MULTI-DISCIPLINARY COLLABORATIVE REVIEW

Application Type:	NDA Supplement
Application Number:	021283-058
Priority or Standard:	Standard
Submit Date:	June 19, 2020
Received Date:	June 19, 2020
PDUFA Goal Date:	April 19, 2021
Division:	Division of Cardiology and Nephrology
Review Team:	See section 5.3
Established Name:	Valsartan
Trade Name:	Diovan®
Applicant:	Novartis Pharmaceuticals Corporation
Formulation:	Oral suspension (extemporaneously prepared from tablets)
Dosing Regimen:	Starting dose of 1 mg/kg once-daily (not to exceed 40 mg) which is adjusted according to blood pressure response and tolerability up to a maximum dose of 4 mg/kg once-daily (not to exceed 160 mg)
Proposed Indication:	Treatment of hypertension in pediatric patients 1 to <6 years of age

Recommendation on Regulatory Action: APPROVAL

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1. Executive Summary

1.1 Summary of Regulatory Action

Valsartan is an orally active angiotensin receptor blocker (ARB) approved in adults for the treatment of hypertension, to reduce the risk of hospitalization in heart failure patients and to reduce the risk of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction. In children, valsartan is approved for the treatment of hypertension from 6 to 18 years. In the current supplement (S-058), Novartis is seeking to extend the indication to treat hypertension in patients 1 to <6 years of age based on study CVAL489K2306 (K2306) and other supportive studies. (b) (4)

Three studies were considered to evaluate the safety and effectiveness of valsartan in pediatric patients 1 to <6 years of age. Studies K2303 and K2306 were reviewed in the current supplement, whereas study A2307 was reviewed earlier by the Division in 2007. All studies had a randomized, double-blind, dose-response phase in duration varying from 2 to 6 weeks. In studies K2303 and A2307, the dose-response phase was followed by a randomized placebo withdrawal phase for 2 weeks. Doses evaluated in these studies were similar, in the range of 0.25 to 4 mg/kg. Studies K2303 and K2306 evaluated body-weight adjusted doses (in 'mg/kg') and study A2307 evaluated body-weight tiered fixed doses. Oral solution was used in study K2306, whereas an extemporaneously made suspension from valsartan tablets was used in studies K2303 and A2307. Additional details on the regulatory history and study design elements can be found in sections 2.2 and 3.2 of the review.

The primary evidence of effectiveness comes from study K2306, where a statistically significant dose-response relationship was demonstrated with a slope estimate of -1.17 and a difference in change from baseline in mean systolic blood pressure (MSBP) between high and low dose of 4.4 mmHg (p=0.0157). The study also showed a statistically significant dose-response relationship in change from baseline in mean diastolic blood pressure (MDBP). A similar slope estimate (-1.05) for dose-response relationship was observed for mean seated SBP (MSSBP) in study K2303, although it was not statistically significant. Study A2307 did not demonstrate a trend for dose-response relationship, however, there was a statistically significant difference in MSSBP between valsartan (pooled) and placebo (-3.9 mmHg; p=0.0217) in the randomized withdrawal phase of the study. While the dose-response portion of studies K2303 and A2307 did not demonstrate a statistically significant slope, clinically meaningful reduction in blood pressure was noted in these studies.

The safety review focused on hepatic adverse events (AEs) and transaminitis which were noted in the previously reviewed study, A2307. A causal relationship to valsartan was not established at the time. In the current safety evaluation, five cases of transaminitis were reported in data from 200 patients of studies K2303, K2303E1 and K2306; however, none of the cases indicate a clear causal relationship to the drug. No deaths were reported. All other AEs were consistent with labeled adverse reactions for this class (hyperkalemia, hypotension, kidney impairment, and hypersensitivity), thus no new safety information for this age group was identified.

The relative bioavailability of valsartan between oral solution and suspension was evaluated in study K2101 following a single-dose. The results show that C_{max} was higher by approximately 30% for oral solution and the total systemic exposure i.e., area under the curve (AUC) was similar between the two formulations which allows bridging of the efficacy and safety findings of study K2306 (conducted using oral solution) to the extemporaneously prepared suspension formulation.

Consistent with how the trials were done, the proposed dosing regimen recommends a starting dose of 1 mg/kg titrated based on blood pressure response and tolerability to a maximum dose of 4 mg/kg. The dosing recommendations in patients 6 to 16 years of age were also revised to be consistent to 1 to <6 years of age and are acceptable.

Overall, the submitted data provide substantial evidence that valsartan is effective in lowering blood pressure in pediatric patients 1 to <6 years of age and reassurance that the risks of valsartan do not outweigh its benefits. The review team recommends approval of valsartan for the treatment of hypertension in pediatric patients 1 to <6 years of age. The cross-discipline team leader and the Division Director (signatory) are in agreement with the review team's recommendation for 'approval' action.

1.2 Benefit-Risk Assessment

Table 1: Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition and Current Treatment Options	Approximately 3.5% of children and adolescents in the United States have hypertension. Clinical diagnosis of hypertension in children 1 to <13 years of age is confirmed when repeated systolic and/or diastolic blood pressure is ≥95th percentile for age, sex and height, or ≥130 and/or 80 mmHg, respectively, whichever is lower. Children <6 years of age are more likely to have secondary hypertension, usually due to kidney parenchymal disease or renovascular hypertension. Apart from lifestyle modifications including weight loss, children and adolescents are usually initiated, as single agent, with ACE inhibitors, angiotensin receptor blocker, long-acting calcium channel blocker or a thiazide diuretic. However, only two drugs are approved for the treatment of hypertension in children <6 years of age: enalapril down to 1 month of age and candesartan down to 1 year of age.	Left untreated, severe hypertension can lead to end organ damage, e.g., kidney failure, stroke, and congestive heart failure. Given the prevalence of pediatric hypertension, there is an unmet medical need for additional treatment options.
Benefit	A statistically significant dose-response relationship was demonstrated in study K2306, with slope estimate of -1.17 and a difference in MSBP between high and low dose of 4.4 mmHg (p=0.0157).	Data from study K2306 provide principle support for effectiveness of valsartan in pediatric patients 1 to <6 years of age. Data from studies K2303 and A2307 are supportive.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Although not statistically significant, dose-dependent reductions in MSSBP was observed in study K2303 with a similar slope estimate of -1.05. While no apparent dose-response relationship was observed in Phase 1 of study A2307, a statistically significant difference in MSSBP between valsartan versus placebo (-3.9 mmHg; p=0.0217) was observed in the randomized withdrawal phase in Phase 2 of study A2307 indicative of treatment effect.	
Risk and Management	The safety review focused on hepatic AEs and transaminitis which were noted in the previously reviewed study, A2307. A causal relationship to valsartan was not established at the time. In the current safety evaluation, five cases of transaminitis were reported in data from 200 patients of studies K2303, K2303E1 and K2306; however, none of the cases indicate a clear causal relationship to the drug. No deaths were reported. All other AEs were consistent with labeled adverse reactions for this class (hyperkalemia, hypotension, kidney impairment, and hypersensitivity), thus no new safety information for this age group was identified.	Adverse Reactions section of the product insert will retain a statement on the observed cases of transaminitis and lack of a causal relationship to valsartan in pediatric patients 1 to <6 years of age. The label includes Warnings and Precautions for hypotension, impaired kidney function including acute kidney failure, and hyperkalemia, known adverse reactions of the angiotensin receptor blocker class. The available data provide reassurance that the risks of valsartan do not outweigh its benefits.

2. Introduction and Regulatory Background

2.1 Disease Background

Approximately 3.5% of children and adolescents in the Unites States have hypertension. The true prevalence is likely higher, given the condition is underdiagnosed. Clinicians make a diagnosis of hypertension in children 1 to <13 years of age when repeated systolic and/or diastolic blood pressure is ≥95th percentile for age, sex and height, or ≥130 and/or 80 mmHg, respectively, whichever is lower.[1] Normal blood pressure is <90th percentile for age, sex and height. For adolescents ≥13 years of age, diagnostic criteria for hypertension (repeated systolic and/or diastolic blood pressure ≥130 and/or 80 mmHg, respectively) and normal blood pressure limits (<120/80 mmHg) are similar to those for adults. Children <6 years of age are more likely to have secondary hypertension, usually due to kidney parenchymal disease or renovascular hypertension. Left untreated, severe hypertension can lead to end organ damage, e.g., kidney failure, stroke, and congestive heart failure. To date, FDA has approved two drugs for use in children <6 years of age: enalapril down to 1 month of age and candesartan down to 1 year of age. Thus, there is an unmet need for additional age-appropriate pediatric formulations with bioavailability, pharmacokinetic, and pharmacodynamic data in children to inform efficacy, safety, and dosing.

2.2 Valsartan and its Regulatory History

Diovan® (valsartan) is a nonpeptide, orally active and specific angiotensin II receptor blocker (ARB) acting on the AT_1 receptor subtype. Valsartan is currently approved for the treatment of hypertension in adults and children 6 to 16 years of age, to reduce the risk of hospitalization for heart failure in adult patients with heart failure (NYHA class II-IV), and to reduce the risk of cardiovascular mortality in clinically stable adult patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

Diovan capsules were initially approved on December 23, 1996 under NDA 020665 and withdrawn in 2018 for reasons unrelated to safety or efficacy. A tablet dosage form was approved on July 18, 2001 under NDA 021283. The label includes instructions for preparation of a 4 mg/mL extemporaneous suspension.

On December 19, 2000, FDA issued a Written Request (WR) to Novartis Pharmaceuticals Corporation to conduct pediatric studies of valsartan for the treatment of hypertension. The WR was amended on November 25, 2002 and June 18, 2003.

On May 29, 2007, Novartis submitted a supplemental NDA (sNDA) S-024 with data from studies CVAL489A2301 (A2301), CVAL489A2305 (A2305), and CVAL489A2307 (A2307) to support the use of valsartan in children 1 to 16 years of age with hypertension. FDA approval of S-024 on November 29, 2007 was limited to children 6 to 16 years of age because of potential safety concerns of two deaths and three cases of transaminase elevations (for which a causal relationship with valsartan could not be established) during the open-label, uncontrolled part of study A2307 and the inability to write clear dosing instructions due to lack of dose-response relationship in study A2307 in children 1 to <6 years of age.

[1] Flynn, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics; Sep 2017, 140 (3) e20171904; DOI: 10.1542/peds.2017-1904

(b) (4)

from 2007 to 2009, Novartis initiated and completed Studies VAL489K2303 (K2303) and VAL489K2303E1 (K2303E1) in 75 children 1 to <6 years of age.

Diovan was approved in Europe on April 19, 2010 to treat pediatric patients 6 to <18 years of age with hypertension. (b) (4)

tudy CVAL489K2306 (K2306) was conducted to establish a dose-response relationship of valsartan oral solution in children 1 to <6 years of age with hypertension, with or without chronic kidney disease. (b) (4)

Based on the information gathered for the European (b) (4) program, Novartis submitted a Prior Approval Supplement on July 11, 2011 (S-035) to add safety information in patients 1 to <6 years of age with hypertension from studies K2303 and K2303E1. S-035 was approved on February 28, 2012.

On February 12, 2019, FDA requested that Novartis consider submitting a sNDA with the results of study K2306 to label valsartan in pediatric patients 1 to <6 years of age. Novartis submitted background information on valsartan's pediatric development program and an overview of the sNDA package. After a request for additional information on November 4, 2019, Novartis submitted sNDA (S-058) containing efficacy and safety results from study K2306 and other supportive studies (K2303 and K2303E1) to expand the indication for treatment of hypertension to children 1 to <6 years of age. In addition to studies K2306, K2303, and K2303E1, study A2307 which was previously reviewed by the FDA in 2007 was also considered towards efficacy evaluation in this review.

3. Interdisciplinary Collaborative Review

3.1 Approach to the Review

This was a joint review between clinical and clinical pharmacology review disciplines. Efficacy review was conducted by staff from Office of Clinical Pharmacology and safety review was conducted by Dr. Kirtida Mistry, Division of Cardiology and Nephrology.

3.2 Trial Design

3.2.1 Study A2307

Reviewer comment: Study A2307 was reviewed by the FDA in 2007 with supplement S-024. The study design of A2307 is briefly summarized based on Clinical and Statistical Review for S-024 dated 10/4/2007.

Title

A double-blind, randomized, multicenter study followed by 12 months open-label treatment to evaluate the dose-response and safety of valsartan in pediatric hypertensive patients 1 to 5 years of age.

Objectives

Primary Objective

- To explore the dose-response relationship of valsartan in MSSBP in hypertensive children 1 to 5 years of age.

Secondary Objective

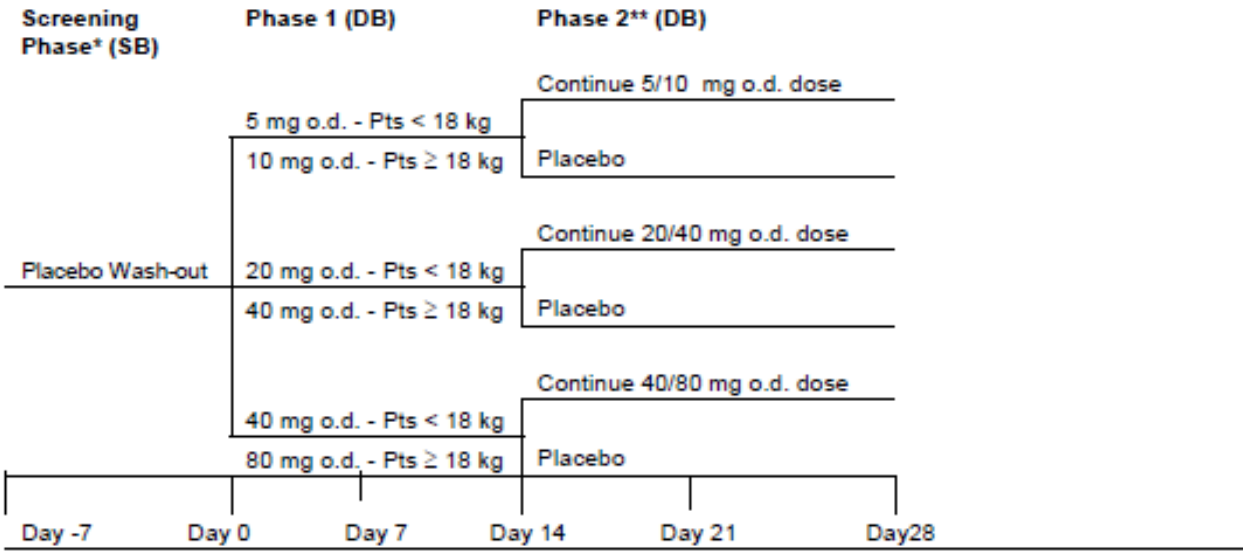
- To determine efficacy, safety and tolerability of short-term (4 week) and long-term (52 week) valsartan administration in hypertensive children 1 to 5 years of age.

Study Design

Study A2307 consisted of:

- A single-blind placebo washout phase for up to one week (Screening).
- A two-week, double-blind phase where patients were randomized in a 2:1:2 ratio to low, medium and high-dose valsartan, respectively (Phase 1). Patients <18 kg received 5, 20 or 40 mg valsartan QD, respectively; patients >18 kg received 10, 40 or 80 mg valsartan QD, respectively.
- A randomized, double-blind, withdrawal phase (Phase 2) of up to 2 weeks. Patients who completed Phase 1 were re-randomized (1:1) to either continue their Phase 1 valsartan dose or switch to placebo.
- An optional 52-week open-label (OL) phase. Patients received 20 mg QD of valsartan, and could be up-titrated, based on to mean sitting trough systolic blood pressure (SSBP) to 40 mg QD, to 80 mg QD, to 80 mg QD plus 12.5 mg QD HCTZ.

Figure 1. Schematic of double-blind phase of study A2307



* Screening Phase duration was a minimum of 3 days (for patients who qualify), up to 7 days.
** Phase 2 duration was ≤ 14 days.
For patients entering the study with inadequately controlled hypertension, previous antihypertensive medications were unchanged during the blinded phases of the study, including single blind placebo run-in phase and double-blind Phases 1 and 2.

Source: CSR for A2307, Figure 3-1, page 26.

Noteworthy features include:

- Continuation of stable doses of other antihypertensive medications was allowed, and valsartan was used as add-on therapy in 1 to 5 years of age patients whose BP had not been adequately controlled.
- Patients were stratified by baseline weight (<18 vs. >18 kg), race (Black vs. non-Black) and concomitant antihypertensive therapy at study entry (use vs. non-use).
- During Phase 1, patients were randomized to low (5 or 10 mg QD), medium (20 or 40 mg QD) or high (40 or 80 mg QD) dose valsartan depending on the body weight group. During the OL phase, patients received 20 mg QD valsartan at Day 0-OL (Visit 6). Patients either remained on this dose or were up-titrated at Week 2-OL (to 40 mg QD), Week 4-OL (to 80 mg QD) and Week 6-OL (to 80 mg QD plus hydrochlorothiazide (HCTZ) 12 mg QD if tolerable) if the mean trough SSBP was >95th percentile for age, sex and height. If at Week 8-OL, the patient had been receiving valsartan 80 mg QD for four weeks without adequate control, then the patient was discontinued, and all end-of-study evaluations were completed.

Treatment

Valsartan suspension (4 mg/mL) was prepared by the study site pharmacist and diluted based on treatment randomization. HCTZ was provided in capsules which were opened and sprinkled onto applesauce or yogurt as directed by the pharmacist.

Study population

Pediatric patients 1 to 5 years of age , >8 kg weight, with SSBP >95th percentile for age, sex and height, who were either newly diagnosed, or had discontinued antihypertensive therapy or were inadequately controlled on current antihypertensive therapy.

Patients were excluded if mean sitting BP at Visit 2 (baseline) was >25% higher than the 95th percentile for age; for clinically significant laboratory abnormalities; for clinically significant ECG abnormalities other than those associated with hypertension, left ventricular hypertrophy and AV block controlled with a pacemaker; aortic coarctation with a gradient >30 mm Hg; bilateral renal artery stenosis; organ transplantation except for renal or heart; clinical illness.

Efficacy Variables
Primary Efficacy Variables

- Change from baseline (Visit 2) to end of Phase 1 (Visit 4) in MSSBP
- Change in MSSBP from end of Phase 1 (Visit 4) to end of Phase 2 (Visit 6)

Secondary Efficacy Variables

- Change in MSSBP from baseline (Visit 2) to the end of Phase 2 (Visit 6)
- Change in MSDBP from baseline (Visit 2) to the end of Phase 1 (Visit 4)
- Change in MSDBP from end of Phase 1 (Visit 4) to the end of Phase 2 (Visit 6)
- Change in MSDBP from baseline (Visit 2) to the end of Phase 2 (Visit 6)

Statistical Analysis Plan
Sample Size Determination
The study was sized to obtain dosing and safety information in children 1 to 5 years of age. Per the Written Request, study A2307 was not considered as standalone and the number of patients enrolled should have accounted for 25% of total population of valsartan pediatric antihypertensive program (children 1 to 16 years of age). A total of 261 children aged 6 to 16 years were enrolled in study A2302, the pivotal trial of the valsartan pediatric program. Therefore, 90 patients were required to be enrolled in study A2307 to meet the 25% criteria.

Analysis of Primary Efficacy Variables
The null hypothesis for Phase 1 was that the slope of the dose-response relationship for change from baseline (Visit 2) in MSSBP was not statistically significant from zero at the end of Phase 1 (Visit 4). For dropouts the last value measured (LOCF) was used. Testing was conducted at the 2-sided significance level of 0.05. An ANCOVA model including effects for treatment, race strata (Black vs. non-Black), weight strata (<18 kg, >18 kg at baseline on Day 0), continuing use of prior antihypertensive treatment (use vs. non-use) as fixed factors, and centered baseline SSBP and dose ratio (1, 4, 8) as continuous covariates was used.

The null hypothesis for Phase 2 was that the change in MSSBP from the end of Phase 1 (Visit 4) to the end of Phase 2 (Visit 6) was not different between the pooled patients who received valsartan and those who received placebo. An ANCOVA model that included effects for treatment, race strata, weight strata, continuing use of prior antihypertensive treatment strata (use vs. non-use) and centered Visit 4 SSBP was carried out at the 2-sided significance level of 0.05.

3.2.2 Study K2303/K2303E1

Title
A randomized, multicenter, double-blind, 6-week study to evaluate the dose-response of valsartan on blood pressure reduction in children 6 months to 5 years of age with hypertension, followed by a 2-week placebo withdrawal period.

Objectives
Primary Objective

- To evaluate a dose dependent reduction in MSSBP when comparing three doses of valsartan (0.25 mg/kg, 1 mg/kg and 4 mg/kg) over a 6 week randomized, double-blind dose-ranging period (Period 1) in children 6 months to 5 years of age with hypertension (≥95th percentile).

Secondary Objectives

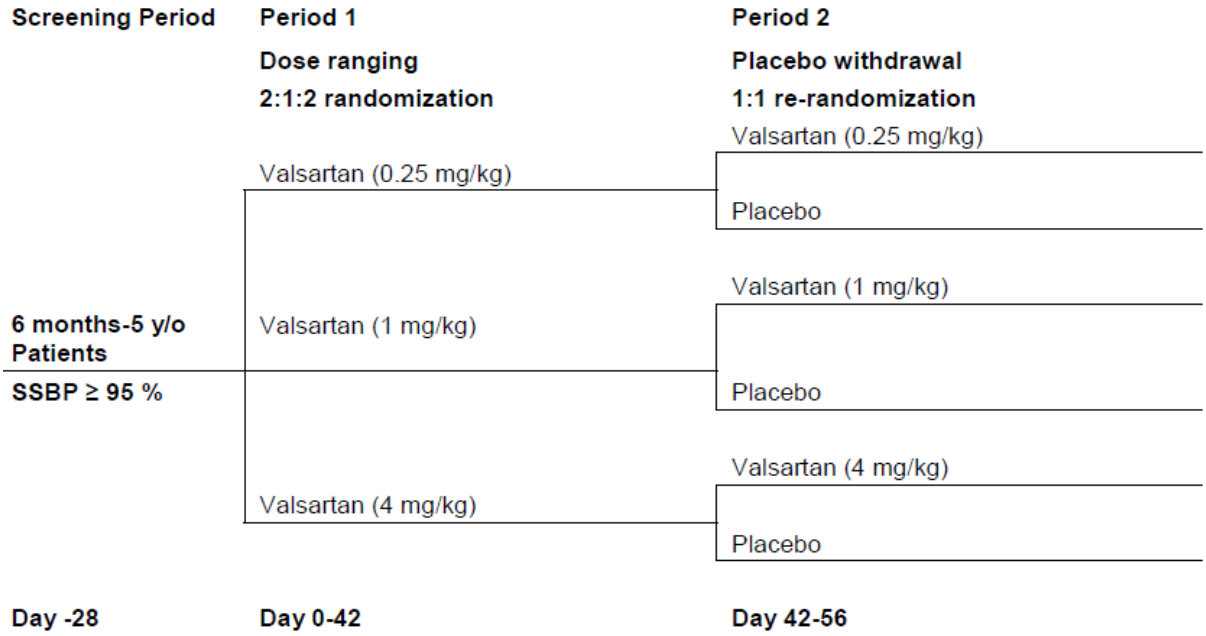
- To evaluate the overall safety and tolerability of valsartan in children 6 months to 5 years of age when treated for up to 6 weeks (Period 1).
- To evaluate BP change at the end of Period 2 (a 2-week randomized double-blind placebo withdrawal period) from the end of Period 1, when comparing pooled valsartan patients vs. pooled placebo patients.

Trial Design
Study K2303 consisted of three periods:

- Screening period was a single-blind placebo run-in period of 4 days to four weeks. All eligible patients, both naive and treated, started on single blind placebo run-in medication for a minimum of 4 days and a maximum of 28 days. Patients whose blood pressure was not adequately controlled (≥95th percentile, while continuing on other antihypertensive therapy) also received the single-blind placebo run-in medication.
- Period 1 was a six-week randomized, double-blind dose-ranging period consisting of 3 valsartan dose groups: low (0.25 mg/kg), medium (1 mg/kg), and high dose (4 mg/kg). Patients were seen in the clinic on a weekly basis after the screening visit, to determine if they met the blood pressure criteria MSSBP ≥ 95th percentile for randomization. At Visit 2 (Week 0), eligible patients were randomized to one of three treatment arms, 0.25 mg/kg, 1 mg/kg, or 4 mg/kg in a 2:1:2 ratio. All patients remained on this dose of study medication for 6 weeks. Continuing prior antihypertensive therapy strata (yes/no) and race strata (Caucasian versus non-Caucasian) were the two stratification factors used for randomization.
- Period 2 was a two-week randomized double-blind placebo withdrawal period consisting of 1:1 re-randomization to placebo or continuation of Period 1 valsartan treatment. Response to the two additional weeks of treatment with valsartan or placebo was compared during this period of the study.

Study K2303E1 was an optional 18 week open-label extension to the study K2303 to evaluate the safety, tolerability and efficacy of valsartan treatment. The starting dose of open-label valsartan was 1 mg/kg for all patients. This dose was taken for the first 2 weeks of the extension. Patients were seen at 2-week intervals during the first 6 weeks of the study, and at 4-week intervals thereafter. If the MSSBP was ≥95th percentile for age, sex and height, the Investigator could increase the dose to 2 mg/kg. The dose could be further increased to 4 mg/kg after two weeks at the next scheduled visit to achieve MSSBP <95th percentile. If the patient's MSSBP remained ≥95th percentile after 2 weeks on valsartan 4 mg/kg, HCTZ or amlodipine could be added at the discretion of the investigator.

Figure 2. Schematic of double-blind phases of study K2303



Source: CSR K2303, Figure 9-1, page 36.

Treatment

Commercial valsartan 160 mg tablets and placebo tablets matching valsartan were supplied to the sites by the applicant. Extemporaneous suspension of valsartan was prepared by the study site pharmacist or designated health care professional. Ora-plus™ and Ora-sweet™ preparations were used to prepare the suspension.

Key Eligibility Criteria

Key Inclusion Criteria

- Male or female patients between the ages of 6 months to 5 years, at Visit 1 with a documented history of hypertension.
- Weight ≥6 kg or ≤40 kg.
- Patients, either naïve or treated, with a documented history of a mean seated systolic blood pressure (mean of three measurements), ≥95th percentile for age, sex and height.
- Patients with uncontrolled blood pressure, receiving background antihypertensive therapy, could continue their therapy provided there was no change in dosing regimen.

Key Exclusion Criteria

- MSSBP (mean of three measurements) at baseline (Visit 2) ≥25% higher than the 95th percentile for age, sex and height.
- Use of background ARB therapy.
- Any clinically significant abnormalities or clinically noteworthy abnormal laboratory values other than those relating to renal function, including but not limited to the following:
    - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) >3 times the upper limit of the reference range.
    - Total bilirubin >2 times the upper limit of the reference range.

  - Glomerular filtration rate (GFR) <30 mL/min/1.73m² (calculated using Modified Schwartz formula to estimate GFR, based on the serum creatinine concentration obtained at Visit 1/Screening).
  - Serum potassium >upper limit of the reference range (reference range 3.5 – 5.5 mmol/L).
- Clinically significant ECG abnormalities. Patients with ECG abnormalities associated with left ventricular hypertrophy were permitted to enroll.

Efficacy Variables
Primary Efficacy Variable
- Change from baseline in MSSBP at the end of Period 1

Secondary Efficacy Variables
- Change from Week 6 (Visit 5) in MSSBP at the end of Period 2
- Change from baseline (Visit 2) in MSDBP at the end of Period 1
- Change from Week 6 (Visit 5) in MSDBP at the end of Period 2

Statistical Analysis Plan
Sample Size Determination
A slope of 1.6 mmHg/mg/kg corresponds to a difference of 6 mmHg between the low (0.25 mg/kg) and high (4 mg/kg) doses. Sample size of 27 patients in each of the low and high dose groups provided a power of >80% to achieve statistical significance for testing the null hypothesis of no difference between low and high doses under the alternative hypothesis of a 6 mmHg difference between low and high doses in change from baseline in MSSBP, at a 2-sided significance level of 0.05, assuming a standard deviation of 7.5 mmHg for change from baseline in MSSBP. Therefore, the planned sample size was to obtain a total of 67 completed patients, or 27, 13, and 27 on valsartan low, medium, and high doses, respectively. With an estimated dropout rate of 10% from randomization to Week 8, a total of 75 patients were planned to be randomized to valsartan low (0.25 mg/kg), medium (1 mg/kg), and high (4 mg/kg) doses in 2:1:2 ratio, or 30, 15, and 30 subjects per treatment dose group, respectively.

Key Analysis Sets
- Period 1 Intent-to-treat population (ITT1): All randomized patients that had both the Week 0 baseline and at least one post-baseline assessment of any efficacy variable during Period 1.
- Period 2 Intent-to-treat population (ITT2): All re-randomized patients that had both Visit 5 (Week 6) and at least one post-re-randomization assessment of any efficacy variable during Period 2.
- Period 1 Per-protocol population (PP1): All ITT1 patients who completed the study Period 1 and did not have a protocol deviation in a manner liable to affect the efficacy assessment during Period 1.

Analysis of Primary Efficacy Variable
- *Change from baseline in MSSBP to end of Period 1*

The primary analysis assessed the dose dependent SBP reduction in Period 1 comparing valsartan low, medium, and high doses on the ITT1 population. The null hypothesis that the slope of the dose-response relationship for SBP reduction (mmHg) over dose per body weight (mg/kg) was zero was tested against the 2-sided alternative hypothesis that the slope is different from zero as H0: $\beta = 0$ versus H1: $\beta \neq 0$. β is the slope for the assumed linear relationship between change from baseline to end of Period 1 in MSSBP (mmHg), as the dependent variable, and dose per body weight (mg/kg), as an explanatory variable.

The hypothesis test was performed by analyzing change from baseline at the end of Period 1 in MSSBP using an ANCOVA model with continuing prior antihypertensive therapy strata (yes/no) and race strata (Caucasian versus non-Caucasian) as factors, dose per body weight as the main regressor, and baseline MSSBP as a covariate. Baseline was defined as the Week 0 value. End of Period 1 was defined as the Week 6 (Visit 5) value or the last post-baseline observation during Period 1 carried forward (LOCF). The least-squares mean estimate for the slope was also calculated at a 2-sided significance level of 0.05.

Analysis of Secondary Efficacy Variables

- *Change in MSSBP from Week 6 to end of Period 2*

The further reduction of SBP in Period 2 was evaluated to compare the pooled valsartan patients with the pooled placebo patients, and each valsartan dose with the corresponding placebo from the same Period 1 dose arm (low, medium, or high). The end of Period 2 is defined as the Week 8 (Visit 7) value or the last post-Week 6 observation during Period 2 carried forward (LOCF). The change from Week 6 (Visit 5) to the end of Period 2 in MSSBP was analyzed by testing the null hypothesis of no treatment difference versus the alternative hypothesis of a non-zero difference in mean change from Week 6. The analysis was performed on the ITT2 population using the same ANCOVA model with treatment, continuing prior antihypertensive therapy strata (yes/no) and race strata (Caucasian versus non-Caucasian) as factors and the centered Week 6 MSSBP as a covariate. Treatment comparisons were performed by linear contrasts of the model effects at the 2-sided significance level of 0.05.

- *Change from baseline in MSDBP to end of Period 1*

The change from baseline (Visit 2) to end of Period 1 in MSDBP was analyzed to test the slope of dose-response relationship for DBP reduction over dose per body weight and compare the three dose groups using the same ANCOVA model as for MSSBP, on the ITT1 population.

- *Change in MSDBP from Week 6 to end of Period 2*

The further reduction of MSDBP in Period 2 was evaluated to compare the pooled valsartan patients with the pooled placebo patients, and each valsartan dose with the corresponding placebo from the same Period 1 dose arm (low, medium, or high) using the same ANCOVA model as for MSSBP, on the ITT2 population.

Protocol Amendments

- Original protocol dated on 27-Nov-2006
- Amendment 1: 26-Jun-2007
- Amendment 2: 30-Sep-2008
- Study initiation date: 21-Mar-2007 (first patient screened)
- Study completion date: 21-Jan-2009 (last patient completed)

Reviewer Comment: There were no changes that affects the primary efficacy analysis.

3.2.3 Study K2306

Title

A 6 week, randomized, multicenter, double-blind, double-dummy study to evaluate the dose-response of valsartan on blood pressure reduction in children 1 to 5 years of age with hypertension, with or without chronic kidney disease, followed by a 20-week open-label titration phase.

Objectives

Primary Objective

- To evaluate if a dose dependent reduction in MSBP exists when comparing two doses of valsartan solution (0.25 mg/kg/day and 4 mg/kg/day) over a 6-week period in children 1 to 5 years of age with hypertension (MSBP ≥95th percentile for age, sex and height), with or without chronic kidney disease (CKD).

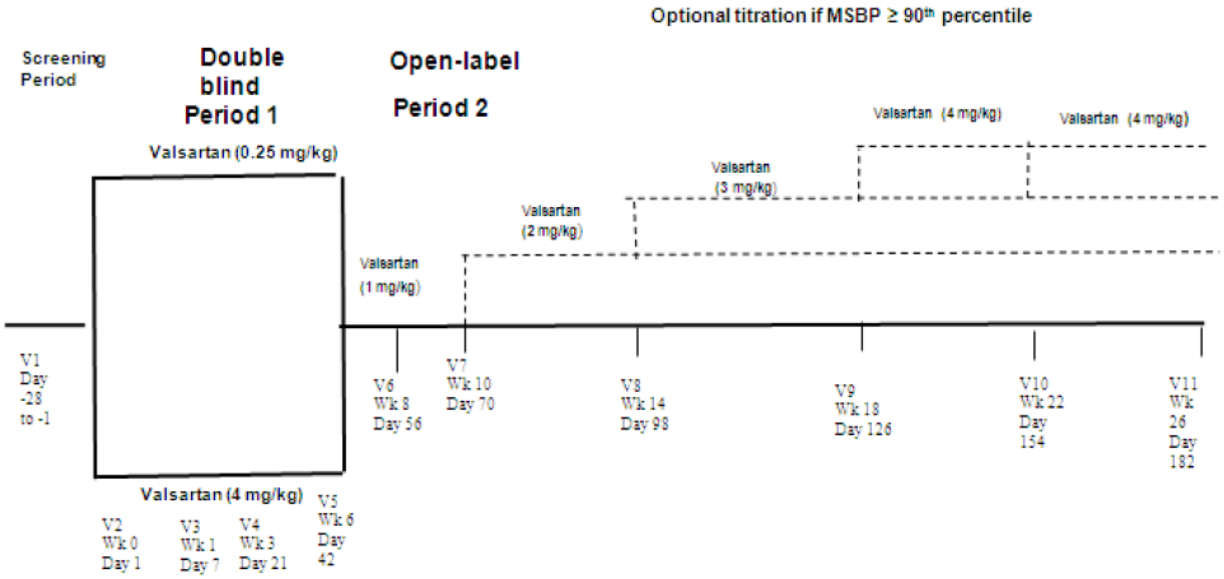
Secondary Objectives

- To assess the efficacy of valsartan in reducing the MDBP in children with hypertension.
- To assess the efficacy of valsartan in controlling the MSBP and MDBP in children with hypertension. The target mean BP is <90th percentile for age, sex and height.
- To assess the safety and tolerability profile of valsartan in children with hypertension, with or without CKD.
- To assess the effect of valsartan on proteinuria and eGFR in a subset of children with hypertension and CKD.

Trial Design

Patients who received background antihypertensive treatments continued on these medications as long as they met the eligibility criteria for MSBP (≥95th percentile). The background therapy and dose remained unchanged for the duration of the study. No patients were permitted in the study with background Renin angiotensin aldosterone system (RAAS) blocker therapy [ARBs, ACEi, and direct renin inhibitors(DRIs)].

Figure 3. Schematic of double-blind period and open-label period of study K2306



Source: Applicant's CSR K2306, Figure 9-1, page 51.

Study K2306 consisted of three periods:

Screening/Washout Period

Screening visit (Visit 1) was performed 1 to 28 days before enrollment to test patient's eligibility for study participation. A wash-out period of 28 days was included for eligible patients on prior treatments with RAAS blockers, including ARBs, ACEi, and DRIs. If there was an increase in MSBP of more than 20%

above the 95th percentile for age, sex and height during wash-out, or if the investigator deemed hypertensive treatment necessary, the patient commenced the study drug treatment early after fulfilling all eligibility criteria.

Patients who were taking antihypertensive medications other than RAAS blockers with MSBP <95th percentile for age, sex and height at screening, were tapered off these medications according to Investigators instruction and manufacturer's labeling, in order to meet entry criteria. Patients who were not on RAAS blockers could enter the treatment phase of the trial (Visit 2) once the patient achieved a MSBP ≥95th percentile for age, sex and height, screening laboratory results, and had met all other inclusion criteria. Patients taking non-RAAS blockers, who had MSBP ≥95th percentile for age, sex and height, continued antihypertensive medications throughout the trial without dose change.

Double-blind Period (Period 1)
At Visit 2, eligible patients were randomized (1:1) into one of the two treatment arms (valsartan 0.25 mg/kg/day or 4 mg/kg/day). Patients remained on their respective dosing regimen for 6 weeks. The randomization was stratified based on CKD status (yes/no).

Open-label Period (Period 2)
All patients moved to the 20-week, open-label phase. All patients started with 1 mg/kg/day of valsartan and remained on this dose for 4 weeks. After 4 weeks, if the patient's MSBP was ≥90th percentile for age, sex and height, the dose of valsartan was increased to 2 mg/kg/day. After 4 weeks, if the patient's MSBP was ≥90th percentile for age, sex and height, the dose of valsartan was increased to 3 mg/kg/day. The dose was further increased to 4 mg/kg/day after 4 weeks, in order to control MSBP (<90th percentile). Patients remained on the 4 mg/kg/day dose through the end of the study. The study medication was down-titrated at the investigator's discretion. After down-titration the investigator could up-titrate again to the maximum dose as necessary. The maximum dose was 4 mg/kg/day for a maximum of 8 weeks.

Treatment
Valsartan 3 mg/mL oral solution and placebo to match valsartan 3 mg/mL oral solution were provided.

Key Eligibility Criteria
Key Inclusion Criteria

- Male or female, 1 to 5 years at baseline (Visit 2), with documented diagnosis of hypertension (National High Blood Pressure Education Program 2004).
- Approximately 50% of enrolled patients were CKD-patients. CKD patients were defined based on the following criteria (Hogg et al 2003):
    - Kidney damage for ≥3 months, defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifested by one or more of the following features:
        - Abnormalities in the composition of urine
        - Abnormalities in imaging tests
        - Abnormalities on kidney biopsy
    - Estimated GFR <60 mL/min/1.73m^2 for ≥3 months, with or without the other signs of kidney damage described above.
        - For all patients, eGFR was calculated using the Modified Schwartz Formula (Schwartz et. al 1987): eGFR [mL/min/1.73m^2] = k * Height [cm] / Serum Creatinine [mg/dL], where k was based on age as following:

Age	K
<1 year	0.45
2 to 12 years	0.55
13 to 21 years (adolescent females)	0.55
13 to 21 years (adolescent males)	0.70

- MSBP (mean of 3 measurements) were ≥95th percentile, and ≤25% above the 95th percentile, for age, sex and height, at baseline (Visit 2), by office automatic blood pressure monitor and cuff. Confirmation of MSBP ≥95th percentile was made using the auscultatory blood pressure method.
- Body weight ≥8 kg and ≤40 kg at baseline.

Key Exclusion Criteria

- Any clinically significant physical abnormality or clinically relevant abnormal laboratory values other than those relating to renal function, including but not limited to:
  - AST/SGOT or ALT/SGPT >3 times the upper limit of the reference range
  - Total bilirubin >2 times the upper limit of the reference range
  - eGFR <30 mL/min/1.73m² (calculated using Modified Schwartz Formula)
  - Serum potassium >5.3 mmol/L
- Uncontrolled diabetes mellitus defined by the investigator.
- Current diagnosis of heart failure (New York heart association [NYHA] Class II-IV).
- Patients taking any of the following concomitant medications including:
  - RAAS blockers other than study drug
  - Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that increased potassium levels
- Patients who demonstrated clinically significant ECG abnormalities.

Efficacy Variables

Primary Efficacy Variable

- Change from baseline (Visit 2) in MSBP to end of Week 6 during the double-blind period

Key Secondary Efficacy Variables

- Change in MDBP from baseline to end of Week 6
- Percentage of patients achieving MSBP <90th (and <95th) percentile for age, sex and height at end of Week 6
- Percentage of patients achieving both MSBP and MDBP <90th percentile of age, sex and height at end of Week 6
- Percentage of patients achieving both MSBP and MDBP <95th percentile for age, sex and height at end of Week 6

Statistical Analysis Plan

Sample Size Determination

The sample size of 116 completed patients was calculated based on the primary efficacy variable, change from baseline in MSBP, and a standard deviation of 11 mmHg (based on previous data). The sample size was calculated to ensure at least 80% power to detect statistical significance for the comparison of valsartan 0.25 mg/kg vs. valsartan 4 mg/kg under the alternative hypothesis that the treatment difference was 6 mmHg at a two-sided significance level of 0.05. Assuming 10% drop-out rate, the total targeted sample size to be randomized was 130 patients.

Key Analysis Sets

- Full-analysis set (FAS): All patients randomized with at least one follow-up efficacy assessment in the double-blind phase. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned at randomization. However, patients who were not qualified for randomization and were inadvertently randomized into the study were excluded from the FAS, provided these patients did not receive the study drug.
- Per-protocol set (PPS): All patients in FAS without any major protocol deviations in the double-blind phase. The major protocol deviations were pre-specified prior to unblinding the treatment codes for analyses.

Analysis of Primary Efficacy Variable

Primary analysis was testing the null hypothesis that there is no treatment difference in the reduction of MSBP (mmHg) between dose groups 0.25 mg/kg (low) and 4 mg/kg (high). The alternative hypothesis was that there is a difference between dose groups valsartan 0.25 mg/kg and valsartan 4.0 mg/kg. The treatment comparison was tested at a two-sided significance level of 0.05. The change from baseline in MSBP at the end of Week 6 during double-blind phase was analyzed on FAS using ANCOVA as the primary analysis model with treatment and CKD strata as factors and baseline MSBP as the covariate. The baseline MSBP values were centered by subtracting the overall mean of all patients included in the analysis for FAS. For patients with missing values at Week 6, the last post-baseline observation during the double-blind period was carried forward (LOCF).

Supportive analyses included the primary analysis performed on the PPS population and a slope analysis where the change from baseline to the end of Week 6 in MSBP was analyzed on FAS by an ANCOVA model with CKD strata as the factor and baseline MSBP as a covariate, and dose per body weight (mg/kg) as the main regressor.

Analysis of Key Secondary Efficacy Variables

- Change from baseline at the end of Week 6 in the double-blind period (using LOCF) in MDBP was analyzed on FAS using an ANCOVA model with treatment and CKD strata as factors and baseline MDBP as the covariate. Treatment comparison was performed at the two-sided significance level of 0.05.
- Following variables were analyzed using a logistic regression model with treatment and CKD strata as factors and baseline MSBP as the covariate. The odds ratio of valsartan 4 mg/kg/ valsartan 0.25 mg/kg was computed, along with the associated 95% CI and p-value. Similar analyses were carried out for the CKD and non-CKD subgroups of patients.
    - Percentage of patients achieving MSBP <90th percentile for age, sex and height at end of Week 6
    - Percentage of patients achieving MSBP <95th percentile for age, sex and height at end of Week 6
    - Percentage of patients achieving both MSBP and MDBP <90th percentile for age, sex and height at end of Week 6
    - Percentage of patients achieving both MSBP and MDBP <95th percentile for age, sex and height at end of Week 6

Subgroup Analysis

Similar analysis of the primary efficacy variable for the treatment comparison was performed for the subgroup of CKD patients and for the subgroup of non-CKD patients (per CKD yes/no strata).

Furthermore, treatment-by-CKD strata interaction in the entire FAS was assessed by inclusion of the additional interaction term to the primary analysis model for the overall analysis in FAS.

Protocol Amendments

There were no protocol amendments during the study.

- Protocol identification: CVAL489K2306
- Original Protocol Release Date: 31-May-2012
- Study initiation date: 07-Nov-2012 (first patient first visit)
- Study completion date: 24-Jan-2017 (last patient last visit)

3.3 Efficacy Results

3.3.1 Study A2307

Reviewer comment: Study A2307 was reviewed by the FDA in 2007 with supplement S-024. The relevant efficacy results are briefly summarized in this section.

Patient Disposition

A total of 130 patients entered the placebo washout phase of the study and 90 patients were randomized into Phase 1 and 87 completed Phase 1. Three randomized patients were discontinued (one each in the low and high-dose groups for unsatisfactory therapeutic effect and one in the medium-dose group for protocol violation). A total of 87 patients were then re-randomized to either valsartan or placebo for Phase 2 and 43 valsartan and 40 placebo patients completed Phase 2. Of the 4 premature discontinuations, 1 patient on valsartan and two patients on placebo discontinued due to unsatisfactory therapeutic effect; 1 patient on placebo discontinued due to administrative problems.

A total of 88 patients entered the OL phase. One patient discontinued from Phase 1 due to unsatisfactory therapeutic effect and entered the OL phase directly without being re-randomized into Phase 2. Eighty (80) patients remained on valsartan monotherapy and 8 patients were on valsartan + HCTZ; eighty-two patients completed the OL phase. Two patients discontinued OL due to AEs (one with hepatitis, and one with renal impairment). One patient died due to viral gastroenteritis. Another patient died due to complications of pneumonitis 11 days after study discontinuation.

Patient Characteristics

The mean age was 3.2 years and the overall population (total N=90) was 60% male, 41% Caucasian, 30% Black, and 18% from the US. A total of 37 patients were randomized to low, 18 to medium, and 35 to high dose groups. Across treatment groups, the population was about 49 to 71% male, 35 to 46% Caucasian, 26 to 33% Black, and 11 to 23% from the US. With respect to other baseline characteristics, the baseline MSSBP was higher (115.1 mm Hg) in the high dose group than the medium dose group (112.1 mm Hg) and the medium dose group appeared to include a higher percentage of patients with mild hypertension. Otherwise, there were no noted imbalances in other characteristics such as weight, BMI (mean 16.8 kg/m^2), use of antihypertensive (16-22%), mean sitting DBP (68-70 mm Hg), or sitting pulse (101.4-104.2 bpm).

In terms of medical history in the randomized Phase 1 population, 57 (63%) patients had a history of renal/urinary disorder. Seventeen (18.9%) had a history of nephrotic syndrome, 6 (6.7%) had a history of acute renal failure, and 13 (14.4%) had a history of chronic renal failure. Thirty-eight (42.2%) of patients had a history of a congenital, familial or genetic disorder, including 7 (7.8%) with congenital cystic kidney disease. Six (6.7%) of patients had a history of ventricular hypertrophy.

A majority (71%) of the randomized population was on antihypertensive medication prior to the start of study medication. The most frequently used antihypertensives were ACE inhibitors (48%) and dihydropyridines (28.9%). Antihypertensive medications were continued by 18.9% of the patients (N=90) during double-blind; the most frequently used during double-blind were dihydropyridines (10%). Seventy-three percent of randomized patients were taking non-antihypertensive therapies prior to the start of study medication. The most frequently used non-antihypertensive medications was corticosteroids (16.7%). After start of study medication, the most frequently used classes were anilides (24%). During OL, 87.5% of patients took non-antihypertensive therapies; the most frequently used classes of medications were anilides (52%), cephalosporins (34%), and other antibiotics; 13.6% were taking glucocorticoids and 12.5% were taking corticosteroids.

Protocol Deviations
Protocol violations were noted in 33 patients (36.7% of the Phase 1 population); eighteen patients had major protocol violations which excluded them from the per-protocol analysis. The most frequent major violation during Phase 1 was that the end of Phase 1 (Visit 4) BP was measured outside the 20 to 30 hour post-dosing window (15 patients, 16.7%). Eighteen patients (20.7%) had at least one protocol violation during Phase 2; 15 patients had major protocol violations. The most frequent major violation for both Phase 1 and Phase 2 was that the end of Phase BP measurement was taken outside the 20 to 30 hour post-dosing window.

Efficacy Results
Primary Efficacy Variables
Change from baseline (Visit 2) to end of Phase 1 (Visit 4) in MSSBP

Table 2 shows the baseline, end of Phase 1, and change from baseline to end of Phase 1 in MSSBP. All three treatment groups showed a statistically significant mean decrease from baseline. However, no obvious dose-response relationship was observed, and the slope analysis yielded a slope estimate of -0.10 mmHg per unit increase in dose (p=NS). Similar results were seen in the PP1 population, where the slope estimate was -0.28 mmHg (p=NS). For the LSM change from baseline to end of Phase 1 in MSSBP, no statistically significant difference between treatments (low vs. high, low vs. medium, medium vs. high) was seen in the ITT1 or PP1 populations for between-group comparisons.

Table 2. Change in MSSBP (mmHg) from baseline to end of Phase 1 by treatment (ITT1)

	Low Dose N = 37	Medium Dose N = 18	High Dose N = 35
Baseline/Visit 2			
n	37	18	35
Mean (SD)	116.8 (6.88)	112.1 (8.56)	115.1 (6.34)
End of Phase 1			
n	37	18	35
Mean (SD)	108 (11.04)	103.7 (7.40)	106.5 (8.67)
Change from baseline to End of Phase 1			
n	37	18	35
Mean (SD)	-8.4 (8.44)	-8.3 (7.63)	-8.6 (7.55)
95% CI [1]	-11.18, -5.55	-12.13, -4.54	-11.18, -6.00
p-value [1]	<0.0001*	0.0002*	<0.0001*

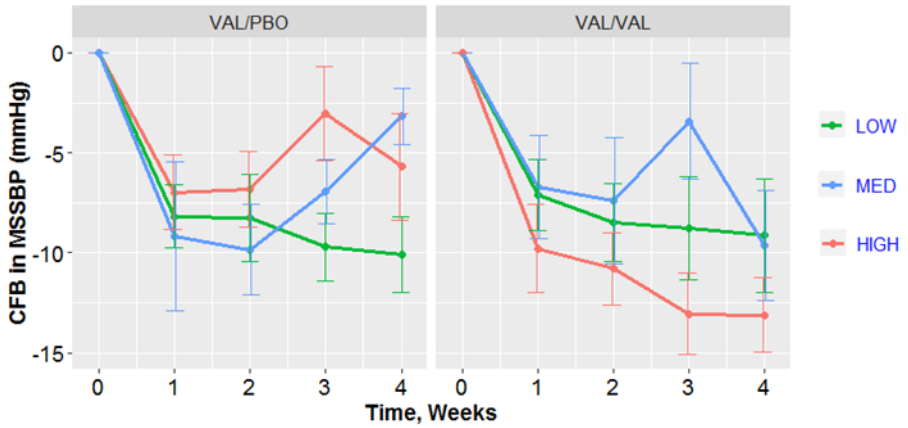
[1] p-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
*indicates statistical significance at the 0.05 level

Source: CSR for A2307. Table 9-1. Page 65

Reviewer Comment: It is plausible that a 2-week treatment duration may not be long enough to observe the maximum BP lowering effect of valsartan and capture potential dose-dependent BP reduction. In patients who continued their valsartan dose for additional 2 weeks in the placebo withdrawal phase, further reduction in SBP was observed (

Figure 4*, right panel) from the end of dose-response period (2 weeks). At the end of Week 4, the high dose appears to be associated with greater reduction in MSSBP compared to the lower dose group.*

Figure 4. SBP change from baseline through the end of placebo withdrawal phase for A2307

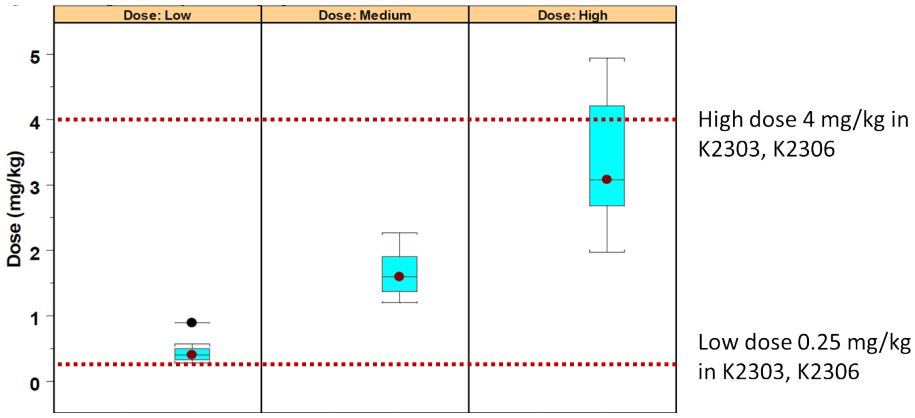


Source: Reviewer's figure. VAL/PBO: patients received valsartan (high, medium, low) dose during dose-response period and switched to placebo at Week 2. VAL/VAL: patients received valsartan (high, medium, low) dose during dose-response period and continued the same dose during placebo withdrawal phase. Dots present arithmetic means of SBP reduction and error bars represent standard errors of means.

*Moreover, the doses studied in A2307 were fixed doses: 5/10 mg (low dose), 20/40 mg (medium dose), and 40/80 mg (high dose) for body weight <18 kg/ ≥ 18kg. The range of corresponding weight adjusted dose (*Figure 5*) in A2307 is narrower than those studied in other two studies. Particularly, the low dose (mean of 0.4 mg/kg) in A2307 is higher than 0.25 mg/kg, the lowest studied dose in K2306 and K2303. A ratio between the low dose and the high dose of valsartan was 1:8 for study A2307 compared to 1:16 for*

studies K2303 and K2306. Valsartan exposures in study A2307 may be near to the plateau of the exposure-response relationship.

Figure 5. Comparison of weight-adjusted dose (mg/kg) between A2307 and other studies (K2303, K2306)



Source: Adapted from Pharmacometrics Review for NDA 02183 S-24.

Change in MSSBP from end of Phase 1 (Visit 4) to end of Phase 2 (Visit 6)

For the analysis of Phase 2, the difference in the change in sitting SBP from end of Phase 1 to end of Phase 2 is statistically significant between the pooled valsartan and placebo (p=0.02) (Table 3), supporting the presence of a treatment effect. When analyzed as three separate dose groups (Table 4), the difference in the change from baseline in sitting SBP between valsartan and placebo is statistically significant only for the medium dose; however, in the high dose group the trend is in a similar direction and the p-value narrowly missed the statistical significance.

Table 3. Change in MSSBP (mmHg) from end of Phase 1 to end of Phase 2 by pooled treatment (ITT2)

	Valsartan N = 44	Placebo N = 43
End of Phase 1/Visit 4		
n	44	42
Mean (SD)	106.5 (11.03)	106.7 (8.17)
Range	86-129	91-124
End of Phase 2		
n	44	42
Mean (SD)	105.0 (11.92)	108.5 (8.98)
Range	75-133	90-125
Change from end of Phase 1 to End of Phase 2		
n	44	42
Mean (SD)	-1.5 (7.92)	1.5 (7.76)
95% CI [1]	-3.91, 0.90	-0.95, 3.89
Within-treatment p-value [1]	0.2135	0.2273
Between-group p-value [2]	0.0217*	

[1] p-values and 95% CI are based on the paired t-test of the null hypothesis of no change from the end of Phase 1 within each treatment group.
[2] p-value is from the ANCOVA model with treatment, race strata, weight strata and continuing use of prior antihypertensive treatment strata as factors, and centered Visit 4 SSBP as a covariate.
* indicates statistical significance at the 0.05 level.
Only patients who had both end of Phase 1 and end of Phase 2 values are included.

Source: CSR for A2307. Table 9-3. Page 67.

Table 4. Least-square (LS) mean and treatment comparison for change in MSSBP (mmHg) from end of Phase 1 to end of Phase 2 (ITT2)

	N	LS Mean Change [1]	LS Mean [2]	95% CI [2]	p-value [2]
Low/Low	19	-0.0			
Low/Placebo	17	-1.4	1.4 (2.40)	(-3.37, 6.21)	0.5565
Med/Med	8	-2.5			
Med/Placebo	9	5.6	-8.1(3.53)	(-15.17, -1.10)	0.0241*
High/High	17	-2.9			
High/Placebo	16	2.0	-5.0 (2.53)	(-10.00, 0.06)	0.0529

[1] LS mean change from end of phase to end of phase 2 within each dose group
[2] LS mean, 95% CI, and p-values are for the difference between valsartan and placebo for each dose level based on the ANCOVA model with treatment, race strata, weight strata, continuing use of prior antihypertensive treatment strata as factors, and centered Visit 4 SSBP as a covariate.
* indicates statistical significance at the 0.05 level.

Source: CSR for A2307. Table 9-4. Page 68.

Secondary Efficacy Variables

Change in MSSBP from baseline to end of Phase 2

All groups showed a decrease from baseline (Table 5). A statistically significant decrease from baseline is seen in all the dose groups who continued to stay on valsartan in Phase 2.

Table 5. Change in mean SSBP (mmHg) from baseline to end of Phase 2 (ITT population)

		SSBP (mmHg)			
Treatment	**n**	**Baseline**	**End of Phase 2**	**Change**	**P-value [1]**
Low/Low	19	116.6	107.5	-9.1	0.0048*
Low/Placebo	17	116.5	106.4	-10.1	<0.0001*
Medium/Medium	8	112.3	102.7	-9.6	0.0102*
Medium/Placebo	9	112.1	108.9	-3.2	0.0554
High/High	17	116.3	103.3	-13.0	<0.0001*
High/Placebo	17	114.1	110.9	-3.2	0.2337

[1] p-values correspond to a paired t-test of the mean change from baseline versus zero, i.e., no change from baseline, within each treatment; * indicates statistical significance at the 0.05 level.

Source: CSR for A2307. Table 9-5. Page 69.

Change in MSDBP from baseline to end of Phase 1

All three dose groups showed a significant decrease from baseline with what appears to be a flat dose-response relationship. These results are consistent with the results for MSSBP. When the changes from baseline in MSDBP between groups were compared (low vs. high, low vs. medium, and medium vs. high), none of the differences were statistically significant (Table 6).

Table 6. Change in MSDBP (mmHg) from baseline to end of Phase 1 by treatment (ITT1 population)

	Low Dose N = 37	**Medium Dose N = 18**	**High Dose N = 35**
Baseline/Visit 2			
n	37	18	35
Mean (SD)	70.5 (8.52)	68.1 (8.60)	68.8 (7.60)
End of Phase 1			
n	37	18	35
Mean (SD)	65.0 (7.78)	61.7 (7.64)	63.3 (6.78)
Change from baseline to End of Phase 1			
n	37	18	35
Mean (SD)	-5.5 (6.06)	-6.4 (4.23)	-5.5 (8.47)
95% CI [1]	-7.50, -3.46	-8.55, -4.34	-8.39, -2.58
p-value [1]	<0.0001*	<0.0001*	0.0005*

[1] p-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.

Source: CSR for A2307. Table 9-6. Page 69.

Change in MSDBP from end of Phase 1 to end of Phase 2 (randomized placebo withdrawal)

A statistically significant decrease in MSDBP in the valsartan group as well as a statistically significant increase in MSDBP in the placebo group is observed. The difference between the two groups is statistically significant (p=0.009), supporting the presence of a treatment effect (Table 7).

Table 7. Change in mean SDBP (mmHg) from end of Phase 1 to end of Phase 2 by pooled treatment (ITT2 population)

	Valsartan N = 44	Placebo N = 43
End of Phase 1/Visit 4		
n	44	42
Mean (SD)	64.2 (6.87)	63.3 (8.19)
End of Phase 2		
n	44	42
Mean (SD)	61.7 (7.89)	65.3 (6.81)
Change from end of Phase 1 to End of Phase 2		
n	44	42
Mean (SD)	-2.5 (7.51)	2.0 (5.86)
95% CI [1]	-4.77, -0.20	0.19, 3.84
p-value [1]	0.0336*	0.0312*
Between-group p-value [2]	0.0089*	

[1] p-values and 95% CI are based on the paired t-test of the null hypothesis of no change from the end of Phase I within each treatment group.
[2] p-value is from the ANCOVA model with treatment, race strata, weight strata and continuing use of prior antihypertensive treatment strata as factors, and centered Visit 4 SDBP as a covariate.
* indicates statistical significance at the 0.05 level.

Source: CSR for A2307. Table 9-7. Page 70.

Change in mean SDBP from baseline to end of Phase 2

The results were consistent with the results for the change in MSSBP (Table 8). A statistically significant decrease from baseline is seen in all the dose groups who continued to stay on valsartan in Phase 2.

Table 8. Change in mean SDBP (mmHg) by double-blind treatment (Phases 1 & 2 combined) (ITT)

	SDBP (mmHg)			
Treatment	**Baseline**	**End of Phase 2**	**Change**	**P-value [1]**
Low/Low	72.3	63.3	-9.0	0.0012*
Low/Placebo	68.0	64.7	-3.3	0.0260*
Medium/Medium	68.8	62.7	-6.1	0.0380*
Medium/Placebo	66.9	64.9	-1.9	0.3290
High/High	69.4	59.5	-9.9	<0.0001*
High/Placebo	68.4	67.3	-1.1	0.6378

[1] P-values correspond to a paired t-test of the mean change from baseline versus zero, i.e., no change from baseline, within each treatment; * indicates statistical significance at the 0.05 level.

Source: CSR for A2307. Table 9-8. Page 71.

3.3.2 Study K2303/K2303E1

Patient Disposition

A total of 81 patients were enrolled into the single-blind placebo period of the study. A total of 75 patients completed the single-blind period and were randomized to the double-blind Period 1 to receive

low, medium, or high doses of valsartan. One patient included in the randomized and re-randomized populations was excluded from all analyses (Patient (b) (6)) because no CRF data was available due to site closing and critical GCP issues. Thus, a total of 74 patients who completed Period 1 were re-randomized (1:1) to either valsartan or placebo for Period 2. Following Visit 5, one patient (Patient (b) (6) who was re-randomized to continue valsartan treatment during Period 2 discontinued the study due to an AE of hyperkalemia and did not have any more blood pressure assessments. Therefore, a total of 73 patients entered Period 2.

Patient Characteristics

Patient demographics and baseline characteristics by treatment arm in randomized population in Period 1 presented in Table 9 and Table 10, respectively. Majority of the patients were Caucasian (56%) and male (64%). Antihypertensive medications were continued by 19% of the patients (N=75) during double-blind and the most frequently used during double-blind were calcium channel blockers in 10 patients (13%). There were fewer males in the low dose treatment group compared to the other two groups. Sitting pulse was higher in the medium dose group than in the low and high dose groups and MSSBP was higher in the high dose group than in the low and medium dose groups (Table 10).

A total of 97% of randomized patients had at least one medical history abnormality or current medical condition recorded at the time of study entry, besides hypertension. A total of 61% patients had at least one renal or urinary disorders. The most the most frequently reported conditions were urinary tract infection (19%) and vesicoureteric reflux (19%) followed by nephrotic syndrome (17%), chronic renal failure (15%) and congenital cystic kidney disease (12%).

Table 9. Demographics by treatment for patients in Period 1 (Randomized population)

Variable	Low N=30	Medium N=15	High N=30	Total N=75
Age (years)				
N	30	14	30	74
Mean (SD)	3.4 (1.28)	3.2 (1.48)	3.3 (1.53)	3.3 (1.41)
Median	4.0	3.0	4.0	4.0
Min, Max	1, 5	1, 5	1, 5	1, 5
Gender: n (%)				
Male	17 (56.7)	10 (66.7)	21 (70.0)	48 (64.0)
Female	13 (43.3)	4 (26.7)	9 (30.0)	26 (34.7)
Ethnicity: n (%)				
Hispanic	4 (13.3)	2 (13.3)	4 (13.3)	10 (13.3)
Non-Hispanic	26 (86.7)	12 (80.0)	26 (86.7)	64 (85.3)
Race: n (%)				
Caucasian	17 (56.7)	8 (53.3)	17 (56.7)	42 (56.0)
Black	3 (10.0)	2 (13.3)	4 (13.3)	9 (12.0)
Asian	8 (26.7)	4 (26.7)	8 (26.7)	20 (26.7)
Other	2 (6.7)	0 (0.0)	1 (3.3)	3 (4.0)
Race Strata: n (%)				
Caucasian	17 (56.7)	8 (53.3)	17 (56.7)	42 (56.0)
Non-Caucasian	13 (43.3)	6 (40.0)	13 (43.3)	32 (42.7)
Region group: n (%)				
Europe	14 (46.7)	7 (46.7)	12 (40.0)	33 (44.0)
Non-Europe	16 (53.3)	7 (46.7)	18 (60.0)	41 (54.7)

Percentage (%) is calculated using the randomized population (RAN1) as the denominator.
'Low'= Valsartan 0.25 mg/kg; 'Medium' = Valsartan 1.0 mg/kg; 'High' = Valsartan 4.0 mg/kg.

Source: CSR for K2303. Table 11-3. Page 66.

Table 10. Baseline characteristics for patients in Period 1 (Randomized population)

Variable	Low N=30	Medium N=15	High N=30	Total N=75
Weight (kg)				
N	30	14	30	74
Mean (SD)	16.1 (6.26)	14.6 (5.22)	16.9 (6.91)	16.2 (6.33)
Min, Max	8, 34	8, 28	9, 37	8, 37
Height (cm)				
N	30	14	30	74
Mean (SD)	97.5 (12.74)	93.8 (13.41)	97.6 (14.65)	96.9 (13.56)
Min, Max	78, 126	72, 120	77, 121	72, 126
BMI (kg/m**2)				
N	30	14	30	74
Mean (SD)	16.4 (2.48)	16.1 (1.75)	17.2 (3.24)	16.7 (2.71)
Min, Max	13, 26	13, 19	13, 30	13, 30
Head Circumference (cm)				
N	29	13	30	72
Mean (SD)	49.5 (2.56)	48.7 (2.18)	49.5 (2.33)	49.3 (2.39)
Min, Max	44, 55	45, 53	45, 55	44, 55
Continuing Prior Antihypertensive Therapy Strata , n (%)				
Non, use	26 (86.7)	12 (80.0)	22 (73.3)	60 (80.0)
Use	4 (13.3)	2 (13.3)	8 (26.7)	14 (18.7)
Continuing Prior Antihypertensive Therapy by ATC Class , n (%)				
ACE, Inhibitor	0 (0.0)	0 (0.0)	2 (6.7)	2 (2.7)
Beta Blocker	1 (3.3)	1 (6.7)	0 (0.0)	2 (2.7)
Calcium Channel Blocker	4 (13.3)	1 (6.7)	5 (16.7)	10 (13.3)
Diuretics	0 (0.0)	0 (0.0)	2 (6.7)	2 (2.7)
Other	0 (0.0)	0 (0.0)	1 (3.3)	1 (1.3)
MSSBP (mmHg)				
N	30	14	30	74
Mean (SD)	113.3 (8.45)	112.0 (5.97)	117.2 (9.88)	114.6 (8.84)
Min, Max	85, 130	101, 121	97, 139	85, 139
MSDBP (mmHg)				
N	30	14	30	74
Mean (SD)	69.5 (10.99)	71.3 (11.88)	70.8 (11.16)	70.4 (11.10)
Min, Max	50, 99	46, 93	48, 92	46, 99
Sitting Pulse (beats/minute)				
N	30	14	30	74
Mean (SD)	99.5 (13.66)	107.1 (17.52)	98.5 (11.18)	100.5 (13.75)
Min, Max	67, 121	80, 144	78, 123	67, 144

* Baseline values are collected at Visit 1 for Height and Head Circumference, other baseline values are collected at Visit 2 (randomization visit)
Percentage (%) is calculated using the randomized population (RAN1) as the denominator.
'Low'= Valsartan 0.25 mg/kg; 'Medium' = Valsartan 1.0 mg/kg; 'High' = Valsartan 4.0 mg/kg

Source: CSR for K2303. Table 11-4. Page 68.

Reviewer Comment: Period 1 treatment groups (low, med, high doses) were generally similar with regard to patient demographics and baseline characteristics except for baseline MSSBP which was higher in the high dose group than in the low and medium dose groups. Primary analysis was performed adjusted for the baseline MSSBP. No obvious difference across the dose groups with respect to the types and frequencies of abnormalities were noted.

Protocol Deviations

Protocol deviations occurred in 41 patients (55%) of the overall randomized population and occurred more often in the high and low dose groups than in the medium dose group. Twenty patients (27%) had major protocol deviations leading to exclusion from the per-protocol analysis. The most frequently reported major violations were MSSBP at time of randomization <95th percentile for age, sex and height (11%) and Visit 5 blood pressure taken <20 or >30 hours after the previous study medication dose (11%). Thirty patients (40%) had minor deviations. The most frequently reported were visits occurring outside the prescribed visit window in relation to Visit 2, and mis-stratification in IVRS (to include incorrect assignment as Continuing or Not Continuing on Anti-HTN therapy).

Efficacy Results

Primary Efficacy Variable

Change from baseline in MSSBP at Week 6 (Period 1)

The primary analysis was the dose dependent SBP reduction in Period 1 comparing valsartan low, medium, and high doses on the ITT1 population. The slope analysis yielded a slope estimate of -1.05 (mmHg) per unit increase in dose per body weight (p = 0.099) for change from baseline in MSSBP (Table 11). Higher doses of valsartan were associated with numerically greater reductions in SBP; however, a statistical significance was not achieved. At the end of Period 1, the reductions from baseline in MSSBP of 8.3, 10.3 and 14.4 mmHg, respectively, were observed in the 3 treatment groups (low, medium and high dose) (Table 12).

Table 11. Slope analysis for changes from baseline in MSSBP (mmHg) at end of Period 1 by treatment (ITT1)

	Estimate	Standard error	95% CI	P-value
Slope (ß)[1] (mmHg per unit increase in dose per body weight)	-1.05	0.630	(-2.31, 0.20)	0.0990

1 Slope is based on the regression model with terms including continuing prior antihypertensive therapy strata, race strata, baseline MSSBP, and dose per body weight.
* Indicates statistical significance at 0.05 level.

Source: CSR for K2303. Table 11-9. Page 73.

Table 12. Changes from baseline in MSSBP (mmHg) at end of Period 1 by treatment (ITT1)

	Low N=30	Medium N=14	High N=30
Baseline			
n	30	14	30
Mean (SD)	113.3 (8.45)	112.0 (5.97)	117.2 (9.88)
Median	114.7	112.7	118.7
Min, Max	85.3, 129.7	101.0,121.3	97.3, 138.7
End of period 1			
n	30	14	30
Mean (SD)	105.0 (9.52)	101.8 (13.16)	102.8 (9.08)
Median	104.0	101.5	102.0
Min, Max	90.0, 123.3	77.0, 122.7	87.7, 123.3
Change from baseline to End of Period 1			
n	30	14	30
Mean (SD)	-8.3 (10.44)	-10.3 (9.83)	-14.4 (10.93)
Median	-8.3	-8.2	-12.5
Min, Max	-33.7, 14.0	-29.7, 4.0	-46.7, 2.7
95% CI[1]	(-12.2, -4.4)	(-15.9, -4.6)	(-18.4, -10.3)
P-value[1]	0.0002 *	0.0018 *	<0.0001 *

[1]P-values and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
* Indicates statistical significance at 0.05 level.
-Baseline is the Visit 2 value, and endpoint of Period 1 is the value at Visit 5 or LOCF.
-Only patients who had both baseline and Period 1 endpoint values are included.
- 'Low'= Valsartan 0.25 mg/kg; 'Medium' = Valsartan 1.0 mg/kg; 'High' = Valsartan 4.0 mg/kg

Source: CSR for K2303. Table 11-8. Page 73.

Reviewer Comment: The results were verified by the reviewer. While the primary analysis of dose-response slope was not met, there was a numerical trend for dose-dependent reduction in MSSBP. In all dose groups, there were statistically significant reductions in MSSBP from baseline to end of Period 1.

It is plausible that the lack of statistical significance may be due to lower sample size when compared to study K2306 which is similar in design but enrolled more patients. The sample size in study K2303 was determined assuming a standard deviation of 7.5 mmHg in SBP which is lower than those observed (approximately 10 mmHg) in the three trials.

Secondary Efficacy Variables

Change in MSSBP from Week 6 to end of Period 2

Increase in MSSBP from the end of Period 1 to end of Period 2 were observed in both treatment groups (pooled valsartan and placebo). The magnitude of increase was marginally greater in valsartan group compared to placebo (Table 13).

Table 13. Between treatment comparison for change in MSSBP (mmHg) from end of Period 1 to end of Period 2 (ITT2)

Treatment	N	LSM change (SE) [1]	LSM difference (SE) [2]	95% CI [2]	P-value [2]
Valsartan	35	3.0 (1.62)	0.6 (1.95)	(-3.3, 4.5)	0.7575
Placebo	38	2.3 (1.53)			
Low/Low	15	-0.3 (2.18)	-3.8 (2.83)	(-9.4, 1.9)	0.1845
Low/Placebo	15	3.5 (2.24)			
Medium/Medium	6	6.1 (3.25)	8.0 (4.23)	(-0.4, 16.5)	0.0627
Medium/Placebo	8	-1.9 (2.91)			
High/High	14	3.1 (2.18)	-2.4 (2.89)	(-8.2, 3.4)	0.4084
High/Placebo	15	5.5 (2.04)			

1] LSM Change from Period 1 endpoint to endpoint of Period 2 within each treatment group, is from the model in [2].
[2] LSM difference, 95% CI, and p-values are for the difference between valsartan and placebo for each assigned dose level based on the ANCOVA model with treatment, race strata, continuing prior antihypertensive therapy strata as factors, and the centered Visit 5 MSSBP as a covariate.
* Indicates statistical significance at 0.05 level.
'Low/Low'= Val 0.25 mg/kg / Val 0.25 mg/kg; 'Low/Placebo'= Val 0.25 mg/kg / Placebo; 'Medium/Medoum'= Val 1.0 mg/kg / Val 1.0 mg/kg; 'Medium/Placebo'= Val 1.0 mg/kg / Placebo; 'High/High'= Val 4.0 mg/kg /Val 4.0 mg/kg; 'High/Placebo'= Val 4.0 mg/kg / Placebo.

Source: CSR for K2303. Table 11-11. Page 76.

Reviewer Comment: During Period 2, numerically higher increase in MSSBP was noted in the pooled valsartan group compared to placebo. This appears to be driven by the large difference between medium/medium (increase by 6.1 mmHg) and medium/placebo (decrease by 1.9). Difference between valsartan and placebo in low and high dose groups trended in the right direction.

The magnitude of the increase (3.1 mmHg) in high/high group during the 2-week of Period 2 is relatively small compared to the magnitude of reduction (-14.3 mmHg) observed in the high dose in Period 1. Therefore, the increase in MSSBP in high/high group may not indicate a loss of efficacy. No clear explanation can be provided for the medium/medium group except that it had the fewest patients.

Change in MSDBP from baseline to end of Period 1

The slope analysis yielded a slope estimate of -0.33 mmHg per unit increase in dose per body weight (p = 0.608) for the dose-response relationship for change from baseline in MSDBP. At the end of Period 1, MSDBP were reduced by 4.7, 8.6 and 6.7 mmHg for the low, medium and high dose group, respectively in the ITT1 population.

Table 14. Change in MSDBP from baseline to end of Period 1 by treatment group (ITT1)

	Low N=30	Medium N=14	High N=30
Baseline			
n	30	14	30
Mean (SD)	69.5 (10.99)	71.3 (11.88)	70.8 (11.16)
Median	68.7	68.7	67.0
Min, Max	50.3, 98.7	46.0, 92.7	48.0, 92.0
End of period 1			
n	30	14	30
Mean (SD)	64.8 (12.59)	62.7 (14.30)	64.1 (7.46)
Median	63.3	62.5	62.7
Min, Max	41.3, 91.3	40.0, 90.0	51.3, 81.3
Change from baseline to End of Period 1			
n	30	14	30
Mean (SD)	-4.7 (9.53)	-8.6 (12.43)	-6.7 (10.61)
Median	-4.2	-7.0	-5.3
Min, Max	-32.7, 11.3	-31.0, 9.3	-29.3, 11.7
95% CI[1]	(-8.3, -1.2)	(-15.8, -1.4)	(-10.7, -2.7)
P-value[1]	0.0113 *	0.0222 *	0.0017 *

[1]P-value and 95% CI are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
* Indicates statistical significance at 0.05 level.
-Baseline is the Visit 2 value, and endpoint of Period 1 is the value at Visit 5 or LOCF.
-Only patients who had both baseline and Period 1 endpoint values are included.
- 'Low'= Valsartan 0.25 mg/kg; 'Medium' = Valsartan 1.0 mg/kg; 'High' = Valsartan 4.0 mg/kg

Source: CSR for K2303. Table 11-13. Page 77.

Change in MSDBP from Week 6 to end of Period 2

Increase in MSDBP from the end of Period 1 to end of Period 2 were observed in both treatment and placebo groups. The increase was numerical greater in the placebo group, but the between group difference was not statistically significant.

Table 15. Between treatment comparison for change in MSDBP (mmHg) from end of Period 1 to end of Period 2 (ITT2)

Treatment	N	LSM change (SE) [1]	LSM difference (SE) [2]	95% CI [2]	P-value [2]
Valsartan	35	2.5 (1.61)	-0.4 (1.95)	(-4.3, 3.5)	0.8524
Placebo	38	2.9 (1.53)			
Low/Low	15	-0.3 (2.16)	-4.6 (2.84)	(-10.3, 1.0)	0.1081
Low/Placebo	15	4.3 (2.21)			
Medium/Medium	6	6.0 (3.25)	6.3 (4.24)	(-2.2, 14.7)	0.1445
Medium/Placebo	8	-0.3 (2.91)			
High/High	14	1.9 (2.17)	-2.7 (2.88)	(-8.5, 3.0)	0.3457
High/Placebo	15	4.7 (2.05)			

[1] LSM Change from Period 1 endpoint to endpoint of Period 2 within each treatment group, is from the model in [2].
[2] LSM difference, 95% CI, and p-values are for the difference between valsartan and placebo for each assigned dose level based on the ANCOVA model with treatment, race strata, continuing prior antihypertensive therapy strata as factors, and the centered Visit 5 MSDBP as a covariate.
* Indicates statistical significance at 0.05 level.
'Low/Low'= Val 0.25 mg/kg / Val 0.25 mg/kg; 'Low/Placebo'= Val 0.25 mg/kg / Placebo; 'Medium/Medoum'= Val 1.0 mg/kg / Val 1.0 mg/kg; 'Medium/Placebo'= Val 1.0 mg/kg / Placebo; 'High/High'= Val 4.0 mg/kg /Val 4.0 mg/kg; 'High/Placebo'= Val 4.0 mg/kg / Placebo.

Source: CSR for K2303. Table 11-16. Page 80.

Reviewer Comment: A dose-response relationship for MSDBP was not noted during the dose-response period. For the 2 weeks of randomized placebo withdrawal, MSDBP increased in both pooled valsartan and placebo arms. Similar to the observations for SBP, the increase in the pooled valsartan treatment group appears to be driven by medium/medium dose group which showed 6 mmHg increase compared to 0.3 mmHg decrease in the respective placebo group. The difference in MSDBP between valsartan and placebo trended in the right direction for low and high dose groups.

Efficacy Results – MSSBP and MSDBP in K2303E1
A total of 66 patients enrolled in the open-label extension trial, of which 60 (91%) patients completed the open-label phase while 6 (9%) patients discontinued. The most common reason for discontinuation was AEs, which occurred in 3 (5%) patients. All patients were required to start the extension on valsartan 1 mg/kg; however, 4 patients were started on valsartan 4 mg/kg due to a dosing error by the site pharmacist. These patients remained on valsartan 4 mg/kg for the entire study duration. Two patients (3.0%) initiated antihypertensive medications after starting extension study drug. Two patients (3%) took amlodipine and one of these two patients also took HCTZ as add-on therapy.

At endpoint (Week 26), the mean reduction in MSSBP/MSDBP was -11.2/-6.6 mmHg compared to baseline (Visit 2). The systolic BP control rate (MSSBP < 95th percentile for sex, age and height) for all patients who continued into the extension was 64%. At the end of the extension period, when all patients were taking valsartan (with or without adding amlodipine or HCTZ), the systolic BP control rate increased to 76%.

3.3.3 Study K2306

Patient Disposition
A total of 156 patients were screened, of which 127 patients were randomized in the study. A total of 120 patients (95%) completed the study. Two patients discontinued from the study due to AEs, both in

the valsartan 0.25 mg/kg group. There was 1 additional patient, in valsartan 0.25 mg/kg arm) counted as discontinued during the double-blind phase as a result of data entry error but the patient was discontinued during the open-label phase. Four patients (3%) withdrew consent from the study (1 patient from the valsartan 0.25 mg/kg and 3 patients from the valsartan 4 mg/kg treatment arm).

Patient Characteristics

Patient demographics were generally similar between both valsartan arms (Table 16). Approximately two thirds of patients were male (63%) and the majority of patients were Caucasian (75%). There were 8 Black patients (13%), all of whom were assigned to valsartan 4 mg/kg arm.

Baseline disease characteristics were generally similar between both valsartan arms (Table 17). The MSBP at baseline was slightly higher in the valsartan 0.25 mg/kg arm compared to valsartan 4 mg/kg arm (116.0 mmHg vs. 113.3 mmHg). The mean Schwartz eGFR was 143.2 mL/min/1.73m^2 and majority of patients (87.4%) had eGFR ≥90 mL/min/1.73m^2. A total of 70 patients (55%) received prior antihypertensive medication prior to the start of the study medication. Overall, ACE inhibitors were the most frequently used class of antihypertensives medication received prior to the start of study medication (46 patients, 36%).

During the double-blind phase of the study, a total of 24 patients (19%) used concomitant antihypertensive medications, the majority of which were dihydropyridine derivatives (18 patients, 14%). A slightly higher percentages of patients in the valsartan 4 mg/kg (21%) compared to valsartan 0.25 mg/kg arm (17%) used antihypertensive medication.

Table 16. Patient demographics (all randomized patients)

Characteristic	Valsartan 0.25 mg/kg N=65	Valsartan 4.0 mg/kg N=62	Total N=127
Age (years)			
n	65	62	127
Mean (SD)	3.35 (1.523)	3.17 (1.409)	3.26 (1.466)
Median	3.29	2.96	3.12
Min	1.02	1.00	1.00
Max	5.97	5.82	5.97
Gender – n (%)			
Male	39 (60.0)	41 (66.1)	80 (63.0)
Female	26 (40.0)	21 (33.9)	47 (37.0)
Race – n (%)			
Caucasian	50 (76.9)	45 (72.6)	95 (74.8)
Black	0	8 (12.9)	8 (6.3)
Asian	1 (1.5)	0	1 (0.8)
Native American	9 (13.8)	5 (8.1)	14 (11.0)
Other	5 (7.7)	4 (6.5)	9 (7.1)
Ethnicity – n (%)			
Hispanic/Latino	26 (40.0)	31 (50.0)	57 (44.9)
Other	39 (60.0)	31 (50.0)	70 (55.1)

Source: CSR for K2306, Table 11-3, page 80.

Table 17. Baseline and disease characteristics (all randomized patients)

Characteristic	Valsartan 0.25 mg/kg N=65	Valsartan 4.0 mg/kg N=62	Total N=127
Weight (kg)			
n	65	62	127
Mean (SD)	16.4 (6.94)	17.2 (7.42)	16.8 (7.16)
Median	14.5	15.1	14.7
Min - Max	8.1-37.4	8.0-37.6	8.0-37.6
Height (cm)			
n	65	62	127
Mean (SD)	95.8 (13.92)	97.0 (13.37)	96.4 (13.61)
Median	97.0	95.5	96.2
Min - Max	71.0-126.0	72.0-124.0	71.0-126.0
BMI (kg/m^2)			
n	65	62	127
Mean (SD)	17.2 (2.95)	17.4 (3.52)	17.3 (3.23)
Median	16.7	16.1	16.3
Min-Max	13.0-28.3	13.2-29.8	13.0-29.8
Head Circumference (cm)			
n	65	61	126
Mean (SD)	49.0 (4.50)	49.6 (2.51)	49.3 (3.67)
Median	50.0	50.0	50.0
Min-Max	19.0-55.0	44.0-55.0	19.0-55.0
Mean SBP (mmHg)			
n	65	62	127
Mean (SD)	116.0 (6.97)	113.3 (5.86)	114.7 (6.56)
Median	114.7	112.5	114.0
Min-Max	103.3-138.3	100.0-127.3	100.0-138.3
Mean DBP (mmHg)			
n	65	62	127
Mean (SD)	69.6 (7.18)	68.9 (6.39)	69.3 (6.79)
Median	68.7	68.8	68.7
Min-Max	51.7-88.7	49.7-83.0	49.7-88.7
Pulse (bpm)			
n	65	62	127
Mean (SD)	103.4 (14.81)	103.1 (11.94)	103.3 (13.43)
Median	102.0	103.5	102.0
Min-Max	50.0-146.0	73.0-130.0	50.0-146.0
CKD status – n (%)			
Yes	32 (49.2)	31 (50.0)	63 (49.6)
No	33 (50.8)	31 (50.0)	64 (50.4)
Schwartz eGFR ($mL/min/1.73m^2$)			

n	65	62	127
Mean (SD)	141.4 (41.88)	145.1 (42.94)	143.2 (42.27)
Median	144.6	145.9	145.9
Min-Max	45.8-235.0	36.8-235.4	36.8-235.4
Schwartz eGFR (mL/min/1.73m^2)- n (%)			
eGFR ≥30 to <60	3 (4.6)	3 (4.8)	6 (4.7)
eGFR ≥60 to <90	7 (10.8)	3 (4.8)	10 (7.9)
eGFR ≥90	55 (84.6)	56 (90.3)	111 (87.4)
Prior Antihypertensive Therapy Strata - n (%)			
No-use	32 (49.2)	25 (40.3)	57 (44.9)
Use	33 (50.8)	37 (59.7)	70 (55.1)
Prior antihypertensive therapy by ATC class - n (%)			
ACE Inhibitor	25 (38.5)	21 (33.9)	46 (36.2)
Beta Blocker	3 (4.6)	5 (8.1)	8 (6.3)
Calcium Channel Blocker	17 (26.2)	20 (32.3)	37 (29.1)
Diuretics	3 (4.6)	3 (4.8)	6 (4.7)
ARB	3 (4.6)	4 (6.5)	7 (5.5)
Others	2 (3.1)	2 (3.2)	4 (3.1)

BMI: body mass index; CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; ATC: anatomical therapeutic chemical.

Source: CSR for K2306. Table 11-5. Pages 82-83

Subgroup by CKD Status

The baseline demographics (Table 18) and baseline characteristics (Table 19) were generally balanced between the dose arms of both CKD and non-CKD patient populations. In the CKD subgroup, the percentage of male was slightly higher in 4 mg/kg arm compared to 0.25 mg/kg arm (74% and 63%, respectively), while the percentage of Caucasians were less in valsartan 4 mg/kg arm than valsartan 0.25 mg/kg arm (68% and 84%, respectively). The MSBP was slightly higher in the valsartan 0.25 mg/kg arm compared to 4 mg/kg arm in CKD subgroup (116.1 mmHg vs. 112.1 mmHg). In the non-CKD subgroup, the baseline demographics were generally balanced between the treatment arms.

A higher percentage of CKD patients used prior antihypertensives compared to non-CKD patients (67% vs. 44%). Overall, the most frequently used class of antihypertensives was ACE inhibitors (44% in CKD patients and 28% in non-CKD patients) followed by calcium channel blockers (32% in CKD patients and 27% in non-CKD patients).

During the double-blind phase, a higher percentage of CKD patients used concomitant antihypertensive medication compared to non-CKD patients (15 patients, 24% vs. 9 patients, 14%, respectively). Dihydropyridine derivatives were the most frequently used antihypertensive medication in both subgroups with a higher frequency of usage among CKD patients (12 patients, 19%) compared to non-CKD patients (6 patients, 9%).

Table 18. Patients demographics (all randomized patients by CKD and non-CKD subgroup)

	CKD patients			Non-CKD patients		
Variable	**Valsartan 0.25 mg/kg N=32**	**Valsartan 4.0 mg/kg N=31**	**Total N=63**	**Valsartan 0.25 mg/kg N=33**	**Valsartan 4.0 mg/kg N=31**	**Total N=64**
Age (years)						
N	32	31	63	33	31	64
Mean (SD)	2.99 (1.47)	2.72 (1.33)	2.86 (1.40)	3.70 (1.51)	3.62 (1.36)	3.66 (1.43)
Median	3.05	2.55	2.67	3.6	3.59	3.59
Min-Max	1.02-5.97	1.0-5.35	1.0-5.97	1.2-5.94	1.08-5.82	1.08-5.94
Gender n (%)						
Male	20 (62.5)	23 (74.2)	43 (68.3)	19 (57.6)	18 (58.1)	37 (57.8)
Female	12 (37.5)	8 (25.8)	20 (31.7)	14 (42.4)	13 (41.9)	27 (42.2)
Race n (%)						
Caucasian	27 (84.4)	21 (67.7)	48 (76.2)	23 (69.7)	24 (77.4)	47 (73.4)
Black	0	5 (16.1)	5 (7.9)	0	3 (9.7)	3 (4.7)
Asian	0	0	0	1 (3.0)	0	1 (1.6)
Native American	4 (12.5)	4 (12.9)	8 (12.7)	5 (15.2)	1 (3.2)	6 (9.4)
Other	1 (3.1)	1 (3.2)	2 (3.2)	4 (12.1)	3 (9.7)	7 (10.9)
Ethnicity n (%)						
Hispanic/Latino	12 (37.5)	16 (51.6)	28 (44.4)	14 (42.4)	15 (48.4)	29 (45.3)
Other	20 (62.5)	15 (48.4)	35 (55.6)	19 (57.6)	16 (51.6)	35 (54.7)

Source: CSR for K2306, Table 11-4, page 81.

Table 19. Baseline and disease characteristics (All randomized patients by CKD and non-CKD subgroup)

	CKD patients			Non-CKD patients		
Variable	Valsartan 0.25 mg/kg N=32	Valsartan 4.0 mg/kg N=31	Total N=63	Valsartan 0.25 mg/kg N=33	Valsartan 4.0 mg/kg N=31	Total N=64
Weight (kg)						
n	32	31	63	33	31	64
Mean (SD)	13.7 (3.15)	14.1 (4.13)	13.9 (3.64)	19.0 (8.52)	20.3 (8.67)	19.6 (8.55)
Median	14.3	13.2	13.5	18.0	18.1	18.0
Min - Max	8.3-20.4	8.0-24.2	8.0-24.2	8.1-37.4	8.6-37.6	8.1-37.6
Height (cm)						
n	32	31	63	33	31	64
Mean (SD)	91.6 (11.77)	92.5 (11.79)	92.1 (11.69)	99.9 (14.78)	101.5 (13.52)	100.7 (14.09)
Median	92.5	92.0	92.0	100.0	105.0	102.5
Min - Max	71.0-116.0	72.0-113.0	71.0-116.0	75-126	77-124	75-126
BMI (kg/m^2)						
n	32	31	63	33	31	64
Mean (SD)	16.2 (1.59)	16.1 (1.66)	16.2 (1.61)	18.1 (3.65)	18.8 (4.33)	18.4 (3.98)
Median	16.6	15.7	15.9	17.6	17.4	17.5
Min - Max	13.4-18.5	13.2-22.0	13.2-22.0	13.0-28.3	13.6-29.8	13.0-29.8
Mean systolic blood pressure (mmHg)						
n	32	31	63	33	31	64
Mean (SD)	116.1 (7.7)	112.1 (4.89)	114.1 (6.72)	115.9 (6.3)	114.6 (6.55)	115.2 (6.4)
Median	114.3	111.0	113.0	114.7	114.3	114.7
Min - Max	105.3-138.3	103.7-127.0	103.7-138.3	103.3-132.7	100-127.3	100-132.7
Mean diastolic blood pressure (mmHg)						
n	32	31	63	33	31	64
Mean (SD)	69.9 (5.59)	68.8 (5.44)	69.3 (5.5)	69.3 (8.53)	69.1 (7.31)	69.2 (7.9)
Median	69.2	69.0	69.0	68.7	68.7	68.7
Min - Max	60.0-84.7	60.3-81.0	60.0-84.7	51.7-88.7	49.7-83.0	49.7-88.7
Pulse (bpm)						
n	32	31	63	33	31	64
Mean (SD)	105.2 (13.5)	105.1 (10.44)	105.2 (11.99)	101.6 (15.98)	101.2 (13.15)	101.4 (14.56)
Median	106.0	106.0	106.0	102.0	102.0	102.0
Min - Max	85.0-141.0	89.0-130.0	85.0-141.0	50.0-146.0	73.0-130.0	50.0-146.0
Schwartz eGFR (mL/min/1.73m^2)						
n	32	31	63	33	31	64
Mean (SD)	125.7 (44.09)	124.7 (40.82)	125.2 (42.17)	156.5 (33.81)	165.4 (35.0)	160.8 (34.41)
Median	126.7	132.4	132.4	156.7	161.6	157.3
Min - Max	45.8-222.6	36.8-206.0	36.8-222.6	69.9-235.0	90.3-235.4	69.9-235.4
Schwartz eGFR (mL/min/1.73m^2) n (%)						
eGFR ≥30 to <60	3 (9.4)	3 (9.7)	6 (9.5)	0	0	0
eGFR ≥60 to <90	6 (18.8)	3 (9.7)	9 (14.3)	1 (3.0)	0	1 (1.6)
eGFR ≥ 90	23 (71.9)	25 (80.6)	48 (76.2)	32 (97.0)	31 (100)	63 (98.4)
CGFR (mL/min/1.73m^2)						

	CKD patients			Non-CKD patients		
Variable	Valsartan 0.25 mg/kg N=32	Valsartan 4.0 mg/kg N=31	Total N=63	Valsartan 0.25 mg/kg N=33	Valsartan 4.0 mg/kg N=31	Total N=64
n	30	30	60	NA	NA	NA
Mean (SD)	81.7 (24.39)	86.8 (27.78)	84.3 (26.05)	NA	NA	NA
Median	86.5	89.5	88.0	NA	NA	NA
Min - Max	34.0-128.0	29.0-144.0	29.0-144.0	NA	NA	NA
cGFR (mL/min/1.73m^2) n (%)						
cGFR <30	0	1 (3.2)	1 (1.6)	NA	NA	NA
cGFR ≥30 to <60	7 (21.9)	4 (12.9)	11 (17.5)	NA	NA	NA
cGFR ≥60 to <90	9 (28.1)	10 (32.3)	19 (30.2)	NA	NA	NA
cGFR ≥90	14 (43.8)	15 (48.4)	29 (46.0)	NA	NA	NA
Prior antihypertensive therapy strata - n (%)						
No-use	12 (37.5)	9 (29.0)	21 (33.3)	20 (60.6)	16 (51.6)	36 (56.3)
Use	20 (62.5)	22 (71.0)	42 (66.7)	13 (39.4)	15 (48.4)	28 (43.8)
Prior antihypertensive therapy by ATC Class - n (%)						
ACE Inhibitor	16 (50.0)	12 (38.7)	28 (44.4)	9 (27.3)	9 (29.0)	18 (28.1)
Beta Blocker	3 (9.4)	2 (6.5)	5 (7.9)	0	3 (9.7)	3 (4.7)
Calcium channel blocker	11 (34.4)	9 (29.0)	20 (31.7)	6 (18.2)	11 (35.5)	17 (26.6)
Diuretics	2 (6.3)	3 (9.7)	5 (7.9)	1 (3.0)	0	1 (1.6)
ARB	0	3 (9.7)	3 (4.8)	3 (9.1)	1 (3.2)	4 (6.3)
Others	2 (6.3)	2 (6.5)	4 (6.3)	0	0	0

BMI: body mass index; CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate, cGFR cystatin glomerular filtration rate, NA: Not applicable; ATC: anatomical therapeutic chemical.

Source: CSR for K2306. Table 11-6. Pages 84-85

Reviewer Comment: The baseline demographics were generally balanced between the treatment arms of both CKD and non-CKD patient populations except for race (Black patients). Baseline disease characteristics were generally similar between valsartan arms (4 mg/kg and 0.25 mg/kg) within the CKD groups with noteworthy difference in baseline MSBP. This imbalance was adjusted in the pre-defined primary analysis by including baseline MSBP as a covariate.

The applicant used the modified Schwartz formula (Schwartz et al. 1987) to calculate eGFR for all patients. This formula was developed based on the Jaffe assay (colorimetric) to measure serum creatinine (SCr). SCr can also be measured using an enzymatic essay. Using the 1987 Schwartz equation to estimate GFR using SCr measured by an enzymatic assay tends to overestimate eGFR. Because SCr in study K2306 was measured using an enzymatic assay, the reviewer corrected the eGFR using the Schwartz et al. 2009 equation which has been developed based on an enzymatic SCr assay. With use of the 2009 Schwartz equation, only one patient who was previously classified as non-CKD was now classified as having CKD; hence, grouping based on 1987 Schwartz equation as was done in study K2306 is not expected to affect subgroup analyses based on CKD status.

Protocol Violations/Deviations

Protocol deviations occurred in 65 patients (51.2%) in the double-blind phase. The majority of protocol deviations were due to vital signs (blood pressure and pulse) collected in a position other than as specified in the protocol (lying down or sitting or being held in parent's arms or lap, 24 patients [19%]).

Eighteen patients (14%) failed to follow visit schedule and 6 patients (5%) were <75% compliant taking study medication during the double-blind phase.

One CKD patient was excluded from FAS and the safety set as the guardian did not sign the informed consent. Twenty-one patients (17%) were excluded from PPS in the double-blind phase. The most frequently cited reason for exclusion was "study dose not taken or incorrect dose volume taken" (eight patients, 6%) followed by "patient <75% compliant with taking study medication during double-blind phase" (6 patients, 5%).

Efficacy Results

Primary Efficacy Variable

Change in MSBP from baseline to end of Week 6

The primary efficacy analysis was a between treatment comparison of two dose levels using pre-defined ANCOVA model. At Week 6, a decrease from baseline in MSBP was observed with a larger decrease in the valsartan 4 mg/kg group compared to the valsartan 0.25 mg/kg group (8.5 mmHg vs 4.1 mmHg). This difference was statistically significant (p=0.0157) (Table 20).

Table 20. Between treatment comparison for change from baseline in MSBP (mmHg) at Week 6 in double-blind phase (FAS)

				Difference in LS-mean change (valsartan 4.0 mg/kg - valsartan 0.25 mg/kg)		
Treatment	**n**	**Baseline mean (SE)**	**LS-mean change (SE)**	**mean (SE)**	**95% CI**	**p-value**
Valsartan 4.0 mg/kg (N=62)	62	113.3 (0.74)	-8.5 (1.27)	-4.4 (1.80)	-7.96, -0.85	0.0157*
Valsartan 0.25 mg/kg (N=64)	64	116.0 (0.88)	-4.1 (1.25)			

Source: CSR for K2306. Table 11-7. Page 87

Baseline is the Visit 2 value and endpoint of double-blind phase is the value at Visit 5 or LOCF. Only patients who had both baseline and double-blind phase endpoint values are included. LS means, 95% CIs, and p-values were based on an ANCOVA model with treatment and CKD strata as factors and centered-baseline MSBP as the covariate. * indicates statistical significance at 0.05 level.

The randomization was stratified based on CKD status (yes/no). Comparison between two dose levels for change from baseline in MSBP in CKD and non-CKD subgroups are presented in Table 21. In the CKD subgroup, a larger decrease in MSBP from baseline was observed in the valsartan 4 mg/kg group (9.2 mmHg) compared to the valsartan 0.25 mg/kg group (1.2 mmHg). This difference between the two dose arms was statistically significant (p=0.0096). In the non-CKD subgroup, a numerically larger decrease in MSBP from baseline was observed in the valsartan 4.0 mg/kg group compared to valsartan 0.25 mg/kg group (7.8 mmHg vs. 6.9 mmHg). However, this difference was not statistically significant.

Table 21. Between treatment comparison for change from baseline in MSBP (mmHg) at Week 6 by CKD status in double-blind phase (FAS)

				Difference in LS-mean change (valsartan 4.0 mg/kg - valsartan 0.25 mg/kg)		
Subgroup Treatment	**n**	**Baseline mean (SE)**	**LS-mean change (SE)**	**Mean (SE)**	**95% CI**	**p-value**
CKD						
Valsartan 4.0 g/kg (N=31)	31	112.1 (0.88)	-9.2 (2.05)	-7.9 (2.96)	-13.86, -2.01	0.0096*
Valsartan 0.25 mg/kg (N=31)	31	116.1 (1.40)	-1.2 (2.05)			
Non-CKD						
Valsartan 4.0 mg/kg (N=31)	31	114.6 (1.18)	-7.8 (1.48)	-0.9 (2.07)	-5.07, 3.20	0.6531
Valsartan 0.25 mg/kg (N=33)	33	115.9 (1.10)	-6.9 (1.44)			

Source: CSR Table 11-10. Page 89-90. P value of treatment by CKD interaction: 0.0354. Baseline is the Visit 2 value, and endpoint of double-blind phase is the value at Visit 5 or LOCF. Only patients who had both baseline and double-blind phase endpoint values are included. LS means, 95% CIs, and p-values were based on an ANCOVA model with treatment, CKD strata, treatment by CKD strata interaction as factors and centered-baseline MSBP as the covariate. * indicates statistical significance at 0.05 level.

Reviewer Comment: The primary analysis was verified by the reviewer. The results confirm dose-dependent reductions in MSBP when comparing the two doses of valsartan at the end of 6 weeks. The primary analysis was performed based on LOCF imputed data which was prespecified in the SAP of the original protocol.

The reviewer performed a slope analysis of the dose-response data. A slope estimate of -1.17 was obtained. The slope estimate is to be interpreted as the change in MSBP per unit increase in dose i.e., 1 mg/kg. Since there are only two dose levels, the slope analysis is expected to yield similar results as the between-treatment comparisons of two dose levels. Increasing from the low dose (0.25 mg/kg) to high dose (4 mg/kg), the treatment difference was 4.4 mmHg which corresponds to the slope estimate of 1.17 mmHg reduction per 1 mg/kg increase in dose.

*Subgroup analysis by CKD status was verified by the reviewer. The reviewer further conducted a subgroup analysis using pre-defined subgroup analysis incorporating the interaction term (CKD * DOSE) in model. The interaction was significant. LS mean values calculated from the model including the interaction term are similar to applicant's analysis. In the CKD group, a statistically significant dose-response relationship was observed. In the non-CKD group, while a significant dose-response relationship was not observed, both dose groups showed meaningful reductions in MSBP.*

Secondary Efficacy Variables

Change in MDBP from baseline to end of Week 6

At the end of Week 6, a greater decrease from baseline in MDBP was observed with valsartan 4 mg/kg arm compared to 0.25 mg/kg arm (6.8 mmHg vs 0.3 mmHg, respectively). This difference was statistically significant.

Comparison between two dose levels for change from baseline in MDBP were assessed in CKD and non-CKD subgroups. In the CKD subgroup, there was an increase of 1.3 mmHg in 0.25 mg/kg dose group compared to a decrease of 6.5 mmHg in the 4 mg/kg group. In the non-CKD subgroup, a greater reduction in MDBP was seen in 4 mg/kg group compared to 0.25 mg/kg arm. The difference between the two dose arms in both subgroups were statistically significant.

Table 22. Between treatment comparison for change from baseline in MDBP (mmHg) by CKD status at end of Week 6 in double-blind phase (FAS)

					Difference in LS-mean change (4 mg/kg vs. 0.25 mg/kg)		
	Treatment	n	Baseline MDBP (SE)	LS-mean change (SE)	Mean (SE)	95% CI	p-value
Full Analysis Set (FAS)	4 mg/kg	62	68.9 (0.81)	-6.8 (1.10)	-6.5 (1.54)	[-9.54, -3.44]	<0.0001*
	0.25 mg/kg	64	69.7 (0.89)	-0.3 (1.08)	-	-	-
Subgroup							
CKD	4 mg/kg	31	68.8 (0.98)	-6.5 (1.79)	-7.9 (2.54)	[-12.94, -2.78]	0.0030*
	0.25 mg/kg	31	70.2 (0.97)	1.3 (1.79)	-	-	-
Non-CKD	4 mg/kg	31	69.1 (1.31)	-7.2 (1.30)	-5.4 (1.80)	[-8.98, -1.77]	0.0042*
	0.25 mg/kg	33	69.3 (1.48)	-1.9 (1.26)	-	-	-

Source: Adapted from CSR for K2306. Tables 11-11, and 11-12. Pages 92-93.

Percentage of patients achieving MSBP <90th or <95th percentile for age, sex and height at Week 6 endpoint

A numerically larger percentage of patients in the 4 mg/kg arm achieved <90th and <95th percentile at Week 6 endpoint in MSBP compared to 0.25 mg/kg arm (Table 23). In the CKD subgroup, proportion of patients achieving blood pressure target was greater with 4 mg/kg compared to 0.25 mg/kg, however, in the non-CKD subgroup, both dose levels resulted in similar proportion of patients achieving the blood pressure target.

Table 23. Between treatment comparison for proportion of patients achieving MSBP <90th or <95th percentile for age, sex and height at Week 6 endpoint in double-blind phase (FAS)

		Patients achieving MSBP <90th percentile for age, sex and height			Patients achieving MSBP <95th percentile for age, sex and height		
		n/M (%)	Odds Ratio [95%CI]	p-val	n/M (%)	Odds Ratio [95%CI]	p-val
Full Analysis Set (FAS)	4 mg/kg	26/62 (41.9)	1.59 [0.75, 3.37]	0.2251	37/60 (61.7)	2.12 [1.02, 4.43]	0.0450*
	0.25 mg/kg	19/64 (29.7)	-	-	27/64 (42.2)	-	-
CKD	4 mg/kg	14/31 (45.2)	2.04 [0.67, 6.20]	0.2096	20/31 (64.5)	3.56 [1.18, 10.76]	0.0246
	0.25 mg/kg	8/31 (25.8)	-	-	9/31 (29.0)	-	-
Non-CKD	4 mg/kg	12/31 (38.7)	1.24 [0.44, 3.46]	0.6841	17/29 (58.6)	1.20 [0.44, 3.31]	0.7195
	0.25 mg/kg	11/33 (33.3)	-	-	18/33 (54.6)	-	-

Source: Adapted from CSR for K2306. Tables 11-13, 11-14, 11-15, 11-16. Pages 94-96.
n: The number of patients who achieved MSBP <90th (left table) or <95th (right table) percentile for age, sex and height
M: The number of patients with non-missing MSBP at Week 6 endpoint and baseline MSBP ≥95th percentile.

Logistic regression model: Logit (proportion) = treatment + centered-baseline MSBP + CKD strata
An odds ratio >1 favors the treatment in the numerator of the ratio

Percentage of patients achieving <90th or <95th percentile for age, sex and height in both MSBP and MDBP at Week 6 endpoint

Similar trend in results between doses by CKD/non-CKD status were observed when the blood pressure target was set at <90th and <95th percentile for age, sex and height in both MSBP and MDBP (Table 24).

Table 24. Between treatment comparison for proportion of patients achieving <90th, or <95th percentile for age, sex and height at Week 6 endpoint in both MSBP and MDBP (FAS)

		Patients achieving MSBP and MDBP <90th percentile for age, sex and height			Patients achieving MSBP and MDBP <95th percentile for age, sex and height		
		n/M (%)	Odds Ratio [95%CI]	p-val	n/M (%)	Odds Ratio [95%CI]	p-val
Full Analysis Set (FAS)	4 mg/kg	17/62 (27.4)	1.65 [0.70, 3.88]	0.2512	28/61 (45.9)	2.19 [1.02, 4.70]	0.0441
	0.25 mg/kg	13/64 (20.3)	-	-	19/64 (29.7)	-	-
CKD	4 mg/kg	9/31 (29.0)	1.68 [0.49, 5.80]	0.4111	13/31 (41.9)	2.18 [0.69, 6.86]	0.1818
	0.25 mg/kg	6/31 (19.4)	-	-	7/31 (22.6)	-	-
Non-CKD	4 mg/kg	8/31 (25.8)	1.45 [0.44, 4.79]	0.5443	15/30 (50.0)	1.98 [0.70, 5.64]	0.2008
	0.25 mg/kg	7/33 (21.2)	-	-	12/33 (36.4)	-	-

Source: Adapted from CSR for K2306. Tables 11-17, 11-18, 11-19, 11-20. Pages 96-100.
n: The number of patients who achieved both MSBP and MDBP <90th (left table) or <95th (right table) percentile for age, sex and height
M: The number of patients with non-missing both MSBP and MDBP at Week 6 endpoint and baseline MSBP and/or MDBP ≥ 95th percentile
Logistic regression model: Logit (proportion) = treatment + centered-baseline MSBP + CKD strata
An odds ratio >1 favors the treatment in the numerator of the ratio

Reviewer Comment: The results for the secondary efficacy variables suggest a similar trend of dose-dependent BP control as the primary analysis and support the effectiveness of valsartan.

- *A statistically significant difference in MDBP reduction was seen between the two dose arms (0.25 mg/kg and 4 mg/kg).*
- *A dose-response relationship for MDBP was seen in both CKD and non-CKD groups, while dose-response relationship for MSBP was evident in the CKD group.*
- *The proportions of patients achieving <90th or <95th percentile for MSBP were numerically higher with the high dose (4 mg/kg) compared to the low dose (0.25 mg/kg).*
- *The proportions of patients achieving <90th or <95th percentile for both MSBP and MDBP were higher with the high dose (4 mg/kg) compared to the low dose (0.25 mg/kg).*

Efficacy Results – MSBP and MDBP in the Open-label Phase

In the open-label phase, a decrease in MSBP and MDBP was sustained from Week 6 to Week 26 of the last post-baseline value. Following observations can be noted:

- The mean decrease in MSBP from baseline was 8.5 mmHg. Similar results were seen in the subgroup of CKD and non-CKD patients (decrease of 8.3 and 8.7 mmHg, respectively).
- The mean decrease in MDBP from baseline was 5.2 mmHg. Similar results were seen in the subgroup of CKD and non-CKD patients (decrease of 4.4 and 6.0 mmHg, respectively).

- A total of 42% (50/120) of patients achieved <90th percentile for age, sex and height in MSBP. Similar results were seen in the subgroup of CKD and non-CKD patients (41% vs 43%, respectively).
- A total of 65% (77/118) of patients achieved <95th percentile for age, sex and height in MSBP. A higher percentage of non-CKD patients achieved <95th percentile for age, sex and height in MSBP compared to CKD patients (71% vs 59%, respectively).
- A total of 27% (32/120) of patients achieved <90th percentile for age, sex and height in both MSBP and MDBP. A higher percentage of non-CKD patients achieved <90th percentile for age, sex and height in both MSBP and MDBP compared to CKD patients (36% vs 17%).
- A total of 46% (55/119) of patients achieved <95th percentile for age, sex and height in both MSBP and MDBP. A higher percentage of non-CKD patients achieved <95th percentile for age, sex and height in both MSBP and MDBP compared to CKD patients (60% vs 32%).

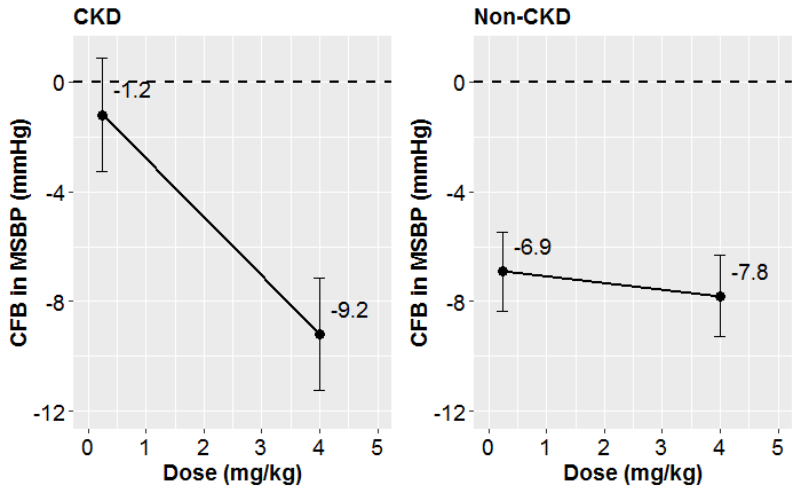
Reviewer Comment: The results from the open-label phase support the sustained effect of valsartan on blood pressure reduction. The magnitude of overall mean decrease in MSBP/MDBP are similar to those observed in the high dose arm (4 mg/kg) at the end of double-blind phase. The proportion of patients achieving <90th or <95th percentile for age, sex and height in MSBP at the end of open-label phase are similar to those observed in the high dose arm (4 mg/kg) at the endpoint of double-blind phase.

3.3.4. Important Patient Subgroups

Chronic Kidney Disease (CKD)

Study K2306 was designed to evaluate dose-response relationship of valsartan in children with hypertension with or without CKD and the randomization was stratified by patient's CKD status predefined by protocol. Approximately 50% of study subjects were categorized as patients with CKD. The subgroup analysis performed for MSBP reduction shows that the dose-response relationships are different between patients with CKD and non-CKD patients (Figure 6). A statistically significant dose-response relationship was only observed in the CKD group, while a dose-dependent reduction was not evident in non-CKD group. A dose-response relationship observed in full analysis population in K2306 (Figure 8) appears to be driven by the steeper relationship in the CKD patients.

Figure 6. Change from baseline in MSBP (mmHg) by CKD and non-CKD status in study K2306



Source: Reviewer's figures based on reviewer's analysis. Dots and annotated numbers represent the least square (LS) means for each dose level calculated from the pre-specified model in protocol for each study. Whiskers represent standard error of means.

It is noteworthy that though dose-response relationship was not observed in non-CKD group, substantial reductions in MSBP were observed with both the low (-6.9 mmHg) and the high dose (-7.8 mmHg) arms. This may imply that the low dose (0.25 mg/kg) and the associated valsartan exposure are at plateau region of the dose (exposure)-response curve in non-CKD patients. This motivated further assessment of efficacy data by CKD/non-CKD status in studies A2307 and K2303.

Descriptive subgroup analysis for studies A2307 and K2303 by CKD/non-CKD status were performed. The CKD status for each study subject was not pre-defined in studies A2307 and K2303. Therefore, the patients who likely had CKD at the time of enrollment were identified by Clinical Reviewer, Dr. Kirtida Mistry, based on the medical history and reported eGFR for each subject using the same criteria used in the protocol of study K2306. All randomized patients in A2307, and K2303 were categorized into three categories (likely CKD patients, non-CKD patients, unable to be determined due to insufficient data). Table 25 summarizes the composition of patients.

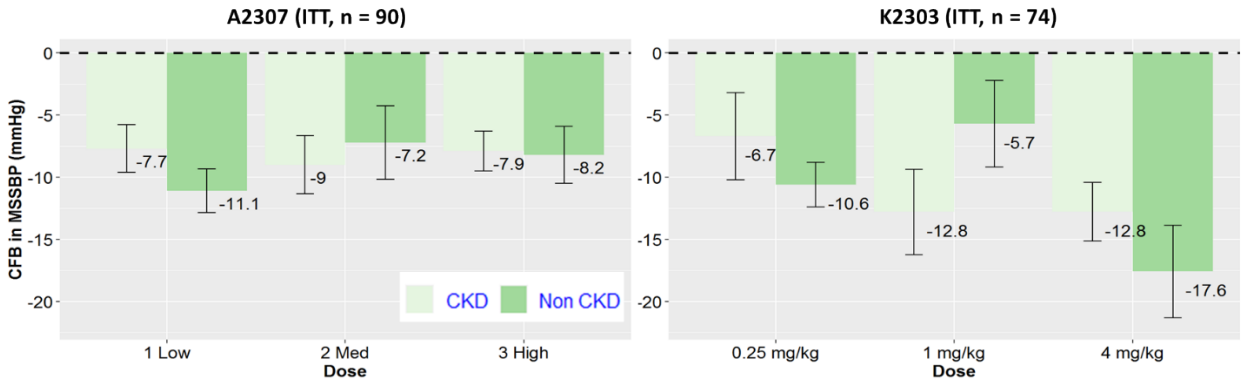
Table 25. Summary of patients identified as likely to have CKD in studies A2307 and K2303

	A2307				K2303			
Dose	5/10 mg	20/40 mg	40/80 mg	Total	0.25 mg/kg	1 mg/kg	4 mg/kg	Total
CKD	19	11	21	51 (57%)	15	9	16	40 (54%)
Non-CKD	15	7	11	33 (37%)	12	5	12	29 (39%)
ND*	3	0	3	6 (7%)	3	0	2	5 (7%)
Total	37	18	35	90 (100 %)	30	14	30	74 (100%)

ND represents "not determined due to insufficient data" and excluded from subgroup analysis.

The results of subgroup analysis by CKD status are presented in Figure 7. For A2307, the dose-response relationship is flat and similar between CKD and non-CKD patients. The lack of dose-response relationship is similar to the primary analysis based on ITT population. For K2303, there is a trend of dose-dependent reduction for both CKD and non-CKD patients, similar to the primary analysis with all randomized patients. The numerical treatment difference between the low dose and the high dose were similar between non-CKD patients (7 mmHg) compared to CKD patients (6.1 mmHg). Due to the small sample size, any formal statistical test for dose-response was not performed. Similar to what was observed in K2306, non-CKD patients tend to have a substantial reduction in SBP reductions with the low dose groups (-11.1 mmHg in the low dose [5/10 mg] for A2303, -10.6 mmHg in the low dose [0.25 mg/kg] for K2303). Taken together with the results from K2306, this suggests a potential benefit of the low dose in SBP reduction for non-CKD patients. This analysis is exploratory and further evaluation may be warranted.

Figure 7. Dose-response by CKD/non-CKD subgroup in studies A2307 and K2303



All randomized population						
	A2307			K2303		
Dose	5/10 mg	20/40 mg	40/80 mg	0.25 mg/kg	1 mg/kg	4 mg/kg
N	37	18	35	30	14	30
Mean SBP Reduction (SE)	-8.4 (1.4)	-8.3 (1.8)	-8.6 (1.3)	-8.3 (1.9)	-10.3 (2.6)	-14.4 (2.0)
Source: Reviewer's analysis.						

Source: Reviewer's analysis. Each bar and annotated text represent the arithmetic mean of SBP reduction for CKD and non-CKD patients for each dose arm. Error bars represent standard errors of the mean.

Race

Race was a stratification factor for Studies A2307 (Black vs. non-Black patients) and K2303 (Caucasian vs non-Caucasian). A descriptive subgroup analysis including K2306 is presented in Table 26. In general, no difference in magnitude of SBP reduction was noted between Black and non-Black patients for A2307. A substantial reduction was noted in Black patients receiving the low dose in K2303; however, it is based on 3 patients. No Black patients received low dose in K2306, and similar reductions were observed in Black and non-Black patients with the high dose. Overall, no apparent difference in SBP reduction is evident based on race.

Table 26. Mean (SD) change in SBP from baseline to the end of dose-response period by race

		A2307			K2303			K2306	
Treatment		Low (N=37)	Med (N=18)	High (N=35)	0.25 mg/kg (N=30)	1 mg/kg (N=14)	4 mg/kg (N=30)	0.25 mg/kg (N=64)	4 mg/kg (N=62)
Black	n	12	6	9	3	2	4	0	8
	Change	-7.9 (8.1)	-7.5 (3.0)	-7.9 (4.4)	-12.9 2.1	-14.5 2.1	-12.5 7.3	n/a	-8.7 (6.4)
Non-Black	n	25	12	26	27	12	26	64	54
	Change	-8.6 (8.7)	-8.8 (9.3)	-8.8 (8.4)	-7.8 (10.9)	-9.6 (10.5)	-14.6 (11.5)	-4.7 (11.2)	-7.9 (9.4)

Source: Reviewer's analysis. Consistent with applicant's analysis reported for studies A2307 and K2303.

Concomitant Antihypertensive Drugs

Continuing prior antihypertensive therapy was a stratification factor for studies A2307 and K2303 and a descriptive subgroup analysis was performed by the applicant. The reviewer performed a similar analysis for study K2306. Concomitant use of antihypertensives in dose-response periods is summarized by study (Table 27). A greater proportion (71%) of patients in study A2307 received antihypertensives prior to randomization compared to studies K2303 (39%), and K2306 (55%). Overall, similar proportions (19%) of patients continued their prior antihypertensive drugs during the dose-response period.

Table 27. Concomitant antihypertensive use in dose-response period

	A2307 (ITT, n= 90)			K2303 (ITT, n=75)			K2306 (FAS, n=126)	
Prior use	64 (71%)			29 (39%)			70 (55%)	
Continuing use	17 (19%)			14 (19%)			24 (19%)	
Treatment	Low (N=37)	Med (N=18)	High (N=35)	0.25 mg/kg (N = 30)	1 mg/kg (N = 15)	4 mg/kg (N = 30)	0.25 mg/kg (N = 64)	4 mg/kg (N = 62)
Total	6 (16%)	4 (22%)	7 (20%)	4 (13%)	2 (13%)	8 (27%)	11 (17%)	13 (21%)
CCB	5 (14%)	2 (11%)	3 (9%)	4 (13%)	1 (7%)	5 (17%)	9 (14%)	9 (14%)
ACEi	1 (3%)	2 (11%)	2 (6%)	0 (0%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)
BB	1 (3%)	0 (0%)	2 (6%)	1 (3%)	1 (7%)	0 (0%)	3 (5%)	3 (5%)
Diuretics†	1 (3%)	0 (0%)	1 (3%)	1 (3%)	0 (0%)	3 (10%)	4 (6%)	2 (3%)
Others	1 (3%)	1 (6%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	3 (5%)	1 (2%)
†	2 furosemide			2 plain thaizide;2 furosemide			5 HCTZ; 1 furosemide	

Source: Adapted from CSR for A2307, Post-Text Table 8.2-2, CSR for K2303, Table 14.3-1.3, CSR for K2306, Table 14.3-1.5.
†Diuretics in this table includes furosemide and thiazides.

SBP reductions during dose-response period are summarized by continuing prior hypertensive therapy (Table 28). Patients on concomitant antihypertensives showed somewhat steeper dose-response relationship in SBP reduction in studies K2303 and K2306. Due to the small sample size for each subgroup and potential confounders such as CKD status, baseline SBP, this analysis is considered exploratory. Also, data from adult hypertension trials of valsartan suggests that the blood pressure-lowering effect of valsartan and thiazide-type diuretics are approximately additive. Because of the small number of subjects who received diuretics (Table 27) in pediatric trials, a subgroup analysis based on concomitant use of diuretics was not assessed.

Table 28. Mean (SD) change in SBP from baseline to the end of dose-response period by concomitant use of antihypertensives

		A2307			K2303			K2306	
Treatment		Low (N=37)	Med (N=18)	High (N=35)	0.25 mg/kg (N=30)	1 mg/kg (N=14)	4 mg/kg (N=30)	0.25 mg/kg (N=64)	4 mg/kg (N=62)
Continued Use	n	6	4	7	4	2	8	11	13
	Change	-5.1 (14.1)	-13.5 (6.8)	-9.4 (9.5)	+4.3 (9.0)	-14.7 (9.9)	-14.5 (6.1)	+3.9 (12.6)	-6.9 (10.9)
No use	n	31	14	28	26	12	22	53	49

	Change	-9.0 (7.1)	-6.9 (7.4)	-8.4 (7.2)	-10.2 (9.3)	-9.5 (10.1)	-14.3 (12.4)	-6.5 (10.1)	-8.2 (8.6)

Source: Reviewer's analysis. Consistent with applicant's analysis reported for studies A2307 and K2303.

3.3.5 Integrated Summary of Efficacy

The antihypertensive effect of valsartan in 290 children aged between 1 to less than 6 years of age has been evaluated in three randomized, double-blind clinical studies (A2303, K2303 and K2306). Salient design features of studies A2303, K2303 and K2306 are listed in Table 29. Because of differences in the patient populations and study designs, a pooled analysis was not conducted. A totality of evidence from these studies supports the effectiveness of valsartan in pediatric patients age 1 to <6 years of age, which are outlined below.

Table 29. Summary of studies conducted in pediatric patients age 1 to <6 years of age

Characteristics		Study A2307	Study K2303/K2303E1	Study K2306
Study design		Dose-response followed by placebo withdrawal	Dose-response followed by placebo withdrawal	Dose-response followed by open-label optional dose titration
Patient age (years)		1-5	1-5	1-5
Number of randomized patients		N=90	N=75	N=127
Efficacy Analysis population		ITT = 90	ITT1 = 74	FAS = 126
Doses (n)	Low	5 mg/10 mg (n=37)	0.25 mg/kg (n=30)	0.25 mg/kg (n=64)
	Med	20 mg/40 mg (n=18)	1 mg/kg (n=14)	-
	High	40 mg/80 mg (n=35)	4 mg/kg (n=30)	4 mg/kg (n=62)
CKD		Not defined in protocol	Not defined in protocol	Pre-defined in protocol
Formulation		Extemporaneous suspension	Extemporaneous suspension	Oral solution
Duration				
Dose-response		2 weeks	6 weeks	6 weeks
Placebo withdrawal		2 weeks	2 weeks	-
Open-label		52 weeks	18 weeks	20 weeks
Background antihypertensive therapy		No other than patients' current antihypertensive treatment known to have a significant effect on BP were allowed	Prohibited ARB	Prohibited RAAS blockers (ARB, ACEi, DRI, aldosterone antagonists)

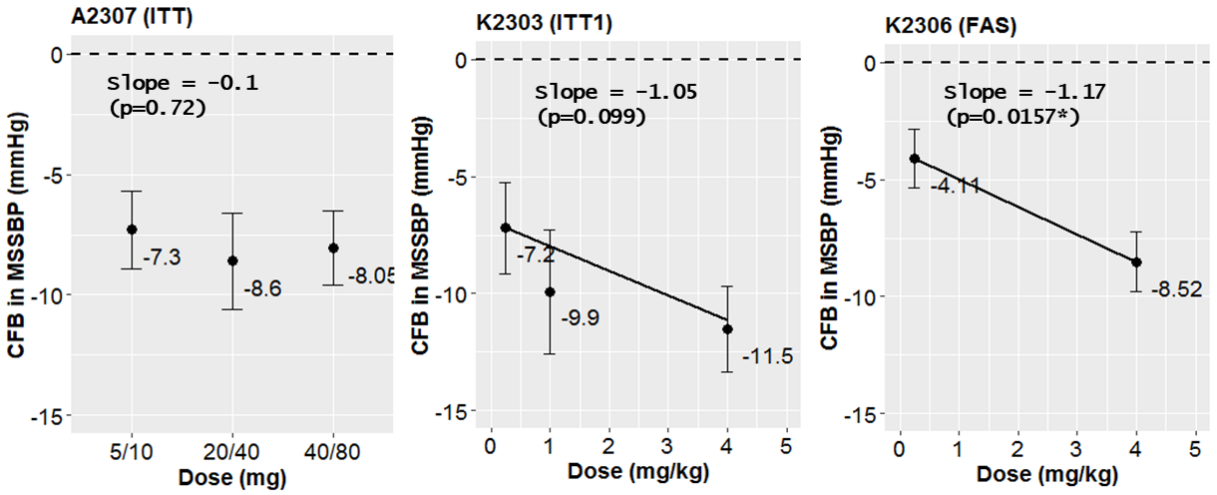
Source: Adapted from Table 1-4, page 16 of Clinical Overview

Dose-Response

The primary objective for studies A2307, K2303, and K2306 was to evaluate a dose-response relationship for change from baseline in systolic blood pressure (SBP) following valsartan treatment in the double-blind, dose-repose period. Primary analysis results for the 3 studies are summarized in Figure 8. A statistically significant dose-response relationship was demonstrated in study K2306, with slope estimate of -1.17 and a difference between high and low dose of 4.4 mmHg (p=0.0157). As only two dose levels were studied in study K2306, a slope analysis and difference between the two dose levels are expected to produce similar results. Dose-dependent reductions in MSSBP were observed in study K2303 with a similar slope estimate (-1.05) as seen in study K2306, though a significance was not

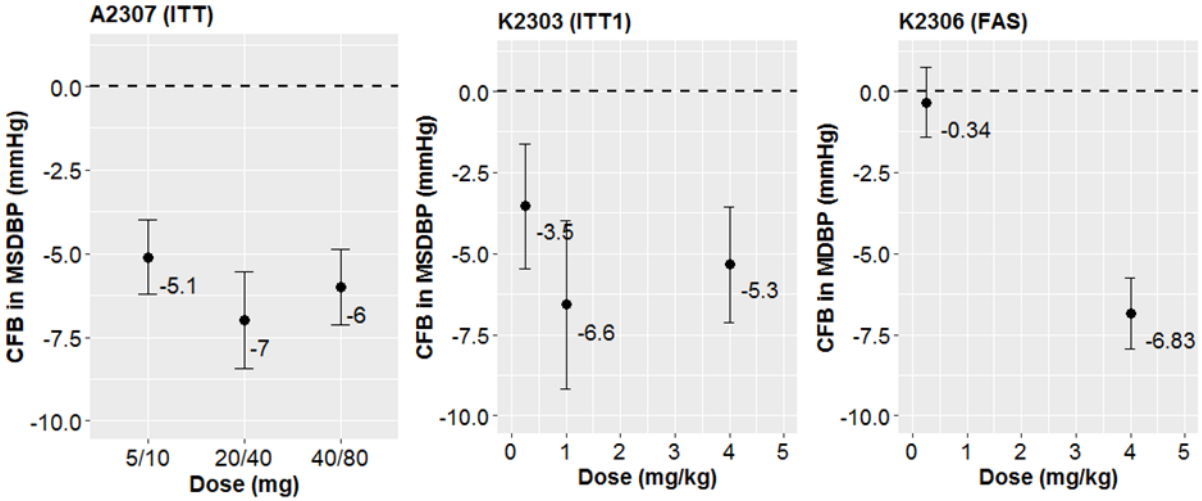
achieved. The dose-response relationship was flat in study A2307. Similar analyses were performed for DBP which was a secondary efficacy variable (Figure 9). A statistically significant dose-response relationship for DBP was observed in study K2306, while no apparent dose-response relationship for DBP was observed in studies A2307 and K2303.

Figure 8. Primary analysis of dose-response for studies A2307, K2303 and K2306



Source: Reviewer's analysis. X-axis for the left panel (A2307) shows doses (mg) for body weight strata (<18 kg/≥18 kg). CFB: Change from baseline. Dots and annotated numbers represent the least square (LS) means for each dose level calculated from the pre-specified model in protocol for each study. Whiskers represent standard error of means. The lines represent the fitted linear regressions from the pre-specified slope analyses for studies K2303, and K2306. *pre-defined significance level of 0.05.

Figure 9. DBP reduction from baseline in the dose-response period for studies A2307, K2303 and K2306



Source: Reviewer's figures. X-axis for the left panel (A2307) shows doses (mg) for body weight strata (<18 kg/≥18 kg). CFB: Change from baseline. Dots and annotated numbers represent the least square (LS) means for each dose level calculated from the pre-specified model in protocol for each study. Whiskers represent standard error of means.

Clinically Meaningful SBP/DBP Reductions

While a dose-response was not demonstrated in studies A2307 and K2303, there were clinically and statistically significant reductions in SBP by 7 to 11 mmHg and DBP by 3.5 to 7 mmHg from baseline to

the end of dose-response period for all dose levels (low, medium, high) evaluated for studies A2307 and K2303 (Figure 8 and Figure 9).

Treatment Effect in Randomized Placebo Withdrawal Phase
In the randomized placebo withdrawal phase of study A2307, there was an additional SBP reduction (1.8 mmHg) in the pooled (low to low, medium to medium, high to high dose) valsartan group compared to an increase of 2.1 mmHg in the pooled placebo group. The LS mean difference between the two pooled groups was -3.9 mmHg (p=0.0217). When analyzed separately by dose groups (Table 4), the difference in the change from baseline in mean sitting SBP between valsartan and placebo was statistically significant for the medium dose. In the high dose group, the difference between valsartan and placebo trended in a similar direction, but the p-value narrowly missed statistical significance.

Sustained Blood Pressure Control
Long-term efficacy data were collected in the open-label period of studies A2307 and K2306 and from the extension study K2303E1. The observations showed a sustained decrease in SBP/DBP from end of dose-response period to the end of open-label periods. At the end of the optional 52-week OL extension of study A2307, the mean decrease in SBP/DBP from baseline were 11.5/7.2 mmHg. In K2303E1, the optional 18-week OL extension study, the mean decrease in SBP/DBP from baseline was 11.2/6.6 mmHg. At the end of the 20-week OL titration period of study K2306, the mean decrease in SBP/DBP from baseline was 8.5/5.2 mmHg. Similar results were seen in the CKD and non-CKD subgroups i.e., decrease in SBP/DBP by 8.3/4.4 mmHg and 8.7/6.0 mmHg, respectively. The reductions in blood pressure observed at the end of open-label period were consistent with mean reductions observed during the dose-response period of each studies.

3.3.6 Relative Bioavailability Assessment
Out of the three efficacy studies done in children <6 years of age, valsartan extemporaneous suspension was used in studies A2307 and K2303 and valsartan oral solution was used in study K2306 (Table 29). To bridge the clinical efficacy and safety data of the oral solution to the suspension formulation, a relative bioavailability (BA) study (CVAL489K2101 (K2101)) was conducted in healthy adults. Study K2101 is an open-label, randomized, single dose, two period, crossover study evaluating the relative BA of valsartan following administration of valsartan 160 mg oral solution compared to valsartan 160 mg extemporaneous suspension under fasted condition.

The extent (AUC_{0-t}, $AUC_{0-\infty}$) of absorption of valsartan is similar between the oral solution and the extemporaneous suspension. The 90% confidence intervals for the geometric mean ratios of valsartan AUC_{0-t} and $AUC_{0-\infty}$ lie within the bioequivalence limits of 80% and 125%. The rate (C_{max}) of absorption is 32% higher for the oral solution formulation compared to the extemporaneous suspension formulation. Median time (t_{max}) to attain peak plasma concentration of valsartan was 1 h (range: 1 to 2 h) post-dose for the oral solution and 3 h (range: 1 to 4 h) post-dose for extemporaneous suspension. For drugs like antihypertensives which are dosed chronically, AUC or C_{trough} is a more relevant metric that correspond to drug's effect. As the total systemic exposure of valsartan is similar between the oral solution and suspension formulations, the results obtained with oral solution in study K2306 can be extrapolated to the suspension formulation. The mean C_{max} and AUC of extemporaneous suspension are 90% (60 to 130%) and 60% (40 to 80%) higher, respectively, compared to the adult 80 mg tablet. The dose of valsartan may need to be adjusted when switching between suspension and tablet formulations in children who are old enough to swallow tablets.

Table 30. Relative bioavailability assessment results (study K2101)

PK Parameter (unit)	Mean (%CV)		GMR test/reference (%) (90% CI)
	Oral solution (test) (n-=82)	Extemporaneous suspension (reference) (n=82)	
AUC_{0-t} (ng·h/mL)	52410 (28.5%)	48080 (29.4%)	1.09 (1.05, 1.13)
$AUC_{0-\infty}$ (ng·h/mL)	52910 (28.4%)	48540 (29.3%)	1.09 (1.05, 1.13)
C_{max}§ (ng/mL)	8655 (20.1%)	6571 (23.1%)	1.32 (1.27, 1.38)

CI: confidence interval; CV: coefficient of variation; GMR: geometric least squares mean ratio;
§: N= 83; Source: Reviewer's analysis

3.3.7 Acceptability of the Proposed Dosing Recommendations

The current recommended starting dose of valsartan for children 6 to 16 years is 1.3 mg/kg once-daily (not to exceed 40 mg) with titration to a maximum dose of 2.7 mg/kg once-daily (not to exceed 160 mg). In this supplement, the applicant has proposed a starting dose of 1 mg/kg once-daily (not to exceed 40 mg) with titration to a maximum dose of 4 mg/kg once-daily (not to exceed 160 mg) for children 1 to 16 years of age.

Applicant's proposed dosing recommendation in the 1 to <6 years age group is primarily based on study K2306 which evaluated 0.25 mg/kg and 4 mg/kg once-daily dose for 6-weeks during the randomized, double-blind treatment period. This was followed by an open-label extension period of 20 weeks where patients were initiated with valsartan 1 mg/kg and were titrated to 2 mg/kg, 3 mg/kg, and 4 mg/kg at 4-week intervals. The study results suggest dose dependent reductions in MSBP for valsartan over 0.25 mg/kg to 4 mg/kg dose range for the 6-week treatment period. During the open-label phase of study K2306, the number of patients who did not require titration and remained on the 1 mg/kg dose for the entire 20 weeks duration was 38 (31.7%) while 14 (11.7%) required titration to 4 mg/kg. The efficacy and safety data from study K2306 support the proposed starting dose of 1 mg/kg once-daily (not to exceed 40 mg) with titration to a maximum dose of 4 mg/kg once-daily (not to exceed 160 mg) for children 1 to <6 years of age.

The current dosing recommendation for children of age 6 to 16 years of age is based on study A2302 (NDA021283/S-024) which evaluated the efficacy and safety of low, medium and high dose of valsartan administered as body-weight tiered fixed doses. After adjusting for individual body-weight, the median low, medium and high dose correspond to 0.4 mg/kg, 1.3 mg/kg and 2.7 mg/kg daily doses of valsartan. Revision of the starting dose from 1.3 mg/kg to 1 mg/kg in 6 to 16 years of age is acceptable, as 1 mg/kg was well covered within the range of body-weight adjusted doses evaluated in the medium dose group in study A2302. A dose of 4 mg/kg was observed to be overall safe and well tolerated in pediatric

patients <6 years of age in studies K2303, K2303E1 and K2306. Based on the demonstrated safety and tolerability of 4 mg/kg dose of valsartan in pediatric patients <6 years of age, the applicant has proposed body weight adjusted maximum dose of 4 mg/kg (not to exceed 160 mg) for patients 6 to 16 years of age. The applicant has proposed increase in the maximum mg/kg dose of valsartan while keeping the same maximum total dose of 160 mg as the current dosing recommendation. The proposed dosing regimen is suitable particularly for patients who are transitioning to age >6 years and can tolerate 4 mg/kg dose.

The mean dose-normalized exposure of valsartan tends to increase with age in pediatric patients (see Clinical Pharmacology review for NDA012283/S-024). The mean dose normalized C_{max} and $AUC_{0\text{-}inf}$ of valsartan is approximately 20 to 50% higher in patients 12 to 16 years of age compared to younger patients (1 to <12 years of age). However, as valsartan doses will be titrated based on tolerability, the proposed maximum dose of 4 mg/kg (not to exceed 160 mg) for patients 6 to 16 years of age is acceptable.

3.4 Safety Results

Important Safety Issues with Valsartan and Related Drugs

The current valsartan label includes Warnings and Precautions for fetal toxicity, hypotension, impaired kidney function including acute kidney failure, and hyperkalemia, known adverse reactions of the angiotensin receptor blocker class.

Valsartan is currently not labeled for use in pediatric patients under 6 years of age because of safety concerns (deaths and transaminitis) raised in two previous studies (A2307 and K2303) in 164 pediatric patients 1 to 5 years of age. A causal relationship between these events and valsartan could not be established because the events occurred in the open-label extension and were not unexpected in the study population, which often had significant comorbidities. Given the lack of dose-response in this younger group in study A2307, the label states "Diovan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded."[2]

For review of this supplement, safety analyses focused on known and potential toxicities of valsartan including liver transaminase elevations, hyperkalemia, hypotension, kidney impairment, and hypersensitivity.

Safety Analysis Set and Overall Exposure

Safety analyses used the safety population, which included 200 enrolled patients in studies K2303/K2303E1 (74 patients) and K2306 (126 patients) who received at least one dose of study drug. One patient randomized to valsartan 0.25 mg/kg in study K2306 was excluded from the safety population because the guardian did not sign the informed consent, and one patient randomized to valsartan 1 mg/kg was excluded from study K2303 because the study site (b) (4) was closed (critical GCP findings) and no information about the patient was obtained from the site.[3] Safety data from studies K2303/K2303E1 and K2306 were pooled because both studies had a similar design with a 6-week

[2] Efficacy and safety data from study A2307 were reviewed in October 2007 under NDA 021283/S024. Safety data from study K2303 were reviewed in February 2012 under NDA 021283/SLR-035 (a Prior Approval labeling Supplement, which provided additional safety information in pediatric patients 1 to <6 years of age with hypertension).

[3] These patients were also excluded from the full analysis set.

double-blind dose-response period (Pool A) and an open-label extension period (18 and 20 weeks in studies K2303E1 and K2306, respectively [Pool B]). Both studies used weight-based valsartan dosing during the dose-response periods (0.25, 1, and 4 mg/kg in study K2303, and 0.25 and 4 mg/kg in study K2306). The 2-week placebo-withdrawal period of study K2303 was excluded from the pooled safety analyses because study K2306 did not include a similar placebo-withdrawal period, but all serious adverse events (SAEs), study discontinuations due to adverse events (AEs), and significant laboratory abnormalities during that period were reviewed. FDA previously reviewed the safety data from study K2303 in 2012, including the placebo-withdrawal period (labeling supplement 035).

Safety evaluations for studies K2303, K2303E1 and K2306 included vital signs, physical examinations, laboratory tests, and electrocardiograms, which were performed at regular intervals.

Of the 200 patients enrolled at the beginning of studies K2303 and K2306, 192 (96%) and 178 (89%) patients were exposed to valsartan for at least 6 and 20 weeks, respectively. The mean (SD) duration of exposure was 69 (47) days.

In Pool A, of the 200 patients enrolled in the 6-week dose-response phases of studies K2303 and K2306, 195 patients (98%) were exposed to valsartan for ≥28 days (4 weeks), and 139 patients (70%) were exposed to valsartan for ≥42 days (6 weeks) (Table 31). The mean (SD) exposure was 41 (7) days.

In Pool B, of the 186 patients enrolled in the extension phases of studies K2303E1 and K2306, 173 (93%) and 96 (52%) patients received valsartan for ≥16 and ≥20 weeks, respectively. The mean (SD) duration of exposure was 134 (20) days.

Table 31. Duration of Exposure, Pools A and B, Safety Population

	Pool A by valsartan dose				Pool B	
	0.25 mg/kg N=94 n (%)	1 mg/kg N=14 n (%)	4 mg/kg N=92 n (%)	All Patients N=200 n (%)		All Patients N=186 n (%)
Exposure (days)					Exposure (days)	
>0	94 (100)	14 (100)	92 (100)	200 (100)	>0	186 (100)
≥7 (1 week)	93 (99)	14 (100)	90 (98)	197 (99)	≥56 (8 weeks)	184 (99)
≥14 (2 weeks)	92 (98)	14 (100)	90 (98)	196 (98)	≥84 (12 weeks)	181 (97)
≥28 (4 weeks)	91 (97)	14 (100)	90 (98)	195 (98)	≥112 (16 weeks)	173 (93)
≥42 (6 weeks)	61 (65)	12 (86)	66 (72)	139 (70)	≥140 (20 weeks)	96 (52)
Descriptive statistics (days)						
N	94	14	92	200		186
Mean (SD)	41 (8)	42 (1)	41 (7)	41 (7)		134 (20)
Median	42	42	42	42		140
Min, Max	4, 84	39, 45	3, 54	3, 84		7, 168

Source: Sponsor's Table 1-3, Summary of Clinical Safety (SCS) and Table 2.1a, SCS, Appendix 1.
Abbreviations: N = number of patients in treatment arm; n = number of patients with given treatment duration; SD = standard deviation.

Categorization of Adverse Events

The applicant categorized AEs and SAEs by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. An AE was defined as any undesirable sign, symptom, or medical condition irrespective of its relationship with the study drug. A SAE was defined as an event that resulted in death, was life-threatening, required hospitalization or prolonged an existing hospitalization, resulted in persistent or significant disability or incapacity, or was a medically important event. A treatment-emergent adverse event (TEAE) was defined as an AE that occurred or worsened on or after the first dose of study drug, and any AE that was subsequently considered related to study drug.[4] AEs were collected from the time of informed consent.

Overall Adverse Event Summary

The overall incidence of TEAEs was 49% in Pool A and 70% in Pool B (Table 32). Most reported AEs were mild or moderate in severity. SAEs occurred in eight patients (4%) in Pool A and 10 patients (5%) in Pool B. Four patients (2%) in Pool A and six (3%) in Pool B discontinued study drug because of AEs. The most common TEAEs (incidence ≥5%) occurred in Pool B and were pyrexia, nasopharyngitis, cough, upper respiratory tract infection, diarrhea, bronchitis, vomiting, tonsillitis, and ear infection and were not thought by investigators to be related to study drug. TEAEs with a frequency of >1% can be found in 5.1. Appendix A (Table 35 and Table 36). TEAEs considered related to study drug by the investigator were reported in 7% of patients in Pool A and 5% in Pool B. Review of TEAEs by eGFR subgroups (<90 vs. ≥90 mL/min/1.73 m^2) did not reveal significant differences.

Table 32. Overview of Adverse Events, Safety Population

Event Category		Pool A N=200 n (%)	Pool B N=186 n (%)
Any AE		98 (49)	130 (70)
Mild AEs		68 (34)	89 (48)
Moderate AEs		24 (12)	35 (19)
Severe AEs		6 (3)	6 (3)
Any SAE		8 (4)	10 (5)
SAE with fatal outcome		0	0
AE leading to discontinuation of study drug		4 (2)*	6 (3)*
TEAEs thought to be related to investigational product		13 (7)	10 (5)
Most common	Vomiting	3 (2)	1 (0.5)
	Diarrhea	2 (1)	1 (0.5)
	Hyperkalemia	1 (0.5)	1 (0.5)
	Decreased appetite	0	2 (1)

Source: Sponsor's Summary of Clinical Safety (SCS), SCS Appendix 1, and Clinical Study Reports of studies K2303, K2303E1, and K2306.

Abbreviations: AE = adverse event; N = number of patients in treatment arm; n = number of patients with at least one event; SAE = serious adverse event.

[4] The applicant did not provide a definition for a TEAE. The reviewer used the standard commonly used definition in this review.

*The sponsor reports AEs leading to discontinuation of study drug in 2 patients (1%) in Pool A and 4 (2%) in Pool B, however, the clinical reviewer identified additional patients.

Deaths

There were no deaths in Pools A, B, or the 2-week placebo withdrawal period of study K2303.

Non-Fatal Serious Adverse Events

SAEs occurred in 8 patients (4%) in Pool A and 10 patients (5%) in Pool B (Table 33). The most common SAEs were infections including respiratory and viral infections, which are common in children 1 to 5 years of age. Review of all the reported SAEs in Pools A, B, and the placebo-withdrawal phase of study K2303 did not reveal an obvious association with study drug and were generally consistent with the comorbidities of the patient population.

Table 33. Number of Patients with SAEs, by System Organ Class and Preferred Term, Safety Population

	Pool A by valsartan dose				Pool B
	0.25 mg/kg	1 mg/kg	4 mg/kg	All Patients	All Patients
System Organ Class Preferred Term	N=94 n (%)	N=14 n (%)	N=92 n (%)	N=200 n (%)	N=186 n (%)
Patients with Any SAE	3 (3)	1 (7)	4 (4)	8 (4)	10 (5)
Infections and infestations	2 (2)	0	2 (2)	4 (2)	5 (3)
Gastroenteritis	0	0	0	0	2 (1)
Bronchitis	1 (1)	0	1 (1)	2 (1)	0
Upper respiratory tract infection	1 (1)	0	1 (1)	2 (1)	0
Respiratory tract infection	1 (1)	0	0	1 (0.5)	0
Mastoiditis	0	0	0	0	1 (0.5)
Pharyngitis	0	0	0	0	1 (0.5)
Viral infection	0	0	0	0	1 (0.5)
Gastrointestinal disorders	1 (1)	0	2 (2)	3 (2)	0
Gastritis	1 (1)	0	1 (1)	2 (1)	0
Enteritis	0	0	1 (1)	1 (0.5)	0
Injury, poisoning and procedural complications	0	0	0	0	3 (2)
Contusion	0	0	0	0	1 (0.5)
Head injury	0	0	0	0	1 (0.5)
Toxicity to various agents	0	0	0	0	1 (0.5)
Wound	0	0	0	0	1 (0.5)
Renal and urinary disorders	1 (1)	0	1 (1)	2 (1)	2 (1)
Nephrotic syndrome	1 (1)	0	1 (1)	2 (1)	2 (1)
General disorders and administration site conditions	0	0	0	0	1 (0.5)
Oedema peripheral	0	0	0	0	1 (0.5)
Metabolism and nutrition disorders	0	0	1 (1)	1 (0.5)	0
Dehydration	0	0	1 (1)	1 (0.5)	0
Psychiatric disorders	1 (1)	0	0	1 (0.5)	0
Aggression	1 (1)	0	0	1 (0.5)	0

	Pool A by valsartan dose				Pool B
System Organ Class Preferred Term	0.25 mg/kg N=94 n (%)	1 mg/kg N=14 n (%)	4 mg/kg N=92 n (%)	All Patients N=200 n (%)	All Patients N=186 n (%)
Respiratory, thoracic and mediastinal disorders	0	1 (7)	0	1 (0.5)	0
Bronchospasm	0	1 (7)	0	1 (0.5)	0

Source: Sponsor's Tables 2-13 and 2-14, Summary of Clinical Safety.
Abbreviations: AE = adverse event; N = number of patients in treatment arm; n = number of patients with at least one event; SAE = serious adverse event.

Dropouts or Discontinuations Due to Adverse Events

Overall, 10 patients (5%) discontinued study drug because of AEs. The commonest AE leading to study drug discontinuation was hyperkalemia in four patients (2%); all were non-serious. Of these one (ITA/0704/00001) was likely not related to study drug because the patient developed hyperkalemia after receiving placebo during the randomized-withdrawal phase of study K2303. Review of all the study drug discontinuations due to AEs did not identify new safety information.

Adverse Events of Special Interest

The safety review focused on hepatic AEs and transaminitis, which were a safety concern in previously reviewed studies 2307 and K2303/K2303E1. All other AEs were consistent with labeled adverse reactions for this class (hyperkalemia, hypotension, kidney impairment, and hypersensitivity), thus no new safety information for this age group was identified.

1. Hepatic Adverse Events and Abnormal Liver Tests

No AEs mapped to the Drug-related Hepatic Disorders SMQ in Pools A, B, or the placebo-withdrawal phase of study K2303. Overall, four patients (2%) had an increase in ALT of >3 x ULN, and one patient (0.5%) had an increase in ALT of >10 x ULN and AST >3 x ULN (Table 34).

In Pool A, one patient (0.5%) had a transient and sporadic increase in ALT >3 x ULN that resolved spontaneously while remaining on valsartan.

- *Study K2303, IND/* [redacted]: 5-year-old male with a history of steroid-induced gastritis, anemia, dermatomyositis, and myalgia on concomitant prednisolone. ALT was mildly elevated at baseline (36 U/L [ULN 30 U/L]), and increased to 97 U/L (>3 x ULN) on Day 15 of the dose-response period. Bilirubin and AST remained normal throughout. Valsartan was continued. The patient completed the dose-response phase and the extension study K2303E1 and all subsequent ALT measurements were within normal (20 U/L on Day 46, 12 U/L on Day 57, 17 U/L on Day 185).

In Pool B, one patient (0.6%) with CMV infection had an ALT >10 x ULN and AST >3 x ULN. Three patients (2%) had an ALT >3 x ULN, two of which improved while remaining on valsartan. There were no follow up liver assessments reported for the third patient (K2306-[redacted]), whose ALT increased at the end of the study.

- *Study K2303E1,* [redacted]: 1-year-old male with a history of hemolytic uremic syndrome and bronchospasm. No concomitant medications were reported. He was randomized to valsartan 0.25 mg/kg in the dose-response and randomized withdrawal periods. Valsartan dose was increased to 1 mg/kg during the extension period. He had normal liver assessments until the end of study visit, when ALT was >10 x ULN and AST >3 x ULN (bilirubin was normal throughout) in the setting of an approximately 2-week febrile illness secondary to pneumonia

and CMV infection. Three new medications (amoxicillin, clarithromycin, and metamizole sodium) were introduced during this time. Valsartan was discontinued at the end of the study. The investigator assessed the transaminitis to be secondary to CMV infection, and the AST and ALT returned to normal 39 days after the end of study visit.

- *Study K2306, K2306-* (b) (6): 3-year-old male with a history of hypertension and patent ductus arteriosus repair. He was on concomitant amlodipine, enalapril and metamizole. He was randomized to valsartan 4 mg/kg in the dose-response period. Baseline ALT and AST were above the normal range at 55 U/L (ULN 30 U/L) and 92 U/L (ULN 69 U/L), respectively. At the end of the dose-response period, ALT was 32 and AST 49 U/L. On Day 43, the valsartan dose was decreased to 1 mg/kg. On Day 92 of the extension phase ALT and AST were normal (16 and 41 U/L, respectively). On Day 197 (end of study visit), ALT was 109 U/L and AST was 94 U/L. No additional information was available for this patient.

- *Study K2306, K2306-* (b) (6): 5-year-old male with a history of hypertension, chronic kidney disease and kidney dysplasia. He was on concomitant enalapril. He was randomized to valsartan 4 mg/kg in the dose-response period. Baseline ALT and AST were within the normal range (30 and 46 U/L, respectively) and did not change from baseline at the end of the dose-response phase. On Day 106, while on valsartan 1 mg/kg, ALT was 92 (>3x ULN) and AST 96 U/L (>2 x ULN). On Day 127, valsartan was increased to 2 mg/kg and at the end of study visit ALT and AST improved to 33 and 50 U/L, respectively.

- *Study K2306, K2306-* (b) (6) 5-year-old female with a history of hypertension, nephrotic syndrome, and renal tubular acidosis. She was on losartan and amlodipine prior to the study, and concomitant prednisone and phenytoin. No concomitant medications were reported. She was hospitalized for a seizure during the screening period prior to receiving study drug, and was subsequently randomized to valsartan 0.25 mg/kg in the dose-response period. Baseline ALT was above the normal range at 36 U/L (ULN 30 U/L) and AST was 44 U/L (ULN 58 U/L). On Day 92, while on valsartan 2 mg/kg, ALT increased to 106 U/L, and AST was 63 U/L. No action was taken and on Day 100, ALT had improved to 68 U/L and AST was 62 U/L. Valsartan was increased to 3 mg/kg on Day 127 and 4 mg/kg on Day 155 and end of study (Day 183) ALT and AST were 23 and 33 U/L, respectively.

Table 34. Worst Post-baseline Liver Tests, Safety Population

	Pool A by Valsartan Dose				Pool B
	0.25 mg/kg	1 mg/kg	4 mg/kg	All Patients	All Patients
Test	N=94	N=14	N=92	N=200	N=186
Worst Post-Baseline	n/M (%)	n/M (%)	n/M (%)	n/M (%)	n/M (%)
Total bilirubin (µmol/L)					
>2 x ULN	0/73	0/14	0/75	0/162	0/159
AST (U/L)					
>3 x ULN	0/84	0/14	0/86	0/184	1/178 (0.6)
>5 x ULN	0/84	0/14	0/86	0/184	0/178
>8 x ULN	0/84	0/14	0/86	0/184	0/178
>10 x ULN	0/84	0/14	0/86	0/184	0/178
ALT (U/L)					
>3 x ULN	0/90	0/14	1/90 (1)	1/194 (0.5)	3/181 (2)
>5 x ULN	0/90	0/14	0/90	0/194	0/181
>8 x ULN	0/90	0/14	0/90	0/194	0/181
>10 x ULN	0/90	0/14	0/90	0/194	1/181 (0.6)

Source: Sponsor's Summary of Clinical Safety (SCS), Tables 3-6 and 3-11.
Abbreviations: N = number of patients in treatment arm; n = number of patients with abnormality; M = number of patients with at least one post-baseline value for the specified parameter; ULN = upper limit of normal.

The Division reviewed study A2307 in 2007.[5] The clinical reviewer notes four patients had "marked increases in transaminases; one of these patients had a positive serology for hepatitis A. One patient was discontinued from the study due to hepatitis (see Deaths).[6] A third patient was noted to have marked elevations in transaminases (300-500 U/L range) at the end of study visit, with normalization of transaminases 10 days later... A fourth patient (b) (6) with elevated transaminases showed normalization while continuing the same dose of valsartan treatment."

Reviewer comment: In the data from 200 patients in studies K2303, K2303E1 and K2306, five patients had significant transaminitis with an ALT and/or AST >3 x ULN. One patient with an ALT >10 x ULN and AST >3 x ULN had CMV infection/hepatitis, three patients' ALT improved while continuing the same or higher doses of valsartan, and one patient with abnormal ALT and AST at baseline had variable ALT and AST throughout the study including increased measurements at the end of study. These data do not indicate clear drug-related transaminase elevations in these studies.

[5] NDA 021283/S024, review dated October 15, 2007.

[6] One-year-old male with a history of lower respiratory tract infection, bronchopneumonia, hyperbilirubinemia, gastrointestinal reflux, neonatal sepsis, cryptorchism, right solitary pelvic kidney, polydactyly, and developmental delay. His transaminases were mildly elevated on screening. Because of elevated blood pressure, the valsartan dose was increased to 80 mg once-daily. On Day 193, he presented with fever, cough, coryza and vomiting. He was hospitalized two days later with pneumonitis and hepatitis (hepatitis serology was negative). The valsartan dose was decreased to 20 mg once-daily, and by Day 207, his transaminases had markedly improved. The investigator discontinued the patient from the study due to hepatitis. Eleven days later, the patient was readmitted for exacerbation of pneumonitis; he went into respiratory failure and died 8 hours after admission.

Safety Summary and Conclusion
Previously identified safety concerns in pediatric patients 1 to <6 years of age included two deaths and three cases of transaminitis during the open-label, uncontrolled part of study A2307. A causal relationship with valsartan could not be established. Subsequently, in 200 patients 1 to <6 years of age in studies K2303, K2303E1 and K2306, no deaths or significant drug-related liver transaminase increases were observed. No new safety signals were noted in the three studies reviewed. These data provide reassurance that the risks of valsartan do not outweigh the benefits.

The current Diovan label includes reports of "Elevated liver enzymes and very rare reports of hepatitis" under section 6.2 Postmarketing Experience. We recommend retaining a comment in Section 6 Adverse Reactions, informing prescribers of the findings of transaminitis and lack of a clear causal relationship to valsartan in pediatric patients 1 to <6 years of age.

4 Labeling Recommendations
See the Executive Summary.

5 Appendix

5.1. Appendix A

Table 35. Treatment-emergent Adverse Events with an incidence ≥1%, Pool A, Safety Population

Preferred term	Valsartan 0.25 mg/kg N=94 n (%)	Valsartan 1 mg/kg N=14 n (%)	Valsartan 4 mg/kg N=92 n (%)	All Patients N=200 n (%)
Number of patients with at least one AE	50 (53.2)	6 (42.9)	42 (45.7)	98 (49.0)
Cough	5 (5.3)	1 (7.1)	3 (3.3)	9 (4.5)
Diarrhoea	5 (5.3)	0	4 (4.3)	9 (4.5)
Nasopharyngitis	6 (6.4)	1 (7.1)	2 (2.2)	9 (4.5)
Pyrexia	2 (2.1)	0	7 (7.6)	9 (4.5)
Bronchitis	5 (5.3)	0	3 (3.3)	8 (4.0)
Respiratory tract infection	5 (5.3)	0	3 (3.3)	8 (4.0)
Vomiting	6 (6.4)	0	2 (2.2)	8 (4.0)
Abdominal pain	3 (3.2)	0	4 (4.3)	7 (3.5)
Upper respiratory tract infection	4 (4.3)	0	3 (3.3)	7 (3.5)
Headache	4 (4.3)	0	1 (1.1)	5 (2.5)
Rhinitis	4 (4.3)	0	0	4 (2.0)
Tonsillitis	1 (1.1)	0	3 (3.3)	4 (2.0)
Gastroenteritis	1 (1.1)	0	2 (2.2)	3 (1.5)
Nephrotic syndrome	2 (2.1)	0	1 (1.1)	3 (1.5)
Urinary tract infection	2 (2.1)	0	1 (1.1)	3 (1.5)
Urticaria	1 (1.1)	0	2 (2.2)	3 (1.5)
Allergy to arthropod bite	0	1 (7.1)	1 (1.1)	2 (1.0)
Bronchospasm	1 (1.1)	1 (7.1)	0	2 (1.0)
Conjunctivitis	2 (2.1)	0	0	2 (1.0)
Gastritis	1 (1.1)	0	1 (1.1)	2 (1.0)
Gastroenteritis viral	1 (1.1)	1 (7.1)	0	2 (1.0)
Otitis media acute	1 (1.1)	0	1 (1.1)	2 (1.0)
Pharyngitis	1 (1.1)	1 (7.1)	0	2 (1.0)
Rash	1 (1.1)	0	1 (1.1)	2 (1.0)
Tracheobronchitis	1 (1.1)	0	1 (1.1)	2 (1.0)
Varicella	2 (2.1)	0	0	2 (1.0)

- Pooled population includes 6-week double-blind dose-response periods of Study K2303 and Study K2306.
- PTs are sorted in descending frequency of AEs in the 'All patients' column.
- Patient with multiple AEs is counted only once in the at least one AE row.
- MedDRA Version 20.1 has been used for the reporting of AEs.
- Source: [SCS Appendix 1-Table 4.5].

Source: Sponsor's Summary of Clinical Safety (SCS), Table 2-7.

Table 36. Treatment-emergent Adverse Events with an incidence ≥1%, Pool B, Safety Population

Preferred term	Valsartan mono N=184 n (%)	Valsartan+ HCTZ/amlo N=2 n (%)	All Patients N=186 n (%)
Number of patients with at least one AE	128 (69.6)	2 (100)	130 (69.9)
Pyrexia	30 (16.3)	1 (50.0)	31 (16.7)
Nasopharyngitis	15 (8.2)	1 (50.0)	16 (8.6)
Cough	15 (8.2)	0	15 (8.1)
Upper respiratory tract infection	15 (8.2)	0	15 (8.1)
Diarrhoea	13 (7.1)	0	13 (7.0)
Bronchitis	12 (6.5)	0	12 (6.5)
Vomiting	12 (6.5)	0	12 (6.5)
Tonsillitis	11 (6.0)	0	11 (5.9)
Ear infection	10 (5.4)	0	10 (5.4)
Headache	7 (3.8)	1 (50.0)	8 (4.3)
Rhinitis	8 (4.3)	0	8 (4.3)
Pharyngitis	7 (3.8)	0	7 (3.8)
Respiratory tract infection	7 (3.8)	0	7 (3.8)
Viral infection	6 (3.3)	0	6 (3.2)
Stomatitis	5 (2.7)	0	5 (2.7)
Urinary tract infection	5 (2.7)	0	5 (2.7)
Gastroenteritis	4 (2.2)	0	4 (2.2)
Otitis media	4 (2.2)	0	4 (2.2)
Sinusitis	4 (2.2)	0	4 (2.2)
Urticaria	4 (2.2)	0	4 (2.2)
Varicella	3 (1.6)	1 (50.0)	4 (2.2)
Viral upper respiratory tract infection	4 (2.2)	0	4 (2.2)
Allergy to arthropod bite	3 (1.6)	0	3 (1.6)
Conjunctivitis	3 (1.6)	0	3 (1.6)
Decreased appetite	3 (1.6)	0	3 (1.6)
Food allergy	3 (1.6)	0	3 (1.6)
Oropharyngeal pain	3 (1.6)	0	3 (1.6)
Abdominal pain	2 (1.1)	0	2 (1.1)
Alanine aminotransferase increased	2 (1.1)	0	2 (1.1)
Bronchospasm	2 (1.1)	0	2 (1.1)
Dysuria	2 (1.1)	0	2 (1.1)
Epistaxis	2 (1.1)	0	2 (1.1)
Erythema	2 (1.1)	0	2 (1.1)
Fatigue	2 (1.1)	0	2 (1.1)
Gastritis	2 (1.1)	0	2 (1.1)
Hyperkalaemia	2 (1.1)	0	2 (1.1)
Nausea	2 (1.1)	0	2 (1.1)
Nephrotic syndrome	2 (1.1)	0	2 (1.1)
Otitis media acute	2 (1.1)	0	2 (1.1)
Pain in extremity	2 (1.1)	0	2 (1.1)
Wheezing	2 (1.1)	0	2 (1.1)
Wound	1 (0.5)	1 (50.0)	2 (1.1)

- Pooled population includes open-label Study K2303E1 (18 weeks) and Study K2306 open-label period (20 weeks).
- PTs are sorted in descending frequency of AEs in the 'All patients' column.
- Patient with multiple AEs is counted only once in the "at least one AE" row.
- Patient with multiple AEs with the same PT is counted only once for that PT.
- MedDRA Version 20.1 has been used for the reporting of AEs.
- Source: [SCS Appendix 1-Table 4.5a].

Source: Sponsor's Summary of Clinical Safety (SCS), Table 2-10.

5.2 Financial Disclosure

Was a list of clinical investigators provided?	Yes
Total number of investigators identified	69
Number of investigators who are Sponsor employees (including both full-time and part-time employees)	None
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455)	None
Number of investigators with certification of due diligence (Form FDA 3454, box 3)	None

5.3 Review Team

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Division Director (signatory)	Norman Stockbridge

* Participated in relevant discussions during review and/or towards labeling but did not author this collaborative review

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