CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210709Orig1s000

CLINICAL REVIEW(S)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 210709

Submission Date(s): 06/05/2017

Applicant: Noden

Product: Aliskiren oral pellets

Reviewer: Christine Garnett

Date of Review: 10/12/2017

Covered Clinical Study (Name and/or Number): SPP100A2365 and SPP100A2365E1

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: A2365: 89 (US) and 66 (non US); A2365E1: 66 (US) and 49 (non US)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant adequately addressed financial interests.

[1] See [web address].

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/s/

CHRISTINE E GARNETT
11/08/2017

CLINICAL AND CLINCAL PHARMACOLOGY REVIEW

Application Type	NDA
Application Number(s)	0210709
Priority or Standard	Priority
Submit Date(s)	05/15/2017
PDUFA Goal Date	11/15/2017
Division/Office	ODE1/DCRP OTS/OCP/DCP1
Reviewer Name(s)	Christine Garnett, PharmD (clinical) Martina Sahre, PhD (clinical pharmacology)
Review Completion Date	09/15/2017
Established Name	Aliskiren
(Proposed) Trade Name	TEKTURNA
Applicant	Noden Pharma
Formulation(s)	Oral pellets (pediatric formulation)
Dosing Regimen	≥ 20 kg to < 50 kg [redacted] (b) (4) The maximum recommended dose is 150 mg. ≥ 50 kg Starting dose: 150 mg once daily. The maximum recommended dose is 300 mg
Applicant Proposed Indication(s)/Population	Treatment of pediatric hypertension in children aged 6 years and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Oral pellets for the treatment of pediatric hypertension in children aged 6 years and older, and weighing ≥ 20 kg

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Glossary

ABPM	ambulatory blood pressure monitoring
AC	advisory committee
ACE	angiotensin converting enzyme
ACEI	angiotensin-converting-enzyme inhibitor
AE	adverse event
ALT/SGPT	alanine aminotransferase / serum glutamic pyruvic transaminase
ANCOVA	analysis of covariance
Ang I	angiotensin I
Ang II	angiotensin II
ARB	angiotensin II receptor blockers
ASBP	ambulatory systolic blood pressure
AST/SGOT	aspartate aminotransferase / serum glutamic oxaloacetic transaminase
AUC	area under curve
BE	Bioequivalence
BLA	biologics license application
BMI	body mass index
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDS	core data sheet
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHMP	Committee for medicinal products for human use
CI	confidence interval
Cmax	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document

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EMA	European Medicines Agency
EU	European Union
FAS	full analysis set- study A2365E1
FAS1	full analysis set- Phase 1 of study A2365
FAS2	full analysis set- Phase 2 of study A2365
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
GRMP	good review management practice
HCTZ	Hydrochlorothiazide
HPMC	hydroxypropyl methylcellulose
IA	interim analysis
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LFT	liver function test
LOCF	last observation carried forward
LSM	least square mean
LT	long-term
LVH	left ventricular hypertrophy
MADBP	mean ambulatory diastolic blood pressure
MAP	mean arterial pressure
MASBP	mean ambulatory systolic blood pressure
MedDRA	medical dictionary for regulatory activities
mITT	modified intent to treat
msDBP	mean sitting diastolic blood pressure
msSBP	mean sitting systolic blood pressure
NDA	new drug application
NME	new molecular entity
o d.	once a day
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PDCO	Pediatric committee
PI	prescribing information
PIP	Pediatric investigational plan

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PK	Pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PRA	plasma renin activity
PRC	plasma renin concentration
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
RAAS	renin angiotensin aldosterone system
RAN	randomized set
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAF	safety set- study A2365
SAF1	safety set- Phase 1 of study A2365
SAF2	safety set- Phase 2 of study A2365
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
sNDA	supplemental NDA
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
UACR	urine albumin creatinine ratio
ULN	upper limit of normal
US	United States
WR	Written request

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1 Executive Summary

1.1. Product Introduction

The safety and efficacy of aliskiren are well established in adults with hypertension, and it is approved in the United States, the European Union, and other countries for the treatment of hypertension in adults.

The pediatric program was conducted in accordance with the post-marketing study requirements stated in the aliskiren (TEKTURNA) approval letter. The program consisted of three clinical studies, designed and completed in fulfillment of the Written Request and the Pediatric Research Equity Act. All three studies used aliskiren 37.5 mg oral pellets in HPMC capsule. This formulation was developed specifically for conducting studies in the pediatric population, and is the same as the one proposed for marketing.

In addition, a bioequivalence study was conducted, comparing exposures after a 300 mg dose of either the marketed tablet or oral pellets when given with a teaspoon of vanilla ice cream. This study showed that the AUC and Cmax are similar for both formulations and fall within the 80−125% limits to establish bioequivalence.

This review evaluates the pharmacokinetics, efficacy and safety of aliskiren in pediatric hypertensive patients 6 to 17 years of age.

1.2. Conclusions on Effectiveness

The results of studies A2365 and A2365E1 indicate that aliskiren is effective in lowering blood pressure in pediatric patients with hypertension aged 6 and over.

Study A2365 was a multicenter, randomized, double-blind, 8-week study to evaluate the dose response, efficacy and safety of aliskiren in hypertensive patients 6-17 years of age. Phase 1 of this study demonstrated a significant dose-dependent blood pressure (BP) lowering effect with aliskiren over a 4 -week treatment period for mean sitting systolic BP (msSBP) and diastolic BP (msDBP). However in the randomized withdrawal phase (Phase 2), the change in msSBP for the pooled mid/high doses of aliskiren was not statistically significantly different from the change in the corresponding placebo arms (-1.7 mmHg in favor of aliskiren, p=0.12). Additional analyses of the Phase 2 data supported the efficacy of the high dose group (150/300/600mg). Specifically, the LSM change was -2.8 mmHg for aliskiren compared to -0.1 mmHg for placebo (p =0.06). At the end of Phase 2, dose-response for msSBP and msDBP were maintained (p <0.01). Furthermore, a dose-response was also observed (p=0.009) for the percentage of patients receiving a positive treatment response in msSBP (defined as an msSBP < 95th percentile (for age, gender and height) or a 7 mmHg decrease in msSBP from the baseline).

Study A2365E1 was a multicenter, double-blind, randomized, 52-week extension study to evaluate the long-term safety, tolerability and efficacy of aliskiren compared to enalapril in hypertensive patients 6-17 years of age. After 52 weeks of treatment, changes in msSBP from

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baseline were similar with aliskiren compared to enalapril (-7.6 mmHg vs -7.9 mmHg). There were no statistically significant differences between aliskiren and enalapril treatments for changes from baseline to end of study for msSBP (p=0.82) and msDBP (p=0.32) as well as for key secondary endpoints, MAP and 24-h ABPM.

1.3. Conclusions on Proposed Pediatric Doses

The data from both the dose response and placebo controlled withdrawal phases of Study A2365 establish the efficacy of aliskiren in lowering blood pressure in children ages 6–17 years at the high doses of 75 mg, 300 mg, and 600 mg for children weighing ≥20 to <50 kg, ≥50 to <80 kg and ≥80 kg, respectively.

Exposures in the high dose arm were similar to those in adults after a 300 mg dose. The 600 mg dose produced roughly a doubling of exposures compared to adult exposures after a 300 mg dose, as well as compared to pediatric patients taking a 300 mg dose.

The results from the dose titration within each of the 3 different weight groups in the 52-week safety extension Study A2365E1 support the pediatric dosing regimen. The starting doses for each of the three groups were 37.5 mg, 75 mg and 150 mg, respectively. These starting doses correspond to the mid-dose level in study A2365. By week 42, more than 50% of the patients within each weight group were titrated to a higher dose level in an effort to achieve the desired BP level (i.e., msSBP < the 90th percentile for age, gender and height). Approximately 9% of patients in the aliskiren arm required add-on medication for BP reduction which was similar to the percentage of patients (10%) in the enalapril control group.

For the product label, the sponsor has proposed capping the maximum dose at 300 mg (the maximum dose in adults), instead of allowing patients >80 kg to titrate to 600 mg as was done in Study A2565E1. The exposure-response analysis supports the sponsor's proposal. The log10-linear relationship between trough aliskiren concentrations and change from baseline in msSBP is statistically significant but shallow [log10 trough slope = -2.7 (3.9, -1.6), p < 0.001]. The expected mean BP reduction with a 2-fold increase in dose is less than -1 mmHg.

1.4. Benefit-Risk Assessment

The results of studies A2365 and A2365E1 indicate that aliskiren is effective in lowering blood pressure in patients with hypertension 6 to 17 years of age.

There were no new or unexpected safety findings in the two clinical trials that were conducted in pediatric patients. In study A2365E1, there were no important imbalances between aliskiren and enalapril in the number of patients with AEs associated with anaphylactic reactions, hypotension, hyperkalemia or renal injury, potential risks based on the experience in adults. 1% of patients discontinued treatment due to AEs. In the two trials, there were no reports of medication errors (e.g., swallowing the HPMC dispensing capsule) or other findings that might suggest a potential problem with use of the proposed pediatric formulation as described in the proposed product label.

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2 Therapeutic Context

2.1. Analysis of Condition

The prevalence of hypertension in children has been increasing worldwide. This is mostly driven by the increasing prevalence of childhood obesity. The definition of hypertension in children and adolescents is based on the normative distribution of BP in healthy children. Hypertension in children and adolescents is defined as an average SBP or DBP that is ≥ 95th percentile for gender, age, and height on at least three separate occasions.

- Primary (essential) hypertension in children is usually mild or Stage 1 hypertension. As in adults, it is often associated with a positive family history of hypertension or cardiovascular disease, and clusters with other cardiovascular disease risk factors or comorbidities including obesity, dyslipidemia, and insulin resistance.
- Renal parenchymal and renovascular diseases are the most common causes of secondary hypertension in children.

2.2. Analysis of Current Treatment Options

There are 10 drugs approved by the FDA for the treatment of hypertension in children and adolescents. Drugs that are used "off-label" for pediatric hypertension include captopril, atenolol, propranolol, nifedipine, furosemide and hydrochlorothiazide.[1]

3 Regulatory Background

[1] Chu PY et al. Anti-hypertensive drugs in children. World J Cardiol 2014 May 26; 6(5): 234-244

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3.1. U.S. Regulatory Actions and Marketing History

The pediatric program was conducted in accordance with the post-marketing study requirements stated in the TEKTURNA approval letter. The pediatric plan was designed to support a hypertension indication in children 6-17 y ears of age and fulfill the conditions of a Written Request under the BPCA and PREA.

3.2. Summary of Presubmission/Submission Regulatory Activity

The timelines of major regulatory milestones are as follows. Requirements of the pediatric Written Request are summarized in Table 3.

- 03/05/2007: Approval of TEKTURNA tablets for treatment of hypertension in adults.
- 5/13/2008: FDA issues a pediatric WR for TEKTURNA.
- 03/14/2009: Amendment 1 of the WR extends the due date of the report to the Agency.
- 08/06/2012: Amendment 2 of the WR further extends the due date of the report to the Agency.
- 01/28/2016: Novartis submits a pediatric sNDA without a pediatric indication or commercial pediatric formulation. Novartis asserts that study A2365 did not meet its primary objective and failed to establish efficacy. Upon review of the data, FDA disagreed with the interpretation of the efficacy results and advised Novartis to develop a commercial pediatric formulation to meet the requirements of the WR.
- 03/25/2016: Novartis withdraws the sNDA for the purpose of resuming the commercial development of a pediatric dosage form and developing a corresponding CMC module.
- 08/09/2016: Amendment 3 to the WR extends the due date for submission of the clinical study report to on or before 04/20/2017.

Table 1: Requirements of Pediatric Written Request

WR Section	Requirement
Type of Studies	• Pharmacokinetic sampling in patients spanning the same age range as those to be studied for effectiveness, • Dose-response trial of effectiveness in hypertensive pediatric patients; and • Safety data derived from a controlled trial and a 1-year open treatment phase following the effectiveness trial, and a summary of all available information on the safety of the drug in hypertensive pediatric patients. The safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data.
PK Trials	• Pharmacokinetic data must be obtained over the range of doses and ages studied for effectiveness. Patients must have grossly normal metabolic function. • Data must be collected with respect to aliskiren and any metabolites that make substantial contributions to its efficacy 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, Cmax, and tmax in pediatric subjects

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	of the various age groups.
Dose-Ranging Trial	• The dose-ranging study must be double-blind in design and it must evaluate at least three dose levels of aliskiren. You must obtain agreement from the Division on the doses incorporated into this study. • The duration of the parallel portion of the study must be at least 2 weeks after titration to target doses is completed. The primary end point must be either absolute or percentage change in systolic or diastolic pressure. • The primary analysis must include all patients with data on randomized treatment. • If the pharmacokinetics of the drug in children, derived from the pharmacokinetic trial described above, differ substantially from the reported pharmacokinetics in adults, such that the serum half-life is appreciably altered, the trial must include an assessment of the effect of varying dosing interval on trough antihypertensive effect. This must include measurement of the effects of the drug throughout the dosing interval. You must consistently measure both systolic pressure and diastolic pressure in all patients. You must prospectively identify either the systolic or diastolic blood pressure as the primary end point. For the trial designs other than randomized withdrawal from active drug (see above), the primary efficacy measurement must be the change in blood pressure from baseline to the time of the last dose plus the inter-dosing interval. • For randomized withdrawal trial designs, the primary efficacy measurement must be the change in blood pressure at the interdosing interval from the last on-treatment visit to the end of the withdrawal period, or to the time at which an acceptable blood pressure is exceeded. • An age-appropriate formulation must be used in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test one, and, if it is found safe and effective in the studied pediatric populations, you must seek marketing approval for that age appropriate formulation. • If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. • Bioavailability of any formulation used in the studies must be characterized • The trial must be performed in patients of both sexes. • If adolescents are included, at least one additional age group must be included, and 50% of the patients in the trial must be ≤12 years old. • They must not be recruited if other interventions known to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. • The trial must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance. You must obtain agreement on the final statistical analysis plan, including handling of missing data, prior to 25% enrollment. • Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. • This requires you to show that if the true treatment effect for one of the treatment groups were minimally "clinically meaningful", the pre-planned analysis would have at least 90% power to infer that at least one dose or the high dose is significantly different from placebo. • However, to ensure that the study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed at >90% of initially planned enrollment.

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Extraordinary Results	If you believe this is the case, you must contact the Agency to seek an amendment.
Labeling	Under section 505A(j) of the Act, regardless of whether the studies demonstrate that aliskiren is safe and effective, or whether such study results are inconclusive in the studied pediatric population, you must submit labeling to include information about the results of the studies.
Response to Written Request	Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.
Reporting	• You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. • Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. • Reports of the above studies must be submitted to the Agency on or before 04/20/2017.

Reviewer's Comment: The sponsor has fulfilled the requirements of the WR because the study results can be viewed as interpretable.

3.3. Foreign Regulatory Actions and Marketing History

The pediatric formulation (37.5 mg oral pellets in HPMC dispensing capsules) is not approved in any other country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Product Quality

There was extensive internal discussion on the acceptability of using a "dispensing" capsule to deliver oral pellets (i.e., a capsule that is not intended to be swallowed by patients). See the Product Quality Review for additional information.

Reviewer's comment: The clinical trial data do not suggest that the dispensing capsule posed a choking risk in pediatrics. There were no protocol violations, treatment discontinuations or adverse events related to the dosage form or administration.

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4.2. Nonclinical Pharmacology/Toxicology

According to Dr. Jagadeesh's Pharmacology and Toxicology Review (dated 09/14/2017), data obtained in juvenile rats indicate that there is a distinct age-dependent relationship between dose and exposure in aliskiren-treated animals. The high aliskiren exposure in very young rats accounted for the observed morbidity and mortality. Studies of the ontogeny of Multidrug-resistant protein 1 (MDR1) and Organic anion transporting polypeptide 2 (OATP2) mRNA expression in rats, and the intravenous (IV) juvenile rat PK study, all indicate that the substantial aliskiren exposure increase in very young juvenile rats correlates with the process of maturation of the drug transporters involved in aliskiren absorption and disposition. Expression levels (mRNA) for MDR1 and OATP2 in intestine, liver and brain were much lower in rats aged 14 days compared to rats aged ≥21 days. Immaturity of MDR1a in enterocytes appears to be the most important mechanism responsible for the high exposure following oral aliskiren administration to very young rats.

Reviewer's comments: Aliskiren should be contraindicated in children <2 years and should not be used in children aged 2 to less than 6 years of age because of the potential for a substantial increase in aliskiren exposure.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies included in this submission are provided in Table 2.

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Table 2: Summary of Clinical Studies

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
A2365	Multicenter, randomized, double-blind, 8-week study to evaluate the efficacy and safety of aliskiren in pediatric hypertensive patients 6-17 years of age. The study consisted of 3 phases: (1) 3-week wash-out; (2) 4-week randomized, double-blind dose-response consisting of 3 aliskiren dose groups; and (3) a randomized double-blind placebo-controlled withdrawal phase of up to 4 weeks.	low dose (6.25/12.5/25 mg), mid dose (37.5/75/150 mg), and high dose (150/300/600 mg) according to weight cut-offs <50 kg/≥50 kg and <80kg/≥80kg and ≤150 kg	Changes in msSBP from baseline to end of Phase 1 and from end of Phase 1 to end of Phase 2, as measured by office blood pressure reading	Duration of treatment was up to 8 weeks.	268	Male and female children 6 to 17 years with msSBP ≥95th percentile for age, gender and height by office BP. Patients were required to weigh ≥20 kg and ≤150 kg and safety wash out of prior anti-hypertensive medications.	51 centers in 8 countries
A2365E1	Multicenter, double-blind, randomized; 52 week extension study to evaluate the safety, tolerability and efficacy of aliskiren compared to enalapril in hypertensive patients aged 6-17 years of age	Children ≥20 kg to <50 kg: aliskiren 37.5 mg or enalapril 2.5 mg; Children ≥50 kg to < 80 kg: aliskiren 75 mg or enalapril 5 mg; Children ≥ 80 kg to ≤150 kg: aliskiren 150 mg or enalapril 10 mg	Change from baseline of A2365 in msSBP	52 weeks	208	Patients who had successfully completed Phase 1 (dose response phase) and at least 1 week of Phase 2 (placebo withdrawal phase) of A2365, with no serious and drug-related AEs	38 centers in 6 countries
Studies to Support Safety							
A2365E2 (on-	1-2 year observational extension study aimed to			1-2 years		hypertensive children 6 to 17	

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Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
going)	evaluate the long term growth and development of hypertensive children 6 to 17 years of age previously treated with aliskiren.					years of age previously treated with aliskiren	
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
A2256	open-label, multiple-dose, multi-center study to evaluate the safety/tolerability and pharmacokinetics of aliskiren in hypertensive pediatric patients 6-17 years of age	Low dose: 2mg/kg High dose: 6mg/kg	PK	8 days	39	Hypertensive pediatric and adolescent patients 6 - 17 years of age	14 centers in 5 countries
A2109	An open label, randomized, three-periods, single dose, crossover study in healthy male and female subjects to assess the bioavailability of 300 mg aliskiren (b) (4) (minitablets) relative to the 300 mg aliskiren market film coated tablet and the effect of food on the PK of 300 mg aliskiren (b) (4)	300 mg	PK	1	69	Healthy adult volunteers	1 center

Reference ID: 4166471

5.2. Review Strategy

The sponsor's efficacy and safety results were confirmed through independent analyses of the data using R version 3.3.2. Additional analyses were conducted to explore dose-response relationships for efficacy in studies A2365 and A2365E1. Analysis of adverse events was performed using MAED Release Version 1.7.0. The coding from verbatim to MEDRA preferred terms for AEs were verified. SAE/AEs were summarized by a FDA customized grouping of preferred terms (Appendix, Table 24).

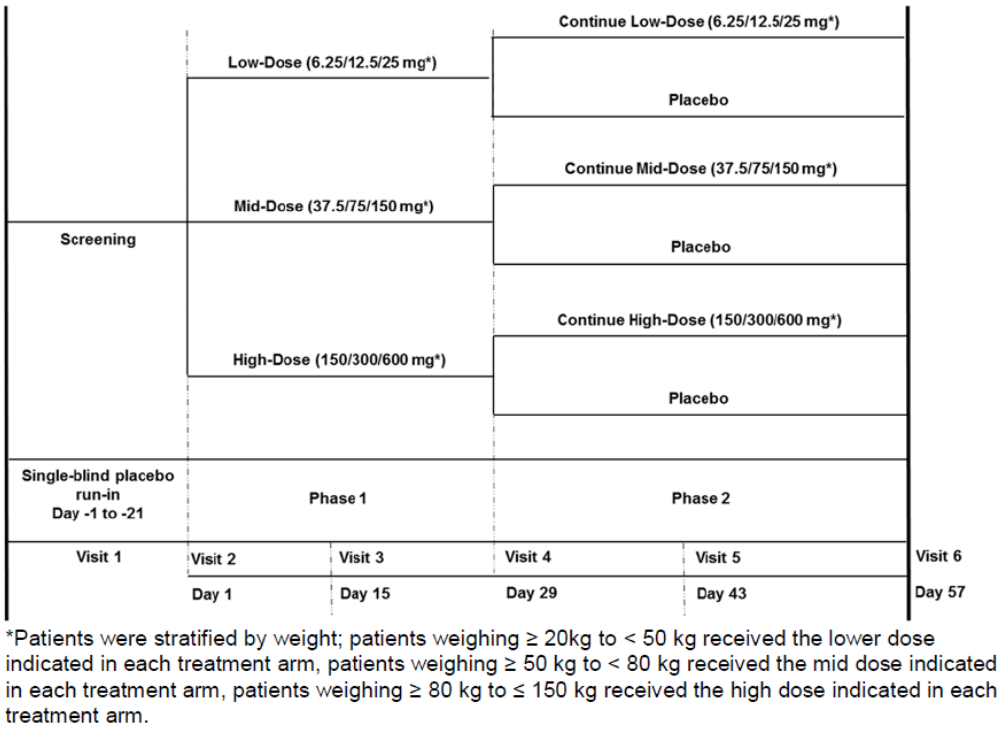
6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. SPP100A2365

6.1.1. Study Design

A schematic of the study design for A2365 and the extension study, A2365E1, is shown in Figure 1.

Figure 1: Study Design of A2365 and the Extension Study A2365E1



*Patients were stratified by weight; patients weighing ≥ 20kg to < 50 kg received the lower dose indicated in each treatment arm, patients weighing ≥ 50 kg to < 80 kg received the mid dose indicated in each treatment arm, patients weighing ≥ 80 kg to ≤ 150 kg received the high dose indicated in each treatment arm.

Source: Figure 9-1 in CSR for A2365

Reference ID: 4166471

Overview and Objective

The primary objectives of this study were:

- In Phase 1 (dose response phase), to evaluate the dose response of aliskiren in msSBP change at end of Phase 1 from the baseline, as measured by office BP reading, in children 6 to 17 years old with hypertension.
- In Phase 2 (placebo-controlled withdrawal phase), to evaluate pooled treatment effect of aliskiren (mid and high doses) in msSBP change at end of Phase 2 from the end of Phase 1, compared to placebo pooled from corresponding arms, as measured by office BP reading, in children 6 to 17 years old with hypertension.

Trial Design

This was a multicenter, randomized, double-blind, 8-week study to evaluate the efficacy and safety of aliskiren in pediatric hypertensive patients 6-17 years of age.

- Screening phase: A single-blind placebo wash-out for up to a maximum of three weeks (21 days).
- Phase 1: A four week (28 day) randomized, double-blind dose-response phase consisting of 3 aliskiren dose groups: low (6.25/12.5/25 mg), mid (37.5/75/150 mg), and high dose (150/300/600 mg) according to weight. The dose ratio for all three dose groups were the same for the low-weight (≥ 20 to < 50 kg), the mid-weight (≥ 50 kg to < 80 kg) and the high-weight (≥ 80 kg to ≤ 150 kg) patients with a low: mid: high dose ratio of 1:6:24. Patients were stratified at baseline by weight (≥ 20 to < 50 kg; ≥ 50 kg to < 80 kg and ≥ 80 kg to ≤150 kg), age (6-11 and 12-17 years old), region, and by hypertension etiology (primary vs. secondary). For Phase 1, patients were randomized to aliskiren low, mid and high dosing groups in a 2:1:2 ratio and were dosed based on their weight category at randomization.
- Phase 2: A randomized double-blind placebo-controlled withdrawal phase of up to four weeks (28 days). Patients either continued the aliskiren treatment assigned during Phase 1 or were switched to placebo.

The duration of the dose response phase (4 weeks) was based on data from studies conducted with aliskiren in adults showing that a substantial proportion (85%-90%) of the BP lowering effect was observed within 2 weeks of initiation of treatment, and near-maximal effect was reached by 4 weeks.

The duration of the placebo-controlled withdrawal phase (4 weeks) was based on the long half-life (34-41 hours) of aliskiren and the results of withdrawal trials in adults which showed that 60% of the BP reduction effect was maintained at week 2 following cessation of treatment.

The study population consisted male and female children, 6 to 17 years of age at randomization (Visit 2), with msSBP ≥ 95th percentile for age, gender and height measured by office BP. Patients had to weigh between 20 kg to 150 kg, inclusive, and had to be safely able to wash out prior antihypertensive therapy for a minimum of 7 days. Patients were excluded if they had clinically significant abnormalities laboratory values, history of angioedema, heart failure, heart

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block, atrial fibrillation, or creatinine clearance < 30 mL/min/1.73m².

Study Endpoints

Mean sitting systolic blood pressure (msSBP) was the primary endpoint. Secondary endpoints included msDBP, MAP, rates of responders and ambulatory blood pressure (MASBP and MADBP).

Reviewer Comment: Similar study endpoints have been used in other pediatric hypertension trials and meet the requirements of the pediatric WR.

Statistical Analysis Plan

The following populations were used for analyses:

- The randomized sets (RAN1 and RAN2) consisted of all patients who received a randomization number at respective phases.
- The full analysis sets (FAS1 and FAS2) consisted of all patients who were randomized into Phase 1 and Phase 2 respectively. Following the intent-to-treat principle, patients were analyzed according to the treatment they were assigned to at randomization. However, patients who did not qualify for randomization and were inadvertently randomized into the study phase were excluded from the FAS1 or FAS2, respectively, provided these patients did not receive study drug during that study phase.
- The per-protocol sets (PPS1 and PPS2) consisted of all FAS patients who completed the respective study phases without any major protocol deviations that impacted on efficacy assessment. The major protocol deviations were pre-specified prior to unblinding treatment codes for analyses.
- The safety sets (SAF1 and SAF2) consisted of all patients who received at least one dose of double-blind study drug at respective phases. Patients were analyzed according to the treatment received.

Primary efficacy endpoints were:

- Change in msSBP from baseline to end of Phase 1, as measured by office BP reading.
- Change in msSBP from end of Phase 1 to end of Phase 2, as measured by office BP reading.

Baseline was defined as Week 0 value.

The primary dose-response relationship was evaluated at the conclusion of Phase 1 and determined by the slope for change from baseline in msSBP. If the slope was statistically significant, then a difference among the doses had been identified. The null hypothesis for Phase 1 was that the slope of the dose-response curve for change from baseline in msSBP was not statistically different from zero at the end of Phase 1. The tests were conducted at a 2-sided significance level of 0.05. An ANCOVA model including weight, age strata, region, and baseline hypertension status (primary vs. secondary) as factors, and baseline msSBP and dose ratio as covariates, was carried out at a 2-sided significance level of 0.05.

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The analysis results in Phase 2 were used to evaluate whether there is a blood pressure effect due to placebo washout. The null hypothesis for Phase 2 was that the change from end of Phase 1 in msSBP was not different between the pooled aliskiren high and mid doses, and placebo pooled from corresponding arms at the end of Phase 2. An ANCOVA model that included treatment, weight, age strata, region, and hypertension status (primary vs. secondary) as factors and end of Phase 1 msSBP as a covariate, was carried out at a 2-sided significance level of 0.05.

For patients with missing values at Week 8, the last post-baseline observation was carried forward (LOCF). A Similar method was also applied to end of Phase 1.

A penalty-free estimate of variability of the sitting BP was completed when 50% and 90% of patients were recruited. The aim of these interim analyses was to assess the sample size using the information of the common variance estimate and make adjustments as needed. Results from the interim analysis conducted at 90% recruitment (11 Mar 2014, 91.3% of patients randomized) showed a total sample of 178 randomized patients would be needed to power the study. Thus no changes were made to the sample size as 251 randomized patients were included in the interim analysis.

Protocol Amendments

The original protocol was finalized on December 18, 2009. The protocol was amended four times as summarized below.

Amendment 1 (effective date: January 19, 2010)

- Deletion of the requirement to collect pregnancy outcomes for partners of patients who took study drug
- Echocardiography must be performed at baseline, prior to the administration of study drug; results do not need to be interpreted prior to randomization
- Addition of medical history to the assessment schedule

Amendment 2 (effective date: April 5, 2010)

- Clarification of age at randomization (Visit 2)
- Clarification of echocardiography requirements
- Addition of 4 study visits for the purpose of collecting weekly trough blood pressure
- Addition of trough PK collection at Visit 4
- Addition of glucose to clinical chemistry parameters
- Removal of alkaline phosphatase from the clinical chemistry parameters
- Addition of sodium, potassium, chloride and BUN collection at Visit 2

Amendment 3 (effective date: September 29, 2010)

- Addition of itraconazole to list of prohibited concomitant treatments
- Clarification of Visit 2 procedures timing
- Clarification of Visit 4A timing
- Clarification of height measurement

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- Addition of IVRS entry to note core study completion to Visit 6 study procedures
- Removal of glucose from Appendix 2: Visit 1 Laboratory alerts

Amendment 4 (effective date: June 24, 2013)

- Text updated to indicate that, at randomization, at least 10% of the patient population will have secondary hypertension by history

Reviewer Comment: Protocol amendments are appropriate and do not impact the interpretation of trial results.

Data Quality and Integrity: Sponsor's Assurance

Clinical audits were performed by Novartis Quality Assurance (QA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. Audits were conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and were performed according to written QA SOPs. The frequency of audits was based on the category and risk assessment. Investigator sites were considered for audit based on the criticality and complexity of the trial, number of patients enrolled in the trial, and other factors derived from the knowledge/risk-based approach.

Audits were conducted at four sites in three countries: Site 0607 in Hungary, Site 1728 in Slovakia, Site 1729 in USA, Site 431069 in USA.

6.1.1. Study Results

Compliance with Good Clinical Practices

The study protocol and the amendment were reviewed by the Independent Ethics Committee or Institutional Review Board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each subject or guardian in writing prior to performing any study-specific procedures.

Financial Disclosure

A statement regarding financial certification (FDA Form 3454) was provided.

Reviewer Comment: No disclosable financial information was reported by any of the clinical investigators participating in the trials.

Patient Disposition

A total of 268 patients were randomized in Phase 1 including 1 mis-randomized patient who did not take double blind medication (PID 0517/00004) and thus was not included in the safety (SAF1 and SAF2) or full analysis (FAS1 and FAS2) sets. The majority of patients completed the study with 260 patients (97.0%) completing Phase 1 and 255 patients (98.1%) completing Phase 2. The rate of discontinuation due to any reason overall during both Phase 1 and 2 was

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4.5%, generally balanced between the phases. Three patients (2 from ALI treatment and 1 from PLB) withdrew from the study due to AEs (see section 7.3.3 for description of the AEs).

Table 3: Patient disposition (for Phase 1)

Disposition	ALI Low 6.25/12.5/25 mg N=108 n (%)	ALI Mid 37.5/75/150 mg N= 54 n (%)	ALI High 150/300/600 mg N=106 n (%)	Total N=268 n (%)
Completed phase1	107 (99.1)	51 (94.4)	102 (96.2)	260 (97.0)
Discontinued phase1	1 (0.9)	3 (5.6)	3 (2.8)	7 (2.6)
Reason for discontinuation				
Subject withdrew consent	0 (0.0)	2 (3.7)	1 (0.9)	3 (1.1)
Protocol deviation	0 (0.0)	1 (1.9)	1 (0.9)	2 (0.7)
Adverse Event(s)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.4)
Unsatisfactory therapeutic effect	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.4)

Percentage (%) was calculated using the randomized set 1 (N) as the denominator.

Source: Sponsor's Table 10-1 in the CSR for A2365

Table 4: Patient disposition (for Phase 2)

Disposition Reason	ALI Low 6.25/12.5/25 mg N= 50 n (%)	PLB Low N= 57 n (%)	ALI Mid 37.5/75/150 mg N= 30 n (%)	PLB Mid N= 21 n (%)	ALI High 150/300/600 mg N= 50 n (%)	PLB High N= 52 n (%)	Total N=260 n (%)
Completed Phase 2	50 (100.0)	54 (94.7)	30 (100.0)	21 (100.0)	49 (98.0)	51 (98.1)	255 (98.1)
Discontinued Phase 2	0 (0.0)	3 (5.3)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.9)	5 (1.9)
Reason for discontinuation							
Adverse Event(s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.9)	2 (0.8)
Subject withdrew consent	0 (0.0)	2 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
Lost to follow-up	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Percentage (%) was calculated using the randomized set 2 (N) as the denominator

Source: Sponsor's Table 10-2 in the CSR for A2365

Protocol Violations/Deviations

Major protocol deviations are summarized in Table 5 for Phase 1 and Table 6 for Phase 2.

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Table 5: Protocol Deviations in Phase 1

Protocol deviation	ALI Low 6.25/12.5/25 mg N=108 n (%)	ALI Mid 37.5/75/150 mg N=54 n (%)	ALI High 150/300/600 mg N=106 n (%)	Total N=268 n (%)
Any protocol deviation	52 (48.1)	23 (42.6)	46 (43.4)	121 (45.1)
Major protocol deviation	6 (5.6)	3 (5.6)	9 (8.5)	18 (6.7)
BP measurement collected not at trough	3 (2.8)	0 (0.0)	3 (2.8)	6 (2.2)
Compliance with study medication <80% during Phase 1	1 (0.9)	1 (1.9)	3 (2.8)	5 (1.9)
Approved antihypertensive drug regardless of indication while on study drug	1 (0.9)	0 (0.0)	1 (0.9)	2 (0.7)
msSBP >= 25% above the 95th percentile for age, height and gender at Visit 2	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.4)
msSBP out of range (< 95th percentile for age, gender and height) at randomization	0 (0.0)	1 (1.9)	1 (0.9)	2 (0.7)
Wrong treatment allocation at V2 to V3	1 (0.9)	2 (3.7)	0 (0.0)	3 (1.1)

Reasons for exclusion are not mutually exclusive.
Major protocol deviation was defined with the severity code of 1 which means patients were excluded from the analysis with Per-protocol set 1.

Source: Table 10-3 in CSR for A2365

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Table 6: Protocol Deviations in Phase 2

Protocol deviation	ALI Low 6.25/12.5/ 25 mg N=50 n (%)	PLB Low N=57 n (%)	ALI Mid 37.5/75/150 mg N=30 n (%)	PLB Mid N=21 n (%)	ALI High 150/300/600 mg N=50 n (%)	PLB High N=52 n (%)	Total N=260 n (%)
Any protocol deviation	23 (46.0)	28 (49.1)	13 (43.3)	7 (33.3)	20 (40.0)	24 (46.2)	115 (44.2)
Major protocol deviation	4 (8.0)	5 (8.8)	3 (10.0)	0 (0.0)	5 (10.0)	3 (5.8)	20 (7.7)
Compliance with study medication <80% during Phase 1	0 (0.0)	1 (1.8)	1 (3.3)	0 (0.0)	2 (4.0)	1 (1.9)	5 (1.9)
Approved antihypertensive drug regardless of indication while on study drug	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	2 (0.8)
BP measurement collected not at trough	2 (4.0)	3 (5.3)	1 (3.3)	0 (0.0)	1 (2.0)	2 (3.8)	9 (3.5)
Compliance with study medication <80% during Phase 2	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	2 (0.8)
msSBP >= 25% above the 95th percentile for age, height and gender at Visit 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.4)
Wrong treatment allocation at V2 to V3	0 (0.0)	1 (1.8)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
Wrong treatment allocation at V4	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Reasons for exclusion are not mutually exclusive.
Major protocol deviation was defined with the severity code of 1 and 7 which means patients were excluded from the analysis with Per-protocol set 2.

Source: Table 10-4 in CSR Study No. SPP100A2365

Reviewer Comment: Similar efficacy results were obtained when the data were analyzed using the Full Analysis and Per-Protocol populations. Therefore, major protocol deviations did not influence study results.

Table of Demographic Characteristics

Patients in the three treatment groups had similar demographic characteristics (Table 7).

Table 7: Table of Key Demographics (FAS1 Population)

Demographic Parameters	Aliskiren			Total (N=268) n (%)
	Low Dose (N=108) n (%)	Mid Dose (N=54) n (%)	High Dose (N=106) n (%)	
Sex				
Male	73 (67.6)	37 (68.5)	66 (62.3)	176 (65.7)
Age				
Mean years (SD)	11.9 (3.3)	11.6 (3.3)	11.8 (3.5)	11.8 (3.4)

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Demographic Parameters	Aliskiren			Total (N=268) n (%)
	Low Dose (N=108) n (%)	Mid Dose (N=54) n (%)	High Dose (N=106) n (%)	
Age Group				
6–12 years	58 (53.7)	30 (55.6)	54 (52.4)	142 (53.0)
13–17 years	50 (46.3)	24 (44.4)	51 (48.6)	125 (46.6)
Weight				
Mean kilograms (SD)	66.7 (28.5)	70.3 (32.3)	69.6 (29.9)	68.6 (29.8)
BMI Group				
<95th percentile	50 (46.3)	21 (38.9)	39 (36.8)	110 (41.0)
≥95th percentile	58 (53.7)	33 (61.1)	66 (62.3)	157 (58.6)
Race				
White	83 (76.9)	39 (72.2)	75 (70.8)	197 (73.5)
Black or African American	9 (8.3)	6 (11.1)	15 (14.2)	30 (11.2)
American Indian or Alaska Native	7 (6.5)	5 (9.3)	6 (5.7)	18 (6.7)
Other	9 (8.3)	4 (7.4)	9 (8.5)	22 (8.2)
Hypertension Etiology				
Primary	89 (82.4)	44 (81.5)	86 (81.1)	219 (81.7)
Secondary[1]	19 (17.6)	10 (18.5)	19 (17.9)	48 (17.9)
msSBP				
Mean mmHg (SD)	134 (9.4)	134 (11.0)	134 (9.5)	134 (9.8)
msDBP				
Mean mmHg (SD)	78 (8.0)	78 (8.5)	79 (8.8)	78 (8.4)
eGFR (ml/min/1.73m^2)				
≥30 and <60	2 (1.9)	1 (1.9)	2 (1.9)	5 (1.9)
≥60 and <90	23 (21.3)	9 (16.7)	21 (19.8)	53 (19.8)
≥90	83 (76.9)	43 (79.6)	82 (77.4)	208 (77.6)
Region				
United States	50 (46.3)	23 (42.6)	46 (43.9)	119 (44.4)
Rest of the World	58 (53.7)	31 (57.4)	59 (56.2)	148 (55.2)

Reviewer's analysis based on applicant's dataset, admg.xpt.
Note: Low dose (6.25/12.5/25), Mid dose (37.5, 75,150) and High Dose (150/300/600)
Secondary etiology includes renal disorders such as enuresis, proteinuria, chronic renal failure, vesicoureteric reflux and hydronephrosis
Cross-reference: Table 11-3,11-6, 11-7 in CSR for Study A2365

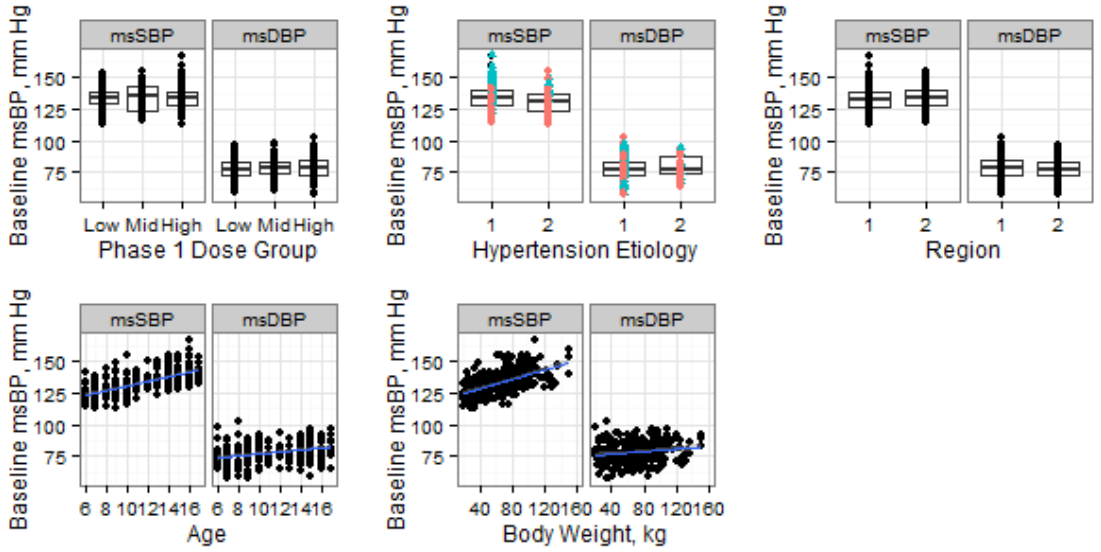
Reviewer Comment: No important imbalances were noted in Phase 1 and Phase 2.

Reference ID: 4166471

Other Baseline Characteristics

Baseline BP levels were comparable across the treatment groups, hypertension etiologies and regions. Baseline BP levels were positively correlated with age and body weight; therefore, older and heavier adolescents had higher baseline BP. Mean (SD) msSBP and msDBP were 128 (8.0) and 76 (8.1) mmHg for children 6–12 years and 140 (7.6) and 81 (8.0) mmHg for adolescents 13–17 years.

Figure 2: Baseline Blood Pressure by Covariates (FAS1 Population)



Reviewer's analysis based on applicant's datasets admg.xpt and adef.xpt.
Note: Hypertension etiology (1=Primary, 2=Secondary); Region (1=US, 2=Outside US). Abbreviations: msSBP=mean sitting systolic blood pressure; msDBP=mean sitting diastolic blood pressure.

Medical conditions reported in at least 10% of patients at baseline were obesity (20%), asthma (16%) and headache (13%). A total of 21% of patients had an abnormality in the renal or urinary SOC (such as enuresis, hematuria, proteinuria, renal failure chronic, vesicoreteric reflux, hydronephrosis).

Reviewer Comment: The patients enrolled in the study are reasonably representative of the pediatric population with hypertension age 6 -17 years.2 Adolescents (13-17 years) were more likely to have primary hypertension and have BMI >95th percentile and the younger children were more likely to have secondary hypertension. Both renal disease and obesity are known to be contributing factors to hypertension in pediatric patients.

[2] Flynn J, Zhang Y, Solar-Yohay S, Shi V. Clinical and demographic characteristics of children with hypertension. Hypertension. 60:1047-54 (2012).

Reference ID: 4166471

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were 159 patients (61%) who used concomitant medications during the study. The most commonly used concomitant medications were anilides (i.e., acetaminophen-related products, 14%), other antihistamines for systemic use (11%) and selective beta-2 adrenoceptor agonists (10%). Three patients required non-study antihypertensive medication after early discontinuation from the study.

Reviewer Comment: Per the inclusion criteria, enrolled patients were to discontinue prior antihypertensive therapy during the single-blind placebo washout period.

Efficacy Results

There was a statistically significant dose-response with a slope estimate of -0.17 (p-value <0.001). The LSM change from baseline was -4.52, -5.99 and -8.03 mmHg for the low, mid and high doses (Table 8). The difference in LS mean (-3.52 mmHg) was statistically significant between the high and low doses (p< 0001).

Table 8: Analysis of Dose-Response in Phase 1 for msSBP (FAS1 population)

Response variable	Label	Estimate	p-value	95% confidence interval	R-square
Change in msSBP (mmHg)	Intercept	-2.59		(-6.48, 1.31)	0.1957
	Slope	-0.17	< 0.001	(-0.27, -0.07)	
	Prediction at				
	dose ratio 1	-4.78	< 0.001	(-6.47, -3.08)	
	dose ratio 6	-5.64	< 0.001	(-7.10, -4.17)	
	dose ratio 24	-8.74	< 0.001	(-10.61, -6.88)	

For change from baseline to end of Phase 1 in msSBP, the ANCOVA model is fitted with weight, age, region and hypertension etiology as factors and baseline msSBP and dose ratio as covariates.
Dose ratio 1 corresponds to low dose level in Phase 1
Dose ratio 6 corresponds to mid dose level in Phase 1
Dose ratio 24 corresponds to high dose level in Phase 1

Source: Applicant's Table 11-9 in CSR for A2365

Analysis of the dose response by weight-based normalized dose also revealed a significant slope of -0.87 (p < 0.001). Dose-response is evident when evaluating weight based dose (Figure 3) and total dose (Figure 4).

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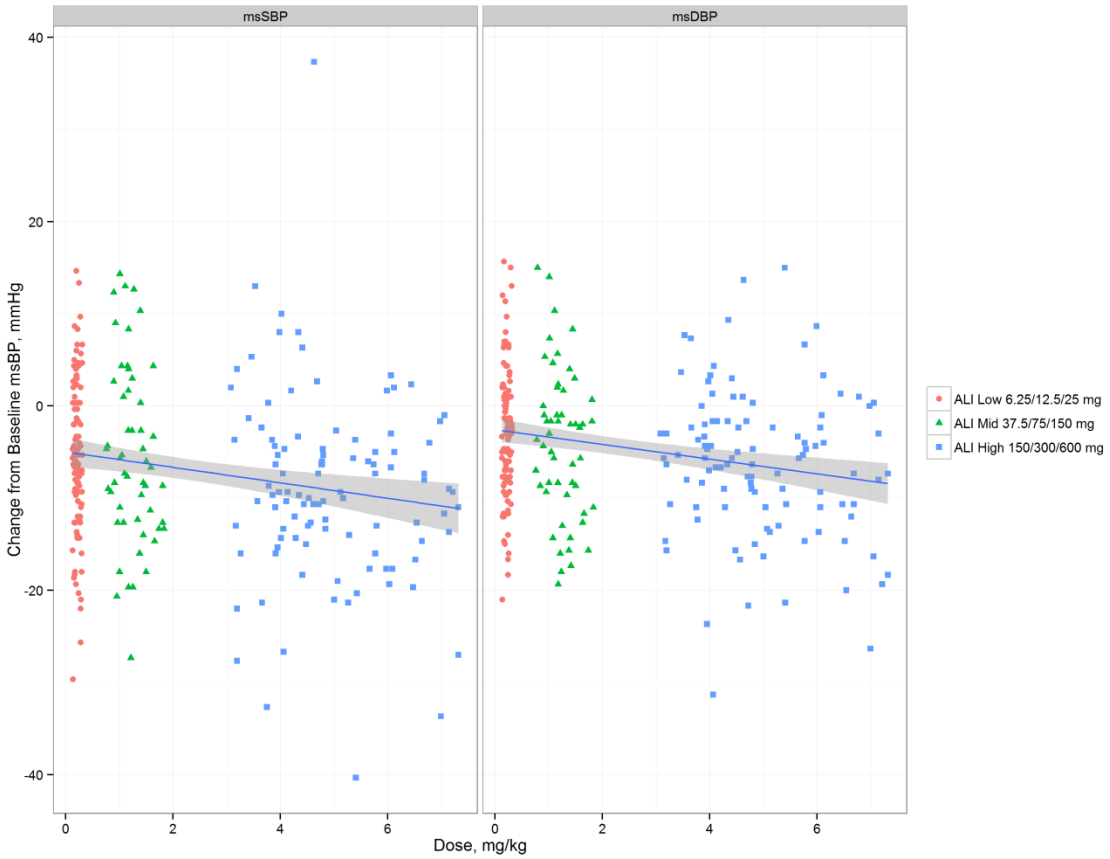
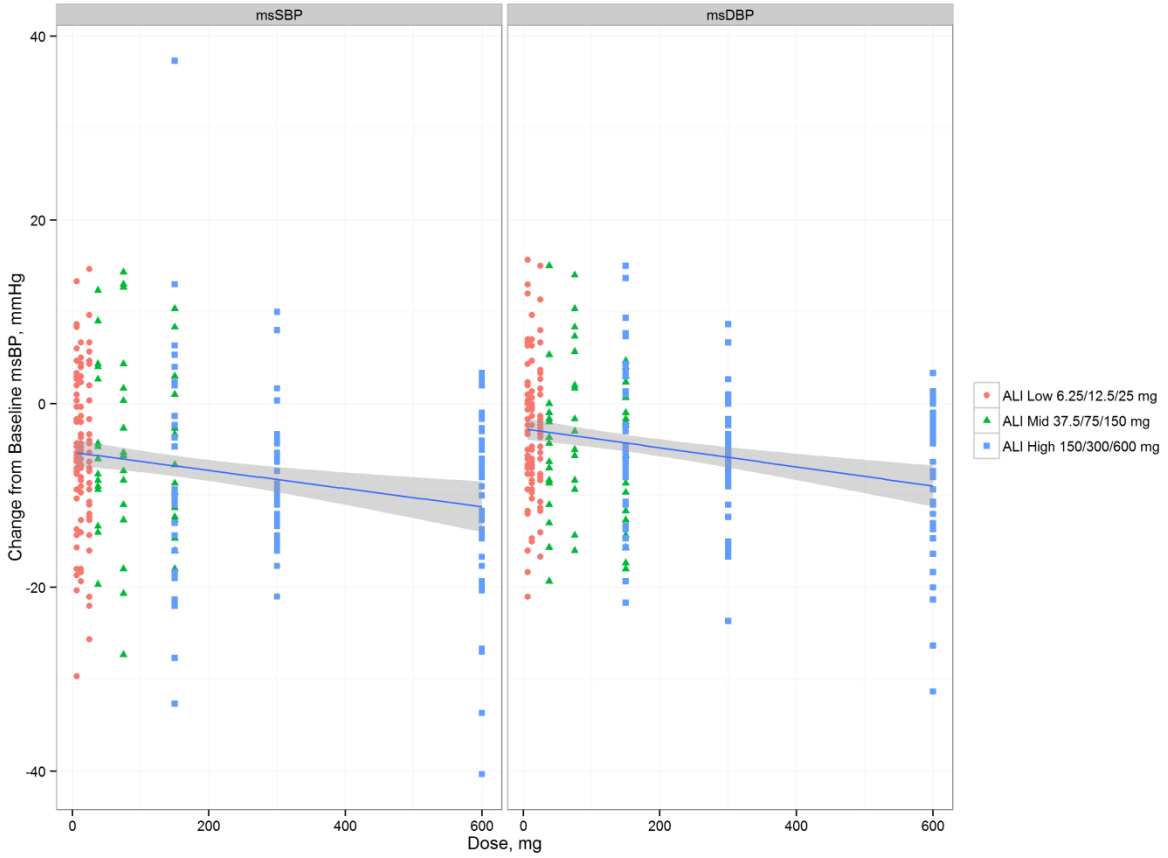
Figure 3: Dose-Response Relationship for msSBP (left) and msDBP (right) by Weight-Based Dose (FAS1 population)



Reviewer's analysis based on applicant's dataset, AEFF.xpt. Weight normalized dose computed as the total dose in Phase 1 divided by baseline body weight. Regression slope = -0.84 (p-value <0.001) for msSBP and -0.79 (p-value <0.001) for msDBP.

Reference ID: 4166471

Figure 4: Dose-Response Relationship for msSBP (left) and msDBP (right) by Total Dose (FAS1 population)



Reviewer's analysis based on applicant's dataset, AEFF.xpt. Regression slope = -0.01 (p-value <0.001) for msSBP and -0.01 (p-value <0.001) for msDBP.

The LSM change in msSBP from end of Phase 1 to end of Phase 2 in the pooled aliskiren mid/high doses was -2.31 mmHg compared to -0.59 mmHg in placebo pooled from corresponding arms. The difference in LSM between these two pooled treatment groups (-1.72 mmHg in favor of aliskiren) was not statistically significant (p=0.12). The LSM change was -2.84 mmHg for the aliskiren high dose group compared to -0.13 mmHg for the placebo high dose group (p=0.06).

Reference ID: 4166471

Table 9: Treatment comparison in msSBP at end of Phase 2 (FAS2 population)

Pairwise Comparison		N		LS Mean (SE)		Difference in LS mean (Change)		
A VS.	B	A	B	A	B	Mean (SE)	(95% CI)	p-value*
ALI pooled	PLB pooled	79	73	-2.31 (0.875)	-0.59 (0.919)	-1.72 (1.088)	(-3.87, 0.43)	0.1152

Mid and high dose groups in each treatment were pooled for analysis.

LS mean = Least squares mean; SE = Standard error of mean; CI=Confidence interval

N is the number of Full Analysis Set 2 patients with non-missing measurement at Week 8 or LOCF value.

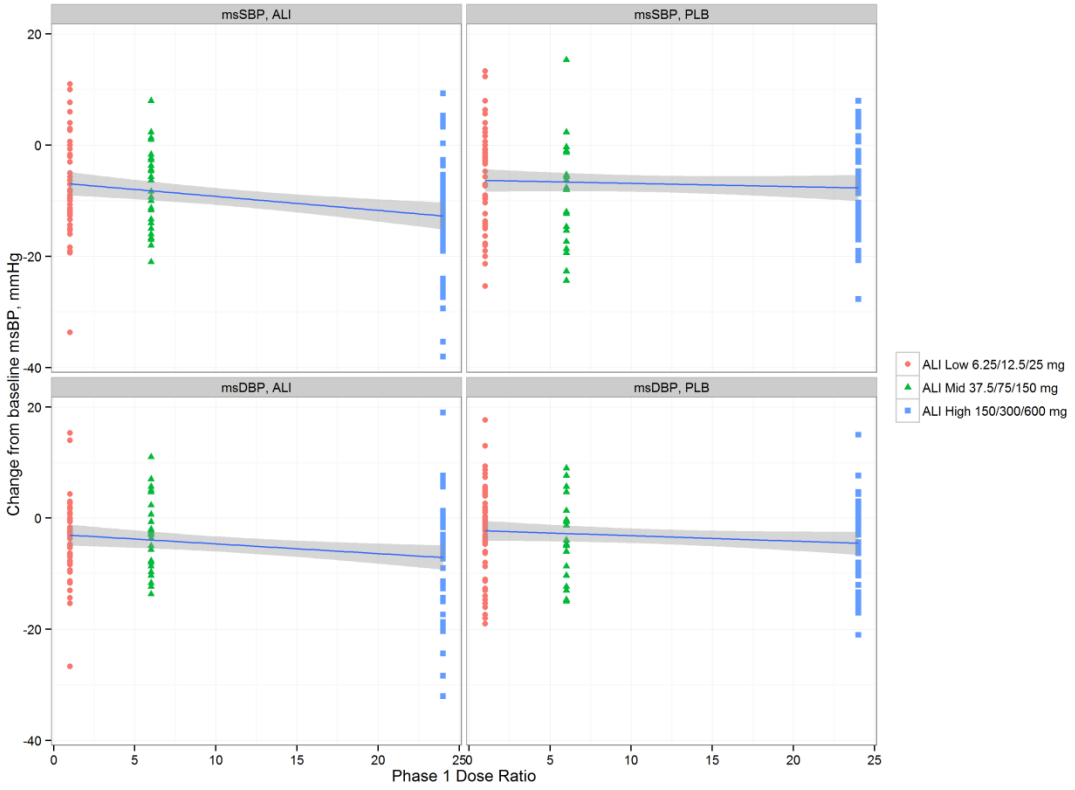
Least squares mean, confidence interval, and p-value were from the ANCOVA model with weight, age, region, and hypertension etiology as factors and msSBP at end of Phase 1 as a covariate.

* Indicates statistical significance at 0.05 level.

Source: Applicant's Table 11-11 in CSR for A2365

At the end of Phase 2, dose response was maintained for msSBP and msDBP in patients who remained on aliskiren. Dose-response is shown for dose ratio (Figure 5), weight-based dose (Figure 6) and total dose (Figure 7).

Figure 5: Phase 2 dose-response relationship for msSBP (top panel) and msDBP (bottom panel) by dose ratio (FAS2 population)



Reviewer's analysis based on applicant's dataset, AEFF.xpt. Regression slopes for aliskiren are -0.25 (p-value <0.001) for msSBP and -0.17 (p-value =0.009) for msDBP. Regression slopes are not statistically significant for placebo.

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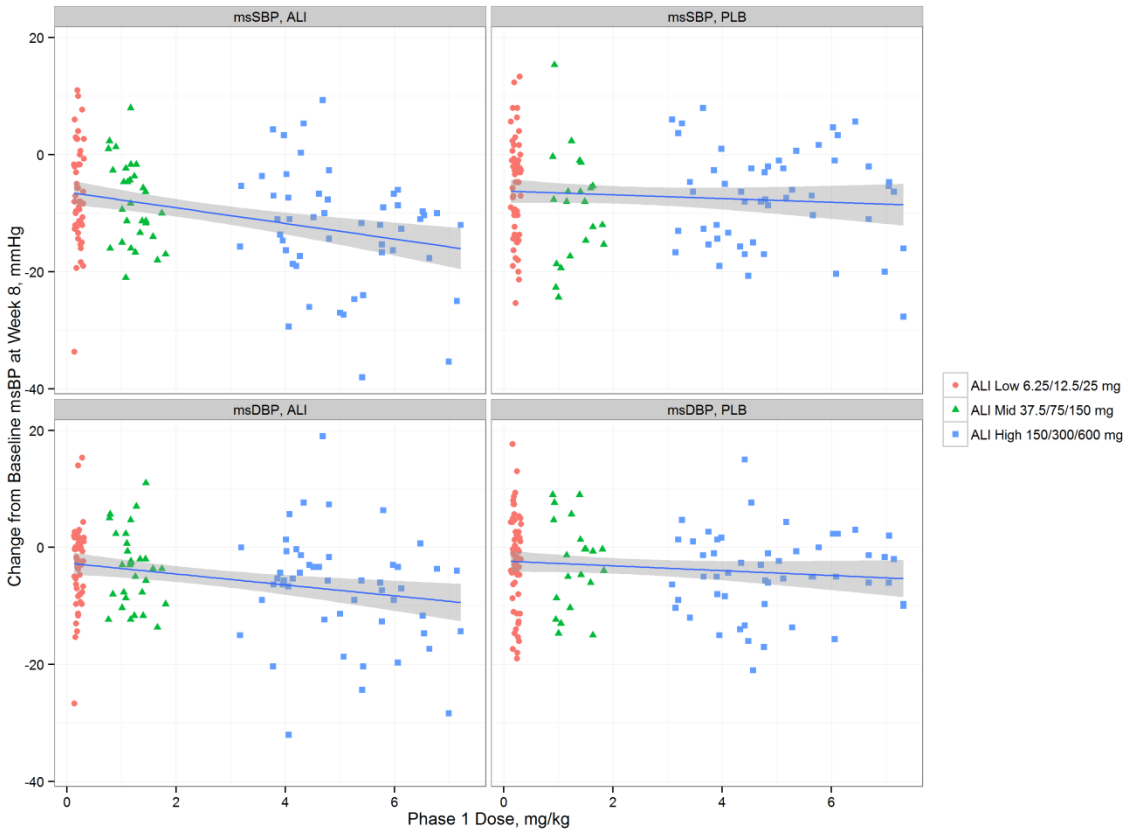
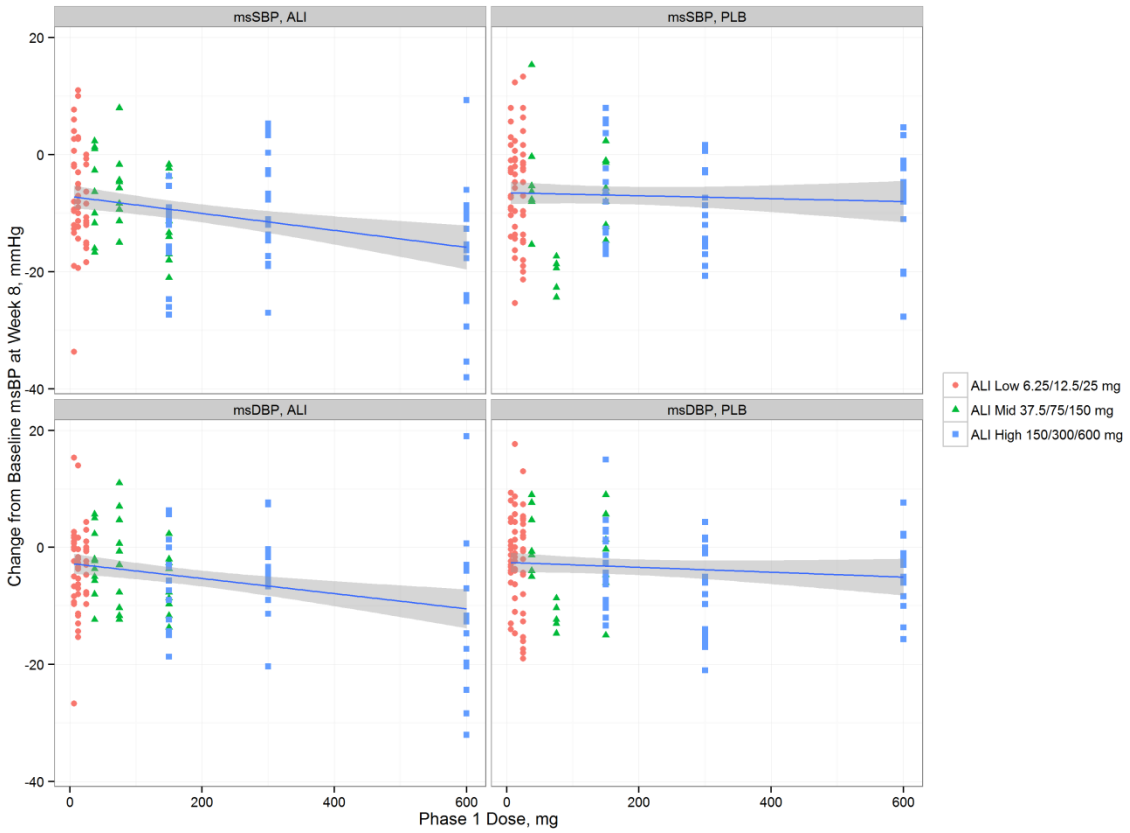
Figure 6: Phase 2 dose-response relationship for msSBP (top panel) and msDBP (bottom panel) by weight-based dose (FAS2 population)



Reviewer's analysis based on applicant's dataset, AEFF.xpt. Weight normalized dose computed as the total dose in Phase 1 divided by baseline body weight. Regression slopes for aliskiren are -1.3 (p-value <0.001) for msSBP and -0.93 (p-value =0.002) for msDBP. Regression slopes are not statistically significant for placebo.

Reference ID: 4166471

Figure 7: Phase 2 dose-response relationship for msSBP (top panel) and msDBP (bottom panel) by total dose (FAS2 population)



Reviewer's analysis based on applicant's dataset, AEFF.xpt. Regression slopes for aliskiren are -0.01 (p-value <0.001) for msSBP and -0.01 (p-value <0.001) for msDBP. Regression slopes are not statistically significant for placebo.

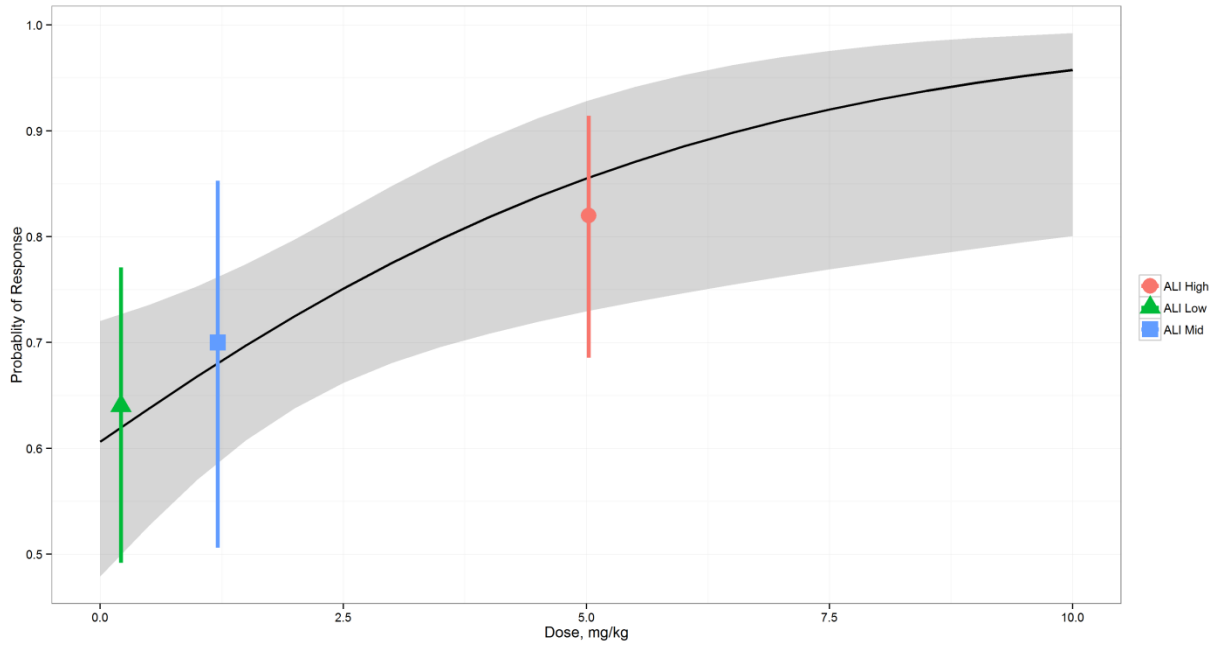
Reviewer Comment: The dose-response analysis of change from baseline msSBP/msDBP show that aliskiren at the high dose group demonstrates efficacy at the end of Phase 2.

A positive response was defined as an msSBP < 95th percentile (for age, gender and height) or a 7 mmHg decrease in msSBP from the baseline. At the end of Phase 2, response rates in patients who continued to receive aliskiren were 64%, 70%, and 82% in the aliskiren low mid and high dose groups. In patients who switched to placebo in Phase 2, the response rates were 47%, 62% and 62% for the placebo low, mid and high dose groups.

Dose-response for positive msSBP response rates is shown in Figure 8 for weight based dose. A similar dose-response relationship was detected for total dose and dose ratio.

Reference ID: 4166471

Figure 8: Probably of positive msSBP response at end of Phase 2 by weight based dose (FAS2 population)



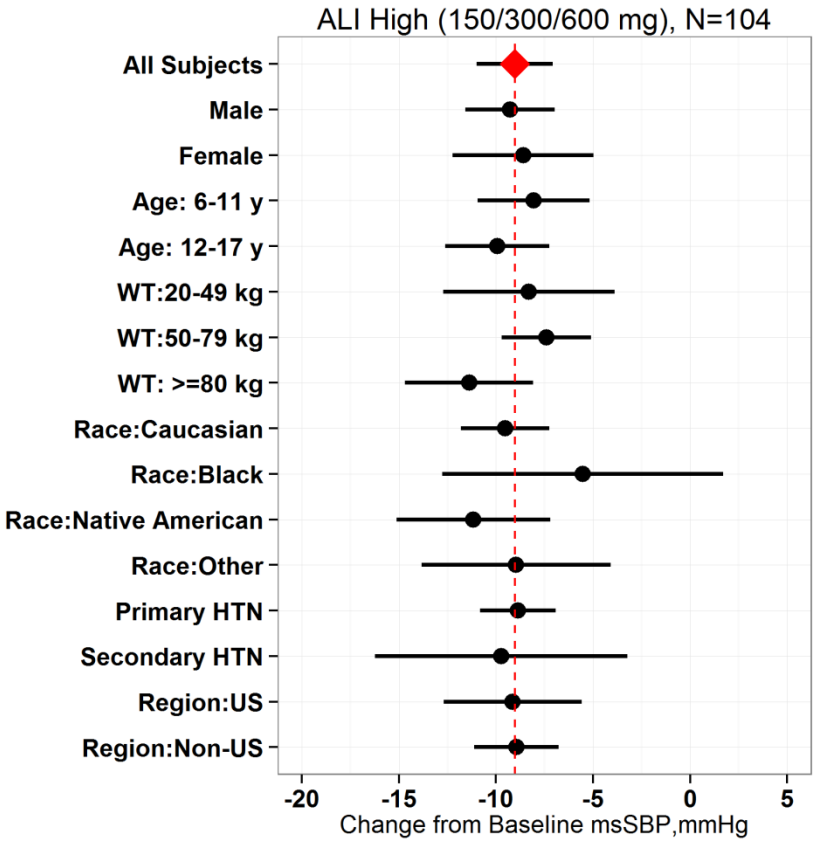
Reviewer's analysis based on applicant's dataset, AEFF.xpt. Logistic regression slope for aliskiren is 0.27 (p-value=0.009). Logistic regression slope was not statistically significant for placebo.

Efficacy Subgroup Analysis

In Phase 1, the results of the mean change from baseline in msSBP were generally consistent across subgroups, and were similar to those reported for the primary efficacy analysis (Figure 9). Similar results were found for the low and mid dose groups for msSBP (Applicant's Table 11-23) as well as across dose levels for msDBP (Applicant's Table 11-25).

Reference ID: 4166471

Figure 9: Forest plot of mean change from baseline msSBP at end of Phase 1 for ALI high dose (FAS1 population)



Reviewer's analysis based on applicant's datasets, AEFF.xpt, ADGN.xpt, and ADMG.xpt. Abbreviations: WT=weight group, HTN=hypertension, ALI=aliskiren, msSBP=mean sitting systolic blood pressure.

Cross-reference: Table 11-23 in CSR for A2365.

As shown in Figure 10, reductions in msSBP in the high dose group at the end of Phase 2 were generally consistent across subgroups irrespective of sex, age group, weight group, race, hypertension etiology and region. Similar results were reported by the applicant.

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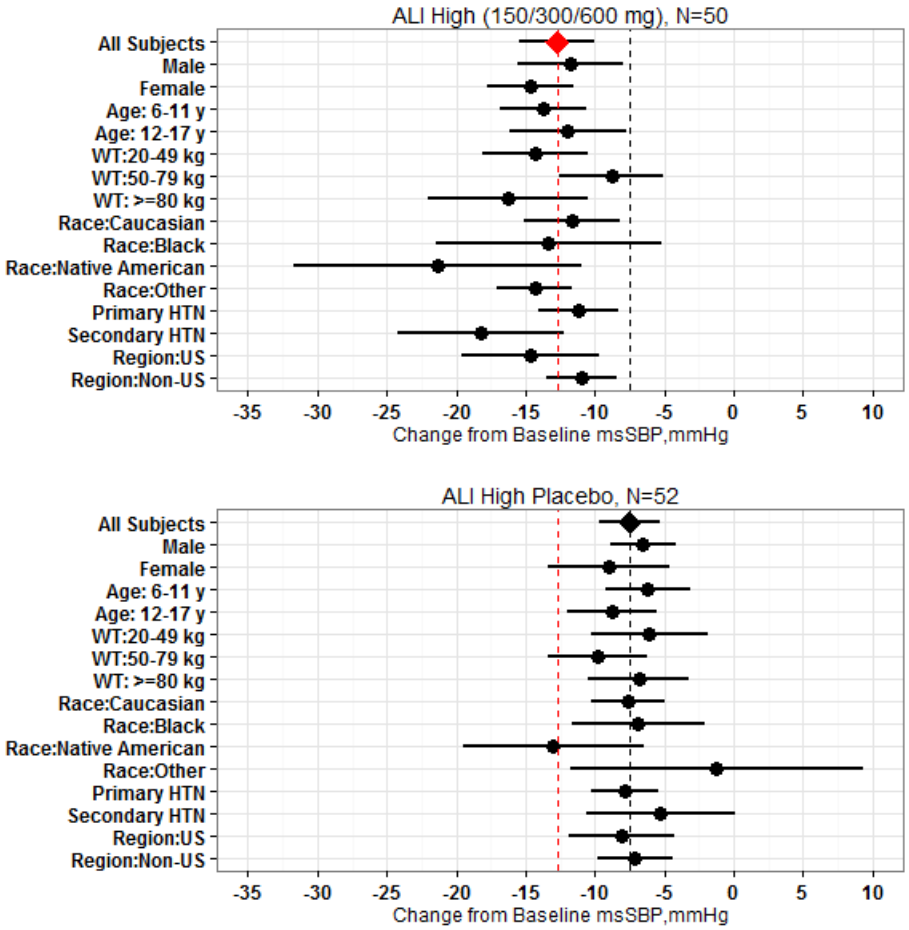
Figure 10: Forest plot of mean change from baseline msSBP at end of Phase 2 for ALI high dose (top panel) and ALI high placebo (bottom panel) (FAS2 population)



Reviewer's analysis based on applicant's datasets, AEFF.xpt, ADGN.xpt, and ADMG.xpt. Abbreviations: WT=weight group, HTN=hypertension, ALI=aliskiren, msSBP=mean sitting systolic blood pressure. Cross-reference: Table 11-24 in CSR for A2365.

6.2. SPP100a2365E1

6.2.1. Study Design

Overview and Objective

The primary objective of this study was:

- To evaluate the safety and tolerability of long term administration (52 weeks) of aliskiren compared to enalapril in hypertensive children aged 6-17 years (age at baseline in Study CSPP100A2365).

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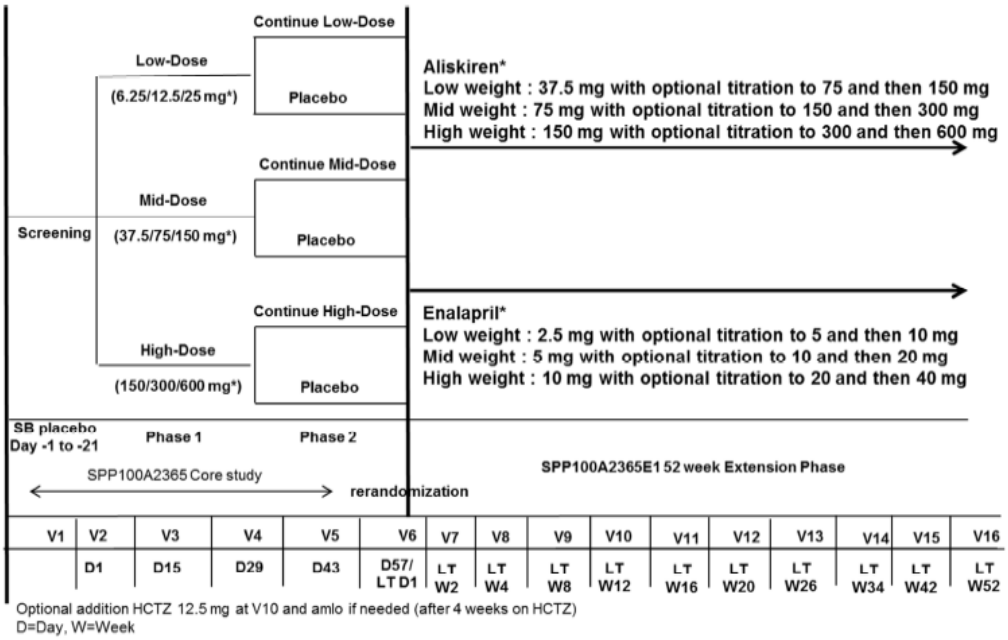
The secondary objectives of the study were:

- To evaluate the efficacy (reduction in mean sitting systolic blood pressure (msSBP)) of long-term administration (52 weeks) of aliskiren compared to enalapril in hypertensive children aged 6-17 years (age at baseline in Study CSPP100A2365) by testing the hypothesis of noninferiority of aliskiren to enalapril
- To evaluate the efficacy (reduction in mean sitting diastolic blood pressure (msDBP)) of long-term administration (52 weeks) of aliskiren compared to enalapril in hypertensive children aged 6-17 years (age at baseline in Study CSPP100A2365)
- To evaluate the efficacy as assessed by calculated mean arterial pressure (MAP), of long-term administration (52 weeks) of aliskiren compared to enalapril in hypertensive children aged 6 to 17 years (age at baseline in Study A2365).]

Trial Design

A multicenter, double-blind, randomized, 52 week extension study to evaluate the safety, tolerability and efficacy of aliskiren compared to enalapril in pediatric hypertensive patients 6-17 years of age (age at baseline in Study CSPP100A2365). Patients who had successfully completed Phase 1 (dose response phase) and at least 1 week of Phase 2 (placebo withdrawal phase) of the CSPP100A2365 protocol, with no serious and drug-related adverse event(s), were eligible for entry into the extension study.

Figure 11: Schematic of Study Design



Source: Applicant's Figure 9-1in CSR for A2365E1

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The mid dose level (0.75-1.88 mg/kg) for A2365 was chosen as starting dose as it was expected to result in blood levels similar to lowest studied dose in adults (75 mg). Optional dose titrations (Table 10) were allowed to be added for BP control if deemed necessary by the investigator, by doubling the dose with each dose titration, up to 600 mg (highest studied dose in adults) with the ≥ 80 to ≤ 150 kg weight group. Dose selection for enalapril was based on doses that were previously studied and confirmed to be efficacious and well tolerated in hypertensive children aged 6-17 years.

Table 10: Dosing with Optional Up-Titration

	Aliskiren			Enalapril		
	Dose at randomization	1st up-titration	2nd up-titration	Dose at randomization	1st up-titration	2nd up-titration
≥20 to <50 kg	37.5 mg	75 mg	150 mg	2.5 mg	5 mg	10 mg
≥50 to <80 kg	75 mg	150 mg	300 mg	5 mg	10 mg	20 mg
≥ 80 to ≤ 150 kg	150 mg	300 mg	600 mg	10 mg	20 mg	40 mg

Patients had to be on each dose level for at least four weeks, before being titrated up to the next dose level. Exception for patients up-titrated at Visit 7, who had to remain on the up-titrated dose for 6 weeks before 2nd up-titration.

Source: Applicant's Table 9-1in CSR for A2365E1

If msSBP was still not controlled after titration to the highest weight-based dose level, then open-label hydrochlorothiazide (HCTZ, 12.5 mg) was allowed to be added for BP control, starting at Visit 10 (LT Week 12). In case, msSBP was still not controlled after treatment at the highest weight-based dose level with HCTZ (12.5 mg) for four weeks, then amlodipine (5 mg) could be added for BP control.

Study Endpoints

The primary objective of the study and was based on the reporting of any adverse events and serious adverse events including death.

Key efficacy endpoints were mean changes in msSBP, msDBP, and MAP from baseline of the core study (CSPP100A2365, Visit 2) to end of the extension study (Visit 16 or LOCF). Other efficacy endpoints evaluated included changes in mean ambulatory blood pressure measurements from baseline (Visit 2) to Visit 13 (LT Week 26) and Visit 16 (LT Week 52, end of study for CSPP100A2365E1) and from end of phase 1 of CSPP100A2365 (Visit 4) to Visit 13 (LT Week 26) and Visit 16 (LT Week 52, end of study for CSPP100A2365E1) and percentage of patients achieving a positive treatment response (defined as msSBP < 95th percentile (for age, gender and height) or a 7 mmHg decrease in msSBP from baseline (Visit 2 of CSPP100A2365).

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Statistical Analysis Plan

For the non-inferiority assessment of change in msSBP, the statistical test was made at a one-sided significance level of 0.025. The non-inferiority margin was defined as 4 mmHg in msSBP change, which corresponded to 50% of the expected decline in BP in the enalapril group. Non-inferiority for the aliskiren regimen versus the enalapril regimen was to be considered achieved if the non-inferiority test was statistically significant.

If the non-inferiority test was statistically significant, the superiority test was performed at two-sided significance level of 0.05. The superiority for the aliskiren regimen versus the enalapril regimen was to be considered achieved if the test was statistically significant in favor of the aliskiren regimen. The statistical tests were performed using an analysis of covariance (ANCOVA) model with treatment regimen, region, age strata, and hypertension etiology (primary, secondary) as factors, and with baseline msSBP as covariate.

Changes from baseline in msDBP and MAP were also tested using the above model for superiority testing.

The safety assessment was based mainly on the frequency of adverse events and the number of laboratory values that fall outside of pre-specified ranges. Descriptive summary statistics was presented for all safety measurements.

Reviewer's comment: A non-inferiority analysis was not specified in the WR and it does not appear that FDA commented on this approach or endorsed the margin that was used.

Protocol Amendments

The study protocol was amended once (**Amendment 1, 12-Oct 2010**). At the time this amendment came into effect, the study was ongoing with 8 of the 220 planned patients randomized. These changes were not expected to affect the study population or study results.

- Added itraconazole as a prohibited concomitant medication.
- Added a standing BP measurement to visits 11, 12, 14 and 15. With this addition, standing BP was taken at every clinic visit, which increased the margin of safety ensuring that the patients were evaluated for orthostatic hypotension at every visit.
- Clarified exclusion of patients taking cyclosporine (already included in disallowed concomitant medication) and those with atrial fibrillation noted at visit 6 (already noted for visit 1).
- Simplified study medication packaging description and clarified the possible number of capsules/tablets per bottle/box.
- Clarified discontinuation criteria regarding laboratory values.
- Clarified that the Week 104 long term follow up details would be provided in a separate protocol.
- Required IVRS call to be made at visit 7 for all patients, regardless of whether or not their study medication was up titrated.

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6.2.2. Study Results

Patient Disposition

Of the 255 patients who completed study CSPP100A2365, a total of 208 patients were randomized in this extension study (CSPP100A2365E1) with the majority of patients (88%) completing the study. The rate of discontinuation was 13% overall in the study with a higher rate in the enalapril group (14%) compared to the aliskiren group (11%). Most common reasons for discontinuations were withdrawal of consent and lost to follow up.

Protocol Violations/Deviations

Protocol deviations occurred in 56 patients (27%) of the randomized population and occurred more often with aliskiren (33%) compared to enalapril (21%). Major protocol deviations occurred in 6 patients (3%) of the overall randomized population.

Table 11: Protocol Deviations

Protocol Deviation	Aliskiren N=104 n(%)	Enalapril N=104 n(%)	Total N=208 n(%)
Any protocol deviation	34 (32.7)	22 (21.2)	56 (26.9)
Major protocol deviation	3 (2.9)	3 (2.9)	6 (2.9)
BP measurement collected not at trough	1 (1.0)	1 (1.0)	2 (1.0)
Compliance with study medication <80%	1 (1.0)	0	1 (0.5)
Cross-over treatment	0	1 (1.0)	1 (0.5)
Use of antihypertensive medication regardless of indication while on study drug (excluding allowed add-on medications, administered per protocol)	1 (1.0)	1 (1.0)	2 (1.0)

Source: Table 14.1-1.3
Reasons for exclusion are not mutually exclusive.
Major protocol deviation was defined with the severity code of 1 which means patients were excluded from the analysis with Per-protocol set.
Percentage (%) was calculated using the count of randomized patients in that treatment group as the denominator

Source: Table 10-2 from CSR for Study A2365E1

Table of Demographic Characteristics

Patients in the two treatment groups had comparable demographic and baseline characteristics (Sponsor's Table 11-2). Overall, the mean age of the patients was 11.8 years with 48.6% of patients being in the 6-11 years age-group and 51% in the 12-17 years age-group. The majority of patients were males (65%) and Caucasians (75%). There were 19 (9%) black patients. Thirty seven patients (18%) had secondary hypertension. Mean weight was 68 kg with 58% of patients having BMI ≥ 95th percentile for age and gender (60% aliskiren compared to 56% in enalapril group).

Efficacy Results

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At the end of the study, changes in msSBP from baseline of the core study (A2365 Visit 2) were similar in aliskiren and enalapril arms (-7.6 mmHg vs -7.9 mmHg). The treatment difference between aliskiren and enalapril was not statistically significant (p=0.82).

Table 12: Treatment differences in msSBP at end of study (primary efficacy endpoint)

Pairwise comparison			n		LS Mean (SE)		Difference in LS mean (Change)			
A	vs	B	A	B	A	B	mean	(95% CI)	p-value (non-inferiority)	p-value (superiority)
Aliskiren		Enalapril	104	104	-7.63 (1.16)	-7.94 (1.14)	0.31	(-2.40, 3.03)	0.0040*	0.8205

Source: Table 14.2-1.1
- End of study is the visit 16 or LOCF value. SE = Standard error.
- Least squares (LS) mean, confidence interval, and p-value were from the ANCOVA model with treatment regimen, region, age strata, weight strata, and hypertension etiology (primary, secondary) as factors, and baseline msSBP as covariate.
* Indicates statistical significance at 0.025 level for one sided non-inferiority testing at 4mmHg margin.
** Indicates statistical significance at 0.05 level for two sided superiority testing

Source: Applicant's Figure 11-5 in CSR for A2365E1

The LS mean change in msDBP from baseline to end of study was -3.9 mmHg with aliskiren compared to -4.9 mmHg with enalapril. The difference in LS mean between the two treatment groups was not statistically significant (p=0.32).

Decreases from baseline in msSBP and msDBP for Aliskiren were maintained over 52 weeks as shown in Figure 12. The decreases in BP were similar between Aliskiren and Enalapril.

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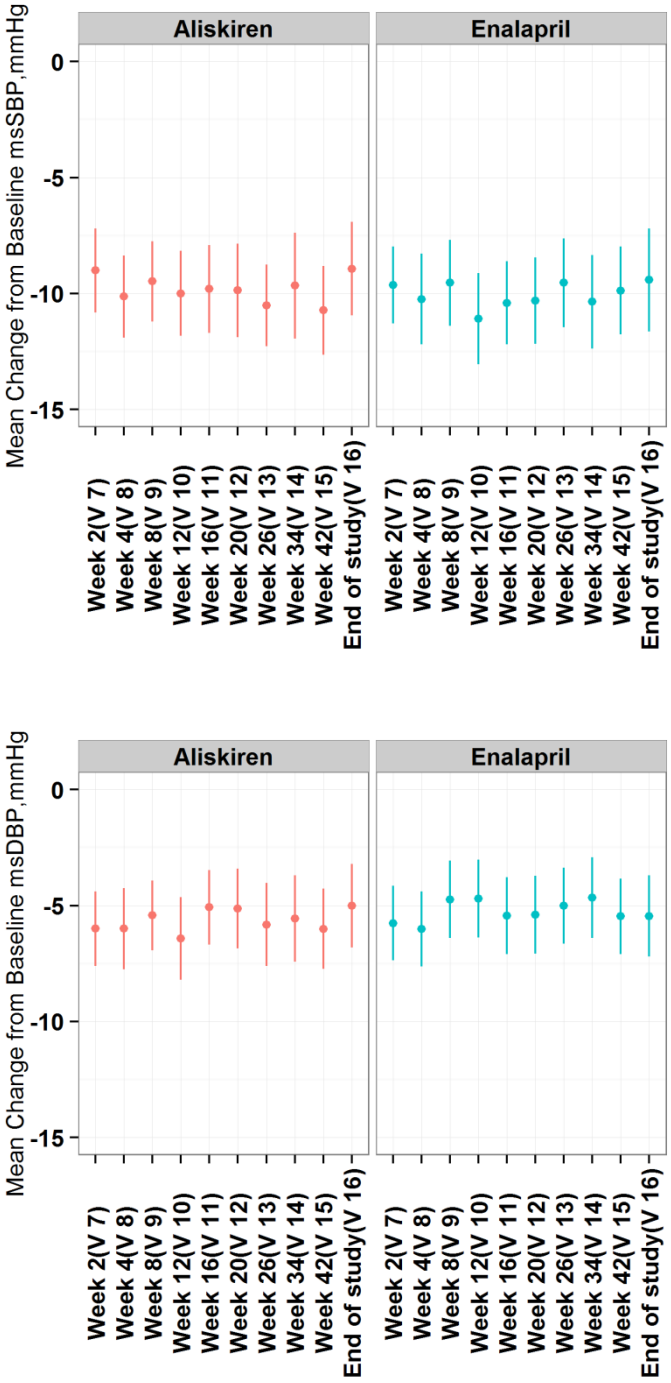
Figure 12: Mean ± 90% CI for msSBP (top) and msDBP (bottom)



Reviewer's analysis based on applicant's datasets, AEFF.xpt. Cross-reference: Table 14.2-2.1 in CSR for A2365E1. Baseline BP was obtained at Week 2.

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7 Review of Safety

7.1. Safety Review Approach

A total of 268 patients were randomized in study A2365 and out of these, 208 patients enrolled in the 52 -week double -blind, randomized extension study A2365E1 designed to evaluate the long term safety of aliskiren compared to enalapril. Therefore, the primary source of the safety database of aliskiren in pediatric patients is from study A2365E1. Due to the differences in study duration, the safety data were not pooled with the 8-week study, A2365.

All safety results are presented for A2365E1. Deaths, SAEs and drug discontinuations due to AEs are also presented for study A2365. The AE terms used are the preferred terms included in the Medical Dictionary for Drug Regulatory Affairs (MedDRA). In study A2365, MedDRA version 16.1 was used, while in study A2365E1, MedDRA version 18.0 was used.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Study A2365 was an 8-week study. Mean and median exposure to double-blind study drug was similar across treatments.

In the long-term safety study A2365E1, optional titration of study drug doses to the next highest weight-based dose level was available if medically necessary to control the msSBP, to obtain a target for msSBP of <90th percentile for age, gender and height (Table 10).

By the end of the study, a higher proportion of patients in the aliskiren group had dose up-titrations (59%) compared to enalapril (49%). Frequency distributions of aliskiren titrations by dose level, weight group, and visit are shown in Figure 13. By the end of the study 31% of patients remained on the initial dose, 26% had one up-titration and 24% patient had a second up-titration (Table 13). The number of patient requiring add-on treatment in the aliskiren arm was 9%, and was similar to enalapril (10%).

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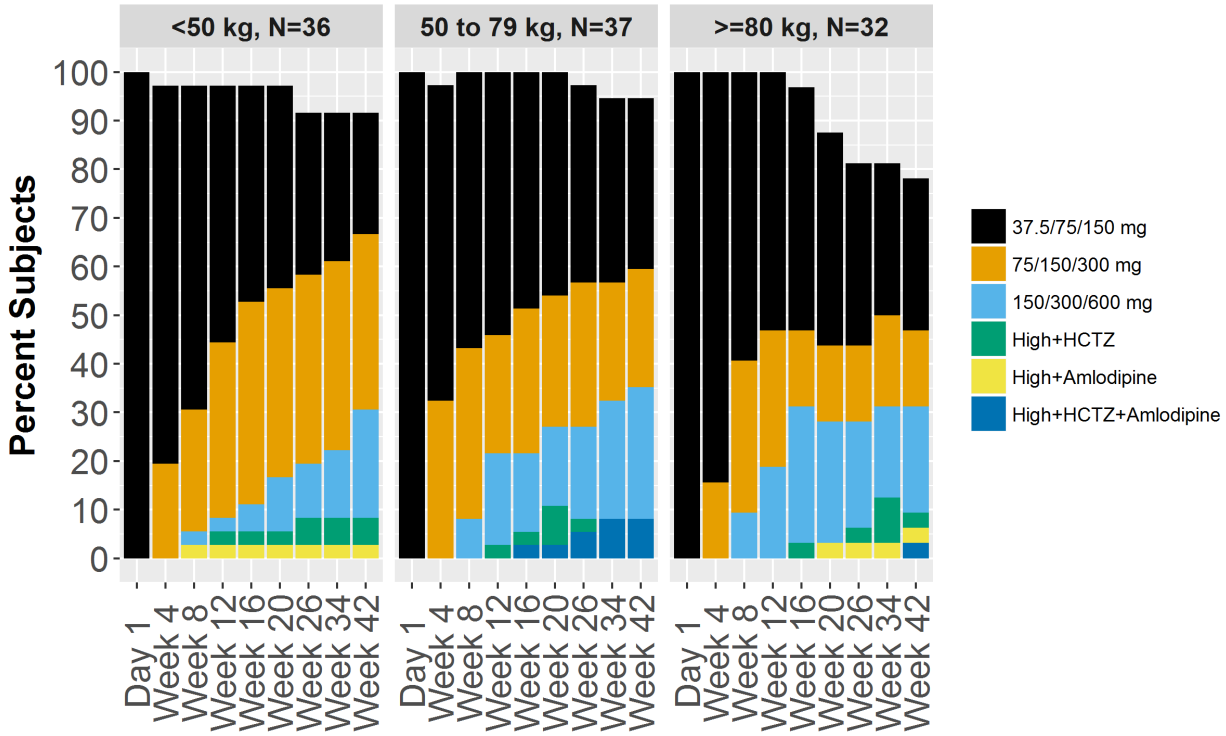
Figure 13: Frequency Distribution of Aliskiren Dose Level



Reviewer's analysis based on applicant's dataset, AIVR.xpt. Cross-reference: Table 12-1 in CSR for SPP100A2365E1.

Table 13: Dose Titrations by Weight Group

		Aliskiren N=105 n (%)	Enalapril N=103 n (%)
Week 42	Overall	93(88.6)	91(88.3)
	Low dose	32(30.5)	40(38.8)
	Medium dose	27(25.7)	20(19.4)
	High dose	25(23.8)	21(20.4)
	High dose with add-on	9(8.6)	10(9.7)

Source: Table 14.3-1.1

Source: Table 12-1 in CSR for A2365E1.

Reviewer Comment: The 8-week study did not show efficacy at the starting dose level (37.5/75/150 mg). Therefore, it is expected that a majority of patients would up-titrate to higher dose levels to achieve blood pressure reduction. More patients (n=7) discontinued treatment in the high weight group compared to the lower weight groups (2 subjects in each

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group). Of the 7 who discontinued in the high weight group, 4 were taking 600 mg, 1 taking 300 mg and 2 taking 150 mg.

Mean and median exposure to study medication was similar in the two treatment groups (Table 14).

Table 14: Exposure by Treatment Group

Duration of exposure (days)	Aliskiren N=105	Enalapril N=103	Total N=208
n	105	103	208
Mean	343.1	338.2	340.7
SD	69.01	75.62	72.22
Median	364.0	364.0	364.0
Min	16	29	16
Max	399	427	427
Exposure categories – n (%)			
≥1 day	105 (100.0)	103 (100.0)	208 (100.0)
≥8 weeks	104 (99.0)	101 (98.1)	205 (98.6)
≥12 weeks	104 (99.0)	101 (98.1)	205 (98.6)
≥ 20 weeks	101 (96.2)	97 (94.2)	198 (95.2)
≥26 weeks	97 (92.4)	97 (94.2)	194 (93.3)
≥34 weeks	96 (91.4)	94 (91.3)	190 (91.3)
≥42 weeks	95 (90.5)	90 (87.4)	185 (88.9)
≥52 weeks	73 (69.5)	69 (67.0)	142 (68.3)

Source: Table 14.3-1.2
Percentages were computed using the safety set number in that treatment group as the denominator.

Source: Table 12-2 in CSR for A2365E1

7.2.2. Categorization of Adverse Events

An AE was defined as the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event was not considered to be related to study drug. Study drug included the investigational drug under evaluation (aliskiren) and the comparator drug (enalapril) or placebo that is given during any phase of the studies. Medical conditions/diseases present before starting study drug were only considered AEs if they worsened after starting study drug. Abnormal laboratory values or test results constituted AEs only if they induced clinical signs or symptoms, were considered clinically significant or required therapy.

An SAE was defined as an event which was fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability or incapacity, constituted a congenital anomaly or a birth defect, or was medically significant in that it may have jeopardized the subject and could have required medical or surgical intervention to prevent one of the outcomes listed above. SAEs occurred in the 30 day follow-up period.

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AEs were assessed overall, by SOC, by preferred term, by maximum severity, by relationship to the trial treatment, and by discontinuation due to AEs for the safety set.

7.2.3. Routine Clinical Tests

Laboratory data (hematology and biochemistry) are summarized by treatment for change from baseline and for occurrence of any abnormalities.

7.3. Safety Results

7.3.1. Deaths

No deaths occurred in the aliskiren pediatric program.

7.3.2. Serious Adverse Events

Three patients reported an SAE in study A2365:

- PID A23565-0103-00001 (9 year old white male on aliskiren high dose) was hospitalized with head injury due to a fall on Day 8. The event was not suspected to be study drug related and resolved on Day 15 upon treatment. The patient completed the study.
- PID A2365-0531-00004 (10 year old black female on aliskiren high dose) complained of headache and syncope (lost consciousness for 1-3 min) on Day 55. She was taken to emergency room where physical exam was unremarkable and diagnostic tests were negative (including brain CT). She was treated with ibuprofen and discharged home on the same day. The event was not suspected to be study drug related and the patient completed the study.
- PID A2365-0534-00001 (13 year old white male on aliskiren high dose) attempted suicide on Day 60 after breaking up with his girlfriend. The patient entered the study with a medical history of depression, treated with trazodone and fluoxetine. The subject was hospitalized and study drug <u>was permanently discontinued due to this SAE</u>. The event was not suspected to be study drug related and was considered resolved on Day 65.

In study A2365E1, the incidence of SAEs was lower in the aliskiren group (n=3; 2.9%) compared to the enalapril group (n=12; 11.7%). None of the SAEs led to study drug discontinuation. Brief descriptions of the SAEs for the 3 patients taking aliskiren are provided below.

- PID A2365E1-0506-00003 (16 year old male of Other race on aliskiren) was hospitalized with acute appendicitis on Day 94. The event was not suspected to be study drug related and resolved on Day 95 after a laparoscopic appendectomy. The patient completed the study.
- PID A2365E1-0607-00019 (7 year old Caucasian female on aliskiren) was hospitalized with mild chest pain, headache on Day 110. Study drug was temporarily interrupted. The events were not suspected to be study drug related and resolved on Day 112 without treatment. On Day 160, the patient was hospitalized again with suspected appendicitis

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that led to temporary interruption of study drug and resolved after 4 days upon treatment. The patient completed the study.

- PID A2365E1-0607-00021 (6 year old Caucasian female on aliskiren) was hospitalized with gastroenteritis and tachycardia on Day 53. The events were not suspected to be study drug related and resolved on Day 54. The patient completed the study.

Table 15: SAEs in Study A2365E1

Preferred term	Aliskiren N=105 n(%)	Enalapril N=103 n(%)	Total N=208 n(%)
Any preferred term	3(2.9)	12(11.7)	15(7.2)
Appendicitis	2(1.9)	1(1.0)	3(1.4)
Tachycardia	1(1.0)	0	1(0.5)
Chest pain	1(1.0)	1(1.0)	2(1.0)
Gastroenteritis	1(1.0)	0	1(0.5)
Headache	1(1.0)	0	1(0.5)
Lymphadenopathy	0	1(1.0)	1(0.5)
Paraesthesia oral	0	1(1.0)	1(0.5)
Device malfunction	0	1(1.0)	1(0.5)
Viral infection	0	1(1.0)	1(0.5)
Concussion	0	1(1.0)	1(0.5)
Dislocation of vertebra	0	1(1.0)	1(0.5)
Head injury	0	1(1.0)	1(0.5)
Skull fractured base	0	1(1.0)	1(0.5)
Weight decreased	0	1(1.0)	1(0.5)
Tetany	0	1(1.0)	1(0.5)
Paraesthesia	0	1(1.0)	1(0.5)
Abnormal behaviour	0	1(1.0)	1(0.5)
Psychosomatic disease	0	1(1.0)	1(0.5)
Nephrolithiasis	0	1(1.0)	1(0.5)
Urethral stenosis	0	1(1.0)	1(0.5)

Source: Table 14.3.1-1.3
Preferred terms were sorted in descending frequency, as reported in the Aliskiren group.
Percentages are calculated using the number of patients in safety set in respective treatment group as the denominator.

Source: Table 12-7 in CSR for A2365E1

Reviewer Comment: Based on review of the cases, it is not obvious that aliskiren played a role in any of these serious events.

7.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

In study A2365, 3 patients discontinued due to an AE. One patient (PID A2365-0101-0001) discontinued from Phase 1 due to an AE (stomach cramping) in the aliskiren high dose group. One patient in the aliskiren high dose group discontinued to an SAE of suicide attempt (PID

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A2365-0534-00001, described above). Another patient (PID A2365-0545-00001, 10 year old, Black male) in the placebo high dose group discontinued the study due to events of generalized rash, generalized pruritus, cough, and fever, all moderate in severity.

In study A2365E1, 3 patients discontinued due to AEs (Table 16). One patient in the aliskiren group discontinued due to suspected AEs of pain in extremity, hypoesthesia and paresthesia (all mild). Two patients discontinued in the enalapril group: one patient due to suspected AE of moderate diarrhea and another patient for non-suspected AE of severe coarctation of the aorta.

Table 16: AEs leading to discontinuation in Study SPP100A2365E1

Preferred term	Aliskiren N=105 n(%)	Enalapril N=103 n(%)	Total N=208 n(%)
Any preferred term	1(1.0)	2(1.9)	3(1.4)
Pain in extremity	1(1.0)	0	1(0.5)
Hypoesthesia	1(1.0)	0	1(0.5)
Paresthesia	1(1.0)	0	1(0.5)
Coarctation of the aorta	0	1(1.0)	1(0.5)
Diarrhea	0	1(1.0)	1(0.5)

Preferred terms were sorted in descending frequency, as reported in the Aliskiren group.
Percentages are calculated using the number of patients in safety set in respective treatment group as the denominator.
Source: [A2365E1 Table 14.3.1-1.4]

Source: Table 12-8 in CSR for A2365E1

Reviewer Comment: It is not obvious that aliskiren played a role in any of these AEs that led to treatment discontinuation

7.3.4. Treatment Emergent Adverse Events and Adverse Reactions

Study A2365E1 provides information on aliskiren's safety profile during extended treatment relative to enalapril and was used to explore AEs.

The overall incidence of AEs was 75% for aliskiren and 70% for enalapril. Most commonly affected SOCs overall were infections and infestations, followed by respiratory, thoracic and mediastinal disorders, and gastrointestinal disorders (Table 17).

Table 17: Adverse Events by SOC (sorted by decreasing incidence in Aliskiren group)

	Aliskiren (N = 105)			*Enalapril (N = 103)*		
SOC	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Infections and infestations	114	58	55	105	51	50
Respiratory, thoracic and mediastinal disorders	32	17	16	31	20	19

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	Aliskiren (N = 105)			*Enalapril (N = 103)*		
SOC	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Gastrointestinal disorders	33	16	15	23	14	14
Nervous system disorders	22	11	11	23	17	17
General disorders and administration site conditions	14	10	10	14	12	12
Injury, poisoning and procedural complications	9	7	7	15	10	10
Investigations	9	6	6	10	6	6
Skin and subcutaneous tissue disorders	7	5	5	6	6	6
Ear and labyrinth disorders	6	4	4	2	2	2
Musculoskeletal and connective tissue disorders	6	4	4	7	4	4
Immune system disorders	4	4	4	6	6	6
Metabolism and nutrition disorders	3	3	3	5	4	4
Vascular disorders	2	2	2	0	0	0
Cardiac disorders	2	2	2	3	2	2
Eye disorders	2	2	2	2	2	2
Renal and urinary disorders	2	2	2	4	2	2
Endocrine disorders	1	1	1	0	0	0
Social circumstances	1	1	1	0	0	0
Psychiatric disorders	1	1	1	4	3	3
Congenital, familial and genetic disorders	0	0	0	1	1	1
Blood and lymphatic system disorders	0	0	0	2	2	2
Reproductive system and breast disorders	0	0	0	4	4	4

Reviewer's analysis based on applicant's datasets, admg.xpt and aaev.xpt using the MAED adverse event tool. Cross-reference: Table 12-3 in CSR for A2365E1.

Reviewer's comment: Although evaluating AEs by SOC is not very informative because related AEs can be split over several SOCs, a sensitivity analysis was conducted using a FDA customized grouping of preferred terms (Appendix, Table 24). No new or unexpected AEs were detected. Most of these AEs would be expected events in a pediatric population.

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7.3.5. Laboratory Findings

The numbers and percentages of patients with notable changes from baseline in LFTs are presented in Table 18. One patient (PID 0705/00007) in the enalapril group was discontinued from the study due to elevated AST and ALT. While elevations in liver function tests were seen in few patients, the data do not show any evidence of liver injury with aliskiren.

Laboratory findings corresponding to renal function are discussed together with renal-relate AEs in section 7.4.3 below.

Table 18: Categorical analysis of LFTs

Criterion	Aliskiren N=105 n/N' (%)	Enalapril N=103 n/N' (%)
Total Bilirubin >100% increase	6/104 (5.8)	4/103 (3.9)
High*	0/104 (0.0)	0/103 (0.0)
ALT >150% increase	5/104 (4.8)	3/103 (2.9)
High*	5/104 (4.8)	3/103 (2.9)
AST>150% increase	1/104 (1.0)	2/103 (1.9)
High*	1/104 (1.0)	2/103 (1.9)
ALT or AST > 3xULN	2/105* (1.9)	1/103* (1.0)
ALT or AST > 5xULN	1/105* (1.0)	0/103
ALT or AST > 8xULN	0/105	0/103
ALT or AST > 3xULN and total Bilirubin > 2xULN	0/105	0/103
Total Bilirubin >3x ULN and AST/ALT <3x ULN	0/105	0/103

Source: Table 14.3-2.11, Table 14.3-2.2

Source: Table 12-13 in CSR for A2365E1

7.3.6. Vital Signs

Evaluation of vital signs did not reveal clinically relevant or unexpected adverse trends in patients receiving aliskiren. Hypotension, a safety issue of interest, is discussed in section 7.4.

7.4. Analysis of Submission-Specific Safety Issues

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7.4.1. Anaphylactic Reactions and Head and Neck Angioedema

Hypersensitivity reactions are AEs of special interest because anaphylactic reactions and angioedema of the face, extremities, lips, tongue, glottis and/or larynx have been reported in patients treated with aliskiren and have necessitated hospitalization and intubation. These AEs may occur at any time during treatment and have occurred in patients with and without a history of angioedema with ACEIs or angiotensin receptor antagonists.

The percentage of subjects reporting at least one AE within the SMQ for anaphylactic reaction was 11% for aliskiren and 10% for enalapril (Table 19). There were no cases of angioedema and none of the AEs in the aliskiren arm appear to reflect anaphylactic reactions.

Table 19: Evaluation of MedDRA SMQ: Anaphylactic reaction

Preferred Term	Aliskiren (N=105)		Enalapril (N=103)	
	n	%	n	%
Total Subjects	***12***	***11%***	***10***	***10%***
Cough	8	8%	9	9%
Rash	3	3%	0	0%
Sneezing	2	2%	0	0%
Asthma	1	1%	1	1%
Dyspnoea	0	0%	1	1%
Bronchospasm	0	0%	1	1%

Reviewer's analysis based on applicant's datasets, admg.xpt and aaev.xpt using the MAED adverse event tool.

7.4.2. Hypotension-Related AEs

Symptomatic hypotension has occurred in adult patients with marked volume depletion, patients with salt depletion, or with combined use of aliskiren and other agents acting on the renin angiotensin-aldosterone system. Therefore, the incidence of hypotension-related AEs (including dizziness, dizziness postural, hypotension, or syncope) was evaluated in pediatrics.

In A2365, 2 patients reported dizziness (1 in the aliskiren mid-dose and 1 in the aliskiren high-dose group) and 1 patient each reported dizziness postural (aliskiren mid-dose group) and hypotension (aliskiren high-dose group) during Phase 1. In addition, two patients reported dizziness (1 in the aliskiren mid-dose and 1 in the aliskiren high-dose group), and one patient (0.4%) in the aliskiren high-dose group reported syncope, during Phase 2.

In A2365E1, dizziness was reported in one patient in the aliskiren and 2 patients in the enalapril group. Syncope occurred in one aliskiren patient in the high weight/low-dose level. Orthostatic hypotension was reported in one aliskiren patient in the mid weight/high-dose aliskiren level plus HCTZ and amlodipine. No patients in the enalapril group reported orthostatic hypotension.

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7.4.3. Renal Impairment

Changes in renal function, including acute renal failure, can be caused by drugs that affect the RAAS. Adverse events suggestive of worsening renal impairment were not reported in any patient, either in A2365 or A2365E1. In the long term safety study, there were no changes in creatinine, potassium or BUN suggestive of worsening of renal function (Table 20).

Table 20: Percentage of patients with elevated laboratory parameters

Laboratory test	Criterion	Aliskiren N=105 n(%)	Enalapril N=103 n(%)	Total N=208 n(%)
Potassium	< 3.5 mmol/L	1 (1.0)	2 (1.9)	3 (1.4)
	> 5.5 mmol/L	2 (1.9)	5 (4.9)	7 (3.4)
	≥ 6.0 mmol/L	0	0	0
Creatinine	> 176.8 µmol/L	0	1 (1.0)	1 (0.5)
Blood Urea Nitrogen (BUN)	> 14.28 mmol/L	1 (1.0)	0	1 (0.5)

Source: Table 14.3-2.3

Source: Table 12-12 in CSR for A2365E1

7.4.4. Hyperkalemia

Drugs that affect the RAAS can cause hyperkalemia. One AE associated with hyperkalemia (including hyperkalemia or blood potassium increased) occurred in one patient in A2365 Phase 2 in the aliskiren high dose group. In A2365E1, 2 patients in the aliskiren group had serum potassium >5.5 mmol/L compared to 5 patients in enalapril group (Table 20). All patients had potassium levels within normal range in subsequent laboratory testing. There were no hyperkalemia-related AEs reported in the aliskiren group in A2365E1; 1 patient in the enalapril mid weight/mid-dose level reported hyperkalemia.

7.5. Safety Analyses by Demographic Subgroups

The sponsor conducted a subgroup analysis of pooled AEs. The results of the subgroup analysis are not very informative because of the low number of patients within each subgroup.

7.6. Specific Safety Studies/Clinical Trials

Study A2365E2 is a 1-2 year observational extension study aimed to evaluate the long term growth and development of hypertensive children 6 to 17 years of age previously treated with aliskiren. All patients successfully completing Study A2365E1 were eligible to participate in this observational study. The study is currently ongoing.

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A total of 106 patients were randomized into this observational study. As of 1-Mar-2017, no deaths were reported in this study. One SAE occurred in a 10 year old patient who was hospitalized for a planned surgery for phimosis.

7.7. Safety in the Postmarket Setting

A cumulative search in the Novartis Argus Safety Database retrieved a total of 22 reports in children 6 to 17 years old: 10 cases were from spontaneous reports, 8 cases were reported from clinical trials and 3 cases were from the literature.

Of the 22 cases, 13 were reported as serious case reports and nine were reported as non-serious case reports. No fatal cases were reported in children 6 to 17 years of age. The sponsor concluded that the postmarket reports do not suggest new safety findings in pediatrics. The sponsor did not provide narratives of serious reports.

Reviewer's comment: An Information Request was sent to the Sponsor requesting narratives for each of the 13 serious case reports.

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8 Clinical Pharmacology

The Office of Clinical Pharmacology has reviewed the submission for quality and accuracy of the submitted material and to support the labeling statements in Sections 2 and 12.3.

The sponsor has conducted a relative bioequivalence study (A2109), a pharmacokinetics and pharmacodynamics study (A2256) and a pivotal efficacy study (A2365, A2365E1) to support this submission.

8.1. Relative Bioequivalence Study (A2109)

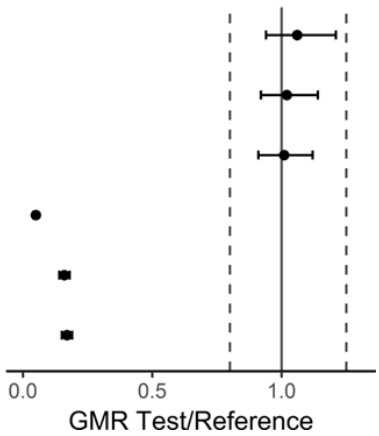
The study was an open-label, single dose, 3-period, 3-sequence crossover study in healthy males; females could have been enrolled per protocol, but were not. The study compared aliskiren exposure after single dose administration of three treatments, (1) 300 mg mini-tablets administered with a teaspoon of low-fat vanilla ice cream after an overnight fast, (2) 300 mg aliskiren marketed tablets (overnight fast), and (3) 300 mg aliskiren mini-tablets administered with a tablespoon of low-fat vanilla ice cream after consuming a high-fat, high-calorie breakfast.

The analytical method used for sample analysis was validated prior to use and performed within acceptable limits during sample analysis.

The results show that mini-tablets are bioequivalent to the marketed 300 mg tablet, as the point estimates and 90% confidence intervals for Cmax and AUC fall within the established limits of 80 to 125% (see Figure 14). The food effect seen with mini-tablets is was an 85% reduction in AUC and a 95% reduction in Cmax. These results are similar to the 85% reduction in AUC and Cmax seen with aliskiren tablets.

Figure 14: Results from Study A2109 showing geometric mean ratio and 90% confidence intervals for the following comparisons (1) Fasted: 300 mg mini-tablets vs 300 mg marketed tablet, (2) 300 mg mini-tablets fed vs fasted

Treatment	Parameter	GMR (90% CI)
Fasted	Cmax	1.06 (0.94, 1.21)
	AUClast	1.02 (0.92, 1.14)
	AUCinf	1.01 (0.92, 1.14)
Food Effect	Cmax	0.05 (0.04, 0.05)
	AUClast	0.16 (0.14, 0.18)
	AUCinf	0.17 (0.15, 0.18



Source: Table 11-4 in CSR for Study A2109

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8.2. Pharmacokinetic and Pharmacodynamic Study A2256

8.2.1. Study Design

The study was an open-label, randomized study in pediatric hypertensive patients. A study schematic is shown in Figure 15.

8.2.2. Objectives

- Safety and tolerability of aliskiren in children 6 to 17 years of age
- Effect of age on aliskiren pharmacokinetics (PK)
- Dose proportionality
- Dose response for change in plasma renin activity and blood pressure

8.2.3. Treatments and Dosing Strategy

This study was conducted to evaluate the pharmacokinetics and pharmacodynamics of aliskiren in children 6 to 17 years of age after single and after 8 days treatment with doses of 2 and 6 mg/kg. The doses in this study were based on weight-based matching to adult dose. A 150 mg dose for a 75 kg adult translated to 2 mg/kg, which was considered as a low end of dosing, likewise, for a patient weighing 50 kg, a 300 mg dose translates to 6 mg/kg, which represents the higher end of weight-based dose in adults. The study drug was administered in the form of aliskiren 3.125 mg mini-tablets (or oral pellets), batch number U0070808 (basis/variant number 7007250.001.

This type of dosing was considered acceptable, given the anticipated similarity of PK between adults and pediatrics.

A total of 39 children were randomized, 19 to 2 mg/kg, 20 to 6 mg/kg with equal distribution between children ages 6 to 11 and 12 to 17 years for both doses.

8.2.4. Population

- 36 male and female hypertensive children aged 6 to 17 years, with equal allocation to groups from 6 to 11 and 12 to 17 years, respectively
- Hypertension defined as SBP or DBP $\geq 95^{th}$ percentile for age, gender, and height, as measured on three separate occasions (guideline driven)
- Body weight $\geq$21 kg and $\leq$100 kg at randomization

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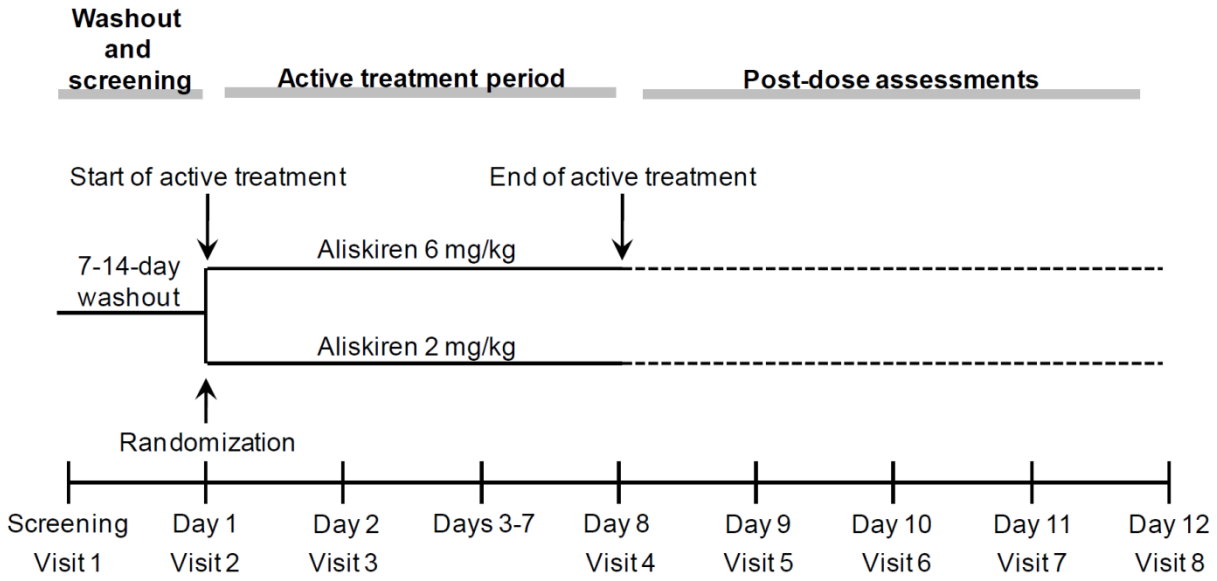
Figure 15: Schematic of planned visits for Study A2256



Source: Clinical Study Report cspp100a2256, Figure 9-1

8.2.5. Study Assessments

Plasma Sampling Times

PK: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 24 h post-dose at visits 2 (randomization), 3, 4, and 5 and at 48, 72, 96 h after the last dose (Visits 6, 7, 8)

PRA: pre-dose, 2, 10 h at Visit 2 (randomization), and pre-dose, 2, 10, 24 h post-dose Visit 4 (last dose)

Reviewer's Note: The sampling times appear reasonable based on aliskiren half-life and feasibility of returning to study site multiple times.

Pharmacodynamic assessments:

Blood pressure was measured using an automated blood pressure measuring device or a mercury sphygmomanometer at trough, i.e. prior to the next dose

Pharmacodynamic endpoints

- Plasma renin activity (PRA)
- Change from pre-dose baseline PRA
- Mean sitting SBP and DBP
- Change from mean pre-dose SBP and DBP
- Mean arterial pressure (MAP)

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Analytical Method: Methods were validated according to FDA Guidance, bioanalytical report shows that the method performed within limits set forth in FDA Guidance.

8.2.6. Results

Table 21: Study Population

	2 mg/kg		**6 mg/kg**	
	6-11 y	***12-17 y***	**6-11 y**	**12-17 y**
Randomized/Completed/Discontinued*	10/9/1	9/9/0	10/10/0	10/10/0
Age [Median (range)]	12.2 (3.12)		11.8 (3.78)	
Weight [Mean (range)]	69.6 (20.8)		56.7 (17.3)	
Male/Female	9/10		12/8	
Race (Caucasian/Black)	15/4		16/4	
BMI	27.3 (5.42)		24.0 (4.23)	
eGFR	108 (20.4)		98.2 (21.1)	
Blood pressure				
msSBP	135.8 (11.56)		131.7 (9.46)	
msDBP	78.7 (9.95)		70.9 (8.94)	

**Discontinued: 1 patient withdrew consent. Source: CSR Tables 10.1, 10-2, 11-2, 11-3*

Pharmacokinetics/Pharmacodynamics

Pharmacokinetics in pediatric patients were variable and suggested a trend for higher exposures with increasing age, attaining exposures in the range observed in adults (Table 21). Plasma renin activity was reduced from baseline by 76% and 87% for the 2 and 6 mg/kg doses, respectively (Figure 16). This mimics the range of PRA reduction observed in adults (50-80%). Blood pressure reductions were variable, but there did not appear to be obvious dose response, which is likely due to the small sample size (Table 23).

Table 22: Summarized pharmacokinetic parameters in Study A2256

Parameter	***6-11 years***		***12-17 years***	
	2 mg/kg	***6 mg/kg***	***2 mg/kg***	***6 mg/kg***
N				
Day 1	10	10	9	10
Day 8	9	10	9	10
Tmax [h]				
Day 1	1.0 (0.5-4.1)	1.5 (0.5-4.1)	1.0 (0.5-3.0)	1.8 (0.5-4.0)
Day 8	1.0 (0.5-4.)	1.5 (0.5-6.0)	1.0 (0.5-3.0)	2.0 (0.5-3.0)
Cmax [ng/mL]				
Day 1	76.8 (78.2)	393.3 (377.4)	136.5 (132.6)	424.3 (188.8)
Day 8	82.2 (97.9)	397.1 (187.1)	278.7 (357.5)	485.7 (300.6)
AUCtau [ng*h/mL]				
Day 1	278.3 (237.3)	1231.0 (728.5)	390.9 (264.5)	1808.7 (806.8)
Day 8	403.6 (326.8)	1959.9 (821.4)	847.2 (803.4)	2087.0 (999.1)

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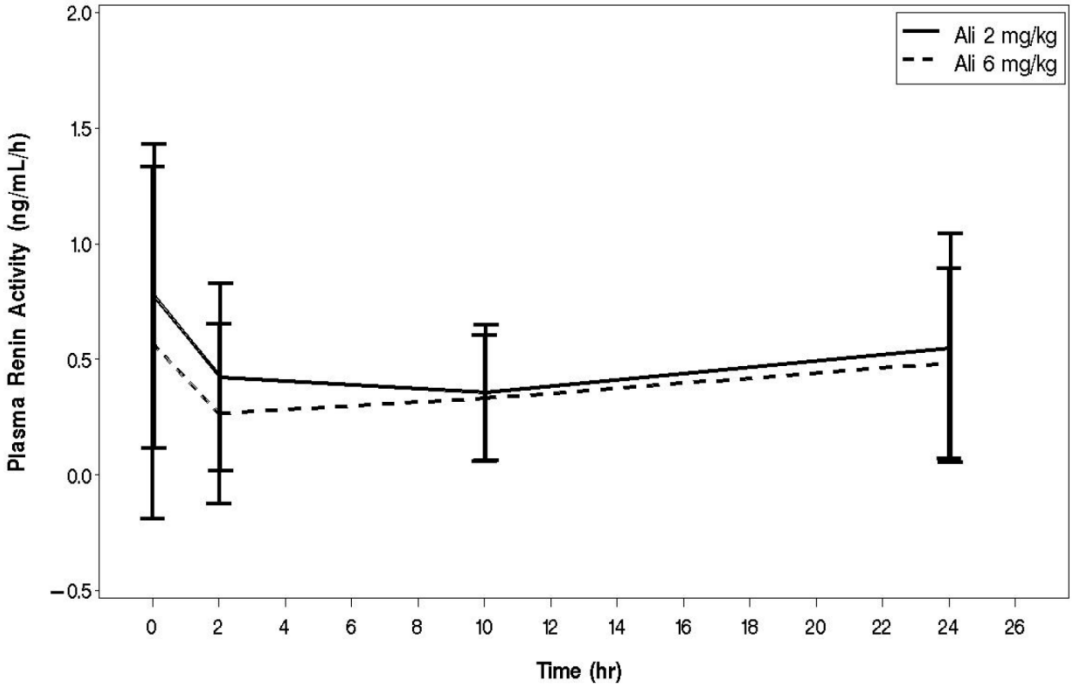
T1/2 [h]	38.8	45.1	39.2	42.9
CL/F [mL*h/kg]	9694.0 (8704.7)	3905.4 (2628.5)	5388 (5580.6)	3539.0 (1587.5)

Source: CSR Table 11-5

Figure 16: Plasma renin activity (PRA) by dose group throughout the study



Source: CSR Figure 11-10]

Table 23: Change from baseline mean seated systolic and diastolic blood pressure (msSBP, msDBP)

Mean Change from Baseline (SD) Blood Pressure [mmHg]	***2 mg/kg***	***6 mg/kg***
msSBP		
6-11 y	-4.5 (14.6)	-7.7 (11.8)
12-17 y	-7.6 (9.01)	-7.7 (9.38)
msDBP		
6-11 y	-1.7 (4.7)	0.0 (8.9)
12-17 y	-5.3 (8.8)	-5.8 (8.0)

Source: Reproduced from CSR Table 11-9

Based on an interim analysis conducted in 24 patients, the sponsor modelled the dose-response data. The model predicted that the low dose (0.13-0.31 mg/kg) would show mean SBP reductions of 7.3 mmHg, 10.2 mmHg for the mid dose (0.75-1.88 mg/kg) and 13.6 mmHg for the

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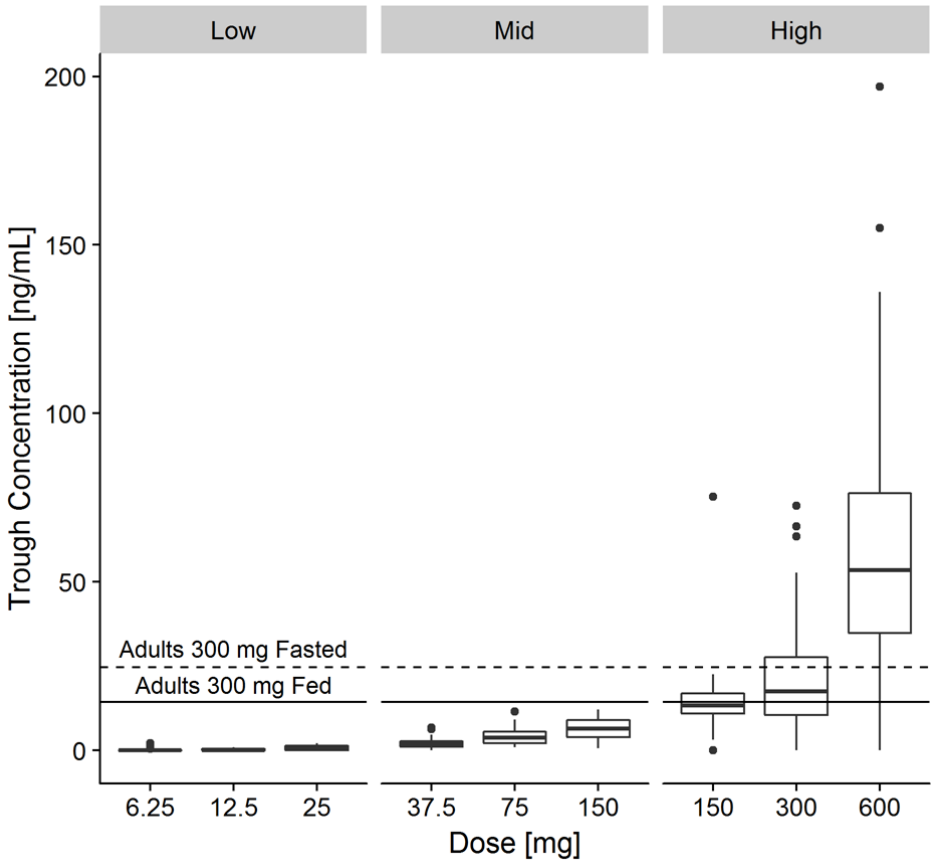
high dose (3-7.5 mg/kg). In addition, the mid dose was predicted to produce a 3 mmHg reduction in SBP relative to placebo. Based on these analyses, doses were chosen for the pivotal efficacy study (A2365).

8.3. PK Part 1 for Study A2365

Analysis of trough PK by dose groups shows that the low and mid doses produced trough concentrations far below what was seen in adults, which likely explains the lack of effect seen at these doses.

Figure 17: Analysis of trough concentrations during Part 1 (dose-response) of Study A2365



Source: Reviewer's analysis (dataset: sppedpk.xpt)

Data from studies A2256 and A2365 were also used for population pharmacokinetic/pharmacodynamic modelling of the blood pressure lowering effect. The applicant found that there was a shallow exposure-response relationship based on simulated AUC and observed trough concentrations. The applicant is planning to limit doses to those used in adults, i.e. the highest dose would be 300 mg. Patients in study 2365 were able to receive

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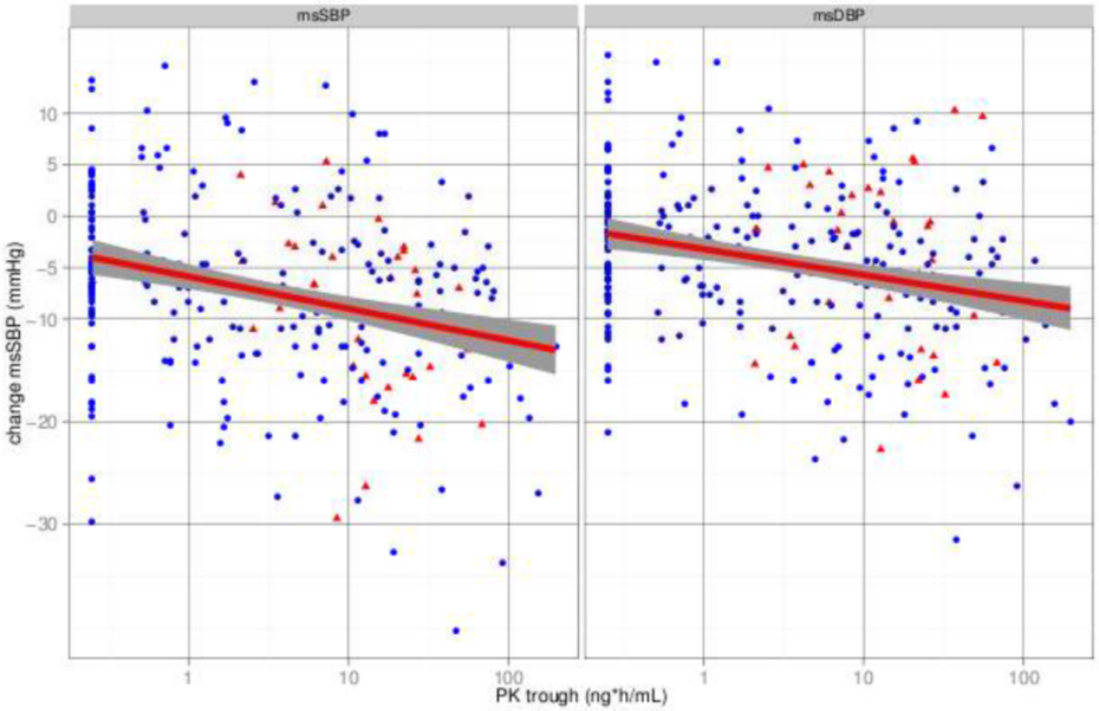
doses up to 600 mg, if deemed necessary. As seen in study 2365 Part 1, exposures did increased about two-fold in the high dose when 300 and 600 mg are compared (Figure 17). However, based on the analysis summarized in Figure 18, the expected additional change in blood pressure when doubling the exposure is less than 1 mmHg systolic and diastolic and a 2.7 and 2.3 mmHg change in blood pressure is seen for every 10-fold increase in trough concentrations of aliskiren. Therefore, capping the dose at 300 mg in pediatric patients weighing more than 50 kg appears acceptable.

Figure 18: Applicant's analysis of changes in trough exposure vs change in msSBP



Source: SPP100a-poppk-modeling-report, Figure 5-15

8.4. Potential Impact on Bioavailability of the Dispensable Capsule if Swallowed Whole

During the review cycle, the Division of Medication Error Prevention and Analysis commented about the use of a capsule shell as a dispensing aid leading to potential risk that a patient might not understand that the capsule needs to be opened, and in turn swallows the capsule whole.

The clinical pharmacology reviewer was consulted as to the potential for the ingestion of the whole capsule to reduce bioavailability. As a preliminary assessment, the Applicant was asked to provide in vitro dissolution data of drug product with and without the dispensing capsule shell. These results showed that at pH 2, dissolution of drug substance from the whole capsule is about

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20% after 60 min, compared to 100% from the mini-tablets (without capsule shell). At pH 6.8, approximately 100% of drug product is dissolved within 30 min from the mini-tablets whereas when the capsule is left to dissolve whole, about 20% of the drug substance is dissolved after 30 min and ~80% after 60 min (data presented in Figure 4 of Biopharmaceutics review) . Further, the Biopharmaceutics reviewer presented data that the sponsor had collected when multiple oral pellet formulations under development were compared in in vitro dissolution tests as well as in clinical relative bioavailability assessments (data presented in Figure 2 and Table 4 of Biopharmaceutics review). These results indicate that the slow rate of dissolution that was seen with the whole capsule when compared to the mini-tablets is expected to reduce the bioavailability of aliskiren by at least 50% or potentially more. Given these findings, the value of an in vivo study to further assess the relative bioavailability of the intact capsule is less.

The bioavailability of aliskiren is low, about 2-4%, and is further reduced when given with food. A high-fat, high-calorie meal reduces bioavailability by 85%. The label currently recommends that patients keep a routine when it comes to taking aliskiren, i.e., always with, or always without food.

In the case of pediatric patients potentially taking the whole capsule with food, the effect would likely be even more pronounced. Therefore, these results clearly support the proposed labeling instructions by the applicant not to swallow the capsule whole. Refer the OPQ review for further discussion on this topic.

9 Appendix

The analysis of AEs by a FDA customized grouping did not reveal any new or unexpected safety findings. In adults, aliskiren is known to cause GI upset which could be reflected by over-reporting in pediatrics of the grouping nausea/vomiting and the grouping of dyspepsia/nausea/vomiting/indigestion/epigastric pain/gastritis/duoden. Some AEs over-reported in the aliskiren arm compared to enalapril are common events in the pediatric population (e.g., infection, URI, cold) and it's not clear, from a mechanistic perspective, how aliskiren might cause or increase the risk of such events.

Table 24: AEs Summarized by a FDA Customized Grouping Sorted by Descending Percent Difference Between Aliskiren and Enalapril Arms (Study A2365E1)

FDA AE Grouping	Aliskiren (N=105)		Enalapril N=103)		Grand Total (N=208)		Difference (A-E)
	n	%	n	%	n	%	
Sum of N(infection, all)	58	55.2%	51	49.5%	109	52.4%	5.7%
Sum of N(dyspepsia, N, V, indigestion, epigastric pain, gastritis, duoden)	10	9.5%	5	4.9%	15	7.2%	4.7%
Sum of N(Nausea, vomiting)	9	8.6%	5	4.9%	14	6.7%	3.7%

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FDA AE Grouping	Aliskiren (N=105)		Enalapril N=103)		Grand Total (N=208)		Difference (A-E)
	n	%	n	%	n	%	
Sum of N(URI, cold, rhinitis, upper resp tract infection, flu-like illne)	35	33.3%	31	30.1%	66	31.7%	3.2%
Sum of N(eczema)	2	1.9%	0	0.0%	2	1.0%	1.9%
Sum of N(diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria,)	2	1.9%	0	0.0%	2	1.0%	1.9%
Sum of N(rash, eruption, dermatitis)	3	2.9%	1	1.0%	4	1.9%	1.9%
Sum of N(diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff)	11	10.5%	9	8.7%	20	9.6%	1.7%
Sum of N(infestation, parasite, amoeba)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(dysarthria, dyslalia, speech disorder)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(reflux, GERD)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(GI bleed)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(constipation)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(sleep apnea)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(hypertension, BP increased)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(orthostasis)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(pre-syncope or syncope)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(syncope)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(seizure)	1	1.0%	0	0.0%	1	0.5%	1.0%
Sum of N(appendicitis)	2	1.9%	1	1.0%	3	1.4%	0.9%
Sum of N(vertigo; vestibular dysfunction)	2	1.9%	1	1.0%	3	1.4%	0.9%
Sum of N(GOT, GPT, GGTP, LFTs)	2	1.9%	1	1.0%	3	1.4%	0.9%
Sum of N(arthralgia, arthritis, arthrosis)	2	1.9%	1	1.0%	3	1.4%	0.9%
Sum of N(influenza)	3	2.9%	2	1.9%	5	2.4%	0.9%
Sum of N(weight gain)	3	2.9%	2	1.9%	5	2.4%	0.9%
Sum of N(fever, rigors)	6	5.7%	5	4.9%	11	5.3%	0.9%
Sum of N(infection, viral)	15	14.3%	14	13.6%	29	13.9%	0.7%
Sum of N(diverticular disease)	0	0.0%	0	0.0%	0	0.0%	0.0%
Sum of N(abscess, boil, furuncle)	1	1.0%	1	1.0%	2	1.0%	0.0%
Sum of N(paresthesia, hypoaesthesia)	1	1.0%	1	1.0%	2	1.0%	0.0%
Sum of N(confusion, delirium, altered mental status, disorientation, coma)	1	1.0%	1	1.0%	2	1.0%	0.0%

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FDA AE Grouping	Aliskiren (N=105)		Enalapril N=103)		Grand Total (N=208)		Difference (A-E)
	n	%	n	%	n	%	
Sum of N(infection, bacterial)	2	1.9%	2	1.9%	4	1.9%	0.0%
Sum of N(pneumonia)	2	1.9%	2	1.9%	4	1.9%	0.0%
Sum of N(eye other)	2	1.9%	2	1.9%	4	1.9%	0.0%
Sum of N(arrhythmia)	2	1.9%	2	1.9%	4	1.9%	0.0%
Sum of N(tachycardia)	2	1.9%	2	1.9%	4	1.9%	0.0%
Sum of N(abdominal pain, distension, bloating, spasm, IBS, megacolon)	5	4.8%	5	4.9%	10	4.8%	-0.1%
Sum of N(autoimmune disease)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(infection, fungal)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(cellulitis, erysipelas)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(weight loss, catabolic state, cachexia, failure to thrive)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(dyspnea, SOB, respiratory distress)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(polycythemia)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(stone, renal colic)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(elevated BUN or Cr, anuria, ARF, CRF, oliguria)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(dehydration, volume depletion)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(ventricular arrhythmia)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(PVCs)	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(emotional mood disturbance (non-depressive))	0	0.0%	1	1.0%	1	0.5%	-1.0%
Sum of N(fall, dizziness, balance disorder, gait disturbance, difficulty walking)	1	1.0%	2	1.9%	3	1.4%	-1.0%
Sum of N(fall, dizziness, balance disorder)	1	1.0%	2	1.9%	3	1.4%	-1.0%
Sum of N(wheeze, bronchospasm, asthma)	1	1.0%	2	1.9%	3	1.4%	-1.0%
Sum of N(dizziness, light-headedness)	1	1.0%	2	1.9%	3	1.4%	-1.0%
Sum of N(dermatitis)	1	1.0%	2	1.9%	3	1.4%	-1.0%
Sum of N(gout, high uric acid)	1	1.0%	2	1.9%	3	1.4%	-1.0%
Sum of N(fracture)	2	1.9%	3	2.9%	5	2.4%	-1.0%
Sum of N(asthenia, fatigue, malaise, weakness, narcolepsy)	2	1.9%	3	2.9%	5	2.4%	-1.0%
Sum of N(bleeding)	3	2.9%	4	3.9%	7	3.4%	-1.0%

Reference ID: 4166471

FDA AE Grouping	**Aliskiren (N=105)**		**Enalapril N=103)**		**Grand Total (N=208)**		**Difference (A-E)**
	n	**%**	**n**	**%**	**n**	**%**	
Sum of N(UTI)	5	4.8%	6	5.8%	11	5.3%	-1.1%
Sum of N(cough)	8	7.6%	9	8.7%	17	8.2%	-1.1%
Sum of N(hematuria)	0	0.0%	2	1.9%	2	1.0%	-1.9%
Sum of N(epistaxis)	2	1.9%	4	3.9%	6	2.9%	-2.0%
Sum of N(somnolence, fatigue, sedation)	2	1.9%	4	3.9%	6	2.9%	-2.0%
Sum of N(bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis)	6	5.7%	8	7.8%	14	6.7%	-2.1%
Sum of N(allergic RXN, hypersensitivity)	1	1.0%	4	3.9%	5	2.4%	-2.9%
Sum of N(headache)	8	7.6%	15	14.6%	23	11.1%	-6.9%

Reference ID: 4166471

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

/s/

CHRISTINE E GARNETT
10/12/2017

MARTINA D SAHRE
10/12/2017

SUDHARSHAN HARIHARAN
10/12/2017

ALIZA M THOMPSON
10/12/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 210079 **Applicant: Noden Pharma** **Stamp Date: 06/05/2017**

Drug Name: Aliskiren **NDA/BLA Type: NDA (pediatrics)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159 htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			Benefit-risk statement in 2.5 Clinical Overview
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1) Pediatric WR
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: A2365 Sample Size: 268 Treatment Arms: Aliskiren dose-response; placebo-control washout	X			Dose response was assessed in the pivotal Phase 3 trial.
EFFICACY					

Reference ID: 4115254

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			Per pediatric WR
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Per pediatric WR
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Per pediatric WR
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Post-marketing experience in children was provided.
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Long term safety study
29.	For Rx-to-OTC switch and direct-to-OTC applications, are			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 4115254

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?				
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Defer in pediatrics <6 y.
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?			X	
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 4115254

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

I do not have any comments for the 74-day letter.

Christine Garnett, PharmD	6/16/2017
Reviewing Medical Officer	Date
Aliza Thompson, MD	6/19/2017
Clinical Team Leader	Date

Reference ID: 4115254

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

/s/

CHRISTINE E GARNETT
06/22/2017

ALIZA M THOMPSON
06/22/2017