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NOVARTIS

Clinical Development

SPP100A/Aliskiren

Clinical Trial Protocol CSPP100A2365E2

A multicenter, 52 to 104 week extension study to evaluate the long term growth and development of pediatric hypertensive patients 6 – 17 years of age treated previously with aliskiren

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
eCRF	Electronic Case Report Form
CPO	Country Pharma Organization
CRO	Contract Research Organization
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EFS	Enrolled to follow-up set
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
PIP	Pediatric Investigational Plan
SAE	serious adverse event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Protocol synopsis

Title of study: A multicenter, 52 to 104 week off-therapy extension study to evaluate the long term growth and development of pediatric hypertensive patients 6 – 17 years of age previously treated with aliskiren in studies CSPP100A2365 and/or CSPP100A2365E1

Purpose and rationale: The purpose of this 52 to 104 week off-therapy follow-up to studies CSPP100A2365 and CSPP100A2365E1 is to evaluate the long term growth and development of children 6 – 17 years old (6 to less than 18 years old at baseline in study CSPP100A2365) with hypertension (msSBP ≥ 95th percentile for age, gender and height) at baseline in study CSPP100A2365, previously treated with aliskiren. Patients identified in study CSPP100A2365 to have primary hypertension will be followed for 52 weeks (1 year) after the completion of study CSPP100A2365E1. Patients identified in study CSPP100A2365 to have secondary hypertension will be followed for 104 weeks (2 years) after the completion of study CSPP100A2365E1. The assessment of growth and development through height and weight measurement will be performed on all patients for 52 weeks, after which patients with primary hypertension will complete. The assessment of patients with secondary hypertension will continue for an additional 52 weeks during which growth and development will continue to be assessed with added neurocognitive and renal function evaluations.

This study is in compliance with the EMA PIP Positive Opinion in support of the monotherapy registration of aliskiren for the treatment of hypertension in pediatric patients 6 – 17 years of age.

Objectives:

- To evaluate the long term growth and development of pediatric hypertensive patients 6 – 17 years of age when previously treated with aliskiren

Population: The study population will consist of male and female hypertensive pediatric patients who have completed the CSPP100A2365E1 protocol. These patients were 6 – 17 years old and had an msSBP ≥ 95th percentile for age, gender and height at baseline (randomization) in study CSPP100A2365. Patients will continue to be stratified by CSPP100A2365 baseline weight, age, hypertension etiology and region. Centers from the US and EU participating in CSPP100A2365 and CSPP100A2365E1 will participate in this off-therapy follow-up.

Inclusion/Exclusion criteria:

All patients are to have met entry inclusion and exclusion criteria for CSPP100A2365 and CSPP100A2365E1.

- Successful completion of the CSPP100A2365E1 protocol
- Written informed consent; patients who are eligible to participate in this long-term off-therapy extension and whose parent(s)/guardian (s) consent in writing to their doing so after the purpose and nature of this investigation has been clearly explained to them. An assent will be obtained for some patients depending upon their age, maturity, capacity for understanding, and the local requirements regarding assents. Written informed consent must be obtained before any assessment is performed.

Investigational and reference therapy:

- Investigational therapy: none
- Reference therapy: none

Study medication is not used in this trial.

Study design: This is a multicenter, 52 to 104 week off-therapy extension to evaluate long-term growth and development in pediatric hypertensive patients 6 – 17 years of age at initiation of treatment with aliskiren in study CSPP100A2365. Eligible patients will continue to be stratified by age (6 to 11 years and 12 to 17 years) at study CSPP100A2365 baseline (Visit 2) and by etiology of hypertension

(primary and secondary). Likewise, stratifications by weight group and region assigned at study CSPP100A2365 will remain.

Efficacy assessments: Not applicable.

Safety assessments:

- At LT weeks 104 and 156 height and weight measurements
- At LT weeks 104 and 156 renal function evaluation only in patients with secondary hypertension

Other assessments:

- At LT weeks 104 and 156 neurocognitive evaluation only in patients with secondary hypertension

Data analysis: Demographics and baseline characteristics, safety data (height, weight, derived BMI, laboratory evaluations, SAE) and other data as appropriate, will be summarized descriptively by treatment regimen from CSPP100A2365E1.

For the superiority assessment of change in weight, the null hypothesis to be tested is that the mean change of weight in the aliskiren regimen is equal to that in the enalapril regimen, versus the alternative hypothesis that they are not equal:

H_0: $\mu_1 = \mu_2$ versus H_1: $\mu_1 \neq \mu_2$

The statistical test for change from baseline in weight will be performed using an analysis of covariance (ANCOVA) model with treatment regimen from CSPP10AE1, region (US, EU), age strata (6 to 11 years, 12 to 17 years), and hypertension etiology (primary, secondary) as factors, and with baseline weight as covariate. The statistical test will be made at two-sided significance level of 0.05. The 95% confidence interval will be provided.

Changes from baseline in height and derived BMI will be analyzed using the similar model.

1 Introduction

1.1 Background

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

Blocking RAS with an ACE inhibitor or angiotensin II receptor blocker (ARB) has been commonly used in clinical practice for the treatment of patients with hypertension. An alternative approach to blockade of the RAS is inhibition of renin, the rate limiting enzyme for the formation of angiotensin II. Until recently, the introduction of renin inhibitors into clinical practice was limited by low oral bio-availability, short duration of action and high cost of chemical synthesis. Aliskiren (SPP 100) is the first new, orally active, non-peptide, specific direct renin inhibitor and has been approved for use in adults in the treatment of hypertension.

Aliskiren is a non-peptide with a low molecular weight (609.8). In vitro, it is a potent direct inhibitor of human renin (IC50 = 0.6 nM). In vivo, aliskiren administered both orally (p.o.) or intravenously (i.v.) in several studies with sodium-depleted marmosets caused complete inhibition of plasma renin activity (PRA), sustained reductions in mean arterial pressure (MAP), and significant increases in plasma concentrations of active and total renin. In humans, plasma concentrations of aliskiren increase rapidly after administration reaching peak levels usually within 1-3 hours. The half-life of aliskiren is approximately 40 hours and its bioavailability is approximately 2.6%. Renal and hepatic clearance of aliskiren is minimal. Changes in renal and hepatic function related to age are not anticipated to alter aliskiren elimination within the proposed range of 6 to 17 years. Aliskiren is excreted mostly unchanged by the fecal route (~90%). About 0.6% of an oral dose is renally excreted.

In the adult population, aliskiren has been studied in clinical trials involving over 12,000 patients with hypertension. It has been demonstrated to be efficacious and safe when used alone or in combination with other antihypertensives for the treatment of hypertension. In a clinical study in patients with mild to moderate hypertension, 652 patients were randomized to receive placebo, aliskiren 150, 300 or 600 mg or 150 mg of irbesartan once daily for 8 weeks. Patients receiving aliskiren 150 mg and 300 mg demonstrated dose related decreases in both systolic and diastolic blood pressure. No additional blood pressure lowering effects were seen with aliskiren 600 mg as compared with aliskiren 300 mg. Aliskiren 150 mg was comparable to irbesartan 150 mg in reducing diastolic blood pressure (DBP) while aliskiren 300 mg and 600 mg showed a significantly greater DBP reduction than irbesartan 150 mg. The overall incidences of adverse events seen in patients receiving aliskiren (150 mg and 300 mg) were similar to placebo. There was a slight increase in GI adverse events (especially diarrhea) at the 600mg aliskiren dose.

In a 26-week, randomized, double-blind study with 1124 randomized patients, the combination of aliskiren with amlodipine was demonstrated to be effective and well tolerated. In addition, the efficacy and safety of the combination of aliskiren with HCTZ were shown in a 26-week, double-blind, randomized active-controlled study with a total number of 842 patients with hypertension.

The effect of aliskiren on the development of the juvenile rat was explored in three toxicology studies. The effects of aliskiren have been tested in rats treated by gavage at 50, 150 or 300 mg/kg/day from days 14 to 34 post-partum. Effects on mortality, clinical signs, and body weight were measured, and following euthanasia at day 34, gross and microscopic pathology were examined. No deaths were noted. Diarrhea was present in most animals at the higher doses. Dose-related 15-50% reductions in body weight gain as compared to controls were found early in the course of treatment, but tended to be slightly higher than controls thereafter. In other studies in which rats were treated by gavage with aliskiren at 30, 100, or 300 mg/kg/day from post-partum day 8 to 35 and 14 to 70, respectively, morbidity (12-57% weight loss, diarrhea, and 20-30% reduction in the absolute lymphocyte count) and mortality (1 death at 100 mg/kg/day and 4 deaths at 300 mg/kg/day) were observed as in the 34 day study. Pharmacokinetic measurements in these studies showed that aliskiren exposure (AUC in ng-h/ml) was 19-36% greater in 8 day old than in 14 day old rats at the 30 mg/kg/day dose, but more than 350% (3.5 fold) greater at the 100 mg/kg/day dose. Remarkably, the AUC was more than 350-fold greater in 14 day old than the 64 day old rats at the 30 mg/kg/day dose, 150-fold greater at the 100 mg/kg/day dose, and 85-fold greater in 14 day old than the 64 day old rats at the 300 mg/kg/day dose. Moreover, the variability in exposure was more than twice as great when the animals were younger than when they were older.

These findings demonstrate that aliskiren exposure is age related with declining exposure possibly related to the maturation of transporters and/or metabolizing systems.

In humans, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus when administered to pregnant women. When pregnancy is detected, aliskiren should be discontinued as soon as possible. For complete details of the toxicology program for aliskiren please refer to the SPP100 Aliskiren Investigator's Brochure.

As the first direct renin inhibitor for the treatment of hypertension in adults, aliskiren is proposed for use in hypertensive children 6-17 years of age, as an alternative to currently available therapies. Aliskiren may offer a therapeutic profile distinct from that of ACE inhibitors and ARBs (Frampton and Curran 2007). The course of hypertension and the effects of antihypertensive medications in adolescents are not likely to differ from the course of the disease and the effects of antihypertensive medications in adults. The pediatric study for which this is an off-therapy follow-up will include a reasonable proportion of school-age, pre-pubertal children with at least 50% of the children being 6-11 years of age.

As the prevalence of hypertension in children increases (Soroff, et al 2004) treatment alternatives to those currently available will be of increasing significance. It is known that hypertension prevalence increases progressively with increased BMI and in the pediatric population hypertension is detectable in approximately 30% of overweight children (NHLBI 12th Report, 2004). Obesity is thought to be a major contributor to essential hypertension in school age children and adolescents (Weinberger, et al 2008). Primary essential hypertension in children is generally mild and associated with a positive family history of hypertension or

CVD and mild/moderate/severe obesity. Aliskiren may therefore be particularly important in children 6-17 years of age with essential hypertension since it has been shown to be of comparable efficacy in obese adult patients compared to those of normal body mass index (BMI) (Jensen, et al 2008).

In summary, the efficacy and tolerability of aliskiren alone or in combination with other agents are comparable to other commonly used antihypertensive medications in adults. Given the results reported with aliskiren in adults with hypertension, a similar efficacy and tolerability of aliskiren in children 6-17 years of age would be anticipated, providing an additional treatment option for children with hypertension.

This study is intended to evaluate the off-therapy long term growth and development of children 6 – 17 years old after exposure to aliskiren for at least one year in studies CSPP100A2365 and CSPP100A2365E1, and was developed to comply with the EMA Pediatric Committee Pediatric Investigational Plan (PIP).

In study CSPP100A2365 the dose-response, efficacy and safety of aliskiren was evaluated in double-blind fashion over 8 weeks. Study CSPP100A2365E1 provided double blind evaluation of the long-term safety, tolerability and efficacy of aliskiren compared to enalapril in the same patient population.

1.2 Purpose

The purpose of this 52 to 104 week off-therapy extension to studies CSPP100A2365 and CSPP100A2365E1 is to evaluate the long term growth and development of children 6 – 17 years old (6 to less than 18 years old at baseline in study CSPP100A2365) with hypertension (msSBP $\geq 95^{th}$ percentile for age, gender and height) at baseline in study CSPP100A2365, previously treated with aliskiren. Patients identified in study CSPP100A2365 to have primary hypertension will be followed for 52 weeks (1 year) after the completion of study CSPP100A2365E1. Patients identified in study CSPP100A2365 to have secondary hypertension will be followed for 104 weeks (2 years) after the completion of study CSPP100A2365E1. The assessment of growth and development through height and weight measurement will be performed on all patients for 52 weeks after which patients with primary hypertension will complete. The assessment of patients with secondary hypertension will continue for an additional 52 weeks during which growth and development will continue to be assessed with added neurocognitive and renal function evaluations as follow-up measures.

This study is in compliance with the EMA PIP Positive Opinion in support of the monotherapy registration of aliskiren for the treatment of hypertension in pediatric patients 6 – 17 years of age.

2 Study objectives

2.1 Primary objectives

- To evaluate the long term growth and development of pediatric hypertensive patients aged 6 – 17 years when treated previously with aliskiren

2.2 Secondary objectives

Not applicable.

2.3 Exploratory objectives

Not applicable.

3 Investigational plan

3.1 Study design

This is a multicenter 52 to 104 week off-therapy extension to evaluate long-term growth and development in pediatric hypertensive patients 6 – 17 years of age at initiation of treatment with aliskiren in study CSPP100A2365. Eligible patients will continue to be stratified by age (6 – 11 years and 12 – 17 years) at study CSPP100A2365 baseline (Visit 2) and by etiology of hypertension (primary and secondary). Likewise, stratifications by weight group and region assigned in study CSPP100A2365 will remain.

Table 3-1 Study design

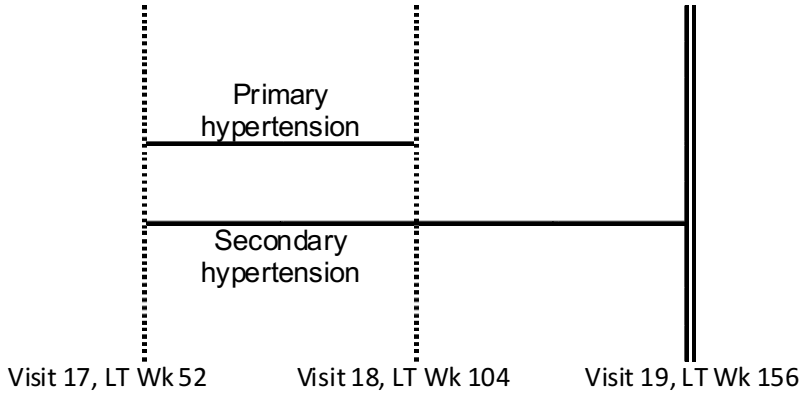
CSPP100A2365E2 LT Safety Follow-up		
Week 52 LT (end of study visit CSPP100A2365E1)	Week 104 LT	Week 156 LT
Day 365 (LT)	Day 730 (LT)	Day1095 (LT)
Visit 17*	Visit 18**	Visit 19***

* Long-term (LT) safety extension visit numbers continue from CSPP100A2365E1

** End of study for patients with primary hypertension

*** End of study for patients with secondary hypertension

Figure 3-1 Study design



3.2 Rationale of study design

This study is being conducted to comply with the EMA PIP Positive Opinion for the provision of long-term growth and development data including renal function and neurocognitive function data in children with secondary hypertension.

3.3 Rationale of dose/regimen, duration of treatment

Not applicable.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

4 Population

The study population will consist of male and female hypertensive pediatric patients who have completed the CSPP100A2365E1 protocol. These patients were 6 – 17 years old and had an msSBP $\geq 95^{th}$ percentile for age, gender and height at baseline (randomization) in study CSPP100A2365. Patients will continue to be stratified by CSPP100A2365 baseline weight, age, hypertension etiology and region. Centers from the US and EU participating in CSPP100A2365 and CSPP100A2365E1 will participate in this off-therapy follow-up.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Informed consent form (approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), signed by the parent(s)/legal guardian(s), after the purpose and nature of the investigation has been clearly explained to the parents and the patient. An assent will be obtained for some patients depending upon their age, maturity, capacity for understanding, and the local requirements regarding assents. Written informed consent must be obtained before any assessment is performed.
2. Male or female patients ages 6 – 17 years at Visit 2 (randomization) in study CSPP100A2365, with a documented diagnosis of hypertension as defined in the NHLBI 12^{th} Report 2004
3. msSBP (mean of 3 systolic blood pressure measurements) $\geq 95^{th}$ percentile for age, gender and height at Visit 2 (randomization) in study CSPP100A2365
4. $\geq$ 20 kg and $\leq$ 150 kg at Visit 2 (randomization) in study CSPP100A2365
5. Successful completion of study CSPP100A2365E1

4.2 Exclusion criteria

1. Patients who did not successfully complete study CSPP100A2365 and CSPP100A2365E1 are excluded from participation in CSPP100A2365E2.
2. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Treatment

5.1 Investigational and control treatment

Not applicable.

5.2 Treatment arms

Not applicable.

5.3 Treatment assignment

Not applicable.

5.4 Treatment blinding

Not applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number was assigned by Novartis to the investigative site in trial CSPP100A2365. Upon signing the informed consent form and assent form, if applicable, the patient will continue to use the patient number assigned by the investigator in trial CSPP100A2365. Only the assigned patient number should be entered in the field labeled "Patient ID" on the EDC data entry screen (e.g. enter '1', '2', etc.).

5.5.2 Dispensing the study treatment

Not applicable.

5.5.3 Supply, storage and tracking of study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Not applicable.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Not applicable.

5.5.6 Rescue medication

Not applicable.

5.5.7 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study. All medications and significant non-drug therapies

(including physical therapy and blood transfusions) administered must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

5.5.8 Prohibited treatment

Not applicable.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion eCRF.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.5.10 Emergency unblinding of treatment assignment

Not applicable.

5.5.11 Study completion and post-study treatment

Patients identified in study CSPP100A2365 as having primary hypertension should complete Visit 18 with assessments. Patients identified in study CSPP100A2365 as having secondary hypertension should complete Visit 19 with assessments. The study will end when all enrolled patients have completed last visit, last assessment.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 Assessment schedule

Visit	**C[4]**	**LT17[1]**	**LT18**	**LT19[3]**
Week		**52**	**104**	**156**
Informed consent/child assent	S	X		
Height	D	X	X	X
Weight	D	X	X	X
Concomitant Medication	D	X	X	X
Neurocognitive Evaluation	D		X[3]	X
Chemistry	D		X[3]	X
Study Completion Form	D		X[2]	X

[1] Extension 2 – Visit LT (long term) 17 should occur on the same day as CSPP100A2365E1 "end of study" V16. Data for other identified evaluations will be obtained from Study CSPP100A2365E1.

[2] Visit LT18 is the end of study visit for patients identified in the core study (CSPP100A2365) as having primary hypertension.

[3] For patients with secondary hypertension only.

[4] C is the category; D = eCRF data, S = source document data

6.1 Information to be collected on screening failures

Not applicable.

6.2 Patient demographics/other baseline characteristics

Patient demographic data and baseline characteristic data will have been collected in study CSPP100A2365. The stratifications applied in the core study will remain in place.

6.3 Treatment exposure and compliance

Not applicable.

6.4 Efficacy

Not applicable.

6.5 Safety

6.5.1 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at all visits. BMI will be derived.

6.5.2 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.3 Clinical chemistry

Serum creatinine, blood urea, sodium, potassium, chloride and calcium will be measured at LT Visits 18 and 19 (patients with secondary hypertension only).

6.5.4 Pregnancy and assessments of fertility

Not applicable.

6.5.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

6.6.1 Neurocognitive evaluation

All patients who were determined to have secondary hypertension in study CSPP100A2365 and have a baseline (Visit 2) neurocognitive assessment will receive a neurocognitive assessment at LT V18 and LT V19.

The neurocognitive assessment of development will include assessment of the following abilities:

- Attention
- Processing speed
- Working memory
- Motor speed

These assessments were chosen based on their validity and reliability, ease and efficiency of administration and scoring by non-psychologists, availability, appropriateness for the age span included in this study and ability to be repeated without significant practice effect (defined as improvement in performance based solely on previous exposure to or practice with the test). A manual for standardized administration of the neurocognitive evaluation and scoring procedures for all assessments will be provided separately to each site. The same battery of tests administered in the same order, where possible, will be used for each patient.

Appendix 2 further outlines the neurocognitive assessment of development as it applies to this protocol and study population.

6.6.2 Resource utilization

Not applicable.

6.6.3 Health-related Quality of Life

Not applicable.

6.6.4 Pharmacokinetics

Not applicable.

6.6.5 Pharmacogenetics/pharmacogenomics

Not applicable.

6.6.6 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

This trial will **only collect the occurrence of serious adverse events** as defined below and in Section 7.2. An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring until 30 days after the patient has completed study CSPP100A2365E1 (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Within this 30 day period, recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurred. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

SAE information is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Pregnancies

Not applicable.

8 Data review and database management

8.1 Site monitoring

A Novartis representative will review this protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the

patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

CRO staff working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff to make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to the Novartis designated CRO.

9 Data analysis

Unless otherwise stated, baseline refers to the core study (CSPP100A2365) baseline and treatment regimen to what was taken in CSPP100A2365E1 study.

9.1 Analysis sets

The enrolled to follow-up set (EFS) will consist of all patients who sign the informed consent form for CSPP100A2365E2 study.

9.2 Patient demographics and other baseline characteristics

Patient demographics and relevant baseline characteristics will be obtained from the core study (CSPP100A2365) and summarized for EFS by treatment regimen in CSPP100A2365E1. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, median minimum and maximum) and categorical variables will be summarized with frequency by treatment regimen in CSPP100A2365E1.

9.3 Treatments

Concomitant medication and significant non-drug therapies will be summarized with frequency for EFS by treatment regimen in CSPP100A2365E1.

9.4 Analysis of the primary variable(s)

9.4.1 Variable

The primary assessment is the reporting of changes in weight, height and neurocognitive assessments for enrolled to follow-up set (EFS).

9.4.2 Statistical model, hypothesis, and method of analysis

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) of baseline, post-baseline values and changes from baseline will be summarized by treatment regimen in CSPP100A2365E1 and visit for EFS.

For the superiority assessment of change in weight, the null hypothesis to be tested is that the mean change of weight in the aliskiren regimen is equal to that in the enalapril regimen, versus the alternative hypothesis that they are not equal:

H_0: $\mu_1 = \mu_2$ versus H_1: $\mu_1 \neq \mu_2$

The statistical test for change from baseline in weight will be performed using an analysis of covariance (ANCOVA) model with treatment regimen, region (US, Euro), age strata (6 to 11 years, 12 to 17 years), and hypertension etiology (primary, secondary) as factors, and with baseline weight as covariate. The statistical test will be made at two-sided significance level of 0.05. The 95% confidence interval for the pairwise comparison will be provided.

Changes from baseline in height and derived BMI will be analyzed using the similar model.

9.4.3 Handling of missing values/censoring/discontinuations

Not planned.

9.4.4 Supportive analyses

Not planned.

9.5 Analysis of secondary variables

9.5.1 Key secondary variables

Not applicable.

9.5.2 Efficacy variables

Not applicable.

9.5.3 Safety variables

The assessment of safety will be based primarily on the frequency of SAEs occurring within the first 30 days after the patient has completed study CSPP100A2365E1 (defined as time of last dose of study drug taken or last visit whichever is later). SAEs experienced after this 30 day period are to be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Occurrence and frequency of SAEs collected within this timeframe will be summarized by treatment regimen in CSPP100A2365E1, primary organ class and preferred term, and will be narrated if any.

Summary statistics by treatment regimen in CSPP100A2365E1 and visit for laboratory values (in patients with secondary hypertension only) will be provided. Occurrence of significant abnormalities in laboratory values from baseline will be summarized by treatment regimen in CSPP100A2365E1.

9.5.4 Pharmacokinetics

Not applicable.

9.5.5 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.6 Biomarkers

Not applicable.

9.5.7 PK/PD

Not applicable.

9.6 Sample size calculation

All patients who successfully complete CSPP100A2365 and 2365E1 studies will be offered enrollment into the study CSPP100A2365E2 for 52 or 104 weeks follow-up.

9.7 Power for analysis of key secondary variables

Not applicable.

9.8 Interim analyses

Not applicable.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

12 References

Available upon request.

Bornkamp B, Pinheiro J, Bretz F. (2009) MCPMod - An R Package for the design and analysis of dose-finding studies. Journal of Statistical Software; 29 (7): 1-23.

Frampton JE, Curran MP. (2007) Aliskiren: A review of its use in the management of hypertension. Drugs; 67 (12): 1767-1792.

Jensen C, Herold P, Brunner HR. (2008) Aliskiren: The first renin inhibitor for clinical treatment. Nature Reviews; 7: 399-410.

McMurray JV, Pitt B, Latini R, et al. (2008) Effects of the oral renin inhibitor aliskiren in patients with symptomatic heart failure. Circ Heart Fail; 1: 17 – 24.

Muldoon MF, Waldstein SR, Ryan CM, et al. (2002) Effects of six anti-hypertensive medications on cognitive performance. J Hypertens; 20(8):1643-52.

Murray MD, Lane KA, Gao S, et al. (2002) Preservation of cognitive function with antihypertensive medications: a longitudinal analysis of a community-based sample of African Americans. Arc Inter Med; 162(18): 2090-6.

NHLBI (2004) The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents: National High Blood Pressure Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics; 114: 555 – 576.

Parving H, Persson F, Lewis JB, et al. (2008) Aliskiren combined with losartan in Type 2 diabetes and nephropathy. N Engl J Med; 358: 2433 – 46.

Sorof JM, Lai D, Turner J, et al. (2004) Overweight, ethnicity, and the prevalence of hypertension in school-aged children. Pediatrics; 113: 475-482.

Starr JM, Whalley LJ, Deary IJ. (1996) The effects of antihypertensive treatment on cognitive function: results from the HOPE study. J Am Ger Soc; 44(4): 411-5.

Tapaninen T, Backman JT, Kurkinen KJ, et al. (2010) Itraconazole, a P-Glycoprotein and CYP3A4 inhibitor, markedly raises the plasma concentrations and enhances the renin inhibiting effect of aliskiren. J Clin Pharmacol; published online 16 April 2010, DOI: 10.1177/0091270010365885.

Weinberger M. (2008) Are children doomed by what they eat and drink? Hypertension; 51: 615-616.

Williams B, Poulter NR, Brown MJ, et al. (2004) Guidelines for management of hypertension: report of the forth working party of the British Hypertension Society, 2004 BHS IV. J Hum Hypertens; 18(3): 139 – 185.

13 Appendix 1: Clinically notable laboratory values

Table 13-1 Clinically notable laboratory values

Parameter	CU Alert Value	CU Units	SI Alert Value	SI Units
Chemistry				
BUN	>50% increase	mg/dL	>50% increase	mmol/L
Creatinine	>50% increase	mg/dL	>50% increase	umol/L
Sodium	>5% increase	mEq/L	>5% increase	mmol/L
Potassium	>20% increase, >20% decrease, or any value >5.3	mEq/L	>20% increase, >20% decrease, or any value >5.3	mmol/L
Chloride	>10% increase, >10% decrease	mEq/L	>10% increase, >10% decrease	mmol/L
Calcium	>10% increase, >10% decrease	mg/dL	>10% increase, >10% decrease	mmol/L

Note: Clinically notable laboratory values drawn after LT Visit 17 will be flagged on the laboratory reports sent to sites by the Central Laboratory at the same time that Novartis is notified (see Central Laboratory Manual for the Notable Laboratory Value Notification Process).

14 Appendix 2: Neurocognitive assessment

The neurocognitive assessment of development is a sensitive marker of a cognitive change resulting from an insult to the brain such as head injury, toxin exposure and medication effect. Although it was previously thought that treatment with antihypertensive medication was a risk for cognitive decline in adults, there is more recent evidence that the treatment of hypertension with antihypertensive medication can improve functioning and has no effect on cognition or may be associated with mild decrements in performance on specific tasks of motor speed (Muldoon, et al 2002); (Murray, et al 2002); (Star, et al 1996). Neurocognitive growth and development will be monitored during the investigation of aliskiren in the treatment of pediatric hypertension.

The following neurocognitive evaluations will be documented at LT V18 and at LT V19 in patients with secondary hypertension only.

Table 14-1 Neurocognitive tests

Function	Test	Applicable age for test	Administration time
Attention	CMS Digits Forward	5 – 16	2 minutes
Processing speed	WJIII Visual Matching	3 +	5 minutes
Working memory	CMS Digits Backwards CMS Sequences	5 – 16 5 – 16	2 minutes 7 minutes
Motor speed	Timed gait and tapping	6 +	2 minutes

CMS = Children's Memory Scale

WJIII = Woodcock Johnson Tests of cognitive ability

Summary statistics of the raw scores and a frequency table for the number of patients with changes from LT V16 of raw test scores (positive, negative or no change) will be presented. No formal inferential analysis is planned.