Medical-Statistical Review

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Drug: Valsartan
Trade Name: Diovan
NDA: 21-283
Submission Number: SE5-024
Letter Date: May 29, 2007

Executive Summary:

The assigned medical officer and statistician jointly reviewed two clinical studies in the valsartan pediatric submission. Each study employed the Written Request type C design, with a double-blind two-week dose-ranging phase and a double-blind two-week placebo withdrawal; both trials included an optional 52-week open-label extension. Study A2302 randomized 261 hypertensive patients, aged 6-16 years; study A2307 randomized 90 hypertensive patients, aged 1-5 years.

In study A2302 a dose-response is supported by the statistically significant slope analysis in the dose-ranging phase. Study A2307 showed decreases from baseline in BP with a flat dose-response (p=NS). The placebo withdrawal phase for both A2302 and A2307 showed a significant difference between pooled valsartan and placebo for the change in BP, supporting a treatment effect.

In the safety analysis of A2302, an increased incidence of BUN (> 50%) was seen with higher doses during double-blind. Hyperkalemia (> 5.5 mmol/L) was reported in 6 patients (2.3%) during double-blind; during open-label, hyperkalemia was reported in 3.8% of patients. Five out of 6 patients with hyperkalemia at end of double-blind had a history of chronic kidney disease, and four of them were renal transplant patients. Otherwise, the most common adverse events were headache and dizziness, and the safety profile appeared similar to that seen in adults.

In A2307, two patients during open-label exhibited marked transaminase elevations without other obvious attributable reasons (such a positive serology); a third patient displayed elevated transaminases (3-10x ULN range) at the open-label end-of-study visit (#061-00006).

The results support a treatment effect for valsartan (via placebo withdrawal phases). Due to the cases of elevated transaminases in the younger patients, this reviewer does not recommend use unless the sponsor can show convincing proof of safety in this population.

VAL489A2302:

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
(First patient recruited: 12/12/2002, Last patient completed: 3/15/2006)

Primary Objective: Evaluate the dose-response of valsartan in sitting systolic blood pressure (SBP) in children 6-16 years-old with hypertension.

Secondary Objective: Determine efficacy of short-term (4 week) and safety/tolerability of short term (4 weeks) and long-term (52 weeks) administration of valsartan in children 6-16 years-old with hypertension.

Study Summary: This study followed the Written Request type C design.
This was a double-blind, randomized study with 4 phases: a single-blind placebo washout (screening phase) of up to one week; a two-week, double-blind phase (Phase 1) in which eligible patients were randomized (2:1:2) to low, medium and high dose valsartan; a randomized, double-blind placebo withdrawal phase of up to two weeks (Phase 2) where patients either continued their Phase 1 valsartan dose or were switched to placebo; and an optional 52-week open-label (OL) treatment phase, where patients received valsartan 40 mg QD and were titrated according to their mean seated trough systolic blood pressure (SSBP).

In all phases, study visits took place at 22-26 hours post-dose; study medication was withheld on the day of a visit until after measurements and evaluations were completed. For the screening and Phases 1 and 2, patients were given three tablets taken once daily, with double-dummy packaging, based on the dose of valsartan. During the open-label phase, patients received valsartan 40 mg QD at Day 0-OL (Visit 6). Patients could be up-titrated, through Visit 10 (Week 8-OL), based on mean trough SSBP measurements; if this value was $\geq 95^{th}$ percentile for age, gender and height, the investigator could up-titrate the valsartan dose every 2 weeks to the next higher dose. Upward titration of valsartan from 40 to 80 to 160 mg QD to 160 mg QD plus hydrochlorothiazide 12.5 mg QD was allowed during the open-label phase of the study.

If at Visit 10, the patient had been receiving valsartan 160 mg QD (with or without HCTZ) for four weeks without adequate control, the patient was discontinued from the study and all end-of-study evaluations were completed.

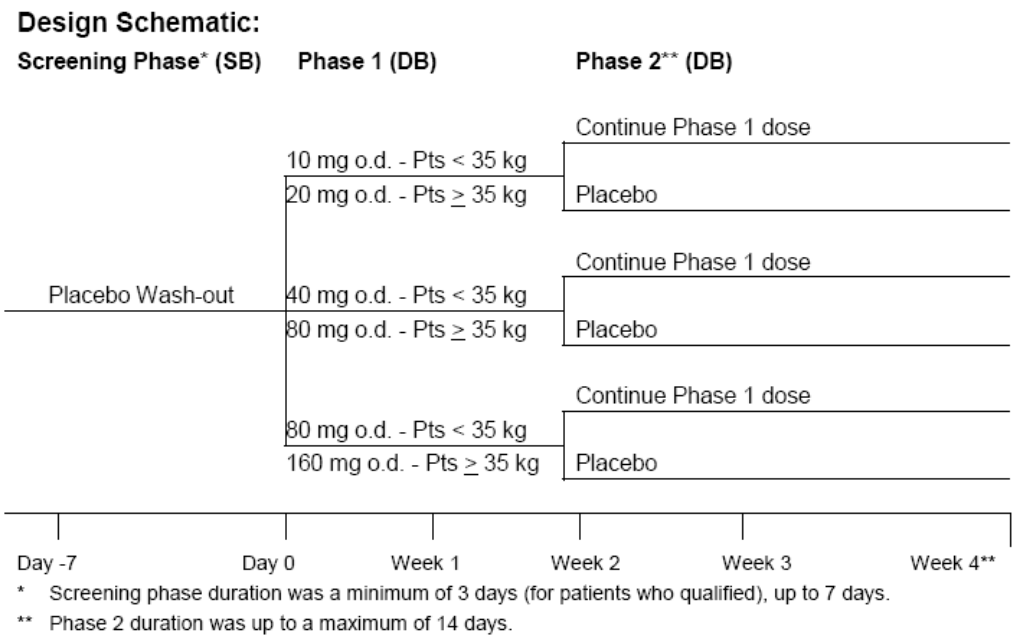


Figure 1. Study Design: A2302: screening and double-blind phases.

Study Population: Male and female patients, 6-16 years old, > 20 kg, able to swallow tablets, with baseline mean (average of 3 consecutive measurements) sitting systolic blood pressure (SSBP) $\geq$ 95th percentile for age, gender and height were eligible for study enrollment. Patients were stratified by region, race (Black vs. Non-black) and weight at baseline ($\geq$ 35 and < 35 kg).
Patients with a mean seated BP at the baseline visit $\geq$ 5% higher than 99th percentile for age were excluded. Patients were also excluded if they had clinically significant laboratory abnormalities; significant electrocardiogram (ECG) abnormalities other than left ventricular hypertrophy and AV block controlled with a pacemaker; coarctation of the aorta with a gradient of > 30 mmHg; and renal artery stenosis.
Renal transplant patients on stable doses of oral prednisone and/or stable doses of immunosuppressive therapy could continue at those doses and were eligible for the study.

Discontinuations:

- At any visit after Visit 2, a patient with mean SSBP after start of randomized study medication $\geq$ 10% greater than the 99th percentile for age with related symptoms.
- For a patient in Phase 2 of the study, if the trough mean SSBP in less than 14 days $\geq$ 95th percentile for age, gender, and height, then the Phase 2 study medication could be discontinued at the discretion of the investigator and all Week 4 evaluations would be completed; these patients were eligible to enter the open-label treatment phase of the study as long as the patient was not discontinued due to an adverse event (AE).
- Study medication could be interrupted for up to 3 days in succession during Phase 1 or 2; after interruption, the patient could return to study medication if considered medically advisable. If treatment was interrupted for 4 or more days

in succession during these phases, the patient was to be discontinued from the study.

Efficacy Assessments:
Mean SSBP was calculated as the average of 3 consecutive readings at each clinic visit. Blood pressure (BP) was measured in the same arm at each evaluation, preferably the right arm.

Safety Assessments:
Safety assessments consisted of adverse event (AE) monitoring; laboratory testing; vital sign measurement; and the performance of physical examinations, neurocognitive testing, Tanner stage assessments, pregnancy testing, and ECGs.

There were no pharmacokinetic assessments in this study and no interim analyses were performed.

Protocol Amendment: (July 3, 2003):

- The open-label phase was extended from 6 to 12 months.
- The power of the study was increased from 80 to 90% and standard deviation changed from 15 to 13.5 mmHg, with the sample size increasing from 230 to 254 randomized patients.
- Stratification by race was added.
- The percentage of Black patients was increased from 10-30% to 40-60%; the age groups were changed from 6-12 and 13-16 to 6-11 and 12-16 years.
- An upper limit for BP at entry and during the study was added.
- The dosing was expanded from "morning only" to same time of day, and electronic BP monitoring equipment was allowed.
- Clarified that BP evaluations were to be done at 22-26 hours post-dosing.
- Concomitant medications were modified and examples of clinically significant ECG abnormalities were added.
- Neurocognitive testing was added.
- Obligations regarding home BP monitoring were added. Home BP monitoring should be used as directed by the investigator; however, home BP monitoring units were not to be used for clinic visit BP measurements.

Statistics:
For Phase 1, the sample size of 228 was calculated to detect a non-zero slope of 0.93 for change from baseline in mean SSBP as a linear function of valsartan dose ratio at a two-sided significance of 0.05. This calculation assumed a standard deviation of 13.5 mmHg and a 2:1:2 allocation ratio to the low, medium, and high dosing groups, respectively. A slope of 0.93 (mmHg/unit increase in dose ratio) corresponded to a difference of 6.5 mmHg for low dose compared with high dose.
For the analysis of Phase 2, a sample size of 206 patients was required to detect a treatment difference in change from baseline in mean SSBP of at least 6.25 mmHg, with a standard deviation of 13.5 mmHg and a two-sided significance level of 0.05.

The primary dose-response relationship at the conclusion of Phase 1 was determined by the slope for change from baseline in mean SSBP. The change from baseline was calculated as SSBP at Visit 4 (Day 14) minus the SSBP at the baseline randomization Visit 2 (Day 0). For dropouts, the last value measured (LOCF) was used for the ITT1 population only. Similar measurements were made for Phase 2.

The null hypothesis for Phase 1 was that the slope of the dose-response curve for change from baseline in mean SSBP was not statistically different from zero at the end of Phase 1. The tests were conducted at the 2-sided significance level of 0.05. An ANCOVA model including effects for region, race (Black vs. non-Black) and weight (< 35 vs. ≥ 35 kg at baseline on Day 0) as fixed factors, and centered baseline SSBP (individual patient deviation from the mean of all ITT1 or PP1 patients) and dose ratio (1, 4, 8) as continuous covariates was used. Patients < 35 kg received 10, 40 or 80 mg QD valsartan; high-weight patients ($\geq$ 35 kg) received 20, 80 or 160 mg QD valsartan. Within each weight group, doses were assigned a ratio of 1, 4, or 8 for low/medium/high/doses, respectively.

The null hypothesis for Phase 2 was that the change from end of Phase 1 (Visit 4) in mean SSBP was not different between the pooled valsartan and placebo groups at the end of Phase 2 (Visit 6). An ANCOVA model that included effects for treatment, region, race strata, weight strata, and centered Visit 4 SSBP was carried out at the 2-sided significance level of 0.05.

Secondary efficacy variables included:

1. change in mean SSBP from baseline (Visit 2) to end of Phase 2 (Visit 6);
2. change in mean sitting diastolic BP (SDBP) from baseline (Visit 2) to the end of Phase 1 (Visit 4);
3. change in mean SDBP from end of Phase 1 (Visit 4) to the end of Phase 2 (Visit 6);
4. change in mean SDBP from baseline (Visit 2) to end of Phase 2 (Visit 6).

Missing values were not imputed unless otherwise indicated.

Results:

Patient Disposition: A total of 322 patients entered placebo washout; of these patients, 261 were randomized in Phase 1 and 245 completed Phase 1. About 90-96% completed Phase 1; no dose-related trends for premature discontinuations are seen.

Table 1. A2302: Disposition Phase 1 (randomized population)

Disposition	Low dose (N=103) n (%)	Medium dose (N=53) n (%)	High dose (N=105) n (%)
Randomized Phase 1	103	53	105
Completed Phase 1	93 (90)	51 (96)	101 (96)

Reasons for discontinuation:			
Adverse event	2 (2)	0	0
Unsatisfactory therapeutic effect	3 (3)	0	1 (1)
Protocol violation	0	1 (2)	2 (2)
Withdrew consent	2 (2)	1 (2)	1 (1)
Lost to follow-up	1 (1)	0	0
Administrative	2 (2)	0	0

Of the patients entering the randomized withdrawal phase, one patient in each treatment arm withdrew due to adverse events.

Table 2. A2302: Disposition Phase 2 (randomized population)

Disposition:	Valsartan (N=123)	Placebo (N=122)
Re-randomized Phase 2	123 (100)	122 (100)
Completed Phase 2	116 (94)	116 (95)
Reasons for discontinuation:		
Adverse event	1 (0.8)	1 (0.8)
Unsatisfactory therapeutic effect	3 (2)	5 (4)
Protocol violation	2 (2)	0
Withdrew consent	1 (0.8)	0

A total of 235 patients entered the open-label phase; of these patients, 195 (83%) received valsartan and 40 (17%) received valsartan and HCTZ. With respect to the valsartan monotherapy group, 151 (77%) completed the open-label phase; of the 44 (23%) who discontinued, seven (4%) did so because of AE, 18 (9%) discontinued for administrative reasons, 6 (3%) patients withdrew consent, and 4 (2%) had protocol violations. In the valsartan + HCTZ group, fourteen (35%) discontinued prior to completion; 13 patients (33%) had an unsatisfactory effect and one (3%) was lost to follow-up.

Protocol deviations/violations:
The most common protocol violations were mean baseline SSBP < 95th percentile for age, gender and height (3%), Visit 4 BP < 20 or > 30 hours post-baseline (3%) and Phase 1 exposure < 7 days (2%). A total of 25 patients (9.6%) in Phase 1 and 16 patients (6.5%) in Phase 2 had major protocol violations which excluded them from the per-protocol analysis. For a given study phase, there were no gross imbalances across treatment groups in the percentage of protocol violations.

Baseline characteristics: For Phase 1, no gross imbalances were noted with respect to baseline characteristics across low, medium and high-dose groups. For the patients randomized in Phase 2, a higher percentage of placebo patients were low-weight than those on valsartan; otherwise no imbalances were noted.

Of the patients randomized into the study, the mean (SD) age was 11.4 years (3) for all three dose groups; about 49-51% were 6-11 years, about 55-63% were male (45% in the medium dose group), 32-37% were Hispanic and 47-51% were Black; about 49-51% were enrolled in the USA.
In Phase 1, the mean (SD) weight was 65-66 (SD 34-36) kg; about 17-18% in each dose group was < 35 kg; mean BMI was 26-27 kg/m^2, and 47-54% were < Tanner stage 3. The mean (SD) SSBP was 131 -133 (10-11) mmHg, mean (SD) SDBP 77-78 (9-13) mmHg, and sitting pulse 86-87 (13-16) bpm. The mean (SD) weight-adjusted dose was 0.4 (0.32), 1.3 (0.48) and 2.7 (0.96) mg/kg for the low, medium, and high-dose groups, respectively.
In the randomized withdrawal phase, 16 (13%) valsartan patients and 29 (24%) placebo patients, were < 35 kg, and 107 (87%) valsartan patients and 93 (76%) placebo patients were ≥ 35 kg. BMI, Tanner stage, mean SSBP, SDBP and sitting pulse were similar between groups and similar to the range in Phase 1.
The population enrolled in the open-label phase showed similar demographic characteristics to those in the double-blind phases of the study.

Of the reported medical history, 37.9% (99/261) of the randomized population had a renal/urinary disorder; 7.7% of the randomized population had chronic renal failure, and 8% of the randomized population had a history of renal transplant. In addition, 21.5% of the randomized population (56/261) had a history of obesity (considered by the investigator).[1] Eleven (11%) patients in the low-dose valsartan group had a history of ventricular hypertrophy, as opposed to 1 (2%) in the medium and 6 (6%) in the high-dose groups (Phase 1); and 17% of low-dose patients had a history or urinary tract infection, as opposed to 8% in the middle and high-dose groups. Otherwise, this reviewer did not see any imbalances across groups.

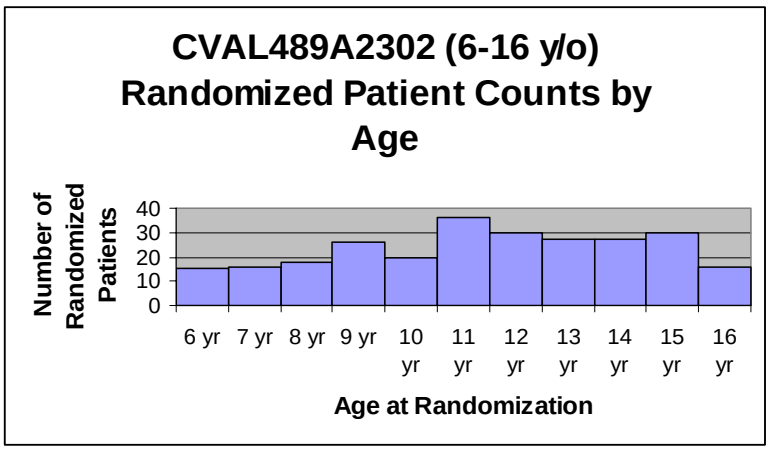


Figure 2. Randomized patient counts by age

Duration of Exposure:
No meaningful difference in duration of exposure by treatment group was seen. The mean exposure to valsartan in Phase 1 was 14.1 (2.93 SD) days. During Phase 2, the

[1] The Sponsor has noted that 54% of patients had a baseline BMI that was ≥ 95th percentile for gender and age which is considered obese.

mean exposure to valsartan was 13.8 (2.39 SD) days and 13.5 (2.59 SD) days for placebo. For each blinded phase (Phase 1 and Phase 2), over 90% of patients took study drug for at least 10 days.
During the OL phase, the mean exposure for any dose was 315.3 (SD 103.68) days. Less than half of the OL population (N=235) were exposed to any dose of valsartan for at least one year.

Table 8-3 Duration of exposure to study drug by dose in Open-label phase (Open Label population)

	Valsartan 40 mg N=234	Valsartan 80 mg N=150	Valsartan 160 mg N=90	Valsartan+HCTZ 160/12.5 mg N=37	Non-protocol defined dose N=7	Total exposure of any dose N=235
Days of Exposure						
> 0	234 (100.0%)	150 (100.0%)	90 (100.0%)	37 (100.0%)	7 (100.0%)	235 (100.0%)
>= 7	234 (100.0%)	150 (100.0%)	89 (98.9%)	36 (97.3%)	6 (85.7%)	235 (100.0%)
>= 14	219 (93.6%)	143 (95.3%)	86 (95.6%)	35 (94.6%)	5 (71.4%)	235 (100.0%)
>= 28	154 (65.8%)	117 (78.0%)	70 (77.8%)	33 (89.2%)	4 (57.1%)	234 (99.6%)
>= 56	115 (49.1%)	89 (59.3%)	66 (73.3%)	29 (78.4%)	3 (42.9%)	227 (96.6%)
>= 182	95 (40.6%)	45 (30.0%)	29 (32.2%)	15 (40.5%)	1 (14.3%)	202 (86.0%)
>= 294	76 (32.5%)	26 (17.3%)	10 (11.1%)	9 (24.3%)	0 (0.0%)	179 (76.2%)
>= 365	36 (15.4%)	2 (1.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	95 (40.4%)
Descriptive Statistics						
(Days)						
n	234	150	90	37	7	235
Mean	156.9	133.1	129.3	155.8	65.6	315.3
SD	157.60	119.53	105.88	118.15	87.70	103.68

Source: Post-text table 8.1-4

Concomitant Medication: Prior to the start of double-blind, about 55-65% of patients were on an antihypertensive (without gross imbalances across Phase 1 treatment group).

The most common antihypertensives were ACE inhibitors (40%), followed by dihydropyridines (22%).

Efficacy:
From Table 9-1 (source: study report), the changes from baseline for low, medium, and high doses are statistically significant. Since there was no concurrent placebo arm in this phase, one cannot distinguish a placebo effect. However, the progressive decrease in SSBP with dose suggests a dose-response relationship. Results for the per-protocol (PP) population were similar to the intent-to-treat (ITT) analysis.

Table 9-1 Changes from baseline in mean SSBP (mmHg) in Phase 1 by treatment (ITT1 population)

	Low Dose (N = 102)	Medium Dose (N = 52)	High Dose (N = 105)
Baseline/Visit 2			
Mean (SD)	131.4 (10.54)	133.3 (9.91)	133.2 (9.70)
End of Phase 1			
Mean (SD)	123.4 (11.43)	123.7 (11.92)	121.7 (12.53)
Change from baseline to end of Phase 1			
Mean (SD)	-7.9 (10.41)	-9.6 (9.12)	-11.5 (11.16)
95% CI [1]	(-9.98,-5.89)	(-12.16,-7.08)	(-13.66,-9.34)
p-value [1]	< 0.0001*	< 0.0001*	< 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: Post-text table 9.1-3a

These results were verified by the statistical reviewer.

The primary analysis, the slope of the change from baseline in SSBP as a function of increasing dose, was significantly different from zero, as seen below.

Table 9-2 Slope analysis for changes from baseline in sitting systolic blood pressure in Phase 1 (ITT1 population)

	Estimate	Standard Error	95% CI	P-value
Slope (β) [1] (mmHg per unit increase in dose ratio)	-0.43	0.193	(-0.81,-0.05)	0.0256*

[1] Slope is based on the regression model with terms including region strata, weight strata, race strata, baseline SSBP, and dose ratio.

* indicates statistical significance at the 0.05 level.

Source: Post-text table 9.1-1a

These results were verified by the statistical reviewer.

The slope result for the per-protocol population was consistent with the ITT analysis (p=0.02).

Comparisons between low, medium and high-dose groups with respect to the change from baseline to end of Phase 1 are shown below. A statistically significant difference was demonstrated only for the low vs. high-dose group. Analysis of the per-protocol population showed similar results. These exploratory between-group comparisons support (and do not contradict) the primary analysis.

Table 3. Comparison for changes from baseline in sitting SBP in Phase 1 (ITT1 population)

Dose Group 1 vs. 2	N1	N2	LSM (SE)1	LSM (SE)2	LSM Diff (SE)	95% CI	p-value
Low vs. High	102	105	-9.9 (1.14)	-12.9 (1.09)	3 (1.36)	(0.35, 5.69)	0.0270
Low vs. Medium	102	52	-9.9 (1.14)	-11 (1.45)	1.1 (1.66)	(-2.19, 4.34)	NS

Medium vs. High	52	105	-11 (1.45)	-12.9 (1.09)	1.9 (1.64)	(-1.30, 5.18)	NS

LSM, SE, 95% CI and p-values from ANCOVA model with treatment, region strata, weight strata, and race strata

At the medical reviewer's request, the sponsor provided analyses of the sitting systolic and diastolic BP changes from baseline to end of Phase 1 as a function of valsartan mg/kg, using linear, log-linear and Emax models.
The results (below) show a consistently significant slope for weight-adjusted dose on sitting SBP.

a. Linear model

Table 1 Slope analysis for change from baseline in sitting systolic/diastolic blood pressure in Phase 1 (ITT1 population)

	Estimate	SE	p-value
Slope for weight-adjusted dose (mg/kg) on SSBP	-1.199	0.4969	0.0166
Slope for weight-adjusted dose (mg/kg) on SDBP	-1.005	0.4401	0.0232

Slope is based on an ANCOVA model with terms including region strata, race strata as factors, and centered baseline SSBP/SDBP and weight-adjusted dose as covariates.

b. Log-Linear model (linear model on log transformed weight-adjusted dose)

Table 2 Slope analysis for change from baseline in sitting systolic/diastolic blood pressure in Phase 1 (ITT1 population)

	Estimate	SE	p-value
Slope for log (weight adjusted dose (mg/kg)) on SSBP	-1.500	0.5972	0.0126
Slope for log (weight adjusted dose (mg/kg)) on SDBP	-0.963	0.5323	0.0715

Slope is based on an ANCOVA model with terms including region strata, race strata as factors, and centered baseline SSBP/SDBP and log(weight-adjusted dose) as covariates.

c. E_{max} model

Table 3 E_{max} model for change from baseline in sitting systolic/diastolic blood pressure in Phase 1 (ITT1 population)

	Parameter	Estimate	SE	p-value
E_{max} Model on SSBP	ED_{50} (mg/kg)	0.152	0.0861	0.0796
	E_{max}	-11.85	1.2051	<0.0001
E_{max} Model on SDBP	ED_{50} (mg/kg)	0.254	0.1867	0.1757
	E_{max}	-7.94	1.3230	<0.0001

At the medical reviewer's request, the sponsor provided scatter plots for the change from baseline to end of Phase 1 in SBP and DBP as a function of weight-adjusted dose. The results are shown below (next page). The reviewer requested analysis of "best fit" for linear, log-linear and Emax models. According to the sponsor, these models did not fit the data.

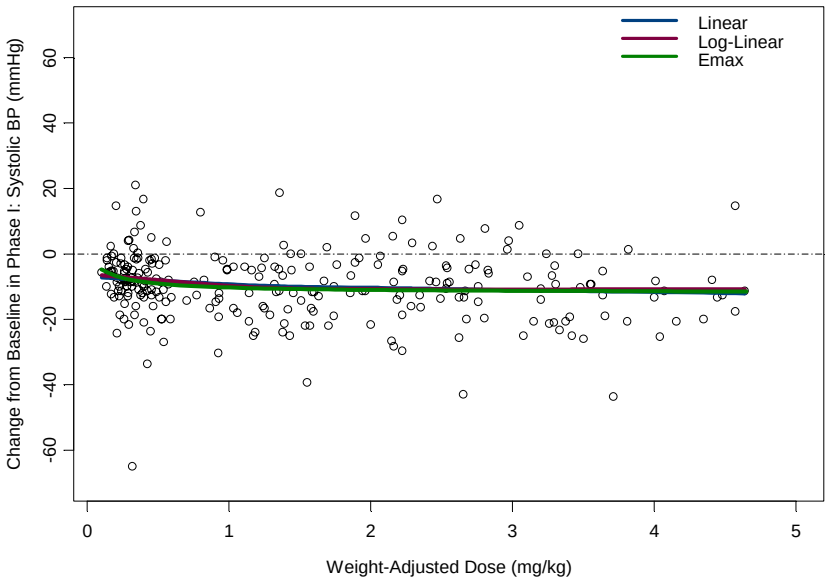


Figure 3. Scatter plot for the change from baseline to end of Phase 1 in mean sitting SBP vs. weight-adjusted dose (mg/kg)

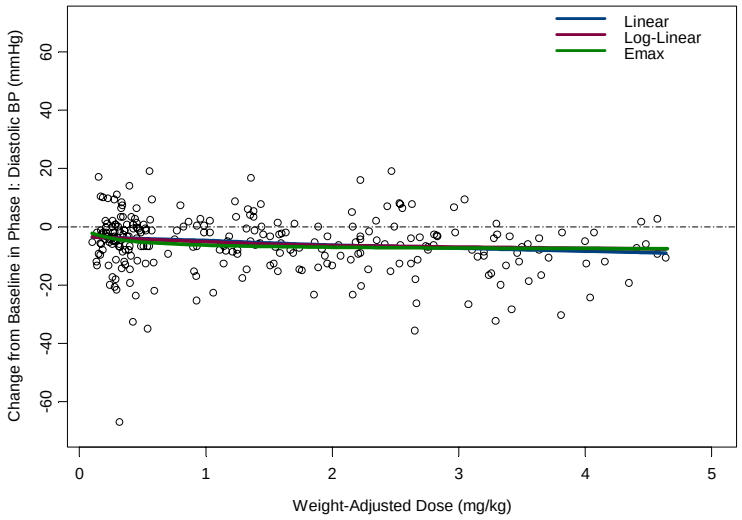


Figure 4. Scatter plot for the change from baseline to end of Phase 1 in mean sitting DBP vs. weight-adjusted dose (mg/kg)

Randomized Withdrawal Phase (Phase 2):
Results for Phase 2 are presented below. An increase in SSBP was seen in both groups, more with placebo than with pooled valsartan, and the difference in the change from baseline was statistically significant between the groups. These results support the presence of a treatment effect.

Table 9-3 Changes from end of Phase 1 to end of Phase 2 in mean SSBP (mmHg) by pooled treatment (ITT2 population)

	Valsartan (N = 123)	Placebo (N = 122)
End of Phase 1/Visit 4		
Mean (SD)	122.2 (12.07)	122.2 (11.51)
End of Phase 2		
Mean (SD)	123.3 (13.05)	126.1 (12.09)
Change from end of Phase 1 to end of Phase 2		
Mean (SD)	1.2 (9.42)	3.9 (9.66)
95% CI [1]	(-0.52,2.84)	(2.15,5.61)
p-value [1]	0.1758	< 0.0001*
p-value [2]	0.0368*	

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

[2] p-value is from the ANCOVA model with treatment, region strata, weight strata, and race strata as factors, and centered Visit 4 SSBP as a covariate.

* indicates statistical significance at the 0.05 level.

Source: Post-text table 9.2-1a, Post-text table 9.2-2a

In the unpooled valsartan groups, the SSBP increase in the placebo group is most marked in the high/placebo group; the high/high vs. high/placebo comparison was the only comparison that was significantly different. However, the subgroups are smaller, and no unexpected findings are seen.

Table 9-4 Least squares mean and treatment comparison for changes from end of Phase 1 to end of Phase 2 in mean SSBP (mmHg) (ITT2 population)

	N	LS Mean Change [1]	LS Mean (SE) [2]	95% CI [2]	P-Value [2]
Low/Low	44	2.7	0.8 (1.87)	(-2.87, 4.48)	0.6673
Low/Placebo	49	1.9			
Medium/Medium	25	-0.0	-3.5 (2.53)	(-8.46,1.52)	0.1717
Medium/Placebo	26	3.4			
High/High	54	1.9	-5.4 (1.82)	(-8.96,-1.80)	0.0034*
High/Placebo	47	7.3			

[1] LS mean change from end of phase 1 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 terms of treatment, region strata, weight strata, race strata, and centered Visit 4 SSBP.

* indicates statistical significance at the 0.05 level.

Source: Post-text table 9.2-1a

Secondary Efficacy results:

1. Change in mean SSBP from baseline to end of Phase 2:

Results for this analysis are shown below. The baseline SSBP in the medium/medium group (134.6 mmHg) appears to be higher than that seen in the low/low (130.7 mm Hg) or low/placebo (130.9 mmHg) groups; the change from baseline is highest in this subgroup.
The p-values were calculated as change from baseline, and do not account for placebo effects. In addition, the analysis (paired t-test) did not adjust for baseline SSBP.
For the medium and high dose groups, the change from baseline is higher in the groups maintained on valsartan than the groups randomized to placebo.

These results do not contradict the primary analysis.

Table 9-5 Mean changes in SSBP (mmHg) by double-blind treatment (Phases 1 & 2 combined) (ITT population)

	SSBP			
Treatment	**Baseline**	**End of Phase 2**	**Change**	**P-value [1]**
Low/Low	130.7	123.8	-6.9	0.0009*
Low/Placebo	130.9	124.8	-6.1	0.0002*
Medium/Medium	134.6	122.1	-12.4	< 0.0001*
Medium/Placebo	132.5	126.6	-5.9	0.0016*
High/High	132.9	123.5	-9.4	< 0.0001*
High/Placebo	133.1	127.1	-5.9	0.0023*

[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: Post-text table 9.3-1

2. Change from baseline to end of Phase 1 in mean sitting diastolic blood pressure (SDBP)

Results for this analysis are consistent with the analysis of SSBP. One cannot distinguish a placebo effect, and the decreases from baseline increase with dose, suggesting a dose-response relationship.

Table 9-6 Changes from baseline in mean SDBP (mmHg) in Phase 1 by treatment (ITT1 population)

	Low Dose (N = 102)	Medium Dose (N = 52)	High Dose (N = 105)
Baseline/Visit 2			
n	102	52	105
Mean (SD)	77.0 (13.04)	77.2 (9.31)	78.4 (11.25)
End of Phase 1			
n	102	52	105
Mean (SD)	72.4 (12.05)	71.4 (10.52)	71.0 (9.79)
Change from baseline to end of Phase 1			
n	102	52	105
Mean (SD)	-4.6 (10.98)	-5.8 (8.87)	-7.4 (9.51)
95% CI [1]	(-6.75,-2.44)	(-8.26,-3.33)	(-9.19,-5.51)
p-value [1]	0.0001*	< 0.0001*	< 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: Post-text table 9.4-2

The LS mean changes from baseline in SDBP was -4.9 mm Hg for the low dose group, -6.1 mm Hg for the medium dose group, and -7.1 mm Hg for the high dose group; none of the comparisons (low vs. medium, medium vs. high, low vs. high) were statistically significant (difference between low and high was 1.0 [SE 1.47] mm Hg, with a p-value of 0.0654).

3. Change in mean SDBP from end of Phase 1 to end of Phase 2:

In this analysis, too the results are consistent with the results for SSBP.

Table 9-7 Changes in mean SDBP (mmHg) from the end of Phase 1 to the end of Phase 2 by treatment (ITT2 population)

	Valsartan (N = 123)	Placebo (N = 122)
End of Phase 1/Visit 4		
n	123	122
Mean (SD)	70.7 (11.26)	71.8 (10.04)
End of Phase 2		
n	123	122
Mean (SD)	71.2 (11.30)	75.3 (10.83)
Change from end of Phase 1 to end of Phase 2		
n	123	122
Mean (SD)	0.5 (8.47)	3.5 (9.37)
95% CI [1]	(-1.05,1.98)	(1.87,5.23)
p-value [1]	0.5451	0.0001*
p-value [2]	0.0047*	

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

[2] p-value is from the ANCOVA model with treatment, region strata, weight strata, and race strata as factors, and centered Visit 4 SSBP as a covariate.

* indicates statistical significance at the 0.05 level.

Source: Post-text table 9.5-1, Post-text table 9.5-2

4. Change in mean SDBP from baseline to end of Phase 2:

The change in mean SDBP during the double-blind period are shown below. Statistically significant decreases from baseline are seen in the groups maintained on valsartan during phase 2. The decreases in SDBP between medium and high dose groups are similar. These results do not contradict the primary analysis.

Table 9-8 Mean changes in SDBP (mmHg) by double-blind treatment (Phases 1 & 2 combined) (ITT population)

	SDBP			
Treatment	**Baseline**	**End of Phase 2**	**Change**	**P-value [1]**
Low/Low	77.1	72.9	-4.2	0.0055*
Low/Placebo	75.7	73.4	-2.4	0.1158
Medium/Medium	76.9	69.8	-7.2	0.0011*
Medium/Placebo	77.7	76.2	-1.5	0.4107
High/High	77.4	70.4	-7.0	< 0.0001*
High/Placebo	78.7	76.9	-1.8	0.2411

[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: Post-text table 9.3-2

Subgroup Analyses:

Subgroup efficacy analyses are presented below for SSBP and SDBP and for Phases 1 and 2. All subgroups trended in a direction similar to the overall population (for SDBP, Phase 2 results showed little change in the group remaining on valsartan). This reviewer noted that in Table 9-10, the change in mean SDBP is lower in the low-weight medium dose group; in Table 9-11, the rise in SSBP (both valsartan and placebo) is greater in the low-weight subgroup. However, the smaller sample size in these low-weight subgroups makes these findings difficult to interpret.

Table 9-9 Subgroup analysis: Change from baseline in mean SSBP (mmHg) in Phase 1 by treatment and subgroup (ITT1 population)

Subgroup	Valsartan Dose		
	Low (N=102) Mean (SD), n	Medium (N=52) Mean (SD), n	High (N=105) Mean (SD), n
Weight			
< 35 kg (N=45)	-7.5* (12.57), 17	-10.3* (8.77), 9	-12.9* (6.84), 19
≥ 35 kg (N=214)	-8.0* (10.01), 85	-9.5* (9.28), 43	-11.2* (11.92), 86
Gender			
Female (N=103)	-6.9* (8.05), 40	-10.6* (8.36), 24	-14.1* (11.05), 39
Male (N=156)	-8.6* (11.71), 62	-8.8* (9.79), 28	-10.0* (11.03), 66
Age			
6-11 years (N=129)	-8.1* (9.50), 49	-10.8* (8,56), 26	-11.1* (11.81), 54
12-16 years (N=130)	-7.8* (11.28), 53	-8.4* (9.65), 26	-11.9* (10.54), 51
Tanner Stage			
< 3 (N=130)	-8.5* (9.48), 55	-10.2* (8.58), 24	-10.9* (10.13), 51
≥ 3 (N=129)	-7.3* (11.48), 47	-9.1* (9.68), 28	-12.0* (12.13), 54
Race			
Black (N=126)	-7.1* (6.48), 47	-7.8* (8.49), 27	-11.1* (10.54), 52
Non-Black (N=133)	-8.6* (12.88), 55	-11.6* (9.54), 25	-11.8* (11.83), 53
Region			
USA (N=129)	-5.9* (6.58), 49	-8.1* (9.97), 26	-9.2* (12.03), 54
Non-USA (N=130)	-9.8* (12.78), 53	-11.1* (8.09), 26	-13.9* (9.71), 51

Note: Only patients who had both baseline and end of phase 1 values are included.

* indicates statistical significance at the 0.05 level within the treatment group.

Source: Post-text table 9.6-1, Post-text table 9.6-2, Post-text table 9.6-3, Post-text table 9.6-4, Post-text table 9.6-5, and Post-text table 9.6-6

Table 9-10 Subgroup analysis: Change from baseline in mean SDBP (mmHg) in Phase 1 by treatment and subgroup (ITT1 population)

Subgroup	Dose Group		
	Low (N=102) Mean (SD), n	Medium (N=52) Mean (SD), n	High (N=105) Mean (SD), n
Weight			
< 35 kg (N=45)	-6.0 (11.80), 17	-3.1 (10.45), 9	-10.0* (10.08), 19
≥ 35 kg (N=214)	-4.3* (10.86), 85	-6.4* (8.53), 43	-6.8* (9.34), 86
Gender			
Female (N=103)	-4.4* (8.61), 40	-6.2* (9.03), 24	-10.2* (10.18), 39
Male (N=156)	-4.7* (12.33), 62	-5.4* (8.88), 28	-5.6* (8.74), 66
Age			
6-11 years (N=129)	-3.7* (9.03), 49	-5.6* (8.42), 26	-8.1* (10.38), 54
12-16 years (N=130)	-5.4* (12.55), 53	-6.0* (9.46), 26	-6.6* (8.55), 51
Tanner Stage			
< 3 (N=130)	-4.0* (9.79), 55	-5.6* (8.52), 24	-8.3* (8.92), 51
≥ 3 (N=129)	-5.3* (12.29), 47	-6.0* (9.31), 28	-6.5* (10.05), 54
Race			
Black (N=126)	-4.1* (6.61), 47	-4.3* (9.04), 27	-7.0* (9.62), 52
Non-Black (N=133)	-5.1* (13.70), 55	-7.4* (8.56), 25	-7.7* (9.49), 53
Region			
USA (N=129)	-3.4* (7.16), 49	-5.7* (9.58), 26	-5.0* (9.40), 54
Non-USA (N=130)	-5.7* (13.58), 53	-5.9* (8.29), 26	-9.8* (9.09), 51

Note: Only patients who had both baseline and end of phase 1 values are included.

* indicates statistical significance at the 0.05 level within the treatment group.

Source: Post-text table 9.7-1, Post-text table 9.7-2, Post-text table 9.7-3, Post-text table 9.7-4, Post-text table 9.7-5, and Post-text table 9.7-6

Table 9-11 Subgroup analysis: Change in mean SSBP (mmHg) from the end of Phase 1 to the end of Phase 2 by treatment and subgroup (ITT2 population)

Subgroup	Treatment Group	
	Valsartan (N=123) Mean (SD), n	Placebo (N=122) Mean (SD), n
Weight		
< 35 kg (N=45)	5.3 (10.35), 16	6.7* (10.05), 29
≥ 35 kg (N=200)	0.5 (9.17), 107	3.0* (9.43), 93
Gender		
Female (N=97)	1.9 (9.19), 52	5.6* (9.27), 45
Male (N=148)	0.6 (9.63), 71	2.9* (9.80), 77
Age		
6-11 years (N=124)	1.8 (8.47), 62	4.5* (10.80), 62
12-16 years (N=121)	0.5 (10.34), 61	3.3*, (8.38), 60
Tanner Stage		
< 3 (N=125)	0.7 (7.81), 59	3.9* (10.59), 66
≥ 3 (N=120)	1.6 (10.74), 64	3.9* (8.54), 56
Race		
Black (N=122)	0.5 (9.69), 60	4.5* (7.96), 62
Non-Black (N=123)	1.8 (9.20), 63	3.2* (11.19), 60
Region		
USA (N=122)	1.2 (9.99), 61	3.0* (8.98), 61
Non-USA (N=123)	1.1 (8.91), 62	4.8* (10.30), 61

Note: Only patients who had both end of phase 1 and end of phase 2 values are included.

* indicates statistical significance at the 0.05 level within the treatment group.

Source: Post-text table 9.9-1, Post-text table 9.9-2, Post-text table 9.9-3, Post-text table 9.9-4, Post-text table 9.9-5, and Post-text table 9.9-6

Table 9-12 **Subgroup analysis: Change in mean SDBP (mmHg) from the end of Phase 1 to the end of Phase 2 by treatment and subgroup (ITT2 population)**

Subgroup	Treatment Group	
	Valsartan (N=123) Mean (SD), n	Placebo (N=122) Mean (SD), n
Weight		
< 35 kg (N=45)	-0.1 (10.29), 16	7.8* (9.15), 29
≥ 35 kg (N=200)	0.5 (8.22), 107	2.2* (9.09), 93
Gender		
Female (N=97)	0.2 (8.03), 52	6.0* (9.68), 45
Male (N=148)	0.7 (8.83), 71	2.1* (8.94), 77
Age		
6-11 years (N=124)	-0.5 (9.08), 62	4.6* (9.05), 62
12-16 years (N=121)	1.4 (7.76), 61	2.5 (9.65), 60
Tanner Stage		
< 3 (N=125)	-0.5 (9.54), 59	4.0* (9.36), 66
≥ 3 (N=120)	1.3 (7.31), 64	3.0* (9.43), 56
Race		
Black (N=122)	0.5 (9.31), 60	3.7* (10.08), 62
Non-Black (N=123)	0.4 (7.65), 63	3.4* (8.66), 60
Region		
USA (N=122)	1.7 (7.08), 61	1.9 (9.17), 61
Non-USA (N=123)	-0.7 (9.55), 62	5.2* (9.36), 61

Note: Only patients who had both end of phase 1 and end of phase 2 values are included.

* indicates statistical significance at the 0.05 level within the treatment group.

Source: Post-text table 9.10-1, Post-text table 9.10-2, Post-text table 9.10-3, Post-text table 9.10-4, Post-text table 9.10-5 and Post-text table 9.10-6

Safety:

Adverse Events (AE): Overall, 105/259 patients (40.5%) reported at least one AE in Phase 1, 87/245 (35.5%) reported at least one AE in Phase 2, and 214/235 patients (91.1%) reported at least one AE in the OL phase.

Of the reported Phase 1 AEs occurring in at least 2% of the safety population (N=259), the most commonly occurring AE was headache (30/259, or 12%), followed by vomiting (10/259, or 4%), cough (8/259, or 3%), dizziness (7/259, or 3%), and nasopharyngitis (7/259, or 3%).
During Phase 1, dizziness was the only AE in which the frequency was higher in the high-dose group, suggesting the possibility of a relationship with dose.

During Phase 2 (randomized withdrawal) (N= 245), AEs occurring in at least 2% of the SAF2 population were: headache (24/245, or 10%), cough (5/245, or 2%), upper respiratory infection (5/245, or 2%), nasal congestion (6/245, or 2%), and dizziness (5/245, or 2%).

During the OL phase (total N=235), the most common AEs were headache (33%), pyrexia (20%), nasopharyngitis (19%), cough (18%), upper respiratory infection (12%), diarrhea (10%), vomiting (9%), abdominal pain (9%), influenza (9%), sinusitis (8%), nausea (7%), nasal congestion (7%), pharyngolaryngeal pain (7%), dizziness (6%), epistasis (6%), rhinitis (6%), tonsillitis (5%). Some reported events may be related to the

same underlying process (e.g., upper respiratory infection, pyrexia, nasopharyngitis, nasal congestion, rhinitis, pharyngolaryngeal pain).

When Phases 1 and 2 are combined, the most common AEs are headache and dizziness.

Table 10-6 Summary of most frequent [1] adverse events by preferred term and treatment in double-blind phase (Safety population)

	Low/ Low	Low/ Placebo	Medium/ Medium	Medium/ Placebo	High/ High	High/ Placebo
	N=44	N=48	N=26	N=25	N=54	N=48
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with at least one AE	22 (50.0)	27 (56.3)	15 (57.7)	14 (56.0)	31 (57.4)	23 (47.9)
Headache	10 (22.7)	9 (18.8)	2 (7.7)	7 (28.0)	11 (20.4)	3 (6.3)
Dizziness	1 (2.3)	0 (0.0)	0 (0.0)	2 (8.0)	5 (9.3)	2 (4.2)
Vomiting	1 (2.3)	3 (6.3)	2 (7.7)	1 (4.0)	4 (7.4)	0 (0.0)
Abdominal pain	2 (4.5)	1 (2.1)	1 (3.8)	0 (0.0)	3 (5.6)	0 (0.0)
Nausea	1 (2.3)	1 (2.1)	0 (0.0)	1 (4.0)	3 (5.6)	0 (0.0)
Cough	2 (4.5)	6 (12.5)	2 (7.7)	1 (4.0)	1 (1.9)	0 (0.0)
Nasal congestion	1 (2.3)	4 (8.3)	2 (7.7)	2 (8.0)	1 (1.9)	1 (2.1)
Pharyngolaryngeal pain	1 (2.3)	2 (4.2)	0 (0.0)	2 (8.0)	1 (1.9)	1 (2.1)
Diarrhea	1 (2.3)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	3 (6.3)
Nasopharyngitis	2 (4.5)	3 (6.3)	2 (7.7)	1 (4.0)	0 (0.0)	2 (4.2)
Upper respiratory tract infection	1 (2.3)	0 (0.0)	3 (11.5)	0 (0.0)	0 (0.0)	4 (8.3)

[1] Reported by at least 5% of patients in a given dose category (patients in low, medium and high only groups, not shown).

Source: Post-text table 10.1-3

In adult hypertensives, the most common reasons for discontinuation of therapy were headache and dizziness.

AE Severity: All of the reported Phase 1 AEs were mild or moderate. During Phase 2, there was one patient in the valsartan group with severe gastroenteritis, and one patient in the placebo group with severe headache. All of the other reported AEs were mild or moderate.

AE by Gender:
The Sponsor provided an analysis of adverse events by gender and treatment phase. As with the overall population, headache was the most common AE by gender, across all phases of the study. This reviewer did not see any consistent gender-related AE trends.

AE by Age: During the randomized withdrawal phase of the study (Phase 2), a higher percentage of AE were reported in the 6-11 year group (41%) than the 12-16 year group; (30%). During the OL phase, a higher percentage of tonsillitis was reported in the 6-11 year group (7%) than in the 12-16 year group (3%) (perhaps an age-related phenomenon). Also in OL, a higher percentage of pharyngolaryngeal pain was reported in the 12-16 year group (14/114, 12.3%) compared to the 6-11 year group (2/121, 2%).

AE by Race: During the randomized withdrawal phase (Phase 2), a higher percentage of Black patients (49/122, 40%) reported at least one AE compared to the non-Black

subgroup (38/123, 31%); otherwise, the incidence of patients reporting at least one AE were similar between Black and non-Black subgroups.
As with the overall population, the most common AE for each subgroup was headache. During phases 2 and OL, a higher percentage of Black patients reported headache (Phase 2: 15/122, 12% of Black patients; 9/123 or 7% of non-Black patients. OL Phase: 44/116, 38% of Black patients; 34/119, 29% of non-Black patients).
During the OL phase, a higher percentage of non-Black patients reported pyrexia (28% non-Black vs. 11% Black), cough (27% non-Black vs. 10% Black), diarrhea (13% non-Black vs. 6% Black) and pharyngolaryngeal pain (10% non-Black, 3% Black); these patterns were not seen during the double-blind portion of the study.

AE by Location (US vs. non-US): During Phases 1 and 2, a higher incidence of patients reporting at least one AE was seen in the non-US population (Phase 1: 45% non-US vs. 36% US; Phase 2: 41% non-US vs. 30% US). Consistent with the overall results, the most common reported AE was headache. During the OL phase, a higher percentage of non-US patients reported cough (25% vs. 11% US), nasopharyngitis (24% vs. 14% US), diarrhea (15% vs. 4% US), influenza (13% vs. 4% US), nausea (10% vs. 4% US), vomiting (14% vs. 4% US), abdominal pain (14% vs. 4% US), dizziness (9% vs. 3% US), rhinitis (9% vs. 2% US), and tonsillitis (9% vs. 0.9% US). However, these subgroup differences were not seen during the double-blind phase.

Deaths: No patients died during the study.

Serious Adverse Events (SAE): One patient in the high/high dose group experienced 3 SAEs during the double-blind phase (vomiting, infectious diarrhea, and dehydration, all on Day 6).

Eighteen patients experienced a total of 34 SAEs during the OL phase. The highest number of OL SAEs occurred within the Infections and infestations class; the most common SAEs were gastroenteritis, pyrexia and diarrhea.
An increased creatinine (SAE) and hyperkalemia was reported in a renal transplant patient who was hospitalized for diarrhea and dehydration (SAEs) during the OL phase; this patient was discontinued from the study due to drug-related hyperkalemia.

Table 4. Serious AE in the Open-Label phase (safety population)

Patient #	Age/Race/Gender (region)	Dose QD	Event	Day	Outcome
1002-00004	11/W/M (Europe)	Val 40 mg Val 80 mg Val 80 mg	Fever, increased creatinine Increased creatinine Increased creatinine, nephritis	193 212 219	Continued drug Continued drug Continued drug
0502-00014	13/W/M (Europe)	Val 40 mg Val 40 mg	Mycoplasma pneumonia Gastroenteritis	73 287	Valsartan interrupted Continued drug
0106-00004	12/B/F (US)	Val 80 mg Val 80 mg	Partial amputation L toe Necrosis of partially	115 120	Continued drug Continued drug

			amputated toe		
0138-00001	13/B/M (US)	Val 160 mg	Depression/psychosis	207	Continued drug*
0501-00001	14/W/F (Europe)	Val 40 mg	Worsening hypocalcemia	153	Continued drug
0502-00003	16/W/M (Europe)	Val 40 mg Val 40 mg Val 40 mg Val 80 mg Val 80 mg	Acute Gastroenteritis Acute Diarrhea Anal Hemorrhage Acute Gastroenteritis Sepsis	30 126 162 284 187	Continued drug Continued drug Continued drug Continued drug Continued drug
0603-00009	14/W/F (LA)	Val 40 mg	Shingles Seizure	47 221	Continued drug Discontinued due to AE
0610-00005	11/W/F (LA)	Val 40 mg	Hypertensive Crisis, L. arm pain	266	Continued drug
0502-00004	8/W/F (Europe)	Val 160 mg Val 160 mg Val 160 mg	Gastritis Viral meningitis C difficile in stool	229 236 262	Continued drug Discontinued due to AE
0123-00003	11/Other/M (US)	Val 80 mg	Diarrhea Dehydration, hyperkalemia	74 82	Discontinued due to AE
0129-00022	11/Other/F (US)	Val 80 mg	Depression	329	Continued drug
0502-00009	12/W/F (Europe)	Val 40 mg	Acute tonsillitis	160	Continued drug
0123-00002	15/B/F (US)	Val 80 mg	Pilonidal cyst	98	Continued drug
0129-00005	12/B/F (US)	Val 160 mg	Cholelithiasis	159	Dose adjusted/temporarily interrupted
0610-00003	6/W/M (LA)	Val 40 mg	Hydatid torsion	45	Continued drug
0503-00001	12/W/F (Europe)	Val 40 mg	Chronic sinusitis	241	Continued drug
0603-00002	9/W/M (LA)	Val + HCTZ 160/12.5 mg	Back pain, fever, pyelonephritis, turbid urine	185	Continued drug
0125-00009	14/B/M (US)	Val 160 mg	Asthma	311	Continued drug

*According to dataset, valsartan therapy was not interrupted. According to the CRF, patient/parent was unsure of amount of study medication taken in last month of OL due to hospitalization for severe depression/psychosis. End of study ECG and laboratory testing was refused by the patient. According to the CRF, this patient did not complete the study.

Discontinuations due to AE:

During Phase 1, one patient (#0123-00001) in the low-dose valsartan group discontinued due to facial rash.

During Phase 2, one valsartan patient (#0608-00008) discontinued to due symptomatic hypotension; two placebo patients (but previously on valsartan) experienced 4 AEs that

led to discontinuation (#1002-00003 developed proteinuria[2]; and #0105-00002 developed pharyngeal edema, pruritis and urticaria). During the OL phase, 7 patients discontinued due to AE (5 SAEs in 3 patients or 4 AEs in 4 patients). Of the three patients discontinuing due to SAEs, one patient developed hyperkalemia, diarrhea and dehydration; one developed viral meningitis; and one was discontinued due to convulsion (see SAE table, above). Four patients on OL discontinued due to "non-serious" AE (1 patient each with elevated creatinine [#503-00003]; colitis [#601-00006]; neutropenia [#0125-00007]; and L. hand swelling [#149-00001]).

Pt # 00502-00001 developed hypertensive encephalopathy and was hospitalized during the placebo screening phase; he was randomized to Phase 1, but was withdrawn on Day 2 due to elevated BP.[3]

Laboratory Results:
Laboratory tests were collected at screening (Day -7, Visit 1), end of Phase 1 (Day 14, Visit 4), and end of Phase 2 (Up to Day 28, Visit 6); during OL, laboratory tests were done during Visits 12 (Day 182) and 15 (Day 365).

Laboratory results were reviewed via measures of central tendency (mean and median changes from baseline) as well as shift tables (from normal to low/high).
For the measures of central tendency, the mean and median changes appeared to be small.

As seen in the next table (from the sponsor), an increased incidence in BUN (> 50%) was seen in groups exposed to medium and high doses of valsartan (including those randomized to placebo but with a history of drug exposure); a dose-related change in potassium, glucose or creatinine is not demonstrated.
During the double-blind phase, hyperkalemia (> 5.5 mmol/L) was reported in 6 patients (2.3%); during OL, hyperkalemia was reported in 3.8% of patients. Five out of 6 patients with hyperkalemia at end of double-blind had a history of chronic kidney disease, and four of them were renal transplant patients.

[2] This patient developed proteinuria and elevated BP during Phase 2, and was discontinued during OL due to unsatisfactory therapeutic effect, but was noted to have persisting proteinuria as related to reason for discontinuation; patients could have only one reason for discontinuation.
[3] From the CRF, it appears that this patient was randomized before the hypertensive encephalopathy had resolved.

Table 10-11 Specified percent change from baseline for laboratory tests in Double-blind Phase

Laboratory Test and Criterion	Double Blind Phase Dose Groups (% patients meeting the criterion)					
	Low/Low (N = 44)	Low/Pbo (N = 48)	Med/Med (N = 26)	Med/Pbo (N = 25)	High/High (N = 54)	High/Pbo (N = 48)
Urea (BUN)> 50% increase	9.3	6.3	3.8	12.5	11.3	12.5
Creatinine > 50 increase	2.3	4.2	0	8.3	0	2.1
Potassium > 20% increase	2.4	4.2	16.0	0	5.6	4.2
Potassium > 20% decrease	0	8.3	0	8.3	3.7	2.1
Glucose > 50% increase	14.3	4.2	3.8	4.2	3.7	2.1
Glucose > 50% decrease	0	0	0	4.2	0	0
Uric acid > 50 % increase	2.3	2.1	7.7	0	5.7	2.1

Source: Post-text table 10.3-6

Pulse: No meaningful changes were noted in mean or median pulse.

Vital Signs (OL): A review of SSBP and SDBP during OL showed that decreases from baseline appear to have been maintained or decreased further at Visit 15 (end of study). For the OL population, mean baseline SSBP/SDBP was 132.2/77.4 mm Hg. At Visit 15, mean SSBP/SDBP was 119.5/68.6 mm Hg.

Height/Weight/BMI: During OL, increases in mean height and weight were seen (this might be expected). Mean BMI was 27.1 kg/m2 at baseline and at end of double-blind; at Day 182-OL (visit 12), mean BMI was 27.5 kg/m2 and at Day 365-OL (visit 15), mean BMI was 27.3 kg/m2.

ECG: The mean changes from baseline in QT and QTc to the end of Phase 1 were < 5 msec for each dose group; no dose relationship was demonstrated. One patient in the low-dose group (0501/00001) experienced a QTcB and QTcF > 60 msec increase from baseline; another patient (102/00003) had ventricular ectopy. One patient in the low-dose group was noted to have PR > 200 msec that was not seen at baseline; however, no patients on medium or high-dose valsartan had similar changes.

Neurocognitive Assessments: Neurocognitive assessments were measured at baseline and the end of open-label (or last visit). Patients' abilities were evaluated for: attention, processing speed, working memory, cognitive flexibility, memory, and motor speed. Since neurocognitive assessments were implemented after a protocol amendment, not all patients underwent testing.

Table 5. Neurocognitive Test results (randomized population with baseline and post-baseline tests)

Test	Statistics	Baseline (visit 2)	End of study visit	Change from baseline
Trails:Time to complete (sec) (N=90)	Mean (SD)	80.1 (54)	68.1 (46)	-12.1 (44)
Word pairs (US and UK only)	5-8 years (N=11)			
	Mean (SD)	16.3 (10)	17.1 (10)	0.8 (9)
	9-16 years (N=46)			

	Mean (SD)	24.5 (10)	24.2 (11)	-0.3 (9)
Sequence (US and UK only) total raw score (N=58)	Mean (SD)	46.8 (18)	51.4 (15)	4.7 (10)
Time tapping right/left hand number of seconds (N=103/103)	Mean (SD)	12.9 (12)/13 (12)	10 (9)/10 (9)	-2.9 (9)/-2.7 (9)
Timed gait (no. seconds) N=101	Mean (SD)	10.7 (5)	10.5 (5)	-0.2 (4)

Of the summary of changes from baseline, a majority had either no change or an improvement in scores; the exception was the word pairs test in children 9-16 years old, where 50% performed the same or better, and 50% performed worse (there was no difference in baseline demographics between the two groups).

Pregnancy: No patients during this study had a positive pregnancy test.

Reviewer Comments/Conclusions:

1. Study A2302 followed the Trial C design.
2. The primary efficacy measurements in Phases 1 and 2 showed a statistically significant slope in the change in SSBP; in addition, a statistically significant difference between pooled valsartan and placebo was seen in the randomized withdrawal phase.
3. Results for SDBP were consistent with SSBP in the slope analysis in Phase 1 and the difference between pooled valsartan and placebo in the randomized withdrawal phase.
4. The results of A2302 randomized withdrawal phase support a treatment effect of valsartan in lowering SBP and DBP in the study population.
5. The most common adverse event was headache.
6. The percentage of patients with > 50% increase in BUN was higher in the high-dose groups.
7. During double-blind, hyperkalemia (>5.5mmol/L) was reported in 6 patients (2.3%) and during OL, it was noted in 3.8% of patients. Five of 6 patients with hyperkalemia at end of double-blind had a history of chronic renal disease, and four of them were renal transplant patients.

VAL489A2307:

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 1-5 years of age. (protocol date: October 10, 2003)
(First patient recruited: 1/12/2004; Last patient completed 11/6/2006).

Objectives: The primary objective of this study was to explore the dose-response of valsartan in mean sitting systolic blood pressure (SSBP) in hypertensive children 1-5 years old.
The secondary objective was to determine efficacy, safety and tolerability of short-term (4 week) and long-term (52 week) valsartan administration in hypertensive children 1-5 years old.

Study Summary: The study design of 2307 was almost identical to the study design of 2302, with the following differences:

1. Since 90% of the patient population in the 1-5 year age group was found to have severe and/or symptomatic hypertension due to underlying diseases, continuation of stable doses of other antihypertensive medications was allowed, and valsartan was used as add-on therapy in 1-5 year old patients whose BP had not been adequately controlled.[4]
2. Patients were stratified by a different baseline weight (< 18 vs. ≥ 18 kg). Patients were also stratified by race (Black vs. Non-Black) and use or non-use of concomitant antihypertensive therapy at study entry.
3. The administered doses were different. During Phase 1, patients were randomized to low (valsartan 5 or 10 mg QD), medium (valsartan 20 or 40 mg QD) or high (valsartan 40 or 80 mg QD) depending on weight. 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 to at Week 2-OL (40 mg QD), Week 4-OL (80 mg QD) and Week 6-OL (80 mg QD plus HCTZ 12 mg QD if tolerable) if the mean trough SSBP was $\geq 95^{th}$ percentile for age, gender, 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.
4. In this study, valsartan was administered as a suspension (see next section).
5. This study randomized fewer patients.

This study consisted of:

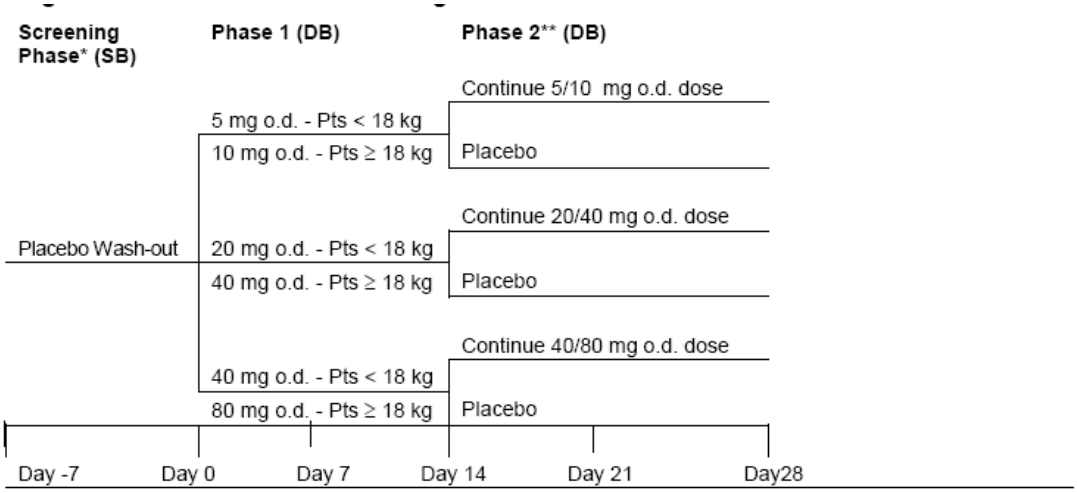
1. A single-blind placebo washout phase for up to one week (Screening);
2. A two-week, double-blind phase where patients were randomized in a 2:1:2 ratio to low, medium and high-dose valsartan, respectively (Phase 1). Patients < 18 kg received 5, 20 or 40 mg valsartan QD, respectively; patients > 18 kg received 10, 40 or 80 mg valsartan QD, respectively;

[4] No change in dosing was permitted during the double-blind period.

3. 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 to switch to placebo.
4. An optional 52-week open-label (OL) phase. Patients received 20 mg QD of valsartan, and could be up-titrated, according 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.

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 medication could be interrupted for up to 3 days in succession during Phase 1 or Phase 2.



* 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.

Figure 5. A2307 Study Design.

Study Population: Males or females, 1-5 (inclusive), ≥ 8 kg weight, with SSBP > 95th percentile for age, gender 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 DBP 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.

	Screening	Baseline	Phase 1 [b]		Phase 2 [b]	
			Week 1	Week 2	Week 3	Week 4 (End of blinded phase)
	Day -7	Day 0[a]	Day 7	Day 14	Day 21	Up to Day 28
Examination	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Informed consent	X					
Background information	X					
Inclusion/exclusion criteria	X	X				
Height, weight and head circumference [c]	X	X				X
Vital signs	X	X	X	X	X	X
Physical Examination		X				X
ECG		X		X		X
Laboratory test (blood chemistry, hematology, urinalysis)	X			X		X
Placebo wash-out medication dispensed	X					
Determine eligibility for randomization		X				
IVRS Call	X	X		X		X
Pt randomized and randomized medication dispensed		X		X		
Concomitant/prior medications	X	X	X	X	X	X
AE/SAE Monitoring		X	X	X	X	X
Developmental Evaluation		X				
End of Study : Blinded Phase						X

a. A patient could be randomized after three days of placebo wash-out dosing as long as his/her previous antihypertensive therapy had been washed out for at least 5 drug half-lives and all entry criteria were met.

b. Patients whose trough sitting systolic blood pressure is $\geq 95^{th}$ percentile for age, gender and height, during the Phase 2 could complete End of Blinded Phase visit (Visit 6) early and then continue in the OL treatment Phase.

c. Head circumference measured at Visit 2

Table 6. A2307: Visit schedule (Screening, Phase 1 and Phase 2)

Table 7. A2307: Visit schedule (Open label phase)

	Day 0-OL (same visit as End of blinded phase)	Week 2-OL	Week 4-OL	Week 6-OL	Week 8-OL	Week 16-OL	Week 26-OL	Week 34-OL	Week 42-OL	Week 52-OL/ End of Study
		Day 14	Day 28	Day 42	Day 56	Day 112	Day 182	Day 238	Day 294	Day 365
Examination	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Vital signs	X	X	X	X	X	X	X	X	X	X
Height, Weight and head circumference[a]	X						X			X
Physical Examination	X				X	X	X	X	X	X
ECG	X						X			X
Laboratory test (blood chemistry, hematology, urinalysis)	X						X			X
IVRS Call	X							X	X	X
Dispense OL medication[b]	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X
AE/SAE Monitoring	X	X	X	X	X	X	X	X	X	X
Developmental Evaluation										X
End of Study: OL Phase										X

a. Head circumference measured at Visit 15
b. OL medication was dispensed as necessary for dose adjustment.

Efficacy Assessments:
The primary efficacy variable was the change in mean SSBP. The primary efficacy analyses were the change from baseline (visit 2) to end of Phase 1 (visit 4) in mean SSBP and the change in mean SSBP from end of Phase 1 (visit 4) to end of Phase 2 (visit 6).

Secondary efficacy variables were:

- the change in mean SSBP from baseline (visit 2) to the end of Phase 2 (visit 6)
- the change in mean SDBP from baseline (visit 2) to the end of Phase 1 (visit 4)
- the change in mean SDBP from end of Phase 1 (visit 4) to the end of Phase 2 (visit 6)
- the change in mean SDBP from baseline (visit 2) to the end of Phase 2 (visit 6)

Safety:
Safety assessments included adverse event recording, laboratory tests, vital signs, physical examinations and ECGs. Developmental assessments (height, weight and head circumference) were performed at baseline (visit 2) and Week 52 (visit 15). In addition, the Child Development Inventory Test was given to the patient's parent/guardian and responses were filled out by the study staff at Visits 2 and 15.

Pharmacokinetic testing was not performed in this study.

Statistics: The null hypothesis for Phase 1 was that the slope of the dose-response curve for change from baseline (Visit 2) in mean SSBP 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

(non-use vs. use) as fixed factors, and centered baseline SSBP and dose ratio (1, 4, 8) as continuous covariates was used.

The analysis results in Phase 2 were used to evaluate whether valsartan had an effect on BP. The null hypothesis for Phase 2 was that the change in mean SSBP 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 (non-use vs. use) and centered Visit 4 SSBP was carried out at the 2-sided significance level of 0.05.

The study was sized to obtain dosing and safety information in children 1-5 years old and to fulfill the FDA Written Request requirement that children 1-5 years old should account for at least 25% of the overall patient population. At least 85 randomized patients would provide at least 45% power for both Phase 1 and Phase 2, with a standard deviation of 13.5 mmHg.

Protocol Amendment (January 27, 2004):

- The sample size was increased from 64 to 85 randomized patients.
- Total number of planned centers increased from 35 to 50.
- Patients on continuing antihypertensive therapy will not be excluded provided their dose is not changed throughout the study.
- Stratification based on use or non-use of concomitant antihypertensive therapy was added.
- Measurement of standing systolic and diastolic BP was eliminated.
- HCTZ 12.5 mg QD was added to the final phase of open-label treatment (in the event that BP was inadequately treated with OL valsartan monotherapy); HCTZ was administered as capsules that were opened and sprinkled onto applesauce or yogurt as directed by the pharmacist.
- The developmental assessment section described administration of the Child Development Inventory Questionnaire
- Inclusion criteria for weight lowered from 10 to 8 kg.
- The protocol originally called for pooling data with study A2302; in this amendment, pooling was made optional.

Results:

Patient Disposition: A total of 130 patients entered the placebo washout phase of the study; 90 patients were randomized into Phase 1 and 87 completed Phase 1. Three randomized patient 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).

Eighty-seven patients were then re-randomized to either valsartan or placebo for Phase 2; forty-three valsartan and 40 placebo patients completed Phase 2. Of the 4 premature discontinuations, one valsartan patient and two patients on placebo discontinued due to

unsatisfactory therapeutic effect; one patient on placebo discontinued due to administrative problems.

Eighty-eight 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 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 AE (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 (see Safety section for further details).

Protocol deviations/violations: 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 PP analysis. The most frequent major violation during Phase 1 was that the end of Phase 1 (visit 4) BP was measured outside the 20-30 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 20-30 hour post-dosing window.

Baseline characteristics:
The mean age was 3.2 years; 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 49-71% male, 35-46% Caucasian, 26-33% Black, and 11-23% from the USA. With respect to other baseline characteristics, the baseline mean sitting SBP 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, this reviewer did not see imbalances in other characteristics such as weight, BMI (mean 16.8 kg/m2), 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.

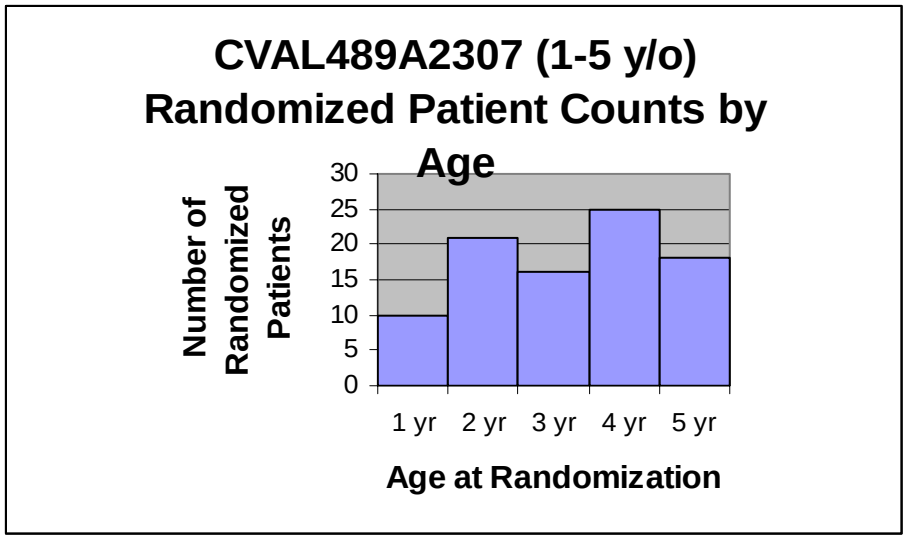


Figure 6. A2307: Histogram of Randomized Patients by Age

Exposure: Mean duration of exposure for each double-blind phase was about 14 days across the treatment groups. During Phase 1, fewer patients in the high dose group (27, or 77%) were exposed to study drug for ≥ 14 days, compared to 32 (87%) of the low-dose and 17 (94%) of the medium dose groups; given the small sample size, larger variations in percentage are seen. Otherwise, the exposure across groups appeared to be similar across groups.

During the OL phase, 96.6% of patients took study drug for at least 182 days, 92% for at least 294 days, and 33% for at least 365 days. The mean number of days on treatment was 346.3. Numerically, most patients in OL were taking valsartan monotherapy in the 20-80 mg QD range. Four patients in OL were taking non-protocol specified valsartan doses (e.g., valsartan 60 mg QD, valsartan 20 mg + HCTZ 12.5 mg, valsartan 5 mg QD).

Concomitant Medication: 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%). No prior valsartan use was noted. 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-hypertensive therapies prior to the start of study medication. The most frequently used non-antihypertensive medications were 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.

Efficacy:

The following table, provided by the sponsor, depicts the baseline, end of Phase 1, and change from baseline to End of Phase 1 in SSBP. All three treatment groups showed a statistically significant mean decrease from baseline However, no obvious dose-response

is seen; the slope analysis yielded a slope estimate of -0.10 mmHg per unit increase in dose ratio for the dose-response curve for change from baseline (p=NS). Similar results were seen in the PP1 population, where the slope estimate was -.28 mmHg (p=NS). Based on this Phase 1 design, one cannot distinguish a placebo effect; however, all groups trended in the right direction.

Table 9-1 Changes in SSBP (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)	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: Post-text table 9.1-3a

These results were verified by the statistical reviewer.

For the LSM change from baseline to end of Phase 1 in SSBP, 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.

For the Phase 2 (randomized withdrawal) analysis, 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), supporting the presence of a treatment effect.

Table 9-3 Changes in mean SSBP (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)	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: Post-text table 9.2-2a, Post-text table 9.2-1a

These results were verified by the statistical reviewer.

When this analysis was performed in the per-protocol population, the mean change from end of Phase 1 to end of phase 2 in SSBP for the valsartan (N=30) group was -0.7 (SD 6.95) mm Hg and for placebo (N=36) the mean change was 0.7 (SD 8.04) mm Hg (p=NS between pooled valsartan and placebo). The trend in the PP2 population was in a similar direction as the ITT2 population.

When viewed as three separate dose groups, 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 is marginally significant (the study was not powered to show statistical significance for this analysis).

Table 9-4 **Least squares mean and treatment comparison for changes in mean SSBP (mmHg) from end of Phase 1 to end of Phase 2 (ITT2 population)**

	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: Post-text table 9.2-1a

Secondary Efficacy results:

1. Change in mean SSBP from baseline to end of Phase 2:

Results are shown below. The sample sizes for each subgroup are smaller, especially in the medium dose subgroup. All groups show a decrease from baseline; a statistically significant decrease from baseline is seen except in the medium/placebo and high/placebo groups.

Table 9-5 **Changes in mean SSBP (mmHg) by double-blind treatment (Phases 1 and 2 combined) (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: PTT 9.3-1

2. Change in mean SDBP from baseline to end of Phase 1:

Results of this analysis are shown below. All three dose groups show a significant decrease from baseline with what appears to be a flat dose-response; a placebo effect cannot be distinguished in this design. These results are consistent with the results for SSBP.

Table 9-6 Changes in mean SDBP (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: Post-text table 9.4-2

When the changes from baseline in SDBP between groups were compared (low vs. high, low vs. medium, and medium vs. high), none of the differences were statistically significant.

3. Change in mean SDBP from end of Phase 1 to end of Phase 2 (randomized withdrawal):

Results of this analysis are shown below. A statistically significant decrease in mean DBP in the valsartan group, as well as a statistically significant increase in SDBP in the placebo group, is seen; the difference between the two groups is statistically significant (p=0.009), supporting the presence of a treatment effect.

Table 9-7 Changes 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: Post-text table 9.5-2; Post-text table 9.5-1

These results were verified by the statistical reviewer.

4. Change in mean SDBP from baseline to end of Phase 2:

Results are shown below and are consistent with the results for the change in sitting SBP.

Table 9-8 Changes in mean SDBP (mmHg) by double-blind treatment (Phases 1 & 2 combined) (ITT population)

	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: PTT 9.3-2

Subgroup Analyses:

For the weight, gender, race, prior antihypertensive treatment, and hypertension severity, all subgroups showed a decrease from baseline to end of Phase 1 in mean SSBP. No unusual patterns were discerned by the reviewers. During Phase 2, mean SSBP remained about the same or decreased further. It should be noted that the sample sizes in some of the subgroups were small.

Table 8. A2307: Subgroup Analysis: Change in mean SSBP (mm Hg) in Phase 1 and Phase 2 by treatment

	Phase 1 (ITT1 population) Change, baseline to end of Phase 1			Phase 2 (ITT2 population) Change, end of Phase 1 to end of Phase 2	
	Low Dose 5 mg/10 mg (N = 37) Mean, (SD), n	Medium Dose 20 mg/40 mg (N = 18) Mean. (SD), n	High Dose 40 mg/80 mg (N = 35) Mean, (SD), n	Pooled Valsartan (N = 44) Mean (SD), n	Pooled Placebo (N = 43) Mean (SD), n
Overall	-8.4* (8.44) 37	-8.3* (7.63) 18	-8.6* (7.55) 35	-1.5 (7.92), 44	1.5 (7.76), 42
Subgroup					
Weight					
< 18 kg	-9.0* (9.73) 24	-7.5* (6.63) 12	-9.6* (8.13) 22	-0.7 (7.22), 28	-0.6 (7.42), 27
≥ 18 kg	-7.2* (5.48) 13	-9.9 (9.83) 6	-6.9* (6.37) 13	-2.9 (9.09), 16	5.2* (7.13), 15
Gender					
Female	-6.7* (8.45) 19	-6.1 (8.64) 7	-7.5* (6.52) 10	-3.0 (8.06), 18	0.1 (7.85), 18
Male	-10.1* (8.29) 18	-9.8* (6.97) 11	-9.0* (8.00) 25	-0.5 (7.81), 26	2.5 (7.70), 24
Race					
Black	-7.9* (8.13) 12	-7.5* (2.97) 6	-7.9* (4.40) 9	-3.9 (7.91), 13	-0.3 (8.92), 12
Non-Black	-8.6* (8.74) 25	-8.8* (9.25) 12	-8.8* (8.43) 26	-0.5 (7.84), 31	2.2 (7.29), 30
Prior antihypertensive treatment					
Use	-5.1 (14.13) 6	-13.5* (6.79) 4	-9.4* (9.46) 7	-0.9 (7.59), 6	0.2 (9.45), 10
Non-use	-9.0* (7.05) 31	-6.9* (7.42) 14	-8.4* (7.19) 28	-1.6 (8.06), 38	1.9 (7.29), 32
Region					
USA	-7.4 (8.14) 6	-5.5 (3.54) 2	-5.2 (9.63) 8	-2.2 (8.52), 9	3.3 (4.12), 6
India	-12.1* (10.16) 10	-8.0 (0.95) 2	-10.6* (8.56) 8	-0.6 (6.08), 7	-1.4 (6.86), 12
Lat Am	-7.6* (6.11) 10	-9.6* (8.61) 10	-12.4* (5.59) 9	-2.1 (8.39), 15	4.7* (7.63), 13
Other	-6.2* (8.74) 11	-6.7 (9.43) 4	-6.3* (4.84) 10	-0.8 (8.59), 13	-0.2 (9.38), 11

Lat Am = Latin America

* indicates statistical significance at the 0.05 level within the treatment group.

Source: [Study A2307-PTT 9.1-3a; PTT 9.6-1 to PTT 9.6-6; PTT 9.2-2a; PTT 9.8-1 to PTT 9.8-6]

Safety:

Adverse Events (AE): In Phase 1, 32% (29/90 total) patients reported AEs in Phase 1 and 45% (39/87) reported AEs in Phase 2; the most common in Phase 1 and Phase 2 were in the category of Infections and infestations (18/90, or 18% in Phase 1; 22/87, or 25% in Phase 2).

In Phase 1, the most frequently reported AEs were cough (total 6/90, or 7%) and pyrexia (5/90, or 6%). Most AEs in Phase 1 were ≤2 per dose group without an obvious dose-relationship.

In Phase 2, the most frequently reported AEs were pyrexia (7/87, or 8%), upper respiratory infection (6/87, or 7%), diarrhea (5/87, or 6%) and cough (5/87, or 6%); of these AEs, a higher percentage was noted in the placebo group.

During the OL phase, 81 patients (92%) experienced AE. The most commonly reported AE were within the category of Infections and infestations (79.5%), followed by respiratory, thoracic and mediastinal disorders (55%) and general disorders and administration site conditions (42%). The most frequently reported adverse events during OL were cough, pyrexia, diarrhea, nasopharyngitis, vomiting, upper respiratory tract

infection, influenza, rhinitis, headache, and tonsillitis. Since most patients were on valsartan monotherapy (80 out of a total N=88), it is difficult to compare the frequency of AE with the frequency on valsartan + HCTZ (N=8). However, no numerical increases in AE were seen with the addition of HCTZ.

AE Severity: One patient in Phase 1 (low-dose group) experienced vomiting that was described as severe. Otherwise, AEs reported during the double-blind period were mild or moderate in severity.

AE Subgroups: AE by gender, race (Black vs. non-Black), and region during Phases 1 and 2 were reviewed; no trends or unusual differences were seen (the absolute numbers of a particular AE by subgroup were small). AE during OL were examined by gender, race (Black vs. non-Black), and region; no unusual results were seen.

Discontinuations due to AE: During double-blind, there were no discontinuations due to AE. During the open-label phase, three patients were discontinued to AE. One of these discontinuations was patient # 0085-00003/ , who died (see below). The second discontinuation was patient #0061-00001, who also died (see below). The third patient, #064-00001 (valsartan 20 mg + HCTZ 12.5 mg QD), a 1 yr old BF (S. Africa) with a history of immune complex glomerulonephritis, was discontinued on Day 247 due to elevated BUN noted on Day 239.

Deaths:
There were no deaths during the double-blind phases. One patient died during the OL phase; a second patient died 11 days after premature discontinuation from the study.

Patient #0061 00001/ was a one year-old Black female with a history of hypertension, urinary tract infection, bilateral hydronephrosis, duplex right kidney, bilateral vesicoureteric reflux and metabolic acidosis; prior to the study, she was taking propranolol for hypertension (which was continued through the study). Other pre-study medications included sodium citrate, Bactrim, amikacin and cefalexin.
The patient was randomized to Phase 1 (Day 1 mean sitting BP =109/71) and completed 2 week treatment with valsartan 40 mg QD (high-dose group); due to site error, Phase 2 randomization was delayed for one week (patient continued on Phase 1 study medication) but was then re-randomized into Phase 2 and received placebo. Seven days after beginning Phase 2, her mean sitting BP was 105/76 with no noted clinically significant changes from baseline. Additional concomitant medication during double-blind included Technetium-99m mercaptoacetyltriglycine (MAG3) for a scan to determine renal function.
On January 10, 2005 she entered open-label and was started on valsartan 20 mg QD as increased to valsartan 40 mg QD on January 17, 2005. On she experienced severe vomiting and diarrhea; the next day at home; no autopsy was performed. The last dose of study drug was The death was coded as gastroenteritis.

Patient # 0085-00003/ was a one year-old Asian male who died of exacerbated pneumonitis 11 days after being discontinued from OL due to hepatitis (SAE). This patient was not coded as a death during the study.

This patient had a history of hypertension, wheezing associated with lower respiratory tract infection, bronchopneumonia, hyperbilirubinemia, gastrointestinal reflux, neonatal sepsis, cryptorchism, right-sided solitary pelvic kidney, right hand polydactyly and developmental delay. Prior to the study, he was taking spironolactone/furosemide for hypertension; other concomitant medications included budesonide, montelukast, salbutamol, ceftriaxone, epinephrine, metronidazole, augmentin, prednisolone, prednisone, ipratropium bromide and azithromycin dehydrate.

At screening, LFTs were mildly elevated: ALT (SGPT) = 28 U/L (NR = 5-25 U/L), AST (SGOT) = 31 U/L (NR 8-25 U/L); his platelet count was elevated at 514 x 10^9/l (NR=135-400 x 10^9/L) and this elevation persisted throughout the study.

On July 6, 2005, he was randomized to high-dose valsartan (40 mg QD) which he took until July 19, 2005; he was prematurely discontinued from double-blind due to unsatisfactory therapeutic effect (BP = 113/63 mm Hg) and started taking open-label valsartan 20 mg QD. At the time ALT was normal and AST mildly elevated (26 U/L). His potassium was 5.1 nmol/L (NR 2.5-5.0 nmol/L) and his ECG showed a QT of 300 msec, QTcF 390 msec and QTcB 450 msec. On August 3, 2005, the patient was titrated to valsartan 40 mg QD due to lack of efficacy (BP 107/61 mm Hg) and with an improvement in BP 2 weeks later (BP 97/57 mm Hg).

On the next scheduled visit (September 1, 2005; Day 58), his valsartan dose was increased to 80 mg QD due to elevated BP (111/67 mm Hg). On January 14, 2006 (Day 193), the patient presented with fever, cough, coryza and vomiting. He was hospitalized on with pneumonia and hepatitis; ALT was 2130 U/L, AST 95 U/L, alkaline phosphatase 2095 U/L (NR = 60-270 U/L), WBC elevated at 19 x 10^9/L (NR=5-15 x10^9/L), low total serum protein (61 g/L) and slightly elevated potassium (4.6 mEq/L; NR = 3.5-4.5 mEq/L). Creatinine and bilirubin levels were reportedly not elevated. Valsartan dose was decreased to 20 mg QD. A CXR showed pneumonitis and the patient was treated with nebulized salbutamol, cefepime injection and oral paracetamol. On the patient underwent Visit 12 evaluation in the hospital; mean sitting Hg and his ECG was reportedly unchanged from baseline. His ALT was 542 U/L and AST 53 U/L; no alkaline phosphatase levels were determined. On January 28, 2006 (Day 207), ALT was 43 U/L and AST was within normal range; potassium and total protein were normal, and white cell and platelet counts were both elevated.

The investigator decided, based on the decrease in liver enzymes after reduction in valsartan dose, as well as the negative hepatitis tests, that the liver enzyme elevations were possibly related to valsartan, and the patient was therefore discontinued from the study (last dose on The patient on oral antibiotics eadmitted on due to exacerbation of pneumonitis. His condition worsened, he went i ure and died 8 hours after admission.

Serious AE (excluding death): Two patients developed SAE during double-blind; 13 (15% of N=88) developed SAE during OL. Patient #071-00001 in the low/low dose

group developed pneumonia (Day 23) and patient #031-00018 in the high/high dose group had a urinary tract infection that started on Study Day 1 (see Table 3, below). Both patients were hospitalized, and neither patient was discontinued from the study.

During OL, most of the SAE fell into the category of infections and infestations.

Table 9. Nonfatal serious adverse events (double-blind and open-label phases) (safety population)

Patient #	Age/race/ gender (country)	Phase/study drug/ daily dose	SAE	Study Day	Outcome
0071-00001	2/W/F (Poland)	2/val/5 mg OL/val/20 mg OL/val/20 mg	Pneumonia Palmar erythema/epistaxis Diagnostic investigation for recurrent URIs	23 80 272	Continued drug Continued drug Continued drug
0031-00018	4/W/F (Brazil)	1/val/80 mg OL/val 20 mg	Worsening UTI UTI	1 58	Continued drug Continued drug
0019-00001	1/W/M (US)	OL/val/20 mg OL/val/ 20 mg OL/val+H/20/12.5 mg Same	Diarrhea, dehydration, swollen abdomen (dx: gastroenteritis) Diarrhea Central line infection Hypoalbuminemia	263 275 343 348	Val interrupted Val restarted (day 280) Continued drug Continued drug
0062-00004	1/W/M (S. Africa)	OL/val 20 mg	Gastroenteritis (due to Shigella and Giardia)	38	Continued drug
072-00008	4 /W/F (Poland)	OL/val 20 mg OL/val 20 mg	Severe diarrhea Urinary tract infection	355 359	Continued drug Continued drug
0083-00002	3/Other/M (India)	OL/val 20 mg	Fever, productive cough (dx viral fever)	209	Val dose adj/temp. interrupted
0084-00004	4/Other/F (India)	OL/val 20 mg	Varicella	67	Continued drug
0061-00001	1/M/F (S. Africa)	OL/val 40 mg	Gastroenteritis	84	Discontinued drug due to AE
0060-00001	3/B/F (S. Africa)	OL/val 40 mg	Convulsions	179	Continued drug
0062-00002	4/W/M (S. Africa)	OL/val 40 mg	Gastroenteritis (Giardia and blastocystis)	126	Continued drug
0062-00003	2/B/F (S. Africa)	OL/val 20 mg OL/val 40 mg OL/val 40 mg OL/val 80 mg OL/val 80 mg	Sepsis, bronchopneumonia Bronchopneumonia Sepsis Bronchopneumonia Bronchopneumonia	30 153 263 307 392	Continued drug Continued drug Continued drug Continued drug 1 day after study completed
0029-00002	5/W/F (Brazil)	OL/val 80 mg OL/val + HCTZ/ 80/12.5 mg	Abdominal wall cellulitis Bacterial tracheobronchitis	210 279	Continued drug Continued drugs

		Same Same Same Same Same	Pneumonia Nephrotic syndrome (decompens) Nephrotic syndrome (decompens) Nephrotic syndrome (decompens) Nephrotic syndrome (decompens)	303 338 348 366 396	Continued drugs Continued drugs Continued drugs Continued drugs AE Ongoing
0062-00001	3/W/F (S. Africa)	OL/val + HCTZ/ 80/12.5 mg	Gastroenteritis	128	Continued drug

URI=upper respiratory infection; UTI=urinary tract infection; decompens = decompensated; SAE = serious adverse event

Laboratory Results:

Mean changes from baseline by treatment in ALT, AST, bilirubin, creatinine, BUN, sodium, potassium, chloride, total protein, albumin, and glucose during double-blind period (Phases 1 and 2) and OL were reviewed.

During Phase 1 of the study, no meaningful changes in biochemistry were seen. During the double-blind phase (Phases 1 and 2), a mean increase of 8.0 U/L SGPT in the medium/medium dose group (n=8) was seen; according to the sponsor, this increase was likely due to one patient (#031-00019) with baseline mildly elevated SGPT 37 U/L (NL =10-35 U/L) and SGPT 119 U/L at the end of double-blind (Visit 6). It should be noted that this patient continued in the OL phase, on valsartan 20 mg QD, with follow-up SGPT 41 U/L and 34 U/L on Visits 12 and 15, respectively.

When examined from baseline to end of study (including OL phase), the mean SGOT value increased from baseline (27.0 U/L) to end of study (37.5 U/L); SGPT increased from 13.8 U/L to 25.6 U/L. According to the sponsor, these increases stemmed from three patients with markedly elevated transaminases during OL.

Patients during OL with markedly elevated transaminases (> 10 x ULN):

- Patient #030-00003 (Brazil) had hepatitis A based on serology; SGPT=708 U/L and SGOT =571 U/L on Study Day 393 (scheduled end-of-study visit); previous SGOT and SGPT values at other study visits were normal. Follow-up liver enzyme tests (at local laboratory) 6 months later showed normal transaminases.
- Patient #080-00003 (India) had SGPT =339 U/L and SGOT=502 U/L on Study Day 393 (end-of-study visit). (On the prior visit 12, SGOT was mildly elevated at 33 U/L with normal SGPT, Day 210 and transaminases prior to Visit 12 were normal). Repeat enzymes at the central laboratory 10 days later were normal.
- Patient #085-00003 (India) had SGPT = 542 U/L and SGOT=53 U/L on valsartan 80 mg QD (high dose) on Study Day 198 (scheduled visit). His valsartan dose was decreased to 20 mg QD; liver enzymes repeated 9 days later showed mildly elevated SGPT (43 U/L) and normal SGOT. This patient died 11 days after discontinuation (see Deaths).

In addition, the medical reviewer has noted the following case:

- Patient #082-00003 (India) (valsartan 40 mg) was diagnosed with hepatitis based on elevated transaminases on Day 148 (SGPT 1197 U/L, SGOT 1095 U/L); however, the transaminases apparently normalized when rechecked during a scheduled visit 2 months later (Visit 12: SGPT 5 U/L, SGOT 20 U/L) and the patient completed the study without a change in dose. Transaminases were also normal on scheduled visits prior to Day 148. This case was not included in the laboratory test results section because the visit was unscheduled and the liver enzymes were analyzed at a local laboratory. **(Reviewer: since the transaminases normalized while the patient continued the same dose of valsartan, the reviewer considers this case unlikely to be drug-related.)**

When the patients with markedly elevated transaminases were excluded, mean transaminases decreased slightly (< 2.0 U/L) during OL.

Two patients (#031-00019, 061-00006) with elevated screening SGOT (one with elevated SGPT as well) had transaminase elevation 3-10 x ULN which increased from baseline while on treatment (#031-00019 at Visits 4 and 6; #061-00006 at Visit 15 [OL]).

Reviewer: #061-00006 (4 yr old BM) had elevated transaminases at the end-of-study visit.

According to current valsartan labeling, "Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (<0.1%) treated with valsartan discontinued treatment for elevated liver chemistries" (section 7.1).

Otherwise, no meaningful change was seen in the changes from baseline (Table 10.3-2, not shown).
No meaningful change was seen with respect to the OL mean change from baseline in cholesterol, triglycerides, or hematocrit (Table 10.3-3, not shown).

Table 10-10 Change from baseline in laboratory parameters during the OL phase (OL population)

Parameter	n*	Baseline Mean (SD)	Baseline Median	End of OL Mean (SD)	End of OL Median	Change from baseline Mean (SD)	Change from baseline Median
ALT (SGPT) U/L	85	13.8 (6.87)	12.0	25.6 (83.10)	12.0	11.8 (82.82)	0.0
ALT (SGPT) U/L**	82	13.6 (6.81)	12.0	13.2 (6.45)	12.0	-0.3 (4.98)	0.0
AST (SGOT) U/L	85	27.0 (9.62)	26.0	37.5 (78.69)	25.0	10.5 (78.17)	-2.0
AST (SGOT) U/L**	82	26.9 (9.77)	25.5	25.5 (9.73)	24.5	-1.4 (9.21)	-2.0
Bilirubin µmol/L	84	6.8 (5.56)	5.5	6.1 (3.69)	5.0	-0.8 (5.78)	0.0
Creatinine µmol/L	85	60.2 (25.43)	53.0	59.4 (27.59)	53.0	-0.8 (15.75)	0.0
BUN (Urea) mmol/L	85	5.46 (2.73)	5.00	6.25 (3. 88)	5.00	0.79 (3.04)	0.20
Uric Acid µmol/L	85	257 (74.21)	240	289 (108.9)	255	32.0 (74.51)	20.0
Glucose mmol/L	79	4.68 (0.82)	4.50	4.59 (0.92)	4.50	-0.09 (1.05)	-0.10
Cholesterol mmol/L	85	4.49 (1.57)	4.14	4.85 (2.91)	4.14	0.36 (1.78)	-0.10
Triglycerides mmol/L	85	1.77 (1.23)	1.39	1.81 (1.67)	1.25	0.04 (1.28)	0.02
Potassium mmol/L	81	4.36 (0.44)	4.30	4.42 (0.46)	4.40	0.06 (0.54)	0.0
Hemoglobin g/L	82	125 (12.10)	126	122 (13.51)	122	-2.3 (11.13)	-2.5
Hematocrit L/L	82	8.35 (15.7)	0.39	9.40 (16.60)	0.38	1.05 (8.56)	0.0

*Only patients with both baseline and post-baseline values were included in the analysis
**These analyses of SGOT and SGPT exclude 3 patients with SGOT/SGPT >10 x UL during the OL phase
Source: Post-text table 10.3-3; Appendix 8.1 Table 1-17

<u>Pre-specified percent change from baseline in laboratory parameters:</u>

Of the pre-specified percent changes from baseline, the highest incidence occurred with respect to > 50% increases in BUN (double-blind and open-label) and > 20% increases in potassium during open-label. In addition, >50% increase in uric acid was seen during open-label but not as consistent during double-blind.

According to current labeling, “in heart failure trials > 50% increases in BUN were seen in 16.6% of Diovan-treated patients compared to 6.3% of placebo patients.”

Table 10-11 Specified percent change from baseline in laboratory tests during double-blind and OL phases (Safety population)

	Double-blind phase (N=90)			Open-label phase (N=88)		
Laboratory test and specified criterion	N*	Meeting the criterion n (%)	Meeting the criterion and out of normal range[1] n (%)	N*	Meeting the criterion n (%)	Meeting the criterion and out of normal range[1] n (%)
BUN (Urea) >50% increase	88	11 (12.5)	7 (8.0)	85	22 (25.9)	10 (11.8)
Creatinine >50% increase	87	3 (3.4)	2 (2.3)	85	5 (5.9)	2 (2.4)
Potassium >20% increase	84	7 (8.3)	3 (3.6)	81	11 (13.6)	6 (7.4)
Potassium >20% decrease	84	2 (2.4)	1 (1.2)	81	4 (4.9)	3 (3.7)
Glucose >50% increase	80	5 (6.3)	3 (3.8)	79	6 (7.6)	5 (6.3)
Glucose >50% decrease	80	1 (1.3)	1 (1.3)	79	1 (1.3)	1 (1.3)
Uric acid >50% increase	88	4 (4.5)	1 (1.1)	85	11 (12.9)	3 (3.5)

* Only patients with both baseline and post-baseline values were included in the analysis.
[1]Higher than normal range for increased values and below normal range for decreased values.
Source: Post-text table 10.3-6 and Post-text table 10.3-7

Shift Tables:

From the shift tables, an increase in SGOT from low/normal to high post-baseline was seen in 14% of patients during double-blind; increases in SGPT were not consistent with the SGOT increases. Increases from low/normal to high post-baseline were also seen with respect to BUN, glucose, cholesterol, triglycerides, and potassium.

Table 10-12 Shifts from baseline to the most extreme value at any time point post-baseline in selected laboratory parameters during the double-blind phase (Safety population)

Laboratory tests for which *high* values are clinically important

Parameter	Total n*	High levels at baseline n (%)	Post-baseline shift: From Low/Normal to High n (%)	Post-baseline shift: From High to Normal/Low n (%)	High levels post baseline n (%)
ALT (SGPT)	88	4 (5)	2 (2)	2 (2)	4 (5)
AST (SGOT)	88	36 (41)	12 (14)	11 (13)	37 (42)
Bilirubin	86	1 (1)	3 (3)	1 (1)	3 (3)
Creatinine	87	22 (25)	6 (7)	2 (2)	26 (30)
BUN (Urea)	88	20 (23)	10 (11)	3 (3)	27 (31)
Uric Acid	88	2 (2)	5 (6)	0 (0)	7 (8)
Glucose	80	9 (11)	9 (11)	8 (10)	10 (13)
Cholesterol	88	35 (40)	11 (13)	8 (9)	38 (43)
Triglycerides	88	44 (50)	12 (14)	11 (13)	45 (51)
Potassium	84	4 (5)	10 (12)	1 (1)	13 (15)

Laboratory tests for which *low* values are clinically important

Parameter	Total n*	Low levels at baseline n (%)	Post-baseline shift: From High/Normal to Low n (%)	Post-baseline shift: From Low to High/Normal n (%)	Low levels post baseline n (%)
Glucose	80	3 (4)	7 (9)	2 (3)	8 (10)
Hemoglobin	84	4 (5)	4 (5)	0 (0)	8 (10)
Hematocrit	84	7 (8)	5 (6)	2 (2)	10 (12)

* Only patients with both a baseline and post-baseline values were included in the analysis.
Source: Post-text table 10.3-4

During OL, increases from low/normal to high were seen with respect to SGOT, BUN, glucose, cholesterol, triglycerides, and potassium. Decreases from high/normal to low were seen with respect to glucose, hematocrit and hemoglobin.

Table 10-13 Shifts from baseline to the most extreme value at any time point post-baseline in selected laboratory tests during the OL phase (OL population)

Laboratory tests for which *high* values are clinically important

Parameter	Total n*	High levels at baseline n (%)	Post-baseline shift		High levels post baseline n (%)
			From Low/Normal to High n (%)	From High to Normal/Low n (%)	
ALT (SGPT)	85	4 (5)	4 (5)	2 (2)	6 (7)
AST (SGOT)	85	36 (42)	15 (18)	14 (17)	37 (44)
Bilirubin	84	1 (1)	3 (4)	1 (1)	3 (4)
Creatinine	85	22 (26)	4 (5)	5 (6)	21 (25)
BUN (Urea)	85	19 (22)	11 (13)	3 (4)	27 (32)
Uric Acid	85	2 (2)	6 (7)	0 (0)	8 (9)
Glucose	79	8 (10)	9 (11)	7 (9)	11 (14)
Cholesterol	85	34 (40)	11 (13)	9 (11)	36 (42)
Triglycerides	85	42 (49)	18 (21)	11 (14)	49 (58)
Potassium	81	4 (5)	10 (12)	3 (4)	11 (14)

Laboratory tests for which *low* values are clinically important

Parameter	Total n*	Low levels at baseline n (%)	Post-baseline shift		Low levels post baseline n (%)
			From High/Normal to Low n (%)	From Low to High/Normal n (%)	
Glucose	79	3 (4)	12 (15)	3 (4)	12 (15)
Hemoglobin	82	4 (5)	7 (8)	0 (0)	11 (13)
Hematocrit	82	7 (8)	10 (12)	1 (1)	16 (20)

* Only patients with both a baseline and post-baseline values were included in the analysis.
Source: Post-text table 10.3-5

Vital Signs:
Safety results for vital signs in the open-label population are presented graphically. These data do not take into account changes in dosage or addition of HCTZ.

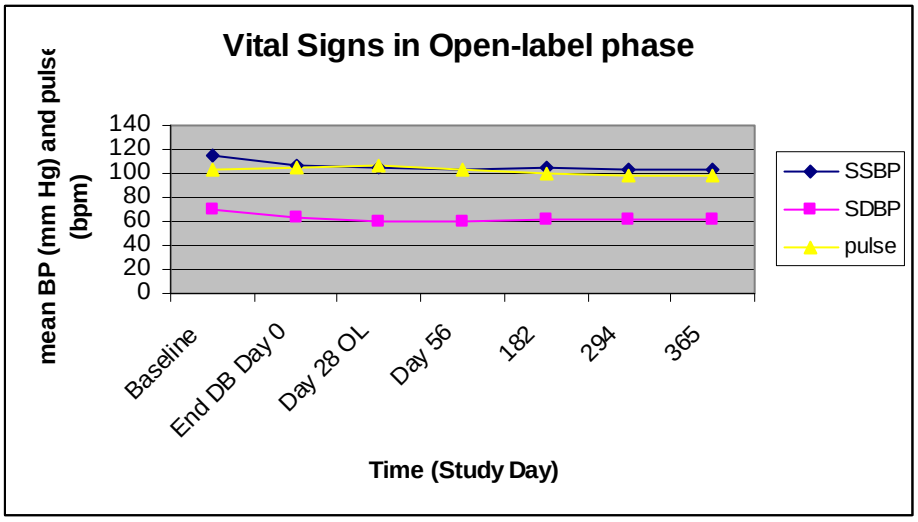


Figure 7. A2307: Vital signs in OL phase

Electrocardiograms:
During double-blind, one patient (#0062-00004) with baseline tachycardia (HR 125 bpm) became more tachycardic (HR 162 bpm) at study Day 15, which improved on Day 21. Another patient (ZAF/0062/00003) with baseline QTcB 430 developed QTcB of 470 (though QTcF 420). The other 8 patients with notably abnormal ECG values (e.g., QT prolongation, tachycardia) had these abnormalities on Day 1 with improvement/without worsening during double-blind.
No dose-related ECG abnormalities were detected.

During OL, no unusual ECG trends were noted.

Developmental Assessments:
A parent/guardian questionnaire (Child Development Inventory Test) was used at baseline (Visit 2 and at the end of OL (Visit 15) or the last visit (for early discontinuations); the same questionnaire was administered at each of these two time points. Mean scores increased for all measured parameters (social development, self help, gross motor, fine motor, expressive language, language comprehension, letters and numbers); >50% of patients showed a positive change for each of these assessments. Since there is no control group, this reviewer does not know how these changes compare to the background population; however, no obvious adverse trend is seen.

Growth Assessments:
Length/height-for-age Z-scores and BMI-for-age Z-scores were provided by the sponsor. The Z-scores were calculated by comparing the patient's length/height and BMI, respectively, with that of gender-matched children of the same gender and age (from WHO Child Growth Standards for age < 60 months and 2000 CDC Growth Charts for age > 50 months at some point during the study).[5]
The mean Z-score of length/height-for-age was -0.649 at baseline (Visit 2) and -0.633 at the end of study (a mean increase of 0.016).
The mean Z-score of BMI-for-age was 0.491 at baseline (Visit 2) and 0.423 at the end of study (a mean change of -0.068).
These mean changes appear to be small and do not raise concern.

Mean head circumference increased from a mean baseline measurements of 49.6 (SD 2.74) cm to a Day 365 (Visit 15) measurement of 50.9 (SD 2.68) cm.

Reviewer Comments/Conclusions:
1. Study A2307 followed the Written Request type C design.
2. Results for Phase 1 (dose-response) showed a slope for the change in SSBP that was not significantly different from zero (p=NS).
3. Results for Phase 2 (randomized withdrawal) showed a statistically significant difference for the change in SSBP (end of Phase 1 to end of Phase 2) between

[5] One is assuming that this study population is comparable with healthy subjects.

pooled valsartan and placebo (ITT population). In the PP population, valsartan and placebo showed nonsignificant trends similar to the ITT population.

4. Results for mean SDBP were consistent with SSBP results.
5. Two patients were noted with markedly elevated transaminases; one patient (085-00003) was discontinued due to elevated transaminases (see Deaths, above); another patient (080-00003) developed elevated transaminases at the end-of-study visit, with subsequent normal transaminases. A third patient (#061-00006) developed elevated transaminases (3-10x ULN) at the end-of-study visit.
6. One patient discontinued OL due to elevated BUN.
7. Two deaths were noted; one occurred during the open-label phase and the other occurred 11 days after discontinuation from the study.
8. The results of the study support a treatment effect, but do not establish a dose-response relationship.
9. Markedly elevated transaminases were seen in two OL patients (one at the end-of-study visit, and one discontinued due to hepatitis), and elevated transaminases (3-10X ULN) were seen in a third OL patient (end-of-study visit).

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/s/

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