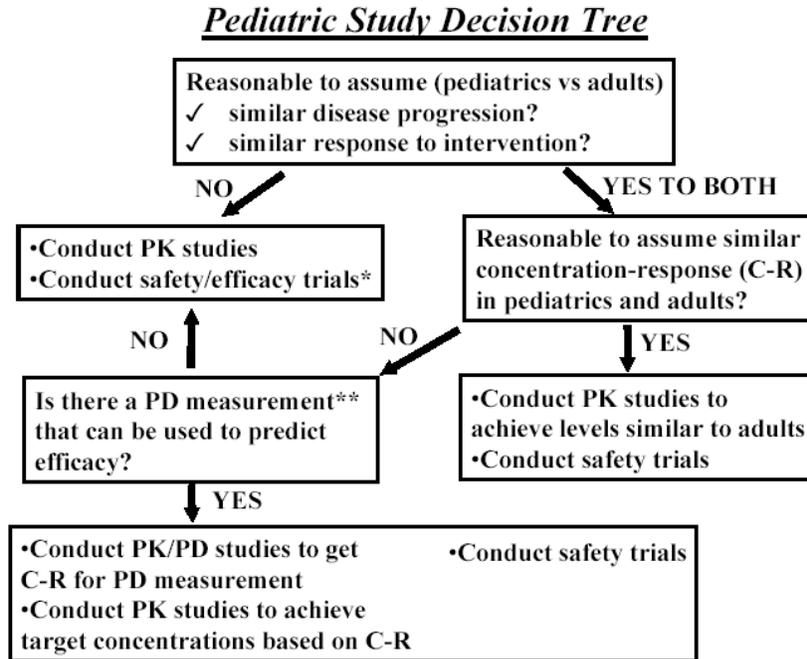
Pharmacokinetic Parameters (a)	Least Squares Means (b)			Ratio of Means (6-16 Yrs./Adult)	90% CI for Ratio of Means	P-Value
	6-11 Yrs. Eplerenone 50 mg SD N = 6	12-16 Yrs. Eplerenone 100 mg SD N = 8	Adult Eplerenone 100 mg SD N = 8			
<b>Not Adjusted For Body Weight</b>						<b>P-Value (c)</b>
<b>SC-66110</b>						
AUC(0-24) (hr*ng/mL)	4909.5	5757.7	5291.6	1.00	(0.77, 1.32)	0.9763
Cmax (ng/mL)	1121.8	1047.1	845.5	1.28	(1.07, 1.54)	0.0304
Tmax (hr)	2.0	0.9	1.7	--	--	0.3081
<b>SC-70303</b>						
AUC(0-24) (hr*ng/mL)	288.1	251.1	243.0	1.11	(0.84, 1.46)	0.5305
Cmax (ng/mL)	62.7	53.3	43.1	1.34	(1.09, 1.64)	0.0232
Tmax (hr)	1.8	1.1	3.9	--	--	0.0201
<b>SC-71597</b>						
AUC(0-24) (hr*ng/mL)	3419.2	2610.3	2230.6	1.34	(1.12, 1.61)	0.0123
Cmax (ng/mL)	517.5	300.4	229.9	1.72	(1.33, 2.22)	0.0018
Tmax (hr)	3.3	2.8	2.4	--	--	0.2649
<b>Adjusted For Body Weight</b>						<b>P-Value (d)</b>
<b>SC-66110</b>						
AUC(0-24) (hr*ng/mL)	5493.2	5731.1	4886.6	1.15	(0.71, 1.86)	0.6262
Cmax (ng/mL)	996.9	1052.2	919.3	1.11	(0.81, 1.54)	0.5679
Tmax (hr)	1.8	0.9	1.8	--	--	0.2724
<b>SC-70303</b>						
AUC(0-24) (hr*ng/mL)	308.3	250.4	231.6	1.20	(0.73, 1.96)	0.5291
Cmax (ng/mL)	60.0	53.4	44.5	1.27	(0.88, 1.83)	0.2727
Tmax (hr)	3.2	1.0	2.9	--	--	0.6406
<b>SC-71597</b>						
AUC(0-24) (hr*ng/mL)	2621.8	2639.1	2692.4	0.98	(0.73, 1.30)	0.8898
Cmax (ng/mL)	311.3	306.8	329.5	0.94	(0.66, 1.33)	0.7536
Tmax (hr)	3.7	2.7	2.2	--	--	0.2607
(a) AUC and Cmax were dose-normalized to the 50 mg dose group and then log-transformed prior to analysis. (b) Least squares means have been back-transformed to the original scale for the log-transformed PK parameters. (c) P-value comparing the 6-16 yr. olds and the Adult group from an analysis of variance (ANOVA) with effect for age group. (d) P-value comparing the 6-16 yr. olds and the Adult group from an analysis of covariance (ANCOVA) with effect for age group and body weight as a covariate. Source: <a href="#">Tables T7.1 through T7.6.</a>						

**Figure 1 Relationship between interindividual variability of Vc/F and body weight**



The sponsor did not claim the pediatric use for eplerenone. no dose was recommended in the pediatric patients in the label by the sponsor.

## 1.4 Pediatric Decision Tree



**Indication:** Eplerenone tablets are indicated in the treatment of adults with hypertension, in which it may be used alone or in combination with other antihypertensive agents. In this application, the Sponsor is proposed for its use for the treatment of juvenile hypertension.

### 1. Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression?

- No. Juvenile hypertension is diagnosed according to the standards of local practice, usually by sorting in the highest few percentiles of age-specific tables of expected blood pressure.

### 2. Is it reasonable to assume that pediatric patients are similar to adults with regard to response to intervention?

- No. Juvenile hypertension is considered more refractory to the medicine intervention than adult hypertension.

Because two “No” to the two questions in Box 1, the Pediatric Study Decision Tree suggests:

- Conducting PK studies
- Conducting safety and efficacy trials

These studies were performed by the Sponsor.

## 1.5 Written Request (WR) Fulfillment-Clinical Pharmacology Related

The following table lists summarized CP-related WR requests and information submitted:

<i>WR Items</i>	<i>Information Submitted</i>
<i>Appropriate formulation for pediatric patient</i>	<i>Clinical Overview: Formulation comparison between the commercial tablet and clinical trial tablet Dissolution profile comparison (Report EPLA-0501-271-SUI from original NDA 21-437 submission)</i>
<i>Pharmacokinetic sampling in patients spanning the same age range as those to be studied for effectiveness</i>	<i>PK Study Reports for Protocol: NE3-01-02-055, patients aged 4 – 14 yr Protocol: A6141077, patients aged 5 -16 yr Effectiveness Study Report for Protocol: A614001, patients aged 6 -16 yr</i>
<i>The sponsor should enroll no less than 25% black patients</i>	<i>PK Study Reports for Protocol: NE3-01-02-055, 100% black subjects Protocol: A6141077, 11% black subjects Total: 40.7% black subjects in the PK group</i>
<i>The sponsor may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters Data must be collected with respect to eplerenone and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected must provide estimates of the exposure (AUC), half-life, oral apparent clearance, volume of distribution, C<sub>max</sub>, and t<sub>max</sub> in pediatric subjects of various age groups.</i>	<i>PK Study Reports for Protocol: NE3-01-02-055, Traditional intensive sampling Protocol: A6141077, Sparse sampling PK Study Reports for Protocol: NE3-01-02-055, eplerenone (SC-66110) and two major metabolites (i.e. SC-70303 and SC-71597) were measured  PK Study Reports for Protocol: NE3-01-02-055 Protocol: A6141077  PK parameters can be obtained from the concentration time profile.</i>

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Office of Clinical Pharmacology

Concurrence: \_\_\_\_\_

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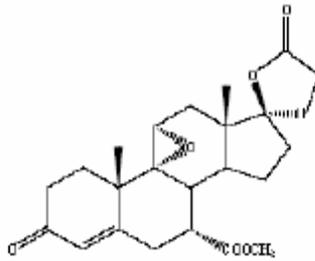
Patrick J Marroum, Ph.D.  
Clinical Pharmacology Team Leader  
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## 2 QUESTION BASED REVIEW

### 2.1 General Attributes

*2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?*

Eplerenone is described chemically as Pregn-4-ene-7, 21- dicarboxylic acid, 9, 11-epoxy-17-hydroxy-3-oxo-,  $\gamma$ -lactone, methyl ester, (7 $\alpha$ , 11 $\alpha$ , 17 $\alpha$ )-. Its empirical formula is C<sub>24</sub>H<sub>30</sub>O<sub>6</sub> and it has a molecular weight of 414.50. The following is its chemical structure:



Eplerenone is an odorless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

There is one approved formulation of eplerenone with two dose strengths – tablet (25 and 50 mg).

*2.1.2 What is the proposed mechanism of drug action? What are therapeutic indications of Eplerenone?*

Eplerenone is a steroid nucleus-based mineralocorticoid receptor (MR) antagonist with a high degree of selectivity. Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotrophic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium

reabsorption and possibly other mechanisms (eplerenone product labeling, Module 1).

Eplerenone produces sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone. In vitro, eplerenone has been shown to selectively bind to recombinant human mineralocorticoid receptors with high affinity relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Eplerenone is indicated in the treatment of adult patients with congestive heart failure post-myocardial infarction to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction  $\leq 40\%$ ) and clinical evidence of congestive heart failure after an acute myocardial infarction. It is also indicated in the treatment of adults with hypertension, in which it may be used alone or in combination with other antihypertensive agents.

### *2.1.3 What are the approved doses and route of administration in adults?*

Eplerenone is administered orally. The recommended dose for congestive heart failure post-myocardial infarction is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks as tolerated by the patient.

Eplerenone may be used alone or in combination with other antihypertensive agents. The recommended starting dose is 50 mg administered once daily. The full therapeutic effect of eplerenone is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily the dosage of eplerenone should be increased to 50 mg twice daily. Higher dosages of eplerenone are not recommended either because they have no greater effect on blood pressure than 100 mg or because they are associated with an increased risk of hyperkalemia.

### *2.1.4 What are the proposed doses for pediatric patients for hypertension?*

The sponsor did not claim the pediatric use for eplerenone. No dose was recommended in the pediatric patients in the label by the sponsor.

## **2.2 General Clinical Pharmacology**

### *2.2.1 What were the major PK parameters obtained from pediatric subjects of various age groups*

The PK parameters in pediatric subjects aged 6 – 16 (divided by two groups: 6 -11, and 12 -16) were summarized based on the pediatric study written request, which required that PK samples/parameters should be obtained in patients spanning the same age range as those in effectiveness study (6-16 years). PK parameters from subjects aged 4-6 were also available. It is to note that 80% of the subjects (4 out of 5 subjects) in this age group likely received different formulations (i.e. crushed tablet together with applesauce rather than tablet). Furthermore, fewer PK samples with shorter sampling duration were

taken in this age group. (PK samples were taken at 0.5, 4, 6 hour post-dose for patients aged 4-6, whereas samples were taken at 0.5, 1, 2, 4, 8, 24 hour post-dose for patients aged 6 -16). Then, PK parameters (especially Ka and CL/F) in this age group should not be directly compared to the other age groups, because formulation is a confounding factor with this age group and clearance can not be reliably estimated due to lack of PK information in elimination phase.

From intensive PK sampling data, the AUC<sub>(0-24)</sub>, C<sub>max</sub>, and T<sub>max</sub> in pediatric patients at various age groups were demonstrated in Table 4 . Other PK parameters including CL/F, Vc/F, and Ka were derived from population PK analysis and presented in Table 3. Terminal half-life was obtained by using WinNonlin ® and was presented in Table 3. The results suggested that Vc/F remarkably differed among different age groups, - subjects aged 12 to 16 had about 2-fold higher of Vc/F compared to age 6 – 11 yr. Further population PK analysis indicated that body weight is associated with the Vc/F change at different age groups.

**Table 3 Summary of PK Parameters by various Age Groups**

PK Parameters	Age			Note
	2 – 6 yr	6 - 11 yr	12 - 16 yr	
Number of subjects	5	15	31	Derived from Population PK Including Study NE3-01-02-055 and Study A6141077
CL/F (L/hr)				
Geometric Mean (CV %)	6.04 (24.02)	4.90 (110.69)	6.69 (75.27)	
Vc/F (L)				
Geometric Mean (CV %)	17.21 (15.45)	18.77 (29.67)	35.75 (39.58)	
Ka (1/hr)				Derived from NCA analysis Including Study NE3-01-02-055
Geometric Mean (CV %)	2.38 (129.39)	0.92 (87.74)	1.54 (178.55)	
Number of Subjects	4	6	8	
Terminal t <sub>½</sub> (hr)				
Harmonic Mean (Pseudo SD)	1.64 (0.33) *1	1.68 (0.48)	4.08 (1.02)	

Note: \*1: Only 2 PK samples were collected at 2 terminal time points for subjects aged 2-6, the estimation of terminal t<sub>½</sub> is not reliable.

**2.2.2 How does the pharmacokinetics of eplerenone in pediatric patients with juvenile hypertension compared to PK of adult hypertensive patients?**

When dose was normalized to 50 mg, no significant different AUCs were observed in the pediatric patients aged 6 -16 compared to adults. However, 27% higher C<sub>max</sub>s were shown in the pediatric patients in this age group compared to adults. This difference is statistically significant (P = 0.03) (Table 4).

Body weight, which was identified as a significant covariate for PK parameters in separate studies from pediatric and adult patients alone, appears to drive the PK parameter difference observed between pediatric and adult patients. After body weight was adjusted, the ANCOVA analysis indicated that there were no statistical significant differences between the adults and pediatric patients (aged 6-16 years)

with regard to AUC<sub>0-24</sub>, C<sub>max</sub> or T<sub>max</sub>, values for eplerenone and its major metabolites (SC70303 and SC71597) (P ≥ 0.2607). The outcomes were listed in Table 4. The results were based on a pharmacokinetic study with intensive PK samples (Study NE3-01-02-055). Because different doses (50 mg and 100 mg) were used in the PK studies in pediatric patients and adults and the dose proportionality was established from 25 to 100 mg from previous studies, all calculated C<sub>max</sub> and AUC values were normalized to 50 mg dose group before ANCOVA analysis.

**Table 4** Ratios and 90% Confidence Intervals for SC-66110, SC-70303, and SC-71597 Pharmacokinetic Parameters for Patients ≥ 6 Years of Age

Pharmacokinetic Parameters (a)	Least Squares Means (b)			Ratio of Means (6-16 Yrs./Adult)	90% CI for Ratio of Means	P-Value
	6-11 Yrs. Eplerenone 50 mg SD N = 6	12-16 Yrs. Eplerenone 100 mg SD N = 8	Adult Eplerenone 100 mg SD N = 8			
<b>Not Adjusted For Body Weight</b>						P-Value (c)
<b>SC-66110</b>						
AUC(0-24) (hr*ng/mL)	4909.5	5757.7	5291.6	1.00	(0.77, 1.32)	0.9763
Cmax (ng/mL)	1121.8	1047.1	845.5	1.28	(1.07, 1.54)	0.0304
Tmax (hr)	2.0	0.9	1.7	--	--	0.3081
<b>SC-70303</b>						
AUC(0-24) (hr*ng/mL)	288.1	251.1	243.0	1.11	(0.84, 1.46)	0.5305
Cmax (ng/mL)	62.7	53.3	43.1	1.34	(1.09, 1.64)	0.0232
Tmax (hr)	1.8	1.1	3.9	--	--	0.0201
<b>SC-71597</b>						
AUC(0-24) (hr*ng/mL)	3419.2	2610.3	2230.6	1.34	(1.12, 1.61)	0.0123
Cmax (ng/mL)	517.5	300.4	229.9	1.72	(1.33, 2.22)	0.0018
Tmax (hr)	3.3	2.8	2.4	--	--	0.2649
<b>Adjusted For Body Weight</b>						P-Value (d)
<b>SC-66110</b>						
AUC(0-24) (hr*ng/mL)	5493.2	5731.1	4886.6	1.15	(0.71, 1.86)	0.6262
Cmax (ng/mL)	996.9	1052.2	919.3	1.11	(0.81, 1.54)	0.5679
Tmax (hr)	1.8	0.9	1.8	--	--	0.2724
<b>SC-70303</b>						
AUC(0-24) (hr*ng/mL)	308.3	250.4	231.6	1.20	(0.73, 1.96)	0.5291
Cmax (ng/mL)	60.0	53.4	44.5	1.27	(0.88, 1.83)	0.2727
Tmax (hr)	3.2	1.0	2.9	--	--	0.6406
<b>SC-71597</b>						
AUC(0-24) (hr*ng/mL)	2621.8	2639.1	2692.4	0.98	(0.73, 1.30)	0.8898
Cmax (ng/mL)	311.3	306.8	329.5	0.94	(0.66, 1.33)	0.7536
Tmax (hr)	3.7	2.7	2.2	--	--	0.2607
(a) AUC and Cmax were dose-normalized to the 50 mg dose group and then log-transformed prior to analysis. (b) Least squares means have been back-transformed to the original scale for the log-transformed PK parameters. (c) P-value comparing the 6-16 yr. olds and the Adult group from an analysis of variance (ANOVA) with effect for age group. (d) P-value comparing the 6-16 yr. olds and the Adult group from an analysis of covariance (ANCOVA) with effect for age group and body weight as a covariate. Source: <a href="#">Tables T7.1 through T7.6.</a>						

### 2.2.3 How were the doses chosen for the pediatric clinical trials?

The doses for the pediatric efficacy and safety trials reflected the pediatric written request that doses chosen should result in blood levels that range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved

adult dose. Following the written request, the sponsor conducted two effectiveness and safety clinical trials in this pediatric submission: The first study is a randomized, double-blinded, placebo withdrawal, parallel group, dose-response study to evaluate the efficacy and safety of eplerenone in the treatment of hypertension in children (Study A6141001). The second study is an open-label, long term study to evaluate the safety of eplerenone in the treatment of hypertension-cognitive function (Study A614077). Three doses were selected in the Study A6141001; 25 mg QD, 25 mg BID, and starting dose of 25 mg BID for 2 weeks and then dose was escalated to 50 mg BID for 4 weeks. Dosing-adjustment was allowed in Study A614077, the subjects were exposed to as low as 25 mg QD dose to as high as 50 mg BID dose. The approved adult dose for the treatment of hypertension is 50 mg QD and 50 mg BID for the treatment of hypertension. The dose range tested in the pediatric studies covers the exposure range of the approved adult dose.

## 2.3 Intrinsic Factors

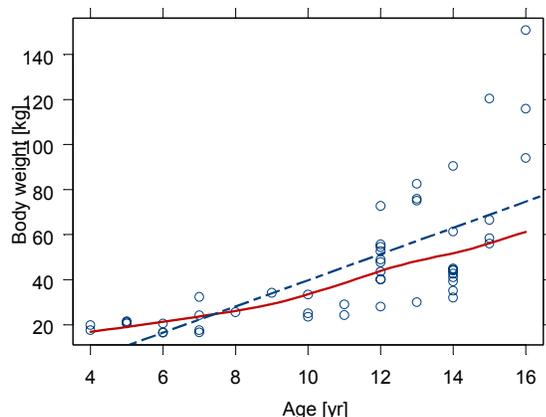
### 2.3.1 What intrinsic factors influence PK of eplerenone?

Population PK analysis indicated that total body weight for  $V_d/F$  as a statically significant covariates. The analysis further confirmed that body weight (or age) did not have statistically significant effects on  $CL/F$  in the pediatric population studied.

#### Body weight (or Age effect):

Body and age were highly correlated in the pediatric patients studied, with the relationship demonstrated in Figure 2. To simplify the covariate selection, body weight, rather than age, was chosen for evaluation.

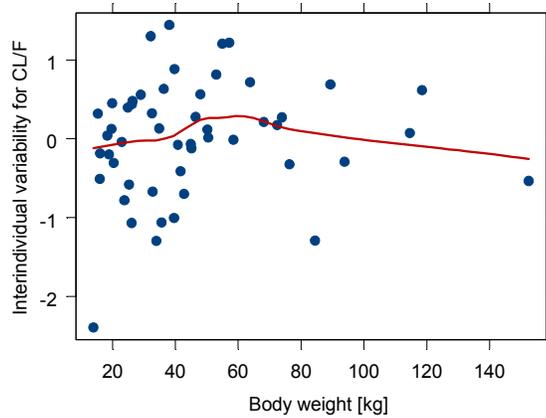
**Figure 2 Body weight and age were highly correlated in the pediatric patient studied**



Note: Red line = lowess smooth line  
Blue line = linear regression line

No statistical significant body weight effect was identified on  $CL/F$ . The relationship between interindividual variability of  $CL/F$  from the final base model and body weight was demonstrated in Figure 3.

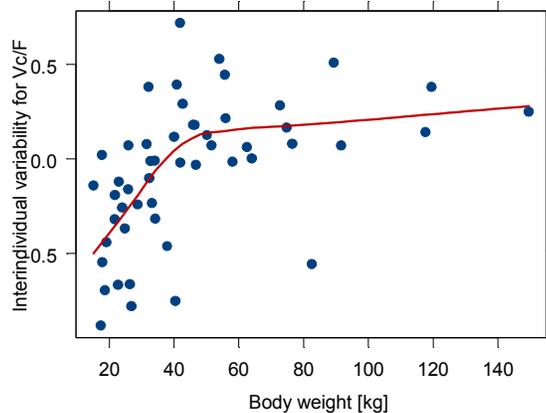
**Figure 3 Relationship between interindividual variability of CL/F and body weight**



Note: red line = lowess smooth line

Statistical significant body weight effect was identified on  $V_c/F$ . The relationship between interindividual variability of  $V_c/F$  from final base model and body weight was demonstrated in Figure 5.

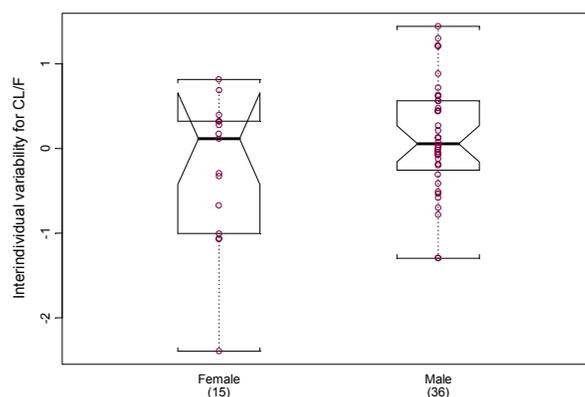
**Figure 4 Relationship between interindividual variability of  $V_c/F$  and body weight**



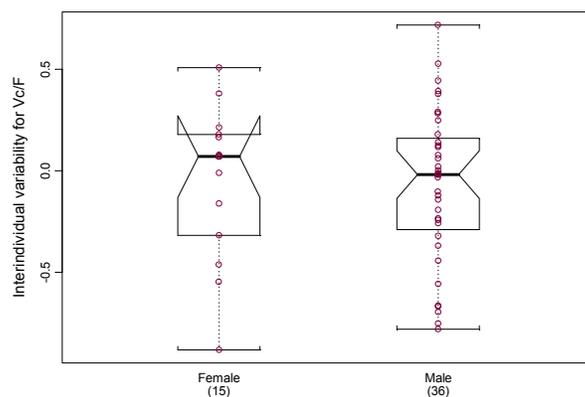
Gender:

No statistical gender effect was identified by population PK approach. The relationships between gender and interindividual variabilities of  $V_c/F$  and  $CL/F$  were presented in Figure 5. The distribution of interindividual variabilities of  $V_c/F$  and  $CL/F$  are similar between the male and female pediatric patients.

**Figure 5 Relationship between interindividual variability of  $CL/F$  (A),  $V_c/F$  (B) and gender**



(A)



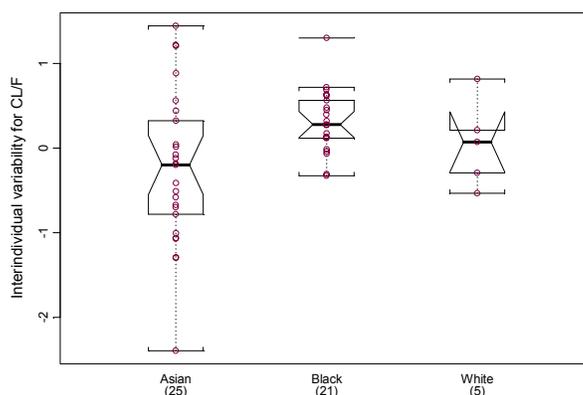
(B)

Race:

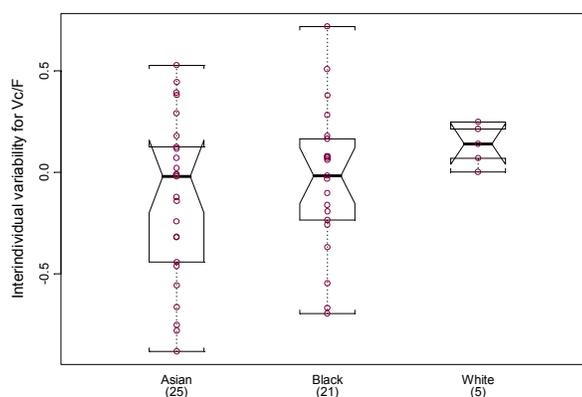
It is to note that most pediatric subjects with PK samples available were from Asian and the black, with only 5 (about 9.8% of the total subjects) white subjects. Therefore, the PK difference for the white subjects compared to the other race groups may not be identified due to the imbalanced design.

No statistically significant race effect was identified by using population PK analysis. The relationship between interindividual variabilities of Vc/F and CL/F and race were demonstrated in Figure 6. The distribution of interindividual variability of Vc/F was similar among different race groups. However, the Mean of interindividual variability of CL/F was higher in the black patients compared to the other 2 races, even though the difference was not statistically significant. The results were consistent with the observations of lower AUC in the adult black subjects.

**Figure 6 Relationship between interindividual variability of CL/F (A), Vc/F (B) and race**



**(A)**



**(B)**

## 2.4 Extrinsic Factors

None that were pertinent to the pediatric population were identified.

## 2.5 General Biopharmaceutics

### 2.5.1 *Is an adequate link established between the clinical and commercial tablets?*

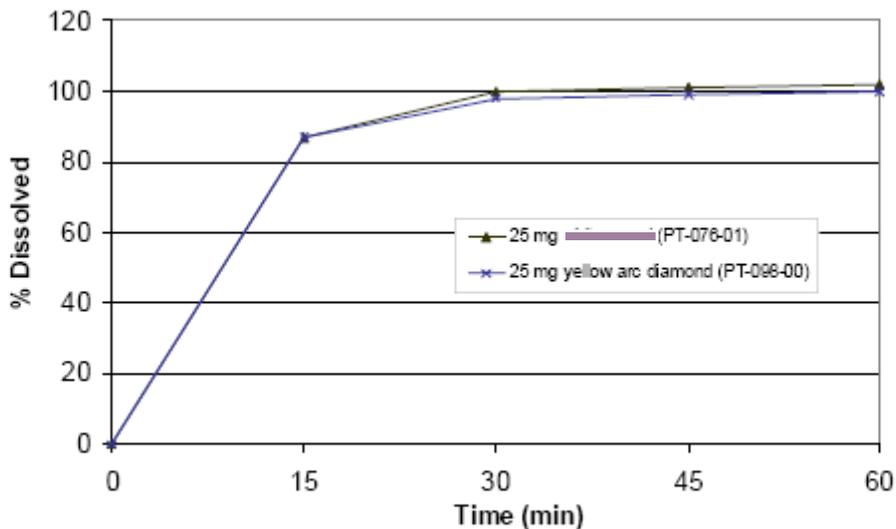
Yes. The tablet cores of the clinical and commercial presentations are formulated identically, with the only difference in the finished tablets being the tablet shape, the color, and the composition of the tablet coating (Table 5). The differences between the clinical tablets and the commercial tablets had no effect on release characteristics of eplerenone drug substance as demonstrated by the similarity in the in vitro dissolution profiles of the 2 tablets (Figure 7). Furthermore, the same clinical tablet formulation has been used previously in the clinical trials in the prior applications of NDA-21437.

**Table 5 Formulation Compositions of Commercial and Late-Phase Clinical Trial Eplerenone 25 mg Tablets**

Ingredient	Function	Clinical Tablet (mg/tablet) 25	Commercial Tablet (mg/tablet) 25
Drug Substance: Eplerenone	Active Ingredient	25.00	25.000
Inactive Ingredients:			
Lactose			
Microcrystalline Cellulose			
Croscarmellose Sodium			
Hypromellose			
Sodium lauryl sulfate			
Talc			
Magnesium Stearate			
Core Weight			
Total Tablet Weight			
			88.825
Tablet Shape			Arc Diamond

Source: Report Number EPLA-0501-271-SU1 (12-JUN-2003), See NDA 21-437

**Figure 7 Dissolution Profiles of Eplerenone Late-Phase Clinical ( ) and Commercial (Yellow, Arc Diamond) 25 mg Film-Coated Tablets**



Source: Report Number EPLA-0501-271-SU1 (12-JUN-2003), See NDA 21-437

**2.5.2** *What is the effect of food on the bioavailability of the drug from the dosage forms?*

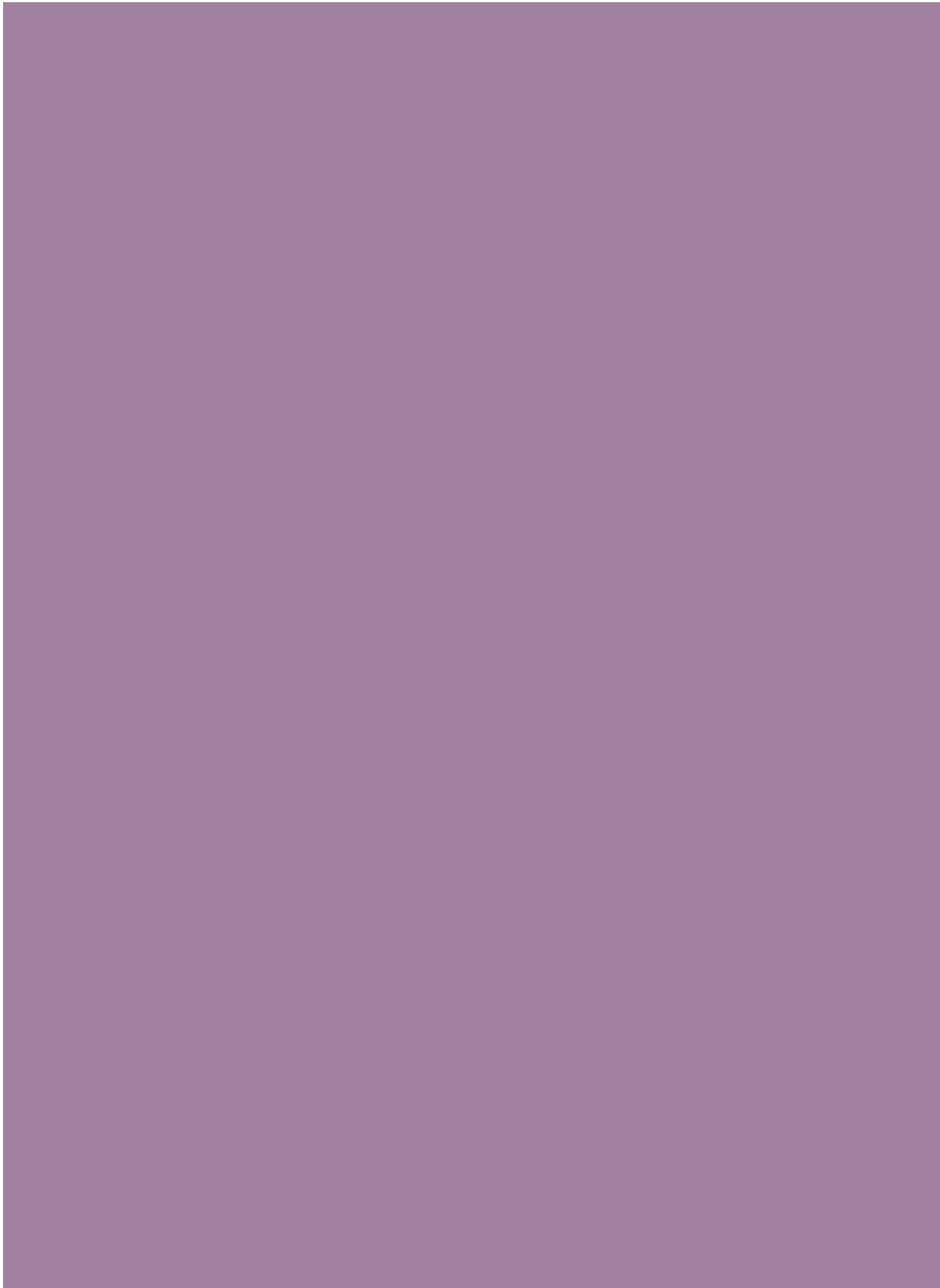
In adults, coadministration of high-fat meal or antacid did not affect the pharmacokinetics of eplerenone. Please refer to the original submission of NDA 21-437.

The food effect has not been studied in pediatric patients.

**3 DETAILED LABELING RECOMMENDATIONS**

(Underlines represent added text and strikethroughs represent deleted text.) Please refer to Dr. Marciniak’s review for recommended changes to the “Clinical Studies” and “Adverse Reactions” sections of the labeling and Patient Package Insert (PPI). At the time of this review, labeling negotiation is on-going. Please refer to the final approval letter for final version of the Package Insert (PI) and PPI.



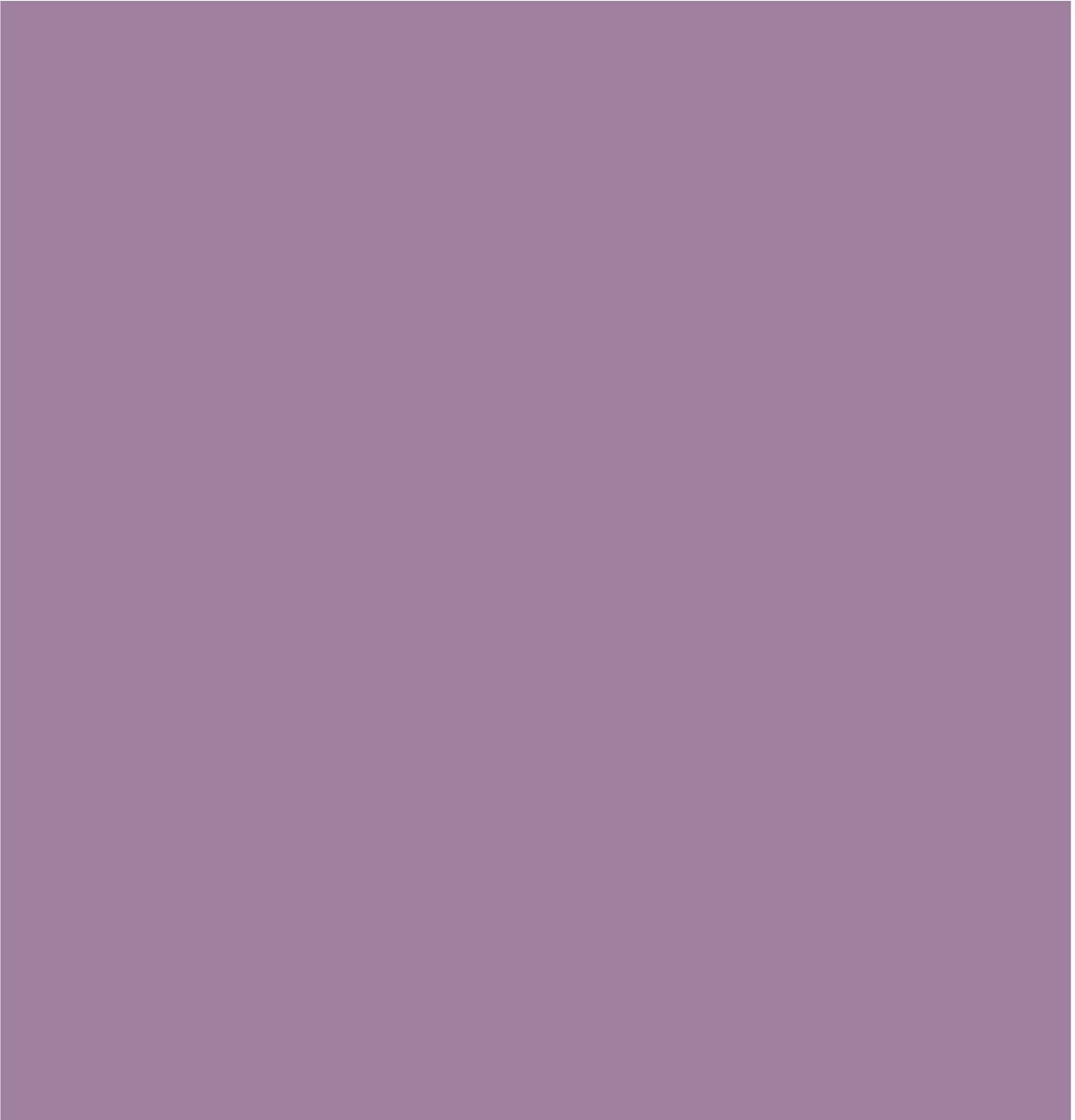






## **4 APPENDICES**

### **4.1 Proposed Package Inserts from the Sponsor**



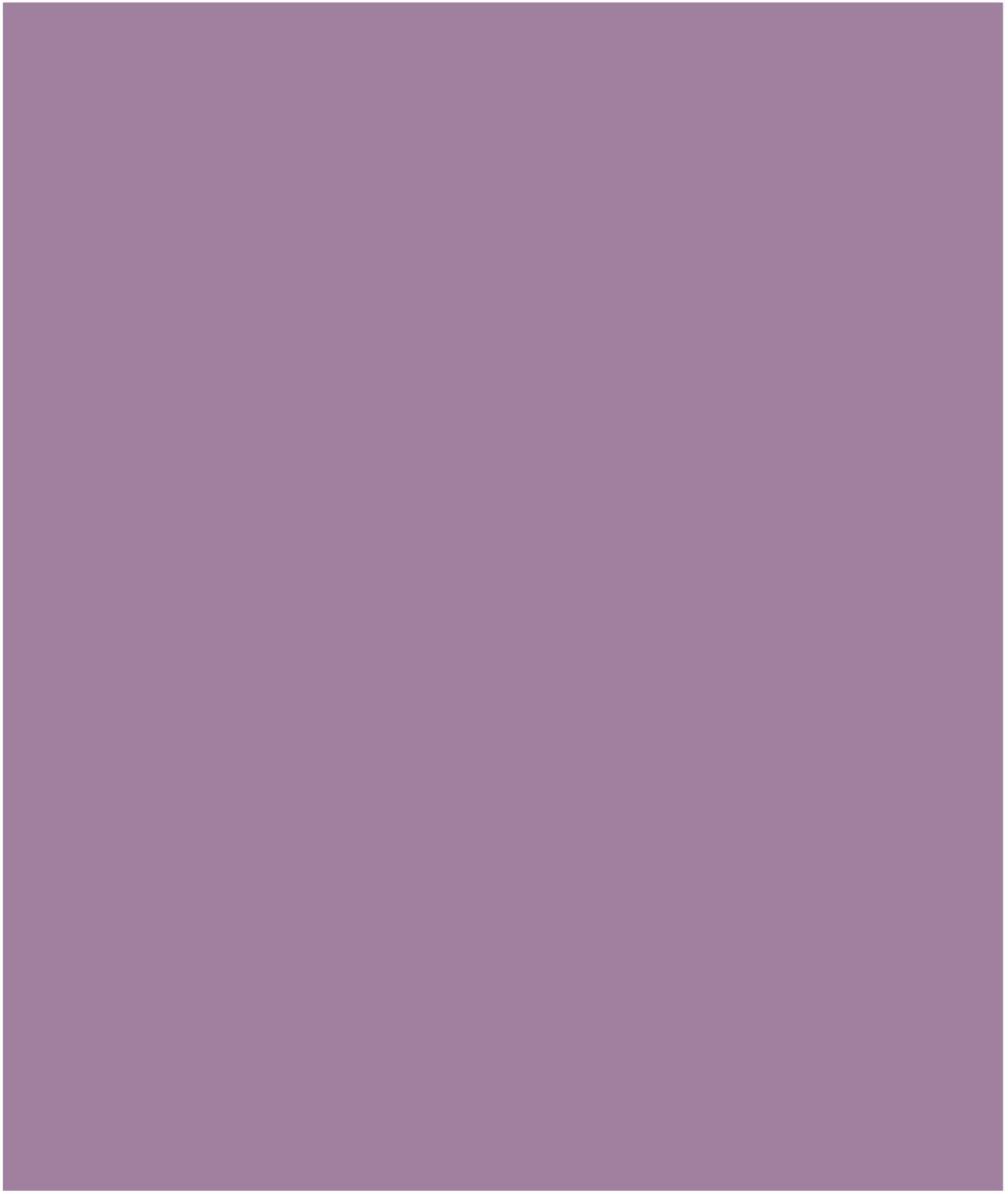


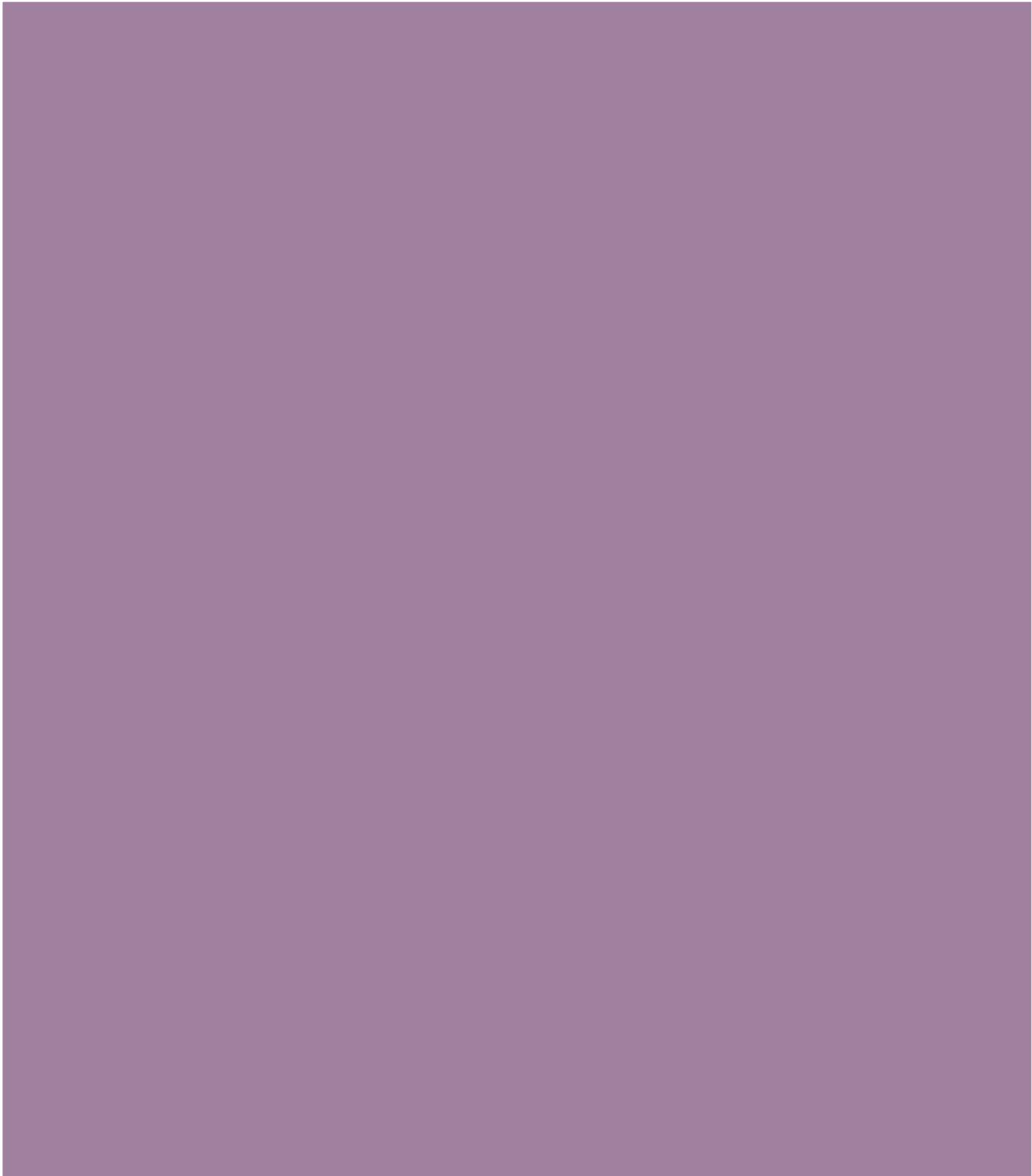




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**Duration of Treatment:** Single Dose

**Reference Therapy, Dose and Mode of Administration, Batch Number:** None.

**Criteria for Evaluation:**

Pharmacokinetic: SC-66110, SC-70303 and SC-71597 pharmacokinetic parameters.

Safety: Adverse events, vital signs, clinical laboratory parameters and physical examinations.

**Statistical Methods:**

An analysis of covariance (ANCOVA) with effect for age group and body weight as a covariate was performed on eplerenone T<sub>max</sub>, and the natural logarithms of C<sub>max</sub> and AUC<sub>0-24</sub>.

For the population pharmacokinetics, nonlinear mixed effects modeling as implemented in the NONMEM software were used to develop a population pharmacokinetic model for eplerenone plasma concentrations in the juvenile and adult hypertensive patient populations receiving single 12.5 mg, 50 mg and 100 mg eplerenone doses. A covariate analysis was performed to investigate the influence of selected patient factors on the primary pharmacokinetic parameter apparent clearance (CL/F) and the secondary pharmacokinetic parameter apparent central volume of distribution (V<sub>c</sub>/F). Specific factors for investigation included: patient population (pediatric vs. adult), body weight, body surface area, age and gender. Likelihood ratio tests were performed to assess the statistical significance of the covariate effects.

**PHARMACOKINETIC RESULTS:**

**Population Pharmacokinetic Results**

A two-compartment model adequately described the eplerenone plasma concentrations. A covariate analysis was performed on this model to investigate the influence of age, body weight, body surface area, sex, and race on the key pharmacokinetic parameters, apparent clearance (CL/F) and apparent central volume of distribution (V<sub>c</sub>/F). A 50 kg patient was predicted to have a V<sub>c</sub>/F of 37.7 L with a 45% predicted increase in V<sub>c</sub>/F for each doubling of body weight. The peak concentration, C<sub>max</sub>, which is influenced by V<sub>c</sub>/F was predicted to decrease by approximately 28% for each doubling of body weight. Inclusion of weight into the model reduced the between-patient variability estimate of V<sub>c</sub>/F by 38%, resulting in an estimate of 21.7% CV (coefficient of variation). The population mean estimate for CL/F was 8.19 L/hr with a 34.9% CV. No covariates were found to influence CL/F, and hence the patients' exposure (in terms of AUC) to eplerenone for a given dose. Overall, no differences between pediatric and adult patients were found that could not be explained by body weight.

**ANCOVA Results**

The results of the ANCOVA indicate there were no statistically significant differences between the adult and pediatric populations regarding AUC<sub>0-24</sub>, C<sub>max</sub> or T<sub>max</sub> values for SC-66110, SC-70303 or SC-71597 when adjusted for body weight (p≥0.2607 for all comparisons).

**RATIOS AND 90% CONFIDENCE INTERVALS FOR SC-66110, SC-70303, AND SC-71597  
PHARMACOKINETIC PARAMETERS FOR PATIENTS ≥ 6 YEARS OF AGE**

Pharmacokinetic Parameters Adjusted for Body Weight (a)	Least Squares Means (b)			Ratio of Means (6-16 Yrs./Adult)	90% CI for Ratio	P-Value (c)
	6-11 Yrs. Eplerenone 50 mg SD N = 6	12-16 Yrs. Eplerenone 100 mg SD N = 8	Adult Eplerenone 100 mg SD N = 8			
SC-66110						
AUC(0-24) (hr*ng/mL)	5493.2	5731.1	4886.6	1.15	(0.71, 1.86)	0.6262
C <sub>max</sub> (ng/mL)	996.9	1052.2	919.3	1.11	(0.81, 1.54)	0.5679
T <sub>max</sub> (hr)	1.8	0.9	1.8	–	–	0.2724
SC-70303						
AUC(0-24) (hr*ng/mL)	308.3	250.4	231.6	1.20	(0.73, 1.96)	0.5291
C <sub>max</sub> (ng/mL)	60.0	53.4	44.5	1.27	(0.88, 1.83)	0.2727
T <sub>max</sub> (hr)	3.2	1.0	2.9	–	–	0.6406
SC-71597						
AUC(0-24) (hr*ng/mL)	2621.8	2639.1	2692.4	0.98	(0.73, 1.30)	0.8898
C <sub>max</sub> (ng/mL)	311.3	306.8	329.5	0.94	(0.66, 1.33)	0.7536
T <sub>max</sub> (hr)	3.7	2.7	2.2	–	–	0.2607
(a) AUC and C <sub>max</sub> were dose-normalized to the 50 mg dose group and then log-transformed prior to the ANCOVA. (b) Least squares means have been back-transformed to the original scale for the log-transformed PK parameters. (c) P-value comparing the 6-16 yr. olds and the Adult group from an analysis of covariance (ANCOVA) with effect for age group and body weight as a covariate. Source: Tables T7.4 through T7.6.						

**SAFETY RESULTS:**

Adverse events were reported for two patients between the ages of 12 and 16 years receiving the 100 mg dose and for two adult patients receiving the 100 mg dose. All of the adverse events were mild in severity and were considered by the Investigator to have no relationship to the study medication. No adverse events causing withdrawal or serious adverse events were reported. No clinically significant findings were noted in the clinical laboratory, physical examination, EKG or vital sign data.

**CONCLUSION(S):**

1. The only statistically significant covariate found to influence the pharmacokinetics of eplerenone was weight. Increases in weight were correlated to increases in the apparent central volume of distribution. No significant differences in eplerenone's total exposure for pediatric hypertensive patients were observed when compared to adult hypertensive patients.
2. There were no statistically significant differences between the adult and pediatric populations regarding AUC<sub>0-24</sub>, C<sub>max</sub> or T<sub>max</sub> values for SC-66110, SC-70303 or SC-71597 when adjusted for body weight (p ≥ 0.2607 for all comparisons).
3. Single doses of eplerenone were well tolerated in pediatric and adult patients.

4.2.2 *Population pharmacokinetic study in pediatric patients following long-term therapy (Protocol A6141077 and report RR754-00063)*

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**Protocol Title:** An Open-Label, Long Term Study to Evaluate the Safety of Eplerenone in the Treatment of Hypertension in Children

**Investigators:** [REDACTED]

**Study Center(s):** Four sites in the United States, 5 sites in India, and 11 sites in the Russian Federation

**Publications Based on the Study:** None

**Study Initiation and Completion Dates:** 05 October 2004 to 20 June 2006

**Phase of Development:** Phase 3

**Study Objective(s):** To assess the long-term safety and toleration of eplerenone in children aged 6 to 16 years; to document the changes in growth, over a period of 1 year or more, and the changes in cognitive function over 1 year, in children aged 6 to 16 years treated with eplerenone; and to characterize the pharmacokinetics (PK) of eplerenone in children aged 6 to 16 years with hypertension.

The results for the cognitive function data are written in a separate report.

The results for the population PK data are presented in a separate report (RR 754-00063).

#### **METHODS**

**Study Design:** This was an open-label, long-term safety study. It included a Screening visit, followed by a dose-adjustment phase of approximately 6 weeks, followed by chronic therapy for a minimum of 1 year's duration. Subjects completing 1 year of treatment were encouraged to remain in the study until its completion in order to assess the longer-term safety of eplerenone. During and after the titration phase of the study, dosing was adjusted as clinically indicated at the discretion of the investigator.

**Diagnosis and Main Criteria for Inclusion:** Males and females aged 6 to 16 years. Subjects younger than 6 years of age were enrolled if they could swallow tablets in their entirety. Females of childbearing potential must have been able to use an acceptable method of nonhormonal contraception from at least 14 days prior to the start of study medication administration until completion of all study follow-up procedures. Subjects had to have a history of seated systolic blood pressure (SBP) greater than or equal to the 95<sup>th</sup> percentile for age, gender, and height, measured on at least 3 separate occasions (at least 1 day apart) prior to entry into the study. Subjects were excluded from the study if their stage of chronic kidney disease

(CKD) was equal to a 4 or 5 based on the National Kidney Foundation’s Kidney Disease/Kidney Disease Outcomes Quality Initiative (K/DOQI) classifications; or their serum or whole blood potassium was >5.5 mEq/L (mmol/L).

**Study Treatment:** Subjects initially received eplerenone 25 mg per day (QD) for the first 2 weeks. After 2 weeks, the dose was increased to eplerenone 25 mg twice daily (BID) (50 mg per day), if clinically indicated. After 2 additional weeks, the dose could have been increased to eplerenone 50 mg BID (100 mg per day), if clinically indicated. For the remainder of the study, the dose of eplerenone could have been adjusted downward or upward within the range of 25 mg QD and 50 mg BID at the discretion of the investigator. The sponsor supplied eplerenone as 25- or 50-mg capsules. Study drug lot numbers are presented in Table S1.

**Table S1. Eplerenone Lot Numbers**

Tablet Strength	Lot Number
Eplerenone	
25 mg	C301692, R13209, C050395, C050437
50 mg	R13211, C301695, C050399

**Efficacy Evaluations:** Not applicable.

**Pharmacokinetic Evaluations:** The evaluation of the population PK data is available as a separate report (RR 754-00063).

**Other Evaluations:** Data for cognitive function was collected and analyzed at [REDACTED]. The methods and results are available as a separate report.

**Safety Evaluations:** Safety was assessed by description of adverse events (AEs), clinical laboratory measurements, physical examinations, and vital signs. Assessment of growth was performed at screening, at one year, and at the end of the study. Testicular volume for male subjects and Tanner stages were recorded at specified visits.

## RESULTS

**Subject Disposition and Demography:** One hundred fifty subjects entered the study. Seventyone of the 150 subjects enrolled into this study from the preceding 10-week double-blind study (A6141001). One subject enrolled in the study but withdrew from the study prior to taking study medication and was not included in any safety evaluations. Therefore, 149 subjects assigned to study medication comprise the intent-to-treat (ITT) study population. Twenty (13.4%) subjects withdrew.

There were 106 males and 43 females ranging in age from 5 to 17 years. Two male subjects were enrolled after their 17<sup>th</sup> birthday. Fifty three subjects were 5 to 12 years of age and 94 subjects were 13 to 16 years of age. There were 97 white, 4 black, and 48 Asian subjects. Ten of the white subjects were Hispanic. The subjects had a median duration of treatment of 365 days and 106 subjects completed a year or more of follow-up.

**Efficacy Results:** Not applicable.

**Pharmacokinetic Results:** The results of the population PK data are available as a separate report (RR 754-00063).

**Safety Results:** Eighty-six subjects (58%) experienced at least 1 AE and 24 subjects (16%) experienced AEs considered treatment-related to eplerenone. The most frequent treatment-related AE, occurring in at least 7.4% of subjects, was headache. Most AEs were considered mild to moderate. Six subjects (4%) experienced at least 1 severe AE with the most frequent severe AE being headache (2 subjects).

There was 1 death and 11 subjects experienced at least 1 nonfatal serious adverse event (SAE). One subject died due to exacerbation of systemic lupus erythematosus and lupus nephritis more than 30 days after she discontinued from the study. The death was not considered treatment related.

Eleven subjects (7.4%) experienced SAEs with the most frequent SAEs being pneumonia and decrease in serum cortisol. Three subjects had SAEs that were considered related to eplerenone (decrease in cortisol; increase in estradiol, increase in progesterone, and decrease in cortisol; and elevated blood urea nitrogen [BUN] and elevated creatinine).

Interpretation of causation of the decrease in cortisol was confounded by concomitant treatment with exogenous glucocorticoids known to suppress cortisol secretion. Five subjects withdrew due to SAEs – 3 withdrawals were considered related to eplerenone treatment. Seven subjects (4.7%) withdrew due to AEs. Five subjects (3.4%) withdrew due to AEs that were considered treatment-related. Treatment-related AEs that led to withdrawal were decrease in cortisol, increase in estradiol, and increase in progesterone; increase in creatinine, increase in BUN; breast enlargement; and vomiting and acidity in the stomach.

There was 1 occurrence (0.7%) of a subject with an AE of hyperkalemia. The AE was considered mild; the subject recovered. The investigator considered the hyperkalemia possibly related to treatment. Seven subjects (4.8%) had potassium laboratory values >5.5 mEq/L (mmol/L) and 3 subjects (2.1%) had potassium laboratory values >6.0 mEq/L (mmol/L). The site investigator did not consider these laboratory abnormalities to be AEs. All of the subjects with laboratory evidence for serum potassium >6.0 mEq/L (mmol/L) had CKD (eg, chronic renal failure, nephrotic syndrome, renal hypoplasia). More than half (4 of 7) of those with serum potassium >5.5 mEq/L (mmol/L) also had CKD. The most frequent potentially clinically important increases in laboratory values occurred in triglycerides, eosinophils-absolute count, testosterone, uric acid, and bicarbonate. The most common potentially clinically important decreases in laboratory values were cortisol, and DHEAS. Sporadic abnormalities and small changes in mean values from baseline were observed for several hormonal factors. Further description and analysis of the hormonal results are included in a separate report.

### **Summary and Conclusion(s):**

1. Eplerenone 25 to 100 mg, total daily dose administered once or twice daily was well tolerated in 149 pediatric patients aged 5 to 17 years with hypertension.
2. One hundred six (106) children were followed for at least 1 year of eplerenone exposure.
3. Compared to previous findings in adults, no unique or unexpected adverse events emerged during eplerenone treatment in children. Hyperkalemia and sex-hormone related adverse effects (eg, gynecomastia, impotence, breast pain, and menstrual disorder) occurred infrequently and at an incidence similar to or lower than reported in adults. Most of the AEs were mild or moderate in intensity.
4. A greater incidence of respiratory illnesses and symptoms were observed in children as compared to adults; this finding might be expected for pre-school and adolescent children.

5. Cortisol was reported to decrease and be related to drug treatment at 1 study site. Interpretation of causation was confounded by concomitant treatment with exogenous glucocorticoids known to suppress cortisol secretion.
6. Safety of chronic administration of eplerenone 25 to 100 mg total daily dose in children ages 5 to 17 years with hypertension appears to be similar to that of adults treated with eplerenone for hypertension.

#### 4.2.3 Population PK study report in pediatric patients (754-00063)

**Report Title:** Population Pharmacokinetics of Eplerenone in Pediatric Hypertensive Subjects

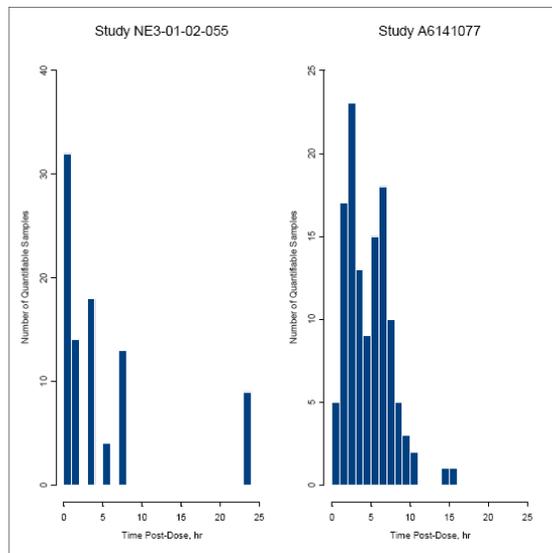
**OBJECTIVE(S):** The main objectives of this analysis are to characterize the population pharmacokinetics (PK) of eplerenone in pediatric hypertensive subjects and to evaluate the effect of important covariates including age, gender, race, and body size on the main pharmacokinetic parameters such as oral clearance and volume of distribution.

#### **STUDY OVERVIEW**

**Study Design:** The PK data collected during Studies NE3-01-02-055 and A6141077 in pediatric hypertensive subjects were pooled for the population analysis. In Study NE3-01-02-055, 18 pediatric subjects received single 12.5-, 50-, or 100-mg doses of eplerenone based on their age. In Study A6141077, 149 pediatric subjects assigned to the study initially received 25 mg of eplerenone once daily with subsequent dose increases up to 50 mg twice daily only if clinically indicated. Further dose adjustments were allowed to achieve final doses ranging from 25 mg once daily to 50 mg twice daily.

**Study Assessments:** In Study NE3-01-02-055, serial blood samples were collected at predose and at 0.5, 0, 1, 2, 4, 8, and 24 hours following single-dose administration. In Study A6141077, at selected PK sites, at Week 6 and again at Week 12, 2 blood samples were collected. In odd-numbered subjects, the samples were drawn between 8:00 AM and 12:00 PM at Week 6 and between 2:00 PM and 6:00 PM at Week 12. In even-numbered subjects, the specimens were drawn between 2:00 PM and 6:00 PM at Week 6 and between 8:00 AM and 12:00 PM at Week 12. The resulted sampling time distribution was demonstrated in Figure 8.

**Figure 8 Sampling time distribution, by study**



Source: /A614 SC66110 Eplerenone Inspira/A614-1077 & NE3-01-02-055 Cross-Study Analysis/Final Data/Final PK Analyses/Run 61/diagnostic\_plot21.wmf

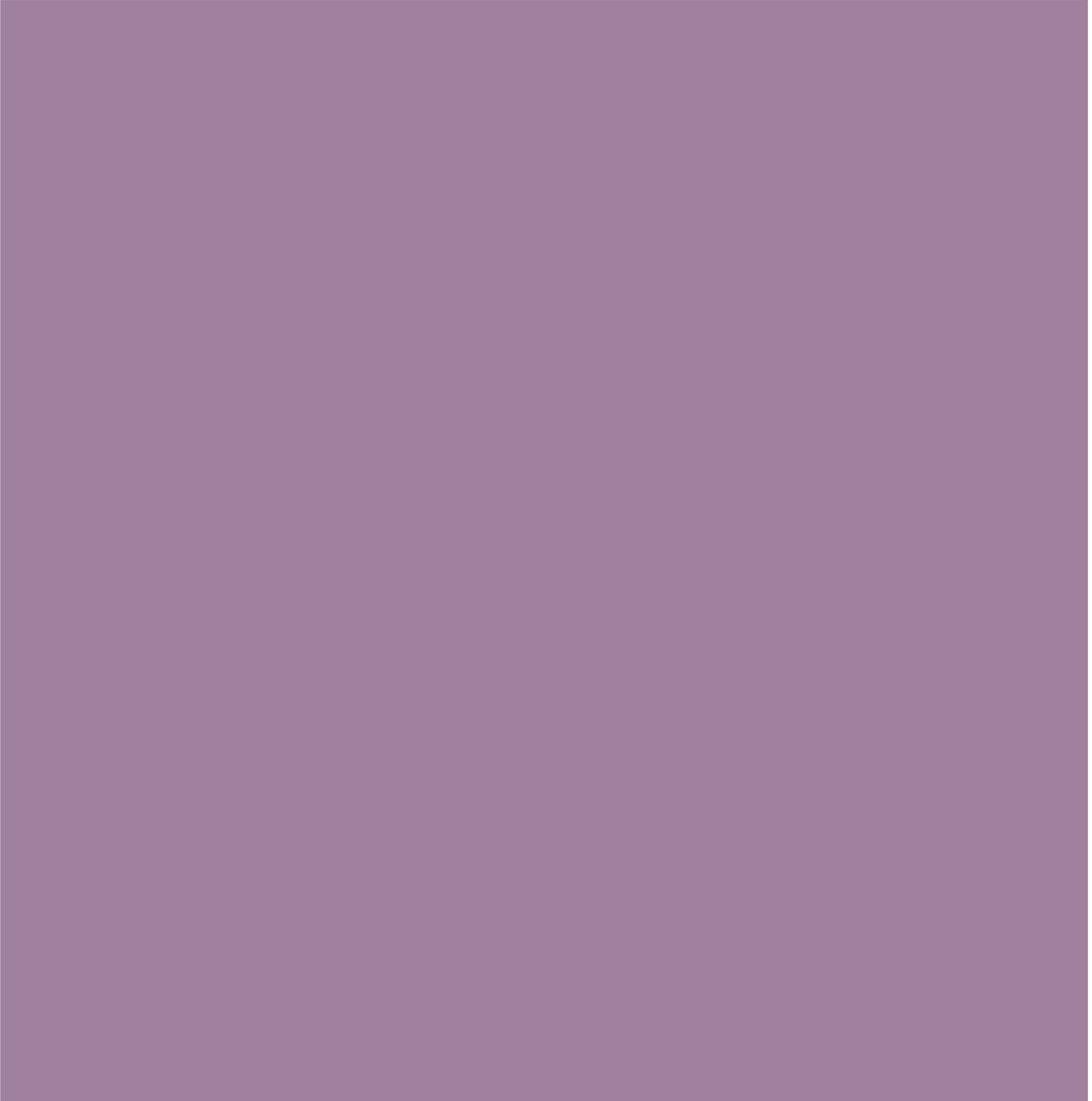
**DATA FOR ANALYSIS:** The derived dataset was created and validated for nonlinear mixed effects modeling (NONMEM) analysis by the pharmacokinetic/pharmacodynamic (PK/PD) Support team in the [REDACTED] following departmental standard operating procedures (SOPs) and Work Instructions. Subject identification, dosing information, time of sample collection, eplerenone concentrations, demographic, physiologic characteristics, and the most common concomitant antihypertensive agents were also included in the combined dataset.

**METHODS:** A 2-compartment model with first-order absorption and absorption lag time ( $t_{lag}$ ) was used as the final base (also referred to as basic) model to fit to the eplerenone concentrations. The first order conditional estimation (FOCE) method was used to estimate all the parameters with the exception of intercompartmental apparent clearance ( $Q/F$ ) and peripheral compartment apparent volume of distribution ( $V_p/F$ ) which were fixed to values obtained from modeling of rich sampling data, also the same values as the ones used in the population analysis of the Study NE3-01-02-055 complete dataset. In the current model, the intersubject variability for apparent clearance ( $CL/F$ ), central compartment apparent volume of distribution ( $V_c/F$ ), and absorption rate constant ( $k_a$ ) were modeled with a study-dependent additive error on the log-transformed concentration data (i.e., proportional error on the untransformed data) and reported as the approximate coefficient of variation (CV [%]). In building the final model and covariate selection, forward selection and backward elimination procedures were used at  $\alpha=0.01$  and  $\alpha=0.001$  levels, respectively. Among the body size related covariates, baseline body weight (BWT) was selected as the covariate of choice since it would be easier to dose as a function of that covariate. Other body size related parameters such as lean body weight, body surface area, body mass index, and height were highly correlated with BWT; therefore, they were not included in the covariate analyses. In addition, there was no major change in WT with time and as a result, BWT instead of WT was used.

Goodness of fit of different models to the data was evaluated using the following criteria: change in objective function, visual inspection of different diagnostic plots, precision of parameter estimates, and decreases in both interindividual variability and residual variability. The goodness of fit plots for the final base model and the final covariate model were shown in Figure 9 and Figure 10 respectively. The assumption checks for the final covariate model were presented Figure 11 and Figure 12. Furthermore, the weighted residual and individual weighted residual was assessed in Figure 13 and Figure 14.

**RESULTS:** The parameter estimates for the base and final models are provided in the following table (Table 6).

**Figure 9 Goodness of fit for the final base model**



**Figure 10 Goodness of fit for the final covariate model**

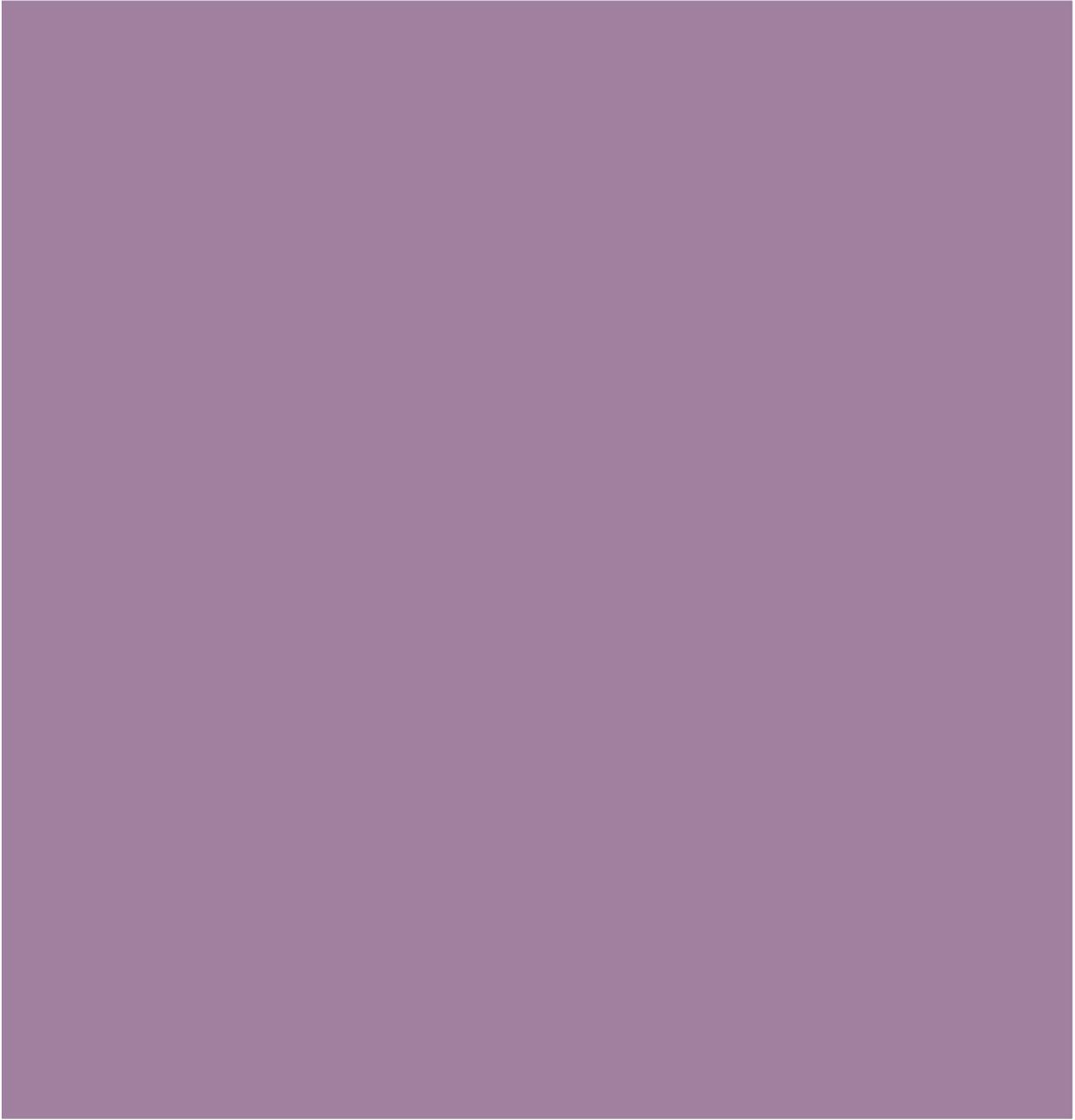


Figure 11 Distribution plots for CL/F, Vc/F, and Ka

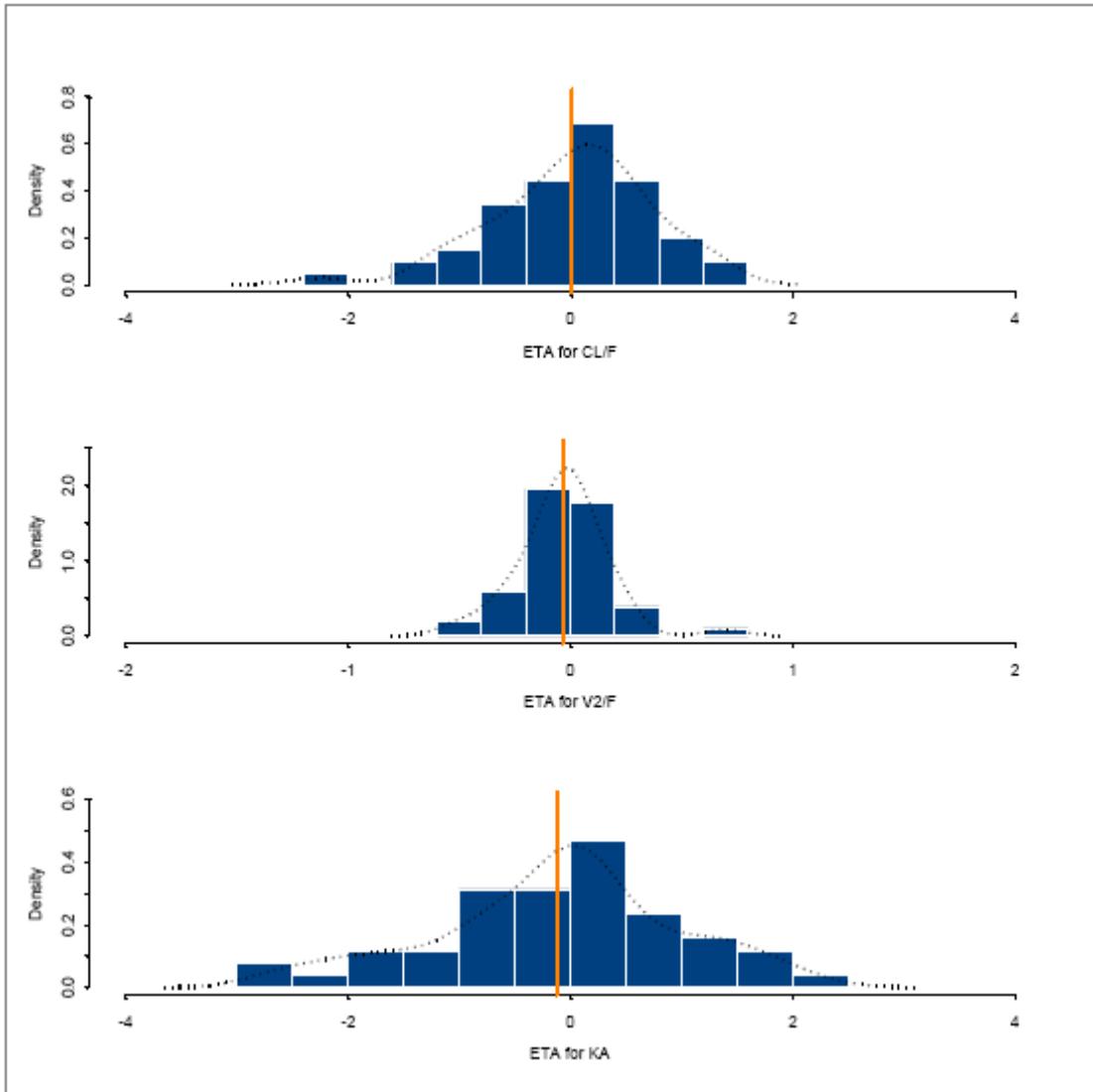
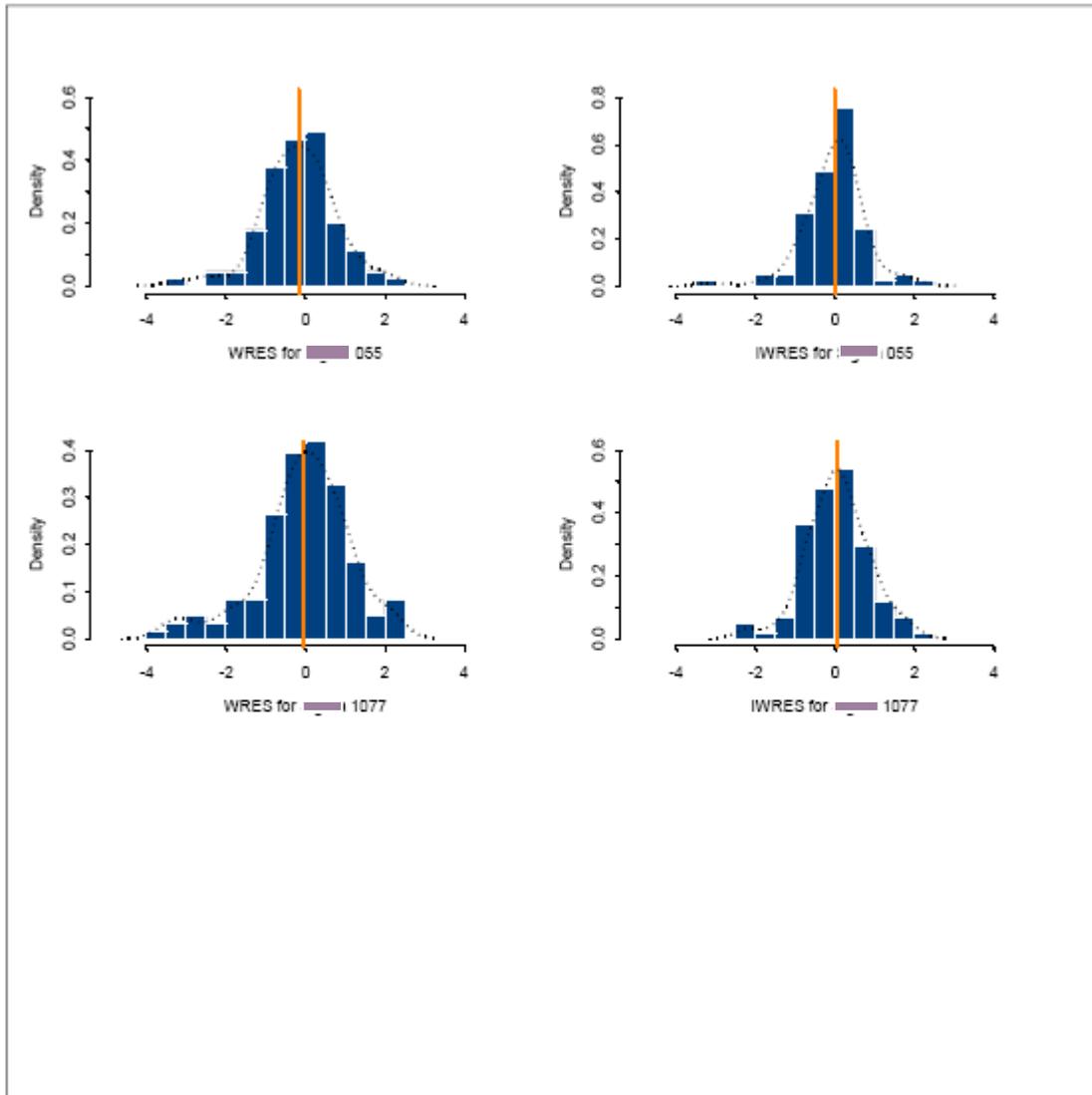


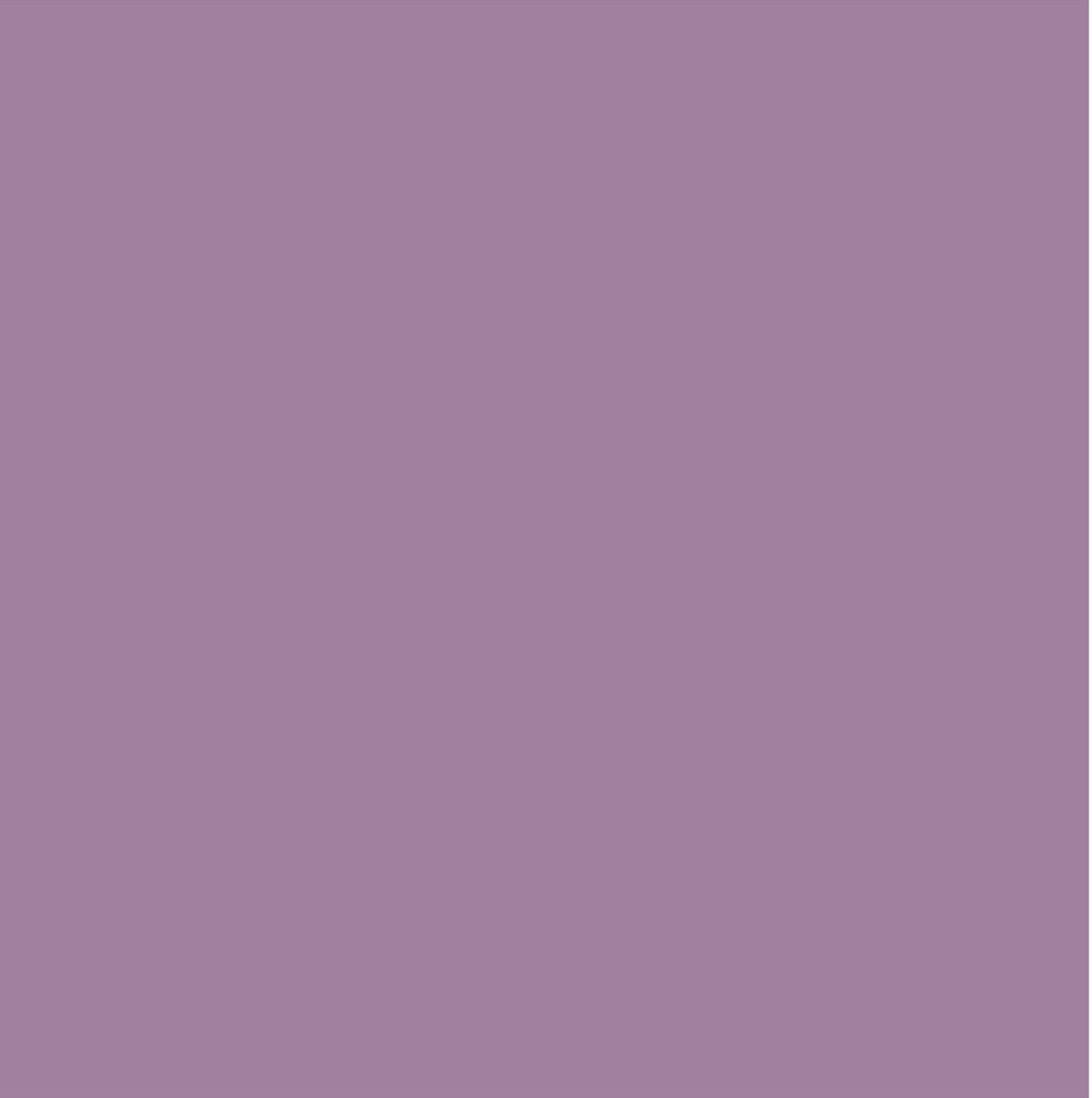
Figure 12 Distribution plots of WRES and IWRES, by study



Source: /A614 SC66110 Eplerenone Inspra/A614-1077 & NE3-01-02-055 Cross-Study Analysis/Final Data/Final PK Analyses/Run 61/diagnostic plots2.wmf



**Figure 14 Plots of WRES vs. PRED, by DOSE**



**Table 6 Mean and 95% Confidence Interval Results for the Base and Final Models**

Parameter	Base Model		Final Model	
	Model Results <sup>a</sup>	Bootstrap Results <sup>b</sup>	Model Results <sup>a</sup>	Bootstrap Results <sup>c</sup>
Population Mean Estimates (95% CI)				
CL/F ( $\theta_1$ ), L/hr	5.96 (4.72–7.20)	5.93 (4.78–7.37)	5.95 (4.72–7.18)	5.95 (4.83–7.38)
V <sub>c</sub> /F ( $\theta_2$ ), L	28.0 (17.8–38.2)	28.7 (19.6–41.4)	30.7 (24.6–36.8) <sup>d</sup>	31.2 (25.0–42.6) <sup>d</sup>
k <sub>e</sub> ( $\theta_3$ ), hr <sup>-1</sup>	1.55 (0.053–3.05)	1.93 (0.66–5.33)	1.56 (0.53–2.59)	1.70 (0.77–4.64)
t <sub>lag</sub> ( $\theta_4$ ), hr	0.270 (0.117–0.423)	0.244 (0–0.356)	0.273 (0.097–0.449)	0.247 (0.000–0.357)
V <sub>p</sub> /F ( $\theta_5$ ), L	42.1 (FIXED)	42.1 (FIXED)	42.1 (FIXED)	42.1 (FIXED)
Q/F ( $\theta_6$ ), L/hr	0.856 (FIXED)	0.856 (FIXED)	0.856 (FIXED)	0.856 (FIXED)
$\theta_{BWT(Vc/F)}$ ( $\theta_9$ ), L/kg	--		0.500 (0.298–0.702)	0.513 (0.310–0.804)
t <sub>1/2<math>\alpha</math></sub> <sup>e</sup> , hr	2.81 (1.27) <sup>f</sup>		3.14 (2.05) <sup>f</sup>	
t <sub>1/2<math>\beta</math></sub> <sup>e</sup> , hr	41.3 (7.76) <sup>f</sup>		41.5 (8.15) <sup>f</sup>	
Residual Variability CV (95% CI)				
$\sigma_{33}$	18.2 (11.2–25.2)	17.2 (11.0–24.3)	17.7 (10.7–24.7)	16.5 (10.8–23.3)
$\sigma_{1077}$	28.1 (16.4–39.8)	28.4 (19.7–37.9)	29.3 (20.4–38.2)	29.5 (20.5–38.8)
Intersubject Variability CV (95% CI)				
$\omega_{\eta(CL/F)}$	75.4 (13.5–106)	73.6 (52.6–95.4)	73.6 (53.4–89.4)	72.8 (54.8–92.4)
$\omega_{\eta(Vc/F)}$	57.4 (0–118)	62.4 (30.0–97.8)	33.0 (0–52.4)	38.8 (2.3–78.2)
$\omega_{\eta(k_a)}$	155 (66.3–209)	147 (74.1–215)	157 (56.9–214)	153 (85.4–218)
$\rho_{\eta(CL/F), \eta(Vc/F)}$	0.460		0.327	

<sup>a</sup> 95% confidence interval was estimated as (mean-1.96\*SE–mean+1.96\*SE).

<sup>b</sup> 24% Run Failure with a single attempt; only runs with successful covariance step were included.

<sup>c</sup> 33% Run Failure with a single attempt; only runs with successful covariance step were included.

<sup>d</sup> For a 45-kg subject.

<sup>e</sup> Calculated based on the micro-constants derived from macro-constants.

<sup>f</sup> Arithmetic mean (standard deviation).

The inclusion of the covariate total body weight on V<sub>c</sub>/F reduced the intersubject variability in this parameter from a CV of 57.4% for the base model to 33.0% for the final model. For pediatric hypertensive subjects, the estimated covariate effect is 0.500 ± 0.103, meaning that their V<sub>c</sub>/F and consequently their total volume of distribution is increased or decreased by 0.5 L for every kg of total body weight increase or decrease, respectively.

**CONCLUSIONS:** A two-compartment model with lag time was successfully used to describe the eplerenone pharmacokinetic data from two studies in 51 pediatric hypertensive subjects. Consistent with population analyses results of the complete dataset from Study NE3-01-02-055, the covariate analyses identified total body weight for V<sub>c</sub>/F as a statistically significant covariate. Similarly, the analyses confirmed that age and body weight did not have statistically significant effects on CL/F in the pediatric population studied. Pharmacokinetics of eplerenone in pediatric hypertensive subjects was not substantially different from those in adult hypertensive subjects.

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their  $V_c/F$  and consequently their total volume of distribution is increased or decreased by 0.5L for every kg of total body weight increase or decrease, respectively.

#### **4.3 REVIEWER'S COMMENTS ON THE POPULATION PK ANALYSIS**

The sponsor performed population PK study in pediatric patients (Report: 754-00063), we found that:

- The population PK analysis based on the two pediatric PK studies is acceptable.
- The sponsor should provide PRED vs. DV and IPERD vs. DV plots under normal scale in addition to those under log-transformed scale, in order to assist the evaluation of the goodness of fit of the model.
- PK parameters from subjects aged 4-6 can be derived from population PK approach. It is to note that 80% of the subjects (4 out of 5 subjects) in this age group likely received different formulations (i.e. crushed tablet together with applesauce rather than tablet). Furthermore, fewer PK samples with shorter sampling duration were taken in this age group. (PK samples were taken at 0.5, 4, 6 hour post-dose for patients aged 4-6, whereas samples were taken at 0.5, 1, 2, 4, 8, 24 hour post-dose for patients aged 6 -16). Then, PK parameters (especially  $K_a$  and  $CL/F$ ) in this age group should not be directly compared to the other age groups, because formulation is a confounding factor with age group and clearance can not be reliably estimated due to lack of PK information in elimination phase.

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