14 January 2015
EMA/262230/2016
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Rasilez

aliskiren

Procedure no: EMEA/H/C/000780/P46/039

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested type IB variation

Pursuant to Article 15 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 18 June 2015 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.z	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	Type IB	I

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC according to the outcome of the recently completed Article 46 procedure EMA/H/C/780/P46/039 which reviewed the results of the aliskiren paediatric study CSPP100A2365 in children 6-17 years with hypertension.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.3.z	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	Type IB	I

☒ is recommended for approval.

3. Scientific discussion

3.1. Quality aspects

N/A

3.2. Safety, Efficacy, Pharmacovigilance aspects

Introduction

On February 2015, the MAH submitted a completed paediatric study for Rasilez (aliskiren), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview has also been provided.

Prevalence of hypertension in children has been increasing worldwide driven by the increasing prevalence of childhood obesity (Din-Dzietham et al, 2007, Flynn, 2008). Hypertension in children and adolescents is defined as average systolic blood pressure (SBP) or diastolic blood pressure (DBP) that is ≥ 95th percentile for gender, age, and height on at least three separate occasions (NHBPEP 4th Report, 2004). Primary (essential) hypertension in children is usually 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 (Riley et al, 2012).

The renin angiotensin aldosterone system (RAAS) plays a major role in the regulation of blood pressure (BP) and the pathogenesis of hypertension. Renin is secreted by the kidney in response to a decrease in circulating volume and BP. It cleaves the substrate angiotensinogen to form the inactive decapeptide angiotensin I (Ang I). Angiotensin I is converted to the active octapeptide Angiotensin II (Ang II) by angiotensin converting enzyme (ACE). Angiotensin II interacts with cellular receptors (Ang II receptors) and through different mechanisms increases total peripheral resistance, resulting in the elevation of BP.

Blocking the RAAS with an ACE inhibitor (ACEI) or Angiotensin II receptor blocker (ARB) has been commonly used in clinical practice for the treatment of patients, including children, with hypertension (Chu et al, 2014). An alternative approach to blockade of the RAAS is inhibition of renin, the rate limiting enzyme for the formation of Ang II. Aliskiren (SPP100) is the first in class, orally active, non-peptide, specific direct renin inhibitor and blocks the conversion of angiotensinogen to Ang I.

It is approved in EU for treatment of hypertension in adults.

Information on the development program

Aliskiren's safety and efficacy are well established in adults and it is approved for treatment of hypertension in adults, except in patients who have type 2 diabetes mellitus and are receiving an ACEI or an ARB [aliskiren Investigator Brochure, edition 16]. The study CSPP100A2365 was designed to evaluate the efficacy and safety/tolerability of aliskiren in the pediatric population aged 6-17 years.

The MAH stated that study title and number is part of a clinical development program.

Information on the pharmaceutical formulation used in the study<ies>

The investigational drug (SPP100, aliskiren) was provided by Novartis Drug Supply Management (DSM) equaling 6.25 mg/37.5 mg/150 mg dosage strengths.

Clinical study

Methods

<u>Study number and title</u>

CSPP100A2365 - A multicenter, randomized, double-blind, 8 week study to evaluate the dose response, efficacy and safety of aliskiren in peadiatric hypertensive patients 6-17 years of age.

The study CSPP100A2365 is a multicenter, randomized, double-blind, 8-week study in pediatric hypertensive patients with ages 6-17 years.

Objective(s)

The *primary objectives* of this study were:

- In Phase 1 (dose response phase), to evaluate the dose response of aliskiren in mean sitting systolic blood pressure (msSBP) change at end of Phase 1, from the baseline to Week 4, as measured by office BP.

- 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 (at the beginning of Week 5),compared to placebo pooled from corresponding arms, as measured by office BP.

The *secondary objectives* of this study were the followings: safety and tolerability of aliskiren, dose response of aliskiren in mean sitting diastolic blood pressure (msDBP, office BP), effect of aliskiren (mid and high doses) in msDBP change compared to placebo, dose response of aliskiren in calculated mean arterial pressure (MAP, office BP), treatment effect of aliskiren (mid and high doses) in calculated MAP change compared to placebo, the rate of positive treatment response by dose group (positive response = msSBP < 95th percentile or a 7 mmHg decrease in msSBP from the baseline), the effect of aliskiren on the 24 hour ambulatory blood pressure monitoring (ABPM) with focus on mean systolic and diastolic ABPM, daytime and nighttime ABPM, dipper vs. non-dipper pattern (nondipper = < 10% decline in nighttime mean vs. the daytime mean in ABPM).

The exploratory objectives of this study were the followings: the relationship between change in PRA and the dose of aliskiren, the relationship between change in PRA from baseline at the end of Phase 1 and age, the relationship between baseline PRA, disease factors and BP response, age and dose.

Patients successfully completing this study were offered to participate in a 52-week, double-blind, randomized extension study (CSPP100A2365E1) aimed to evaluate the long-term safety, tolerability and efficacy of aliskiren compared to enalapril.

Study 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. The study consisted of 3 phases as defined below (Figure 9-1):

- 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 ($\geqslant$ 20 to < 50 kg), the mid-weight ($\geqslant$ 50 kg to < 80 kg) and the high-weight ($\geqslant$ 80 kg to $\leqslant$ 150 kg) patients with a low: mid: high dose ratio of 1:6:24. Patients were stratified at baseline by weight ($\geqslant$ 20 to < 50 kg; $\geqslant$ 50 kg to < 80 kg and $\geqslant$ 80 kg to $\leqslant$150 kg), age (6-11 and 12-17 years old), region (US, EU and ROW, as applicable), and by hypertension etiology (primary vs. secondary). For Phase 1,

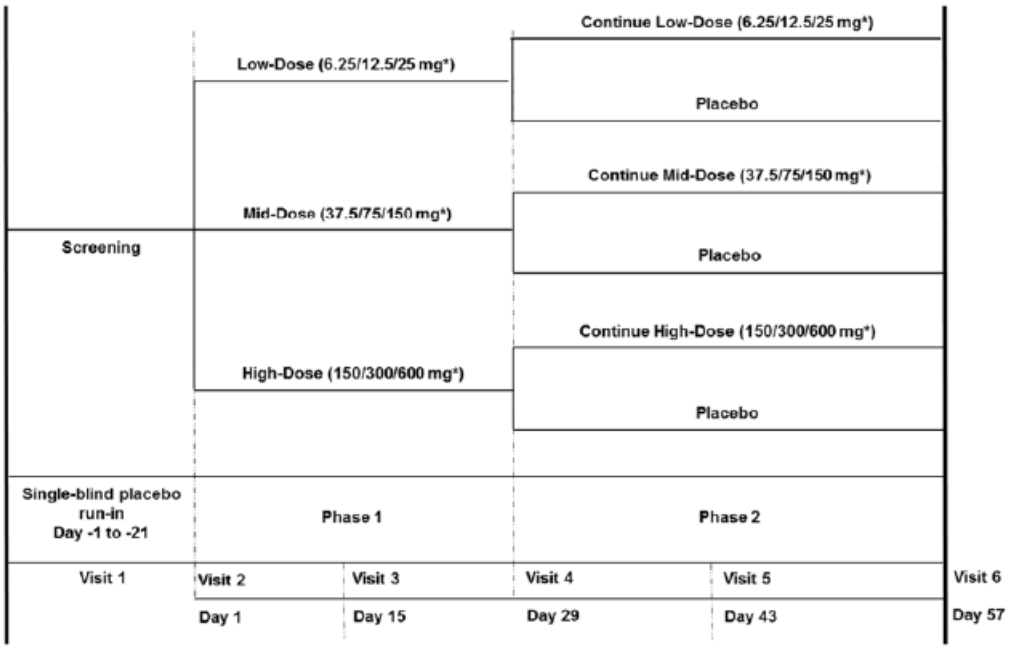
patients were randomized to aliskiren low, mid and high dosing groups in a 2:1:2 ratio and were dosed based on their weight category at randomization as shown in Table 9-1.

- 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 I or were switched to placebo.

Table 9-1 Dosing Regimen in Phase 1

	Dosing Groups		
Weight Category	Low Dose	Mid Dose	High Dose
≥20 to <50 kg	6.25 mg o.d (0.13 – 0.31 mg/kg)	37.5 mg o.d (0.75 – 1.88 mg/kg)	150 mg o.d (3.0 – 7.5 mg/kg)
≥50 to <80 kg	12.5 mg o.d (0.16 – 0.25 mg/kg)	75 mg o.d (0.94 – 1.5 mg/kg)	300 mg o.d (3.75 – 6.0 mg/kg)
≥ 80 to ≤ 150 kg	25 mg o.d (0.17 – 0.31 mg/kg)	150 mg o.d (1.0 – 1.88 mg/kg)	600 mg o.d (4.0 – 7.5 mg/kg)

Figure 9-1 Study design



*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.

The study design was discussed and agreed with US Food and Drug Administration (FDA) and Pediatric Committee (PDCO) of the European Medicines Agency (EMA) as an adequate design to characterize the efficacy and safety of aliskiren in pediatric patients. The study follows the FDA trial design C which avoids use of a true placebo arm and ensures interpretability of results. A negative slope of the dose response phase would indicate that the study was successful (Pasquali et al, 2002). In case the dose response phase is uninterpretable (zero slope, drug effective at all studied doses), the placebo-controlled withdrawal phase would be used to help differentiate the efficacy of the drug. Study design C is the most commonly used trial design in pediatric hypertension (Benjamin et al, 2008).

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 [aliskiren Investigator Brochure, edition 16].

msSBP was the primary endpoint (and entry criteria) because systolic hypertension is more prevalent than diastolic hypertension in children. Clinical studies indicate that SBP change is often better correlated with clinical outcome (cardiovascular mortality and morbidity) than DBP, although no such data is available in children. Secondary endpoints included msDBP, MAP, rates of responders and ambulatory blood pressure (mean arterial systolic BP [MASBP] and mean arterial diastolic BP [MADBP]).

Study population

The study population consisted of approximately 275 male and female children, 6 to 17 years of age at randomization (Visit 2), with msSBP $\geqslant$ 95th percentile for age, gender and height measured by office BP. It was estimated that, at randomization:

- at least 50% of patients would be 11 years old or younger

- at least 10% of the patient population would have secondary hypertension by history

- at least 80% of the patient population would be $\leqslant$ 100 kg.

A total of 255 patients were expected to complete Phase 1, and approximately 237 patients were expected to complete Phase 2.

Inclusion criteria were the followings:

- Male or female, aged 6-17 years with a documented diagnosis of hypertension as defined in the NHBPEP 4th Report, 2004 (msSBP as mean of 3 measurements) must have been $\geqslant$ 95th percentile for age, gender and height, at Visit 2)

- Weighed $\geqslant$ 20 kg and $\leqslant$ 150 kg at randomization (Visit 2)

- Were able to safely wash out prior antihypertensive therapy for a minimum of 7 days if already receiving treatment

- Were able to swallow

- written informed consent of their parent(s)/guardian(s) consented.

Exclusion criteria were clinically abnormalities or abnormal lab values including the followings:

- high AST/SGOT or ALT/SGPT or high total bilirubin

- creatinine clearance < 30 mL/min/1.73m² (modified Schwartz formula),

- low White Blood Cells (WBC) count, low Platelet count,

- high serum potassium (> 5.2 mEq/L),

- renal artery stenosis, history of angioedema, heart failure (NYHA Class II-IV) or cardio-myopathy or obstructive valvular disease, severe hypertension (msSBP $\geqslant$ 25% above the 95th percentile),

- second or third degree heart block without a pacemaker or atrial fibrillation or atrial flutter or any symptomatic arrhythmia

- solid organ transplantation

- treatment with immunosuppressant medication (e.g. cyclosporine, MMF, etc.) other than oral/topical steroids, for any medical condition

- treatment with atorvastatin, cholestyramine or colestipol resins, monoamine oxidase (MAO) inhibitors, ketoconazole, itraconazole, or antiarrhythmic medications (other than digoxin)

- child-bearing potential or pregnancy or nursing (lactating) women,

- hypersensitivity to study medication or to any drug of similar chemical class.

For detailed exclusion criteria, please refer to Appendix 16.1.1–Study Protocol–Section 5.2.

Sample size

For the analysis of Phase 1, a total sample size of 200 patients was required to provide at least 90% power to detect a non-zero slope of 0.239 for change from baseline in msSBP (mmHg) as a linear function of aliskiren dose ratio (1:6:24) at a two-sided significance level of 0.05. This calculation assumed a 2:1:2 patient allocation ratio to aliskiren low, mid and high dosing groups respectively. The (pooled) standard deviation from valsartan study CVAL489A2302 was estimated as 11 mm Hg, so this was used in the current calculation. A slope of 0.239 (mmHg per unit increase in dose ratio) corresponds to 5.5 mmHg reduction in SBP from low dose (6.25/12.5 mg) to high dose (150/600 mg). Considering a 7% dropout rate, a total of 216 patients were required for Phase 1 to achieve 90% lower.

For the analysis of Phase 2, a total sample size of 237 patients (with 1:1 patient allocation ratio for placebo and aliskiren) was required to provide at least 90% power to detect a treatment difference in change from end of Phase 1 in msSBP of 5.5 mmHg, with a standard deviation of 10 mmHg at a two-sided significance level of 0.05. The standard deviations for the change from end of Phase 1 in mean sitting SBP for the primary and secondary hypertension groups in the valsartan study CVAL489A2302 were estimated as 9.40 mmHg and 9.98 mmHg, respectively. The standard deviations in both hypertension groups were smaller than the standard deviation considered in this calculation. Considering a 7% dropout rate, a total of 255 patients were required for Phase 2 to achieve 90% power. This required that 275 patients be entered into Phase 1, so that the expected 255 patients continued into Phase 2.

The sample size of 275 patients was required to achieve at least 90% power for testing the primary hypothesis in each phase at a two-sided significance level of 0.05. It was expected that the proportion of patients with primary hypertension would be at least 60%, so based on the assumptions of the standard deviation and treatment effects, the planned sample size of 275 randomized patients should result in at least 90% power for testing the primary hypothesis in each phase, at a two-sided significance level of 0.05.

Treatments

The following study medications were provided in a double-blind fashion:

- Investigational drug: SPP100 (aliskiren) 6.25, 37.5 mg and 150 mg

- Control drug: placebo to SPP100 (aliskiren)

All test materials were supplied by Novartis Drug Supply Management (DSM).

A dose ratio of 1:6:24 (low : mid : high) was selected to try to ensure no efficacy overlap between the three dose groups selected for this study, which has been shown to be a factor in the success of dose response trials of antihypertensive agents in a pediatric population (Benjamin et al, 2008).

Aliskiren in adults was studied in doses of 75 mg, 150 mg, 300 mg and 600 mg. Once daily doses of aliskiren 150 mg and 300 mg were recommended and approved for use as monotherapy or in combination with other anti-hypertensive agents in adults [aliskiren Investigator Brochure, edition 16].

In addition, in study CSPP100A2256, doses of 2 and 6 mg/kg were studied in 39 hypertensive patients aged 6-17 years with results showing that the overall pharmacokinetic (PK) findings in pediatric patients are similar to those seen in adults based on the body weight normalized plasma apparent total body clearance. As with adults, age, body weight, and gender appeared to have no significant effect on aliskiren systemic exposure. The exposure levels in these pediatric patients were within or slightly below the exposure range found in adults. The aliskiren doses selected in study CSPP100A2365 (3.0-7.5 mg/kg for high, 0.75-1.88 mg/kg for mid and 0.13-0.31 mg/kg for low dose groups) were selected with the intention of covering a wider dose range from a highly effective dose (inclusive of a dose higher than that used in adults (i.e. 600mg)), and also to ensure a minimally effective dose. This is consistent with recommendations for dose response studies to include a low dose that is less than the lowest approved adult dose and a high dose that is at least two-fold higher than the maximum approved adult dose (Benjamin et al, 2008).

A modelling and simulation analysis was done on interim data from CSPP100A2256 to predict a BP dose response in CSPP100A2365. Results showed that a dose response slope would be generated with mean SBP reductions of 7.3 mmHg, 10.2 mmHg and 13.6 mmHg for the low, medium and high dose groups, respectively.

Treatment blinding: Patients, investigator staff, persons performing the assessments, and data analysts remained blind to the identity of the treatment from the time of randomization until database lock, using the following methods:

Instructions for prescribing and taking study treatment: Patients were instructed to withhold study medication on the day of their next clinic visit and to bring all remaining study medication to their next clinic visit.

Permitted dose adjustments and interruptions of study treatment: Study drug dose adjustments were not permitted. If a temporary interruption of study medication occurred, every attempt to re-initiate study medication was made.

Rescue medication: The use of rescue medication was not permitted in this study.

Concomitant treatment: Use of the following treatments was not allowed: anti-hypertension drugs, cyclosporine, Itraconazole, potassium sparing diuretics, and/or potassium supplement, MAO inhibitors.

Uses of the following treatments were conditionally permitted after the start of the washout Period: chronic use of NSAIDS/COX-2, over the counter decongestants, stimulant therapy such as methylphenidate for attention deficit disorder/attention deficit hyperactivity disorder, chronic use of steroids, other drugs provided the need for such medication(s) was a continuation of a need that existed prior to entry into the study and the manner in which the medication(s) were used remained essentially unchanged.

Patients were not discontinued from the study until the study monitor had been contacted. The decision to discontinue a patient who had taken any of these concomitant medications (with the exception of cyclosporine and itraconazole) was evaluated on a case by case basis by Novartis in

consultation with the investigator. Any patient who had taken cyclosporine or itraconazole, for any indication, was to be discontinued immediately.

Discontinuation of study treatment and premature patient withdrawal: Study drug was discontinued (and the patient withdrawn from the trial) if the investigator determined that continuing would have resulted in a significant safety risk for that patient or if, on balance, he/she thought that continuation would have been detrimental to the patient's wellbeing.

The following circumstances required study drug discontinuation: withdrawal of informed consent, inability to discontinue prior antihypertensive therapy for a minimum of 7 days during the SB placebo run-in, positive pregnancy test, lack of baseline (Visit 2) msSBP measurement, use of the prohibited concomitant medication, emergence of adverse events (AEs). The list of AEs included the followings:: msSBP is ≥ 25% above the 95th percentile at any time, symptomatic hypotension or msSBP ≤ 50th percentile for gender, age and height at any time, severe anemia defined as Hemoglobin < 8 gm/dL, severe leucopenia defined as WBC < 3000/mm3, pregnancy, allergic reaction to study medication, protocol deviation resulting in significant risk, liver enzymes >3 times the upper limit of the reference range not due to viral hepatitis.

Patients had the possibility to voluntarily withdraw from the study for any reason at any time.

Emergency unblinding did not occur in this study.

Treatment exposure and compliance: Treatment exposure and compliance was assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient.

Outcomes/endpoints

Efficacy, safety and pharmacokinetic/pharmacodynamic assessments - Visit schedule: The study visits and procedures are presented in Table 9-3 which lists all of the assessments and indicates with an "X" the visits at which they were performed.

Table 9-3 Evaluation and visit schedule

		Day -21 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
	Category[5]	Visit 1 SCR	Visit 2 BL	Visit 2A	Visit 3	Visit 3A	Visit 4	Visit 4A	Visit 5	Visit 5A	Visit 6
Assessment			**Phase 1**					**Phase 2**			
Informed consent	S	X									
Inclusion/Exclusion	S	X									
Demography	D	X									
Medical History	D	X									
Physical Exam*	S	X									X
Hematology*	D	X					X				X
Chemistry*	D	X					X				X
Cystatin C*	D		X								X
Creatinine, BUN electrolytes	D		X								
PK[1]	D				X		X				
PRA*	D		X				X				X
PRC[6]	D		X				X				X
ABPM[2]	D		X				X				X
Serum Pregnancy*	S	X									X
Urine Pregnancy	D	X	X								X
Urinalysis*	D	X					X				X
Urine UACR[3]	D		X				X				X
Height*	D	X	X		X		X		X		X
Weight*	D	X	X		X		X		X		X
Blood pressure*	D	X	X	X	X	X	X	X	X	X	X
Pulse*	D	X	X	X	X	X	X	X	X	X	X
ECG*	S		X								X
Echocardiography[4]	D		X								
Tanner stage evaluation*	D		X								X

		Day -21 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
	Category[5]	Visit 1 SCR	Visit 2 BL	Visit 2A	Visit 3	Visit 3A	Visit 4	Visit 4A	Visit 5	Visit 5A	Visit 6
Assessment			**Phase 1**					**Phase 2**			
Neurocognitive developmental evaluation	D		X								X[7]
IVRS	S	X	X				X				X
Prior/concomitant medications*	D	X	X	X	X	X	X	X	X	X	X
Dispense study medication	S	X	X				X				X**
AE/SAE*	D		X	X	X	X	X	X	X	X	X
Drug administration record*	D	X	X		X		X		X		X
Study completion CRF*	D										X

SCR=Screening, BL=Baseline

Office BP measurements were done using an automated BP monitoring device and calibrated regularly in accordance with the Guidelines for Management of Hypertension: Report of the fourth working party of the British Hypertension Society, 2004 – BHS IV (Williams, et al 2004). Post-dose measurements were made at trough (24 hours ± 3 hours post-dose), i.e. just prior to taking the daily dose of study medication. The measurements were done using the non-dominant arm; however, if a clinically-relevant difference (≥ 10 mmHg in SBP and/or ≥ 5 mmHg in DBP) was noted between the two arms at study entry, the arm with higher BP reading was used for subsequent study assessments. The arm used was documented in source documentation.

Sitting BP was measured after the patient had been sitting for 5 minutes and the average of three sitting BP measurements was used as the mean sitting office BP. Standing BP was measured only once

at each visit, after the patient had been standing for 3 minutes and within 3-5 minutes after the last sitting BP measurement.

Self-measured blood pressure: At the first study visit all patients who were dispensed SB run-in study medication were also provided with an automated self-measuring BP device (SMBP). SMBP information was not analyzed. It was intended to be used as a guide to monitor the patient's home BP throughout the course of the trial.

Ambulatory Blood Pressure Monitoring (ABPM): ABPM assessments were anticipated to be done in at least 50% of the randomized patient population. Patients at pre-selected sites had ABPM collected over a 24-hour period at Visits 2, 4 and 6. Following office BP measurements, patients were instructed to wear the ABPM device for 24 hours. The ABPM device was pre-set to collect readings every 20 minutes. All ABPM readings remained blinded to the patients.

Assessment of safety: Safety assessments consisted of collecting all AEs, including serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They also included the regular monitoring of laboratory tests (hematology, clinical chemistry, and urinalysis) and regular assessments of vital signs, body height/weight and physical condition. Electrocardiograms (ECGs) were performed at baseline (Visit 2) and Visit 6. Echocardiography was offered to all patients at baseline, but was only required for patient with left ventricular hypertrophy (LVH). Other safety assessments included pregnancy tests at screening, baseline, and Visit 6, Tanner stages evaluation for growth at baseline and Visit 6. Neurocognitive assessment was performed at baseline for all patients and at Visit 6 only for patients who discontinued early or did not enter the extension study. Clinically notable laboratory values were pre-defined.

Drug concentration measurements: At Week 2 (Visit 3), PK blood samples were planned to be collected in 30 to 50% of the patient population at a random time point post dose for population PK analysis. One (1) fasting trough PK sample was planned to be collected from every patient at the completion of the dose-response phase (Week 4 (Visit 4)).

Pharmacodynamic and biomarker assessments: Biomarkers related to hypertension and renal functions were collected. These included markers such as PRA, plasma renin concentration (PRC), urinary albumin-to-creatinine ratio (UACR), and Cystatin C.

Data quality assurance – Monitoring: The responsibility for site monitoring resided with field monitors from Novartis or from Research Pharmaceutical Services Inc (RPS).

Statistical Methods

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.

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 safety sets (SAF1 and SAF2) consisted of all patients who received at least one dose of double-blind study drug at respective phases.

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. If a flat dose-response curve was found (i.e., the slope is not

statistically different than zero), it would indicate that there are no significant differences among the aliskiren doses during the four weeks of treatment in Phase 1; then the analyses performed in Phase 2 would be used to further interpret whether there is an effect on BP due to placebo wash-out. The primary efficacy analyses were performed on the FAS1 and FAS2. Additional analyses were performed using the PPS1 and PPS2. 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, were carried out at the 2-sided significance level of 0.05.

Results

Recruitment/ Number analysed

Summary of patient disposition for Phase 1 is presented in Table 10-1 and for Phase 2 in Table 10-2. A total of 268 patients were randomized in Phase 1 including 1 mis-randomized patient who did not take double blind medication 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 low (4.5%), generally balanced between the phases, and lower than the protocol projected discontinuation rate of 14%.

In Phase 1, 7 patients (2.6%) discontinued from the study (Table 10-1). The rate of discontinuation due to an AE was low with only 1 patient discontinuing in the aliskiren high dose group. This patient discontinued the study medication on Day 1 due to an AE that started during the single-blind placebo wash-out (stomach cramping).

Table 10-1 Patient disposition by treatment group for Phase 1 (Randomized set 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: Table 14.1-1.1

Five patients (1.9%) discontinued from Phase 2 (Table 10-2); 4 of these were in the placebo group and 1 in the aliskiren high dose group. Withdrawal of consent (0.8%) and AEs (0.8%) were the most common reasons for discontinuation (1 in the aliskiren high dose group and 1 in the placebo high dose group).

Table 10-2 Patient disposition by treatment group for Phase 2 (Randomized set 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: Table 14.1-1.2

Patient disposition for Phase 1 and Phase 2 were also presented by region, center, and treatment group.

Patients successfully completing this study were offered the opportunity to participate in a 52-week, double-blind, randomized extension study (CSPP100A2365E1) aimed to evaluate the long-term safety, tolerability and efficacy of aliskiren compared to enalapril. A total of 208 of the 255 patients (81.6%) completing study CSPP100A2365 enrolled in CSPP100A2365E1.

Protocol deviations are summarized for Phase 1 in Table 10-3 and for Phase 2 in Table 10-4.

In Phase 1, protocol deviations occurred in 121 patients (45.1%) of the overall randomized population, and occurred more often in the low dose group than in the mid and high dose groups. The majority of the reported protocol deviations were minor, with use of NSAIDS and visit occurring out of window being the most commonly reported minor protocol deviations. The relatively high number of minor protocol deviations might be attributable to the longer than expected time to complete the study (4 years).

Major protocol deviations occurred in 18 patients (6.7%) of the overall randomized population that excluded them from the per-protocol analysis. The most common major protocol deviation was BP measurement collected not at trough in 6 patients (2.2%) followed by compliance with study medication less than 80% in Phase 1 in 5 patients (1.9%).

Table 10-3 Summary of protocol deviation by treatment group for Phase 1 (Randomized set 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 14.1-1.5

In Phase 2, protocol deviations occurred in 115 patients (44.2%) of the overall randomized population. Major protocol deviations occurred in 20 patients (7.7%) of the overall randomized population that excluded them from per-protocol analysis. Similar to Phase 1, the most common major protocol deviation was BP measurement collected not at trough in 9 patients (3.5%). Five patients had compliance with study medication less than 80% in Phase 2.

Table 10-4 Summary of major protocol deviation by treatment group for Phase 2 (Randomized set 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 150/300/6 00 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 14.1-1.6

Baseline data

The key baseline demographic and background characteristics of the randomized patients in Phase 1 are shown in Table 11-3. Patients in the three treatment groups had comparable demographic and baseline characteristics, including age, gender, race, weight, and hypertension etiology. The majority of patients were male and Caucasian with a mean age of 11.8 years. 47.8% of patients were in the 6-11 years age group and 51.9% in the 12-17 years age group. 53% of the patients were 12 years of age or younger. There were 30 (11.2%) black patients. Forty-eight patients (17.9%) had secondary hypertension. Mean weight was 68.6 kg with 58.6% of patients having body mass index (BMI) ≥ 95th percentile for age and gender.

Table 11-3 Patient background characteristics by treatment group for Phase 1 (Randomized set 1)

Demographic Characteristic category/statistic	ALI Low 6.25/12.5/25 mg N=108	ALI Mid 37.5/75/150 mg N=54	ALI High 150/300/600 mg N=106	Total N=268
Age (Years)				
n	108	54	105	267
Mean	11.9	11.6	11.8	11.8
SD	3.27	3.29	3.50	3.36
Age Group (years) n(%)				
6 – 11	49(45.4%)	28(51.9%)	51(48.1%)	128(47.8%)
12 – 17	59(54.6%)	26(48.1%)	54(50.9%)	139(51.9%)
6 – 12	58(53.7%)	30(55.6%)	54(50.9%)	142(53.0%)
13 – 17	50(46.3%)	24(44.4%)	51(48.1%)	125(46.6%)
Sex n(%)				
Male	73(67.6%)	37(68.5%)	66(62.3%)	176(65.7%)
Female	35(32.4%)	17(31.5%)	39(36.8%)	91(34.0%)
Race n(%)				
Caucasian	83(76.9%)	39(72.2%)	75(70.8%)	197(73.5%)
Black	9(8.3%)	6(11.1%)	15(14.2%)	30(11.2%)
Native American	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%)
Ethnicity n(%)				
Hispanic or Latino	16(14.8%)	12(22.2%)	19(17.9%)	47(17.5%)
Mixed ethnicity	5(4.6%)	0(0.0%)	3(2.8%)	8(3.0%)
Other	87(80.6%)	42(77.8%)	83(78.3%)	212(79.1%)
Hypertension etiology n(%)				
Primary	89(82.4%)	44(81.5%)	86(81.1%)	219(81.7%)
Secondary	19(17.6%)	10(18.5%)	19(17.9%)	48(17.9%)
Height (cm)				
n	108	54	105	267
Mean	155.6	155.1	154.5	155.0
SD	20.36	21.57	19.16	20.08
Weight (kg)				
n	108	54	105	267
Mean	66.7	70.3	69.6	68.6
SD	28.45	32.34	29.93	29.78
Weight category n(%)				
>=20 kg and < 50kg	35(32.4%)	18(33.3%)	34(32.1%)	87(32.5%)
>=50 kg and < 80 kg	36(33.3%)	17(31.5%)	36(34.0%)	89(33.2%)
>=80 kg and < 150 kg	36(33.3%)	19(35.2%)	35(33.0%)	90(33.6%)
>= 150 kg	1(0.9%)	0(0.0%)	0(0.0%)	1(0.4%)
Body Mass Index (kg/m^2)				
n	108	54	105	267
Mean	26.2	27.8	27.9	27.2
SD	7.38	9.11	7.93	7.98
BMI status n(%)				
< 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%)
eGFR (ml/min/1.73 m^2)				
n	108	53	105	266
Mean	105.6	109.7	110.0	108.2
SD	23.98	23.61	25.94	24.70
eGFR category n(%)				
< 60 ml/min/1.73 m^2	2(1.9%)	1(1.9%)	2(1.9%)	5(1.9%)
>= 60 and < 90 ml/min/1.73 m^2	23(21.3%)	9(16.7%)	21(19.8%)	53(19.8%)
>= 90 ml/min/1.73 m^2	83(76.9%)	43(79.6%)	82(77.4%)	208(77.6%)

SD = standard deviation

Height and weight were reassessed at Visit 4 before re-randomization in Phase 2 of the study and considered as baseline values for Phase 2. The overall characteristics for patients in Phase 2 were comparable to those reported for the full patient population in Phase 1. As in Phase 1, there was no meaningful difference in most of the baseline demographic parameters between aliskiren and corresponding placebo groups across dose groups in Phase 2, except in the distribution of weight, BMI and hypertension etiology. (Table 11-4).

Table 11-4 Patient background characteristics by treatment group for Phase 2 (Randomized set 2)

Demographic Characteristic category/statistic	ALI Low 6.25/12.5/25 mg N=50	PLB Low N=57	ALI Mid 37.5/75/150 mg N=30	PLB Mid N=21	ALI High 150/300/600 mg N=50	PLB High N=52	Total N=260
Age (Years)							
n	50	57	30	21	50	52	260
Mean	12.1	11.6	11.2	12.7	11.9	11.8	11.8
SD	3.40	3.19	3.41	2.99	3.46	3.60	3.37
Age Group (years) n(%)							
6 - 11	22(44.0%)	26(45.6%)	17(56.7%)	8(38.1%)	22(44.0%)	26(50.0%)	121(46.5%)
12 - 17	28(56.0%)	31(54.4%)	13(43.3%)	13(61.9%)	28(56.0%)	26(50.0%)	139(53.5%)
6 - 12	24(48.0%)	33(57.9%)	18(60.0%)	9(42.9%)	25(50.0%)	26(50.0%)	135(51.9%)
13 - 17	26(52.0%)	24(42.1%)	12(40.0%)	12(57.1%)	25(50.0%)	26(50.0%)	125(48.1%)
Sex n(%)							
Male	31(62.0%)	41(71.9%)	22(73.3%)	13(61.9%)	33(66.0%)	32(61.5%)	172(66.2%)
Female	19(38.0%)	16(28.1%)	8(26.7%)	8(38.1%)	17(34.0%)	20(38.5%)	88(33.8%)
Race n(%)							
Caucasian	38(76.0%)	44(77.2%)	22(73.3%)	15(71.4%)	35(70.0%)	39(75.0%)	193(74.2%)
Black	2(4.0%)	7(12.3%)	4(13.3%)	1(4.8%)	6(12.0%)	7(13.5%)	27(10.4%)
Native American	4(8.0%)	3(5.3%)	3(10.0%)	2(9.5%)	3(6.0%)	3(5.8%)	18(6.9%)
Other	6(12.0%)	3(5.3%)	1(3.3%)	3(14.3%)	6(12.0%)	3(5.8%)	22(8.5%)
Ethnicity n(%)							
Hispanic or Latino	10(20.0%)	6(10.5%)	5(16.7%)	6(28.6%)	11(22.0%)	8(15.4%)	46(17.7%)
Mixed ethnicity	0(0.0%)	5(8.8%)	0(0.0%)	0(0.0%)	3(6.0%)	0(0.0%)	8(3.1%)
Other	40(80.0%)	46(80.7%)	25(83.3%)	15(71.4%)	36(72.0%)	44(84.6%)	206(79.2%)
Hypertension etiology n(%)							
Primary	39(78.0%)	49(86.0%)	26(86.7%)	15(71.4%)	39(78.0%)	45(86.5%)	213(81.9%)
Secondary	11(22.0%)	8(14.0%)	4(13.3%)	6(28.6%)	11(22.0%)	7(13.5%)	47(18.1%)
Height (cm)							
n	50	57	30	21	49	52	259
Mean	155.3	157.0	153.7	159.4	156.4	153.9	155.7
SD	20.74	20.08	22.67	20.46	20.97	17.65	20.14
Weight (kg)							
n	50	57	30	21	49	52	259
Mean	62.7	71.4	70.3	72.7	69.6	72.1	69.5
SD	25.48	30.00	33.47	32.09	28.99	31.25	29.76
Weight category n(%)							
>=20 kg and < 50kg	17(34.0%)	15(26.3%)	10(33.3%)	7(33.3%)	14(28.0%)	17(32.7%)	80(30.8%)
>=50 kg and < 80 kg	20(40.0%)	18(31.6%)	11(36.7%)	5(23.8%)	17(34.0%)	16(30.8%)	87(33.5%)
>=80 kg and < 150 kg	13(26.0%)	23(40.4%)	9(30.0%)	9(42.9%)	17(34.0%)	18(34.6%)	89(34.2%)
>= 150 kg	0(0.0%)	1(1.8%)	0(0.0%)	0(0.0%)	1(2.0%)	1(1.9%)	3(1.2%)

Body Mass Index (kg/m^2)							
n	50	57	30	21	49	52	259
Mean	24.8	27.6	28.2	27.3	27.2	29.1	27.3
SD	6.33	7.68	8.95	9.85	7.23	8.45	7.92
BMI status n(%)							
< 95th percentile	26(52.0%)	23(40.4%)	11(36.7%)	10(47.6%)	22(44.0%)	15(28.8%)	107(41.2%)
>= 95th percentile	24(48.0%)	34(59.6%)	19(63.3%)	11(52.4%)	27(54.0%)	37(71.2%)	152(58.5%)
eGFR (ml/min/1.73 m^2)							
n	50	57	30	20	50	52	259
Mean	106.3	104.7	108.1	106.6	112.1	107.2	107.5
SD	25.36	22.99	18.94	27.07	29.65	20.99	24.32
eGFR category n(%)							
< 60 ml/min/1.73 m^2	1(2.0%)	1(1.8%)	0(0.0%)	1(4.8%)	2(4.0%)	0(0.0%)	5(1.9%)
>= 60 and < 90 ml/min/1.73 m^2	10(20.0%)	13(22.8%)	5(16.7%)	4(19.0%)	10(20.0%)	10(19.2%)	52(20.0%)
>= 90 ml/min/1.73 m^2	39(78.0%)	43(75.4%)	25(83.3%)	15(71.4%)	38(76.0%)	42(80.8%)	202(77.7%)

SD = standard deviation

Source: Table 14.1-3.2

Tables 11-5 and 11-6 summarizes baseline descriptive statistics for blood pressure status for Phase 1 and Phase 2.

Table 11-5 Summary of baseline blood pressures by treatment group for Phase 1 (Randomized set 1)

Baseline variable	ALI Low 6.25/12.5/25 mg N=108	ALI Mid 37.5/75/150 mg N=54	ALI High 150/300/600 mg N=106	Total N=268
Mean sitting SBP (mmHg)				
n	108	54	105	267
Mean	133.7	134.1	133.8	133.8
SD	9.41	11.07	9.47	9.75
Median	134.3	134.8	134.0	134.0
Minimum	108.3	115.3	113.0	108.3
Maximum	153.0	155.3	167.3	167.3
Mean sitting DBP (mmHg)				
n	108	54	105	267
Mean	78.0	78.0	78.5	78.2

SD	8.03	8.54	8.79	8.41
Median	77.0	78.0	78.3	77.3
Minimum	59.0	60.7	57.0	57.0
Maximum	96.0	98.0	102.7	102.7
Standing systolic BP (mmHg)				
n	108	54	104	266
Mean	134.8	133.4	134.3	134.3
SD	13.03	16.06	11.91	13.25
Median	134.5	134.5	134.0	134.0
Minimum	88.0	69.0	104.0	69.0
Maximum	168.0	157.0	176.0	176.0
Standing diastolic BP (mmHg)				
n	108	54	104	266
Mean	81.5	79.5	82.4	81.5
SD	9.63	11.09	10.38	10.25
Median	81.5	81.0	82.0	81.0
Minimum	57.0	51.0	56.0	51.0
Maximum	104.0	102.0	109.0	109.0
Sitting pulse (bpm)				
n	108	54	105	267
Mean	83.7	87.3	82.8	84.1
SD	13.77	14.09	13.45	13.76
Median	82.0	86.5	82.0	84.0
Minimum	53.0	48.0	55.0	48.0
Maximum	124.0	124.0	128.0	128.0

SD = standard deviation

Source: Table 14.1-3.3

Table 11-6 Summary of baseline blood pressures by treatment group for Phase 2 (Randomized set 2)

Baseline variable	ALI Low 6.25/12.5/25 mg N=50	PLB Low N=57	ALI Mid 37.5/75/150 mg N=30	PLB Mid N=21	ALI High 150/300/600 mg N=50	PLB High N=52	Total N=260
Mean sitting SBP (mmHg)							
n	50	57	30	21	50	52	260
Mean	127.7	128.7	127.7	131.1	124.9	123.8	126.9

SD	9.98	10.71	12.36	10.31	10.86	9.97	10.77
Median	126.8	128.0	129.7	132.0	124.3	123.2	126.5
Minimum	102.7	107.0	101.0	107.0	98.7	99.7	98.7
Maximum	148.3	150.3	152.0	148.0	150.3	143.3	152.0
Mean sitting DBP (mmHg)							
n	50	57	30	21	50	52	260
Mean	73.8	76.6	73.6	75.4	73.0	71.5	73.9
SD	8.26	7.93	9.61	6.65	8.11	7.11	8.12
Median	73.3	76.7	72.7	76.3	74.0	71.8	74.5
Minimum	59.0	61.3	52.0	63.3	56.7	57.7	52.0
Maximum	90.3	94.3	86.7	83.7	92.7	86.7	94.3
Standing systolic BP (mmHg)							
n	50	57	30	21	50	52	260
Mean	130.8	131.8	126.1	128.4	126.3	126.9	128.6
SD	12.38	13.16	12.57	18.08	12.75	13.20	13.42
Median	132.5	132.0	123.5	130.0	127.5	128.0	130.0
Minimum	101.0	100.0	91.0	69.0	99.0	100.0	69.0
Maximum	163.0	176.0	150.0	154.0	154.0	154.0	176.0
Standing diastolic BP (mmHg)							
n	50	57	30	21	50	52	260
Mean	80.4	81.4	75.5	80.3	75.6	75.9	78.2
SD	9.12	11.20	10.87	12.38	11.00	9.43	10.73
Median	79.5	81.0	78.5	80.0	75.0	76.0	79.0
Minimum	57.0	59.0	50.0	45.0	52.0	56.0	45.0
Maximum	104.0	131.0	92.0	99.0	98.0	98.0	131.0
Sitting pulse (bpm)							
n	50	57	30	21	50	52	260
Mean	84.7	82.7	84.6	87.9	82.5	84.5	84.1
SD	14.85	12.33	13.56	14.02	12.94	13.58	13.43
Median	83.0	84.0	85.0	90.0	81.5	84.0	84.0
Minimum	60.0	54.0	47.0	56.0	55.0	55.0	47.0
Maximum	123.0	112.0	111.0	109.0	117.0	128.0	128.0

SD = standard deviation

Source: Table 14.1-3.4

Baseline BP levels were generally similar among the 6 treatment groups except for 3.4 mmHg higher baseline msSBP in the placebo mid dose group (compared to aliskiren mid dose group). (Table 11-6).

Most of patients had at least one co-morbidity (metabolism and nutrition disorders, respiratory, thoracic and mediastinal disorders , renal and urinary disorders, nervous system disorders, surgical and medical procedures, infections and infestations, and congenital, familial, and genetic disorders). Frequent conditions (≥ 10% of patients in any group) were obesity, asthma, headache, and seasonal allergy (Table 11-7). A total of 20.9% of patients had an abnormality in the renal or urinary SOC and 20.1% were considered obese by the investigator while 58.6% had baseline BMI≥95th percentile for age and gender.

Table 11-7 Medical histories and continuing medical conditions by primary system organ class, preferred term and treatment group (RAN1)

Primary system organ class Preferred term	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 primary system organ class	88(81.5)	46(85.2)	93(87.7)	227(84.7)
Congenital, familial and genetic disorders	18(16.7)	7(13.0)	17(16.0)	42(15.7)
Atrial septal defect	3(2.8)	1(1.9)	2(1.9)	6(2.2)
Congenital cystic kidney disease	3(2.8)	2(3.7)	2(1.9)	7(2.6)
Infections and infestations	19(17.6)	8(14.8)	15(14.2)	42(15.7)
Urinary tract infection	6(5.6)	3(5.6)	2(1.9)	11(4.1)
Metabolism and nutrition disorders	35(32.4)	18(33.3)	33(31.1)	86(32.1)
Obesity	19(17.6)	12(22.2)	23(21.7)	54(20.1)
Dyslipidaemia	6(5.6)	1(1.9)	5(4.7)	12(4.5)
Hypercholesterolaemia	4(3.7)	1(1.9)	3(2.8)	8(3.0)
Metabolic syndrome	4(3.7)	1(1.9)	5(4.7)	10(3.7)
Hypertriglyceridaemia	2(1.9)	3(5.6)	3(2.8)	8(3.0)
Nervous system disorders	20(18.5)	9(16.7)	21(19.8)	50(18.7)
Headache	16(14.8)	6(11.1)	13(12.3)	35(13.1)
Migraine	3(2.8)	2(3.7)	2(1.9)	7(2.6)
Renal and urinary disorders	22(20.4)	10(18.5)	24(22.6)	56(20.9)
Enuresis	4(3.7)	1(1.9)	4(3.8)	9(3.4)
Haematuria	4(3.7)	1(1.9)	1(0.9)	6(2.2)
Proteinuria	4(3.7)	3(5.6)	4(3.8)	11(4.1)
Renal failure chronic	4(3.7)	3(5.6)	5(4.7)	12(4.5)
Vesicoureteric reflux	3(2.8)	1(1.9)	3(2.8)	7(2.6)
Hydronephrosis	2(1.9)	2(3.7)	2(1.9)	6(2.2)
Respiratory, thoracic and mediastinal disorders	25(23.1)	14(25.9)	28(26.4)	67(25.0)
Asthma	17(15.7)	8(14.8)	19(17.9)	44(16.4)
Rhinitis allergic	7(6.5)	5(9.3)	5(4.7)	17(6.3)
Epistaxis	5(4.6)	1(1.9)	3(2.8)	9(3.4)
Surgical and medical procedures	19(17.6)	9(16.7)	17(16.0)	45(16.8)
Tonsillectomy	6(5.6)	2(3.7)	4(3.8)	12(4.5)
Vesicoureteral reflux surgery	4(3.7)	1(1.9)	2(1.9)	7(2.6)
Adenoidectomy	3(2.8)	1(1.9)	4(3.8)	8(3.0)

For a SOC to be included in the table, at least 15% of patients must have reported an abnormality within that SOC. For a preferred term to be included in the table a) the SOC must pass the criterion for inclusion and b) at least 2% of the patients must have reported the preferred term.

Primary system organ classes are presented alphabetically; preferred terms were sorted within primary system organ class in descending frequency, as reported in the ALI Low 6.25/12.5/25 mg column.

For each patient, multiple conditions of any primary SOC or preferred term were counted only once.

Source: Table 14.1-3.5

Efficacy results

Primary objectives

At the end of Phase 1, there was a statistically significant decrease from baseline in msSBP in all 3 dose groups ($p<0.001$, Table 11-8). The reduction in msSBP was larger in the high dose group (-9.03 mmHg) than in the low (-5.54 mmHg) and mid dose (-5.42 mmHg) groups. Similar results were seen in the PPS1 population (-5.61, -6.13 and -9.89 mmHg, respectively, Table 14.2-1.1a).

Table 11-8 Within treatment comparison for change from baseline in mean sitting systolic blood pressure (msSBP) (mmHg) at the end of Phase 1 (Full analysis set 1)

Treatment group	n	Baseline Mean (SE)	Endpoint Mean (SE)	Change from Baseline		
				Mean (SE)	95% CI for mean	p-value*
ALI Low 6.25/12.5/25 mg	108	133.82 (0.883)	128.28 (0.990)	-5.54 (0.780)	(-7.09, -3.99)	< 0.001 *
ALI Mid 37.5/75/150 mg	53	134.24 (1.532)	128.82 (1.587)	-5.42 (1.331)	(-8.09, -2.75)	< 0.001 *
ALI High 150/300/600 mg	104	133.85 (0.931)	124.82 (1.052)	-9.03 (1.008)	(-11.03, -7.03)	< 0.001 *

Baseline is the week 0 value. Endpoint is the value at week 4 or LOCF value in Phase 1.

n, Means (SE), and the associated confidence intervals for changes are based on paired data; p-values are from the paired t-test.

* indicates statistical significance at 0.05 level.

Source: Table 14.2-1.1

The primary efficacy slope analysis yielded a slope estimate of -0.17 (mmHg per unit increase in dose ratio P<0.001) for the dose-response curve for change from baseline to end of Phase 1 in msSBP (Table 11-9). Results were similar in the per protocol population (PPS1).

Table 11-9 Analysis of dose-response for change from baseline in mean sitting systolic blood pressure (msSBP) (mmHg) at the end of Phase 1 (Full analysis set 1)

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

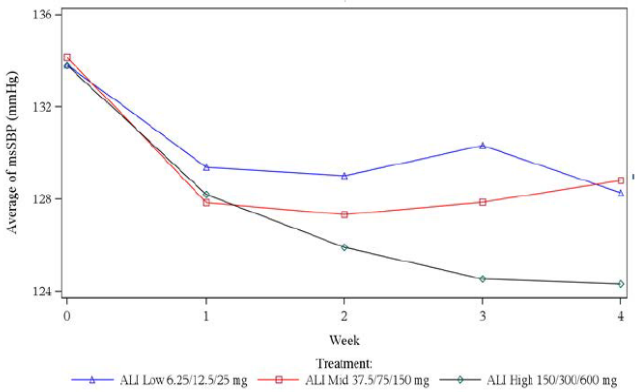
Dose ratio 6 corresponds to mid dose level in Phase 1

Dose ratio 24 corresponds to high dose level in Phase 1

Source: Table 14.2-1.3

The reductions in msSBP were observed as early as Week 1 in all three dose groups. Further reductions after Week 2 were seen with the high dose up to Week 4 (end of Phase 1).

Figure 11-1 **Average of mean sitting systolic blood pressure (msSBP) (mmHg) during Phase 1 by treatment group and visit (FAS1)**



Week 0 =Visit 2
Source: Table 14.2-1.5

A summary of the changes in msSBP from end of Phase 1 to the end of Phase 2 is presented in Table 11-10. At the end of Phase 2, reductions in msSBP from end of Phase 1 were seen in all three aliskiren dose groups but was significant in the aliskiren mid dose group only (-2.59 mmHg, p=0.028). For patients that switched to placebo in Phase 2, the msSBP change from Phase 1 end was an increase only in the placebo high dose group and was not significant (+1.11 mmHg, P=0.354). The msSBP change was a further decrease in the placebo low group (-0.64 mmHg) and in the placebo mid dose group (-2.90 mmHg). The decrease in msSBP of the placebo mid dose group was borderline significant (P=0.064) and actually numerically greater compared to the aliskiren mid dose group. Similar results were seen with the PPS2 population.

Table 11-10 **Within treatment comparison for change from end of Phase 1 in mean sitting systolic blood pressure (msSBP) (mmHg) at the end of Phase 2 (Full analysis set 2)**

Treatment group	n	Baseline Mean (SE)	Endpoint Mean (SE)	Change from Baseline Mean (SE)	95% CI for mean	p-value*
ALI Low 6.25/12.5/25 mg	50	127.73 (1.411)	127.21 (1.553)	-0.53 (0.947)	(-2.43, 1.38)	0.581
PLB Low	57	128.74 (1.419)	128.11 (1.285)	-0.64 (1.256)	(-3.15, 1.88)	0.614
ALI Mid 37.5/75/150 mg	30	127.68 (2.257)	125.09 (2.032)	-2.59 (1.119)	(-4.88, -0.30)	0.028*
PLB Mid	21	131.13 (2.251)	128.22 (2.316)	-2.90 (1.481)	(-5.99, 0.18)	0.064
ALI High 150/300/600 mg	49	124.85 (1.565)	122.88 (1.665)	-1.97 (1.071)	(-4.13, 0.18)	0.072
PLB High	52	123.81 (1.382)	124.92 (1.144)	1.11 (1.185)	(-1.27, 3.49)	0.354

Baseline is the week 4 value. Endpoint is the value at week 8 or LOCF value in Phase 2.
n, Means (SE), and the associated confidence intervals for changes are based on paired data; p-values are from the paired t-test.
* indicates statistical significance at 0.05 level.
Source: Table 14.2-1.2

Between-group comparisons of msSBP changes from the end of Phase 1 to the end of Phase 2 for the 3 different dose groups are shown in Table 11-12. The difference for the aliskiren high dose group as compared to placebo did not meet statistical significance (p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were < 0.2 mmHg and not significant as well.

Table 11-12 Between treatment comparisons for change from end of Phase 1 in mean sitting systolic blood pressure (msSBP) (mmHg) at the end of Phase 2 (Full Analysis set 2)

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 Low	PLB Low	50	57	-0.33 (1.066)	-0.14 (1.031)	-0.19 (1.381)	(-2.91, 2.53)	0.8894
ALI Mid	PLB Mid	30	21	-2.02 (1.368)	-1.89 (1.574)	-0.12 (2.026)	(-4.11, 3.87)	0.9511
ALI High	PLB High	49	52	-2.84 (1.061)	-0.13 (1.082)	-2.70 (1.411)	(-5.48, 0.07)	0.0563

- Baseline is the week 4 value.
- LS mean= Least squares mean; SE = Standard error of mean.
- 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 pooled treatment, 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: Table 14.2-1.4b

In pooled analyses for mid-high doses, the difference in msSBP change between aliskiren groups and placebo groups was not significant (Table 11-11).

Table 11-11 Between treatment comparisons for change from end of Phase 1 in mean sitting systolic blood pressure (msSBP) (mmHg) at the end of Phase 2 (Full analysis set 2)

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: Table 14.2-1.4

Subgroup analyses did not indicate clinically significant trends.

Secondary objectives

- *msDBP*: At the end of Phase 1, there was a statistically significant decrease from baseline in msDBP in all 3 dose groups (p<0.001) with a larger reduction observed with increasing aliskiren dose (-2.71 mmHg, -4.05 mmHg and -6.33 mmHg for the low, mid and high dose groups, respectively). The msDBP slope analysis presented in Table 11-14 yielded a slope estimate of -0.14 (mmHg per unit increase in dose ratio) for the dose-response curve for change from baseline. Between-group comparisons of msDBP changes from the end of Phase 1 to the end of Phase 2 between aliskiren and placebo did not meet statistical significance in analyses separate per dose and in pooled analyses. Findings were similar for msMAP.

- *Responders*: At the end of phase 2, the proportion of responders for msSBP was 26% higher in the aliskiren pooled group compared to the placebo pooled group (62/80 vs 45/73, P=0.038).

- *ABPM*: A total of 152 patients (56.7%) were included in final analysis for ABPM. All three aliskiren dose group showed reductions from baseline in post-dosing 24-hour mean ambulatory systolic blood pressure (MASBP) at the end of Phase 1 (high group, mid group, and low group = -6.02, -6.01, and -2.66 mmHg, respectively). The mid and high dose groups had similar MASBP reductions. The mid and high dose groups had statistically significant greater reductions than the low dose group (P<0.001). In pooled analyses for all doses, the difference in MASBP change between aliskiren groups and placebo groups was significant (-2.86 mHg, P=0.0022). Results were similar for MADBP. The differences in

MASBP and MADBP associated with aliskiren treatment were explained by differences in daytime BP not in night time BP.

UACR levels were measured for all patients at randomization. For patients with albuminuria, testing was also done at Visit4 (end of Phase 1) and Visit 6 (end of Phase 2). No specific trends were seen with UACR changes at end of Phase 1 or Phase 2 (low number of patients with albuminuria at randomization and the uneven distribution of patients with albuminuria among the different treatment groups, Tables from 14.3-2.11 to 14.3-2.18).

- *PK*: Weight-based dose of aliskiren significantly correlated with plasma levels of aliskiren.

Safety results

Duration of exposure was similar among groups of Phase 1 and Phase 2 (Table 12-1 and Table 12-2, respectively).

Table 12-1 Duration of exposure for Phase 1 (Safety set 1)

Duration of exposure (days)	ALI Low 6.25/12.5/25 mg N=108	ALI Mid 37.5/75/150 mg N= 54	ALI High 150/300/600 mg N=105	Total N=267
N	108	54	105	267
Mean	28.4	27.9	27.8	28.1
SD	2.49	4.97	4.18	3.79
Median	28.0	28.0	28.0	28.0
Min	9	3	1	1
Max	35	35	37	37

SD=standard deviation
Source: Table 14.3-1.1

Table 12-2 Duration of exposure for Phase 2 (Safety set 2)

Duration of exposure	ALI Low 6.25/12.5/25 mg N= 50	PLB Low N= 57	ALI Mid 37.5/75/150 mg N= 30	PLB Mid N= 21	ALI High 150/300/600 mg N= 50	PLB High N= 52	Total N=260
N	50	57	30	21	50	52	260
Mean	27.1	27.1	27.9	27.3	28.6	28.0	27.7
SD	5.81	5.30	3.57	1.71	1.25	5.19	4.48
Median	28.0	28.0	28.0	28.0	28.0	28.0	28.0
Min	5	8	14	21	27	2	2
Max	46	40	35	29	33	43	46

SD=standard deviation
Source: Table 14.3-1.2

Overall, 159 patients (61.2%) used concomitant medications. The most commonly used concomitant medications were anilides (13.8%), other antihistamines for systemic use (10.8%) and selective beta-2 adrenoceptor agonists (10.0%).

Three patients (1.2%) required non-study antihypertensive medication after early discontinuation from the study.

Newly occurring AEs were reported by 30.3% of patients in Phase 1 and 35.8% of patients in Phase 2 (Tables 12-3 and 12-4). AEs were more common in the aliskiren high dose group.

Table 12-3 Number (%) of patients with overall adverse events starting during Phase 1 by treatment group and primary system organ class (Safety set 1)

Primary system organ class	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=105 n (%)	Total N=267 n (%)
Any system organ class	30(27.8)	14(25.9)	37(35.2)	81(30.3)
Infections and infestations	17(15.7)	7(13.0)	14(13.3)	38(14.2)
Gastrointestinal disorders	6(5.6)	4(7.4)	8(7.6)	18(6.7)
Nervous system disorders	5(4.6)	4(7.4)	10(9.5)	19(7.1)
Respiratory, thoracic and mediastinal disorders	5(4.6)	5(9.3)	7(6.7)	17(6.4)
Cardiac disorders	2(1.9)	0(0.0)	0(0.0)	2(0.7)
Injury, poisoning and procedural complications	2(1.9)	0(0.0)	2(1.9)	4(1.5)
Ear and labyrinth disorders	1(0.9)	0(0.0)	1(1.0)	2(0.7)
General disorders and administration site conditions	1(0.9)	1(1.9)	0(0.0)	2(0.7)
Psychiatric disorders	1(0.9)	0(0.0)	0(0.0)	1(0.4)
Renal and urinary disorders	1(0.9)	0(0.0)	0(0.0)	1(0.4)
Skin and subcutaneous tissue disorders	1(0.9)	0(0.0)	3(2.9)	4(1.5)
Eye disorders	0(0.0)	0(0.0)	1(1.0)	1(0.4)
Immune system disorders	0(0.0)	0(0.0)	1(1.0)	1(0.4)
Musculoskeletal and connective tissue disorders	0(0.0)	0(0.0)	3(2.9)	3(1.1)
Reproductive system and breast disorders	0(0.0)	1(1.9)	0(0.0)	1(0.4)
Social circumstances	0(0.0)	1(1.9)	0(0.0)	1(0.4)
Vascular disorders	0(0.0)	0(0.0)	1(1.0)	1(0.4)

System organ classes were sorted in descending frequency, as reported in the Aliskiren Low column.
A patient with multiple adverse events within a primary system organ class was counted only once.
Source: Table 14.3.1-1.1

Table 12-4 Number (%) of patients with overall adverse events starting during Phase 2 by treatment group and primary system organ class (Safety set 2)

Primary system organ class	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 system organ class	18(36.0)	22(38.6)	10(33.3)	5(23.8)	21(42.0)	17(32.7)	93(35.8)
Infections and infestations	9(18.0)	8(14.0)	6(20.0)	1(4.8)	9(18.0)	6(11.5)	39(15.0)
Respiratory, thoracic and mediastinal disorders	5(10.0)	6(10.5)	2(6.7)	1(4.8)	6(12.0)	2(3.8)	22(8.5)
Nervous system disorders	4(8.0)	3(5.3)	2(6.7)	2(9.5)	5(10.0)	3(5.8)	19(7.3)
Gastrointestinal disorders	2(4.0)	3(5.3)	1(3.3)	1(4.8)	2(4.0)	3(5.8)	12(4.6)
Renal and urinary disorders	2(4.0)	1(1.8)	0(0.0)	0(0.0)	2(4.0)	0(0.0)	5(1.9)
Injury, poisoning and procedural complications	1(2.0)	1(1.8)	0(0.0)	0(0.0)	0(0.0)	2(3.8)	4(1.5)
Investigations	1(2.0)	0(0.0)	1(3.3)	1(4.8)	1(2.0)	2(3.8)	6(2.3)
Musculoskeletal and connective tissue disorders	1(2.0)	1(1.8)	0(0.0)	3(14.3)	1(2.0)	1(1.9)	7(2.7)
Vascular disorders	1(2.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Ear and labyrinth disorders	0(0.0)	2(3.5)	0(0.0)	1(4.8)	0(0.0)	0(0.0)	3(1.2)
Eye disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(2.0)	1(1.9)	2(0.8)
General disorders and administration site conditions	0(0.0)	2(3.5)	1(3.3)	1(4.8)	1(2.0)	0(0.0)	5(1.9)
Immune system disorders	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(3.8)	2(0.8)
Metabolism and nutrition disorders	0(0.0)	0(0.0)	0(0.0)	1(4.8)	0(0.0)	0(0.0)	1(0.4)
Psychiatric disorders	0(0.0)	1(1.8)	0(0.0)	0(0.0)	1(2.0)	0(0.0)	2(0.8)
Skin and subcutaneous tissue disorders	0(0.0)	0(0.0)	1(3.3)	0(0.0)	1(2.0)	3(5.8)	5(1.9)

Source: Table 14.3.1-1.2
System organ classes were sorted in descending frequency, as reported in the Aliskiren Low column.
A patient with multiple adverse events within a primary system organ class was counted only once.

The investigator defined as drug-related the AEs of 2 patients (0.7%) in Phase 1 and 3 patients (1.2%) in Phase 2. The two suspected AEs in Phase 1 were mild hypotension (aliskiren high dose, resolved same days) and mild flatulence (aliskiren high dose, study drug interrupted for 1 day). In Phase 2, one

patient (placebo high dose) had rash, pruritus, cough, and fever that led to study discontinuation. Another patient (aliskiren low dose group) had headache (treated with acetaminophen and resolved in 1 day). The third patient (placebo high dose group) had mild pharyngitis, treated with clarithromycin and resolved in 7 days).

Analysis by hypertension etiology is summarized in Table 12-13. Patients with secondary hypertension had higher rate of AEs compared to patients with primary hypertension in both phases of the study (comorbidities more frequent in the secondary hypertension).

Table 12-13 Summary of most frequent [1] adverse events by preferred term, hypertension etiology, and treatment phase

Study Phase	Phase 1		Phase 2	
Hypertension etiology	Primary N=219	Secondary N=48	Primary N=213	Secondary N=47
Any preferred term	57(26.0)	24(50.0)	71(33.3)	22(46.8)
Headache	11(5.0)	4(8.3)	12(5.6)	5(10.6)
Upper respiratory tract infection	7(3.2)	4(8.3)	11(5.2)	4(8.5)
Diarrhoea	5(2.3)	3(6.3)	1(0.5)	0 (0.0)
Cough	3(1.4)	2(4.2)	5(2.3)	3(6.4)

Preferred terms were sorted in descending frequency, as reported in the patients with primary hypertension in Phase 1
[1] Reported by at least 5% of patients in any phase
Source: Table 14.3.1-1.19a and Table 14.3.1-1.19b

There were no deaths reported in the study. Serious adverse events and AEs resulting in study discontinuation are summarized in Table 12-15 for Phase 1 and Table 12-16 for Phase 2. No patient discontinued the study prematurely due to a laboratory abnormality.

Table 12-15 Number (%) of patients with deaths, serious adverse events and discontinuation due to adverse events and abnormal laboratory values during Phase 1 (Safety Set 1)

	ALI Low 6.25/12.5/25mg N=108 n (%)	ALI Mid 37.5/75/150mg N=54 n (%)	ALI High 150/300/600mg N=105 n (%)	Total N=267 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.4)
AE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drug-related AE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Tables 14.1-1.1 and 14.3.1-1.7, Listing 14.3.2-1.2 and 14.3.2-1.3.

Table 12-16 Number (%) of patients with deaths, serious adverse events and discontinuation due to adverse events and abnormal laboratory values during Phase 2 (Safety set 2)

	ALI Low 6.25/12.5/25mg N=50 n (%)	PLB Low N=57 n (%)	ALI Mid 37.5/75/150mg N=30 n (%)	PLB Mid N=21 n (%)	ALI High 150/300/600mg N=50 n (%)	PLB High N=52 n (%)	Total N=260 n (%)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)	2 (0.8)
AE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.9)	2 (0.8)
Drug-related AE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.4)
SAE discontinuations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.4)
Discontinuations for abnormal lab values	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Tables 14.1-1.2 and 14.3.1-1.8, Listing 14.3.2-1.2 and 14.3.2-1.3.

Among the serious AEs, there was one patient with head injury (fall), one patient with headache and syncope, and one patient with attempted suicide. None of these event was considered aliskiren-related.

Three patients discontinued the treatment: one in Phase 1 (stomach cramping during placebo run-in phase) and two in Phase 2 (the patient with treatment-unrelated attempted suicide and another placebo-treated patient with rash-pruritus).

Lab test

No patient discontinued the study due to a lab abnormality.

Small, insignificant changes in the hematology and biochemistry parameters were seen in both phases of the study. The % of patients with notable changes in Phase 1 and 2 is shown in Table 12-20 and 12-21, respectively. There was an increase in the proportion of patients with AST values above upper limit of normal (ULN) in the aliskiren mid dose group (7.8% to 19.6%) at end of Phase 1, but most of the patients returned to normal ranges by end of Phase 2 (3.3% on aliskiren mid dose and 0.0% on placebo mid dose).

Table 12-20 Percentage of patients with notable change from baseline in Biochemistry tests with associated distribution from the normal range by laboratory parameter and treatment group (Safety set 1)

	Criterion	ALI Low 6.25/12.5/25 mg (N=108) n %,N'	ALI Mid 37.5/75/150 mg (N=54) n %,N'	ALI High 150/300/600 mg (N=105) n %,N'
Blood Urea Nitrogen (BUN)	>50% increase	5 4.7, 106	3 5.8, 52	3 3.0, 101
	High*	0 0.0, 106	1 1.9, 52	1 1.0, 101
Creatinine	>50% increase	0 0.0, 106	0 0.0, 52	1 1.0, 101
	High*	0 0.0, 106	0 0.0, 52	1 1.0, 101
Glucose	>50% increase	0 0.0, 105	0 0.0, 51	1 1.0, 101
	High*	0 0.0, 105	0 0.0, 51	1 1.0, 101
Bilirubin (total)	>100% increase	5 4.8, 105	3 5.9, 51	4 4.0, 101
	High*	1 1.0, 105	0 0.0, 51	0 0.0, 101
AST	>150% increase	0 0.0, 105	1 2.0, 51	0 0.0, 101
	High*	0 0.0, 105	1 2.0, 51	0 0.0, 101
ALT	>150% increase	1 1.0, 105	1 2.0, 51	0 0.0, 101
	High*	1 1.0, 105	1 2.0, 51	0 0.0, 101
Potassium	>20% increase	0 0.0, 106	2 3.9, 51	0 0.0, 101
	High*	0 0.0, 106	1 2.0, 51	0 0.0, 101
	>20% decrease, or any value >5.3 mmol/L	0 0.0, 106	1 2.0, 51	1 1.0, 101
	High*	0 0.0, 106	1 2.0, 51	1 1.0, 101
Calcium	>10% increase	1 0.9, 106	0 0.0, 51	1 1.0, 101
	High*	0 0.0, 106	0 0.0, 51	0 0.0, 101
	>10% decrease	0 0.0, 106	2 3.9, 51	0 0.0, 101
	Low*	0 0.0, 106	2 3.9, 51	0 0.0, 101

Baseline is the Week 0 value or the previous screening value if Week 0 value is not available.
N': number of patients with both baseline and at least one post-baseline value during Phase 1
n=number of patients meeting the above criteria
*A further classification of patients who met the specified criterion with respect to laboratory normal ranges. It indicates that the extreme (highest/lowest) post-baseline test value is either above or below the normal range.
Source: Table 14.3-2.3

Table 12-21 Percentage of patients with notable change from baseline in Biochemistry tests with associated distribution from the normal range by laboratory parameter and treatment group (Safety set 2)

	Criterion	ALI Low 6.25/12.5/25 mg (N=50) n %,N'	PLB Low (N=57) n %,N'	ALI Mid 37.5/75/150 mg (N=30) n %,N'	PLB Mid (N=21) n %,N'	ALI High 150/300/600 mg (N=50) n %,N'	PLB High (N=52) n %,N'
Blood Urea Nitrogen (BUN)	>50% increase	2 4.2, 48	4 7.1, 56	1 3.3, 30	0 0.0, 21	1 2.0, 49	1 2.0, 51
	High*	0 0.0, 48	2 3.6, 56	0 0.0, 30	0 0.0, 21	0 0.0, 49	1 2.0, 51
Creatinine	>50% increase	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
Glucose	>50% increase	0 0.0, 48	0 0.0, 56	0 0.0, 30	1 5.0, 20	0 0.0, 49	0 0.0, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 20	0 0.0, 49	0 0.0, 51
Bilirubin (total)	>100% increase	0 0.0, 48	0 0.0, 56	1 3.3, 30	4 20.0, 20	2 4.1, 49	1 2.0, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 20	0 0.0, 49	0 0.0, 51
AST	>150% increase	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 20	0 0.0, 49	1 2.0, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 20	0 0.0, 49	1 2.0, 51
ALT	>150% increase	0 0.0, 48	1 1.8, 56	0 0.0, 30	0 0.0, 20	0 0.0, 49	1 2.0, 51
	High*	0 0.0, 48	1 1.8, 56	0 0.0, 30	0 0.0, 20	0 0.0, 49	1 2.0, 51
Sodium	>5% decrease	0 0.0, 48	1 1.8, 56	1 3.3, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
	High*	0 0.0, 48	1 1.8, 56	1 3.3, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
Potassium	>20% increase	1 2.1, 48	1 1.8, 56	0 0.0, 29	0 0.0, 21	1 2.0, 49	1 2.0, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 29	0 0.0, 21	1 2.0, 49	0 0.0, 51
	>20% decrease, or any value >5.3 mmol/L	0 0.0, 48	1 1.8, 56	0 0.0, 29	0 0.0, 21	2 4.1, 49	2 3.9, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 29	0 0.0, 21	2 4.1, 49	1 2.0, 51
Chloride	>10% increase	0 0.0, 48	1 1.8, 56	1 3.3, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
	High*	0 0.0, 48	1 1.8, 56	1 3.3, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
Chloride	>10% decrease	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 21	0 0.0, 49	1 2.0, 51
	Low*	0 0.0, 48	0 0.0, 56	0 0.0, 30	0 0.0, 21	0 0.0, 49	1 2.0, 51
Calcium	>10% increase	1 2.1, 48	0 0.0, 56	0 0.0, 30	0 0.0, 21	1 2.0, 49	0 0.0, 51
	High*	1 2.1, 48	0 0.0, 56	0 0.0, 30	0 0.0, 21	0 0.0, 49	0 0.0, 51
	>10% decrease	0 0.0, 48	1 1.8, 56	1 3.3, 30	1 4.8, 21	1 2.0, 49	1 2.0, 51
	Low*	0 0.0, 48	1 1.8, 56	1 3.3, 30	0 0.0, 21	1 2.0, 49	0 0.0, 51
Uric Acid	>50% increase	1 2.1, 48	0 0.0, 56	0 0.0, 30	1 5.0, 20	1 2.0, 49	0 0.0, 51
	High*	0 0.0, 48	0 0.0, 56	0 0.0, 30	1 5.0, 20	0 0.0, 49	0 0.0, 51

Baseline is the Week 0 value or the previous screening value if Week 0 value is not available.
N': number of patients with both baseline and at least one post-baseline value during Phase 2
n=number of patients meeting the above criteria
*A further classification of patients who met the specified criterion with respect to laboratory normal ranges. It indicates that the extreme (highest/lowest) post-baseline test value is either above or below the normal range.
Source: Table 14.3-2.4

No specific trends were seen with UACR changes at end of Phase 1 or Phase 2 (low number of patients with albuminuria at randomization and the uneven distribution of patients with albuminuria among the different treatment groups).

Vital signs

Slight changes in body weight were observed at end of Phase 1 (0.3 to 0.5 Kg) and at end of Phase 2 (0.0 to 0.5 Kg).

There were no meaningful changes in sitting pulse rate in Phase 1 and Phase 2.

A decrease of at least 20 mmHg in SBP or a decrease of at least 10 mmHg in DBP when a patient moves from sitting position to a standing position (orthostatic BP changes) in Phase 1 occurred with similar frequency among the 3 aliskiren dose groups. In Phase 2, orthostatic BP changes were more frequent in the aliskiren mid dose group (Table 12-27).

Table 12-27 Frequency of patients with orthostatic blood pressure change in Phase 2 (Safety set 2)

	ALI Low 6.25/12.5/25 mg (N=50) n/N'(%)	PLB Low (N=57) n/N'(%)	ALI Mid 37.5/75/150 mg (N=30) n/N'(%)	PLB Mid (N=21) n/N'(%)	ALI High 150/300/600 mg (N=50) n/N'(%)	PLB High (N=52) n/N'(%)
Baseline	4/50(8.0)	3/57(5.3)	3/30(10.0)	1/21(4.8)	4/49(8.2)	3/52(5.8)
Week 5	4/50(8.0)	2/57(3.5)	3/30(10.0)	0/21(0.0)	5/50(10.0)	5/50(10.0)
Week 6	1/48(2.1)	4/55(7.3)	3/30(10.0)	3/21(14.3)	2/50(4.0)	3/51(5.9)
Week 7	2/48(4.2)	4/51(7.8)	1/29(3.4)	1/20(5.0)	4/49(8.2)	2/49(4.1)
Week 8	3/50(6.0)	3/54(5.6)	5/30(16.7)	0/21(0.0)	5/50(10.0)	3/51(5.9)
Endpoint	3/50(6.0)	3/57(5.3)	5/30(16.7)	0/21(0.0)	5/50(10.0)	3/52(5.8)
Any visit (post-baseline)	9/50(18.0)	11/57(19.3)	12/30(40.0)	3/21(14.3)	11/50(22.0)	10/52(19.2)

Endpoint is the Week 8 value or LOCF in Phase 2
N=number of patients in the treatment groups
N'=number of patients with blood pressure measurements at the corresponding visit
n=number of patients meeting the above criteria
Any visit includes values from both scheduled and unscheduled visit.
Source: Table 14.3-3.10

A review of study reported AEs did not reveal any ECG related AEs.

Scores of tests on neurocognitive assessments did not indicate substantial changes after treatment.

Discussion on clinical aspects

Summary of Efficacy

The results of the study Phase 1 demonstrated a significant dose-dependent BP lowering effect with aliskiren over a 4 week treatment period with consistent findings for msSBP (primary endpoint) and secondary objectives (msDBP, MAP, % of responder, and ABPM in a subset of 152 patients).

The results of the study Phase 2 – that is the changes from end of Phase1 to end Phase 2 – were inconsistent because of a contrast between data for mean changes in msSBP (primary objective) and secondary objectives. For patients that switched to placebo in Phase 2, the mean of the msSBP change from Phase 1 end was an increase only in the placebo high dose group and was not significant (+1.11 mmHg, P=0.354). The mean of the msSBP change was a further decrease in the placebo low group (-0.64 mmHg) and in the placebo mid dose group (-2.90 mmHg). Briefly, Phase 2 results for the primary objective do not exclude the possibility that a substantial fraction of the blood pressure reduction during Phase 1 was accounted for by factors other than the treatment with aliskiren given that the substitution of aliskiren with placebo was followed by a further decrease in the mean of msSBP for the majority of patients. It is noteworthy that the mean of the msSBP decrease in the placebo mid dose group was borderline significant (P=0.064) and numerically greater compared to the aliskiren mid dose group. Findings for secondary objectives were in contrast with findings for msSBP (% of

responders and ABPM). The response rate at the end of Phase 2 increased further in patients who continued to receive aliskiren (64%, 70% and 82% in the aliskiren low, mid and high dose groups respectively) compared to patients who were switched to placebo. The pooled mid/high doses of aliskiren had a significantly higher proportion of patients with BP response compared to placebo pooled from corresponding arms (77.5% vs 61.6%, p=0.038). ABPM at end of Phase 2 showed significantly greater reductions from baseline in MASBP (-2.86 mmHg, p=0.0022) and MADBP (-2.78 mmHg, p<0.0001) for the pooled mid/high doses of aliskiren compared to placebo pooled from corresponding arms.

The change in msSBP and msDBP in both Phase 1 and Phase2 were generally consistent irrespective of age group, gender, race, ethnicity, weight group, and hypertension etiology.

There was a positive correlation between aliskiren trough concentration and dose.

Summary of safety

Aliskiren was generally well tolerated in this patient population. There were no deaths reported in the study. Only 3 SAE were reported in the aliskiren high dose group (head injury in Phase 1 and suicide attempt and syncope in Phase 2). None of these 3 SAE was suspected to be related to study medication.

The incidence of AEs was similar among the different treatment groups with majority of AEs of mild severity.

The discontinuation rate due to any reason was low overall with very few patients discontinuing due to an AE.

The most frequently reported AEs (headache and upper respiratory tract infection) are common in this patient population.

Changes in laboratory parameters were generally minor with no meaningful differences among the different treatment groups.

Discussion: Rapporteur's conclusions

This study was designed to evaluate the efficacy and safety of aliskiren in the paediatric population aged 6-17 years. Three dose levels of aliskiren were evaluated for a total period of 8 weeks: low (0.13-0.31 mg/Kg), mid (0.75-1.88 mg/Kg) and high (3.0-7.5 mg/Kg) with a wide dose ratio between the low, mid and high dose groups (1:6:24). The study included two phases: Phase 1 for evaluation of dose-response curve, and Phase 2 for evaluation of placebo effects (placebo-controlled withdrawal).

The primary objective and the secondary objectives of the study Phase 1 were met.

The primary objective of the Phase 2 study was not met whereas the secondary objectives of the study Phase 2 were partially met. The Applicant concludes that this inconsistency might reflect insufficient washout of aliskiren effect when patients were switched to placebo (long biological half-life of aliskiren). This interpretation does not appear adequate because it does not explain all the inconsistencies such as that between mean changes in msSBP and % of responders (office BP vs office BP) as well as the contrasting results for msSBP and MASBP (office BP vs ABPM). Moreover, the possibility of antihypertensive effects lasting for up to 4 weeks after treatment suspension would rise serious doubts about the manageability of aliskiren in the paediatric population.

Aliskiren was generally well tolerated in this patient population of hypertensive patients aged 6-17 years old. The rate of discontinuation was low. There were no deaths and there were few SAEs (1.1%). Most of the reported AEs were generally mild and transient in nature. Overall, the safety profile of aliskiren in this short term study was similar to placebo.

Rapporteur's overall conclusion and recommendation

The efficacy of aliskiren cannot be considered as fully proved in the paediatric population aged 6 to 17 years old because of inconclusive results of the placebo-controlled Phase 2 of the study CSPP100A2365.

Aliskiren appears safe in the paediatric population aged 6 to 17 years old.

Overall, data from study CSPP100A2365 do not support an indication in the studied population.

The Applicant was required to present a variation application to amend the Product Information of aliskiren containing products with the results from study CSPP100A2365 (see section below).

In view of the available data regarding efficacy and safety of aliskiren in patients aged 6-17 years from study CSPP100A2365, the Rapporteur asked the MAH to either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so.

The above variation application should have amended the relevant sections of the SmPC to include the above discussed findings, in line with the wording reported below (changes to the currently approved text: deleted text is ~~strikethrough~~; added text is in **bold**). The PL should have been updated in line with the SmPC changes.

3.3. Changes to the Product Information

As a result of this type IB variation, sections 4.2, 4.4, 4.8, 5.1 of the SmPC are being updated according to the outcome of the recently completed Article 46 procedure EMA/H/C/780/P46/039 which reviewed the results of the aliskiren paediatric study CSPP100A2365 in children 6-17 years with hypertension.

The proposed amendments to the SmPC were as follows (see Attachment 1) (changes to the currently approved text: deleted text is ~~strikethrough~~; added text is in **bold**; the differences between the wording proposed by the Rapporteur and that proposed by the MAH are highlighted in grey):

Section 4.2

RAPPORTEUR'S PROPOSAL

"Paediatric population
Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

~~Limited data on the use of Rasilez in children aged 6 to less than 18 years are described in sections 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years~~

The safety and efficacy of aliskiren in children aged 6 to 17 years with hypertension has not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2."

CHANGES MADE BY THE MAH ACCORDINGLY

"*Paediatric population*
The safety and efficacy of Rasilez in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.**

Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

~~Limited data on the use of Rasilez in children aged 6 to less than 18 years are described in sections 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.~~"

Section 4.4

RAPPORTEUR'S PROPOSAL

"Paediatric population
Aliskiren is a *P-glycoprotein* (P-gp) substrate, and there is a potential for aliskiren overexposure in children with an immature P-gp drug transporter system. The age at which the transporter system is mature cannot be determined (see sections 5.2 and 5.3). Therefore, Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years.

~~Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).~~ "*(Apply also to Rasilez HCT and Rasilamlo SmPCs)*

CHANGES MADE BY THE MAH ACCORDINGLY

"Paediatric population
Aliskiren is a P-glycoprotein (P-gp) substrate, and there is a potential for aliskiren overexposure in children with an immature P-gp drug transporter system. The age at which the transporter system is mature cannot be determined (see sections 5.2 and 5.3). Therefore, Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years.

~~Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).~~"

Section 4.8

RAPPORTEUR'S PROPOSAL

"Paediatric population
~~Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.~~

In a paediatric multicenter, randomized, double-blind, 8-week study in 267 hypertensive patients aged 6 to 17 years, aliskiren appears to be well-tolerated. The incidence of adverse events was comparable between the three aliskiren dose levels and corresponding placebo groups, regardless of weight, age, gender, and race or hypertension etiology. The majority of adverse events were of mild severity. The most frequently reported adverse events were headache and upper respiratory tract infection (common, i.e. ≥1/100 to <1/10). The frequency, type and severity of adverse reactions in children are expected to be similar to

that seen in hypertensive adults." *(Apply also to Rasilez HCT and Rasilamlo SmPCs under 'Aliskiren' subsection)*

CHANGES MADE BY THE MAH ACCORDINGLY

"Paediatric population
~~Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.~~ **In a paediatric multicentre, randomised, double-blind, 8-week study in 267 hypertensive patients aged 6 to 17 years aliskiren appears to be well-tolerated. The incidence of adverse events was comparable between the three aliskiren dose levels and corresponding placebo groups, regardless of weight group, age group, gender, race or hypertension aetiology. The majority of adverse events were mild. The most frequently reported adverse events were headache and upper respiratory tract infection (common, i.e. ⩾1/100 to <1/10). The frequency, type and severity of adverse reactions in children are expected to be similar to those seen in hypertensive adults.**"

Section 5.1

RAPPORTEUR'S PROPOSAL

"Paediatric population
In a multicenter, randomized, double-blind, 8-week study with aliskiren monotherapy (3 dose groups according to weight: low 6.25/12.5/25 mg [0.13-0.31 mg/kg]; mid 37.5/75/150 mg [0.75-1.88 mg/kg]; and high dose 150/300/600 mg [3.0-7.5 mg/kg], with a wide dose ratio between the low, mid and high dose groups [1:6:24]) in 267 paediatric hypertensive patients aged 6 to 17 years, aliskiren lowered office and ambulatory blood pressure in a dose-dependent manner during the initial 4 week dose-finding phase of the study (Phase 1). However, in the subsequent 4 week randomised withdrawal phase of the study (Phase 2), the effect of aliskiren overlapped with the effects observed in patients switched to placebo in all dose groups (low, p=0.8894; mild, p=0.9511; high, p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were < 0.2 mmHg and not significant as well. The treatment with aliskiren was well tolerated in this study. *(Apply also to Rasilez HCT and Rasilamlo SmPCs under 'Aliskiren' subsection)*

The European Medicines Agency has deferred the obligation to submit the results of studies with Rasilez in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use)."

CHANGES MADE BY THE MAH ACCORDINGLY

"Paediatric population
In a multicentre, randomised, double-blind, 8-week study with aliskiren monotherapy (3 dose groups according to weight: low 6.25/12.5/25 mg [0.13-0.31 mg/kg]; mid 37.5/75/150 mg [0.75-1.88 mg/kg]; and high dose 150/300/600 mg [3.0-7.5 mg/kg], with a wide dose ratio between the low, mid and high dose groups [1:6:24]) in 267 paediatric hypertensive patients aged 6 to 17 years, aliskiren lowered office and ambulatory blood pressure in a dose-dependent manner during the initial 4 week dosefinding phase of the study (Phase 1). However, in the subsequent 4 week randomised withdrawal phase of the study (Phase 2), the effect of aliskiren overlapped with the effects observed in patients switched to placebo in all dose groups (low, p=0.8894; mid, p=0.9511; high, p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were <0.2 mmHg. The treatment with aliskiren was well tolerated in this study.

The European Medicines Agency has deferred the obligation to submit the results of studies with Rasilez in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use)."

Assessor's comment

The recently completed Article 46 procedure EMA/H/C/780/P46/039 reviewed the results of the aliskiren paediatric study CSPP100A2365 in children 6-17 years with hypertension.

Indeed, this study was designed to evaluate the efficacy and safety of aliskiren in the paediatric population aged 6-17 years. Three dose levels of aliskiren were evaluated for a total period of 8 weeks: low (0.13-0.31 mg/Kg), mid (0.75-1.88 mg/Kg) and high (3.0-7.5 mg/Kg) with a wide dose ratio between the low, mid and high dose groups (1:6:24). The study included two phases: Phase 1 for evaluation of dose-response curve, and Phase 2 for evaluation of placebo effects (placebo-controlled withdrawal).

The primary objective and the secondary objectives of the study Phase 1 were met.

The primary objective of the Phase 2 study was not met whereas the secondary objectives of the study Phase 2 were partially met. The Applicant concludes that this inconsistency might reflect insufficient washout of aliskiren effect when patients were switched to placebo (long biological half-life of aliskiren). This interpretation does not appear adequate because it does not explain all the inconsistencies such as that between mean changes in msSBP and % of responders (office BP vs office BP) as well as the contrasting results for msSBP and MASBP (office BP vs ABPM). Moreover, the possibility of antihypertensive effects lasting for up to 4 weeks after treatment suspension would rise serious doubts about the manageability of aliskiren in the paediatric population.

Aliskiren was generally well tolerated in this patient population of hypertensive patients aged 6-17 years old. The rate of discontinuation was low. There were no deaths and there were few SAEs (1.1%). Most of the reported AEs were generally mild and transient in nature. Overall, the safety profile of aliskiren in this short term study was similar to placebo.

In conclusion, the efficacy of aliskiren cannot be considered as fully proved in the paediatric population aged 6 to 17 years old because of inconclusive results of the placebo-controlled Phase 2 of the study CSPP100A2365.

Aliskiren appears safe in the paediatric population aged 6 to 17 years old.

Overall, data from study CSPP100A2365 do not support an indication in the studied population.

The Applicant was required to present a variation application to amend sections 4.2, 4.4, 4.8, 5.1 of the SmPC of aliskiren containing products with the results from study CSPP100A2365.

Regarding the **section 4.2**, the MAH adopted the wording proposed by the Rapporteur, but it would be better to move the following sentence

"Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3)."
before the sentence

"The safety and efficacy of Rasilez in children aged ***6 to 17 years with hypertension*** ~~*below 18 years*~~ *have not yet been established.* ***Currently available data are described in sections 4.8, 5.1, and 5.2.****"*

Moreover, the Rapporteur concluded that "Aliskiren was generally well tolerated in this patient population of hypertensive patients aged 6-17 years old. The rate of discontinuation was low. There were no deaths and there were few SAEs (1.1%). Most of the reported AEs were generally mild and

transient in nature. Overall, the safety profile of aliskiren in this short term study was similar to placebo. … Aliskiren appears safe in the paediatric population aged 6 to 17 years old."

But, there are no data on long-term safety in this age category, hence it is proposed to add *"long-term safety"* in the following sentence ""*The safety and efficacy of Rasilez in children aged* ***6 to 17 years with hypertension*** ~~*below 18 years*~~ *have not yet been established.* ***Currently available data are described in sections 4.8, 5.1, and 5.2.****"*

Therefore, the wording should be as follows:

"Paediatric population
Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

~~*Limited data on the use of Rasilez in children aged 6 to less than 18 years are described in sections 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.*~~

The ***long-term*** *safety and efficacy of aliskiren in children aged* ***6 to 17 years with hypertension*** ~~*below 18 years*~~ *have not yet been established.* ***Currently available data are described in sections 4.8, 5.1, and 5.2.****"*

Regarding the **section 4.4**, the MAH made the changes proposed by the Rapporteur as follow:

"Paediatric population
Aliskiren is a P-glycoprotein (P-gp) substrate, and there is a potential for aliskiren overexposure in children with an immature P-gp drug transporter system. The age at which the transporter system is mature cannot be determined (see sections 5.2 and 5.3). Therefore, Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years.

~~*Limited safety data are available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children aged 6 to less than 18 years (see sections 4.8 and 5.2).*~~*"*

Regarding the **section 4.8**, the MAH only made minor editorial changes (highlighted in grey) that do not modify the meaning of the wording proposed by the Rapporteur (see below) and these changes are endorsed by the Rapporteur:

WORDING PROPOSED BY THE RAPPORTEUR

"*Paediatric population*
~~*Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.*~~

In a paediatric multicenter, randomized, double-blind, 8-week study in 267 hypertensive patients aged 6 to 17 years, aliskiren appears to be well-tolerated. The incidence of adverse events was comparable between the three aliskiren dose levels and corresponding placebo groups, regardless of weight, age, gender, and race or hypertension etiology. The majority of adverse events were of mild severity. The most frequently reported adverse events were headache and upper respiratory tract infection (common, i.e. ≥1/100 to <1/10). The frequency, type and severity of adverse reactions in children are expected to be similar to that seen in hypertensive adults.*" (Apply also to Rasilez HCT and Rasilamlo SmPCs under 'Aliskiren' subsection)*

WORDING PROPOSED BY THE MAH:

"Paediatric population
~~*Based on the limited amount of safety data available from a pharmacokinetic study of aliskiren treatment in 39 hypertensive children 6-17 years of age, the frequency, type and severity of adverse*~~

~~*reactions in children are expected to be similar to that seen in hypertensive adults. As for other RAAS blockers, headache is a common adverse event in children treated with aliskiren.*~~ ***In a paediatric multicentre, randomised, double-blind, 8-week study in 267 hypertensive patients aged 6 to 17 years aliskiren appears to be well-tolerated. The incidence of adverse events was comparable between the three aliskiren dose levels and corresponding placebo groups, regardless of weight group, age group, gender, race or hypertension aetiology. The majority of adverse events were mild. The most frequently reported adverse events were headache and upper respiratory tract infection (common, i.e. ≥1/100 to <1/10). The frequency, type and severity of adverse reactions in children are expected to be similar to those seen in hypertensive adults.***"

Regarding the **section 5.1**, the MAH made an editorial change (highlighted in grey) by deleting *"… and not significant as well."* (see below):

WORDING PROPOSED BY THE RAPPORTEUR

"Paediatric population
In a multicenter, randomized, double-blind, 8-week study with aliskiren monotherapy (3 dose groups according to weight: low 6.25/12.5/25 mg [0.13-0.31 mg/kg]; mid 37.5/75/150 mg [0.75-1.88 mg/kg]; and high dose 150/300/600 mg [3.0-7.5 mg/kg], with a wide dose ratio between the low, mid and high dose groups [1:6:24]) in 267 paediatric hypertensive patients aged 6 to 17 years, aliskiren lowered office and ambulatory blood pressure in a dose-dependent manner during the initial 4 week dose-finding phase of the study (Phase 1). However, in the subsequent 4 week randomised withdrawal phase of the study (Phase 2), the effect of aliskiren overlapped with the effects observed in patients switched to placebo in all dose groups (low, p=0.8894; mild, p=0.9511; high, p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were < 0.2 mmHg and not significant as well. The treatment with aliskiren was well tolerated in this study. *(Apply also to Rasilez HCT and Rasilamlo SmPCs under 'Aliskiren' subsection)*

The European Medicines Agency has deferred the obligation to submit the results of studies with Rasilez in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use)."

WORDING PROPOSED BY THE MAH

"Paediatric population
In a multicentre, randomised, double-blind, 8-week study with aliskiren monotherapy (3 dose groups according to weight: low 6.25/12.5/25 mg [0.13-0.31 mg/kg]; mid 37.5/75/150 mg [0.75-1.88 mg/kg]; and high dose 150/300/600 mg [3.0-7.5 mg/kg], with a wide dose ratio between the low, mid and high dose groups [1:6:24]) in 267 paediatric hypertensive patients aged 6 to 17 years, aliskiren lowered office and ambulatory blood pressure in a dose-dependent manner during the initial 4 week dosefinding phase of the study (Phase 1). However, in the subsequent 4 week randomised withdrawal phase of the study (Phase 2), the effect of aliskiren overlapped with the effects observed in patients switched to placebo in all dose groups (low, p=0.8894; mid, p=0.9511; high, p=0.0563). The average differences between aliskiren and placebo for the low and mid dose groups were <0.2 mmHg. The treatment with aliskiren was well tolerated in this study.

The European Medicines Agency has deferred the obligation to submit the results of studies with Rasilez in one or more subsets of the paediatric population in hypertension (see section 4.2 for information on paediatric use)."

According to the Rapporteur, this editorial change is acceptable and hence the wording of the section 5.1 with the editorial change proposed by the MAH is endorsed.

4. Request for supplementary information

Supplementary information (other concern) is requested to the MAH (see below).

4.1. Other concerns which should be addressed by the applicant

Regarding the **section 4.2**, the MAH adopted the wording proposed by the Rapporteur, but it would be better to move the following sentence

"Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3)."
before the sentence

"The safety and efficacy of Rasilez in children aged ***6 to 17 years with hypertension*** ~~*below 18 years*~~ *have not yet been established.* ***Currently available data are described in sections 4.8, 5.1, and 5.2.****"*

Moreover, the Rapporteur concluded that "Aliskiren was generally well tolerated in this patient population of hypertensive patients aged 6-17 years old. The rate of discontinuation was low. There were no deaths and there were few SAEs (1.1%). Most of the reported AEs were generally mild and transient in nature. Overall, the safety profile of aliskiren in this short term study was similar to placebo. … Aliskiren appears safe in the paediatric population aged 6 to 17 years old."

But, there are no data on long-term safety in this age category, hence it is proposed to add *"long-term safety"* in the following sentence ""*The safety and efficacy of Rasilez in children aged* ***6 to 17 years with hypertension*** ~~*below 18 years*~~ *have not yet been established.* ***Currently available data are described in sections 4.8, 5.1, and 5.2.****"*

Therefore, the wording should be as follows:

"Paediatric population
Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

~~*Limited data on the use of Rasilez in children aged 6 to less than 18 years are described in sections 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.*~~

The ***long-term*** *safety and efficacy of aliskiren in children aged* ***6 to 17 years with hypertension*** ~~*below 18 years*~~ *have not yet been established.* ***Currently available data are described in sections 4.8, 5.1, and 5.2.****"*

5. Assessment of the responses to the request for supplementary information

Question
Regarding the **section 4.2**, the MAH adopted the wording proposed by the Rapporteur, but it would be better to move the following sentence

"Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3)."
before the sentence

*"The safety and efficacy of Rasilez in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.**"*

Moreover, the Rapporteur concluded that "Aliskiren was generally well tolerated in this patient population of hypertensive patients aged 6-17 years old. The rate of discontinuation was low. There were no deaths and there were few SAEs (1.1%). Most of the reported AEs were generally mild and transient in nature. Overall, the safety profile of aliskiren in this short term study was similar to placebo. … Aliskiren appears safe in the paediatric population aged 6 to 17 years old."

But, there are no data on long-term safety in this age category, hence it is proposed to add *"long-term safety"* in the following sentence ""*The safety and efficacy of Rasilez in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.**"*

Therefore, the wording should be as follows:

"Paediatric population
Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

~~Limited data on the use of Rasilez in children aged 6 to less than 18 years are described in sections 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.~~

*The **long-term** safety and efficacy of aliskiren in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.**"*

Summary of the WSA's response

The MAH submitted the updated SmPC as follows:

"Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

*The **long-term** safety and efficacy of Rasilez in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.***

~~Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).~~

~~Limited data on the use of Rasilez in children aged 16 to less than 18 years are described in serious 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.~~"

Assessment of the WSA's response

The MAH submitted the updated SmPC as follows:

"Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

*The **long-term** safety and efficacy of Rasilez in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.***

~~*Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).*~~

~~*Limited data on the use of Rasilez in children aged 16 to less than 18 years are described in serious 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.*~~"

The SmPC update is considered in line with PRAC/CHMP request. But, as the efficacy of aliskiren cannot be considered as fully proved in the paediatric population aged 6 to 17 years old because of inconclusive results of the placebo-controlled Phase 2 of the study CSPP100A2365, in order to avoid confusion in the prescriber, it would be better to write in SmPC section 4.2 as follows:

"*The **efficacy** and **long-term** safety ~~**and efficacy**~~ of Rasilez in children aged 6 to 17 years with hypertension have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2."*

instead of

*"The **long-term** safety and efficacy of Rasilez in children aged 6 to 17 years with hypertension have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2".*

Conclusion

The efficacy of aliskiren cannot be considered as fully proved in the paediatric population aged 6 to 17 years old because of inconclusive results of the placebo-controlled Phase 2 of the study CSPP100A2365.

Aliskiren appears safe in the paediatric population aged 6 to 17 years old.

Overall, data from study CSPP100A2365 do not support an indication in the studied population.

The Applicant was required to present a variation application to amend the Product Information of aliskiren containing products with the results from study CSPP100A2365 (see section below).

In view of the available data regarding efficacy and safety of aliskiren in patients aged 6-17 years from study CSPP100A2365, the Rapporteur asked the MAH to either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so.

The above variation application should have amended the relevant sections of the SmPC to include the above discussed findings, in line with the wording reported below (changes to the currently approved text: deleted text is ~~strikethrough~~; added text is in **bold**). The PL should have been updated in line with the SmPC changes.

The MAH submitted the updated SmPC as follows:

"Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).

*The **long-term** safety and efficacy of Rasilez in children aged **6 to 17 years with hypertension** ~~below 18 years~~ have not yet been established. **Currently available data are described in sections 4.8, 5.1, and 5.2.***

~~*Rasilez is contraindicated in children from birth to less than 2 years and should not be used in children aged 2 to less than 6 years because of safety concerns due to potential aliskiren overexposure (see sections 4.3, 4.4, 5.2, and 5.3).*~~

~~*Limited data on the use of Rasilez in children aged 16 to less than 18 years are described in serious 4.8 and 5.2. No recommendation on a posology can be made for children aged 6 to less than 18 years.*~~"

The SmPC update is considered in line with PRAC/CHMP request. But, as the efficacy of aliskiren cannot be considered as fully proved in the paediatric population aged 6 to 17 years old because of inconclusive results of the placebo-controlled Phase 2 of the study CSPP100A2365, in order to avoid confusion in the prescriber, it would be better to write in SmPC section 4.2 as follows:

"*The **efficacy** and **long-term** safety **~~and efficacy~~** of Rasilez in children aged 6 to 17 years with hypertension have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2."*

instead of

*"The **long-term** safety and efficacy of Rasilez in children aged 6 to 17 years with hypertension have not yet been established. Currently available data are described in sections 4.8, 5.1, and 5.2".*

The MAH agreed to update the SmPC section 4.2 with the above proposed changes.

☒ Overall conclusion and impact on benefit-risk balance has been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance