Document Type:	Statistical Analysis Plan
Official Title:	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
NCT Number:	NCT01420068
Document Release Date:	Final SAP: 18 October 2017

[redacted]

[redacted]

Document Information	
Customer:	Noden Pharma, [redacted]
Protocol Number:	CSPP100A_CSPP100A2365E2
Quanticate Project Number:	Q_02857
Product/Document Title:	Statistical Analysis Plan and Tables, Listing and Figures
Version Number:	2.0.0
Version Date:	18 Oct 2017

The approval of the above mentioned document(s) implies that the document(s) has been reviewed and that the approver is in complete agreement with the content.

[redacted] AUTHOR
Name: [redacted]
Position: [redacted]

[redacted]
Signature

18 OCT 2017
Date

NODEN PHARMA APPROVAL
Name: [redacted]

[redacted]
Signature

25 OCT 2017
Date

Clinical Development

SPP100A/Aliskiren (Tekturna®/Rasilez®)

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

RAP Module 3 – Detailed Statistical Methodology

Author: [redacted]

Document type: SAP Documentation

Document status: Version 2.0.0

Release date: 18-10-2017

Number of pages: 9

Table of contents

Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
Draft V0.1	21JUL2015	First draft version
Draft V0.2	27NOV2015	Updated as per discussion in RAP review meeting
Final 1.0	18MAR2016	First final version
Final 2.0.0	18OCT2017	Changes were made throughout text to aid analysis and presentation of data to those defined in SAP version 1.0 dated 18 March 2016, keeping in line with the final protocol. The primary analysis from v1.0 was changed so that it is an analysis of change from baseline to Visit 18, rather than an analysis of change from baseline to end of study. Analysis of change from baseline to end of study is not considered appropriate as the two groups of patients (primary and secondary hypertensive) have different end of study visits. A secondary analysis was added for the change from baseline to end of study by hypertension group.

1 Statistical methods (will be incorporated into section 9.7 of CSR)

Data will be analyzed by [redacted] according to the data analysis section 9 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

1.1 Development of the Current Version

The Version CSPP100A_CSPP100A2365E2_RAP_Module_3_V2.0.0 is developed under the instruction of current sponsor Noden Pharma whose authorship is effective from 01 September 2017. The current version is developed based on CSPP100A_CSPP100A2365E2_RAP_Module_3_V1.0.0 by Novartis.

1.2 Statistical and analytical plans

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 were followed for 52 weeks (1 year) after the completion of study CSPP100A2365E1(aliskiren vs. enalapril) . Patients identified in study CSPP100A2365 to have secondary hypertension were followed for 104 weeks (2 years) after the completion of study CSPP100A2365E1. The assessment of growth and development through height and weight measurement was performed on all patients for 52 weeks, after which patients with primary hypertension completed the study. The assessment of patients with secondary hypertension continued for an additional 52 weeks during which growth and development was continually assessed with added neurocognitive and renal function evaluations.

The study population consists of male and female hypertensive pediatric patients who have completed study CSPP100A2365E1. 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 at Visit 2, baseline age group, hypertension etiology (primary or secondary) and region. Centers (approximately 70) from the US, EU and ROW participating in CSPP100A2365 and CSPP100A2365E1 will participate in this off-therapy follow-up.

The follow up visits 52 and 104 weeks of the study follow up will be referred to as Week 104 and Week 156, respectively, in the CSPP100A2365E2 study documents and output.

The primary objective of the study is

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

This objective will be evaluated by assessing the following endpoints:

Safety endpoints:

All Patients:

- At LT (long term) weeks 104 and 156 height and weight measurements and derived BMI as weight (kg)/(height (m))^2.

Patients with Secondary Hypertension:

- At LT weeks 104 and 156 renal function evaluation

Other endpoints:

- At LT weeks 104 and 156 neurocognitive evaluation for secondary hypertensive patients only

Patient demographics and relevant baseline characteristics will be obtained from the core study (CSPP100A2365) and summarized by actual treatment regimen at the end of study CSPP100A2365E1 (aliskiren vs. enalapril). Key measurements (weight, height, BMI and neurocognitive assessments), both raw values and their changes from baseline, will be summarized by visit (as recorded in the CRF) and treatment regimen. Safety observations will be summarized by treatment regimen.

Treatment regimen in this document refers to actual treatment regimen at the end of study CSPP100A2365E1 (aliskiren vs. enalapril)

Unless stated otherwise, baseline refers to the core study (CSPP100A2365) baseline.

Unless stated otherwise, statistical tests will be carried out at a two-sided significance level of 0.05 using SAS® statistical software ([redacted].) version 9.3 or higher.

1.2.1 Population of analysis

The **Enrolled to Follow-up Set** (EFS) will consist of all patients who sign the informed consent form for CSPP100A2365E2. Patients will be analyzed according to the treatment received in the CSPP100A2365E1 study.

1.2.2 Protocol deviations

A listing of protocol deviations will be produced by treatment regimen including the date and study day of the deviation occurrence.

1.2.3 Medical history

The number of patients with relevant medical history and/or continuing medical conditions collected at Week 2 (Visit 6) of the extension study (CSPP100A2365E1) and adverse events collected during the extension study (CSPP100A2365E1), regardless of whether they are resolved or on-going at the start of the CSPP100A2365E2, will be combined and summarized by primary system organ class, preferred term, and treatment regimen for the EFS. If there are

any on-going AEs in the CSPP100A2365E1 study which are on-going at the start of CSPP100A2365E2 and have changed in severity during CSPP100A2365E2, it is assumed that they will be reported as new AEs in CSPP100A2365E2.

1.2.4 Baseline and demographic characteristics

Patient demographics and baseline characteristics will be summarized by treatment regimen for the enrolled to follow-up set. Continuous variables will be summarized with descriptive statistics (n, mean, standard deviation, Q1, median, Q3, minimum, maximum). Categorical variables will be summarized with counts and percentages. In addition, all demographic and baseline data will be listed by patient and treatment regimen.

The demographic and baseline characteristics collected at Study CSPP100A2365 baseline (Visit 2) include:

Categorical variables:

- Age groups (6-11 years, 12-17 years, and 6 – 12 years, 13-17 years)
- Sex (Male, Female)
- Race (Caucasian, Asian, Black, Native American, Pacific Islander and Other)
- Ethnicity (Hispanic/Latino, Chinese, Indian (Indian subcontinent), Japanese, Mixed ethnicity and Other)
- Weight category (≥20 kg and < 50kg, ≥50 kg and <80kg, ≥80 kg and ≤150 kg)
- Hypertension etiology (primary, secondary)
- eGFR category (<60, ≥60 ml/min/SA and <90, ≥90 ml/min/SA)
- BMI category (< 95^{th} percentile and ≥ 95^{th} percentile)

Continuous variables:

- Age (years), Height (cm), Weight (kg), BMI (Kg/m^2), eGFR (ml/min/SA)
- msSBP (mmHg), msDBP (mmHg), sitting pulse (bpm), standing systolic/diastolic blood pressure (mmHg)

1.2.5 Concomitant or prior medication

Concomitant medications and significant non-drug therapies will be summarized with counts and percentages by treatment regimen for the EFS.

Concomitant medications from the extension study (CSPP100A2365E1), or from the original study CSPP100A2365 that stopped before the start of this study (CSPP100A2365E2) will be summarized as prior medications using counts and percentages by treatment regimen for the EFS.

1.2.6 Analysis of primary variables

The primary endpoints are the changes in weight, height, BMI and neurocognitive assessments from baseline to visit LT 18 for the EFS.

Baseline is defined as the baseline observation taken from the core CSPP100A2365 study. The changes from baseline in primary endpoints will be calculated as value at visit LT 18 – value at Baseline.

End of CSPP100A2365E2 study is visit LT 18 for the primary hypertension group and visit LT 19 for the secondary hypertension group. Visit LT 17 is end of study visit from CSPP100A2365E1 study.

The secondary endpoints are the changes in weight, height, BMI and neurocognitive assessments from baseline to end of study, by hypertension group.

The changes from baseline in secondary endpoints will be calculated as (value at the End of Study visit) – (value at Baseline).

1.2.6.1 Weight, Height and BMI

The primary endpoint data will be summarised using the descriptive statistics (n, mean, standard deviation, Q1, median, Q3, minimum and maximum). The baseline values, post-baseline values, and changes from baseline will be summarized by treatment regimen used in the CSPP100A2365E1 and visit for the EFS. For patients with primary hypertension, changes from baseline to visit LT 17 (week 52) and visit LT 18 (week 104) will be summarised. For patients with secondary hypertension who are not followed up after LT 17, changes from baseline to visit LT 17 (week 52), visit LT 18 (week 104) and visit LT 19 (week 156) will be summarised.

Primary analysis

The primary analysis will be a superiority assessment of change in weight, height and BMI from baseline to visit LT 18. For the purpose of describing the analysis of primary variables, weight will be used to describe the analysis. Height and BMI will be analysed in exactly the same fashion as described for the weight in this section. The null hypothesis to be tested is that the mean change of weight at visit LT 18, in the aliskiren regimen is equal to that in the enalapril regimen, versus the alternative hypothesis that they are not equal:

$H0: \mu1 = \mu2$ versus $H1: \mu1 \neq \mu2$

Where $\mu1$ and $\mu2$ are the mean of the change in weight from baseline to visit LT 18, for aliskiren and enalapril, respectively. This hypothesis will be tested at a two-sided significance level of 0.05 using an analysis of covariance (ANCOVA) model with treatment regimen, region (US, Euro), age strata at baseline (6 to 11 years, 12 to 17 years), and hypertension etiology (primary, secondary) as factors, and with baseline weight as the baseline covariate (refer to appendix 1). The estimated change from baseline and the 95% confidence interval for $\mu1 - \mu2$ will be presented. For the analysis of change in height, the baseline height will be included as the baseline covariate in the model. For the analysis of change in BMI, baseline BMI will be included as the baseline covariate in the model. Missing values will not be imputed.

No multiplicity adjustment will be performed.

Sensitivity analysis

A sensitivity analysis will be performed by repeating the primary analysis by imputing any missing values of weight/height/BMI at visit LT 18 by LOCF method from visit LT 17. Other missing values in the data will not be imputed.

Secondary analysis

The analysis of secondary endpoints will be similar to the primary analysis. The secondary endpoints, changes in weight, height, BMI from baseline to end of study, will be analysed by hypertension group.

The estimated change from baseline and the 95% confidence interval for the difference between treatment groups at end of study will be presented for each hypertension group.

1.2.6.2 Neurocognitive assessments

Neurocognitive assessments were performed only for patients with secondary hypertension at visit LT 18 (week 104) and visit LT 19 (week 156) in this study and therefore, the corresponding tables will include the secondary hypertension patients only.

Descriptive statistics for visit LT 17 (week 52), visit LT 18 (week 104), visit LT 19 (week 156) and change from baseline and visit LT 17 (week 52) of neurocognitive development evaluations collected will be presented. Visit LT 17(week 52) will be end of study visit from CSPP100A2365E1 study. In addition, number and percentage of patients with positive change, negative change and no change in percentages from baseline and visit LT 17 (week 52) to visit LT 18 (week 104), and visit LT 19 (week 156) for all neurocognitive tests will be presented.

1.2.7 Analysis of secondary variables

Adverse events

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 were reported to Novartis only if the investigator suspected a causal relationship to the study drug.

Occurrence and frequency of SAEs collected will be summarized by treatment regimen in CSPP100A2365E1, primary organ class and preferred term

Clinical chemistry

Laboratory data will be summarized in SI units at baseline, visit LT 18 (week 104), and visit LT 19 (week 156) for absolute values and changes from baseline by treatment regimen. Serum creatinine, blood urea (BUN), sodium, potassium, chloride and calcium will be measured at LT Visits 18 (week 104) and 19 (week 156) (patients with secondary hypertension only). As the evaluations are only specified for patients with secondary

hypertension as per protocol, only patients with secondary hypertension will be included in the summary tables.

The incidence of patients with notable BUN, creatinine, sodium, potassium, chloride, and calcium values based on pre-specified percent change from baseline (defined in Table 1-1 below) will be summarized. In addition, shift tables, based on normal ranges, from baseline to post-baseline assessments will be provided by treatment regimen. Listings of patients with notable laboratory values based on pre-specified percent change from baseline will be provided by laboratory parameter, treatment regimen, and patient number.

Table 1-1 Notable Laboratory Abnormalities

Parameter	Conventional Alert Value	Conventional 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

In addition, the number and percentage of patients with clinically significant values (BUN: >14.28 mmol/L; creatinine > 176.8 µmol/L; potassium <3.5 mmol/L, > 5.5 mmol/L, or ≥ 6 mmol/L) at any post-baseline laboratory evaluation will also be presented.

In addition, clinical chemistry data will be listed by patient and treatment regimen.

1.3 Determination of sample size

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

Appendix 1: SAS code for ANCOVA model

```
Ods graphics on;
proc mixed data=one;
  class treatment region age etiology;
  model change = treatment region age etiology baseline_covariate /
solution residual;
  estimate 'Aliskiren vs Enalapril' treatment 1 -1/CL;
run;
ods graphics off;
```