CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA: Supplement:	210709
Drug Name:	SPP100/Aliskiren (Tekturna®/Rasilez®)
Indication(s):	Hypertension
Applicant:	Noden Pharma DAC
Date(s):	April 6, 2017
Review Priority:	Priority
Biometrics Division:	DBI/OB/OTS
Statistical Reviewer:	Fanhui Kong, PhD
Concurring Reviewers:	Hsien Ming Hung, PhD
Medical Division:	Division of Cardiovascular and Renal Products
Clinical Team:	Christine Garnett, MD.
CDTL	Aliza Thompson, MD.
Project Manager:	Maryam Kord Bacheh Changi

Keywords: Mean Sitting Diastolic Blood Pressure (msDBP), Mean Sitting Systolic Blood Pressure (msSBP), Analysis of Covariance (ANCOVA), Last Observation Carried Forward (LOCF)

Table of Contents

1 EXECUTIVE SUMMARY

The sponsor submitted a pediatric sNDA in fulfillment of the Written Request (WR) and the Pediatric Research Equity Act (PREA) commitments. The submission consisted of three studies: an 8-day open-label, multiple-dose PK study; a multicenter, randomized, double-blind, 8-week efficacy and safety study; and a long-term safety, follow-up study. The pivotal study SPP100A2365 was a two-phase, 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 primary efficacy analysis was the dose-response determined at Phase 1 by the statistical significance of the slope of the change in msSBP from baseline to the Week 4. The analysis results in Phase 2 were used to evaluate whether there was a blood pressure (BP) effect due to placebo withdrawal on the changes in msSBP from the end of Phase 1 to the end of Phase 2.

A sample size of 275 patients was planned in Study SPP100A2365 to be randomized in Phase 1 so 255 and 237 patients were expected to complete Phase 1 and Phase 2 of the study. In reality, 268 patients were randomized in Phase 1, and 260 completed Phase 1 and were randomized in Phase 2. The trial was designed to test a 5.5 mmHg difference in the primary endpoint between low and high dose levels in both phases with 90% power. This did not satisfy the requirement of the Written Request of the Agency that the trial must be designed to detect a "clinically meaningful" treatment benefit on the primary endpoint of a 3-mmHg effect (placebo subtracted change from baseline) on either systolic or diastolic blood pressure. However, sponsor's sample size recalculation suggested that the sample size would have to be increased to 907 randomized patients to satisfy such a requirement, which would have been very difficult to recruit in a reasonable timeframe. Strictly speaking, the study sample size did not meet the terms of the WR. However, since the study results can be viewed as interpretable, the Agency considers the study as being conducted fairly in response to the WR.

The primary efficacy analysis in Phase 1 of the pivotal study yielded a slope estimate of -0.17 (mmHg per unit increase in dose ratio) for the dose-response curve for the change from baseline to the end of Phase 1 in msSBP. The negative slope estimate was statistically different from zero ($p<0.001$), indicating a significant dose-response. According to the study design, this result provided the evidence supporting the effectiveness of aliskiren in the treatment of hypertension in pediatric patients 6-17 years of age. The least square mean (LSM) change in msSBP from the end of Phase 1 to the end of Phase 2 in the pooled aliskiren mid/high dose groups and the corresponding pooled placebo groups gave a difference of -1.72 mmHg in favor of aliskiren but was not statistically significant ($p= 0.1152$). On the other hand, between-group comparisons of the primary endpoint in Phase 2 using the analysis of covariance (ANCOVA) for all 3 dose groups gave a numerical difference of -2.70 mmHg between the aliskiren high dose group and the corresponding placebo group. The numerical difference was not statistical significant ($p=0.0563$).

2 INTRODUCTION

Tekturna® (aliskiren), as a direct renin inhibitor, was first approved by FDA on March 5, 2007. It is currently available as a tablet formulation in the United States for the treatment of hypertension in adult patients, except in patients who have type 2 diabetes mellitus and are receiving an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker. This study was designed to evaluate the efficacy and safety of aliskiren in the pediatric population aged 6-17 years in order to support the registration of aliskiren monotherapy for the treatment of hypertension in this population.

This submission consists of a pediatric supplemental New Drug Application (sNDA) to NDA 21985. It consists of three clinical studies to fulfil the WR and the PREA commitments, along with relevant Chemistry, Manufacturing and Controls (CMC) information. Study SPP100A2256 was an 8-day open-label, multiple-dose, multi-center study to evaluate the safety/tolerability and Pharmacokinetic (PK) of aliskiren in the hypotension patient population of 6-17 years of age. The pivotal Study SPP100A2365 was a multicenter, randomized, double-blind, 8-week study to evaluate the dose response, efficacy and safety of aliskiren in the same population. It was followed by a 52-week extension study, Study SPP100A2365E1, to evaluate the long-term safety, tolerability and efficacy of aliskiren compared to enalapril in the same patient population. As the pivotal study for the efficacy and safety evaluation of aliskiren in hypertensive patients 6-17 years of age, Study SPP100A2365 is selected for full statistical review and evaluation.

2.1 Overview

Tekturna® (aliskiren) was first approved by FDA on March 5, 2007 in the United States for the treatment of hypertension in adult patients. The sponsor was requested to conduct pediatric studies in patients 6 to 17 years of age to fulfill requirements under the PREA as specified in the WR. The WR was initially issued on May 13, 2008, and amended on August 6, 2012. On January 28, 2016, the sponsor submitted a pediatric sNDA as requested in the WR. As advised by the Agency afterward, the sponsor submitted it as a new pediatrics formulation which was considered as a new NDA.

As the pivotal study of the submission, Study SPP100A2365 was a multicenter, randomized, double-blind, 8-week study consisted of two phases. In Phase 1, the dose response of 3 aliskiren dose groups, low, mid, and high doses were evaluated according to three weight categories. It was followed by Phase 2 of a 4 week placebo controlled withdrawal phase. The primary dose-response relationship was determined at Phase 1 by the statistical significance of the slope of the change from baseline in msSBP. The analysis results in Phase 2 were used to evaluate whether there was a BP effect due to placebo withdrawal on the changes in msSBP from the end of Phase 1 to the end of Phase 2.

According to the final protocol, a sample size of 275 patients was planned to be randomized in Phase 1 with 255 and 237 patients expected to complete Phase 1 and Phase 2. In total, 268 patients were randomized in Phase 1, and 260 patients completed Phase 1 and were randomized in Phase 2. The primary efficacy analysis in Phase 1 of the pivotal study yielded a slope estimate

of -0.17 (mmHg per unit increase in dose ratio) for the dose-response curve for the primary endpoint. The negative slope estimate was statistically different from zero ($p<0.001$) and is considered as the evidence supporting the effectiveness of aliskiren in the treatment of hypertension in pediatric patients 6-17 years of age.

2.2 Data Sources

The sponsor's electronic data sources were stored in the directory of \\CDSESUB1\evsprod\NDA210709\0000 of the Center's electronic document room of the Agency. Data sources include all material reviewed, i.e., study reports, raw data sets in SDTM format, analysis data sets in ADAM format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc. The SAS data sets are stored in the directory of \\CDSESUB1\evsprod\NDA210709\0000\m5\datasets\. The analysis software is also stored in the same directory.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor provided high quality data sets along with the programs to produce the analysis data sets and efficacy results which allow the statistical reviewer to duplicate the efficacy results. According to Clinical Study Report (CSR), randomization codes and data about all treatment dispensed to the patient and all dosage changes were tracked using an interactive voice randomization system. At the conclusion of the study, the occurrence of any emergency code breaks were determined after return of all code break reports and unused drug supplies to the sponsor. The occurrence of any protocol deviations was determined. After these actions were completed and the database was declared to be complete and accurate, it was locked and the treatment codes were unblinded and made available for data analysis.

The CSR also indicates that all the clinical sites were carefully monitored before initiating the study and during the study to assure that the standard operating procedures (SOPs) and the Good Clinical Practice (GCP) were fully adhered, and that the data entered into the eCRFs were complete and accurate. The investigators were required to maintain source documents for each patient in the study. All information on eCRFs was required to be traceable to these source documents in the patient's file. Internal system (internal processes, clinical development functions/units, etc.), investigator site, and third party/vendors were audited by the Quality Assurance (QA) group comprising of those who were not involved in conducting, monitoring or performing quality control of the clinical trial, according to written QA SOPs.

The Center of Drug Evaluation and Research (CDER) performed a sponsor monitor inspection between November 9, 2012 and November 30, 2012, which included inspections designed to evaluate the conduct of research and to help ensure that the rights, safety and welfare of the human subjects of those studies had been protected.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

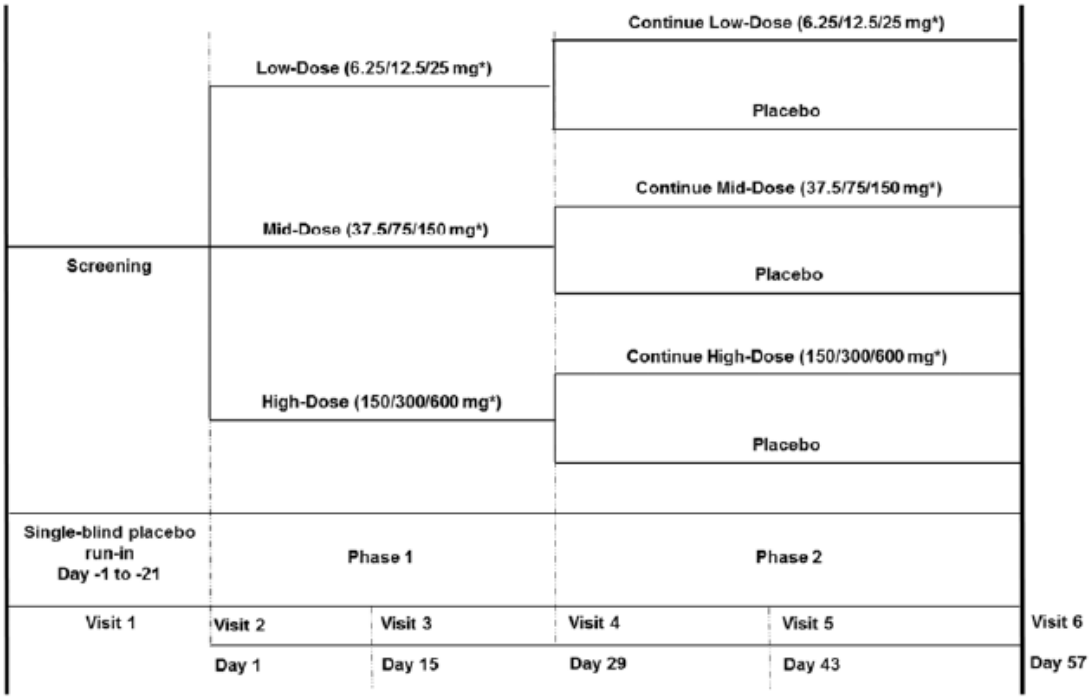
Study SPP100A2365 was a multicenter, randomized, double-blind, 8-week study to evaluate the efficacy and safety of aliskiren in pediatric hypertensive patients 6-17 years of age. After a single-blind placebo wash-out screening phase for up to a maximum of three weeks, the study had two 4-week phases. Phase 1 was a four week 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 their weight. The dose ratios for all three dose groups were the same for the low-weight (≥ 20 to < 50 kg), the mid-weight (≥ 50 kg to < 80 kg) and the high-weight (≥ 80 kg to ≤ 150 kg) patients. The low: mid: high dose ratios in each weight group were 1:6:24. The aliskiren doses selected in the study equate to 0.13-0.31 mg/kg for low dose, 0.75-1.88 mg/kg for mid dose and 3.0-7.5 mg/kg for high dose. Patients were stratified at baseline by weight (≥ 20 to < 50 kg, ≥ 50 kg to < 80 kg, and ≥ 80 kg to ≤ 150 kg), age (6-11 and 12-17 years old), region (US, EU and ROW, as applicable), and by hypertension etiology (primary vs. secondary). Patients were randomized to aliskiren low, mid and high dosing groups in a 2:1:2 ratio based on their weight category. Phase 2 is a randomized, placebo-controlled withdrawal phase of up to four weeks. Patients either continued the aliskiren treatment assigned during Phase I or were switched to placebo. The design of the study is depicted in Figure 3.1.

According to the WR, the trial must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance. An agreement must be obtained on the final statistical analysis plan (SAP), including handling of missing data, prior to 25% enrollment. The study must be powered to be able to detect a “clinically meaningful” treatment benefit on the primary end point of a 3-mmHg effect (placebo subtracted change from baseline) on either systolic or diastolic blood pressure.

The original protocol was finished on December 18, 2009. An amendment was made on January 19, 2010, revised on April 5, 2010, September 29, 2010, and finalized on June 23, 2013. In the protocol, a sample size of 200 patients in Phase 1 was designed to detect a non-zero slope of 0.239 for change from baseline in mean sitting SBP as a linear function of aliskiren dose ratio (1:6:24) at a two-sided significance level of 0.05 with ≥ 90% power. This corresponds to 5.5 mmHg reduction in SBP from low dose to high dose. In Phase 2, a total sample size of 237 patients was required to test a mean sitting SBP of 5.5 mmHg. Given 7% dropout, this required that 275 patients be entered into Phase 1, so that the expected 255 patients would continue into Phase 2. In summary, a sample size of 275 patients was planned to be randomized in Phase 1 with 255 and 237 patients expected to complete Phase 1 and Phase 2.

In total, 268 patients were randomized in Phase 1, all of which were included in the full analysis (FAS1) sets for Phase 1 except for one mis-randomized patient who did not take double blind medication. Overall, 260 patients completed Phase 1 and were randomized in Phase 2 and included the full analysis (FAS2) sets for Phase 2. The first patient was enrolled on June 10, 2010, and the last was enrolled on August 14, 2014.

Figure 3.1 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.
Source: Figure 9-1 in Clinical Study Report: SPP100A2365

Study SPP100A2365 was conducted at a total of 52 sites: 25 in the United States, 4 in Turkey, 4 in Belgium, 1 in Germany, 1 in Poland, 7 in Hungary, 7 in Slovakia, and 2 in Guatemala.

Statistical Comments:

1. *In the statistical analysis plan (SAP) submitted to IND 62976 in October of 2011, the sponsor indicated that the trial was powered for a treatment difference of 5.5 mmHg between aliskiren and placebo instead of 3 mmHg as requested by the WR. In the meantime, the late stage interim analysis of variance would be conducted at 75% of information time in contrast to > 90% of initially planned enrollment as required in the WR. Given the discrepancy between the sponsor's SAP and the requirement of the WR, in August 2013, the Agency warned the sponsor the possibility of precluding granting exclusivity due to the design features. On the other hand, Agency also asked them to provide the technically incomplete summary of the results and would amend the WR if the results provided clinically important information.*

   In July 2014, the sponsor submitted a revised the SAP, reflecting the results of the interim analysis, which took place on March 11, 2014, with 251 randomized patients amounting

to 91.3% of initially planned enrollment. Their sample size recalculation suggested that a study with 90% power to detect a 3 mmHg difference would have increased the sample size to 907 randomized patients, which would have been very difficult to recruit in a reasonable timeframe. The sponsor also suggested that with the standard deviation of 7.96 mmHg in msSBP determined at the interim analysis, a treatment difference of 4.4 mmHg could be detected with 90% power. The sponsor asserted that the study as designed would "allow completion of a comparatively large trial with a high probability of obtaining interpretable and clinically meaningful data in a reasonable timeframe." Strictly speaking, the study sample size did not meet the terms of the WR, the study results can be viewed as interpretable, we consider the study as being conducted fairly in response to the WR.

2. *In the protocol, a penalty-free blinded interim analysis was planned to estimate the variability for the sitting blood pressure when data for approximately 50% and 75% of patients were available to adjust the sample size to ensure 90% power to test the dose response of aliskiren based on a predicted standard deviation. The SAP was submitted in July 2014, revised based on the interim analysis of 91.3% of patients enrolled. This indicates that the SAP was not finalized prior to 25% enrollment as required in the WR. This seems to be a concern.*

Primary and Secondary Endpoints:

As required in the WR, the primary efficacy endpoint for Phase 1 was the change in msSBP from baseline to end of Phase 1, as measured by office blood pressure reading. Primary efficacy endpoint for Phase 2 was the change in msSBP from end of Phase 1 to end of Phase 2, as measured by office blood pressure reading.

Secondary efficacy endpoints for the two phases were the changes in msDBP and MAP from baseline to end of Phase 1 and from end of Phase 1 to end of Phase 2, percentage of patients achieving a positive treatment response (defined as a msSBP at the end of Phase 1 < 95th percentile (for age, gender and height) or a 7 mmHg decrease in msSBP from the baseline), changes from baseline in post-dosing 24-hour mean ambulatory systolic and diastolic blood pressure, daytime and nighttime ambulatory systolic blood pressure change at the end of Phase 1, and dipper and non-dipper at the end of Phase 2.

3.2.2 Statistical Methodologies

The SAP was finalized on March 11, 2014. The change in msSBP was evaluated for Phase 1 for each dose group separately at the significance level of 0.05. The primary dose-response relationship was evaluated by testing the slope of the dose-response curve for the change from baseline in msSBP at the end of Phase 1. According to the protocol and SAP, if the slope is statistically significant at the two-sided significance level of 0.05, then a difference among the doses is identified. If the test fails to reveal significant differences among the aliskiren doses in Phase 1, then the analyses performed in Phase 2 would be used to further identify whether there is an effect on BP due to placebo wash-out. No alpha adjustment is needed for testing these two hypotheses. The primary efficacy analyses were performed on the FAS1 and FAS2. The FAS

population consisted of all subjects randomized into Phase 1 and Phase 2 of the study. Last observation carried forward (LOCF) was used for the patients dropped out of the study.

In Phase 1, an ANCOVA model was used as the primary analysis to test the slope of the dose-response curve that included weight, age strata, region, and baseline hypertension status (primary vs. secondary) as factors, and baseline msSBP and dose ratio as covariates. The primary efficacy analysis of Phase 2 was to compare between the pooled aliskiren mid/high dose group and the corresponding placebo groups. The changes of msSBP from the end of Phase 1 to the end of Phase 2 between the aliskiren groups and the corresponding placebo arms were analyzed using the ANCOVA model with treatment group, weight category at baseline, age strata, region, and hypertension status (primary vs. secondary) as factors and the end of Phase 1 msSBP as a covariate.

3.2.3 Patient Disposition

Patients in Phase 1 in the three treatment groups had comparable demographic and baseline characteristics, including age, gender, race, weight, and hypertension etiology. Sixty-six percent were male and 73.5% were Caucasian; 11.2% were black; the mean age was 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. Mean weight was 68.6 kg with 58.6% of patients having body mass index (BMI) $\geq 95^{th}$ percentile for their age and gender.

The overall demographic and baseline characteristics for the patients in Phase 2 were similar to those in Phase 1. Most of the baseline demographic parameters between aliskiren and corresponding placebo groups across dose groups in Phase 2 were compatible, except in the distribution of weight and BMI.

Table 3.1 Key Demographic/Baseline Characteristics by Treatment Group for Phase 1 (FAS 1)

Demographic/Baseline Characteristic	ALI Low 6.25/12.5/25mg N=108	ALI Mid 37.5/75/150mg N=54	ALI High 150/300/600mg 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 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%)
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%)
Weight Category (%)				
≥20kg and < 50kg	35 (32.4%)	18 (33.3%)	34 (32.1%)	87 (32.5%)
≥50kg and < 80kg	36 (33.3%)	17 (31.5%)	36 (34.0%)	89 (33.2%)
≥80kg and <150kg	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%)
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%)

Source: Table 11-3 in Clinical Study Report: SPP100A2365

Table 3.2 Key Demographic/Baseline Characteristics by Treatment Group for Phase 2 (FAS 2)

Demographic /Baseline Characteristic	**ALI Low 6.25/12.5 /25mg N=50**	**PLB Low N=57**	**ALI Mid 37.5/75 /150mg N=30**	**PLB Mid N=21**	**ALI High 150/300/ 600mg 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 n (%)							
6-11	22 (44%)	26 (46%)	17 (57%)	8 (38%)	22 (44%)	26 (50%)	121 (47%)
12-17	28 (56%)	31 (54%)	13 (43%)	13 (62%)	28 (56%)	26 (50%)	139 (53%)
Sex n (%)							
Male	31 (62%)	41(72%)	22 (73%)	13(62%)	33 (66%)	32 (62%)	172 (66%)
Female	19 (38%)	16(28%)	8 (27%)	8(38%)	17 (34%)	20 (38%)	88 (34%)
Race n (%)							
Caucasian	38 (76%)	44 (77%)	22 (73%)	15 (71%)	35 (70%)	39 (75%)	193 (74%)
Black	2 (4%)	7 (12%)	4 (13%)	1 (5%)	6 (12%)	7 (14%)	27 (10%)
Native							

American	4 (8%)	3 (5%)	3 (10%)	2 (10%)	3 (6%)	3 (6%)	18 (7%)
Other	6 (12%)	3 (5%)	1 (3%)	3 (14%)	6 (12%)	3 (6%)	22 (9%)
Weight Category							
≥20kg and < 50kg	17 (34%)	15 (26%)	10 (33%)	7 (33%)	14 (28%)	17 (33%)	80 (31%)
≥50kg and < 80kg	20 (40%)	18 (32%)	11 (37%)	5 (24%)	17 (34%)	16 (31%)	87 (34%)
≥80kg and <150kg	13 (26%)	23 (40%)	9 (30%)	9 (43%)	17 (34%)	18 (35%)	89 (34%)
≥150 kg	0 (0%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)	1 (2%)	3 (1%)
BMI status							
< 95th percentile	26 (52%)	23 (40%)	11 (37%)	10 (48%)	22 (44%)	15 (29%)	107 (41%)
≥ 95th percentile	24 (48%)	34 (60%)	19 (63%)	11 (52%)	27 (54%)	37 (71%)	152 (59%)

Source: Table 11-4 in Clinical Study Report: SPP100A2365

The baseline BP levels in Phase 1 were comparable across the 3 treatment groups. In the total randomized population, msSBP was 133.8 mmHg and msDBP was 78.2 mmHg. All BP parameters at Visit 4 were considered as baseline for Phase 2. Baseline BP levels were generally comparable among the 6 treatment groups except for a higher baseline msSBP in the placebo mid dose group (3.4 mmHg difference compared to aliskiren mid dose group).

Table 3.3 Baseline Blood Pressure by Treatment Group for Phase 1 (FAS 1)

Baseline BP	**ALI Low 6.25/12.5/25mg N=108**	**ALI Mid 37.5/75/150mg N=54**	**ALI High 150/300/600mg N=106**	**Total N=268**
msSBP (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
msDBP (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

Source: Table 11-5 in Clinical Study Report: SPP100A2365

Table 3.4 Baseline Blood Pressure by Treatment Group for Phase 2 (FAS 2)

Baseline BP	**ALI Low 6.25/12.5 /25mg N=50**	**PLB Low N=57**	**ALI Mid 37.5/75/150 mg N=30**	**PLB Mid N=21**	**ALI High 150/300/ 600mg N=50**	**PLB High N=52**	**Total N=260**
msSBP (mmHg)							
N	50	57	30	21	50	52	260
Mean	127.7	127.8	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
msDBP (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

Source: Table 11-6 in Clinical Study Report: SPP100A2365

3.2.3.1 Disposition in Phase 1

Of the 268 subjects enrolled in Phase 1, 1 mis-randomized patient who did not take double blind medication and thus was not included in the full analysis (FAS1 and FAS2) sets. The majority of patients completed the study with 260 patients (97.0%) completed Phase 1 and 255 patients (98.1%) completed Phase 2. The rate of discontinuation due to any reason overall during both Phase 1 and 2 was 4.5%. The reasons of withdrawal are depicted in Table 3.5. In Phase 1, 7 patients (2.6%) discontinued from the study. Only 1 patient discontinued due to AE in the aliskiren high dose group.

Table 3.5 Patient Disposition by Treatment Group for Phase 1 (FAS1)

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 as the denominator.
Source: Table 10-1 in Clinical Study Report: SPP100A2365

3.2.3.2 Disposition of Subjects in Phase 2

Of the 260 subjects who participated in Phase 2 of the study, 5 patients (1.9%) discontinued; 4 of these were in the placebo group and 1 in the aliskiren high dose group. One in the aliskiren high dose group and 1 in the placebo high dose group withdrew of consent (0.8%) and AEs (0.8%). The reasons for early withdrawal from Phase 2 are depicted in Table 3.6.

Table 3.6 Patient Disposition by Treatment Group for Phase 2 (FAS2)

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 as the denominator.
Source: Table 10-2 in Clinical Study Report: SPP100A2365

3.2.3.3 Protocol Deviations

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, often with use of Non-steroidal anti-inflammatory drugs (NSAIDS) and visit occurring out of window. 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 3.7 Patient 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 10-3 in Clinical Study Report: SPP100A2365

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 3.8 Patient 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 10-4 in Clinical Study Report: SPP100A2365

3.2.4 Results and Conclusions

Analysis of Phase 1 Primary Efficacy Endpoint

A summary for the primary efficacy endpoint of the changes in msSBP from baseline to the end of Phase 1 is presented in Table 3.9. At the end of Phase 1, there was a statistically significant decrease from baseline in msSBP in all 3 dose groups ($p<0.001$). 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.

Table 3.9 Within Treatment Comparison for the Change from Baseline in msSBP (mmHg) at the End of Phase 1 (FAS1)

Treatment Group	n	Baseline Mean (SE)	Endpoint Mean (SE)	Change from Baseline		
				Mean (SE)	95% CI	p-value†
ALI Low 6.25/12.5/25 mg	108	133.8 (0.88)	128.3 (0.99)	-5.54 (0.78)	(-7.09, -3.99)	<0.001
ALI Mid 37.5/75/150 mg	53	134.2 (1.53)	128.8 (1.59)	-5.42 (1.33)	(-8.09, -2.75)	<0.001
ALI High 150/300/600 mg	104	133.9 (0.93)	124.8 (1.05)	-9.03 (1.01)	(-11.03, -7.03)	<0.001

† indicates statistical significance at 0.05 level.
Source: Table 11-8 in Clinical Study Report: SPP100A2365

The primary efficacy analysis yields a slope estimate of -0.17 (mmHg per unit increase in dose ratio) for the dose-response curve for the change from baseline to the end of Phase 1 in msSBP, as depicted in Table 3.10. The negative slope estimate was statistically different from zero (p<0.001), indicating a significant dose-response. The ANCOVA model yields the LSM change from baseline of -4.78, -5.64 and -8.74 mmHg for the low, mid and high aliskiren dose groups respectively, which are all statistically significant (p<0.001).

Table 3.10 Analysis of Dose-response for the Change from Baseline in msSBP (mmHg) at the End of Phase 1 (FAS1)

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 11-9 in Clinical Study Report: SPP100A2365

Analysis of Phase 2 Primary Efficacy Endpoint

The primary efficacy analysis in the Phase 2 of the study gives a LSM change in msSBP from the end of Phase 1 to the end of Phase 2 in the pooled aliskiren mid/high doses of -2.31 mmHg compared to -0.59 mmHg in placebo pooled from corresponding arms as depicted in Table 3.11. The difference in LSM between these two pooled treatment groups of -1.72 mmHg in favor of aliskiren was not statistically significant (p= 0.1152).

Table 3.11 Between Treatment Comparisons for the Change from the End of Phase 1 in msSBP (mmHg) at the End of Phase 2 (FAS2)

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.
N is the number of FAS2 patients with non-missing measurement at Week 8 or LOCF value.
LSM, 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: Tables 11-11 in Clinical Study Report: SPP100A2365

On the other hand, between-group comparisons of the msSBP change from the end of Phase 1 to the end of Phase 2 were performed using the ANCOVA for all 3 dose groups and the results are depicted in Table 3.12. The LSM change was -2.84 mmHg for the aliskiren high dose group compared to -0.13 mmHg for the corresponding placebo group, showing a numerical difference between this two groups, without being statistical significant (p=0.0563). There were no significant differences between aliskiren and placebo for the low and mid dose groups.

Table 3.12 Between Treatment Comparisons for the Change from the End of Phase 1 in msSBP (mmHg) at the End of Phase 2 (FAS 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

N is the number of FAS2 patients with non-missing measurement at Week 8 or LOCF value.
LSM, confidence interval, and p-value were from the ANCOVA model with 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: Tables 11-12 in Clinical Study Report: SPP100A2365

The reviewer confirmed the efficacy results for both Phase 1 and Phase 2 using the analysis data that were provided by the sponsor. According to the protocol and SAP, if the slope is statistically significant at the two-sided significance level of 0.05, then a difference among the doses is identified. Only if the slope test fails to reveal significant differences among the aliskiren doses in Phase 1, the analyses performed in Phase 2 would be used to further identify whether there is an effect on BP due to placebo wash-out. No alpha adjustment is needed for testing these two hypotheses. So according to the predefined analysis procedure, the study provides statistical evidence supporting the effectiveness of aliskiren in the treatment of hypertension in pediatric patients.

Analyses of Phase 1 Secondary Efficacy Endpoints

On the other hand, the sponsor also provided the efficacy results of the secondary endpoints in both phases as supporting evidence for the effectiveness of aliskiren in the treatment of hypertension in pediatric patients. These included the changes in msDBP and MAP from baseline to the end of Phase 1 and from the end of Phase 1 to the end of Phase 2, percentage of patients achieving a positive treatment response, etc. The efficacy results regarding the changes in msDBP in both Phase 1 and Phase 2 are summarized in the following.

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 dosage (-2.71 mmHg, -4.05 mmHg and -6.33 mmHg for the low, mid and high dose groups, respectively). The msDBP slope analysis yielded a slope estimate of -0.14 (mmHg per unit increase in dose ratio) for the dose-response curve of the change from baseline, as depicted in Table 3-14. The negative slope estimate was statistically significantly different from zero ($p<0.001$), indicating a dose-response for the change from baseline to the end of Phase 1 in msDBP. The LSM change from baseline was statistically significant in all 3 dose levels (-2.17 mmHg, -2.90 mmHg and -5.50 mmHg for the low, mid and high aliskiren doses, respectively).

Table 3-14 Between Treatment Comparisons for Change from Baseline in msDBP (mmHg) at the End of Phase 1 (FAS1)

Response variable	Label	Estimate	p-value	95% confidence interval	R-square
Change in msDBP (mmHg)	Intercept	-0.40		(-3.29, 2.48)	0.2933
	Slope	-0.14	< 0.001	(-0.22, -0.07)	
	Prediction at				
	dose ratio 1	-2.17	0.001	(-3.49, -0.86)	
	dose ratio 6	-2.90	< 0.001	(-4.04, -1.76)	
	dose ratio 24	-5.50	< 0.001	(-6.95, -4.04)	

* For change from baseline to end of Phase 1 in msDBP, the ANCOVA model is fitted with weight, age, region and hypertension etiology as factors and baseline msDBP and dose ratio as covariates.
Source: Tables 11-14 in Clinical Study Report: SPP100A2365

Analyses of Phase 2 Secondary Efficacy Endpoint

At the end of Phase 2, the msDBP tended to increase except in the low dose placebo group. For all the aliskiren groups, there were minimal to small increase in msDBP at the end of Phase 2 (1.27, 0.89 and 0.37 mmHg for the aliskiren low, mid and high dose groups, respectively). The LSM change in msDBP from the end of Phase 1 to the end of Phase 2, using the ANCOVA model was 0.42 mmHg in pooled aliskiren mid/high doses compared to 0.88 mmHg in placebo pooled from corresponding arms (Table 3-14). The difference in LSM between the two pooled treatment groups of -0.46 mmHg in favor of aliskiren was not statistically significant ($p=0.6669$).

Table 3-14 Between Treatment Comparisons for Change from the End of Phase 1 in msDBP (mmHg) at the End of Phase 2 (FAS 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	0.42 (0.854)	0.88 (0.891)	-0.46 (1.055)	(-2.54, 1.63)	0.6669

Aliskiren mid and high dose groups were pooled for analysis.
LSM, confidence interval, and p-value were from the ANCOVA model with weight, age, region, and hypertension etiology as factors and msDBP at end of Phase 1 as a covariate.
* Indicates statistical significance at 0.05 level.
Source: Tables 11-16 in Clinical Study Report: SPP100A2365

3.3 Evaluation of Safety

NA.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses in Phase 1

Subgroup analyses of the change in msSBP from baseline to the end of Phase 1 and from the end of Phase 1 to the end of Phase 2 were performed by the following subgroups: age group (6-11 years vs. 12-17 years), gender (female vs. male), race (Caucasian vs Black vs native American vs others) in the FAS data sets. The subgroups and the subgroup analysis results are depicted in Tables 4.1 and 4.2. All subgroup analyses are considered exploratory.

In Phase 1 as depicted in Table 4.1, the results of the analyses were generally consistent across subgroups, and were similar to those reported for the primary efficacy analysis, as reported in Section 3.2.4. The majority of subgroups had a reduction in msSBP from baseline to the end of Phase 1 for all 3 aliskiren doses. There was a trend to greater mean reductions from baseline with increasing aliskiren dose, supporting the evidence of the dose-response in the overall population. The subgroup results must be interpreted with caution due to small number of patients in some subgroups.

Table 4.1 Subgroup Analysis: Change from Baseline in msSBP (mmHg) in Phase 1 by Treatment and Subgroup (FAS 1)

Subgroup	ALI Low 6.25/12.5/25 mg N=108 Mean (SD), n	ALI Mid 37.5/75/150 mg N=53 Mean (SD), n	ALI High 150/300/600 mg N=104 Mean (SD), n
Age			
6-11 Years	-4.2 (7.56), 49	-2.7 (9.79), 27	-8.1 (10.50), 50
12-17 Years	-6.7 (8.42), 59	-8.3 (8.88), 26	-9.9 (10.09), 54
Gender			
Male	-6.0 (7.95), 73	-5.9 (8.67), 36	-9.3 (9.61), 66
Female	-4.5 (8.44), 35	-4.3 (11.77), 17	-8.6 (11.47), 38
Race			
Caucasian	-5.8 (8.11), 83	-6.5 (9.08), 38	-9.5 (10.12), 75
Black	-0.5 (7.79), 9	-2.3 (12.05), 6	-5.5 (13.90), 14
Native American	-3.1 (6.16), 7	-6.9 (12.10), 5	-11.2 (4.97), 6
Other	-10.5 (7.36), 9	1.6 (8.39), 4	-9.0 (7.49), 9

Source: Tables 11-23 in Clinical Study Report: SPP100A2365

4.2 Subgroup Analyses in Phase 2

As depicted in Table 4.2, reductions in msSBP at the end of Phase 2 were generally consistent across subgroups regarding age, gender, race, and also in consistent with the results in the overall population as described in Section 3.2.4. The subgroup results must be interpreted with caution due to small number of patients in some subgroups.

Table 4.2 Subgroup analysis: Change in msSBP (mmHg) from the End of Phase 1 to the End of Phase 2 by Treatment and Subgroup (FAS 2)

Subgroup	ALI Low 6.25/12.5/25 mg N=50 Mean (SD), n	PLB Low N=57 Mean (SD), n	ALI Mid 37.5/75/150 mg N=30 Mean (SD), n	PLB Mid N=21 Mean (SD), n	ALI High 150/300/600 mg N=49 Mean (SD), n	PLB High N=52 Mean (SD), n
Age						
6-11 Years	-1.1 (7.08), 22	-1.0 (9.93), 26	-2.2 (7.13), 17	-3.6 (6.58), 8	-1.8 (8.09), 22	1.2 (8.74), 26
12-17 Years	-0.1 (6.48), 28	-0.4 (9.24), 31	-3.1 (4.75), 13	-2.5 (7.14), 13	-2.1 (7.13), 27	1.0 (8.51), 26
Gender						
Male	0.0 (6.93), 31	1.0 (9.69), 41	-2.5 (5.30), 22	-2.8 (4.15), 13	-1.2 (8.11), 32	2.0 (7.20), 32
Female	-1.4 (6.37), 19	-4.8 (7.72), 16	-2.7 (8.46), 8	-3.1 (10.10), 8	-3.5 (6.10), 17	-0.3 (10.40), 20
Race						
Caucasian	-0.6 (7.00), 38	-0.4 (9.97), 44	-2.4 (5.97), 22	-2.1 (7.19), 15	-1.1 (7.16), 34	1.4 (8.22), 39
Black	3.2 (7.78), 2	-2.7 (9.14), 7	-4.7 (4.79), 4	-11.3 (NA), 1	-2.2 (11.30), 6	0.0 (7.04), 7
Native American	-1.3 (4.85), 4	-2.0 (6.36), 3	2.7 (4.18), 3	-7.3 (7.54), 2	-7.1 (8.90), 3	-4.9 (8.17), 3
Other	-0.4 (6.70), 6	2.2 (7.46), 3	-14.3 (NA), 1	-1.1 (2.36), 3	-4.2 (3.79), 6	5.3 (16.58), 3

Source: Tables 11-24 in Clinical Study Report: SPP100A2365

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

NA

5.2 Collective Evidence

The sponsor submitted a pediatric sNDA in fulfillment of the WR and the PREA commitments. The submission consisted of three studies: an 8-day open-label, multiple-dose PK study; a multicenter, randomized, double-blind, 8-week efficacy and safety study; and a long-term safety, follow-up study. The two-phase pivotal study SPP100A2365 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. In Phase 1, the dose response of 3 aliskiren dose groups were evaluated according to the weight categories. It was followed by a 4 week placebo controlled withdrawal phase in Phase 2.

The primary efficacy analysis in Phase 1 yielded a slope estimate of -0.17 (mmHg per unit increase in dose ratio) for the dose-response curve for the change from baseline to the end of

Phase 1 in msSBP. The negative slope estimate was statistically different from zero ($p<0.001$), indicating a significant dose-response. According to the protocol, the result provided the evidence supporting the effectiveness of aliskiren in the treatment of hypertension in pediatric patients 6-17 years of age. The LSM change in msSBP from the end of Phase 1 to the end of Phase 2 in the pooled aliskiren mid/high dose groups and the corresponding pooled placebo groups gave a difference of -1.72 mmHg in favor of aliskiren but was not statistically significant ($p= 0.1152$). On the other hand, between-group comparisons of the primary endpoint in Phase 2 using the ANCOVA for all 3 dose groups gave a numerical difference of LSM change from the end of Phase 1 to the end of Phase 2 of -2.70 mmHg between the aliskiren high dose group and the corresponding placebo group. The numerical difference was not statistical significant ($p=0.0563$).

5.3 Conclusions and Recommendations

With a total of 265 patients in the FAS1 population, the primary efficacy analysis in Phase 1 of the pivotal study (SPP100A2365) yielded a slope estimate of -0.17 (mmHg per unit increase in dose ratio) for the dose-response curve for the change from baseline to the end of Phase 1 in msSBP. The negative slope estimate was statistically different from zero ($p<0.001$), indicating a significant dose-response. According to the study design, this result provided the evidence supporting the effectiveness of aliskiren in the treatment of hypertension in pediatric patients 6-17 years of age. The analyses of the LSM change of msSBP in Phase 2 gave a numerical difference in favor of the aliskiren high dose group compared to the corresponding placebo group. The numerical difference was not statistical significant therefore was not strong supporting evidence for the efficacy of aliskiren in hypertensive pediatric patients. Strictly speaking, the study sample size did not meet the terms of the WR. However, given the study results can be viewed as interpretable, the Agency considers the study as being conducted fairly in response to the WR.

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/s/

FANHUI KONG
09/22/2017
Just checked it again and did some minor revisions.

HSIEN MING J HUNG
09/22/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 210-709
Supplement #:	NA
Related IND #:	NA
Product Name:	Tekturna® (Aliskiren)
Indication(s):	Treatment of Hypertension
Applicant:	NODEN PHARMA DAC
Dates:	06/05/2017
Review Priority:	Priority
Biometrics Division:	CDER/OB/DBI
Statistical Reviewer:	Fanhui Kong
Concurring Reviewers:	Hsien Ming Hung
Medical Division:	CDER/ODEI/DCRP
Clinical Team:	Christine Garnett, Aliza Thompson
Project Manager:	Maryam Kord Bacheh Changi

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Noden Pharma is submitting a supplemental New Drug Application (sNDA) for Tekturna® Tablets to submit pediatric study reports required to fulfill the conditions of a Written Request under the Best Pharmaceuticals for Children's Act (BPCA), and to fulfill the "assessments" required under the Pediatric Research Equity Act (PREA).

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
SPP100A2365	MC, R, DB, PG, dose response (8 wks)	Ali Low/108 Ali Mid/54 Ali High/106	Primary: Change from baseline in msSBP Key Secondary:	p<0.001(slope)
SPP100A2365E1	MC, R, DB, AC (52 wks extension)	Aliskiren / 104 Enalapril / 104	Primary: long-term safety Key Secondary: changes in msSBP	P= 0.004

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**Yes**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Yes**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes**

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA210709\0000\m5\datasets\spp100a2365\analysis
Were analysis datasets provided?	X
Dataset structure (e.g., SDTM or ADaM)	ADaM
Are the define files sufficiently detailed?	X
List the dataset(s) that contains the primary endpoint(s)	X
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	X

Content Parameter	Response/Comments
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	X
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	X

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

NA

5.1. Refuse-to-File Issues

NA

5.2. Information Requests/Review Issues

We request that you submit the CSR and the associated appendices and datasets for Study CSPP100A2365 and everything to support this regulatory action from NDA 21985 to new NDA 210709.

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

/s/

FANHUI KONG

07/14/2017

I checked in my filing review as an Advice letter. Maryam asked me to re-do it as a reviewer. So I resubmit and she will have the previous one removed. So please sign it. Thanks.

HSIEN MING J HUNG

07/16/2017