CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-283/S-024

Trade Name: Diovan 40, 80, 160, and 320 mg Tablets

Generic Name: valsartan

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: November 29, 2007

Indication: Provides for the use of Diovan for the treatment of hypertension in pediatric patients 6 – 16 years of age

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APPLICATION NUMBER:

21-283/S-024

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-283/S-024

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy A. Price
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Price:

Please refer to your May 29, 2007 supplemental new drug application submitted under section 505(b)(i) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) 40, 80, 160, and 320 mg Tablets.

We acknowledge receipt of your submissions dated July 2, 3, 11 (two), 16, August 2, 6, 16, September 5, 7, 20, 24, October 10, 16, 17, 22, and November 19, 2007.

This supplemental new drug application provides for the use of Diovan for the treatment of hypertension in pediatric patients 6 – 16 years of age.

We have completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and text for the patient package insert). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-283/S-024."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardiovascular and Renal Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

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

/s/

Norman Stockbridge

11/29/2007 05:01:01 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Diovan safely and effectively. See full prescribing information for Diovan.

Diovan (valsartan) Tablets
Initial U.S. Approval: 1996

WARNING: USE IN PREGNANCY

When pregnancy is detected, discontinue Diovan as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus (5.1)

----------RECENT MAJOR CHANGES----------

Dosage and Administration: Use in pediatric hypertension 6-16 years (2.2) 11/2007
Warning and Precautions: Use in pregnancy (5.1) 11/2006

----------INDICATIONS AND USAGE----------

Diovan is a angiotensin II receptor blocker (ARB) indicated for:

- Treatment of **hypertension** (1.1)
- Treatment of **heart failure** (NYHA class II-IV); Diovan significantly reduced hospitalization for heart failure (1.2)
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction **following myocardial infarction** (1.3)

----------DOSAGE AND ADMINISTRATION----------

Indication	Starting dose	Dose Range	Target Maintenance Dose*
Adult Hypertension (2.1)	80 or 160 mg once daily	80-320 mg once daily	---
Pediatric Hypertension (6-16 years) (2.1)	1.3 mg/kg once daily (up to 40 mg total)	1.3-2.7 mg/kg once daily (up to 40-160 mg total)	---
Heart Failure (2.2)	40 mg twice daily	40-160 twice daily	160 mg twice daily
Post-Myocardial Infarction (2.3)	20 mg twice daily	20-160 mg twice daily	160 mg twice daily

* as tolerated by patient

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment. Diovan may be administered with or without food. In **heart failure** patients, consideration should be given to reducing the dose of concomitant diuretics. **Following myocardial infarction**, consideration should be given to a dosage reduction if symptomatic hypotension or renal dysfunction occurs.

----------DOSAGE FORMS AND STRENGTHS----------

Tablets (mg): 40 (scored), 80, 160, 320

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- Avoid fetal or neonatal exposure (5.1)
- Observe for signs and symptoms of hypotension (5.2)
- Use with caution in patients with impaired hepatic (5.3) or renal (5.4) function

----------ADVERSE REACTIONS ----------

Hypertension: Most common adverse reactions are headache, dizziness, viral infection, fatigue and abdominal pain (6.1)
Heart Failure: Most common adverse reactions are dizziness, hypotension, diarrhea, arthralgia, back pain, fatigue and hyperkalemia (6.1)
Post-Myocardial Infarction: Most common adverse reactions which caused patients to discontinue therapy are hypotension, cough and increased blood creatinine (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NOVARTIS PHARMACEUTICALS CORPORATION at 1 888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Potassium sparing diuretics, potassium supplements or salt substitutes may lead to increases in serum potassium, and in heart failure patients, increases in serum creatinine (7)

----------USE IN SPECIFIC POPULATIONS----------

Nursing Mothers: Nursing or drug should be discontinued (8.3); **Pediatrics**: Efficacy and safety data support use in 6-16 year old patients (8.4); **Geriatrics**: No overall difference in efficacy or safety vs younger patients, but greater sensitivity of some older individuals cannot be ruled out (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: November 2007

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: USE IN PREGNANCY

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.

See WARNINGS: Fetal/Neonatal Morbidity and Mortality (5.1)

1. INDICATIONS AND USAGE

1.1 Hypertension

Diovan® (valsartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

1.2 Heart Failure

Diovan is indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor. [See Clinical Studies (14.2)]

1.3 Post-Myocardial Infarction

In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, Diovan is indicated to reduce cardiovascular mortality. [See Clinical Studies (14.3)]

2. DOSAGE AND ADMINISTRATION

2.1 Adult Hypertension

The recommended starting dose of Diovan (valsartan) is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once a day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

2.2 Pediatric Hypertension 6-16 years of age

For children who can swallow tablets, the usual recommended starting dose is 1.3 mg/kg once daily (up to 40 mg total). The dosage should be adjusted according to blood pressure response. Doses higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in pediatric patients 6 to 16 years old.

For children who cannot swallow tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of Diovan, the use of a suspension is recommended. Follow the suspension preparation instructions below (see **Preparation of Suspension**) to administer valsartan as a suspension. When the suspension is replaced by a tablet, the dose of valsartan may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablet.

Diovan is not recommended for treatment of children below the age of 6 years or children of any age with a glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available.

Preparation of Suspension (for 160 mL of a 4 mg/mL suspension)

Add 80 mL of Ora-Plus®* oral suspending vehicle to an amber glass bottle containing 8 Diovan 80 mg tablets, and shake for a minimum of 2 minutes. Allow the suspension to stand for a minimum of 1 hour. After the standing time, shake the suspension for a minimum of 1 additional minute. Add 80 mL of Ora-Sweet SF®* oral sweetening vehicle to the bottle and shake the suspension for at least 10 seconds to disperse the ingredients. The suspension is homogenous and can be stored for either up to 30 days at room temperature (below 30 C/86 F) or up to 75 days at refrigerated conditions (2-8 C/35-46 F) in the glass bottle with a child-resistant screw-cap closure. Shake the bottle well (at least 10 seconds) prior to dispensing the suspension.

*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

2.3 Heart Failure

The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

2.4 Post-Myocardial Infarction

Diovan may be initiated as early as 12 hours after a myocardial infarction. The recommended starting dose of Diovan is 20 mg twice daily. Patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Diovan may be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin, beta-blockers, and statins.

3. DOSAGE FORMS AND STRENGTHS

40 mg are scored yellow ovaloid tablets with beveled edges, imprinted NVR/DO (Side 1/Side 2)

80 mg are pale red almond-shaped tablets with beveled edges, imprinted NVR/DV

160 mg are grey-orange almond-shaped tablets with beveled edges, imprinted NVR/DX

320 mg are dark grey-violet almond-shaped tablets with beveled edges, imprinted NVR/DXL

4. CONTRAINDICATIONS

None

5. WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Diovan can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. *[See Use in Specific Populations (8.1)]*

5.2 Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction patients. Patients with heart failure or post-myocardial infarction patients given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Impaired Hepatic Function

As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan to these patients.

5.4 Impaired Renal Function

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adult Hypertension

Diovan (valsartan) has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with Diovan was similar to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse reactions that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse reactions that occurred in controlled clinical trials of patients treated with Diovan (>0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

Body as a Whole Allergic reaction and asthenia
Cardiovascular: Palpitations
Dermatologic: Pruritus and rash
Digestive: Constipation, dry mouth, dyspepsia, and flatulence
Musculoskeletal: Back pain, muscle cramps, and myalgia
Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence
Respiratory: Dyspnea
Special Senses: Vertigo
Urogenital: Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Pediatric Hypertension

No relevant differences were identified between the adverse experience profile for pediatric patients aged 6-16 years and that previously reported for adult patients. Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with Diovan for up to one year.

In the one study (n=90) of pediatric patients (1-5 years), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These 5 events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to Diovan has not been established.

Heart Failure

The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse reactions vs. 7% of placebo patients.

The table shows adverse reactions in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Other adverse reactions with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long-term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse reactions not previously identified.

Post-Myocardial Infarction

The safety profile of Diovan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the post-myocardial infarction setting. The table shows the percent of patients discontinued in the valsartan and captopril-treated groups in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) with a rate of at least 0.5% in either of the treatment groups.

	Valsartan (n=4,885)	Captopril (n=4,879)
Discontinuation for adverse reaction	5.8%	7.7%
Adverse reactions		
Hypotension NOS	1.4%	0.8%
Cough	0.6%	2.5%
Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: There are rare reports of angioedema;
Digestive: Elevated liver enzymes and very rare reports of hepatitis;
Renal: Impaired renal function;
Clinical Laboratory Tests: Hyperkalemia;
Dermatologic: Alopecia.
Blood and Lymphatic: There are very rare reports of thrombocytopenia.
Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7. DRUG INTERACTIONS

No clinically significant pharmacokinetic interactions were observed when Diovan (valsartan) was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

Transporters The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

7.1 Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver Function Tests: 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.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan-treated patients compared to 6.3% of placebo-treated patients.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D

Diovan, like other drugs that act on the renin angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of pregnancy. Diovan can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. In a retrospective study, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin angiotensin system, was associated with a potential risk of birth defects.

When pregnancy occurs in a patient using Diovan, the physician should discontinue Diovan treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Diovan (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent can not be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Diovan treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to Diovan should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy. *[See Nonclincial Toxicology (13.2)]*.

8.3 Nursing Mothers

It is not known whether Diovan is excreted in human milk. Diovan was excreted in the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from Diovan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The antihypertensive effects of Diovan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1-5 and 6-16 years of age [see Clinical Studies(14.1)]. The pharmacokinetics of Diovan have been evaluated in pediatric patients 1 to 16 years of age (see Pharmacokinetics, Special Populations, Pediatric (12.3)). Diovan was generally well tolerated in children 6-16 years and the adverse experience profile was similar to that described for adults. Diovan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded [see Adverse Reactions, Pediatric Hypertension (6.1)].

Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m^2 basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. Since this period coincides with up to 44 weeks after conception in humans, it is not considered to point toward an increased safety concern in 6 to 16 year old children.

Diovan is not recommended for treatment of children with glomerular filtration rates <30 mL/min/1.73 m^2, as no data are available.

8.5 Geriatric Use

In the controlled clinical trials of valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥65 years and 265 (7.9%) were ≥75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 53% (2,596) of the 4,909 patients treated with valsartan and 51% (2,515) of the 4,885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.

10. OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

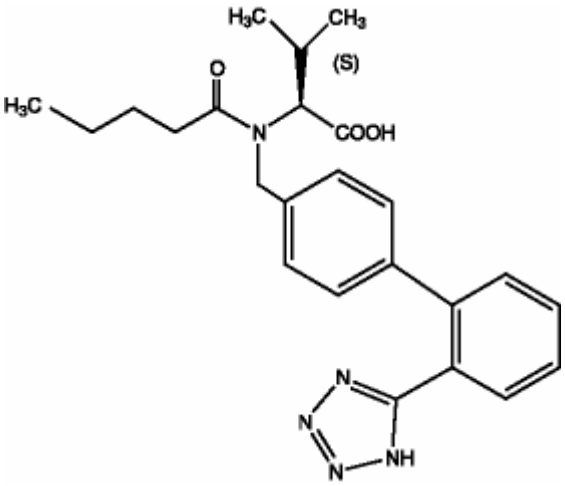
Diovan (valsartan) is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

11. DESCRIPTION

Diovan (valsartan) is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT_1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as tablets for oral administration, containing 40 mg, 80 mg, 160 mg or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Diovan (valsartan) blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

12.2 Pharmacodynamics

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

12.3 Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for Diovan is about 25% (range 10%-35%). The bioavailability of the suspension (see [2.2] Dosage and Administration; Pediatric Hypertension) is 1.6 times greater than with the tablet. With the tablet, food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Distribution: The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations:

Pediatric: In a study of pediatric hypertensive patients (n=26, 1-16 years of age) given single doses of a suspension of Diovan (mean: 0.9 to 2 mg/kg), the clearance (L/h/kg) of valsartan for children was similar to that of adults receiving the same formulation.

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary [see Dosage and Administration (2.1)].

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan [see Dosage and Administration (2.1)].

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease [see Dosage and Administration (2.1)].

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

14. CLINICAL STUDIES

14.1 Hypertension

Adult Hypertension

The antihypertensive effects of Diovan (valsartan) were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2,000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition

of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Pediatric Hypertension

The antihypertensive effects of Diovan were evaluated in two randomized, double-blind clinical studies.

In a clinical study involving 261 hypertensive pediatric patients 6 to 16 years of age, patients who weighed < 35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥ 35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). Renal and urinary disorders, and essential hypertension with or without obesity were the most common underlying causes of hypertension in children enrolled in this study. At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by -8, -10, -12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

In a clinical study involving 90 hypertensive pediatric patients 1 to 5 years of age with a similar study design, there was some evidence of effectiveness, but safety findings for which a relationship to treatment could not be excluded mitigate against recommending use in this age group [See Adverse Reactions (6.1)].

14.2 Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5,010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF < 40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4 mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in the table below.

	Placebo (N=2,499)	**Valsartan (N=2,511)**	**Hazard Ratio (95% CI*)**	**Nominal p-value**
All-cause mortality	484 (19.4%)	495 (19.7%)	1.02 (0.90-1.15)	0.8
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009

* CI = Confidence Interval

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in the following table.

	Without ACE Inhibitor		**With ACE Inhibitor**	
	Placebo (N=181)	**Valsartan (N=185)**	**Placebo (N=2,318)**	**Valsartan (N=2,326)**
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
p-value	0.0002		0.0965	

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Secondary end points in the subgroup not receiving ACE inhibitors were as follows.

	Placebo (N=181)	**Valsartan (N=185)**	**Hazard Ratio (95% CI)**
Components of HF morbidity			
All-cause mortality	49 (27.1%)	32 (17.3%)	0.59 (0.37, 0.91)

Sudden death with resuscitation	2 (1.1%)	1 (0.5%)	0.47 (0.04, 5.20)
CHF therapy	1 (0.6%)	0 (0.0%)	–
CHF hospitalization	48 (26.5%)	24 (13.0%)	0.43 (0.27, 0.71)
Cardiovascular mortality	40 (22.1%)	29 (15.7%)	0.65 (0.40, 1.05)
Non-fatal morbidity	49 (27.1%)	24 (13.0%)	0.42 (0.26, 0.69)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

14.3 Post-Myocardial Infarction

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and either heart failure (signs, symptoms or radiological evidence) or left ventricular systolic dysfunction (ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan (titrated from 20 or 40 mg twice daily to the highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor, captopril (titrated from 6.25 mg three times daily to the highest tolerated dose up to a maximum of 50 mg three times daily), or the combination of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to the highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. Baseline therapy included aspirin (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%) and statins (34%). The mean treatment duration was two years. The mean daily dose of Diovan in the monotherapy group was 217 mg.

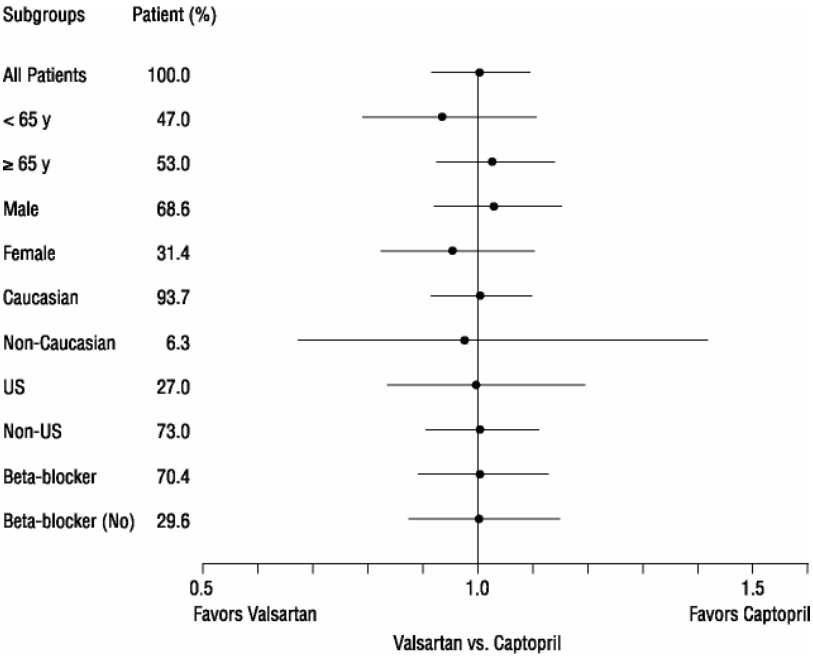
The primary endpoint was time to all-cause mortality. Secondary endpoints included (1) time to cardiovascular (CV) mortality, and (2) time to the first event of cardiovascular mortality, reinfarction, or hospitalization for heart failure. The results are summarized in the table below:

	Valsartan vs. Captopril (N=4,909) (N=4,909)			**Valsartan + Captopril vs. Captopril (N=4,885) (N=4,909)**		
	No. of Deaths Valsartan/Captopril	Hazard Ratio CI	pp-value	No. of Deaths Comb/Captopril	Hazard Ratio CI	p-value
All-cause mortality	979 (19.9%) /958 (19.5%)	1.001 (0.902, 1.111)	0.98	941 (19.3%) /958 (19.5%)	0.984 (0.886, 1.093)	0.73
CV mortality	827 (16.8%) /830 (16.9%)	0.976 (0.875, 1.090)				
CV mortality, hospitalization for HF, and recurrent non-fatal MI	1,529 (31.1%) /1,567 (31.9%)	0.955 (0.881, 1.035)				

There was no difference in overall mortality among the three treatment groups. There was thus no evidence that combining the ACE inhibitor captopril and the angiotensin II blocker valsartan was of value.

The data were assessed to see whether the effectiveness of valsartan could be demonstrated by showing in a non-inferiority analysis that it preserved a fraction of the effect of captopril, a drug with a demonstrated survival effect in this setting. A conservative estimate of the effect of captopril (based on a pooled analysis of 3 post-infarction studies of captopril and 2 other ACE inhibitors) was a 14-16% reduction in mortality compared to placebo. Valsartan would be considered effective if it preserved a meaningful fraction of that effect and unequivocally preserved some of that effect. As shown in the table, the upper bound of the CI for the hazard ratio (valsartan/captopril) for overall or CV mortality is 1.09-1.11, a difference of about 9-11%, thus making it unlikely that valsartan has less than about half of the estimated effect of captopril and clearly demonstrating an effect of valsartan. The other secondary endpoints were consistent with this conclusion.

Effects on Mortality Amongst Subgroups in VALIANT



There were no clear differences in all-cause mortality based on age, gender, race, or baseline therapies, as shown in the figure above.

16. HOW SUPPLIED/STORAGE AND HANDLING

Diovan (valsartan) is available as tablets containing valsartan 40 mg, 80 mg, 160 mg, or 320 mg. All strengths are packaged in bottles and unit dose blister packages (10 strips of 10 tablets) as described below.

40 mg tablets are scored on one side and ovaloid with bevelled edges. 80 mg, 160 mg, and 320 mg tablets are unscored and almond-shaped with bevelled edges.

Tablet	Color	Deboss		NDC 0078-XXXX-XX		
		Side 1	Side 2		Bottle of	Blister
				30	90	
40 mg	Yellow	NVR	DO	0423-15	–	0423-06
80 mg	Pale red	NVR	DV	–	0358-34	0358-06
160 mg	Grey-orange	NVR	DX	–	0359-34	0359-06
320 mg	Dark grey-violet	NVR	DXL	–	0360-34	0360-06

Store at 25 C (77 F); excursions permitted to 15-30 C (59 - 86 F)

[see USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

17. PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Pregnancy: Female patients of childbearing age should be told that use of drugs like Diovan that act on the renin-angiotensin system during pregnancy can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. Women using Diovan who become pregnant should notify their physician as soon as possible.

DIOVAN (DYE'-o-van)
(valsartan) Tablets

Read the Patient Information that comes with DIOVAN before you take it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about DIOVAN, ask your doctor or pharmacist.

What is the most important information I should know about DIOVAN?

Taking DIOVAN during pregnancy can cause injury and even death to your unborn baby. If you get pregnant, stop taking DIOVAN and call your doctor right away. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.

What is DIOVAN?

DIOVAN is a prescription medicine called an angiotensin receptor blocker (ARB). It is used in adults to:

- lower high blood pressure (hypertension) in adults and children, 6 to 16 years of age.
- treat heart failure in adults. In these patients, DIOVAN may lower the need for hospitalization that happens from heart failure.
- improve the chance of living longer after a heart attack (myocardial infarction) in adults.

DIOVAN is not for children under 6 years of age or children with certain kidney problems.

High Blood Pressure (Hypertension). Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. DIOVAN can help your blood vessels relax so your blood pressure is lower.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure and vision problems.

Heart Failure occurs when the heart is weak and cannot pump enough blood to your lungs and the rest of your body. Just walking or moving can make you short of breath, so you may have to rest a lot.

Heart Attack (Myocardial Infarction): A heart attack is caused by a blocked artery that results in damage to the heart muscle.

What should I tell my doctor before taking DIOVAN?

Tell your doctor about all your medical conditions including whether you:

- have any allergies. See the end of this leaflet for a complete list of ingredients in DIOVAN.
- have a heart condition
- have liver problems
- have kidney problems
- **are pregnant or planning to become pregnant.** See "What is the most important information I should know about DIOVAN?"
- are breast-feeding. It is not known if DIOVAN passes into your breast milk. You and your doctor should decide if you will take DIOVAN or breast-feed, but not both. Talk with your doctor about the best way to feed your baby if you take DIOVAN.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (also called "diuretics")
- potassium supplements
- a salt substitute

Know the medicines you take. Keep a list of your medicines with you to show to your doctor and pharmacist when a new medicine is prescribed. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

How should I take DIOVAN?

- Take DIOVAN exactly as prescribed by your doctor.
- For treatment of high blood pressure, take DIOVAN one time each day, at the same time each day.
- If your child cannot swallow tablets, or if tablets are not available in the prescribed strength, your pharmacist will mix DIOVAN as a liquid suspension for your child. If your child switches between taking the tablet and the suspension, your doctor will adjust the dose as needed. Shake the bottle of suspension well for at least 10 seconds before pouring the dose of medicine to give to your child.
- For adult patients with heart failure or who have had a heart attack, take DIOVAN two times each day, at the same time each day. Your doctor may start you on a low dose of DIOVAN and may increase the dose during your treatment.
- DIOVAN can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much DIOVAN, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of DIOVAN?

DIOVAN may cause the following serious side effects:

Injury or death to an unborn baby. See "What is the most important information I should know about DIOVAN?"

Low Blood Pressure (Hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down, if you feel faint or dizzy. Call your doctor right away.

Kidney problems. Kidney problems may get worse in people that already have kidney disease. Some people will have changes on blood tests for kidney function and may need a lower dose of DIOVAN. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing DIOVAN.

The most common side effects of DIOVAN used to treat people with high blood pressure include:

- headache

- dizziness
- flu symptoms
- tiredness
- stomach (abdominal) pain

Side effects were generally mild and brief. They generally have not caused patients to stop taking DIOVAN.

The most common side effects of DIOVAN used to treat people with heart failure include:

- dizziness
- low blood pressure
- diarrhea
- joint and back pain
- tiredness
- high blood potassium

Common side effects of DIOVAN used to treat people after a heart attack which caused them to stop taking the drug include:

- low blood pressure
- cough
- high blood creatinine (decreased kidney function)
- rash

Tell your doctor if you get any side effect that bothers you or that does not go away.

These are not all the possible side effects of DIOVAN. For a complete list, ask your doctor or pharmacist.

How do I store DIOVAN?

- Store DIOVAN tablets at room temperature between 59º to 86ºF (15 C - 30 C).
- Keep DIOVAN tablets in a closed container in a dry place.
- Store bottles of DIOVAN suspension at room temperature less than 86 F (30 C) for up to 30 days, or refrigerate between 35 F - 46 F (2 C - 8 C) for up to 75 days.
- **Keep DIOVAN and all medicines out of the reach of children.**

General information about DIOVAN

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use DIOVAN for a condition for which it was not prescribed. Do not give DIOVAN to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about DIOVAN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DIOVAN that is written for health professionals.

For more information about DIOVAN, ask your pharmacist or doctor, visit www.DIOVAN.com on the Internet, or call **1-866-404-6361**.

What are the ingredients in DIOVAN?

Active ingredient: valsartan

Inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide

Revised: November 2007

Printed in U.S.A.

T2007-109/T2007-110

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

MEDICAL REVIEW(S)

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: November 29, 2007

FROM: Shari L. Targum, M.D.
TO: NDA 21-283, S-024
SUBJECT: Financial Disclosure, Valsartan pediatric submission

Financial Disclosure

A Financial Disclosure certification, dated April 30, 2007, was reviewed.
No clinical investigators were full or part-time employees of the sponsor. Of studies, A2301, A2302, A2304, A2305, A2307, and A2308, 98-100% of the investigators responded to requests for financial disclosure information. No disclosable financial interests were reported that would affect the conduct of the clinical studies.

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/s/

Shari Targum
11/29/2007 11:46:15 AM
MEDICAL OFFICER

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: November 29, 2007

FROM: Shari L. Targum, M.D.

TO: NDA 21-283, S-024

SUBJECT: Safety Update

The sponsor submitted a cover letter, dated September 20, 2007, which comprised the Safety Update for NDA 21-283, S-04; according to the sponsor, as of 9/7/2007, the "ongoing" blinded studies, VAL489K2302 and VAL489K2303, have randomized 34 of 300 planned patients and 6 of 75 planned patients, respectively. For their long-term extensions, there are 10 patients in K2302E and 5 patients in K2303E. According to the sponsor, no deaths, serious adverse events, or adverse events meeting expedited reporting criteria have been observed in these trials.

K2302E is an active-controlled study of valsartan vs. enalapril.

In a teleconference with the sponsor today (with Ms. Price and Mr. Birch), the sponsor notified this reviewer of one SAE occurring in the long-term extension of study 2302E (ongoing in Europe, still blinded, not reviewed by this Agency). A 15 year-old White male with underlying chronic renal insufficiency was hospitalized for hyperkalemia and discontinued from the trial; however, the patient was on either enalapril + placebo or enalapril + valsartan (study drug still blinded). Valsartan contains labeling for hyperkalemia; in addition, hyperkalemia is a known adverse event with ACE inhibitor therapy.
Otherwise, there were 10 discontinuations (8 discontinuations during the core study) in study 2302E (a patient who completed the core study and did not proceed to the long-term extension was considered a "discontinuation"). The sponsor does not know whether these discontinuations occurred due to adverse events. Since this is a blinded trial, it is not known how many of these discontinuations occurred on valsartan (vs. enalapril).
There were no deaths and no discontinuations in the younger patients (1-5 year olds) in the ongoing trials.

Comment: The information in the safety update, as well as the teleconference today, do not preclude an approval action.

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/s/

Shari Targum
11/29/2007 02:24:24 PM
MEDICAL OFFICER

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: November 14, 2007

FROM: Shari L. Targum, M.D.

TO: NDA 21-283, S-024

SUBJECT: Review of case report forms and sponsor's response to Discipline Review Letter (received on November 13, 2007), Valsartan pediatric submission

In the Discipline Review Letter, the concern was raised regarding transaminase elevations seen in the following patients:

A2302:

1. Patient # 0608-00012, with elevated screening transaminases who was discontinued on Day 7 (visit 3) due to a protocol violation (phase 1 exposure < 7 days).
2. Patient #0603-00004, with normal screening transaminases and elevated SGOT (73 U/L) and SGPT (100 U/L) on Visit 12 (Visit Day 70 per electronic dataset).

A2307:

1. Patient #085-00003, hospitalized with pneumonitis and hepatitis, discontinued from the study due to hepatitis (OL); the patient was hospitalized with pneumonitis and fatal respiratory failure 11 days later.
2. Patient #080-00003, with elevated transaminases (SGPT=339 U/L; SGOT = 502 U/L) during the OL end-of-study visit; repeat transaminases 10 days later were normal.
3. Patient #061-00006, with a mildly elevated SGOT (33 U/L) and normal SGPT at screening, an elevated SGOT (77 U/L) at the open-label end-of-study visit (Day 393); the SGOT was improved (27 U/L) on Day 414.

Study A2302:

1. According to the case report form for patient #0603-00004, this patient was on concomitant prednisone, cyclosporine, aspirin, growth hormone, calcium carbonate, Vitamins A, C and D, and growth hormone. It is noted on Visit 4 that the elevated transaminases were "clinically significant and related to high levels of cyclosporine." Abnormal transaminases were also noted on Visit 12 (last visit: September 22, 2003) and were felt due to high levels of cyclosporine. Hepatotoxicity is listed in labeling for cyclosporin (source: labeling for Sandimmune). According to the sponsor response, the patient also had: a history of transfusions, positive IgM titer for CMV (2001), positive serology for hepatitis C (February 2005), and a liver biopsy (February 2005 note) showing chronic hepatitis.

This reviewer agrees that the concomitant cyclosporine could have contributed to the elevated transaminases. It is not clear that events in 2005 exclude a drug effect, as the patient's last visit was in 2003.

2. For patient #0608-00012, the patient was discontinued on Day 8 due to a protocol violation (inappropriately randomized). According to the sponsor's response, this patient received only one dose of study medication before the baseline liver function results, which were > 2 x ULN at baseline, were known.

Reviewer: This patient's abnormal baseline transaminases suggest a liver process unrelated to drug. Discontinuation after only one dose of drug provides some reassurance, although a drug effect cannot be excluded.

A2307:

1. Patient #085-00003, hospitalized with pneumonitis and hepatitis, discontinued from the study due to hepatitis (OL); the patient was hospitalized with pneumonitis and fatal respiratory failure 11 days later. According to the sponsor's response, the on-treatment transaminase elevation was unlikely to be related to valsartan, based on: concomitant conditions (pneumonitis, multiple concomitant medications, congenital anomalies, chronic medical problems), the possibility of endemic anicteric hepatitis, and near normalization of transaminases within 12 days while still on reduced dose valsartan.

Reviewer: The sponsor's points are taken; however, a relationship between the elevated transaminases and valsartan cannot be excluded based on the available information.

2. Patient #080-00003, with elevated transaminases (SGPT=339 U/L; SGOT = 502 U/L) during the OL end-of-study visit; repeat transaminases 10 days later were normal. According to the sponsor, the patient had steroid resistant nephrotic syndrome which relapsed on Day 339. Acetaminophen was used on multiple occasions during OL; hepatitis serologies were negative. The sponsor's experts claimed that: viral etiologies for the transaminase elevations (e.g., CMV, EBV, adenoviruses) were not eliminated; chronic acetaminophen use and high dose steroids can cause/exacerbate liver injury; the patient was on a low dose of valsartan (which does not suggest a dose-related toxic effect); the temporal relationship did not suggest an idiosyncratic reaction; rapid normalization suggested a viral process; the lack of hepatotoxicity in older patients made problems in younger patients less likely.

Reviewer: The sponsor's arguments do not rule out a drug relationship.

3. Patient #061-00006, with a mildly elevated SGOT (33 U/L) and normal SGPT at screening, an elevated SGOT (77 U/L) at the open-label end-of-study visit (Day 393); the SGOT was improved (27 U/L) on Day 414. The sponsor has argued that the normal SGPT (an enzyme that is more specific for liver injury than SGOT) in this case rules out a liver etiology; an isolated elevated SGOT is not liver specific and can be caused by many other factors. The experts' conclusion was that most probable reasons for elevated SGOT include hemolysis, muscle disease, brain disease, and viral infection.

Reviewer: This reviewer accepts the sponsor's argument in this case. The SGOT enzyme is not "liver-specific" and can be found in many tissues.

Reviewer Conclusions: For study A2307, cases #1 and 2 (above), this reviewer is unable to distinguish between possible drug effect and concomitant/underlying disease. It should be noted that in both cases the transaminase elevations occurred during open-label; both patients were enrolled outside the US.

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/s/

Shari Targum
11/19/2007 11:04:04 AM
MEDICAL OFFICER

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel (301) 796-1151

Memorandum

DATE: October 18, 2007

FROM: Shari L. Targum, M.D.
TO: NDA 21-283, S-024
SUBJECT: Addendum to safety review, Valsartan pediatric submission

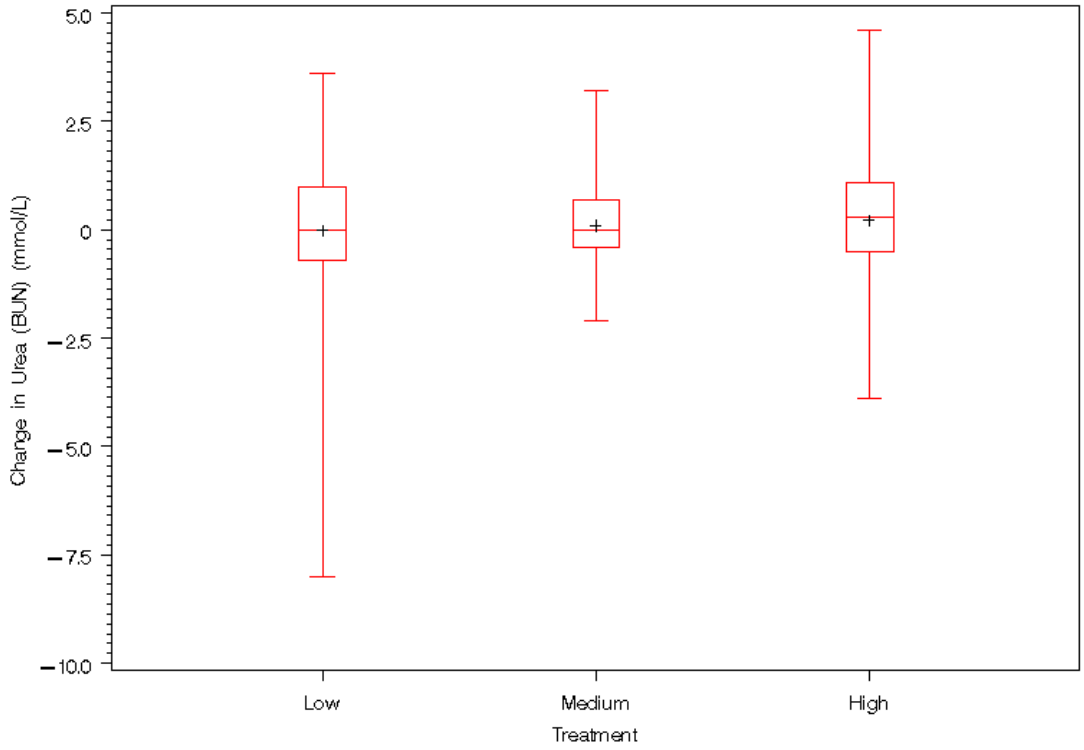
Additional explorations of the following laboratory parameters were conducted:

1. BUN (blood urea nitrogen):
Box and whisker plots for the change in BUN during the double-blind period are shown below for studies A2302 and A2307:

A2302:

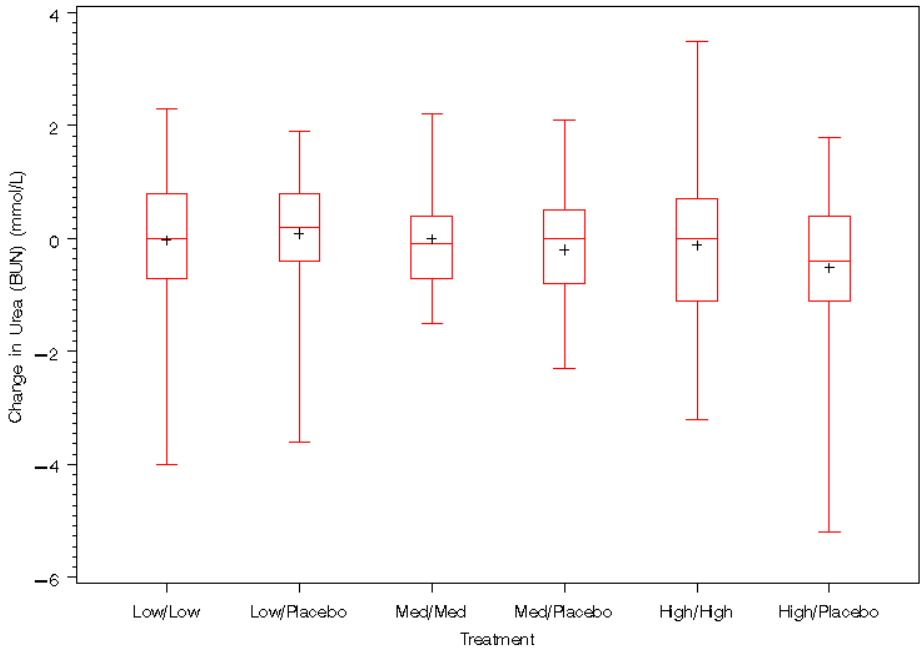
CVAL489A2302

Fig. 1. Box plots for change from baseline to end of phase 1 in urea (BUN) by treatment (safety 1 population)



CVAL489A2302

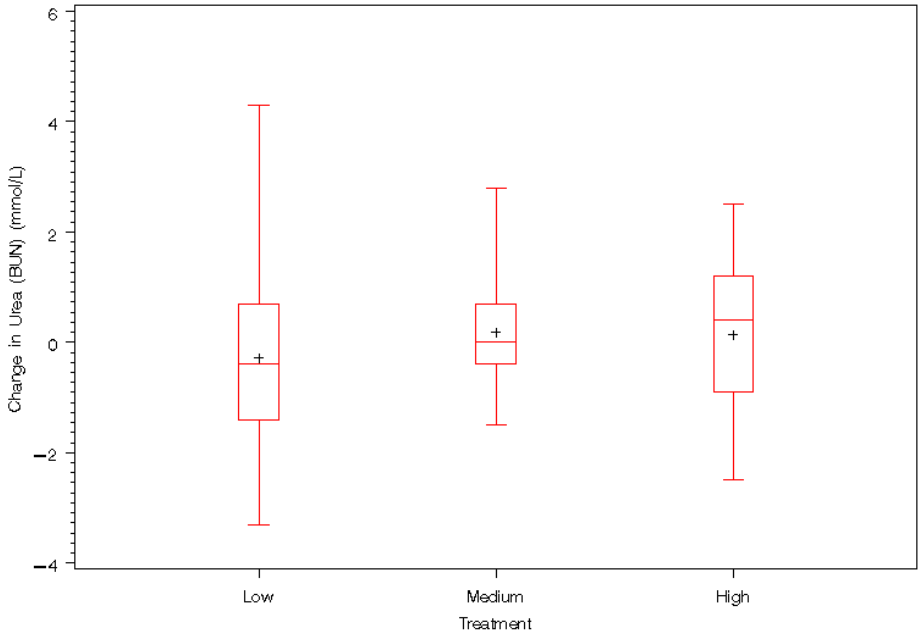
Fig. 2. Box plots for change from end of phase 1 to end of phase 2 in urea (BUN) by treatment (safety 2 population)



A2307:

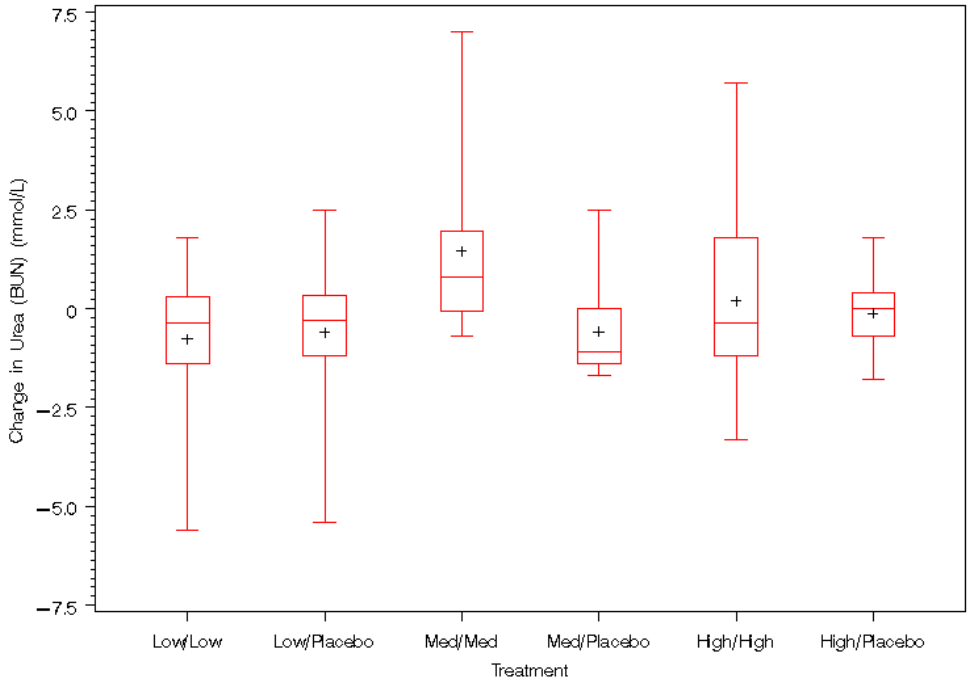
CVAL489A2307

Fig. 1. Box plots for change from baseline to end of phase 1 in urea (BUN) by treatment (safety 1 population)



CVAL489A2307

Fig. 2. Box plots for change from end of phase 1 to end of phase 2 in urea (BUN) by treatment (safety 2 population)



2. Creatinine change in 1 year-olds from study A2307 (n=10):

Supplementary Table 10.3-1 (Page 1 of 1)
One year old patients change from baseline laboratory result by treatment in randomized dose-response phase (Phase 1)
Safety 1 population
Biochemistry: Creatinine (umol/L)

		Baseline			Post baseline: End of phase 1			Post baseline: Change from baseline		
Treatment	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Low (N=4)	3	56.7	30.53	55.0	54.0	35.04	56.0	-2.7	5.51	0.0
Medium (N=2)	2	48.5	6.36	48.5	53.0	0.00	53.0	4.5	6.36	4.5
High (N=4)	3	41.0	5.20	44.0	41.0	10.39	35.0	0.0	9.00	0.0

No dose relationship is seen in this small subgroup.

Supplementary Table 10.3-2 (Page 1 of 1)
One year old patients change from baseline laboratory result by treatment in double blind phases (Phases 1 & 2)
Safety population
Biochemistry: Creatinine (umol/L)

		Baseline			Post baseline: Endpoint			Post baseline: Change from baseline		
Treatment	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Medium (N=1)	1	44.0		44.0	53.0		53.0	9.0		9.0
High (N=1)	1	44.0		44.0	53.0		53.0	9.0		9.0
Low/Low (N=2)	2	54.0	1.41	54.0	44.5	0.71	44.5	-9.5	0.71	-9.5
Low/Placebo (N=2)	2	57.5	43.13	57.5	53.5	37.48	53.5	-4.0	5.66	-4.0
Med/Med (N=1)	1	53.0		53.0	44.0		44.0	-9.0		-9.0
High/High (N=1)	1	35.0		35.0	44.0		44.0	9.0		9.0
High/Placebo (N=2)	1	44.0		44.0	44.0		44.0	0.0		0.0

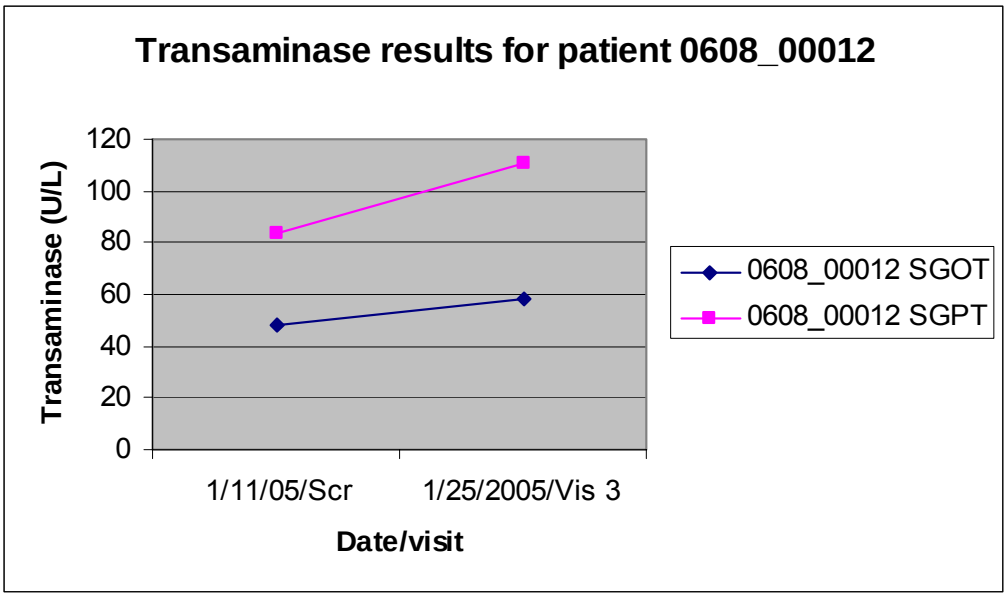
In the above analysis the n per subgroup is even smaller than in the previous analysis.

Supplementary Table 10.3-3 (Page 1 of 1)
One year old patients change from baseline laboratory result in open label phase
Open Label population
Biochemistry: Creatinine (umol/L)

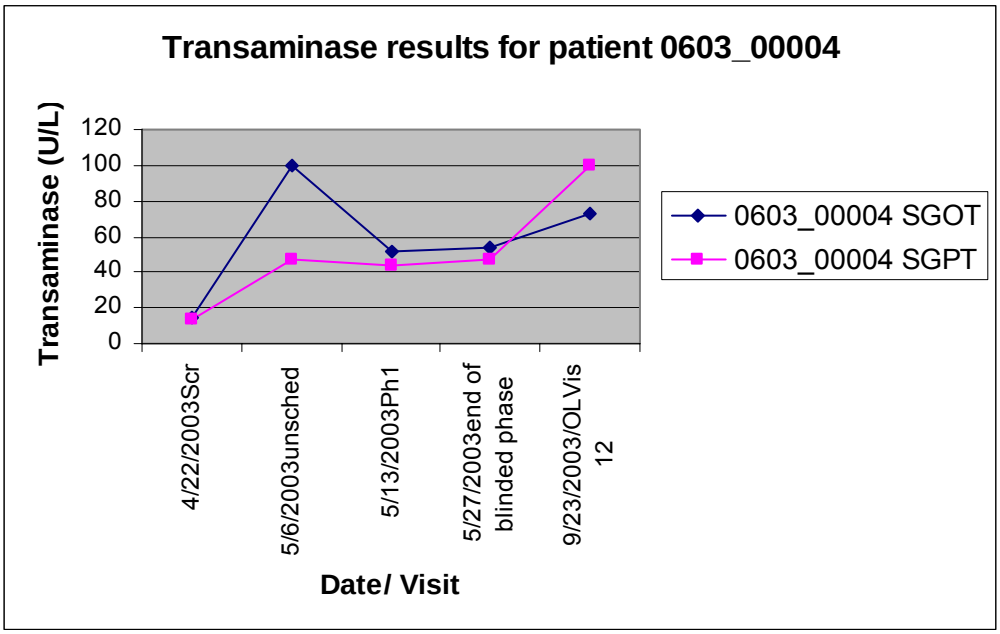
		Baseline			Post baseline: End of open label			Post baseline: Change from baseline		
	n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Total (N=10)	9	49.2	17.12	44.0	53.4	13.65	53.0	4.2	16.80	9.0

In the open-label population, there is a mean increase of almost 10% over the mean baseline value; there is no control group for comparison.

3. Transaminase elevations in study A2302:
Because of transaminase elevations in study A2307, the medical reviewer examined the laboratory datasets for transaminase elevations above 80 U/L. One patient (0139_00001) had a screening SGPT of 130 U/L; otherwise, no patients in study A2302 had transaminase elevations over 111 U/L.
Two patients (0603_00004 and 0608_00012) showed transaminase elevations on treatment and are shown below. In both patients, the bilirubin values were within normal range.



Patient #0608_00012: This 11 year-old WM from Brazil on valsartan 160 mg QD (high dose) had abnormal screening transaminases and an SGPT of 111 U/L (SGPT upper limit of normal = 30 U/L) on Day 7 (Visit 3). He was discontinued at Visit 3 due to a protocol violation (phase 1 exposure < 7 days).



Patient #0603_00004: This 13 year-old WM from Brazil completed Phases 1 and 2 valsartan 80 mg QD /valsartan 80 mg QD (medium dose), and entered open-label, where he was prematurely discontinued after Visit 12 due to unsatisfactory therapeutic effect.

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/s/

Shari Targum
10/19/2007 01:14:32 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA #21-283
Submission Number	SE5-024
Submission Code	
Letter Date	May 29, 2007
Stamp Date	May 29, 2007
PDUFA Goal Date	November 29, 2007
Reviewer Name	Shari L. Targum, M.D.
Review Completion Date	Medical-statistical review completed 10/4/07; template completed 10/10/07
Established Name	Valsartan
(Proposed) Trade Name	Diovan®
Therapeutic Class	Angiotensin II receptor-blocker
Applicant	Novartis
Priority Designation	P
Formulation	Pediatric tablet, oral suspension
Dosing Regimen	(b) (4) -160 mg PO QD
Indication	Treatment of Hypertension
Intended Population	Pediatric patients

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that valsartan be "approvable" for use in pediatric patients. Outstanding issues include: understanding how to dose in order to write appropriate instructions for use; and the sponsor providing convincing evidence of safety with regard to transaminase elevations seen in several cases in study A2307.

In addition, two deaths were seen in the open-label phase of the valsartan study in two 1 year-old patients (severe vomiting and diarrhea in one case with no other available data; in the other case, fatal pneumonitis with respiratory failure occurring 11 days after a hospitalization for pneumonitis and hepatitis with valsartan discontinued due to hepatitis).

The question of dosing arises from study A2307 (1-5 year olds), which showed a flat dose-response in the dose-ranging phase; and the results of weight-adjusted dosing in A2302 (6-16 year olds), which showed a high degree of variability, small effects, and do not appear to fit linear, log-linear, or Emax models.

If dosing and titration can be clarified, then the other outstanding issue involves cases of transaminase elevation in A2307; since similar cases were not seen in the older children, it would then be recommended that valsartan be approved in hypertensive patients aged 6-16 years old. If approved, it is recommended that proposed labeling be amended to include appropriate efficacy and safety information.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

Appropriate information should be communicated to patients and physicians.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor conducted two clinical studies with nearly identical designs (Written Request Trial C). Study A2302 was the pivotal study conducted in hypertensive children aged 6-16 years. Study A2307 was a supportive study in hypertensive children aged 1-5 years. Per the Trial C design, each study incorporated a two-week double-blind dose-response phase (Phase 1), a two-week double-blind placebo-controlled randomized withdrawal phase (Phase 2), and a voluntary open-label extension.

1.3.2 Efficacy

In both studies, results of the randomized withdrawal phase showed a statistically significant different between pooled valsartan and placebo.
In study A2302, results of the two-week dose-ranging phase showed a negative slope of the mm Hg systolic blood pressure per unit increase in dose ratio that was significantly different from zero, supporting a dose-dependent decrease in systolic blood pressure. From additional analyses, these data, when weight-adjusted (mg/kg), showed slope analyses that were significantly different from zero when fit to a linear, linear model on log transformed weight-adjusted dose, and Emax models; however, the data did not "best fit" any of these models.
In study A2307, results of the two-week dose-ranging phase showed a flat dose-response with decreases from baseline in all dose groups (no placebo arm); the slope analyses was not significantly different from zero.

1.3.3 Safety

In A2307 (1-5 years), markedly elevated transaminases were seen at the end-of-study visit in two patients. A third patient subsequently discontinued the study due to hepatitis.

In the A2302 (6-16 years) open-label population, serum creatinine increased by 10% from baseline; in the A2307 open-label population, BUN increased by 15% from baseline. There were two discontinuations from the clinical studies due renal impairment (A2307) and increased creatinine (A2302), respectively.

Two deaths during (or after premature discontinuation from) open-label were noted in A2307. No deaths occurred in A2302.

1.3.4 Dosing Regimen and Administration

Study A2302 employed unapproved tablets. A2307 used an unapproved extemporaneous suspension. According to the clinical pharmacology reviewer, exposure of the 1-5 year old

children receiving the extemporaneous suspension was higher than in adults receiving the adult 80 mg tablet; the exposure of the 6-16 year old children receiving pediatric 10 and 80 mg tablets was comparable to adults receiving the adult tablet.
The dosing regimen in the two clinical studies is summarized in Figure 1-1, below.

Figure 1-1 Study Design, Study A2302 and Study A2307

Screening	Double-blind treatment			Open-Label
Screening Phase[a]	Phase 1[b] (dose-response)		Phase 2[c] (placebo withdrawal)	Open Label[d]
Day -7 to Day 0	Day 0 to Day 14 Randomized 2:1:2 (L: M: H) dose		Days 14 – 28 Re-randomize	Weeks 4 to 52
	Study A2302 (Ages 6 - 16 years)	Study A2307 (Ages 1 – 5 years)	1:1 Ratio	Based on trough blood pressure: 40mg, 80mg , 160mg or 160 +HCTZ 12.5 mg for children 6-16 years old. 20mg, 40 mg, 80mg, and 80mg +HCTZ 12.5 mg for children 1-5 years old
	Dose	Dose		
	Weight < 35 kg	Weight < 18 kg		
Placebo Wash-out	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d.	Low 5 mg o.d Medium 20 mg o.d. High 40 mg o.d.	Continue Phase 1 dose OR Switch to Placebo	
	Weight ≥ 35 kg	Weight ≥ 18 kg		
	Low 20 mg o.d. Medium 80 mg o.d. High 160 mg o.d.	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d		

2 INTRODUCTION AND BACKGROUND

2.1 Product Information:

Valsartan is approved in adults for the treatment of hypertension, heart failure (NYHA Class II-IV), and for the reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or dysfunction after myocardial infarction.
The dose range for adult hypertension is 80-320 mg once daily; the dose range for heart failure is 40-160 mg twice daily; and the dose range in patients following myocardial infarction is 20-160 mg twice daily.

2.2 Presubmission Regulatory Activity

A pediatric Written Request was initially issued on November 25, 2002; an amended written request, superseding the earlier version, was issued on June 18, 2003.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

A CMC review (Kris Raman, Ph.D.) was completed on 9/7/07. According to Dr. Raman, adequate information has been provided in support of the proposed 4 mg/mL oral suspension of Diovan prepared extemporaneously by suspending Diovan 80 mg tablets in ora-Plus oral suspending vehicle and Ora-Sweet SF syrup vehicle. No CMC issues were identified and the supplement can be approved from the CMC perspective.

3.2 Animal Pharmacology/Toxicology

A review of submitted animal data by Dr. Gowra Jagadeesh is pending at this time. The medical reviewer understands that, based on preclinical data (renal effects), dosing in children under 2 years old is not recommended.

3.3 Clinical Pharmacology

Peter Hinderling, M.D. reviewed 4 clinical pharmacology reports: one pharmacokinetic study (PK) in children, 1-16 years, who received a single dose of an oral suspension; and 3 bioavailability studies of 3 unapproved formulations including an oral extemporaneous suspension (4 mg/mL) and pediatric 10 and 80 mg tablets related to the marketed 40 and 80 mg tablets. The relative bioavailability studies were conducted in healthy adults.
The results of the relative bioavailability studies showed that the unapproved pediatric formulations and the adult tablets were not bioequivalent. Mean Cmax and AUC with the extemporaneous suspension were 1.93 and 1.56 times greater, respectively, than with the adult 80 mg tablet. Mean Cmax and AUC with the pediatric 80 mg tablet were 1.06 and 1.08 times greater, respectively, than with the adult 80 mg tablet and mean Cmax and AUC with the pediatric 10 mg tablet were 1.08 and 1.12 times greater, respectively, than with the 40 mg adult tablet. Thus, the exposure of the 1-5 year old children receiving the extemporaneous suspension was higher than in adults receiving the adult 80 mg tablet; the exposure of the 6-16 year old children receiving pediatric 10 and 80 mg tablets was comparable to adults receiving the adult tablet.
According to the sponsor, valsartan exposure (Cmax and AUC), normalized to a standard dose/body weight, does not vary significantly with age over a 1-16 year age range; the body weight-adjusted CL/F values (0.06 to 0.09 L/hr/kg) are comparable across the 1-16 year old children and are similar to those observed in adult subjects (approximately 0.06 L/hr/kg).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The major source of clinical data was the submission by the sponsor. In addition, the reviewer conducted a search of the medical literature. Dr. Szarfman assisted in data mining the AERS database for valsartan use in children 1-16 years.

4.2 Tables of Clinical Studies

The valsartan pediatric clinical development program included the following clinical studies:

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan
Efficacy/safety studies in this submission			**351**	
CVAL489A2302 Pivotal study	Children 6 to 16 years of age with hypertension	Efficacy, dose response, safety, tolerability	261	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Pediatric tablet
CVAL489A2307 Supportive study	Children 1 to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	90	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Oral suspension
Clinical pharmacology studies			**106**	
CVAL489A2301-BA	Healthy volunteers 18 to 45 years of age	Bioavailability of 80 mg valsartan tablets compared to 20 mL of oral valsartan suspension (4 mg/mL)	32	Randomized, single- dose, 80 mg valsartan tablet and 20 mL oral valsartan suspension (4 mg/mL) 2-way crossover design.
CVAL489A2304	Healthy volunteers 18 to 45 years of age	Bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablet	24	Single-dose, two-period, crossover design: 40 mg valsartan tablet and 4 x 10 mg valsartan tablets
CVAL489J2308	Healthy volunteers 18 to 50 years of age	Bioavailability of 80 mg valsartan pediatric tablet (CSF) compared to 80 mg valsartan FMI	24	Single- dose, 80 mg valsartan tablet (80 mg CSF, 80 mg FMI) 2-period crossover design
CVAL489A2305	Children 1 to 16 years of age with hypertension	PK of valsartan given as an oral suspension	26	Single-dose, oral suspension 2.0 mg/kg –> 80 mg (max) valsartan dose age-dependent

4.3 Review Strategy

The reviewer used study protocols, study reports, data summaries, tables and electronic datasets in conducting this review.

4.4 Data Quality and Integrity

From a review of case report forms (CRF), datasets, protocols and study reports, the data quality in this submission appeared to be adequate. The sponsor asked for CRF clarifications when needed.
It should be noted that, in two instances in study A2302, patients with adverse events (proteinuria and hypertensive encephalopathy, respectively) and high blood pressures were coded as "inadequate therapeutic response" rather than "adverse event." The hypertensive encephalopathy event began during the placebo run-in period. Please see individual study review A2302, safety section, for further details.

4.5 Compliance with Good Clinical Practices

According to the sponsor, all studies were conducted in full compliance with Good Clinical Practice; this reviewer saw no evidence to the contrary.

4.6 Financial Disclosures

A Financial Disclosure certification, dated April 30, 2007, was reviewed.
No clinical investigators were full or part-time employees of the sponsor. Of studies, A2301, A2302, A2304, A2305, A2307, and A2308, 98-100% of the investigators responded to requests for financial disclosure information. No disclosable financial interests were reported that would affect the conduct of the clinical studies.

5 INTEGRATED REVIEW OF EFFICACY

5.1 Indication: Treatment of hypertension in pediatric patients

5.1.1 Methods:

Two clinical studies, A2302 and A2307, used study design C (of the study designs recommended by FDA), with a 2-week double-blind dose response (Phase 1) followed by a 2-week double-blind placebo withdrawal (Phase 2). Both studies included a 52-week open-label extension. Study A2302 was considered the "pivotal study" as it was powered at 90% and enrolled the majority of patients.

Figure 1-1 Study Design, Study A2302 and Study A2307

Screening	Double-blind treatment			Open-Label
Screening Phase[a]	Phase 1[b] (dose-response)		Phase 2[c] (placebo withdrawal)	Open Label[d]
Day -7 to Day 0	Day 0 to Day 14 Randomized 2:1:2 (L: M: H) dose		Days 14 – 28 Re-randomize	Weeks 4 to 52
	Study A2302 (Ages 6 - 16 years)	Study A2307 (Ages 1 – 5 years)	1:1 Ratio	Based on trough blood pressure: 40mg, 80mg , 160mg or 160 +HCTZ 12.5 mg for children 6-16 years old. 20mg, 40 mg, 80mg, and 80mg +HCTZ 12.5 mg for children 1-5 years old
	Dose	Dose		
	Weight < 35 kg	Weight < 18 kg		
Placebo Wash-out	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d.	Low 5 mg o.d Medium 20 mg o.d. High 40 mg o.d.	Continue Phase 1 dose OR Switch to Placebo	
	Weight ≥ 35 kg	Weight ≥ 18 kg		
	Low 20 mg o.d. Medium 80 mg o.d. High 160 mg o.d.	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d		

The dosing for A2302 and A2307 was selected based on expected blood pressure (BP) responses rather than plasma level data; no pharmacokinetic sampling was performed in either of these studies. Adult doses were "scaled down" to a corresponding dose for the respective pediatric population based on body surface area of adults vs. children. Three dosing groups (low, medium, high) were selected for Phase 1. Each dosing group included two doses depending on weight. A2302 randomized hypertensive patients aged 6-16 years and included valsartan doses of 10-160 mg once daily ; A2307 randomized hypertensive patients aged 1-5 years and included valsartan doses of 5-80 mg once daily.

	Study A2302 (ages 6 – 16 ys)			Study A2307 (ages 1 – 5 yrs)		
	Low[a] 10 /20 mg	Medium[a] 40 /80 mg	High[a] 80 /160 mg	Low[b] 5 /10 mg	Medium[b] 20 /40 mg	High[b] 40 /80 mg
No. patients randomized	103	53	105	37	18	35
Mean weight (SD), kg	66.1 (33.80)	64.9 (33.26)	65.8 (35.92)	16.4 (6.02)	16.4 (5.41)	17.2 (7.74)
Weight-adjusted dose (SD), mg/kg	0.4 (0.32)	1.3 (0.48)	2.7 (0.96)	0.4 (0.12)	1.6 (0.32)	3.4 (0.84)

a: Doses were determined by randomization, stratified by body weight at baseline: <35 kg, or ≥35 kg. [Study A2302-PTT 7.4-4.]

b: Doses were determined by randomization, stratified by body weight at baseline: <18 kg, or ≥18 kg. [Study A2307-PTT 7.4-4.]

Besides dosing and sample size (power), the study designs of A2302 and A2307 differed with respect to formulation (A2307 used a suspension; A2302 unapproved pediatric tablets) and concomitant use of antihypertensives (allowed in A2307 in patients whose BP remained uncontrolled prior to study entry; prohibited in A2302).

Table 1-2 Comparison of Study A2302 and Study A2307

Characteristic	Study A2302	Study A2307
Study Design	Design C	Design C
Patient age	6 – 16 year old	1 – 5 year old
Number of patients enrolled	N = 261	N = 90
Valsartan used as an add-on therapy	No	Yes (in 18.9% of patients)
Formulation	Tablet	Extemporaneous suspension
Patient population		
Key medical history	Renal and urinary disorders: 37.9% Renal transplantation: 8.0% Obesity: 21.5% (investigator assessment) 54% (BMI >95th percentile)	Renal and urinary disorders, 63.3% Renal transplantation: 0 Obesity: 6.7% (investigator assessment) 23% (BMI >95th percentile)
% of patients previously treated for HTN	63%	71%
Minimum SBP[a] required for study entry	111 mm Hg (age 6) – 134 mm Hg (age 16)	102 mm Hg (age 1) – 110 mm Hg (age 5)

a: ≥95% percentile for age, gender, height

Source: [Study A2302-PTT 7.5-1; Appendix 7.1 Listing 1-15a]; [Study A2307-PTT 7.5-1; Appendix 7.1 Listing 1-15a].

Other differences between A2302 and A2307 included study sites (see Table 1, below, for %USA) and percentage with congenital/familial/genetic disorders (see Table 1, below).

The primary efficacy parameter was the change in trough sitting systolic BP (SSBP). The primary phase 1 analysis was the slope of the change in SSBP from baseline to end of Phase 1 as a function of low, medium and high-doses. The primary phase 2 analysis was the difference between pooled valsartan and placebo in the change in SSBP from end of phase 1 to end of phase 2.
Analyses for sitting diastolic BP (SDBP) were performed as secondary efficacy parameters.

Table 1. Selected baseline characteristics in studies A2302 and A2307

	A2302	A2307
N randomized	261	90
Age range (years)	6-16	1-5
Treated for hypertension prior to study entry	63%	71%
Female	40%	40%
Black	49%	30%
White	46%	41%
USA	50%	18%
Mean (SD) BMI (kg/m2)	27 (10)	17 (3)
Renal/urinary history	38%	63%
Infections and infestations	30%	47%
Metabolism and nutrition	35%	19%
Nervous system	29%	14%

Congenital, familial, genetic	18%	42%
Blood, lymphatic system	6%	18%
Gastrointestinal disorders	13%	22%
Respiratory, thoracic and mediastinal disorders	30%	22%

5.1.2 Efficacy Findings

In study A2302, Phase 1 results showed a decrease from baseline in SSBP which increased with increasing valsartan dose; the slope of the change from baseline in SSBP (mm Hg) per unit increase in dose ratio was -0.43 and significantly different from zero (p= 0.0256). At the end of Phase 2, the change from end of Phase 1 in the pooled valsartan group was significantly different from placebo (see below).
Results for sitting DBP were similar to the results for SSBP.

Table 2. A2302: SSBP (mm Hg) in Phase 1 and Phase 2 by treatment

	Phase 1 (ITT1 population)			Phase 2 (ITT2 population)	
	Low Dose 10 mg/20 mg (N = 102)	Medium Dose 40 mg/80 mg (N = 52)	High Dose 80 mg/160 mg (N = 105)	Pooled Valsartan (N = 123)	Pooled Placebo (N = 122)
Initial timepoint	**Baseline**			**End of Phase 1**	
n	102	52	105	123	122
Mean (SD)	131.4 (10.54)	133.3 (9.91)	133.2 (9.70)	122.2 (12.07)	122.2 (11.51)
Final timepoint	**End of Phase 1**			**End of Phase 2**	
Mean (SD)	123.4 (11.43)	123.7 (11.92)	121.7 (12.53)	123.3 (13.05)	126.1 (12.09)
Change from	**Baseline to end of Phase 1**			**End of Phase 1 to end of Phase 2**	
Mean (SD)	-7.9 (10.41)	-9.6 (9.12)	-11.5 (11.16)	1.2 (9.42)	3.9 (9.66)
p-value[a]	< 0.0001*	< 0.0001*	< 0.0001*	0.1758	< 0.0001*
Between-group p-value[b]	---	---	---	0.0368*	

a: Phase 1: p-values are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
Phase 2: p-values are based on the paired t-test of the null hypothesis of no change from end of Phase 1 within each treatment group.

b: p-value is between treatment comparison 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: [Study A2302-PTT 9.1-3a; PTT 9.2-1a; PTT 9.2-2a]

The sponsor performed a slope analysis as a function of weight-adjusted valsartan (mg/kg) using a linear, log-linear and Emax model. The mean results were consistent with the slope results; however, the data did not fit any of these models.

Table 3. A2302: SDBP (mm Hg) in Phase 1 and Phase 2 by treatment

	Phase 1 (ITT1 population)			Phase 2 (ITT2 population)	
	Low Dose 10 mg/20 mg (N = 102)	Medium Dose 40 mg/80 mg (N = 52)	High Dose 80 mg/160 mg (N = 105)	Pooled Valsartan (N = 123)	Pooled Placebo (N = 122)
Initial timepoint	**Baseline**			**End of Phase 1**	
n	102	52	105	123	122
Mean (SD)	77.0 (13.04)	77.2 (9.31)	78.4 (11.25)	70.7 (11.26)	71.8 (10.04)
Final timepoint	**End of Phase 1**			**End of Phase 2**	
Mean (SD)	72.4 (12.05)	71.4 (10.52)	71.0 (9.79)	71.2 (11.30)	75.3 (10.83)
Change from	**Baseline to end of Phase 1**			**End of Phase 1 to end of Phase 2**	
Mean (SD)	-4.6 (10.98)	-5.8 (8.87)	-7.4 (9.51)	0.5 (8.47)	3.5 (9.37)
p-value[a]	0.0001*	< 0.0001*	< 0.0001*	0.5451	0.0001*
Between-group p-value[b]	---	---	---	0.0047*	

a: Phase 1: p-values are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
Phase 2: p-values are based on the paired t-test of the null hypothesis of no change from end of Phase 1 within each treatment group.

b: p-value is between treatment comparison from the ANCOVA model with treatment, region strata, weight strata, and race strata as factors, and centered Visit 4 SDBP as a covariate.

* indicates statistical significance at the 0.05 level.

Source: [Study A2302-PTT 9.4-2; PTT 9.5-1; PTT 9.5-2]

In study A2307, the Phase 1 slope analysis yielded a slope estimate of -.10 mm Hg per unit increase in dose ratio (p=NS); a dose-response was not seen for SSBP or SDBP.
However, Phase 2 results showed mean decreases in SSBP and SDBP in the pooled valsartan group and increases in the placebo group; the difference between pooled valsartan and placebo was statistically significant for SSBP and SDBP (see next tables).

Table 4. A2307: SSBP (mm Hg) in Phase 1 and Phase 2 by treatment

	Phase 1 (ITT1 population)			Phase 2 (ITT2 population)	
	Low Dose 5 mg/10 mg (N = 37)	Medium Dose 20 mg/40 mg (N = 18)	High Dose 40 mg/80 mg (N = 35)	Pooled Valsartan (N = 44)	Pooled Placebo (N = 43)
Initial timepoint	**Baseline**			**End of Phase 1**	
n	37	18	35	44	42
Mean (SD)	116.8 (6.88)	112.1 (8.56)	115.1 (6.34)	106.5 (11.03)	106.7 (8.17)
Final timepoint	**End of Phase 1**			**End of Phase 2**	
Mean (SD)	108 (11.04)	103.7 (7.40)	106.5 (8.67)	105.0 (11.92)	108.5 (8.98)
Change from	**Baseline to end of Phase 1**			**End of Phase 1 to end of Phase 2**	
Mean (SD)	-8.4 (8.44)	-8.3 (7.63)	-8.6 (7.55)	-1.5 (7.92)	1.5 (7.76)
p-value[a]	<0.0001*	0.0002*	<0.0001*	0.2135	0.2273
Between-group p-value[b]	---	---	---	0.0217*	

a: Phase 1: p-values are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
Phase 2: p-values are based on the paired t-test of the null hypothesis of no change from end of Phase 1 within each treatment group.

b: p-value is between treatment comparison from the ANCOVA model with treatment, weight strata, race 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.

Source: [Study A2307-PTT 9.1-3a; PTT 9.2-1a; PTT 9.2-2a]

Table 5. A2307: SDBP (mm Hg) in Phase 1 and Phase 2 by treatment

	Phase 1 (ITT1 population)			Phase 2 (ITT2 population)	
	Low Dose 5 mg/10 mg (N = 37)	Medium Dose 20 mg/40 mg (N = 18)	High Dose 40 mg/80 mg (N = 35)	Pooled Valsartan (N = 44)	Pooled Placebo (N = 43)
Initial timepoint	**Baseline**			**End of Phase 1**	
n	37	18	35	44	42
Mean (SD)	70.5 (8.52)	68.1 (8.60)	68.8 (7.60)	64.2 (6.87)	63.3 (8.19)
Final timepoint	**End of Phase 1**			**End of Phase 2**	
Mean (SD)	65.0 (7.78)	61.7 (7.64)	63.3 (6.78)	61.7 (7.89)	65.3 (6.81)
Change from	**Baseline to end of Phase 1**			**End of Phase 1 to end of Phase 2**	
Mean (SD)	-5.5 (6.06)	-6.4 (4.23)	-5.5 (8.47)	-2.5 (7.51)	2.0 (5.86)
p-value[a]	<0.0001*	<0.0001*	0.0005*	0.0336*	0.0312*
Between-group p-value[b]	---	---	---	0.0089*	

a: Phase 1: p-values are based on the paired t-test of the null hypothesis of no change from baseline within each treatment group.
Phase 2: p-values are based on the paired t-test of the null hypothesis of no change from end of Phase 1 within each treatment group.

b: p-value is between treatment comparison from the ANCOVA model with treatment, weight strata, race 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: [Study A2307-PTT 9.4-2; PTT 9.5-1; PTT 9.5-2]

In study A2302, subgroup analyses by weight, gender, age (6-11, 12-16 years), Tanner stage (< 3, ≥ 3), race (Black, non-Black) and region (US, non-US) for SSBP and SDBP showed similar trends to the overall results in Phase 1 and Phase 2.
In study A2307, subgroup analyses by weight (< 18 kg, > 18 kg), gender, race (Black, non-Black), prior antihypertensive treatment (use, non-use), and region (US, India, Latin America, Other) showed general trends that were similar to the overall results; some of the subgroups were small. Please see A2302 and A2307 individual study reviews for further details.

A2302 and A2307 included an optional one year open-label period where patients were started on an initial dose of valsartan (40 mg qd in A2302; 20 mg qd in A2307) and were up-titrated if needed; if the highest dose (160 mg qd in A2302; 80 mg qd in A2307) was not efficacious, then 12.5 mg HCTZ cold be added. In A2302, 235 patients entered open-label; 83% remained on valsartan monotherapy, and 75% completed open-label.

In A2307, 88 patients entered open-label; 94% of patients remained on valsartan monotherapy, and 93% completed this phase of the study.

A review of mean SSBP and SDBP at baseline and end of open-label showed that BP lowering was maintained or improved on long-term therapy. However, these data do not take into account change in dosage or addition of HCTZ.

5.1.3 Efficacy Conclusions

- The Phase 1 and Phase 2 results of A2302 and the Phase 2 results of A2307 support a BP-lowering treatment effect of valsartan. The results of SDBP are consistent with the SSBP results and also support the conclusion of a treatment effect.
- The Phase 1 results of A2302 support a dose-dependent BP lowering effect; however, the Phase 1 results of A2307 do not support a dose-dependent BP lowering effect in the doses/formulation/patients studied.
- When the slope analysis was performed for weight-adjusted (mg/kg) valsartan dosing, the slope results were consistent with the prespecified analyses; the data did not fit linear, log-linear, or Emax models.
- Results in subgroups (age, gender, race, region, Tanner stage) show trends that are similar to the overall results.

6 INTEGRATED REVIEW OF SAFETY

6.1 Methods and Findings

The main source for the safety analysis was the two clinical studies in the sponsor's submission. In addition, a literature search was conducted; data mining of AERS was also conducted. Findings were as follows:

1. In A2302 (6-16 years), the most common adverse events were headache, vomiting, cough, dizziness and upper respiratory tract infection, and nasopharyngitis. In A2307 (1-5 years), the most common adverse events were headache, cough, pyrexia, nasopharyngitis, diarrhea, rhinitis, sinusitis, and upper respiratory tract infection.
2. Two deaths occurred during open-label in study A2307; one of the deaths occurred 11 days after discontinuing study drug. No deaths occurred in study A2302.
3. In Table 5-11 (below), showing mean changes from baseline to end of study (OL population), the serum creatinine increased by about 10% and uric acid increased by about 5% in A2302; in study A2307, mean BUN increased by about 15% and uric acid increased by about 10% (see Section 6.1.5, below).
4. Two patients discontinued A2302 for renal events (proteinuria, creatinine increased, respectively); one patient discontinued A2307 due to renal impairment (see Section 6.1.3, below).
5. In A2307, one patient was discontinued from open-label due to hepatitis (see Section 6.1.1, below) and two other patients were noted to have elevated transaminases at the end-of-study visit (see Section 6.1.5, below).

6.1.1 Deaths

There were no deaths in A2302.

In A2307, one patient died during open-label. This 1 year-old Black female with a history of hypertension, urinary tract infection, bilateral hydronephrosis, duplex right kidney, bilateral vesicoureteric reflux and metabolic acidosis experienced severe vomiting and diarrhea on Day 84 of open-label valsartan (40 mg QD). The next day she was found dead at home and no autopsy was performed. The death was coded as gastroenteritis.

The other patient died during open-label, 11 days after discontinuing valsartan therapy. This 1 year-old Asian male with a history of lower respiratory tract infection, bronchopneumonia, hyperbilirubinemia, gastrointestinal reflux, neonatal sepsis, cryptorchism, right-sided solitary pelvic kidney, right hand polydactyly and developmental delay completed double-blind and entered open-label (his transaminases were mildly elevated on screening). Due to elevated BP his valsartan was increased to 80 mg QD. On Day 193, he presented with fever, cough, coryza and vomiting; he was hospitalized two days later with pneumonitis and hepatitis (serology was negative). His valsartan dose was decreased to 20 mg QD. By Day 207, his transaminases had markedly improved; the investigator decided to discontinue the patient from the study due to

hepatitis. Eleven days later, the patient was readmitted due to exacerbation of pneumonitis; he went into respiratory failure and died 8 hours after admission.

6.1.2 Other Serious Adverse Events

Table 5-7 Number (%) of patients who died, had other serious AEs, or discontinued due to AEs, Study A2302 and Study A2307

	Study A2302 (6 – 16 yrs)			Study A2307 (ages 1 – 5 yrs)		
	Phase 1 Safety 1 Population N=259 n (%)	Phase 2 Safety 2 Population N=245 n (%)	Open Label Population N=235 n (%)	Phase 1 Safety 1 Population N=90 n (%)	Phase 2 Safety 2 Population N=87 n (%)	Open Label Population N=88 n (%)
Deaths*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
SAEs	1 (0.4)	0 (0.0)	18 (7.7)	1 (1.1)	1 (1.1)	13 (14.8)
Discontinued due to AE	1 (0.4)	3 (1.2)	7 (3.0)	0 (0.0)	0 (0.0)	3 (3.4)

* excluding death after study discontinuation
Source: [Study A2302-PTL 10.2-2a; PTL 10.2-2b; PTT 10.2-1; PTT 10.2-2; PTT 10.2-3; PTT 10.2-4; PTT 10.2-5; PTT 10.2-6; PTT 10.2-7]; [Study A2307-PTL 10.2-2a; PTL 10.2-2b; PTT 10.2-1; PTT 10.2-2; PTT 10.2-3; PTT 10.2-4; PTT 10.2-5; PTT 10.2-6; PTT 10.2-7]

Listings of SAEs can be found in the individual study reviews. In A2302, diarrhea, pyrexia, and gastroenteritis were the only SAEs reported by more than one patient during open-label. Increased creatinine and hyperkalemia (1 patient each, both renal transplant patients) were reported as SAEs. In A2307, gastroenteritis was the most frequently reported SAE, followed by diarrhea.

6.1.3 Dropouts and Other Significant Adverse Events

The sponsor provided a listing of patients that discontinued due to AE.

In A2302, two patients who were coded as discontinuing due to "unsatisfactory therapeutic effect" also had adverse events (proteinuria beginning in double-blind; hypertensive encephalopathy beginning during placebo run-in). Please see safety section in the individual study reviews for further discussion.

In A2307, there were no discontinuations in double-blind that were due to an AE. Three discontinuations during open-label are listed below:

Table 5-9 Adverse events leading to study discontinuation, Study A2302 and Study A2307

Patient ID	Age-Sex-Race	Preferred term	Study drug related	Drug-dose-phase
Study A2302 (ages 6 – 16 years)				
[A2302-0123-00001]	13-M-BI	Rash	Yes	Val 20mg (L) Ph 1
[A2302-1002-00003]	9-M-Ca	Proteinuria	Yes	Placebo Ph 2
[A2302-0105-00002]	14-M-BI	Pruritus	Yes	Placebo Ph 2
		Pharyngeal oedema	Yes	Placebo Ph 2
		Urticaria	Yes	Placebo Ph 2
[A2302-0608-00008]	11-F-BI	Hypotension	Yes	Val 160mg (H) Ph 2
[A2302-0149-00001]	8-F-Ca	Oedema peripheral	Yes	Val 40mg OL
[A2302-0601-00006]	14-M-BI	Colitis	Yes	Val 40mg OL
[A2302-0603-00009]	14-F-Ca	Convulsion (SAE)	No	Val 40mg OL
[A2302-0502-00004]	8-F-Ca	Meningitis viral (SAE)	No	Val 160mg OL
[A2302-0503-00003]	16-F-Ca	Blood creatinine increased	Yes	Val 40mg OL
[A2302-0123-00003]	11-M-Ot	Diarrhea (SAE)	No	Val 80mg OL
		Dehydration (SAE)	No	Val 80mg OL
		Hyperkalemia (SAE)	Yes	Val 80mg OL
[A2302-0125-00007]	15-M-BI	Neutropenia	Yes	Val 160mg OL
Study A2307 (ages 1 – 5 years)				
[A2307-0085-00003]	1-M-As	Hepatitis (SAE)	Yes	Val 80mg OL
[A2307-0061-00001]	1-F-BI	Gastroenteritis viral (SAE)	No	Val 40mg OL
[A2307-0064-00001]	1-F-BI	Renal impairment	No	Val 20mg + HCTZ OL

Reviewer note: The case of peripheral edema was actually hand swelling per the dataset. Three patients had "renal events" that led to discontinuation: proteinuria, blood creatinine increased, and renal impairment.

6.1.4 Common Adverse Events (AE)

The most common AE in all phases of A2302 was headache. The most common AEs in A2307 were cough and pyrexia. Listed below are AEs by phase and treatment in both clinical studies.

Table 5-3 **Adverse event incidence overall and by preferred term (>= 3% in any group) Phase 1, Study A2302 and Study A2307, (Safety 1 population)**

	Study A2302				Study A2307			
	Low N=101 n (%)	Medium N=52 n (%)	High N=106 n (%)	Total N=259 n (%)	Low N=37 n (%)	Medium N=18 n (%)	High N=35 n (%)	Total N=90 n (%)
Any AE	**46 (45.5)**	**21 (40.4)**	**38 (35.8)**	**105 (40.5)**	**10 (27.0)**	**7 (38.9)**	**12 (34.3)**	**29 (32.2)**
Headache	15 (14.9)	7 (13.5)	8 (7.5)	30 (11.6)	1 (2.7)	1 (5.6)	1 (2.9)	3 (3.3)
Vomiting	4 (4.0)	2 (3.8)	4 (3.8)	10 (3.9)	1 (2.7)	0 (0.0)	0 (0.0)	1 (1.1)
Cough	6 (5.9)	2 (3.8)	0 (0.0)	8 (3.1)	2 (5.4)	1 (5.6)	3 (8.6)	6 (6.7)
Dizziness	1 (1.0)	1 (1.9)	5 (4.7)	7 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nasopharyngitis	3 (3.0)	2 (3.8)	2 (1.9)	7 (2.7)	1 (2.7)	1 (5.6)	1 (2.9)	3 (3.3)
Nasal congestion	3 (3.0)	2 (3.8)	0 (0.0)	5 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (1.0)	0 (0.0)	2 (1.9)	3 (1.2)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.1)
URT infection	1 (1.0)	1 (1.9)	1 (0.9)	3 (1.2)	1 (2.7)	3 (16.7)	0 (0.0)	4 (4.4)
Rhinitis	2 (2.0)	0 (0.0)	1 (0.9)	3 (1.2)	0 (0.0)	2 (11.1)	2 (5.7)	4 (4.4)
Sinusitis	0 (0.0)	2 (3.8)	1 (0.9)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.4)	3 (8.1)	1 (5.6)	1 (2.9)	5 (5.6)
Excoriation	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.4)	1 (2.7)	1 (5.6)	0 (0.0)	2 (2.2)
Influenza	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (5.6)	1 (2.9)	2 (2.2)
Irritability	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.7)	2 (2.2)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.1)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.1)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.1)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	1 (1.1)

URT = Upper respiratory tract.
A subject with multiple AEs is counted only once in the total row. AEs listed in decreasing frequency in valsartan total group, Study A2302.
Source: [Study A2302- PTT 10.1-1a and Study A2307- PTT 10.1-1a]

Table 5-4 **Adverse event incidence overall and by preferred term (>= 3% in any group) Phase 2, Study A2302 and Study A2307 (Safety 2 population)**

	Study A2302			Study A2307		
	Valsartan N=124 n (%)	Placebo N=121 n (%)	Total N=245 n (%)	Valsartan N=44 n (%)	Placebo N=43 n (%)	Total n=87 n (%)
Any AE	**49(39.5)**	**38(31.4)**	**87 (35.5)**	**21 (47.7)**	**18 (41.9)**	**39 (44.8)**
Headache	14 (11.3)	10 (8.3)	24 (9.8)	1 (2.3)	0 (0.0)	1 (1.1)
Dizziness	4 (3.2)	1 (0.8)	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	3 (2.4)	2 (1.7)	5 (2.0)	2 (4.5)	3 (7.0)	5 (5.7)
URT infection	2 (1.6)	3 (2.5)	5 (2.0)	2 (4.5)	4 (9.3)	6 (6.9)
Nasopharyngitis	3 (2.4)	0 (0.0)	3 (1.2)	3 (6.8)	0 (0.0)	3 (3.4)
Influenza	2 (1.6)	1 (0.8)	3 (1.2)	2 (4.5)	0 (0.0)	2 (2.3)
Pyrexia	2 (1.6)	0 (0.0)	2 (0.8)	2 (4.5)	5 (11.6)	7 (8.0)
Diarrhea	1 (0.8)	1 (0.8)	2 (0.8)	3 (6.8)	2 (4.7)	5 (5.7)
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	2 (2.3)

A subject with multiple AEs is counted only once in the total row. AEs listed in decreasing frequency in total group, Study A2302. URT = Upper respiratory tract.
Source: [Study A2302- PTT 10.1-2a and Study A2307- PTT 10.1-2a]

Table 5-5 Adverse event incidence overall and by preferred term (>= 5% in total group, Study A2302 or Study A2307) in open label, (Open label population)

	Study A2302			Study A2307		
	Valsartan Only[a] N=195 n (%)	Valsartan +HCTZ[b] N=40 n (%)	Total N=235 n (%)	Valsartan Only[a] N=80 n (%)	Valsartan +HCTZ[b] N=8 n (%)	Total N = 88 n (%)
Any AE	**177 (90.8)**	**37 (92.5)**	**214 (91.1)**	**74 (92.5)**	**7 (87.5)**	**81 (92.0)**
Headache	58 (29.7)	20 (50.0)	78 (33.2)	8 (10.0)	2 (25.0)	10 (11.4)
Nasopharyngitis	38 (19.5)	6 (15.0)	44 (18.7)	16 (20.0)	0 (0.0)	16 (18.2)
Pyrexia	36 (18.5)	10 (25.0)	46 (19.6)	32 (40.0)	4 (50.0)	36 (40.9)
Cough	33 (16.9)	10 (25.0)	43 (18.3)	33 (41.3)	3 (37.5)	36 (40.9)
URT infection	23 (11.8)	5 (12.5)	28 (11.9)	12 (15.0)	0 (0.0)	12 (13.6)
Diarrhea	20 (10.3)	3 (7.5)	23 (9.8)	17 (21.3)	3 (37.5)	22 (22.7)
Vomiting	19 (9.7)	3 (7.5)	22 (9.4)	12 (15.0)	3 (37.5)	15 (17.0)
Influenza	18 (9.2)	2 (5.0)	20 (8.5)	9 (11.3)	2 (25.0)	11 (12.5)
Sinusitis	16 (8.2)	3 (7.5)	19 (8.1)	5 (6.3)	2 (25.0)	7 (8.0)
Abdominal pain	15 (7.7)	5 (12.5)	20 (8.5)	7 (8.8)	0 (0.0)	7 (8.0)
Rhinitis	12 (6.2)	1 (2.5)	13 (5.5)	8 (10.0)	2 (25.0)	10 (11.4)
Nausea	12 (6.2)	5 (12.5)	17 (7.2)	1 (1.3)	1 (12.5)	2 (2.3)
Nasal congestion	11 (5.6)	5 (12.5)	16 (6.8)	3 (3.8)	1 (12.5)	4 (4.5)
Pharyngolaryngeal pain	11 (5.6)	5 (12.5)	16 (6.8)	1 (1.3)	1 (12.5)	2 (2.3)
Tonsillitis	9 (4.6)	3 (7.5)	12 (5.1)	7 (8.8)	2 (25.0)	9 (10.2)
Dizziness	9 (4.6)	4 (10.0)	13 (5.5)	2 (2.5)	0 (0.0)	2 (2.3)
Epistaxis	8 (4.1)	5 (12.5)	13 (5.5)	5 (6.3)	1 (12.5)	6 (6.8)
Otitis media	4 (2.1)	2 (5.0)	6 (2.6)	4 (5.0)	1 (12.5)	5 (5.7)

URT = Upper respiratory tract.

6.1.5 Laboratory Findings

In study A2302, the mean changes from baseline were small during double-blind.
For A2302 (and A2307), the highest number and percentage of patients with a clinically significant change was seen with respect to BUN increase > 50% (see Table 5-13, below). In Table 5-11 (below), showing mean changes from baseline to end of study (OL population), the serum creatinine increased by about 10% and uric acid increased by about 5% in A2302; in study A2307, mean BUN increased by about 15% and uric acid increased by about 10%.

In A2307 (see Table 5-13, AST and ALT results, and individual study review), an increase from baseline was seen with transaminases. Three patients in A2307 were reported to have marked increases in transaminases; one of these patients had a positive serology for hepatitis A. One patient was discontinued from the study due to hepatitis (see Deaths). A third patient was noted to have marked elevations in transaminases (300-500 U/L range) at the end of study visit, with normalization of transaminases 10 days later.

Two patients with elevated screening SGOT had transaminase elevations 3-10x the upper limit of normal; one of these (#061-00006) developed transaminase elevation at the end of study visit. For further details, please see the individual study report for A2307.

A fourth patient (#082-00003) with elevated transaminases showed normalization while continuing the same dose of valsartan treatment.

Table 5-11 Mean changes from baseline to end of study in selected laboratory values, Study A2302 and Study A2307, Open-label population

	Study A2302 (ages 6 – 16 years) N=235			Study A2307 (ages 1 – 5 years) N=88		
Laboratory parameter	N[a]	Baseline Mean (SD)	Change from baseline Mean (SD)	N[a]	Baseline Mean (SD)	Change from baseline Mean (SD)
ALT (SGPT), U/L	221	20.4 (9.45)	-0.2 (9.16)	85	13.8 (6.87)	11.8 (82.82)
AST (SGOT), U/L	221	25.2 (6.83)	-1.4 (7.45)	85	27.0 (9.62)	10.5 (78.17)
Bilirubin, umol/L	220	6.5 (4.86)	-0.1 (3.74)	84	6.8 (5.56)	-0.8 (5.78)
Creatinine, umol/L	224	62.7 (25.04)	6.3 (15.77)	85	60.2 (25.43)	-0.8 (15.75)
BUN, mmol/L	223	4.99 (2.35)	0.03 (1.91)	85	5.46 (2.73)	0.79 (3.04)
Uric Acid, umol/L	221	317 (91.48)	16.87 (60.12)	85	257 (74.21)	32.0 (74.51)
Glucose, mmol/L	221	4.89 (0.82)	0.06 (1.71)	79	4.68 (0.82)	-0.09 (1.05)
Cholesterol, mmol/L	221	4.43 (0.87)	-0.091 (0.74)	85	4.49 (1.57)	0.36 (1.78)
Triglycerides, mmol/L	220	1.47 (0.93)	-0.02 (0.85)	85	1.77 (1.23)	0.04 (1.28)
Potassium, mmol/L	222	4.18 (0.44)	0.01 (0.49)	81	4.36 (0.44)	0.06 (0.54)
Hemoglobin, g/L	222	133 (12.24)	-1.3 (9.73)	82	125 (12.10)	-2.3 (11.13)
Hematocrit, L/L	222	0.42 (0.04)	-0.005 (0.03)	82	8.35 (15.7)	1.05 (8.56)

BUN = blood urea nitrogen
[a] Only patients with both baseline and post-baseline values were included in the analysis.
Source: [Study A2302-PTT 10.3-3; Study A2307-PTT 10.3-3]

Table 5-13 Number (%) of patients with clinically notable selected laboratory values (most extreme value at any timepoint post-baseline), Study A2302 and Study A2307 (Safety population)

	Patients meeting BOTH the criterion AND outside of lab normal range							
	Study A2302 (ages 6 – 16 years)				Study A2307 (ages 1 – 5 years)			
	DB (N=259)		OL (N=235)		DB (N=90)		OL (N=88)	
Laboratory parameter/criterion	**N[a]**	**n[b] (%)**	**N[a]**	**n[b] (%)**	**N[a]**	**n[b] (%)**	**N[a]**	**n[b] (%)**
BUN, >50% increase	253	9 (3.4)	223	12 (5.4)	88	7 (8.0)	85	10 (11.8)
Creatinine, >50% increase	254	0 (0)	224	5 (2.2)	87	2 (2.3)	85	2 (2.4)
Potassium, >20% increase	251	3 (1.2)	222	5 (2.3)	84	3 (3.6)	81	6 (7.4)
Potassium, >20% decrease	251	2 (0.8)	222	1 (0.5)	84	1 (1.2)	81	3 (3.7)
Glucose, >50% increase	252	6 (2.4)	221	5 (2.3)	80	3 (3.8)	79	5 (6.3)
Glucose, >50% decrease	252	1 (0.4)	221	5 (2.3)	80	1 (1.3)	79	1 (1.3)
Uric acid, >50% increase	253	3 (1.2)	221	6 (2.7)	88	1 (1.1)	85	3 (3.5)

DB = Double blind; OL = Open-label, BUN = blood urea nitrogen

a: N is the number of patients with a value at both baseline and post-baseline. It is used as the denominator in calculating the percentages.

b: n is the number of patients meeting the both the laboratory parameter criterion AND with a laboratory value outside of normal range (Higher than normal range for increased values; below normal range for decreased values).

Source: [Study A2302-PTT 10.3-6, PTT 10.3-7]; [Study A2307-PTT 10.3-6; PTT 10.3-7]

6.1.6 Vital Signs

Hypotension: Orthostatic hypotension was not assessed in study A2307.
In A2302, orthostatic BP changes were defined as a decrease in DBP > 10 mm Hg or decrease in SBP > 20 mm Hg when the patient changed from a sitting to standing position. Results during double-blind are shown below. A slightly increased incidence of orthostatic BP can be seen in the high/high group compared to high/placebo (14.8% compared to 10.4%); a dose-relationship is not seen.

Post-text table 10.7-1 (Page 1 of 1)
Frequency of orthostatic blood pressure changes in double blind phase
Safety Population

			Baseline/ Visit 2	Day 7/ Visit 3	Day 14/ Visit 4	Day 21/ Visit 5	Day 28/ Visit 6	Endpoint	At any visit/ (Post-baseline)
Low	(N=9)	Total	9	9	3	0	0	9	9
		n (%)	1(11.1)	2(22.2)	0			2(22.2)	2(22.2)
Medium	(N=1)	Total	1	1	1	0	0	1	1
		n (%)	0	0	0			0	0
High	(N=4)	Total	4	4	1	0	0	4	4
		n (%)	1(25.0)	0	0			0	0
Low/Low	(N=44)	Total	44	44	44	44	42	44	44
		n (%)	2(4.5)	3(6.8)	3(6.8)	1(2.3)	5(11.9)	5(11.4)	8(18.2)
Low/Placebo	(N=48)	Total	48	48	48	48	42	48	48
		n (%)	6(12.5)	6(12.5)	3(6.3)	2(4.2)	4(9.5)	4(8.3)	9(18.8)
Med/Med	(N=26)	Total	26	26	26	26	25	26	26
		n (%)	2(7.7)	4(15.4)	1(3.8)	2(7.7)	1(4.0)	1(3.8)	7(26.9)
Med/Placebo	(N=25)	Total	25	25	25	25	24	25	25
		n (%)	1(4.0)	1(4.0)	0	0	0	0	1(4.0)
High/High	(N=54)	Total	54	53	54	54	51	54	54
		n (%)	0	4(7.5)	6(11.1)	5(9.3)	7(13.7)	8(14.8)	15(27.8)
High/Placebo	(N=48)	Total	48	48	48	48	45	48	48
		n (%)	4(8.3)	7(14.6)	4(8.3)	5(10.4)	4(8.9)	5(10.4)	11(22.9)

One patient in A2302 discontinued double-blind (high-dose group) due to symptomatic hypotension.
No meaningful effects on pulse were seen in this submission.

6.1.7 Human Reproduction and Pregnancy Data

There were no pregnancies reported in this program.

6.1.8 Assessment of Effect on Growth

Results from growth and neurocognitive assessments did not reveal any negative impact of valsartan.

6.1.9 Overdose Experience

No overdoses were reported.

6.2 Adequacy of Patient Exposure and Safety Assessments

6.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The primary clinical data sources were the two clinical studies A2302 and A2307.
A2302 exposed 261 children, 6-16 years old, to valsartan doses of 10-160 mg QD (per the sponsor, a mean exposure of 0.4 to 2.7 mg/kg). A2307 exposed 90 children, 1-5 years old, to valsartan doses of 5-80 mg QD (per the sponsor, a mean exposure of 0.4 to 3.4 mg/kg).

Table 5-1 Duration of exposure to valsartan by dose in open-label, Study A2302 and Study A2307 (Open Label population)

	Valsartan 20 mg	Valsartan 40 mg	Valsartan 80 mg	Valsartan 160 mg	Valsartan+ HCTZ 80/12.5 mg	Valsartan+ HCTZ 160/12.5 mg	Non-protocol dose	Total of any dose
Study A2302 (Ages 6 – 16 years); N = 235								
Days of Exposure, n (%)								
> 0	NA	234 (100)	150 (100.)	90 (100)	NA	37 (100.0)	7 (100.0)	235 (100)
≥ 7	NA	234 (100)	150 (100.)	89 (98.9)	NA	36 (97.3)	6 (85.7)	235 (100)
≥ 14	NA	219 (93.6)	143 (95.3)	86 (95.6)	NA	35 (94.6)	5 (71.4)	235 (100)
≥ 28	NA	154 (65.8)	117 (78.0)	70 (77.8)	NA	33 (89.2)	4 (57.1)	234 (99.6)
≥ 56	NA	115 (49.1)	89 (59.3)	66 (73.3)	NA	29 (78.4)	3 (42.9)	227 (96.6)
≥ 182	NA	95 (40.6)	45 (30.0)	29 (32.2)	NA	15 (40.5)	1 (14.3)	202 (86.0)
≥ 294	NA	76 (32.5)	26 (17.3)	10 (11.1)	NA	9 (24.3)	0 (0.0)	179 (76.2)
≥ 365	NA	36 (15.4)	2 (1.3)	1 (1.1)	NA	0 (0.0)	0 (0.0)	95 (40.4)
Descriptive Statistics (Days)								

	Valsartan 20 mg	Valsartan 40 mg	Valsartan 80 mg	Valsartan 160 mg	Valsartan+ HCTZ 80/12.5 mg	Valsartan+ HCTZ 160/12.5 mg	Non-protocol dose	Total of any dose
n	NA	234	150	90	NA	37	7	235
Mean	NA	156.9	133.1	129.3	NA	155.8	65.6	315.3
SD	NA	157.60	119.53	105.88	NA	118.15	87.70	103.68
Study A2307 (Ages 1 – 5 years); N = 88								
Days of Exposure, n (%)								
> 0	88 (100)	48 (100)	24 (100)	NA	6 (100)	NA	4 (100)	88 (100)
≥ 7	87 (98.9)	48 (100)	21 (87.5)	NA	6 (100)	NA	3 (75.0)	88 (100)
≥ 14	76 (86.4)	46 (95.8)	20 (83.3)	NA	6 (100)	NA	3 (75.0)	88 (100)
≥ 28	62 (70.5)	37 (77.1)	18 (75.0)	NA	6 (100)	NA	2 (50.0)	88 (100)
≥ 56	50 (56.8)	32 (66.7)	16 (66.7)	NA	6 (100)	NA	2 (50.0)	87 (98.9)
≥ 182	45 (51.1)	23 (47.9)	9 (37.5)	NA	4 (66.7)	NA	0 (0.0)	85 (96.6)
≥ 294	39 (44.3)	20 (41.7)	6 (25.0)	NA	3 (50.0)	NA	0 (0.0)	81 (92.0)
≥ 365	13 (14.8)	0 (0.0)	0 (0.0)	NA	0 (0.0)	NA	0 (0.0)	29 (33.0)
Descriptive Statistics (Days)								
n	88	48	24	NA	6	NA	4	88
Mean	186.9	186.0	144.2	NA	241.8	NA	80.3	346.3
SD	163.10	141.25	124.67	NA	98.73	NA	82.09	64.86

NA = Not applicable (treatment not given in study)
Source: [Study A2302-PTT 8.1-4, Study A2307-PTT 8.1-4]

6.2.1.1 Study type and design

Both A2302 and A2307 employed the type C design of the FDA pediatric Written Request. Please see Section 5.1.1 for further details.

6.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

6.2.2.1 Other studies:

As part of the FDA Written Request, the sponsor was asked to collect safety information from unpublished and published sources.
In order to collect unpublished safety information, the sponsor conducted an international survey of pediatric nephrologists and pediatricians (N=88) from 11 countries. The goal of the survey was to assess frequency of valsartan use over a 5 year period and to identify physicians that had treated a reasonable number of pediatric hypertensive patients with valsartan (outside a clinical trial).

Of 88 physicians, 46 were in the US; 12 in Brazil; 7 in South Africa; 6 in India; 5 in Poland; 3 in Germany; 2 in Argentina; 2 in Belgium; 2 in Chile; 2 in Sweden; and 1 in France. Only 27 (30%) responded after multiple requests.

Of the 27 responders, 8 reported that they did not treat any pediatric patients with valsartan; 8 reported treating 1-5 patients with valsartan within the last 5 years; 6 treated 6-10 patients; and 2 treated 11-20 patients. One responder reported that the number treated with valsartan was

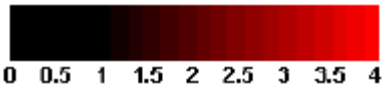
unknown, and two responders did not answer the question regarding valsartan use outside a clinical study.

The sponsor also provided a published survey of 438 North American pediatric nephrologists which reported angiotensin converting-enzyme inhibitors to be the most commonly used first-line antihypertensive agents (46.7%); angiotensin-II receptor blockers were used as a second line agent by 4.9% of respondents.[1]

6.2.2.2 Postmarketing experience

Dr. Szarfman mined the AERS database for valsartan in the pediatric population (1-16 years). Only 17 reports for valsartan were noted (29 and 43 reports were seen with candesartan and losartan, respectively). Nine of the 17 reports involved fetal exposure to valsartan; the other reports were coded as accidental exposures or intentional overdoses. For example, this database included one report of a multiple drug overdose of valsartan, benzafibrate, and amlodipine in a 16 year-old patient who subsequently went into renal failure and was noted to be hypotensive and in shock.

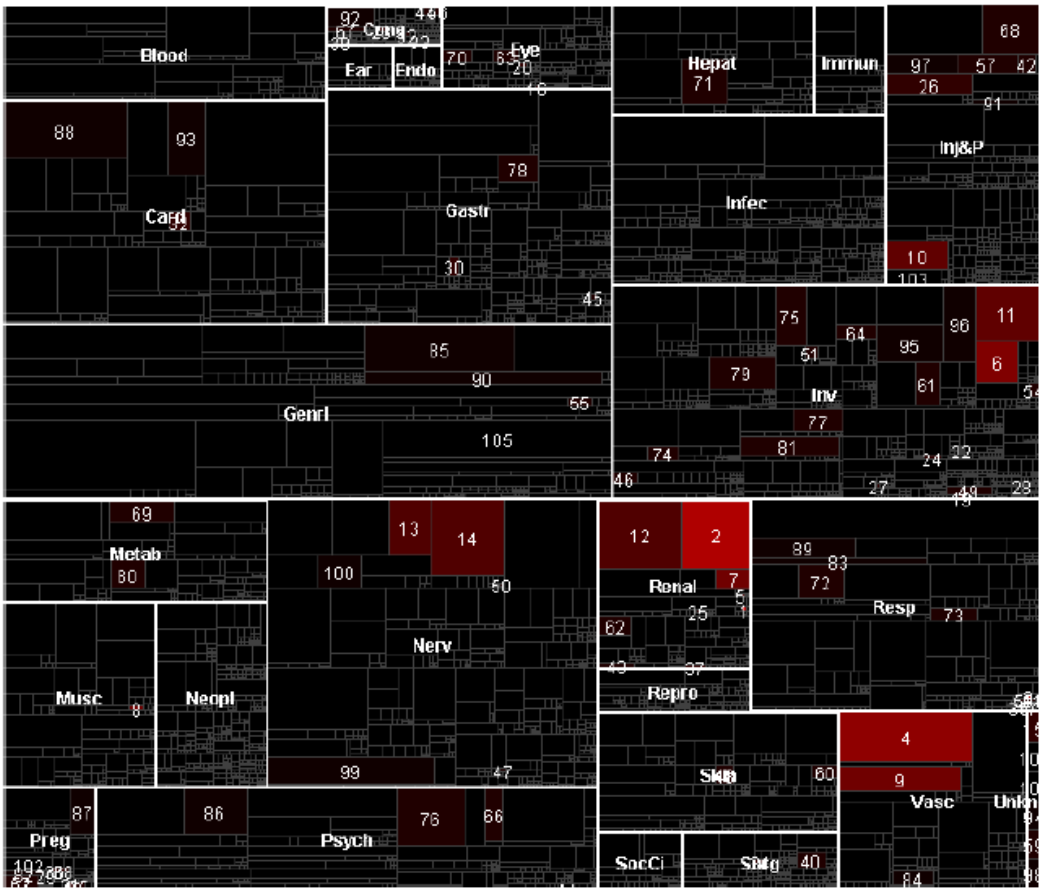
1 Woronieki R, Flynn J. How are hypertensive children evaluated and managed? A survey of North American pediatric nephrologists. Pediatric Nephrology 2005; 20: 791-797.



Rank	SOC	Term (PT)	EBGM
1	Renal	Kidney enlargement	3.380
2	Renal	Renal failure acute	3.050
3	Resp	Neonatal asphyxia	2.861
4	Vasc	Hypotension	2.662
5	Renal	Renal failure neonatal	2.607
6	Inv	Blood urea increased	2.531
7	Renal	Anuria	2.312
8	Musc	Growth retardation	2.286
9	Vasc	Shock	2.233
10	Inj&P	Drug exposure during pregnancy	2.218
11	Inv	Blood creatinine increased	2.149
12	Renal	Renal failure	2.031
13	Nerv	Depressed level of consciousness	1.922
14	Nerv	Dizziness	1.891
15	Unknown	Outcome - Congenital Anomaly (Custom Term)	1.611
16	Eye	Scleral disorder	1.510
17	Resp	Diaphragmatic disorder	1.508
18	Preg	Placental infarction	1.508
19	Inv	Pulmonary function test abnormal	1.508
20	Eye	Ocular icterus	1.502
21	Psych	Body dysmorphic disorder	1.500
22	Inv	Beta 2 microglobulin urine increased	1.499
23	Cong	Persistent foetal circulation	1.497
24	Inv	Renin increased	1.496
25	Renal	Renal vein thrombosis	1.495
26	Inj&P	Medication error	1.492
27	Inv	Echography abnormal	1.491
28	Inv	Blood aldosterone increased	1.490
29	Preg	Weight decrease neonatal	1.490
30	Gastr	Large intestine perforation	1.489
31	Preg	Placental insufficiency	1.486
32	Card	Atrioventricular block	1.479
33	Cong	Congenital pulmonary hypertension	1.479

None of the preferred terms were associated with an EB05 > 1.14; the largest EBGM value was 3.38 for kidney enlargement (N=2).

Valsartan



6.2.2.3 Literature

A Pubmed literature search by the assigned primary medical reviewer, using search terms "valsartan pediatric," "valsartan children," resulted in few publications and did not reveal any new safety issues in the target patient population.

6.2.3 Adequacy of Overall Clinical Experience

According to presubmission meetings, A2307 was designed to support the pivotal study (A2302). The overall clinical experience appears adequate to discern a treatment effect and to exclude a large safety signal. The safety database for 1-5 year-old patients is relatively small.

6.2.4 Adequacy of Routine Clinical Testing

Pharmacokinetic assessments might have been informative in assessing the dose-response results, especially if one suspected that the lack of dose-response in A2307 was related to higher exposures with administration of the extemporaneous suspension.

Otherwise, the routine clinical testing appears to have been adequate in this submission.

6.2.5 Assessment of Quality and Completeness of Data

A DSI audit of one site is pending at the time of this review. However, based on the submission and case report forms, the data appear to be adequate.
A more complete assessment of patient hospitalizations is limited by the lack of hospital records.

6.2.6 Additional Submissions, Including Safety Update

No safety update was submitted since there were no additional clinical data.

6.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

A limitation of the data is the lack of concomitant placebo group in Phase 1 and open-label phases; as a result, it cannot be distinguished whether some of the adverse events (such as nasopharyngitis, pyrexia) are due to age-related background conditions rather than a drug effect. The most common AE in all phases of A2302 was headache. The most common AEs in A2307 were cough and pyrexia.

Headache appears in the labeling as one of the most common reasons for discontinuation of therapy in adult hypertensives.

In the A2302 open-label population, serum creatinine increased by 10% from baseline; in the A2307 open-label population, BUN increased by 15% from baseline. There were two discontinuations from the study due renal impairment and increased creatinine, respectively. The renal events and renal laboratory changes are consistent with current labeling in adults, where postmarketing experience includes impaired renal function as a reported adverse event, and increased serum creatinine was slightly higher in the post-myocardial infarction population on valsartan compared to those on placebo.

The transaminase elevations in the younger hypertensive patients (A2307) during open-label therapy present a safety issue. Current labeling (section 6.2) includes postmarketing experience of elevated liver enzymes and very rare reports of hepatitis. No signal was seen in the larger A2302, involving older children given the unapproved tablet. Since two cases involved transaminase elevation at the end-of-study visit, the medical reviewer cannot tell whether these elevations were related to drug, exposure, younger population, or concomitant condition.

However, the onus is on the sponsor to provide convincing evidence that the elevated transaminases are not a safety issue.

6.4 General Methodology

6.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data from A2302 and A2307 were not pooled. According to the sponsor, the etiology of hypertension was different in the two trials; the normal range of laboratory values were different; the ability to perceive and communicate AEs varies with age; certain types of disease or AE might occur predominantly in one of the two age groups; and variation in the study (e.g., valsartan add-on therapy was allowed in A2307) made pooling problematic in terms of potentially masking potential safety signals.
In view of the above arguments, the primary medical reviewer agrees with the decision not to pool data across the two clinical studies.

7 ADDITIONAL CLINICAL ISSUES

7.1 Dosing Regimen and Administration

Given the flat dose-response in study A2307, it is not clear that additional benefit will be gained by up-titration.
At the time of this review, it is not clear why the data in A2302, adjusted to mg/kg weight does not fit a linear, log-linear, or Emax model.

7.2 Advisory Committee Meeting:

No advisory committee meetings have been scheduled for this application.

8 OVERALL ASSESSMENT

8.1 Conclusions:

1. A treatment effect is supported by Phase 2 results from both clinical studies.
2. A dose-response is not demonstrated in A2307 (hypertensive children aged 1-5 years). It is not clear whether the lack of dose-response reflects the higher exposures seen with the extemporaneous suspension.

3. A dose-response is demonstrated in A2302 (hypertensive children aged 6-16 years); the data, when weight-adjusted on a mg/kg basis, does not fit a linear, log-linear, or Emax model.
4. Results for diastolic blood pressure are consistent with the results for systolic blood pressure and support a treatment effect.
5. Results by subgroup are consistent with the overall results.
6. In study A2307, marked rises in transaminases were seen in two patients at the end-of-study visit; a third patient was discontinued due to hepatitis and was subsequently hospitalized with fatal pneumonitis.
7. As noted, increases in BUN, creatinine, uric acid, and potassium are seen in the database.

8.2 Recommendation on Regulatory Action

It is recommended that valsartan be granted an "approvable" action.
Outstanding issues are:

1. Instructions for use: we would like to further understand how to dose, given the lack of dose-response in A2307 and the relatively flat (albeit with significant mean slope) change from baseline in BP as a function of weight-adjusted valsartan dose.
2. Safety: Given the cases of transaminase elevations, the sponsor should demonstrate safety in the younger age group. From the current database, the reviewer cannot tell whether these transaminase elevations represent a hepatic safety issue in a vulnerable population, or whether these cases are related to an increase in valsartan exposure (with the extemporaneous suspension), or are related to some incidental concomitant condition.

3. Two deaths occurred in 1 year-old patients exposed to valsartan during the open-label phase; while these events might have been related to concomitant conditions, this reviewer is unable to rule out a drug effect.

8.3 Recommendation on Postmarketing Actions

None.

8.4 Labeling Review

A labeling review will follow separately.

9 APPENDICES

9.1 Review of Individual Study Reports

Please see medical-statistical review, filed separately

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/s/

Shari Targum
10/15/2007 03:48:33 PM
MEDICAL OFFICER

Medical-Statistical Review

Medical Reviewer: Shari Targum, M.D.
Statistical Reviewer: Valeria Freidlin, Ph.D.

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.

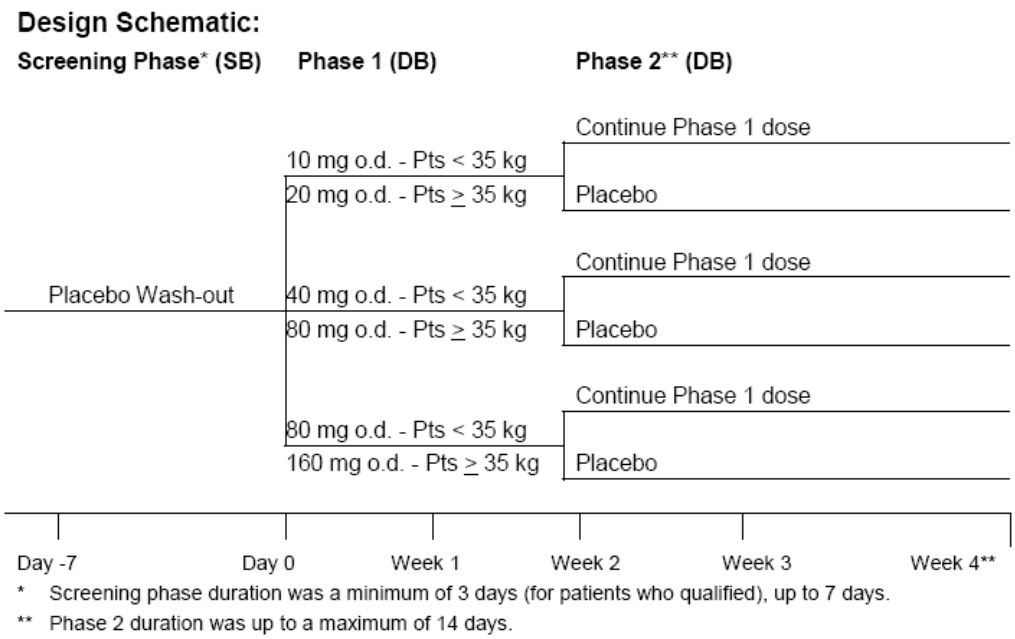


Figure 1. Study Design: A2302: screening and double-blind phases.

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.

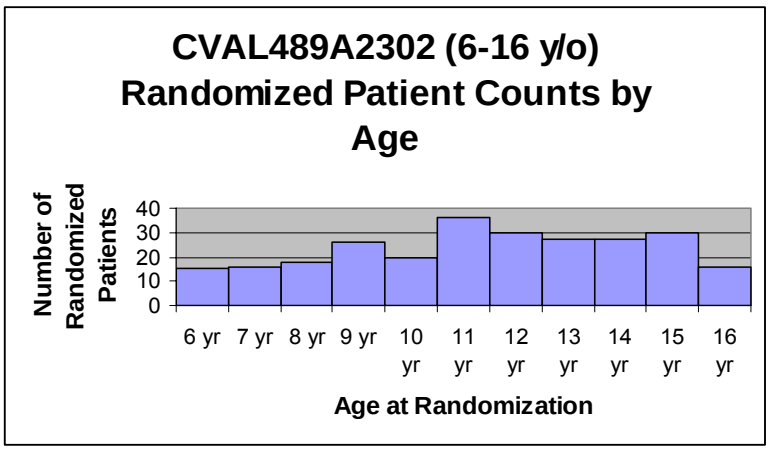


Figure 2. Randomized patient counts by age

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.

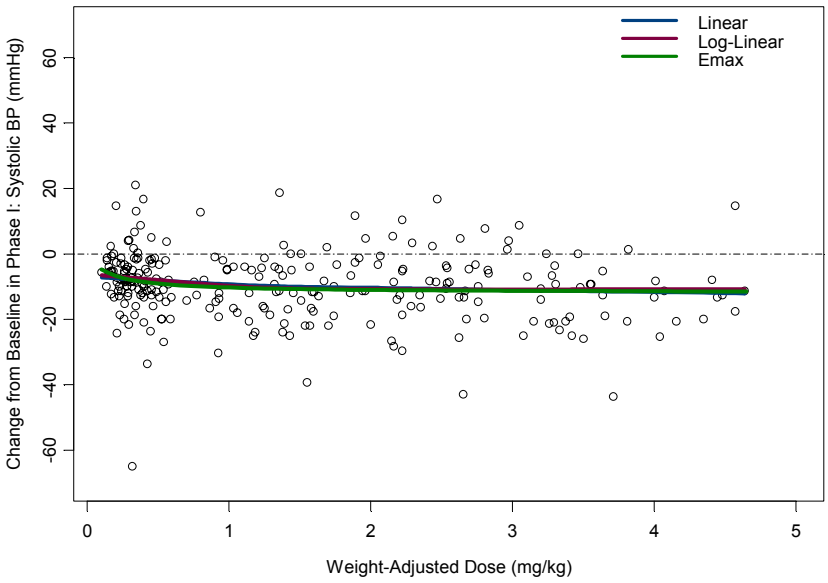


Figure 3. Scatter plot for the change from baseline to end of Phase 1 in mean sitting SBP vs. weight-adjusted dose (mg/kg)

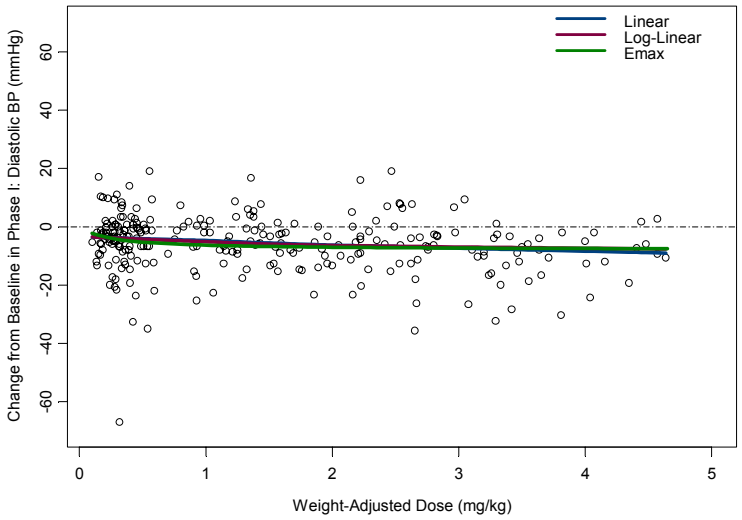


Figure 4. Scatter plot for the change from baseline to end of Phase 1 in mean sitting DBP vs. weight-adjusted dose (mg/kg)

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:

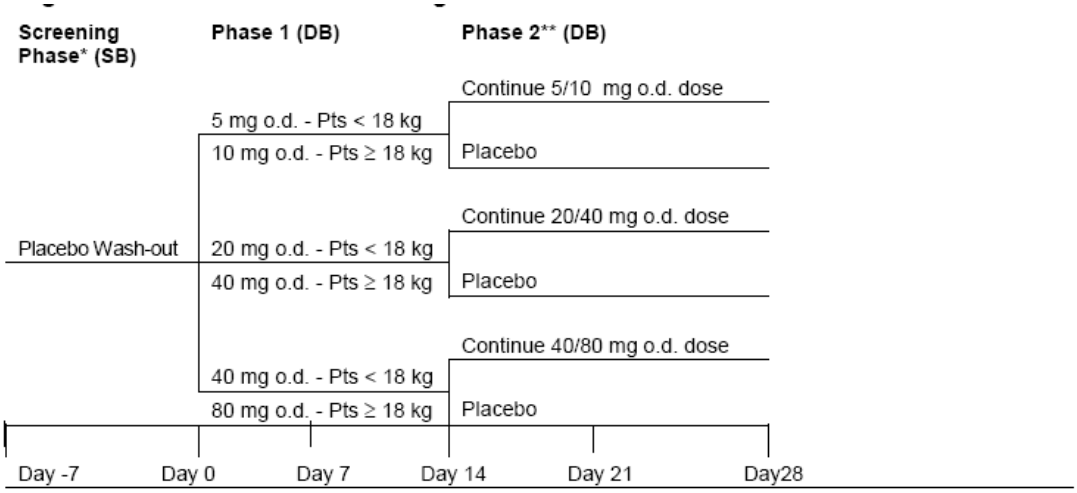
1. A single-blind placebo washout phase for up to one week (Screening);
2. A two-week, double-blind phase where patients were randomized in a 2:1:2 ratio to low, medium and high-dose valsartan, respectively (Phase 1). Patients < 18 kg received 5, 20 or 40 mg valsartan QD, respectively; patients > 18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

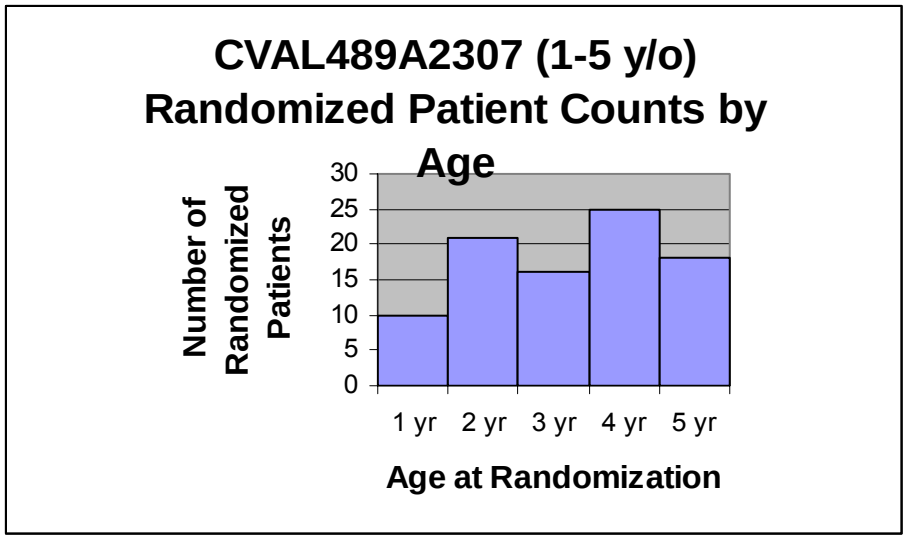


Figure 6. A2307: Histogram of Randomized Patients by Age

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.

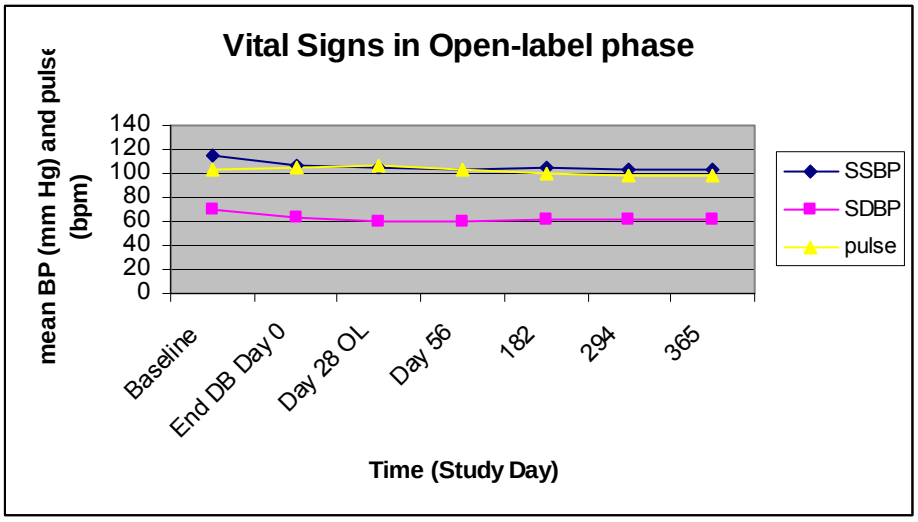


Figure 7. A2307: Vital signs in OL phase

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/

Shari Targum
10/4/2007 11:54:28 AM
MEDICAL OFFICER

Valeria Freidlin
10/4/2007 11:56:56 AM
BIOMETRICS

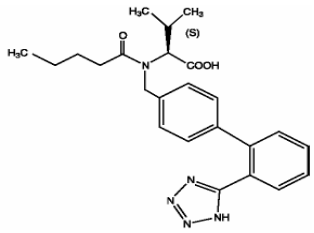
James Hung
10/4/2007 03:05:32 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION: PME	2. NDA Number 21--283
3. Name and Address of Applicant (City & State) Novartis Pharmaceutical Corporation One Health Plaza East Hanover, NJ 07936-1080		**4. Supplement(s)** **Number(s)** **Date(s)** SE5-024 5/29/07
5. Drug Name Diovan®	**6. Nonproprietary Name** Valsartan	**7. Amendments - Dates** SE5-024 (BC) 9/7/07
Supplement Provides For: the treatment of hypertension in pediatric patients.		
9. Pharmacological Category Hypertension-adult (approved) and pediatric (**proposed**) Heart Failure Post-MI	**10. How Dispensed** Rx	**11. Related NDAs** DMF (b) (4)
12. Dosage Form(s) Tablets	**13. Potencies** 80 mg, 160 mg, and 320 mg	
Chemical Name and Structure: N-(1-oxopentyl)-N-[[2'-(1*H*-tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine  Mol. Formula: $C_{24}H_{29}N_5O_3$ Mol. Wt: 435.5		**15. Records/Reports** **Current** **Yes X No** **Reviewed** **Yes No X**
17. Comments: This efficacy supplement is submitted in response to Agency request to provide the efficacy and safety results for valsartan in hypertensive children 1-16 years of age. The drug product for pediatric patients will be prepared extemporaneously by suspending Diovan 80 mg tablets in Ora-Plus oral suspending vehicle and Ora-sweet SF syrup vehicle to a dose of 4 mg/mL. The current submission contains information regarding the suspension, the vehicle, and stability data under long-term and accelerated conditions and labeling information. Review of stability data support a 2.5 month shelf life for the Diovan 4 mg/mL oral suspension when stored in amber glass bottles with child resistant closure at 2-8°C. The application is subject of DMF (b) (4) review, which was reviewed by this reviewer (review # 1) on 8/29/07 and found adequate.		
18. Conclusions and Recommendations: Adequate information has been provided in support of the proposed the 4 mg/mL oral suspension of marketed Diovan (valsartan) tablets prepared extemporaneously by suspending Diovan 80 mg tablets in Ora-Plus oral suspending vehicle and Ora-Sweet SF syrup vehicle. The supplement is "**approved**" from CMC perspective. Please issue an approval letter.		
19. Reviewer:		
Name Kris Raman, Ph.D.	**Signature:**	**Date Completed:** 9/7/07

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Kris Raman
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Jim Vidra
9/14/2007 11:11:11 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	21-283/SE5-024
DATE RECEIVED BY CENTER:	May 29, 2007
DRUG PRODUCT:	DIOVAN® Tablets
DRUG SUBSTANCE:	Valsartan
INTENDED CLINICAL POPULATION:	Hypertensive Children
SPONSOR:	Novartis Pharmaceuticals Corp.
REVIEW DIVISION:	Division of Cardiovascular and Renal Products
PHARM/TOX REVIEWER:	G. Jagadeesh, Ph.D.
PHARM/TOX SUPERVISOR:	Charles Resnick, Ph.D.
DIVISION DIRECTOR:	Norman Stockbridge, M.D., Ph.D.
PROJECT MANAGER:	Quynh Nguyen

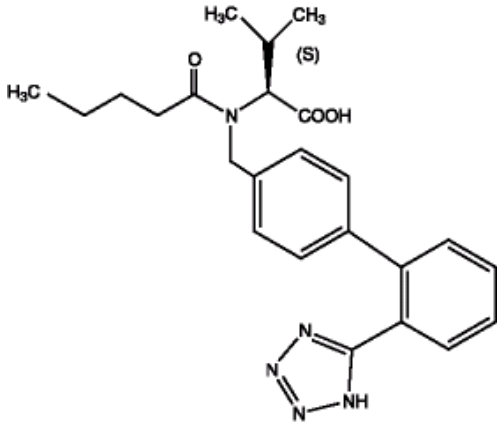
Date of review submission to Division File System (DFS): October 4, 2007

PHARMACOLOGY/TOXICOLOGY REVIEW

NDA Number: 21,283/SE5-024
Date of Supplemental NDA: May 29, 2007 (Amendment Submitted on 7/11/07)
Center Receipt Date: May 29, 2007 (Amendment Received on 7/11/07)
Sponsor: Novartis Pharmaceuticals Corp.
One Health Plaza
East Hanover, NJ 07936
Reviewer: **G. Jagadeesh, Ph.D.**
Division: Cardiovascular and Renal Products
Review Completion Date: October 1, 2007

Drug Product: DIOVAN® Tablets
Drug Substance

Generic name: Valsartan
Chemical name: N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine
CAS registry number: 87333-19-5
Molecular formula/ molecular weight: $C_{24}H_{29}N_5O_3$ /435.5



Related Applications: NDA 20,665 (Diovan® capsules) and NDA 21,283 (Diovan® tablets) were approved for the treatment of hypertension in adults on December 23, 1996 and July 18, 2001, respectively.

Drug Class: Angiotensin II receptor type 1 (AT_1 receptor) antagonist

Indication: Treatment of hypertension in pediatric patients

Clinical Formulation: Diovan® is available as tablets for oral administration, containing 40 mg, 80 mg, 160 mg or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

For children 1 to 5 years old, patients who cannot swallow tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of Diovan, the use of a suspension is recommended. The suspension can be prepared extemporaneously by suspending 8 Diovan® 80 mg tablets in 80 ml Ora-Plus® oral suspending vehicle and 80 ml Ora-Sweet SF® syrup vehicle, in an amber glass bottle. The resulting 160 ml, 4 mg/ml suspension is homogenous and can be stored for either up to 30 days at room temperature (below 30°C) or up to 75 days under refrigerated conditions (2-8°C).

Route of Administration: Oral

Proposed Dosage Regimen: For children who can swallow tablets, the usual recommended starting dose is 1.3 mg/kg once daily (up to 40 mg total). The dose range is 1.3 to 2.7 mg/kg (up to 40 to 160 mg total). The dosage should be adjusted according to blood pressure response.

Disclaimer: Unless indicated otherwise, tables and graphs (some with editorial corrections by the reviewer) are taken directly from the sponsor's submission.

EXECUTIVE SUMMARY

I. Background

Valsartan is an orally effective angiotensin II receptor antagonist approved for the treatment of hypertension, heart failure and reduction of cardiovascular mortality in patients with myocardial infarction. The use of drugs acting on the renin angiotensin system (RAS) in pregnant women has resulted in adverse outcomes for some pregnancies. The most consistent finding reported in the literature with the maternal use of these drugs is fetal renal dysfunction which is manifested prenatally as oligohydramnios and renal tubular dysgenesis, and postnatally as neonatal anuria. These findings are expected, given the fact that angiotensin II plays a critical role in the maintenance of fetal arterial blood pressure, and in the regulation of fetal glomerular filtration rate and renal blood flow.

The purpose of the clinical development program supporting this supplemental NDA was to obtain data on the efficacy and safety of valsartan in children with hypertension aged 1-16 years. To this effect, the sponsor has conducted a toxicity study in neonatal/ juvenile rats. That study, reviewed here, confirms previously published reports on the effects of ACEIs or angiotensin II receptor antagonists on kidney development.

II. Recommendations

A. **Recommendation on Approvability:** Approvable

B. **Recommendations for Additional Nonclinical Studies:** None

Recommendations for Labeling: Based on the 9 week oral toxicity study of valsartan in juvenile rats, we recommend the following text [changes are underlined] be included under

8. USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

The antihypertensive effects of Diovan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1-5 and 6-16 years of age (see CLINICAL STUDIES, Pediatric Hypertension (14.1). The pharmacokinetics of Diovan have been evaluated in pediatric patients 1 to 16 years of age (see Pharmacokinetics, Special Populations, Pediatric (12.3)). Diovan was generally well tolerated and the adverse experience profile was similar to <u>that</u> described <u>for</u> adults (see ADVERSE REACTIONS, Pediatric Hypertension (6.1))

Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (0.035 times the maximum recommended pediatric dose on a mg/m^2 basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage.

Diovan is not recommended for treatment of infants below the age of 24 months or in children with glomerular filtration rates <30 mL/min/1.73 m^2, as no data are available.

III. Summary of Nonclinical Findings

A. Brief Overview of Pediatric Toxicity Study

Male and female neonatal rats were treated orally by gavage from postnatal day (PND) 7 to PND 70 with valsartan at doses of 1, 20 or 150 mg/kg/day followed by a recovery period of 6 to 10 weeks. There were 8 treatment-related deaths in the postweaning period. A dose-dependent and statistically significant increase in serum urea nitrogen and creatinine relative to control were observed at all dose levels at the end of treatment and recovery periods. The changes in BUN and creatinine levels correlated with macroscopically and microscopically observed changes in kidneys that included pale discoloration, pelvic dilatation, irregular surface of the kidney, tubular nephropathy and minimal juxtaglomerular hypertrophy/hyperplasia. Tubular nephropathy was characterized by extensive areas of tubular basophilia with basement membrane thickening, frequent dilated and cystic tubules, interstitial mononuclear cell infiltrates, occasional fibrosis, renal pelvic epithelial hyperplasia and protein casts. All of the renal changes were absent in the control animals and most persisted in the recovery animals. This suggests that the structural renal abnormalities induced during the nephrogenesis period (PND 7 and beyond) may be irreversible. The plasma concentrations of valsartan were substantially higher on PND 7 than on PND 70. This suggests that a large amount of drug may not have been metabolized (drug metabolizing enzymes in the liver are not fully expressed in the rat by PND 7). A NOAEL could not be determined for this study.

B. Nonclinical Safety Issues Relevant to Clinical Use

The developmental toxicity study in neonatal rats demonstrated persistent and irreversible renal tubular and pelvic changes at doses as low as 1 mg valsartan/kg/day.
There is a considerable difference of view in the scientific literature on the vulnerable age interval for the induction of irreversible renal abnormalities in juvenile rats by drugs targeting the RAS. Some report the vulnerability period in rats as the first 24 days of life[1-6] (equivalent to 2 years human) while others conclude vulnerability up to postnatal day 13 (equivalent to 1 month human)[7]. In-house review of the pediatric toxicity study conducted in juvenile rats for ramipril, an ACE inhibitor, has shown vulnerability at PND 14 but not PND 21 (see review of NDA 19,901/SLR-043). Since nephrogenesis and renal functional development are complete in rats by postnatal day 21[8,9] and in humans by 24 months[8,10], it is hypothesized that developing kidneys of human infants less than 2 years old are vulnerable to drugs targeting the RAS. Proposed labeling (b) (4) but non-clinical studies fall short of

demonstrating that it is safe to administer between the ages of 1 and 2. The clinical experience in this age group is insufficient to override this concern. Thus, it is recommended that Diovan® not be administered to children or infants under the age of 2 years.

References

1. Friberg, P. *et al*. *Kidney Int*., **45**: 485, 1994.
2. Guron, G. *et al*. *Hypertension*, **29**: 91, 1997.
3. Guron, G. *et al*. *Am J Physiol.*,**273:** R1421, 1997
4. Guron, G. *et al*. *Acta Physiol Scand*., **164**: 99, 1998
5. Guron, G. *et al*. *Acta Physiol Scand*., **165**: 103, 1999
6. Nilsson A.B. *et al*. *Acta Physiol Scand.*, **173**: 343, 2001.
7. Guron, G. *et al*. *J Am Soc Nephrol.*, **10:** 1550, 1999.
8. Zoetis,, T and Hurtt, M.E. *Birth Defects Res (Part B)*, **68:** 111, 2003.
9. Guidance for Industry: Nonclinical safety evaluation of pediatric drug products. USDHHS, FDA. February 2006.
10. Chevalier, R. *J Urol*., **156:** 714, 1996.

Review of Nine-Week Oral Gavage Study of Valsartan in Juvenile Rats

Key Study Findings: Daily oral dosing of juvenile rats with valsartan at 1, 20 or 150 mg/kg/day from PND 7 to PND 70 resulted in significant toxicity to developing kidneys at all dose levels. Renal tubular changes (tubular nephropathy), pelvic dilatation and, to a lesser extent, juxtaglomerular hypertrophy/hyperplasia persisted in the recovery animals. Increases in BUN and creatinine were noted for both males and females at all dose levels at the end of both the treatment and recovery periods. Of the 13 post-weaning deaths, 12 were attributed to the administration of valsartan, mostly related to renal tubular nephropathy. A NOAEL could not be determined for this study as renal pathology was observed even at the lowest dose level.

Introduction: The objective of the study was to evaluate the adverse effects and to determine the pharmacokinetic profile of valsartan when administered to juvenile rats from postnatal day 7 to PND 70.

Study No.: 900666, Novartis Reference #0680270 and APS-152-095 (TK)
Location of Report: EDR
Conducting Laboratory and Location: (b) (4)

Dates of Study: The pups were initially dosed on August 1 and last necropsied on October 20 (pathology subset), December 6 (recovery subset), December 14 (reproduction subset females) and December 22, 2006 (reproduction subset males).
GLP Compliance: Yes
QA'd Report: yes (X) no ( )
Drug, Batch #: C1302, 99.6% pure
Formulation: Valsartan was suspended in sodium carboxymethylcellulose as a 0.5% (w/v) aqueous solution containing 0.5% (w/v) Tween 80, once a week (refrigerated and protected from light until use). The homogeneity and concentration of each dose suspension prepared on the first day of preparation and in week 3 were analyzed by taking duplicate samples from the top, middle and bottom of the container of each concentration.
Animals

Species/Strain: Wistar Rats, Crl:WI (Glx/BRL/Han) IGS BR (from (b) (4))
#/Animals/Group: On day 4 post partum, the pups were cross-fostered between litters. Each cross-fostered litter was composed of 4 male and 4 female pups. Cross-fostered litters were randomly assigned to the treatment groups using a computer based randomization procedure. There were 52/sex/group for the main study and, of these, 20/sex/group were assigned to the reproductive and the recovery subset and 12/sex/group to the pathology subset. An additional 16 pups/sex/group were assigned for toxicokinetics (see Table 1).
Age: Post partum day 7 at initiation of dosing
Weight: 9 to 20 gm, at initiation of dosing
Husbandry: Pregnant F_0 dams were housed individually in cages. Following weaning on day 21 post partum, the pups were separated from their dams and were housed individually in stainless steel cages. Food and water were available *ad libitum*. Food but

not water was withheld prior to blood sampling, and both were withheld prior to urine collection.

Dosing

Doses: Valsartan was administered at three dose levels: 1, 20 or 150 mg/kg/day (Table 1). Control animals received the vehicle at the same dosage volume as treated animals. Doses were selected on the basis of a 4 week range-finding oral toxicity study in juvenile rats (same strain) dosed from PND 7 to PND 34. In that study, pup body weights prior to weaning were decreased by 13 and 15% for males and 8 and 10% for females at 150 and 300 mg/kg/day, respectively. At terminal sacrifice (on PND 34) there were gross and histopathological findings in kidneys of animals at doses as low as 20 mg/kg/day.

TABLE 1
STUDY DESIGN

Gp #	Test substance	Dose (mg/kg/day)	Dose Conc (mg/ml)	Main Study					Toxicokinetic	
				litters	pups	Reproduct -ive subset	Recovery subset	Pathology subset	No. of litters	No. of pups
1	Vehicle	10 ml/kg	0	13	56M, 59F	20 M, 20F	20 M, 20F	12 M, 12F	2	8 M, 8F
2	Valsartan	1	0.1	13	53M, 53F	20 M, 20F	20 M, 20F	12 M, 12F	4	16 M, 16F
3		20	2.0	13	60M, 56F	20 M, 20F	20 M, 20F	12 M, 12F	4	16 M, 16F
4		150	15.0	13	58M, 56F	20 M, 20F	20 M, 20F	12 M, 12F	4	16 M, 16F

Route, Mode and Duration of Administration: Orally by gavage (10 ml/kg), once daily for 64 days, from day 7 post partum to day 70 post partum. Recovery and reproduction subset animals were treated for the same duration (64 days) but were killed at different times. Recovery animals were necropsied 6 weeks after cessation of dosing or on day 118 post partum, reproduction subset females were necropsied on day 13 of gestation, while males were necropsied between days 134 and 146 post partum.

Observations and Measurements

Clinical Signs: On day 0 post partum, the F_1 pups were examined for malformations, sexed and the numbers of live and dead recorded. Pups were evaluated daily for clinical signs, mortality and moribundity from day 1 post partum.

Body Weight: Individual body weights of pups were recorded at birth, on postnatal days 4, 7 through 21, 24, 28, 31, 35, 38, 42 and 48, and subsequently, twice weekly until termination and on the day of terminal euthanasia. Mated F_1 females assigned to the fertility phase were weighed on gestation days 0, 3, 6, 9 and 13. Offspring dosed for day 7 post partum toxicokinetics were weighed on days 4 and 7 post partum.

Food Consumption: Recorded twice weekly from weaning onwards on days of body weight measurement until termination. For mated F_1 females, it was recorded on gestation days 0-3, 3-6, 6-9, and 9-13.

Postnatal Evaluation: Physical development (including vaginal opening for the females and preputial separation for the males) was assessed on all main study animals from post partum day 26 for females and from partum day 35 for males (Table 2). Auditory startle

and pupillary closure responses were assessed for all main study animals on day 28 and day 35 post partum. Locomotor activity was assessed on all main study animals on PND 93. Neurobehavioral tests for effects on learning and memory were conducted on the Reproduction subset animals of the main study on PND 98, while a passive avoidance test was conducted on animals assigned to the Recovery subset on PND 98 to 100.

F_1 Reproduction: Between PND 106 and 122, F_1 animals assigned to the Reproduction subset were cohabited (1 male and 1 female per litter (sibling mating avoided) in the same dosage group) for a maximum of 7 days. The day of positive identification of spermatozoa was termed gestation day 0. The females and males were separated; females were housed individually until gestation day 13.

Clinical Pathology: Blood samples were collected (from a jugular vein) from fasted animals assigned to the Pathology subset during the last week of treatment (PND 64-70). For the Recovery subset, blood samples were collected from the first ten surviving males and females in each group at the end of the recovery period (postnatal week 15). Specimens were divided for hematology[1] and for clinical chemistry[2] evaluations. Urine samples[3] were collected individually for up to 4 hr during which time food and water was not supplied to the animals.

Toxicokinetics: Single dosed animals assigned exclusively to the toxicokinetics section of the study were bled from the vena cava on PND 7 at 0.5, 2, 8 and 24 hr after dosing. Each animal served for one time point and thus the carcasses were discarded without further examination. Plasma concentrations of valsartan were determined after repeated dosing from animals assigned to both reproduction and recovery subsets (12 animals/sex/group and approximately equal numbers from each subset) on PND 70 at 0.5, 2, 8 and 24 hr after the final dosing (3/sex/time point and each animal was used only once). Blood was obtained from the jugular vein and the animal was returned to the cage for additional evaluations.

Pathology: All treated animals found dead or killed *in extremis* except those assigned to the single dose TK study were subjected to a complete gross pathological examination including examination of the reproductive tract (Reproductive subset only) and tissue samples (Table 1) were preserved. Animals assigned to pathology and recovery subsets were euthanized on PND 70 and in study week 16, respectively. On day 13 of gestation, females assigned to the Reproduction subset were euthanized and laparohysterectomies performed. After a complete necropsy, the uteri and the ovaries were removed, the corpora lutea, live and dead embryos, and resorptions were recorded. No other tissues were collected from these animals. A complete necropsy was conducted on all males assigned to the fertility phase 2 to 3 weeks after the end of the mating period.

[1] erythrocytes, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, reticulocytes, white blood cell count, white blood cell differential and morphology, platelets.

[2] ALT, AST, AP, total bilirubin, total protein, albumin, globulins, glucose, urea, creatinine, creatine kinase, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol, A/G ratio

[3] Specific gravity, pH, blood, protein, bilirubin, glucose, ketones and urobilinogen

TABLE 2
STUDY OBSERVATIONS AND MEASUREMENTS

Arrival of pregnant dams. Acclimation (10 days before start of study)

↓

F_0 dams delivery, F_1 pups evaluated daily from PND 1, on PND 4 pups cross-fostered, randomization

↓

Main Study			**Single dose TK study**
Reproductive subset	**Recovery subset**	**Pathology subset**	
20/sex/gp (1-4)	20/sex/gp (1-4)	12/sex/gp (1-4)	8/sex/control 16/sex/gp (2-4)
Treated from PND 7 to 70 (64 days)			Treated on PND 7
Clinical signs	Clinical signs	Clinical signs	not recorded: clinical signs, body weight, food consumption
Body weight	Body weight	Body weight	
Food consumption	Food consumption	Food consumption	
Postnatal evaluation Physical development Sensory development Motor activity Learning and memory	Postnatal evaluation Physical development Sensory development Motor activity Passive avoidance	Postnatal evaluation Physical development Sensory development Motor activity	
Repeat dose TK evaluation Blood collected at 0.5, 2, 8, 24 hr after dosing on PND 70. n=3/sex/gp/time point (1 animal/time point) Reproduction; Recovery Gp 1 first 7 M, 8 F; Gp 1 first 5 M, 4 F Gp 2 first 6 M, 6 F; Gp 2 first 6 M, 6 F Gp 3 first 7 M, 8 F; Gp 3 first 5 M, 4 F Gp 4 first 7 M, 6 F; Gp 4 first 5 M, 6 F		No TK evaluation	Single dose TK evaluation Blood collected at 0.5, 2, 8, 24 hr after dosing on PND 7. Control: 2 pups/sex/group/time point Treatment groups (2 to 4): 4 pups/sex/group/time point
Fertility assessment PND 106-122 Mating for 7 days Laprotomy on GD 13 Reproduction parameters			
No clinical pathology	Clinical pathology: blood and urine samples obtained at the end of recovery (PND ~112)	Clinical pathology: blood and urine samples obtained on PND 64-70	
Males necropsied 2-3 wk after the end of mating period. Gross pathology on all animals, reproductive tissues from all animals of all groups examined microscopically.	Necropsied 6 weeks after cessation of treatment (PND >112), protocol tissues from all animals of all groups examined microscopically.	Necropsied on PND 70, protocol tissues from all animals of all groups examined microscopically.	After blood collection animals were discarded with no examination.

For each male in the control and high dose groups of the reproduction subset, the right testis was prepared for histopathological examination. Testicular histopathological evaluation included assessment of the spermatogenic cycle. The left cauda epididymis was used for assessing sperm concentration (millions/gm of epididymis) and sperm motility. Following weaning, all F_0 dams and the pups not used in the study were euthanized and discarded without further examination. Representative samples of the protocol tissues (Table 3) were collected from all animals assigned to the Pathology and Recovery subsets and processed for microscopic examination which was performed on all tissues listed in Table 2 from all animals in all dose groups and for all unscheduled deaths/sacrifices in these two subsets.

TABLE 3.
TISSUES/ORGANS SAMPLED FOR HISTOPATHOLOGICAL EXAMINATION

W	P	Adrenal	W	P	Ovaries
	P	Aorta (thoracic)		P	Oviducts
	P	Bone and marrow (sternum) [d]		P	Pancreas
	P	Bone (femorotibial joint) [d]	W	P	Pituitary
W	P	Brain (cerebrum, cerebellum, midbrain and medulla oblongata)	W	P	Prostate
	P	Cecum		P	Rectum
	P	Colon		P	Salivary gland (mandibular)
	P	Duodenum		P	Sciatic nerve
	P	Epididymides [*]		P	Seminal vesicles
	P	Esophagus		P	Skeletal muscle
	P	Eyes [*]		P	Skin (inguinal)
				P	Spinal cord (cervical, thoracic, lumbar)
	P	Harderian gland	W	P	Spleen
W	P	Heart (including section of aorta)		P	Stomach
	P	Ileum	W	P	Testes [+]
	P	Jejunum	W	P	Thymus
W	P	Kidneys	W	P	Thyroid lobes (and parathyroids) [b]
	P	Lacrimal gland		P	Tongue
	P	Larynx		P	Trachea
W	P	Liver (sample of 2 lobes)		P	Urinary bladder
	P	Lungs (sample of 2 lobes)[e]	W	P	Uterus (horns, body, cervix)
	P	Lymph nodes – mandibular, mesenteric, and tracheobronchial		P	Ureters
	P	Mammary gland (inguinal) [b]		P	Vagina
	P	Nasal passage [a,d,e]		P	Macroscopic lesions
	P	Optic nerves [*,b]			Animal identification [a]

[a] Retained but not processed
[b] Examined histopathologically only if present in routine sections of eyes (optic nerves), thyroid lobes (parathyroid glands) or skin (mammary gland)
[d] Bone decalcified prior to sectioning
[e] Infused with neutral buffered 10% formalin
[*] Fixed in Zenker's Fluid for euthanized rats only
[+] Fixed in Bouin's Fluid for euthanized rats only

Results

Analysis of Formulations: The dosing formulations were stable for at least 24 hr at room temperature and for at least 22 days at 6°C. Mean concentrations of all samples analyzed were in the range of 88% to 112% of target concentrations.

Mortality: In the pre-weaning days, 4, 2, 8 and 4 pups were either dead or euthanized in the control, 1, 20 or 150 mg/kg/day groups, respectively. The majority of these pups died on PND 8 and had indications of gavage error. None of the deaths in the pre-weaning period were attributed to an effect of test substance. However, 12 of 13 deaths (or euthanizations) occurring during the post-weaning period (occurred between PND 22 and PND 127; time to death not dose-related) were attributed to the administration of valsartan and these deaths (or euthanizations) were mostly related to renal tubular nephropathy (Table 4).

TABLE 4
MORTALITY

Dose mg/kg/day	Animal no./pup no. Sex (PND)	Study Subset	Total # of decedents/sex	Mortality details
Pups F1 generation (F1) -- Pre-weaning period[1]				
Control	152/8 F (8) 154/6 F (9) 154/7 F (8) 154/8 F (8)	F1 F1 F1 F1	4 F	ED gavage related ED gavage related FD gavage related FD gavage related
1	251/2 M (18) 262/8 F (16)	F1 F1	1M, 1F	FD gavage related FD gavage related
20	354/1 M (8) 354/2 M (10) 354/3 M (8) 359/4 M(8) 351/6 F (15) 354/5 F (8) 354/6 F (8) 354/7 F (8)	F1 F1 F1 F1 F1 F1 F1 F1	4M, 4 F	ED gavage related ED undetermined ED gavage related FD gavage related FD undetermined ED gavage related ED gavage related FD gavage related
150	453/1 M (8) 455/4 M (8) 453/6 F (8) 457/8 F (8)	F1 F1 F1 F1	2M, 2F	ED gavage related ED gavage related FD gavage related FD gavage related
Reproductive subset (RS) -- Post-weaning period[2]				
1	2004 M (137)	RS	1M	FD gavage related
20	3005 M (24) 3006 M (24)	RS RS	2M	FD gastric ulcer ED gastric ulcer
150	4009 M (127) 4513 F (23)	RS RS	1M, 1F	FD tubular nephropathy FD undetermined
Recovery subset (R) -- Post-weaning period[2]				
20	3042 M (86)	R	1 M	ED tubular nephropathy
150	4033 M (23) 4531 F (70)	R R	1M, 1F	FD gastric ulcer FD tubular nephropathy

Pathology subset (P) [3]				
20	3561 F (69)	P	1 F	FD tubular nephropathy
150	4061 M (24)	P	2 M, 2F	FD undetermined
	4067 M (23)	P		FD undetermined
	4563 F (22)	P		FD undetermined
	4569 F (23)	P		FD undetermined

FD: found dead, ED: euthanized, PND: postnatal day: Sex M = male, F = female; F_1 = F_1 generation subset; RS = Reproductive subset; R = recovery subset; P = Pathology subset

1: Mortality in the pre-weaning period (based upon macroscopic observations) was not attributed to the administration of valsartan.

2: Mortality in the post-weaning period (based upon macroscopic observations) was attributed to the administration of valsartan in 7 of 8 animals.

3: Mortality in the pathology subset of animals (based upon macro and microscopic observations) was attributed to the administration of valsartan.

Clinical Signs: There were no test substance-related clinical signs in any of the groups during the pre-weaning period. Dose-related salivation was noted during the post-weaning and recovery periods.

Body Weights: Mean body weight gain between PND 14 and 21 was statistically significantly but non-dose-dependently decreased ($p < 0.05$) for both sexes in all dose groups from the main study relative to control. However during the post-weaning period (PND 24 to 69), a higher than control body weight gain, which was not statistically significant, was noted for all dose groups except for the high dose males (Table 5). There was not much difference between the body weights of valsartan-treated groups and their respective control groups for reproduction and recovery subsets from PND 70 to the end of the study.

TABLE 5
GROUP MEAN BODY WEIGHT GAINS (GRAMS) FOR MAIN STUDY

Dose mg/kg/day	Pre-weaning				Post weaning	
	Postnatal days 7-14		Postnatal days 14-21		Postnatal days 24-69	
	Male	Female	Male	Female	Male	Female
Control	14.78	14.65	17.05	16.68	248.4	137.9
1	15.08	14.69	13.52	12.53	263.6	149.0
20	15.68	15.10	13.73	13.04	250.7	142.0
150	15.28	14.80	13.40	12.80	238.5	142.7

Food Consumption: Food intake was significantly and non-dose-dependently reduced for all dose groups relative to control ($p < 0.05$) up to PND 35. The food consumption recovered thereafter and was higher than control until the end of the dosing period and the tendency continued in the reproduction and recovery subsets.

Postnatal Development: All developmental landmarks and functional test results were similar between treated and control groups.

Reproductive Performance: No effect of treatment on the mean day to mating, the mating and fertility indices and the conception rate. The mean numbers of corpora lutea,

implantation sites, live and dead embryos, resorptions and pre and post implantation losses were unaffected by treatment with valsartan. There was no effect of valsartan on sperm motility, spermatozoa count or spermatozoa morphology.
Hematology: There were no changes in the hematology parameters.
Clinical Chemistry: A statistically significant and dose-related increase in blood urea nitrogen was noted for both sexes at the end of treatment (PND 64-70). A slight but statistically significant elevation in creatinine was noted for females at all dose levels. The changes in urea and creatinine were associated with macroscopic and microscopic renal changes. Non-dose-related increases in cholesterol were noted for both sexes at all dose levels. A mild and non-dose-related increase above concurrent control levels of triglycerides was noted in males at all doses. In recovery subsets, still significant increases in urea and creatinine were noted for both sexes at all dose levels (Table 6).

TABLE 6
NOTEWORTHY CHANGES IN CLINICAL CHEMISTRY PARAMETERS IN PUPS TREATED ORALLY WITH VALSARTAN FOR 9 WEEKS

Daily dose (mg/kg)	0 (Control; Group 1)		1 (Group 2)		20 (Group 3)		150 (Group 4)	
Data from Pathology subset, sampled at the end of treatment, PND 64-70								
Number of animals	M: 12	F: 12	M: 11	F: 11	M: 10	F: 12	M: 11	F: 11
Urea (mg/dL)	16.1	18.8	23.8**	25.1*	29.6***	33.2***	26.4***	34.3***
Creatinine (mg/dL)	0.4	0.4	0.5	0.5**	0.5*	0.5*	0.4	0.5***
Cholesterol (mg/dL)	65.4	57.4	97.9***	70.5*	87.7**	69.4*	85.2**	71.0*
Triglycerides (mg/dL)	104	67	160	76	152	74	128	58
Data from Recovery subset, sampled at the end of recovery, PND ~114								
Number of animals	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10	M: 10	F: 10
Urea (mg/dL)	15.6	17.5	25.8**	23.5*	26.6**	26.3**	28.5***	29.8***
Creatinine (mg/dL)	0.47	0.46	0.55*	0.54	0.55*	0.6**	0.62**	0.6***
Cholesterol (mg/dL)	68.1	55.0	104.5*	61.9	119.4***	60.0	89.8	63.1
Triglycerides (mg/dL)	105.1	62.3	159.1	53.9	186.8	63.5	109.4	85.6

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Urinalysis: A dose-dependent lower than control mean specific gravity was noted for both sexes at all dose levels ($p <0.05$ at 20 or more mg/kg/day) for the pathology subset that continued until the end of the recovery period.
Organ Weights: The following findings were noted for the pathology subset (animals sacrificed at the end of treatment): Dose-dependent decreases in mean absolute brain weight were noted for males at all doses relative to control ($p <0.01$ for mid and high dose groups); both mean absolute and relative (to final body weight) heart weights in high dose males were decreased ($p <0.01$) relative to control; nondose-dependent increases in absolute prostate weights (5% to 19%, $p >0.05$) and dose-dependent elevations in relative prostate weights (7% to 27%, $p <0.01$ at the high dose) were noted relative to control. A similar change was not noted for males sacrificed either at the end of recovery or after the mating periods. There were no histopathological correlates to these increased prostate

weights. For the reproductive subset males, nondose-related increases in mean absolute ($p > 0.05$) and relative (to final body weight, $p < 0.05$ for mid and high dose groups) epididymides weights were noted relative to the control group. The sponsor considers these changes to be secondary to a decrease in final body weights.

Gross Pathology: Macroscopic drug-related pathology was observed in the kidneys with increased incidence at all dose levels for both sexes in all three subsets, at the end of treatment, at the end of recovery period and at the end of the fertility study (Table 7). The dilatation of the pelvis correlated with microscopic pelvic dilatation, the irregular surface correlated with tubular nephropathy and the clear pale fluid was considered to be an accumulation of urine in the dilated renal pelvis. The severity of these renal changes had a dose responsive pattern, was slightly greater in males and considered by the sponsor to reflect an excessive pharmacological action of valsartan on AT-1 receptors in the kidney.

TABLE 7
INCIDENCE OF GROSS PATHOLOGICAL FINDINGS IN ALL RATS

Subsets	**Pathology**				**Recovery**				**Reproductive**			
Group #[1]	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
	MALES											
No. Examined	12	11	10	13	20	20	20	21	20	20	20	20
Kidney												
Area dark	-	-	1	-	-	-	-	1	-			
Area pale	-	-	-	1	-	-	-	-	-			
Cyst					-	-	1	1	-	-	1	-
Dilatation pelvis	2	11	9	11	3	17	20	16	-	20	20	19
Discoloration pale	-	-	-	1	-	-	-	1	-	1	-	1
Fluid pale clear	-	3	1	7	1	-	-	-	-	-	-	-
Surface irregular	-	7	7	7	-	12	19	16	-	19	18	19
	FEMALES											
No. Examined	12	11	12	13	20	20	20	20	20	20	20	21
Kidney												
Area dark	-	-	-	-	-	-	1	-	-	1	-	-
Area pale	-	-	1	-	-	1	-	-	-	3	7	5
Cyst					-	-	-	-	-	1	-	-
Dilatation pelvis	1	7	8	9	2	12	11	11	3	12	16	13
Discoloration pale	-	-	-	1	-	-	-	1	-	-	1	1
Fluid pale clear	1	2	-	3	-	-	-	1	-	-	-	-
Surface irregular	-	3	6	6	-	8	-12	17	-	6	15	15

Groups 1, 2, 3 and 4 are, respectively, Control, 1, 20 and 150 mg valsartan/kg/day

Histopathology: In pathology (Table 8) and recovery (Table 9) subsets, kidneys of all treated groups exhibited a spectrum of test substance-related histopathologic lesions. Kidneys from pathology subset animals in all valsartan-treated groups had tubular nephropathy characterized by extensive areas of tubular basophilia with basement membrane thickening, frequent dilated and cystic tubules, interstitial mononuclear cell infiltrates, occasional fibrosis, renal pelvic epithelial hyperplasia, and protein casts. These changes often resulted in an irregular capsular outline, correlating with the irregular

surface (as noted under Gross Pathology). Some early death animals had increased basophilia with casts, tubular epithelial necrosis, single cell necrosis, and dilated tubules. In a majority of animals, this was accompanied by a varying degree of renal pelvic dilatation. Also observed in most of the drug-treated animals was minimal juxtaglomerular hypertrophy/hyperplasia, characterized by prominent glomerular arterioles. The renal changes were slightly greater in severity in males than females and showed a dose response pattern. In the recovery subset, in all dose groups, kidneys had persistence of tubular nephropathy and pelvic dilatation at approximately equivalent incidences and severities as that of pathology subset animals with minimal reversibility for the tubular nephropathy in females and minimal reversibility of the pelvic dilatation in males. Although many of the changes described for the pathology subset nephropathy were still present, the nephropathy in the recovery group animals additionally had increased lymphoplasmacytic infiltrates and fibrosis, hyperplastic tubules, and hypertrophic tubules as compared to the pathology subset animals. Some glomeruli were sclerotic and senescent. Only two high dose males in the recovery subset had persistence of the juxtaglomerular hypertrophy/hyperplasia, indicating almost complete reversibility of that change. The sponsor considers these renal changes as an exaggerated or excessive pharmacological action of the test article at the dose levels administered in this study. In the stomach, minimal vacuolation of the epithelium of the nonglandular mucosa at and adjacent to the limiting ridge was noted in a few males at all dose levels and in a few females from the high dose group of the pathology subset (Table 8). Vacuoles were intracytoplasmic, unilocular and occasionally multilocular, and often with pale, eosinophilic to amphiphilic fluid content. Due to the minimal degree of change, the low incidence and the absence of either mucosal hyperplasia, erosion or ulceration, the vacuolation of the nonglandular stomach was not considered adverse by the sponsor. In addition, none of stomach changes were noted in the recovery subset animals. There were no adverse findings in the histological examination of the right testis (included assessment of the spermatogenic cycle, spermatozoa count, morphology and sperm motility).

TABLE 8
INCIDENCE AND SEVERITY OF TREATMENT-RELATED HISTOPATHOLOGICAL FINDINGS IN PATHOLOGY SUBSET ANIMALS

Tissue/Finding	Sex	Males				Females			
	Dose (mg/kg/day)	0	1	20	150	0	1	20	150
Kidney	No. examined	12	11	10	13	12	11	12	13
Juxtaglomerular Hypertrophy/hyperplasia									
	Total no. affected	0	11	10	13	0	10	12	12
	Minimal	—	6	2	4	—	8	7	4
	Slight	—	5	8	9	—	2	5	8
Nephropathy, tubular									
	Total no. affected	0	11	10	13	0	10	12	13
	Minimal	—	4	1	—	—	6	3	2
	Slight	—	5	3	6	—	4	8	7
	Moderate	—	2	6	7	—	—	1	4
Dilatation, pelvis									
	Total no. affected	2	11	9	11	1	8	8	9
	Minimal	2	4	1	—	1	2	4	4
	Slight	—	5	3	3	—	6	4	4
	Moderate	—	2	5	8	—	—	—	1
Stomach	no. examined	12	11	10	13	12	11	12	13
Vacuolation: Nonglandular epithelium									
	Total no. affected	—	3	2	4	—	—	—	5
	Minimal	—	3	2	4	—	—	—	5
Infiltration: eosinophilic cell									
	Total no. affected	—	2	1	1	—	—	—	3
	Minimal	—	2	1	1	—	—	—	3

TABLE 9
INCIDENCE AND SEVERITY OF TREATMENT-RELATED HISTOPATHOLOGICAL FINDINGS IN RECOVERY SUBSET ANIMALS

Tissue/Finding	Sex	Males				Females			
	Dose (mg/kg/day)	0	1	20	150	0	1	20	150
Kidney	No. examined	20	20	20	21	20	20	20	20
Juxtaglomerular Hypertrophy/hyperplasia									
	Total no. affected	0	0	0	2	0	0	0	0
	Minimal	—	—	—	2	—	—	—	—
Nephropathy, tubular									
	Total no. affected	0	19	20	21	0	19	18	19
	Minimal	—	7	5	4	—	9	8	6
	Slight	—	9	4	14	—	10	10	12
	Moderate	—	3	9	2	—	—	—	1
	Marked	—	—	2	1	—	—	—	—
Dilatation, pelvis									
	Total no. affected	3	18	20	18	2	13	15	14
	Minimal	3	5	1	2	2	5	8	5
	Slight	—	10	15	9	—	7	6	8
	Moderate	—	3	4	6	—	1	1	1
	Marked	—	—	—	1	—	—	—	—

Toxicokinetics: Peak plasma concentration times were reduced with increase in dose on PND 7, with females (at the low and mid dose levels) developing peak levels later than males. On the other hand, peak levels were reached 0.5 hr post dose at all dose levels after the last dose on PND 70. The plasma concentrations increased with increase in dose but were not dose proportional. The exposure to valsartan was several fold higher on PND 7 (single dose) than on PND 70 at all dose levels (Table 10). There were no gender differences in any groups.

TABLE 10

SUMMARY OF MEAN TOXICOKINETIC PARAMETERS FOR VALSARTAN IN NEONATAL AND JUVENILE MALE (TOP) AND FEMALE (BOTTOM) RATS ON DAY 1 (PND 7) OF TREATMENT AND AFTER 9 WEEKS (PND 70) OF TREATMENT WITH VALSARTAN

Dose Valsartan	1 mg/kg/day		20 mg/kg/day		150 mg/kg/day	
	Group 6	Group 2	Group 7	Group 3	Group 8	Group 4
Parameter (Units)	Day 7 Single dose	Day 70 Last dose	Day 7 Single dose	Day 70 Last dose	Day 7 Single dose	Day 70 Last dose
t_{max} (h)	8	0.5	2	0.5	0.5	0.5
C_{max} (µg/mL)	0.916	0.250	14.0	5.04	117	21.7
C_{max}/Dose (µg/mL)/(mg/kg/day)	0.916	0.250	0.700	0.252	0.780	0.145
AUC_{0-24h} (µg*h/mL)	16.0	0.505	268	15.0	608	82.5
AUC_{0-24h} /Dose (µg*h/mL)/(mg/kg/day)	16.0	0.505	13.4	0.750	4.06	0.550

Dose Valsartan	1 mg/kg/day		20 mg/kg/day		150 mg/kg/day	
	Group 6	Group 2	Group 7	Group 3	Group 8	Group 4
Parameter (Units)	Day 7 Single dose	Day 70 Last dose	Day 7 Single dose	Day 70 Last dose	Day 7 Single dose	Day 70 Last dose
t_{max} (h)	24	0.5	8	0.5	0.5	0.5
C_{max} (ng/mL)	0.653	0.230	15.9	6.51	92.9	28.5
C_{max}/Dose (µg/mL)/(mg/kg/day)	0.653	0.230	0.795	0.326	0.619	0.190
AUC_{0-24h} (µg*h/mL)	14.3	0.430	320	14.9	957	101
AUC_{0-24h} /Dose (µg*h/mL)/(mg/kg/day)	14.3	0.430	16.0	0.744	6.38	0.672

OVERALL SUMMARY AND EVALUATION

Background

Valsartan is a non-peptidic, competitive, potent, orally-effective angiotensin II receptor blocker that selectively blocks the AT-1 receptor located on the blood vessel, heart, adrenal glands and the distal renal tubule. Thus, blockade of AT-1 receptors by valsartan results in decreased vascular resistance and intravascular volume. Valsartan is approved for the treatment of hypertension, reduction of cardiovascular mortality in patients with post-myocardial infarction and treatment of heart failure. The use of drugs acting on the renin angiotensin system among pregnant women in middle and late trimesters has resulted in adverse outcomes for some pregnancies. The most consistent finding reported in the literature with the maternal use of these drugs is fetal renal dysfunction which is manifested prenatally as oligohydramnios, renal tubular dysgenesis, and postnatally as neonatal anuria. These findings are expected given the fact that angiotensin II plays a critical role in the maintenance of normal embryonic and postnatal kidney development, fetal arterial blood pressure, and in the regulation of fetal glomerular filtration rate and renal blood flow. Thus, valsartan therapy in newborns and/or pediatric population is considered with caution. According to the sponsor, valsartan has not been extensively tested in children. The purpose of the present program was to obtain dosing information and data on the efficacy and safety of valsartan in children 1-16 years of age with hypertension. To this effect, Novartis corporation conducted a developmental toxicity study in which 7 day old rats were treated with valsartan for 64 days.

Postnatal Toxicity Study

Valsartan was administered to neonatal rats from postnatal day 7 to postnatal day 70 (64 doses) at doses of 1, 20 or 150 mg/kg/day. At each dose level, the pups were divided into subsets, those that were necropsied at the end of treatment (pathology subset), those that were necropsied 6 weeks after the end of treatment (recovery subset) and those that underwent fertility assessment beginning on PND 106 (reproductive subset). There were 12 treatment-related deaths, all occurring in the post-weaning period and some of which were attributed to valsartan-induced renal tubular nephropathy. Statistically significant reductions in food consumption and body weight gain relative to concurrent control were noted at all dose levels as were statistically significant increases in serum urea nitrogen and creatinine. Macroscopic findings of pale discoloration, pelvic dilatation and irregular surface of kidney, and microscopic findings of renal nephropathy and pelvic dilatation were noted at the end of treatment (PND 70) and in recovery (PND 114) and reproductive (PND >126) subsets of the valsartan treated rats. These findings were equally distributed amongst treated groups irrespective of dose level and were not seen in the control animals (except for 2 males and 1 female which had minimal pelvic dilatation; incidence and severity greater in the treated groups). Tubular nephropathy was characterized by extensive areas of tubular basophilia with basement membrane thickening, frequent dilated and cystic tubules, interstitial mononuclear cell infiltrates, occasional fibrosis, renal pelvic epithelial hyperplasia and protein casts. In the recovery group animals, nephropathy additionally included increased lymphoplasmacytic infiltrates and fibrosis, hyperplastic tubules and hypertrophic tubules. Also observed in most of the drug-treated animals was a minimal juxtaglomerular

hypertrophy/hyperplasia characterized by prominent glomerular arterioles in all drug treated animals at the end of the treatment period. It was absent in the control animals and showed almost complete reversibility as only 2 of 21 high dose recovery group males showed persistence of juxtaglomerular hypertrophy/hyperplasia (13 of 13 high dose males and 12 of 13 high dose females in the pathology subset had presented with juxtaglomerular hypertrophy/hyperplasia) . The renal changes were slightly greater in severity in males than females and showed a dose response pattern. The sponsor contends that all of the above renal effects in neonatal rats represent an expected exaggerated pharmacological effect of drugs affecting the RAS. This reviewer notes that the highest dose administered in this study was not higher than that administered in previous studies in adult rats (up to 600 mg/kg/day for 3 months) in which a minimal increase in incidence of tubular hyperplasia, tubular basophilia and hypertrophy of the renal glomerular afferent arterioles were noted at doses of 200 or more mg/kg/day. Furthermore, these effects were completely reversible. This suggests that the developing kidneys in pups are more sensitive to angiotensin receptor antagonists. A few males at all dose levels and females in the high dose group had minimal vacuolation of the nonglandular mucosa of the stomach. This effect was not noted in the recovery subset. A NOAEL was not determined for this study.

The exposure to valsartan was much higher on PND 7 (single dose) than on PND 70. For doses of 1, 20 and 150 mg/kg/day, the $AUC_{0\text{-}24h}$ decreased between day 7 and day 70 post partum by a factor 32-33, 18-21 and 7-9 (male-female), respectively. The data suggest that in the 7 day old rats, a large portion of the administered valsartan was not metabolized and tended to remain in circulation for an unknown period of time (which was not determined in the study). A similar association of increased metabolism with aging of the pup has been documented for another drug affecting the RAS, ramipril; AUC values were substantially higher when ramipril was administered on PND 14 than when administered on PND 21 (see ramipril pediatric study in our review of NDA 19,901/SLR-043). According to the sponsor, the drug metabolizing enzymes in the rat liver are not fully expressed by PND 7 and/or gastric permeability is greater in 7 day old rats than in adult rats. Thus, systemic exposure to valsartan was particularly high at a time when nephrogenesis was not yet complete.

A literature search reveals that in rats major parts of nephrogenesis occur 7 to 13 days after birth[1,2] whereas in humans, nephrogenesis is a prenatal event, which undergoes marked acceleration in mid gestation and is complete by 34 to 36 weeks of gestation.[3,4] Important indicators of renal function, such as ability to concentrate urine and glomerular filtration rate (GFR), do not mature or reach adult level in either species until well after birth (rats, 2-5 weeks of age[4,8]; human infants, 12-24 months of age[3-5]). Neonatal ACE inhibition or AT-1 receptor antagonism during the first 24 days of life in rats[1] and in pigs[6] induces persistent, irreversible abnormalities in renal morphology including impaired urinary concentrating ability in adult life long after the rats have been taken off treatment.[7] Thus, the vulnerable time frame is restricted to the preweaning period, which coincides with the completion of nephrogenesis, a period of marked tubular growth and differentiation, and functional development, suggesting a pivotal role for angiotensin II in these processes.[1,7] It is not known exactly what postnatal time interval the rat kidney is vulnerable to an interruption of the RAS. In a previously conducted juvenile rat toxicity study for the ACE inhibitor, ramipril (NDA 19,901/SLR-043), a single dose of ramipril (3 mg/kg) on PND 14 (approximately equivalent to a month-old child in development of the

kidney) produced persistent, irreversible histopathological abnormalities in the developing kidney. In contrast, a single dose of ramipril (30 mg/kg) administered on PND 21 (approximately equivalent to an 18-23 month-old child in development of the kidney) did not produce any observable (renal or other) effects. A repeat dose study (daily doses beyond weaning, >PND 21), with measurement of drug effects on overall growth of organ systems that develop postnatally (e.g., skeletal, renal, pulmonary, neurological, immunologic, and reproductive systems) is not available.

Though the kidney damage observed in rats might not have occurred had valsartan treatment been restricted to weanling animals (age equivalent to human infants at least 1 year old), as was the case for ramipril, there is no data available to allow us to conclude such a limitation on vulnerability to valsartan.

In conclusion, daily oral dosing of neonatal/juvenile rats with valsartan from postnatal day 7 (approximately equivalent to 36 weeks of human gestation) to postnatal day 70 at doses as low as 1 mg/kg/day produced persistent, irreversible histopathological abnormalities in the developing kidney. Proposed labeling (b) (4) but non-clinical studies fall short of demonstrating that it is safe to administer between the ages of 1 and 2. Thus, it is recommended that Diovan® not be administered to children or infants under the age of 2 years.

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/s/

Gowra Jagadeesh
10/4/2007 12:07:03 PM
PHARMACOLOGIST

Charles Resnick
10/5/2007 11:32:15 AM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

STATISTICAL REVIEW(S)

Medical-Statistical Review

Medical Reviewer: Shari Targum, M.D.
Statistical Reviewer: Valeria Freidlin, Ph.D.

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.

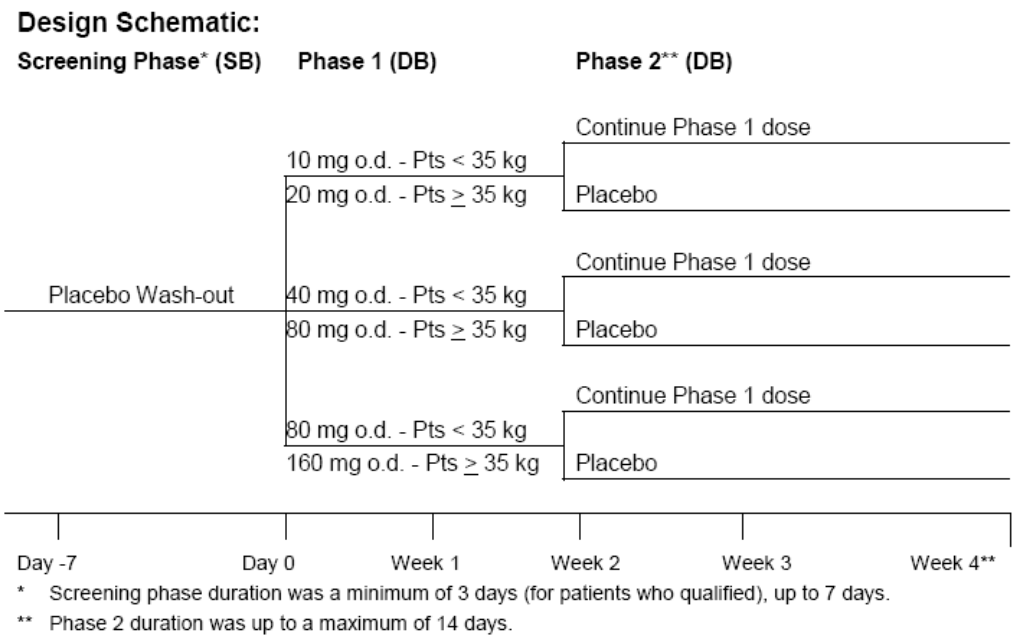


Figure 1. Study Design: A2302: screening and double-blind phases.

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.

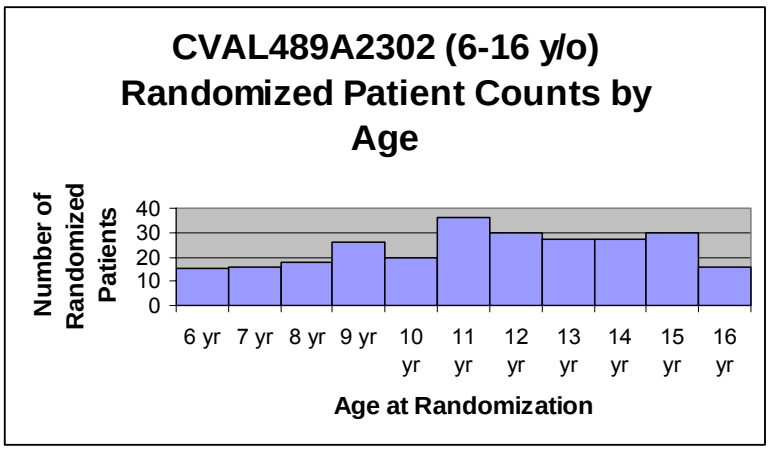


Figure 2. Randomized patient counts by age

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.

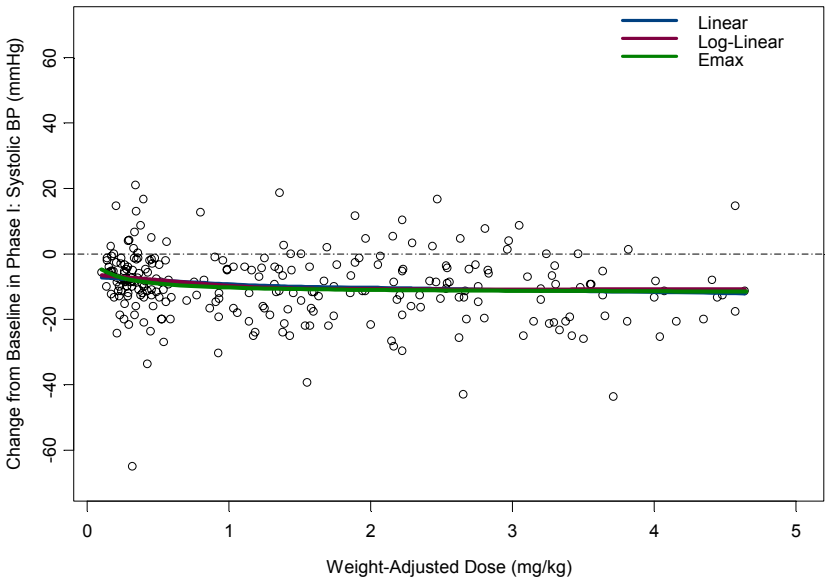


Figure 3. Scatter plot for the change from baseline to end of Phase 1 in mean sitting SBP vs. weight-adjusted dose (mg/kg)

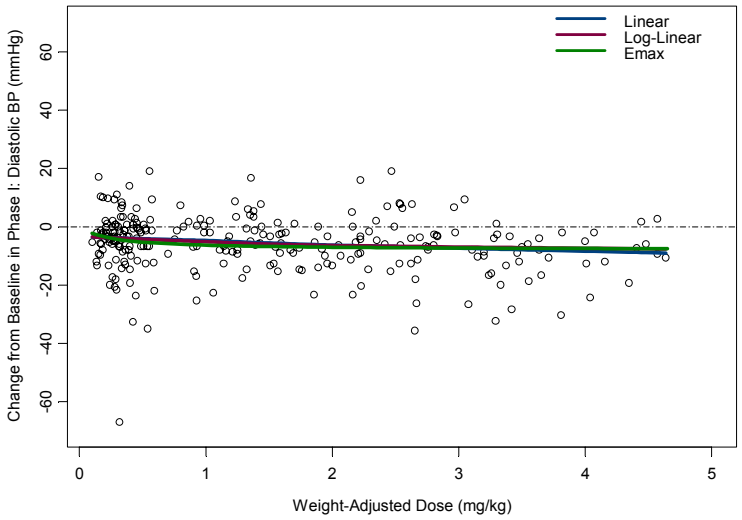


Figure 4. Scatter plot for the change from baseline to end of Phase 1 in mean sitting DBP vs. weight-adjusted dose (mg/kg)

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:

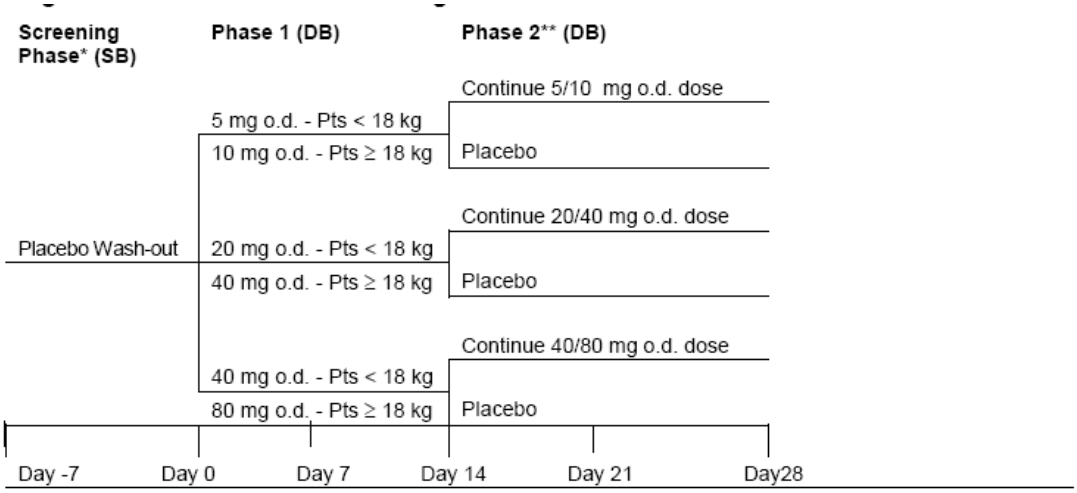
1. A single-blind placebo washout phase for up to one week (Screening);
2. A two-week, double-blind phase where patients were randomized in a 2:1:2 ratio to low, medium and high-dose valsartan, respectively (Phase 1). Patients < 18 kg received 5, 20 or 40 mg valsartan QD, respectively; patients > 18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

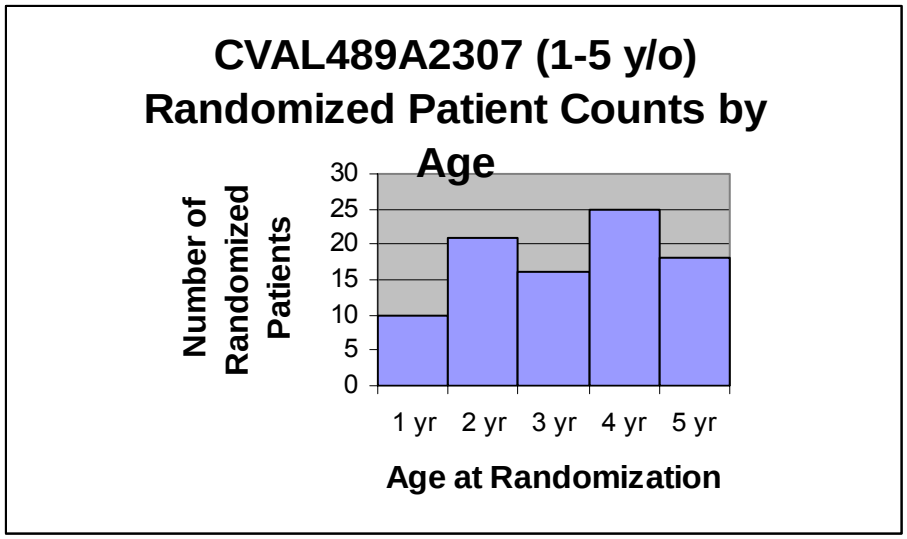


Figure 6. A2307: Histogram of Randomized Patients by Age

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.

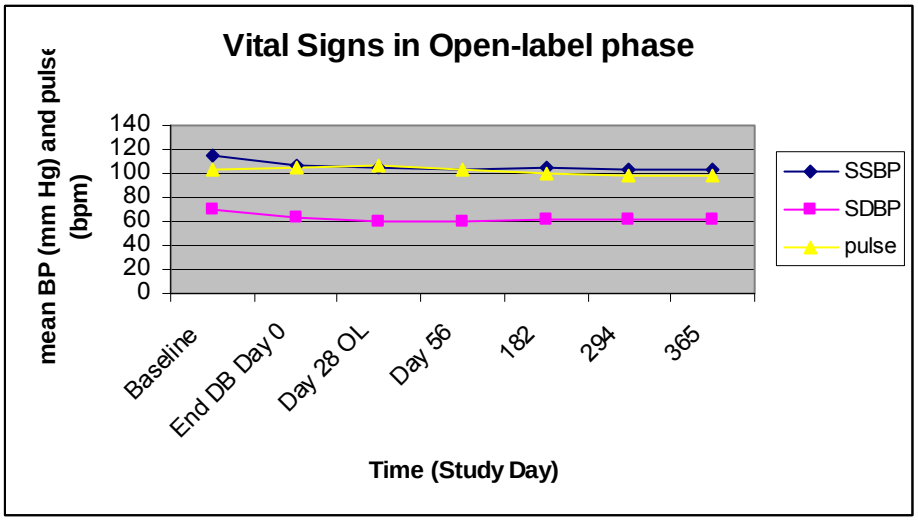


Figure 7. A2307: Vital signs in OL phase

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/

Shari Targum
10/4/2007 11:54:28 AM
MEDICAL OFFICER

Valeria Freidlin
10/4/2007 11:56:56 AM
BIOMETRICS

James Hung
10/4/2007 03:05:32 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Pharmacometrics Review
Office of Clinical Pharmacology

NDA:	**21-283**
Compound:	**Valsartan**
Submission Dates:	**May 31, 2007**
Applicant:	**Novartis**
Type of submission:	**sNDA (pediatrics)**
Pharmacometrics Reviewer:	**Yaning Wang, Ph.D.**
Secondary Reviewer:	**Jogarao Gobburu, Ph.D.**

Question 1:
Explain why there was no relationship between dose and response in one study (A2307), but there was a relationship between dose and response in another study (A2302).

Answer: The lack of dose-response response relationship in A2307 is due to the following reasons:

1. The significantly higher drug exposure levels in A2307 relative to A2302 across low, middle and high dose groups suggest that the exposure range in A2307 is most likely on the plateau region of an exposure response curve, which is one possible result for type C design (doses too high causing no slope but slower withdrawal on active treatment).
2. Younger patients (1-5 years old) in A2307 may have smaller plateau response (change from baseline) than older kids (6-16 years old) in A2302 due to lower baseline blood pressure.
3. Younger patients (1-5 years old) in A2307 may have a different exposure response relationship (plateau response is achieved with lower drug exposure) compared to older kids (6-16 years old) in A2302.

Question 2:
Explain the “flatness” of the weight-adjusted (mg/kg) dose-response curve and why the data did not fit a linear, log-linear, or Emax model.

Answer: Given the large variability in the raw data (SD=9-11 mmHg) relative to the mean signal we are trying to detect (2-3 mmHg) and the lack of a placebo group in the phase 1 period, it is not surprising to see a relatively flat dose-response on the raw data scale. A summarized plot (mean$\pm$SE) will demonstrate the dose-response more clearly (Figure 6). The sponsor applied three different models to fit the data. The intention is to show the significant dose-response relationship irrespective of the model structure.

Technical Details:

Detailed trial designs for A2302 and A2307are referred to the joint review by Dr. Shari Targum and Dr. Valeria Freidlin. Detailed study design for A2305 is referred to Dr. Peter Hinderling's review.

Even though A2302 and A2307 are comparable (slightly higher for A2307) on a mg/kg dosing regimen (Figure 1), the exposure of the drug is expected to be higher for study A2307 because the suspension formulation used in A2307 has 56% higher bioavailability than the tablets used in A2302. Due to the lack of pharmacokinetic measurements in A2302 and A2307, individual drug exposure was predicted based on the following equation:

$$AUC_i = \frac{Dose_i}{CL/F_i} \quad \text{(Equation 1)}$$

where i represents ith subject, AUC_i is the predicted area under the concentration curve for valsartan, $dose_i$ is the dose used, and CL/F_i is the apparent clearance and calculated by $CL/F_i = 0.206 \cdot Weight_i^{0.708}$, a relationship derived by applying linear regression of $\log(CL/F_i)$ against $\log(Weight_i)$ for 26 subjects in A2305 (Figure 2, Table 1).

Figure 1. Comparison of dose (mg/kg) between A2302 and A2307

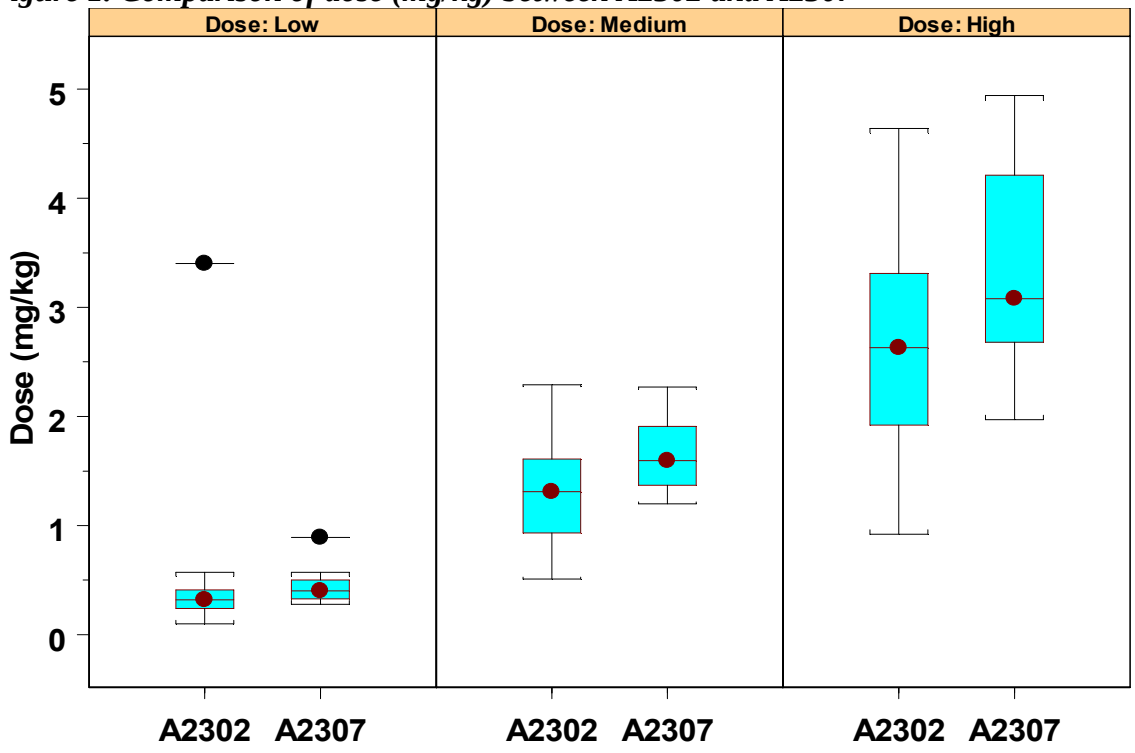


Figure 2. Relationship between apparent clearance (CL/F) and weight in A2305 (circles are observed values, solid line is the model predicted values and shaded area is the 95% confidence interval for mean prediction)

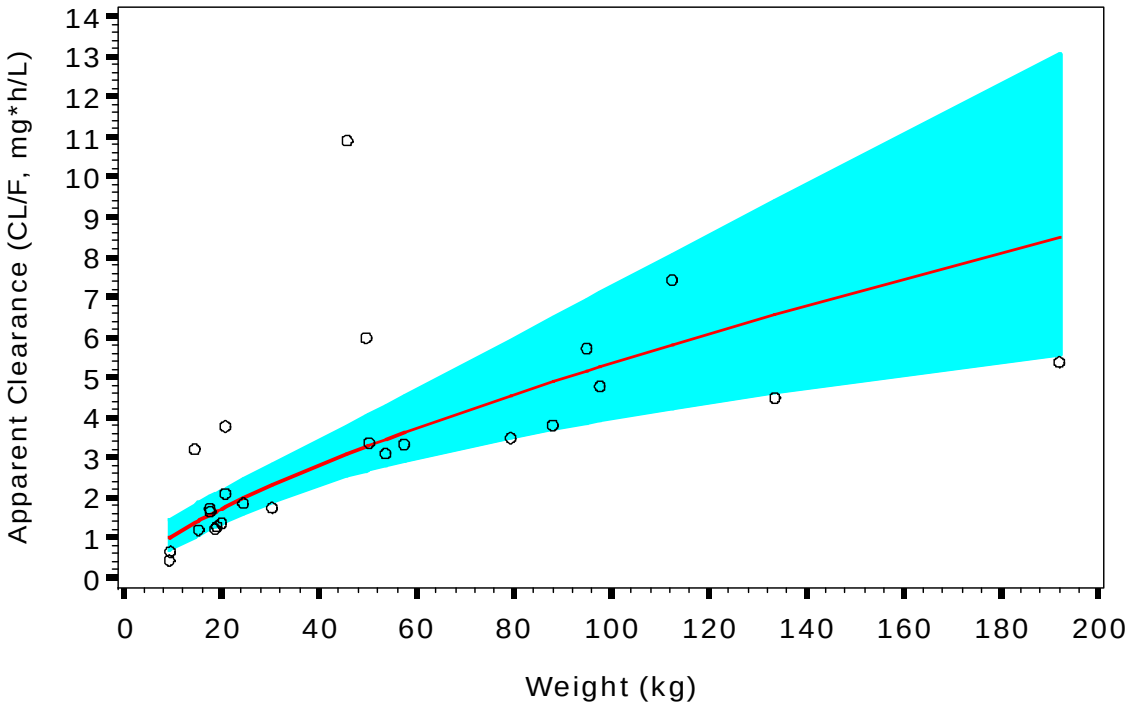


Table 1. Regression analysis of log(CL/F) versus log(Weight)

	Estimate	Standard Error	P-value	exp(Intercept)
Intercept	-1.581	0.409	0.0008	0.206
Slope	0.708	0.111	<.0001	-

Since Equation 1 is derived based on suspension formulation and various strengths of tablets were used in A2302 (Table 2), a factor of 1.56 was used to adjust bioavailability F_i for tablets (F_i/1.56). A factor of 1.12 was further used to adjust F_i (F_i/1.56*1.12) for 10 mg and 20 mg tablets and 1.09 (F_i/1.56*1.09) for 80 mg tablets because 10 mg and 80 mg tablets were specifically developed for study A2302 and they have slightly higher bioavailability compared to the marketed tablets. The adjustment factors (1.56, 1.12 and 1.09) were based on the bioavailability results from CVAL489A2301-BA, CVAL489A2304, and CVAL489J2308 (See Dr. Peter Hinderling's review for details of these 3 studies).

Table 2. Phase 1 dose groups by weight for A2302

Weight	**Low Dose Group**		**Medium Dose Group**		**High Dose Group**	
	Valsartan tablets	**Placebo tablets**	**Valsartan tablets**	**Placebo tablets**	**Valsartan tablets**	**Placebo tablets**
< 35 kg	10 mg (1 round*)	2 placebo (1 round*+ 1 ovaloid**)	40 mg (1 round*)	2 placebo (1 round*+ 1 ovaloid**)	80 mg (1 ovaloid**)	2 placebo (2 round*)
≥ 35 kg	2x10 mg (2 round*)	1 placebo (1 ovaloid**)	80 mg (1 ovaloid**)	2 placebo (2 round*)	160 mg (1 ovaloid**)	2 placebo (2 round*)

* Round tablets were yellow and contained 10 mg, 40 mg or placebo.
** Ovaloid tablets were orange and contained 80 mg, 160 mg or placebo.

The significantly higher drug exposure levels (Figure 3, Table 3) in A2307 relative to A2302 across low, medium and high dose groups suggest that the exposure range in A2307 is most likely on the plateau region of an exposure response relationship (Figure 4). Given the significantly slower withdrawal result in active treatment group compared to placebo group in phase 2 of A2307 (-1.5 mmHg for valsartan and 1.5 mmHg for placebo, p=0.0217), the lack of dose-response in phase 1 is most likely due to too high doses, which is one possible result for type C design. A sensitivity analysis was conducted to show that if the subjects with lower exposure (predicted AUC<3.27 mg*h/L, the minimum AUC in A2307) are removed from A2302, even study A2302 cannot show a significant dose-response relationship (Table 4), suggesting the subjects with low exposure play a key role in establishing the dose-response relationship for phase 1 part of the study where no placebo group was included.

Due to the lower baseline blood pressure for younger patients (1-5 years old) in A2307 (Figure 5), a smaller maximum change from baseline (plateau response) may be expected, which is indicated by the mean changes within each quartile of AUC (Figure 4) or weight-adjusted dose (**Error! Reference source not found.**).

Figure 3. Comparison of individual predicted AUC between A2302 and A2307

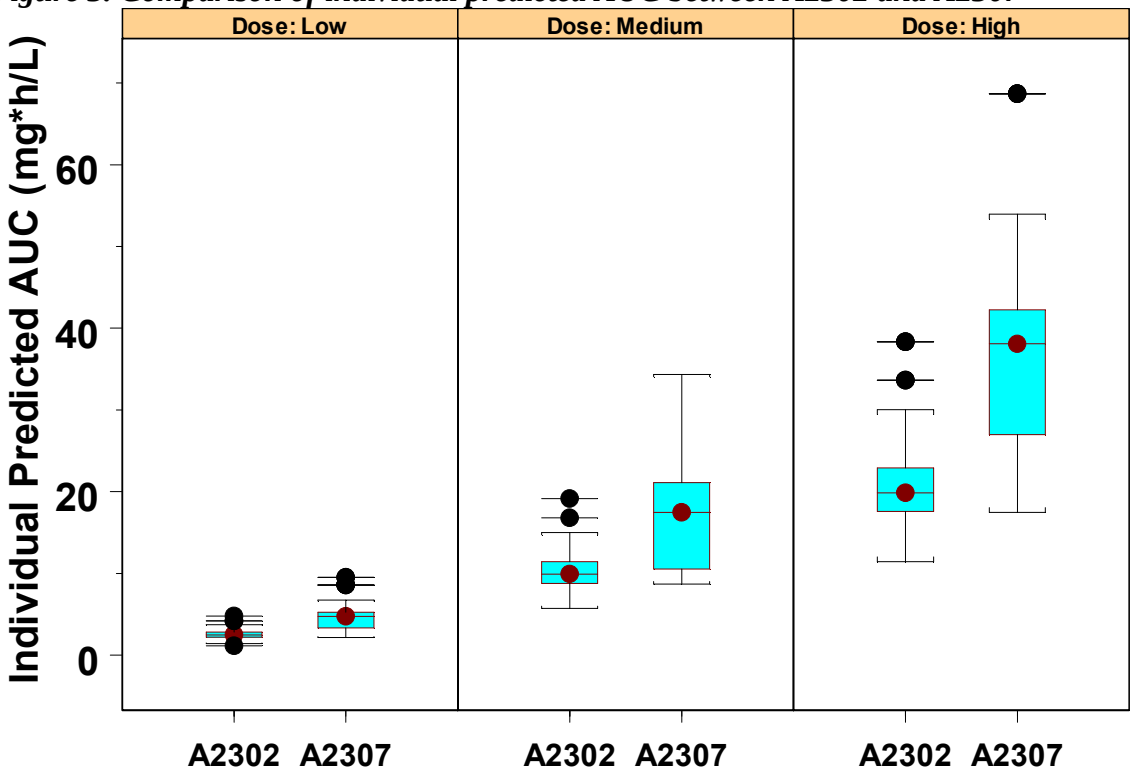


Table 3. Comparison of individual predicted AUC between A2302 and A2307

Group	A2302* (Reference)	A2307* (Test)	Ratio of Geometric Means**	90%CI for Ratio of Geometric Means**
Low Dose	3.2 (0.8)	4.6 (1.2)	1.43	1.32 -1.50
Medium Dose	13 (3.4)	17.8 (3.7)	1.39	1.24 -1.60
High Dose	26 (6.8)	36.4 (8.1)	1.42	1.30 -1.50

*: mean (SD)

**: Log-transformed data were analyzed

Figure 4. Exposure response for A2302 (black dot) and A2307(red circle) (left: raw data; right: mean±SE within each quartile; vertical line at 3.27 in left plot represents the cut-off value for sensitivity analysis)

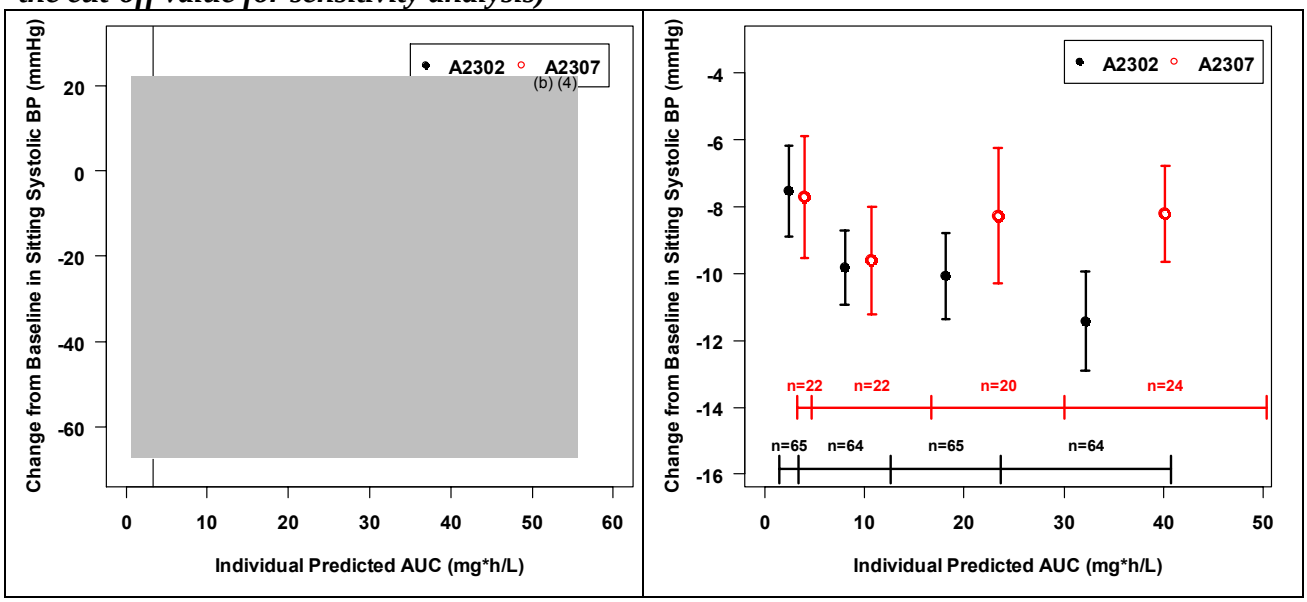


Figure 5. Relationship between age (black circle for A2302 and red triangle for A2307) and baseline sitting systolic blood pressure

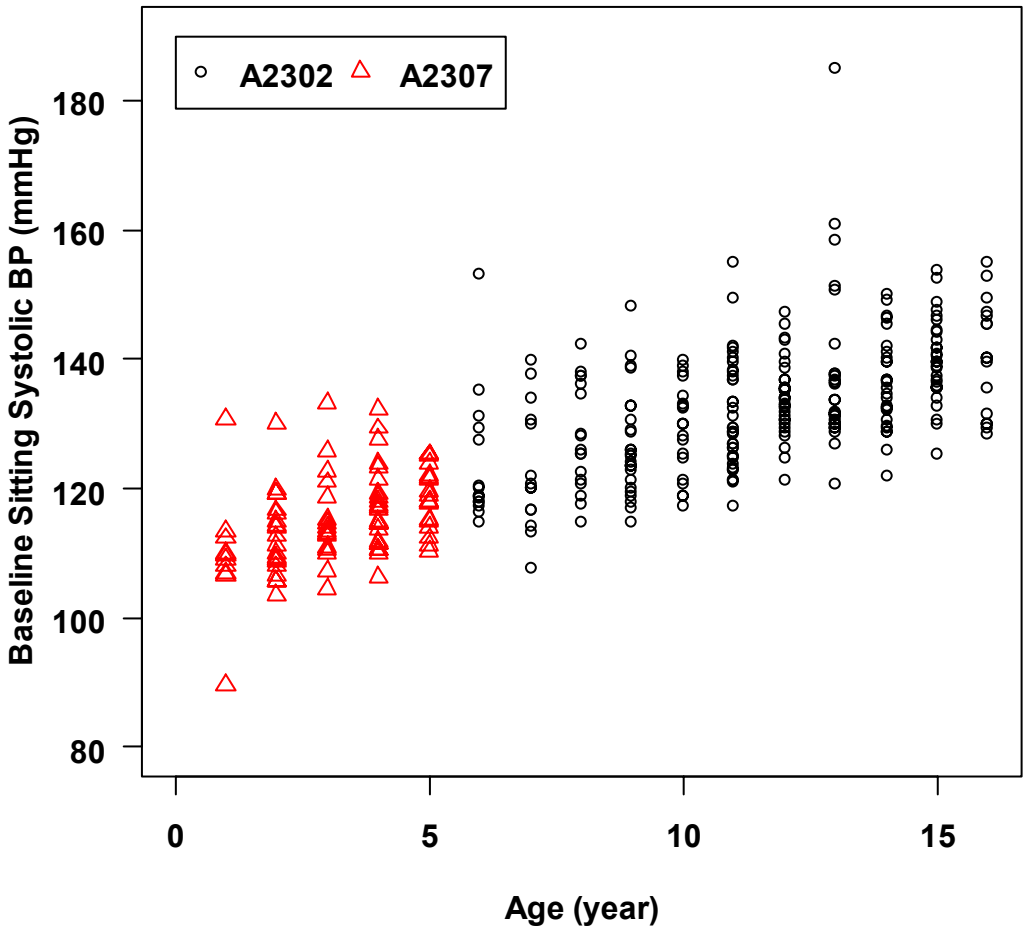
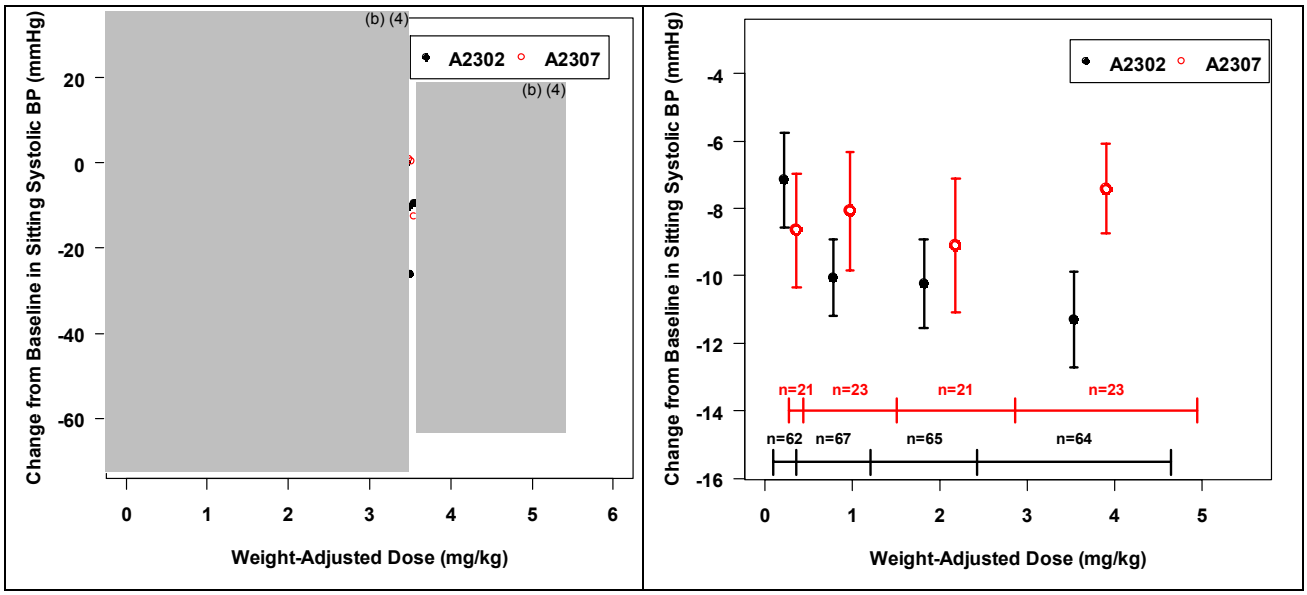


Table 4. Sensitivity analysis for slope analysis for changes from baseline in sitting systolic blood pressure (SSBP) in Phase 1 (ITT1 population)

	Data	Estimate	Standard Error	95% CI	P-value
Slope*	All (N=259)	-0.43	0.19	(-0.81, -0.05)	0.0256
Slope*	Excluding AUC<3.27 mg*h/L (N=202)	-0.25	0.25	(-0.74, 0.24)	0.3138

* Slope is based on linear regression model with terms including region strata, weight strata, race strata, centered baseline SSBP, and dose ratio

Figure 6. Weight-adjusted dose-response for A2302 (black dot) and A2307(red circle) (left: raw data; right: mean±SE within each quartile)


Change from Baseline in Sitting Systolic BP (mmHg)
20
0
-20
-40
-60
(b) (4)
A2302
A2307
(b) (4)
0
1
2
3
4
5
6
Weight-Adjusted Dose (mg/kg)
Change from Baseline in Sitting Systolic BP (mmHg)
-4
-6
-8
-10
-12
-14
-16
A2302
A2307
n=21
n=23
n=21
n=23
n=62
n=67
n=65
n=64
0
1
2
3
4
5
Weight-Adjusted Dose (mg/kg)

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/s/

Yaning Wang
11/29/2007 10:11:58 PM
BIOPHARMACEUTICS

Jogarao Gobburu
12/4/2007 10:26:34 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

Division of Clinical Pharmacology I

NDA 21283 SE5-024 **Submission Dates**: May 29 and September 20, 2007
Type: Pediatric Efficacy Supplement, Priority
Brand Name: Diovan®
Generic Name: Valsartan
Dosage Strength: 40 (scored), 80, 160, 320 mg IR tablets
Sponsor: Novartis
Indication: Treatment of arterial hypertension in children in the age range of 1-16 years
Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110
Reviewer: Peter H. Hinderling, MD
Team Leader: Patrick J. Marroum, Ph.D.

1. EXECUTIVER SUMMARY

The submission contained 11 reports and 1 publication. The 11 reports reported the findings of 2 clinical efficacy studies, 4 clinical pharmacology studies and 5 assay methods. An overview of the clinical studies contained in the pediatric efficacy supplement is given in the below table:

Table 1-1 Clinical studies in the valsartan pediatric clinical development program

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan
Efficacy/safety studies in this submission			**351**	
CVAL489A2302 Pivotal study	Children 6 to 16 years of age with hypertension	Efficacy, dose response, safety, tolerability	261	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Pediatric tablet
CVAL489A2307 Supportive study	Children 1 to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	90	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Oral suspension
Clinical pharmacology studies			**106**	
CVAL489A2301-BA	Healthy volunteers 18 to 45 years of age	Bioavailability of 80 mg valsartan tablets compared to 20 mL of oral valsartan suspension (4 mg/mL)	32	Randomized, single- dose, 80 mg valsartan tablet and 20 mL oral valsartan suspension (4 mg/mL) 2-way crossover design.
CVAL489A2304	Healthy volunteers 18 to 45 years of age	Bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablet	24	Single-dose, two-period, crossover design: 40 mg valsartan tablet and 4 x 10 mg valsartan tablets
CVAL489J2308	Healthy volunteers 18 to 50 years of age	Bioavailability of 80 mg valsartan pediatric tablet (CSF) compared to 80 mg valsartan FMI	24	Single- dose, 80 mg valsartan tablet (80 mg CSF, 80 mg FMI) 2-period crossover design
CVAL489A2305	Children 1 to 16 years of age with hypertension	PK of valsartan given as an oral suspension	26	Single-dose, oral suspension 2.0 mg/kg –> 80 mg (max) valsartan dose age-dependent

a: Details of doses received in Study A2302 and Study A2307 are in Figure 1-1.

The pivotal efficacy study was performed in hypertensive children in the age between 6 and 16 years and used 10 mg and 80 mg unapproved pediatric tablets. A supporting study in hypertensive children in the age between 1 and < 6 years used an oral extemporaneous suspension. The four Clinical Pharmacology reports reported on the PK of valsartan in children in the age between 1 and 16 years who received a single oral dose of an oral suspension and the bioavailability of 3 unapproved clinical service formulations including an oral extemporaneous suspension (4 mg/mL), and pediatric 10 mg and 80 mg tablets relative to the marketed 40 mg and 80 mg tablets. The relative bioavailability studies were conducted in healthy adults. The publication reported in vitro and in vivo animal findings on valsartan as substrate for OATP1B1 and OATP1B3 and MRP2 transporters.

Salient Clinical Pharmacology Facts and Findings

Formulations

The proposed commercial formulations for the pediatric population include the adult 80 mg tablets used for making the extemporaneous suspension (4 mg/mL) and the 40, 80, 160 mg adult tablets. All strengths of the commercial adult tablets are compositionally similar. In a previous bioavailability study and multimedia in vitro dissolution tests it was shown that the 40, 80,160 and 320 mg tablets are bioequivalent**.** The 40 mg and 80 mg commercial adult tablets were the reference formulations in the relative bioavailability studies.

The unapproved extemporaneous suspension and the pediatric 10 mg and 80 mg tablets were the test formulations in the relative bioavailability studies. The pediatric 10 mg and 80 mg tablets were used in the efficacy trial in the 6- 16 year old pediatric patients. The unapproved extemporaneous suspension (4 mg/mL) was used in the efficacy trial in the 1 - < 6 year old pediatric patients and in the PK study in the 1-16 year old children.

Salient Results

Single dose PK of Valsartan in 1-16 year old children

The 1-< 6 year old children received a dose of 2 mg/kg valsartan. The dose administered to the school-age children was 1.6 mg/kg valsartan and the adolescents received a dose of 0.9 mg/kg valsartan. The valsartan formulation used was the extemporaneous suspension. The PK parameters of valsartan obtained are shown in the below tables**:**

Geometric Means of the PK Parameters of Valsartan in the Pediatric Population

PK Parameters	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
Dose, mg/kg	2.0	2.0	1.6	0.9
Cmax, ng/mL	3832	4500	4112	2835
tmax[a], h	2.00	2.00	2.00	2.00
AUC0-∞, ng●h/mL	23517	26071	18994	14988
CL/F, (L/h)	1.23	1.60	3.45	5.34
V/F, L	6.69	9.08	26.32	37.93
t1/2, h	3.77	3.92	5.30	4.92

[a] Median

Oral clearance and volume of distribution of valsartan increase with body weight and/or age. In comparing Cmax and AUC0-∞ it should be noted that the dose in mg/kg in the adolescents and school-age children was smaller (1.6 mg/kg and 0.9 mg/kg), respectively, than in the two younger age groups (2.0 mg/kg).

Dose Adjusted[a] Geometric Mean Exposure Measures in the Four Pediatric Age Groups

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
Cmax, ng/mL	3796	4536	4882	6237
AUC0-∞, ng●h/mL	23294	26333	22544	32997

[a]Adjusted to a dose of 2 mg/kg

The mean dose normalized peak exposure to valsartan tends to increase with body weight/age in the four pediatric groups. The mean dose normalized average exposure appears to be slightly greater in the adolescents than in the younger age groups, but the small number of subjects in the different age groups must be considered. These results may suggest that scaling the dose based on body weight may not result in an identical peak exposure to valsartan in the four studied age groups.

Body Weight Adjusted[a] Geometric Mean Oral Clearance and Volume of Distribution in the Four Pediatric Age Groups

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
CL/F, L/(h ● kg)	0.086	0.076	0.089	0.061
V/F, L/kg	0.465	0.432	0.678	0.429

[a] Adjusted to a unit body weight

The body weight adjusted oral clearance and volume of distribution appear to be comparable among the four age groups.

Comparison of the PK Parameters of Valsartan in Pediatric and Adult Populations

The below table shows the exposure parameters in the pediatric groups receiving the extemporaneous suspension (VAL489A 2305) and adults receiving either the marketed formulation (study VAL489A2304) or the extemporaneous suspension (VAL489A2301–BA):

Dose Adjusted[a] Geometric Mean Exposure Measures in the Pediatric Groups and Adults

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y	Adults	
Cmax, ng/mL	3796	4536	4882	6237	2572[b]	5804[c]
AUC0-∞, ng●h/mL	23294	26333	22544	32997	16791[b]	31256[c]
T1/2, h	3.8	4.0	5.3	5.0	4.6[b]	8.6[c]

[a]Adjusted to a dose of 2 mg/kg [b] 40 mg commercial tablet (study 2304) [c] Suspension (study 2301)

The results indicate that peak and average exposure in adults and adolescents receiving the extemporaneous suspension are similar and slightly greater than in the younger pediatric age groups. In contrast, the exposure in the pediatric population receiving the extemporaneous suspension exceeds clearly that of the adults administered the 80 mg adult tablet. There appears to be a difference in t1/2 for valsartan in adults. However, this is most probably the result of the 24 h blood sampling interval used in study 2304 versus the 36 h blood sampling interval used in study 2301. Blood samples in the PK study were collected only for 24 h after administration. It is more appropriate to compare the mean t1/2 value in the pediatric population with that of the adults in study 2304. It can be concluded that the exposure measures when normalized for body weight are similar in children and adults and the t1/2 estimates are also comparable.

Relative Bioavailability Studies

The bioavailability of the unapproved formulations was tested relative to the adult 40 and 80 mg commercial tablets in healthy adults. The results are shown in the below table:

Relative Bioavailability Studies: Geometric Mean Ratios and 90% Confidence Intervals

Study	Formulation	Cmax	AUC
CVAL489A2301	Extemp. Suspension	1.93 (1.60-2.33)	1.56 (1.36-1.78)
	vs. Adult 80 mg Tablet		
VAL489J2308	Pediatric 80 mg Tablet	1.06 (0.86-1.31)	1.08 (0.93-1.36)
	vs. Adult 80 mg Tablet		
VAL489A2304	Pediatric 10 mg Tablet	1.08 (0.90-1.29)	1.12 (0.97-1.31)
	vs. Adult 40 mg Tablet		

The results show that the unapproved pediatric formulations and the adult tablets are not bioequivalent. Mean Cmax and AUC with the extemporaneous suspension are 1.93 and 1.56 times greater, respectively, than with the adult 80 mg tablet. Mean Cmax and AUC with the pediatric 80 mg tablet are 1.06 and 1.08 times greater, respectively, than with the adult 80 mg tablet and mean Cmax and AUC with the pediatric 10 mg tablet are 1.08 and 1.12 times greater, respectively, than with the 40 mg adult tablet.

Comparing the Respective Exposures to Valsartan in the Clinical Trials in 1- < 6 Year Old and 6-16 Year Old Children

The results from the bioavailability studies can be used to estimate the bioavailability of formulations whose relative bioavailability was not tested directly. The computations, as shown in the below table, indicate that valsartan is significantly more bioavailable from the suspension than from the pediatric 10 mg and 80 tablets and the adult 40 mg and 80 mg tablets:

Bioavailability (90% Confidence Interval) of the Unapproved Pediatric Formulations Relative to the Marketed Adult 40 mg or 80 mg Tablet

	Suspension	**Ped. 10 mg Tablet**	**Ped. 80 mg Tablet**	**80 mg Adult Tablet**
Cmax	1.93 (1.60-2.33)	1.08 (0.90-1.29)	1.06 (0.92-1.26)	1.0
AUC	1.56 (1.36-1.78)	1.12 (0.97-1.31)	1.08 (0.86-1.31)	1.0

Bioavailability of the Pediatric 10 mg and 80 mg Tablets Relative to the Suspension

	Ped. 10 mg Tablet	**Ped. 80 mg Tablet**	**Suspension**
Cmax	0.56	0.55	1.0
AUC	0.72	0.69	1.0

The results indicate that in the clinical trials for a given dose level the exposure of the 1- < 6 year old children receiving the extemporaneous suspension is 1.82 (Cmax) and 1.44 (AUC) fold greater than in the 6-16 year old children receiving the pediatric 80 mg tablet. Similarly, the exposure of the 1 - < 6 year old children receiving the extemporaneous suspension is 1.79 (Cmax) and 1.39 (AUC) fold greater than in the 6-16 year old children receiving the pediatric 10 mg tablet.

The results of bioavailability studies also show that the exposure of the 1- < 6 year old children receiving the extemporaneous suspension in the clinical trial was 1.93 (Cmax) and 1.56 (AUC) times greater than in adults receiving the adult tablets. In contrast, the exposure of the 6-16 year

old children receiving the pediatric 10 mg and 80 mg tablets was comparable to adults receiving the adult tablets.

Therefore, when comparing the exposure of the 1 - < 6 year old children with that of the 6-16 year old children or adults the difference in bioavailability of the clinical service formulations used in the clinical trials must be considered. It should be noted that the valsartan dose in children was scaled down from the adult dose without considering the difference in bioavailability among the different formulations used in the clinical trials.

Bioavailability of the Pediatric Formulations used in the Clinical Trials Relative to the Proposed Commercial Formulations

The extemporaneous suspension used in the clinical trial in 1- < 6 year old children is proposed as commercial formulation in this age group.

The difference in bioequivalence between the pediatric 10 mg and 80 mg clinical service formulations used in the clinical trial in 6-16 year old children and the commercial adult formulations is too small to be relevant. The dose of the commercial adult tablets to be used in the 6-16 year old children does not need to be adjusted.

Labeling

Sponsored Proposed Commercial Formulations for the Pediatric Population

Children in the age between 1 and < 6 years: 4 mg/mL suspension made from adult 80 mg tablets

Children in the age between 6 and 16 years of age: 40, 80 and 160 mg adult tablets

Sponsor Proposed Dose Regimen in Children between 1 and 16 years of Age

Starting dose: 1.3 mg/kg qd (up to 40 mg total)
Dose range: 1.3-2.7 mg/kg qd (up to 40-160 mg total)

The sponsor proposed dose regimens are identical for the 1- < 6 year old and the 6-16 year old children. As pointed out earlier the sponsor did not consider the difference in relative bioavailability and resulting exposure between the extemporaneous suspension and the adult 40, 80 and 160 mg tablets. With the sponsor proposed dose regimens and formulations the exposure to valsartan in the 1- < 6 year old children would be consistently 1.82 (Cmax) and 1.44 (AUC) fold greater than in the 6-16 year old children.

The bioinequivalence of the extemporaneous suspension and the adult tablets must also be considered when the suspension is changed for a tablet when a child becomes old enough to

swallow a tablet. The dose of the tablet must be adjusted for the difference in bioavailability between the extemporaneous suspension and the adult 40, 80 or 160 mg tablets.

Impact of Difference in Bioavailability of the Formulations used in the Clinical trials and in the PK trial and the Formulations Proposed for Marketing

In order to compare the range of the doses studies in the clinical trials and the PK trial the difference in bioavailability of the respective formulations used must be considered. Therefore the respective doses were normalized for the bioavailability of the formulations used. The so corrected doses should result in comparable exposures to valsartan and are tabulated below:

Dose Range used in the Clinical Studies and Proposed for Marketing

Study	Population	Dose Range, mg/kg		
	Age range, years	Tested Formulation		Adult Tablets[a]
2302 Clin Trial	6-16	Pediatric tablets	0.4-2.7	0.4-3.0
2307 Clin Trial	1- < 6	Suspension	0.4-3.7	0.6-5.8
2305 PK Trial	12-16	Suspension	0.9	1.4
	6- < 12	Suspension	1.6	2.5
	1-< 6	Suspension	2.0	3.1
	Adults[b]	Adult tablets	1.6.-3.2	1.6-3.2
Label	6-16	Pediatric tablets	1.3-2.7	1.4-3.0
	1- < 6	Suspension	1.3-2.7	2.0-4.2

[a] Dose range of adult tablets that provides same exposure as that of the pediatric tablets or the suspension
[b] Assuming respective doses of 80 mg and 320 mg are administered to 50 kg and 100 kg individuals, respectively

The review of the Clinical Pharmacology part of the submission indicated the following deficiencies:

1. Failure to consider impact of difference in relative bioavailability among the pediatric clinical service formulations used in the clinical trials

The sponsor states that "the protocol specified doses used in clinical studies 2302 (6-16 year old children) and 2307 (1- < 6 year old children) were selected on the basis of expected blood pressure response rather than plasma concentration levels of valsartan. Adult doses were scaled down to corresponding doses for the respective pediatric population based on the body surface area of adults vs. children." In reality doses were scaled down in the basis of body weight in all

four age groups, but the exposure to valsartan in the two younger age groups was 1.8 times (Cmax) and 1.4 times (AUC) greater than in the two older age groups. The bioavailability of valsartan with the extemporaneous suspension administered to the two younger age groups is significantly greater than with the pediatric 10 and 80 mg tablets given to the two older age groups. The significantly higher exposure of the 1- < 6 years old children in the clinical trial should be considered in comparing the dose-response relationship in trials 2302 and 2307.

2. Label does not consider impact of difference in relative bioavailability between the extemporaneous suspension and the commercial adult 40, 80, 160 and 320 mg tablets

The bioavailability of valsartan with the extemporaneous suspension is about 1.9 times (Cmax) and 1.6 times (AUC) greater than with the commercial adult 80 mg tablet. Similarly, the bioavailability of valsartan with the extemporaneous suspension is about 1.8 times (Cmax) and 1.4 times (AUC) greater than with the commercial adult 40 mg tablet. Despite the significant difference in relative bioavailability between the extemporaneous suspension and the adult tablets the label recommends the same doses corrected for body weight for 1-6 year old children and 6-16 year old children.

Also, the label does not state that the dose of the adult tablets should be increased by a factor of 1.6-1.9 when in a pre-school age child the extemporaneous suspension is changed to an adult tablet.

3. Failure to include in the label results from a published study showing evidence for valsartan to be a substrate of OATP and MRP2

A publication by Yamashiro et al., Drug Metab Dispos 2006;34:1247-1254, shows in vitro evidence for involvement of OATP1B1 and OATP1B3 in hepatic uptake and MRP2 in hepatic extrusion of valsartan. The authors showed further delayed elimination of valsartan using mrp2 deficient rats. The findings suggest that valsartan may be susceptible to interactions when co-administered with OATP inhibitors such as e.g. rifampicin or cyclosporine or drugs interfering with the activity of MRP2, such as e.g. ritonavir or probenecid. The label of valsartan should include the results from this study.

1.1 RECOMMENDATION

From a Clinical Pharmacology viewpoint the submission is acceptable. The sponsor is advised to resolve the above identified issues.

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/s/

Peter Hinderling
11/20/2007 08:43:10 AM
BIOPHARMACEUTICS

Patrick Marroum
11/20/2007 10:00:34 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

Division of Clinical Pharmacology I

NDA 21283 SE5-024 **Submission Dates**: May 29, and September 20, 2007

Type: Pediatric Efficacy Supplement, Priority
Brand Name: Diovan®
Generic Name: Valsartan
Dosage Strength: 40 (scored), 80, 160, 320 mg IR tablets
Sponsor: Novartis
Indication: Treatment of arterial hypertension in children in the age range of 1-16 years
Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110
Reviewer: Peter H. Hinderling, MD
Team Leader: Patrick J. Marroum, Ph.D.

Table of Content

1. EXECUTIVER SUMMARY

The submission contained 11 reports and 1 publication. The 11 reports reported the findings of 2 clinical efficacy studies, 4 clinical pharmacology studies and 5 assay methods. An overview of the clinical studies contained in the pediatric efficacy supplement is given in the below table:

Table 1-1 Clinical studies in the valsartan pediatric clinical development program

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan
Efficacy/safety studies in this submission			**351**	
CVAL489A2302 Pivotal study	Children 6 to 16 years of age with hypertension	Efficacy, dose response, safety, tolerability	261	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Pediatric tablet
CVAL489A2307 Supportive study	Children 1 to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	90	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Oral suspension
Clinical pharmacology studies			**106**	
CVAL489A2301-BA	Healthy volunteers 18 to 45 years of age	Bioavailability of 80 mg valsartan tablets compared to 20 mL of oral valsartan suspension (4 mg/mL)	32	Randomized, single- dose, 80 mg valsartan tablet and 20 mL oral valsartan suspension (4 mg/mL) 2-way crossover design.
CVAL489A2304	Healthy volunteers 18 to 45 years of age	Bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablet	24	Single-dose, two-period, crossover design: 40 mg valsartan tablet and 4 x 10 mg valsartan tablets
CVAL489J2308	Healthy volunteers 18 to 50 years of age	Bioavailability of 80 mg valsartan pediatric tablet (CSF) compared to 80 mg valsartan FMI	24	Single- dose, 80 mg valsartan tablet (80 mg CSF, 80 mg FMI) 2-period crossover design
CVAL489A2305	Children 1 to 16 years of age with hypertension	PK of valsartan given as an oral suspension	26	Single-dose, oral suspension 2.0 mg/kg –> 80 mg (max) valsartan dose age-dependent

a: Details of doses received in Study A2302 and Study A2307 are in Figure 1-1.

The pivotal efficacy study was performed in hypertensive children in the age between 6 and 16 years and used 10 mg and 80 mg unapproved pediatric tablets. A supporting study in hypertensive children in the age between 1 and < 6 years used an oral extemporaneous suspension. The four Clinical Pharmacology reports reported on the PK of valsartan in children in the age between 1 and 16 years who received a single oral dose of an oral suspension and the bioavailability of 3 unapproved clinical service formulations including an oral extemporaneous suspension (4 mg/mL), and pediatric 10 mg and 80 mg tablets relative to the marketed 40 mg and 80 mg tablets. The relative bioavailability studies were conducted in healthy adults. The publication reported in vitro and in vivo animal findings on valsartan as substrate for OATP1B1 and OATP1B3 and MRP2 transporters.

Salient Clinical Pharmacology Facts and Findings

Formulations

The proposed commercial formulations for the pediatric population include the adult 80 mg tablets used for making the extemporaneous suspension (4 mg/mL) and the 40, 80, 160 mg adult tablets. All strengths of the commercial adult tablets are compositionally similar. In a previous bioavailability study

and multimedia in vitro dissolution tests it was shown that the 40, 80,160 and 320 mg tablets are bioequivalent**.** The 40 mg and 80 mg commercial adult tablets were the reference formulations in the relative bioavailability studies.

The unapproved extemporaneous suspension and the pediatric 10 mg and 80 mg tablets were the test formulations in the relative bioavailability studies. The pediatric 10 mg and 80 mg tablets were used in the efficacy trial in the 6- 16 year old pediatric patients. The unapproved extemporaneous suspension (4 mg/mL) was used in the efficacy trial in the 1 - < 6 year old pediatric patients and in the PK study in the 1-16 year old children.

Salient Results

Single dose PK of Valsartan in 1-16 year old children

The 1-< 6 year old children received a dose of 2 mg/kg valsartan. The dose administered to the school-age children was 1.6 mg/kg valsartan and the adolescents received a dose of 0.9 mg/kg valsartan. The valsartan formulation used was the extemporaneous suspension. The PK parameters of valsartan obtained are shown in the below tables**:**

Geometric Means of the PK Parameters of Valsartan in the Pediatric Population

PK Parameters	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**
Dose, mg/kg	2.0	2.0	1.6	0.9
Cmax, ng/mL	3832	4500	4112	2835
tmax[a], h	2.00	2.00	2.00	2.00
AUC0-∞, ng●h/mL	23517	26071	18994	14988
CL/F, (L/h)	1.23	1.60	3.45	5.34
V/F, L	6.69	9.08	26.32	37.93
t1/2, h	3.77	3.92	5.30	4.92

[a] Median

Oral clearance and volume of distribution of valsartan increase with body weight and/or age. In comparing Cmax and AUC0-∞ it should be noted that the dose in mg/kg in the adolescents and school-age children was smaller (1.6 mg/kg and 0.9 mg/kg), respectively, than in the two younger age groups (2.0 mg/kg).

Dose Adjusted[a] Geometric Mean Exposure Measures in the Four Pediatric Age Groups

PK Parameter	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**
Cmax, ng/mL	3796	4536	4882	6237
AUC0-∞, ng●h/mL	23294	26333	22544	32997

[a]Adjusted to a dose of 2 mg/kg

The mean dose normalized peak exposure to valsartan tends to increase with body weight/age in the four pediatric groups. The mean dose normalized average exposure appears to be slightly greater in the adolescents than in the younger age groups, but the small number of subjects in the different age groups must be considered. These results may suggest that scaling the dose based on body weight may not result in an identical peak exposure to valsartan in the four studied age groups.

Body Weight Adjusted[a] Geometric Mean Oral Clearance and Volume of Distribution in the Four Pediatric Age Groups

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y
CL/F, L/(h ● kg)	0.086	0.076	0.089	0.061
V/F, L/kg	0.465	0.432	0.678	0.429

[a] Adjusted to a unit body weight

The body weight adjusted oral clearance and volume of distribution appear to be comparable among the four age groups.

Comparison of the PK Parameters of Valsartan in Pediatric and Adult Populations

The below table shows the exposure parameters in the pediatric groups receiving the extemporaneous suspension (VAL489A 2305) and adults receiving either the marketed formulation (study VAL489A2304) or the extemporaneous suspension (VAL489A2301–BA):

Dose Adjusted[a] Geometric Mean Exposure Measures in the Pediatric Groups and Adults

PK Parameter	1 - 4 y	4 - < 6 y	6 - < 12 y	12-16 y	Adults	
Cmax, ng/mL	3796	4536	4882	6237	2572[b]	5804[c]
AUC0-∞, ng●h/mL	23294	26333	22544	32997	16791[b]	31256[c]
T1/2, h	3.8	4.0	5.3	5.0	4.6[b]	8.6[c]

[a]Adjusted to a dose of 2 mg/kg [b] 40 mg commercial tablet (study 2304) [c] Suspension (study 2301)

The results indicate that peak and average exposure in adults and adolescents receiving the extemporaneous suspension are similar and slightly greater than in the younger pediatric age groups. In contrast, the exposure in the pediatric population receiving the extemporaneous suspension exceeds clearly that of the adults administered the 80 mg adult tablet. There appears to be a difference in t1/2 for valsartan in adults. However, this is most probably the result of the 24 h blood sampling interval used in study 2304 versus the 36 h blood sampling interval used in study 2301. Blood samples in the PK study were collected only for 24 h after administration. It is more appropriate to compare the mean t1/2 value in the pediatric population with that of the adults in study 2304. It can be concluded that the exposure measures when normalized for body weight are similar in children and adults and the t1/2 estimates are also comparable.

Relative Bioavailability Studies

The bioavailability of the unapproved formulations was tested relative to the adult 40 and 80 mg commercial tablets in healthy adults. The results are shown in the below table:

Relative Bioavailability Studies: Geometric Mean Ratios and 90% Confidence Intervals

Study	Formulation	Cmax	AUC
CVAL489A2301	Extemp. Suspension	1.93 (1.60-2.33)	1.56 (1.36-1.78)
	vs. Adult 80 mg Tablet		
VAL489J2308	Pediatric 80 mg Tablet	1.06 (0.86-1.31)	1.08 (0.93-1.36)
	vs. Adult 80 mg Tablet		
VAL489A2304	Pediatric 10 mg Tablet	1.08 (0.90-1.29)	1.12 (0.97-1.31)
	vs. Adult 40 mg Tablet		

The results show that the unapproved pediatric formulations and the adult tablets are not bioequivalent. Mean Cmax and AUC with the extemporaneous suspension are 1.93 and 1.56 times greater, respectively, than with the adult 80 mg tablet. Mean Cmax and AUC with the pediatric 80 mg tablet are 1.06 and 1.08 times greater, respectively, than with the adult 80 mg tablet and mean Cmax and AUC with the pediatric 10 mg tablet are 1.08 and 1.12 times greater, respectively, than with the 40 mg adult tablet.

Comparing the Respective Exposures to Valsartan in the Clinical Trials in 1- < 6 Year Old and 6-16 Year Old Children

The results from the bioavailability studies can be used to estimate the bioavailability of formulations whose relative bioavailability was not tested directly. The computations, as shown in the below table, indicate that valsartan is significantly more bioavailable from the suspension than from the pediatric 10 mg and 80 tablets and the adult 40 mg and 80 mg tablets:

Bioavailability (90% Confidence Interval) of the Unapproved Pediatric Formulations Relative to the Marketed Adult 40 mg or 80 mg Tablet

	Suspension	Ped. 10 mg Tablet	Ped. 80 mg Tablet	80 mg Adult Tablet
Cmax	1.93 (1.60-2.33)	1.08 (0.90-1.29)	1.06 (0.92-1.26)	1.0
AUC	1.56 (1.36-1.78)	1.12 (0.97-1.31)	1.08 (0.86-1.31)	1.0

Bioavailability of the Pediatric 10 mg and 80 mg Tablets Relative to the Suspension

	Ped. 10 mg Tablet	Ped. 80 mg Tablet	Suspension
Cmax	0.56	0.55	1.0
AUC	0.72	0.69	1.0

The results indicate that in the clinical trials for a given dose level the exposure of the 1- < 6 year old children receiving the extemporaneous suspension is 1.82 (Cmax) and 1.44 (AUC) fold greater than in

the 6-16 year old children receiving the pediatric 80 mg tablet. Similarly, the exposure of the 1 - < 6 year old children receiving the extemporaneous suspension is 1.79 (Cmax) and 1.39 (AUC) fold greater than in the 6-16 year old children receiving the pediatric 10 mg tablet.

The results of bioavailability studies also show that the exposure of the 1- < 6 year old children receiving the extemporaneous suspension in the clinical trial was 1.93 (Cmax) and 1.56 (AUC) times greater than in adults receiving the adult tablets. In contrast, the exposure of the 6-16 year old children receiving the pediatric 10 mg and 80 mg tablets was comparable to adults receiving the adult tablets.

Therefore, when comparing the exposure of the 1 - < 6 year old children with that of the 6-16 year old children or adults the difference in bioavailability of the clinical service formulations used in the clinical trials must be considered. It should be noted that the valsartan dose in children was scaled down from the adult dose without considering the difference in bioavailability among the different formulations used in the clinical trials.

Bioavailability of the Pediatric Formulations used in the Clinical Trials Relative to the Proposed Commercial Formulations

The extemporaneous suspension used in the clinical trial in 1- < 6 year old children is proposed as commercial formulation in this age group.

The difference in bioequivalence between the pediatric 10 mg and 80 mg clinical service formulations used in the clinical trial in 6-16 year old children and the commercial adult formulations is too small to be relevant. The dose of the commercial adult tablets to be used in the 6-16 year old children does not need to be adjusted.

Labeling

Sponsored Proposed Commercial Formulations for the Pediatric Population

Children in the age between 1 and < 6 years: 4 mg/mL suspension made from adult 80 mg tablets
Children in the age between 6 and 16 years of age: 40, 80 and 160 mg adult tablets

Sponsor Proposed Dose Regimen in Children between 1 and 16 years of Age

Starting dose: 1.3 mg/kg qd (up to 40 mg total)
Dose range: 1.3-2.7 mg/kg qd (up to 40-160 mg total)

The sponsor proposed dose regimens are identical for the 1- < 6 year old and the 6-16 year old children. As pointed out earlier the sponsor did not consider the difference in relative bioavailability and resulting exposure between the extemporaneous suspension and the adult 40, 80 and 160 mg tablets. With the sponsor proposed dose regimens and formulations the exposure to valsartan in the 1- < 6 year old children would be consistently 1.93 (Cmax) and 1.56 (AUC) fold greater than in the 6-16 year old children.

The bioinequivalence of the extemporaneous suspension and the adult tablets must also be considered when the suspension is changed for a tablet when a child becomes old enough to swallow a tablet. The dose of the tablet must be adjusted for the difference in bioavailability between the extemporaneous suspension and the adult 40, 80 or 160 mg tablets.

Impact of Difference in Bioavailability of the Formulations used in the Clinical trials and in the PK trial and the Formulations Proposed for Marketing

In order to compare the range of the doses studies in the clinical trials and the PK trial the difference in bioavailability of the respective formulations used must be considered. Therefore the respective doses were normalized for the bioavailability of the formulations used. The so corrected doses should result in comparable exposures to valsartan and are tabulated below:

Dose Range used in the Clinical Studies and Proposed for Marketing

Study	Population	Dose Range, mg/kg		
	Age range, years	Tested Formulation		Adult Tablets[a]
2302 Clin Trial	6-16	Pediatric tablets	0.4-2.7	0.4-3.0
2307 Clin Trial	1- < 6	Suspension	0.4-3.7	0.6-5.8
2305 PK Trial	12-16	Suspension	0.9	1.4
	6- < 12	Suspension	1.6	2.5
	1-< 6	Suspension	2.0	3.1
	Adults[b]	Adult tablets	1.6.-3.2	1.6-3.2
Label	6-16	Pediatric tablets	1.3-2.7	1.4-3.0
	1- < 6	Suspension	1.3-2.7	2.0-4.2

[a] Dose range of adult tablets that provides same exposure as that of the pediatric tablets or the suspension
[b] Assuming respective doses of 80 mg and 320 mg are administered to 50 kg and 100 kg individuals, respectively

The review of the Clinical Pharmacology part of the submission indicated the following deficiencies:

1. Failure to consider impact of difference in relative bioavailability among the pediatric clinical service formulations used in the clinical trials

The sponsor states that "the protocol specified doses used in clinical studies 2302 (6-16 year old children) and 2307 (1- < 6 year old children) were selected on the basis of expected blood pressure response rather than plasma concentration levels of valsartan. Adult doses were scaled down to corresponding doses for the respective pediatric population based on the body surface area of adults vs. children." In reality doses were scaled down in the basis of body weight in all four age groups, but the exposure to valsartan in the two younger age groups was 1.8 times (Cmax) and 1.4 times (AUC) greater than in the two older age groups. The bioavailability of valsartan with the extemporaneous suspension administered to the two younger age groups is significantly greater than with the pediatric 10 and 80 mg tablets given to the two older age groups. The significantly higher exposure of the 1- < 6 years old children in the clinical trial should be considered in comparing the dose-response relationship in trials 2302 and 2307.

2. Label does not consider impact of difference in relative bioavailability between the extemporaneous suspension and the commercial adult 40, 80, 160 and 320 mg tablets

The bioavailability of valsartan with the extemporaneous suspension is about 1.9 times (Cmax) and 1.6 times (AUC) greater than with the commercial adult 80 mg tablet. Similarly, the bioavailability of valsartan with the extemporaneous suspension is about 1.8 times (Cmax) and 1.4 times (AUC) greater than with the commercial adult 40 mg tablet. Despite the significant difference in relative bioavailability between the extemporaneous suspension and the adult tablets the label recommends the same doses corrected for body weight for 1-6 year old children and 6-16 year old children.

Also, the label does not state that the dose of the adult tablets should be increased by a factor of 1.6-1.9 when in a pre-school age child the extemporaneous suspension is changed to an adult tablet.

3. Failure to include in the label results from a published study showing evidence for valsartan to be a substrate of OATP and MRP2

A publication by Yamashiro et al., Drug Metab Dispos 2006;34:1247-1254, shows in vitro evidence for involvement of OATP1B1 and OATP1B3 in hepatic uptake and MRP2 in hepatic extrusion of valsartan. The authors showed further delayed elimination of valsartan using mrp2 deficient rats. The findings suggest that valsartan may be susceptible to interactions when co-administered with OATP inhibitors such as e.g. rifampicin or cyclosporine or drugs interfering with the activity of MRP2, such as e.g. ritonavir or probenecid. The label of valsartan should include the results from this study.

1.1 RECOMMENDATION

From a Clinical Pharmacology viewpoint the submission is acceptable. The sponsor is advised to resolve the above identified issues.

2. QUESTION BASED REVIEW

2. 1.1 What are the Stipulations of the Written Request?

The most recent version of the Written Request issued June 18, 2003, stipulated the following key Clinical Pharmacology and related Clinical issues:

Strategy

The requested data will provide guidance for the use of valsartan to reduce blood pressure in pediatric populations. These data will be derived from:

- Pharmacokinetic sampling in patients spanning the same age range as those studied for effectiveness
- A dose ranging trial of effectiveness in hypertensive pediatric patients; and
- Safety data derived from the controlled trial(s) and a 1-year open treatment phase following the effectiveness trial, and a summary of all available information on the safety of the drug in hypertensive pediatric patients. The safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data.

Pediatric Subgroups

Age Groups

- Infants and toddlers (age 1- < 2 y)
- Pre-school children (age 2- < 6 y)
- School age children (age 6- < Tanner stage 3 or age 12), preferred group for effectiveness study
- Adolescents (Tanner stage 3 or age 12 < 17 y)

Regarding effectiveness, studies of anti-hypertensive drugs must include ≥ 50% pre-pubertal patients as the course of disease and the effects of drugs in adolescents are not likely to differ from adults.

School Age Children

- Are usually able to swallow solid dosage forms
- Tolerate doses similar to the smallest doses approved in adults
- Are fairly often diagnosed with hypertension of no specific cause

Pre-School Age Children

For children < 6 years of age formulations issues are more important and hypertension is attributed to renal disease or other specific causes

Racial Groups

Because of antihypertensive response differences in black and non-black adults, 40-60 % black patients should be enrolled

Formulation Issues

Formulations must be well characterized and appropriate to age and clinical setting. Any unapproved formulation will need to be supported by a study of the relative bioavailability of valsartan. These studies can be performed in adults. If a potentially marketable formulation cannot be developed the sponsor must document an attempt to do so and will need to obtain an agreement with Agency regarding the adequacy of the formulation to be used. Full study reports of any relative bioavailability studies must be submitted to the Agency.

Pharmacokinetic Trials

Pharmacokinetic data must be obtained over the range of doses studied for effectiveness. Patients should have a grossly normal metabolic function. Traditional or sparse sampling methods to determine PK parameters can be used.

Data must be collected for valsartan and any metabolites that make substantial contributions to its efficacy and /or toxicity. For parent drug and each metabolite AUC, t1/2, CL/F, V/F, Cmax and tmax in all pediatric groups investigated should be provided.

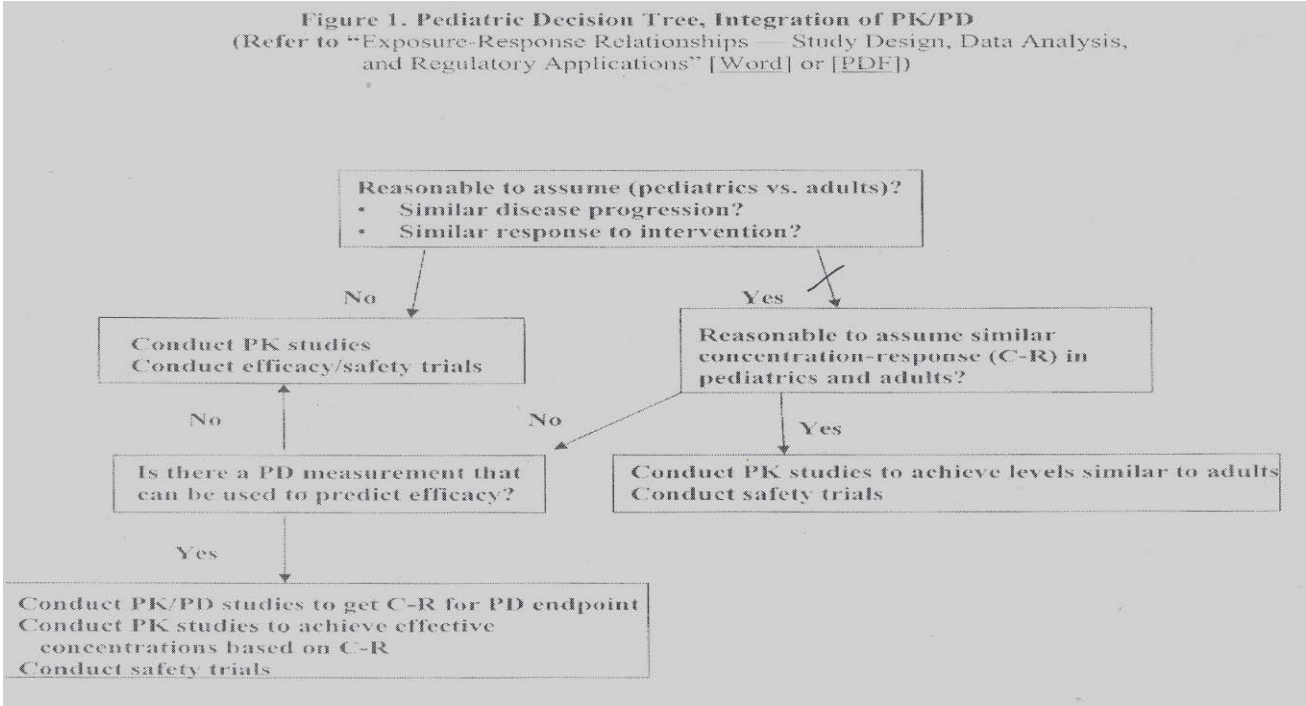
Labeling Changes

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Reporting

Full study reports of the requested trials, including full analysis, assessment, and interpretation, must be submitted in the usual format. The submission must include electronic datasets for all clinical and pharmacokinetic trial data for these studies, submitted according to available guidance.

2.1.2 What is the rationale for the studies requested by the written request?



Hypertension in children may have different causes than in adults. Secondary hypertension is more frequent in < 10 year old children than in adults in whom essential hypertension is the most frequent type of hypertension. A number of past studies with antihypertensive agents have shown that the efficacy of antihypertensive agents in children may be smaller than in adults. Therefore, similar disease progression and response to intervention cannot be assumed. Blood pressure is a PD predictor (surrogate) for cardiovascular events and mortality.
In adults a relation between drug action and plasma concentration does not exist for valsartan. There may also be age/body weight related differences of the pharmacokinetics between pediatric and adult

populations. The clinical trials performed by the sponsor used unapproved clinical service formulations (suspension, 10 and 80 mg tablets) of unknown bioavailability. The requested clinical safety and efficacy studies, the PK study in the pediatric population and the relative bioavailability studies in adults are justified.

2.1.3 Is the submitted clinical pharmacology information in compliance with the Written Request (WR)?

Comparability of age and race of children enrolled in the PK trial and in the effectiveness studies.

The pharmacokinetic samples were collected in children of the same age range as those studied for effectiveness. The PK study in children enrolled infants and toddlers (n=6), pre-school children (n=6), school age children (n=7) and adolescents (n=7). The WR did not define the number of subjects in the different age groups to be enrolled in the PK study, and the number of enrolled subjects is acceptable. More than 50% pre-pubertal patients were enrolled in the PK trial. Thirty one (31) % of the children were black, a slightly smaller percentage than the 40-60% black children recommended by the WR to be enrolled in the clinical trial.

Adequacy of formulations tested

An extemporaneous suspension formulation (4 mg/mL) was used in the clinical trial with pre-school children and pediatric 10 mg and 80 mg tablets were used in the clinical trial with school children and adolescents. The relative bioavailability of all three unapproved formulations was tested relative to the marketed adult 40 mg or 80 mg tablet in healthy adult subjects.

Doses used in the PK trial

A single dose study with the suspension and an extensive sampling schedule was used in hypertensive children in the age between 1 and 16 years. The mean doses of valsartan administered in infants/ toddlers, pre-school children, school age children and adolescents were 30.5 mg, 40.7 mg, 68.4 mg and 80 mg, respectively. When normalized for body weight these values become 2.0 mg/kg, 2.0 mg/kg, 1.6 mg/kg and 0.9 mg/kg, respectively. The individual doses ranged between 30.0 mg to 80.0 mg and when normalized for weight ranged between 0.71 mg/kg to 2.07 mg/kg.

Doses used in the clinical trials and resulting exposure

The three mean dose levels (body weight adjusted) used in clinical trial 2302 in patients 6-16 years of age are 0.4 mg/kg, 1.3 mg/kg and 2.7 mg/kg. The three mean dose levels (body weight adjusted) administered in clinical trial 2307 in patients 1- < 6 years of age are 0.4 mg/kg, 1.6 mg/kg and 3.4 mg/kg indicating a greater range of exposure of the two younger age groups compared to the two older age groups. The true exposure to valsartan in infants/ toddlers and pre-school children was by an additional factor of about 1.81 (Cmax) and 1.42 (AUC) greater in the younger children than in the older ones.

Comparison of doses and resulting exposures in the clinical trials and in the PK trial

The mean doses normalized for body weight in the single dose PK trial in the 1- < 6 year old children is 2.0 mg/kg. The corresponding figure in school children and adolescents is 1.6 mg/kg and 0.9 mg/kg, respectively. The mean doses normalized for body weight tested in the clinical trial in 1- < 6 year old children range between 0.4 mg/kg and 3.4 mg/kg. The mean doses normalized for body weight in 6-16

year old children range between 0.4 mg/kg and 2.7 mg/kg. With the exception of the adolescents the mean dose normalized for body weight used in the PK trial were in the middle of the dose range used in the clinical trial. In the adolescents the mean dose normalized for body weight in the PK trial was in the lower part of the dose range used in the clinical trial. A comparison of the exposures in the clinical and PK trials based on doses normalized for body weight is only appropriate for the children in the age between 1- < 6 years, because they received the same formulation, the suspension, in both the PK and clinical trial. However, it should be noted that the exposure in the PK trial was by factors of 1.81 (Cmax) and 1.42 (AUC) greater than predicted form the mean body weight normalized doses. Thus, the mean exposure to valsartan in the 6-16 year old children in the PK trial was in the upper part of the range of exposures attained in the clinical trial.

Comparison of doses and resulting exposures in children and adults

The minimum and maximum recommended doses of valsartan for the treatment of hypertension in adults are 80 mg and 320 mg qd, respectively. The bodyweight of most hypertensive adults ranges between 50 kg to 100 kg. A 50 kg weighing subject could receive a low dose of 80 mg valsartan and a subject weighing 100 kg could receive a high dose of 320 mg valsartan daily.

The body weight normalized doses for the two adult subjects are 1.6 mg/kg and 3.2 mg/kg, respectively. The dose range tested with the 1-< 6 year children (0.4 mg/kg-3.4 mg/kg) is clearly larger than with the adults as recommended by the WR. Considering the difference in bioavailability between extemporaneous suspension and commercial adult tablets the de facto tested dose range in the 1-< 6 year old children is by a factor of 1.4 greater (0.6- 4.8 mg/kg) than the nominal dose range. The dose range tested with the children 6-16 years of age is (0.4-2.7 mg/kg) starts and ends with a lower value than the adult dose range.

Linearity of PK and PK Parameters

The PK of valsartan have been shown to be dose proportionate and there is no overt evidence challenging this notion in children. In accordance with the WR AUC, t1/2, CL/F, V/F, Cmax and tmax were determined in the children of the 4 age groups. The submission discusses the PK results obtained in the children with those in adults.

Measurement of Active Compounds

Only the parent drug, valsartan, was measured in plasma. The absolute bioavailability of valsartan is about 25 % in adults. About 20% of valsartan is metabolized in adults and the remainder is excreted unchanged in the bile. Valsartan is the major circulating compound in adults. The activity of the metabolites has not been determined. It is reasonable to assume that the extent of metabolism in the 2-16 year old children tested is similar to that in adults.

Reporting

Full study reports were submitted for all PK studies.

The below table summarizes the findings regarding compliance with the Written Request;

Clinical Pharmacology Stipulations of Written Request

Requested	Compliance
PK in patients of same age range as studied for efficacy	√
Infants/toddlers, pre-school, school-age, adolescents	√
40-60% blacks	
>50% pre-pubertal	√
Ped. formulations appropriate for age and characterized	√
PK data over clinical dose range	√
Adult blood levels attained in clinical trials	√
Traditional or sparse sampling	√
Valsartan & active metabolites: AUC, Cmax, tmax, CL/f, V/F	√
Reporting in full study reports	√

2.2 What are the general attributes of the drug in adults

The initial approval for valsartan in the US was in 1996**.** Currently, valsartan in adults is approved for:

- Treatment of hypertension
- Treatment of heart failure (NYHA Class II-IV). Valsartan significantly reduced hospitalization for heart failure
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction

The starting dose in hypertensive adults is 80 mg or 160 mg once daily and the recommended dose range is 80-320 mg once daily.

2.3 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Valsartan is a hydrophilic anionic compound with a log D value of - 0.34.

The marketed drug products in adults are 40 mg (scored), 80 mg,160 mg and 320 mg tablets. The tested pediatric formulations include the pediatric extemporaneous suspension of 4 mg/mL, and pediatric 10 mg and 80 mg tablets.

2.4 What are the proposed mechanism(s)?

Valsartan is an angiotensin II receptor blocker (ARB). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects on vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal re-absorption of sodium.

2.5 General clinical pharmacology

2.5.1 What are the pharmacokinetic characteristics of valsartan in adults?

Peak plasma concentrations of valsartan are reached 2 h to 4 h after administration. After intravenous administration valsartan shows a biexponential decay with an apparent terminal half life of 6 h. Absolute bioavailability of valsartan is about 25%. Food decrease exposure to valsartan by about 40% (AUC) and 50% (Cmax). AUC and Cmax of valsartan increase approximately linearly with increasing dose over the clinical range. The plasma protein binding of valsartan is 95% and the steady-state volume of distribution is 17 L after intravenous administration. Valsartan does not accumulate appreciably in plasma following repeated administration.

Valsartan administered as oral solution is recovered by about 83% and 13% of the dose in feces and in urine, respectively. The recovery is mainly as valsartan, with only about 20% of the dose recovered as metabolites. The primary metabolite accounting for about 9% of the dose is valeryl 4-hydroxy valsartan. The activity of the metabolites is not known. The enzymes responsible for the metabolism of valsartan have not been identified, but do not seem to be CYP 450 isozymes. Total and renal clearances of valsartan are about 33 mL/min and 10 mL/min, respectively.

Special Populations

Elderly

In the elderly exposure to valsartan is increased by 70% and the half-life is 35% longer compared to young subjects.

Sex

The pharmacokinetics of valsartan do not differ significantly between males and females.

Renal Impairment

There is no apparent correlation between creatinine clearance and AUC for valsartan in patients with mild and moderate renal impairment and dose adjustment is not necessary. The impact of severe renal impairment (CLcr <10 mL/min) on the exposure to valsartan has not been investigated and care should be exercised with dosing in these patients. Hemodialysis does not remove valsartan from plasma.

Hepatic Impairment

The exposure (AUC) to valsartan in patients with mild to moderate chronic liver disease, including patients with biliary obstructive disorders, is increased by 100%. Care should be exercised in dosing of patients with liver disease.

Heart Failure

The oral clearance of valsartan in patients with heart failure is 75 mL/min. Valsartan in patients with heart failure accumulates by a factor of 1.7, whereas valsartan in patients without heart failure does not accumulate. Time to peak concentration and half- life in patients with heart failure and healthy subjects appear to be similar.

Drug Interactions

PK

No clinically significant pharmacokinetic drug interactions were observed when Diovan (valsartan) was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. Co-administration of valsartan and warfarin did not change the pharmacokinetics or time course of the anticoagulant properties of warfarin.

The enzymes responsible for valsartan metabolism have not been identified, but CYP 450 enzymes appear not to be involved. The inhibition or induction potential of valsartan is not known either.

PD

The valsartan-atenolol combination is more antihypertensive than either component, but it does not lower heart rate more than atenolol alone.

As with other drugs that block angiotensin or its effects, concomitant use of potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride) potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

2.5.2 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

See table below:

Table 1-1 Clinical studies in the valsartan pediatric clinical development program

Study No.	Patient population	Purpose	n (total)	Dosage of valsartan
Efficacy/safety studies in this submission			**351**	
CVAL489A2302 Pivotal study	Children 6 to 16 years of age with hypertension	Efficacy, dose response, safety, tolerability	261	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Pediatric tablet
CVAL489A2307 Supportive study	Children 1 to 5 years of age with hypertension	Efficacy, dose response, safety, tolerability	90	Phase 1: dose-response; Phase 2: placebo withdrawal; Open-label: dose titration by response. Oral suspension
Clinical pharmacology studies			**106**	
CVAL489A2301-BA	Healthy volunteers 18 to 45 years of age	Bioavailability of 80 mg valsartan tablets compared to 20 mL of oral valsartan suspension (4 mg/mL)	32	Randomized, single- dose, 80 mg valsartan tablet and 20 mL oral valsartan suspension (4 mg/mL) 2-way crossover design.
CVAL489A2304	Healthy volunteers 18 to 45 years of age	Bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablet	24	Single-dose, two-period, crossover design: 40 mg valsartan tablet and 4 x 10 mg valsartan tablets
CVAL489J2308	Healthy volunteers 18 to 50 years of age	Bioavailability of 80 mg valsartan pediatric tablet (CSF) compared to 80 mg valsartan FMI	24	Single- dose, 80 mg valsartan tablet (80 mg CSF, 80 mg FMI) 2-period crossover design
CVAL489A2305	Children 1 to 16 years of age with hypertension	PK of valsartan given as an oral suspension	26	Single-dose, oral suspension 2.0 mg/kg –> 80 mg (max) valsartan dose age-dependent

a: Details of doses received in Study A2302 and Study A2307 are in Figure 1-1.

2.5.3 What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics PD) and how are they measured in clinical pharmacology and clinical studies?

Blood pressure is an established surrogate endpoint. Hypertension is associated with an increased risk for myocardial infarction, stroke and mortality in adults. It is reasonable to assume that hypertension in children is associated with the same increased risk.

2.5.4 Are the active moieties in the plasma (or other biological fluids) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Valsartan is the principal active circulating moiety in adults. It is reasonable to assume that the same is true for children.

2.5.5 Exposure-response

2.5.6. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy in children? What is time of onset and offset of the desirable pharmacological response or clinical endpoint in children?

The hypotensive effect of valsartan increases with increasing dose in adults and in children. After single dose administration of valsartan the time of onset of the hypotensive effect of valsartan is 2 h after dosing. The peak effect occurs at about 6 h after administration and the hypotensive effect lasts for 24 h. With increasing dose the difference between peak and trough effect becomes smaller. After repeated doses given qd a substantial effect on blood pressure is present within 2 weeks of initiation of treatment and a maximum reduction is achieved after 4 weeks. The offset kinetics of the hypotensive effect after multiple dose administration in adults has not been determined. In adults the hypotensive effect of valsartan does not correlate with the plasma concentrations of the drug. The onset and offset of the hypotensive effect of valsartan in the pediatric population is also unknown.

2.5.7 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety?*

The hypotensive effect of valsartan increases with dose. The risk for orthostatic hypotension is small with valsartan, and could increase with increasing dose in adults and children. There was no clear dose dependency of orthostatic hypotension in the tested children. The risk for hyperkalemia is also expected to increase with dose. There was only one case of hyperkalemia in the tested pediatric population.

2.5.8 Does the drug prolong the QT/QTc interval?

The impact of valsartan on the QT/QTc intervals has not been determined in adults or children

2.5.9 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issue

The dose and dose regimens selected by the sponsor are consistent with the dose-efficacy relationship in children. A direct relationship between plasma concentration and efficacy does not appear to exist in adults. The relationship between plasma concentrations and hypotensive effect of valsaratan has not been investigated in children.

2.5.10 What are the PK Characteristics of the drug and its major metabolites?

2.5.10.1 What are the single and multiple dose PK parameters in children and how do they compare to those in adults?

The single and multiple dose pharmacokinetics of valsartan have been determined in adults. In children only single dose PK have been determined. The salient features of the PK of valsartan in children are**:**

Arithmetic Means (SD) of the Uncorrected PK Parameters of Valsartan in the Pediatric Population

PK Parameters	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**
Cmax, ng/mL	4307 (43)	4818 (39)	4254 (27)	3069 (41)
tmax, h	2.00	2.00	2.00	2.00
AUC0-∞, ng●h/mL	25823 (43)	26800 (26)	20214 (36)	15944 (35)
CL/F, (L/h)	1.50 (67)	1.63 (21)	3.80 (43)	5.75 (45)
t1/2, h	3.79 (10)	3.95 (13)	5.33 (12)	4.97 (15)

The results indicate that the oral clearance of valsartan increases with body weight and/or age. The half life shows also a weak trend to increase with body weight and/or age. In comparing Cmax and AUC0-∞ it should be noted that the dose in mg/kg in the oldest children was considerably smaller (0.9 mg/kg) than in the other age groups (2.0 mg/kg).

Dose Adjusted[a] Geometric Mean Exposure Measures in the Four Pediatric Age Groups

PK Parameter	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**
Cmax, ng/mL	3796	4536	4882	6237
AUC0-∞, ng●h/mL	23294	26333	22544	32997

[a] Adjusted to a dose of 2 mg/kg

The results indicate the body weight normalized exposure is largest in the oldest age groups.

Body Weight Adjusted Mean Oral Clearance in the Four Pediatric Age Groups

PK Parameter	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**
CL/F, (L/h ● kg)	0.097	0.078	0.098	0.076

The results indicate that the body weight adjusted oral clearance among the four age groups is comparable.

Dose Adjusted[a] Geometric Mean Exposure Measures in the Pediatric Groups and Adults

PK Parameter	**1 - 4 y**	**4 - < 6 y**	**6 - < 12 y**	**12-16 y**	**Adults**	
Cmax, ng/mL	3796	4536	4882	6237	2572[b]	5804[c]
AUC0-∞, ng●h/mL	23294	26333	22544	32997	16791[b]	31256[c]

T1/2, h	3.8	4.0	5.3	5.0	4.6[b]	8.6[c]

[a] Adjusted to a dose of 2 mg/kg [b] Study 2304 [c] Study 2301

The results indicate that peak and average exposure in adults and adolescents receiving the extemporaneous suspension are similar and slightly greater than in the younger pediatric age groups. In contrast, the exposure in the pediatric population receiving the extemporaneous suspension exceeds clearly that of the adults administered the 80 mg adult tablet. There appears to be a difference in t1/2 for valsartan in adults. However, this is most probably the result of the 24 h blood sample collection interval in study 2304 versus the 36 h blood sampling interval used in study 2301. Since in the PK study blood samples were collected only for 24 h after administration it is more appropriate to compare the t1/2 values in the pediatric population with that of the adults in study 2304. It can be concluded that the exposure measures when normalized for body weight are similar in children and adult and the t1/2 estimates are also comparable.

2.5.10.2 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In adults the PK of valsartan are approximately dose proportionate.

2.5.10.3 How do the PK parameters change with time?

A possible impact of time on the PK of valsartan has not been examined in adults.

2.5.10.4 How do the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The label of valsartan does not indicate whether the PK of the drug in healthy adults and in hypertensive adults are different, but it is probable that the PK in the two populations when matched for age, and body weight are similar. In the pediatric population the pharmacokinetics of valsartan were only investigated in children with hypertension. The existence of active metabolites is unknown.

2.5.10.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject Variation (CV, %) of the Unapproved and Approved Valsartan Formulations in Adults

Formulation	Adult 80 mg		Adult 40 mg	Ext. Suspension	Ped. 10 mg	Ped. 80 mg
Cmax	54.4	30.1	27.6	37.5	36.4	50.3
AUC	42.9	32.4	32.4	39.4	39.6	48.1

In the bioavailability studies submitted in the present submission the inter-subject variation in Cmax and AUC of the unapproved pediatric formulation tested in healthy adults ranges between 28% -54% and 32% and 48%, respectively. In hypertensive children in the age between 1 and 16 years the inter-subject variation of Cmax and AUC with the unapproved extemporaneous suspension ranges between 27-43% and 26-43%, respectively. In healthy adults the inter-subject variation of Cmax and AUC is 38% and 39%, respectively. It can be concluded that the inter-subject variation of the unapproved pediatric

formulations in healthy adults is comparable as is the inter-subject variation of the extemporaneous formulation in healthy adults and hypertensive children.

The labeling does not indicate the inter- and intra-subject variation of the PK parameters for valsartan in adults.

2.6. Intrinsic factors

2.6.1 What intrinsic factors (age, gender, race, disease, genetic polymorphism, pregnancy, organ dysfunction influence exposure?

At comparable doses elderly patients experience greater plasma levels than younger subjects (AUC is increased by a factor of 1.7 and t1/2 by a factor 1.4). In adults mild and moderate hepatic impairment increase the plasma levels by a factor of 2.0. The exposure to valsartan in adult patients with mild and moderate renal impairment is not relevantly increased. The impact of severe renal impairment (CLcr < 10 mL/min) has not been studied. It appears that subjects with CLcr in the range between 11-29 mL/min have not been studied either. Age, gender and race have no effect on the hypotensive effect of valsartan. In adults the hypotensive effect of valsartan is not different between black and white adults.

2.6.2 What pharmacogenetic information is there in the application and is it important or not?

No pharmacogenetic information is provided in adults or children for valsartan.

2.6.3 What is known about drug-drug interactions

No PK based interactions were found when valsartan was co-administered together with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin in adults.

No interaction studies were performed in children.

2.6.4. Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. The results of a published study suggest that the anionic hydrophilic valsartan is a substrate of the OATP and MRP2. Rifampicin and cyclosporine A, known inhibitors of OATP, if co-administered with valsartan, could result in a PK based drug- interaction.

2.7 Extrinsic Factors

2.7.1 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

The enzymes responsible for the metabolism of valsartan have not been identified, but it seems that CYP 450 enzymes are not involved. It is unknown whether the metabolism of valsartan is influenced by pharmacogenetics/genomics.

2.7.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

The status of valsartan as an inhibitor or inducer in vitro or in vivo has not been determined.

2.7.3. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

It is not known whether valsartan is a substrate or inhibitor of P-glycoprotein.

2.7.4 Are there other metabolic/transporter pathways that may be important?

Valsartan is a hydrophilic anionic compound. In vitro data suggest that valsartan may be a substrate of the hepatic uptake transporter OATP and the efflux transporter MRP2.

2.7.5 Does the label specify co-administration of another drug (e.g. combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

No.

2.7.6 What other co-medications are likely to be administered to the target population?

Other antihypertensives, diuretics, hypocholesterinemic drugs.

2.7.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.7.8 Is there a known mechanistic basis for pharmacodynamic dug-drug interactions, if any?

Co-administration of other antihypertensive agents may result in orthostatic hypotension. Co-administration of potassium sparing diuretics, aldosterone antagonists,ACE-inhibitors or potassium containing salts may result in hyperkalemia.

2.7.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Enzymes involved in metabolism of valsartan and activity of main metabolite have not been determined.

2.7.10 What issues related to dose, dose regimens, or administration are unresolved and represent significant omissions?

None (?)

2.8 General biopharmaceutics

This section should summarize the salient points about the attributes of the drug product

2.8.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The BCS classification of valsartan has not been determined. The extemporaneous suspension made form the commercial adult 80 mg tablet is the only new formulation.

2.8.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Two clinical trials were performed: In the first trial 6-16 year old hypertensive children were enrolled. They received the unapproved pediatric 10 mg and 80 mg tablets. In the second trial 1-< 6 year old children were enrolled and were administered the unapproved 4 mg/mL extemporaneous suspension. The bioavailability of the suspension relative to the unapproved pediatric 10 mg and 80 mg tablets is 1.8 times (Cmax) and 1.4 times (AUC) greater. The bioavailability of the suspension relative to the commercial adult 40 mg and 80 mg tablets is 1.9 times greater (Cmax) and 1.6 (AUC) times greater.

2.8.3 What data support or do not support a waiver of in vivo BE data?

- ***BCS classification system***
- ***Formulation ingredient information***
- ***Dissolution profiles***
- ***Others***

NA

2.8.4 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

The 1- < 6 year old children received the same mg/kg doses as the older children, but as a result of the increased bioavailability of the suspension relative to the unapproved and approved solid dosage formulations the exposure of the 1- < 6 year old children in the clinical trial was significantly greater than that of the 6-16 year old children or adults.

2.8.5 If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to be marketed product?

There was no overt evidence for a safety issue of valsartan in the younger and older pediatric age groups. It is critical that the dose be adjusted in accordance with the difference in bioavailability if the suspension is changed to a solid dosage form in a pre-school child old enough to swallow a tablet.

2.8.6 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food decreases Cmax and AUC by about 40% and 50%, respectively, in adults receiving the tablet. It is not known whether food interacts with the drug substance or the drug product. The impact of food was not investigated in children receiving the suspension. An interaction of food with the suspension cannot be excluded.

2.8.5When would a fed BE study be appropriate and was one conducted

NA

2.8.6 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

NA

2.8.7 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to be marketed product?

NA

2.8.8 If the NDA is for a modified release formulation of an approved immediate release product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

NA

2.8.9 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

NA

2.8.10 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None

2.9 Analytical section

This section should address issues related to the analytical and bioanalytical methods used to support the clinical pharmacology and biopharmaceutics studies

2.9.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Valsartan has been shown to be the main active circulating compound in adults. It is reasonable to assume that the same is true for children.

2.9.2 Which metabolites have been selected for analysis and why?

Metabolites of valsartan have not been measured in children. About 20 % of the dose is recovered as metabolites in adults with 9% of the dose as valeryl 4-hydroxy valsartan.

2.9.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (bound + unbound) concentrations of valsartan in plasma were measured in adults and in children. The plasma protein binding of valsartan has been shown to be linear within the therapeutic range in adults. It is reasonable to assume that the same is true for children.

2.9.4 ***What bioanalytical methods are used to assess concentrations?***

2.9.4.1 What is the range of the standard curve?

See below table:

Study	Assay	Calibration Curve		LLOQ	Accuracy Range %	Precision %
		ng/mL	R	ng /mL	interday	interday
CVAL489A2301	HPLC-	50-5000	≥ 0.9992			
VAL489J2308	HPLC-MS/MS	2-10000	≥ 0.9996			
VAL489A2304	HPLCMS/MS	2-5000	≥ 0.9969			
VAL489A2305	HPLC-MS/MS	2-5000	≥ 0.9962			

How does it relate to the requirements for clinical studies?

The range measured represents the range of valsartan concentrations attained under clinical conditions

What curve fitting techniques are used?

Linear functions are fitted to the calibration standard data with the HPLC- detection assay and the HPLC-MS/MS assays. The data are weighted by 1/Y or 1/ Y^2.

2.9.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See above table.

2.9.4.3 What are the accuracy, precision, and selectivity at these limits?

See above table.

2.9.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample handling, sample transport, autosampler)?

Valsartan in plasma is stable when kept for 72 h at room temperature. Valsartan is also stable when stored for 4 weeks at -20 ° C and when exposed to a single freeze-thaw cycle.

2.9.4.5 What is the QC sample plan?

QC samples were measured along with the samples with unknown plasma concentrations of valsartan.

3. LABELING RECOMMENDATIONS

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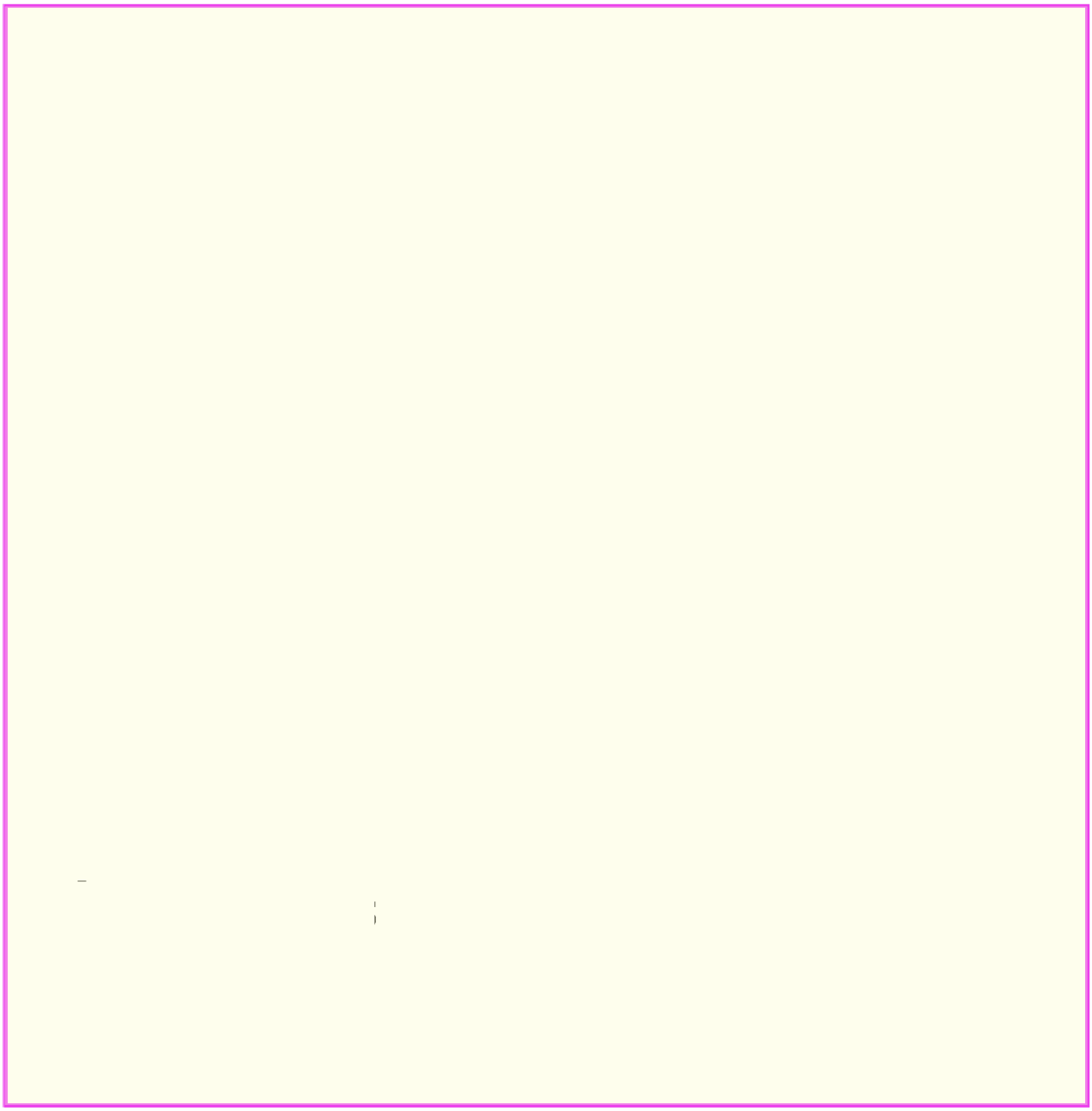


4. INDIVIDUAL STUDY REPORTS

4.1 Study Report: CVAL489A2301-BA " A Randomized, Open-Label, Crossover Study Comparing the Relative Bioavailability of 20 mL of 4 mg/mL Valsartan Oral Suspension and one 80 mg Valsartan Tablet "

Study Site and Investigator

Objectives

The primary objective of this study was to assess the relative bioavailability of 20 mL of 4 mg/mL valsartan extemporaneous oral suspension and one 80 mg valsartan tablet in healthy volunteers

Investigational Drugs/Formulations

Valsartan extemporaneous oral suspension: 20 mL (4 mg/mL) prepared from 80 mg tablets (Lot No.: 01-368US) (Test treatment), Ora Plus suspending vehicle, manufactured by Paddock Laboratories, Inc. Lot No.: 172930, Ora Sweet SF sweetening vehicle, manufactured by Paddock Laboratories, Inc. (Lot No.:132736)

Valsartan 80 mg tablets, manufactured by Novartis Pharmaceutical Corporation, Lot No.: 01-368US (reference treatment)

The pharmacist at the study site prepared the 4 mg/mL valsartan extemporaneous suspension using 80 mg tablets from the bulk supply, according to the instructions given by the sponsor.

Design

The study used a randomized, open-label, two-period, crossover design. A total of 32 male and non-fecund female subjects in the age range 18-45 years and in good health, as determined by past medical history, physical examination, vital signs, ECG, and laboratory test at screening, were to be enrolled in the study. A seven day inter-dose wash-out period was maintained. The subjects were admitted to the study center on the eve of the dosing day and discharged from the unit 36 h after dosing. The subjects fasted 10 h prior to dosing. Study medication was administered together with 180 mL water.

A scheme of the scheduled study activities is shown below:

Table 3.5-1 Evaluation and visit schedule

Study Phase	Screening Day -21 to -1	Period 1 Check-in Day -1	Period 1 Day 0	Washout Days 0-6	Period 2 Check-in Day 6	Period 2 Day 7	End of Study Day 8
Visit number	1	2	3		4	5	6
Evaluation							
Inclusion/Exclusion Criteria	X						
Relevant Medical History Current Medical Conditions	X						
Intervisit Medical History		X					
Demography	X						
Physical Examination	X						X
Hepatitis and HIV Screen	X						
Urine Alcohol & Drug Screen Urine Cotinine	X	X			X		
Pregnancy Test (females only)	X	X			X		X
Drug Administration Record			X			X	
Meal Record			X			X	
Study Completion Information							X
Comments	*	*	*	*	*	*	*
Body Height	X						
Body Weight	X						
Body Temperature	X	X					
Blood Pressure, Pulse Pulse rate	X	X			X		X

Table 3.5-1 Evaluation and visit schedule (continued)

ECG Evaluation	X						
Hematology & Blood Chemistry Urinalysis	X						X
Adverse Events			X	X	X	X	X
Concomitant Meds/Therapies	X	X			X		X
PK Blood Collection			X			X	

* Comments as applicable

Safety and Tolerability

Safety and tolerability were assessed by physical examination, vital signs monitoring, ECGs, safety laboratory evaluations (hematology, serum chemistry, urinalysis) and adverse event recording.

Pharmacokinetic Profiling

Blood samples for the determination of the plasma concentrations of valsartan were collected at the following times: pre-dose, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24 and 36 h after administration.

Bioassay

Valsartan plasma concentrations were measured by a HPLC method with detection that used an internal standard. Calibration curves were generated using 1/y weighted linear least squares regression and were presented as plots of the peak area ratios of valsartan to the internal standard versus the concentrations of the calibration standards. The concentration range of the calibration standards was 50-5000 ng/mL. QC samples with concentrations of 50, 100, 300, 1000 and 5000 ng/mL were used. Inter-day and intra-day accuracy and precision was determined using the QC samples that were analyzed in replicate on each of three analysis days. Sample stability was studied by analyzing duplicate sample aliquots of 50, 1000 and 5000 ng/mL immediately after preparation and then again after 6, 24, 48, and 72 h with the samples kept at room temperature and analyzing duplicate aliquots at time intervals of 7, 14 and 30 days after being frozen at -20°. After storage the samples were thawed and brought to room temperature before analysis. A freeze-thaw study was conducted with duplicate samples at each concentration. The samples that had been frozen for 30 days, were thawed and refrozen for three consecutive days, and then analyzed on the third day.

The correlation coefficient of the calibration curve fits were ≥ 0.9992. The inter-day accuracy of the QC samples ranged between -11.7% and 5.7%. The inter-day precision of the QC samples was ≤ 14.9%. The intra-day accuracy of the QC samples ranged between -11.8% and 14.9% and the intraday precision was ≤ 16.0%. Valsartan was stable in plasma kept at room temperature for 72 h, after storage for 4 weeks at -20° C and after going through a freeze-thaw cycle.
The assay was performed in the laboratories of the sponsor.

PK Data Analysis

The following PK parameters were estimated using non-compartmental methods: AUC0-tlast, AUC0-inf, Cmax, Tmax, Kel, t1/2. The AUC0-tlast was obtained by linear trapezoidal summation.

Statistical Methods

The PK parameters AUC0-tlast, AUC0-inf and Cmax of the test and reference treatments were compared using ANOVA based on the log transformed values. The analysis model contained sequence, formulation, and period as fixed factors and subject (nested in sequence) as random factor. The ratio of treatment means on the original scale was estimated, along with its 90% confidence interval, by the antilog of the difference in least square means on the log scale.

Sample Size

The sample size was calculated based on the criterion that, for an estimated ratio of formulation means (suspension versus tablet) for PK parameters AUC and Cmax there was at least an 80% probability that the 90% confidence interval was within 80%-125% of the true ratio value. In the calculation it was assumed that the true value of mean ratio was between 1 and 1.2, and the PK parameter coefficient of variation (CV) was 0.27 (source CVAL489 Studies 0603 and 0604 which suggested that the CVs for AUC and Cmax were 0.22 and 0.27, respectively).

Results

Thirty two (32) male subjects were enrolled in the study. Thirty (30) subjects completed both treatments. Subject 5110 only received Treatment A (oral suspension) and subject 5130 only received Treatment B (80 mg tablet). Subject 5110 had a positive drug screen at Period 2 check-in, and subject 5130 withdrew consent after the Period 1 dose. The 30 subjects who completed both treatments were included in the PK analysis. All 32 subjects were included in the safety evaluation.

The demographic of the subjects is shown in the table below:

Table 7.4-1 Demographics

Race (N)	
Black	17
Caucasian	9
Other	6
Age (years)	
Mean ± SD	33.8 ± 6.8
Range	21–45
Gender	
Male	32
Weight (kg)	
Mean ± SD	79.7 ± 10.2
Range	54.7–101.3
Height (cm)	
Mean ± SD	178.8 ± 6.1
Range	169–191

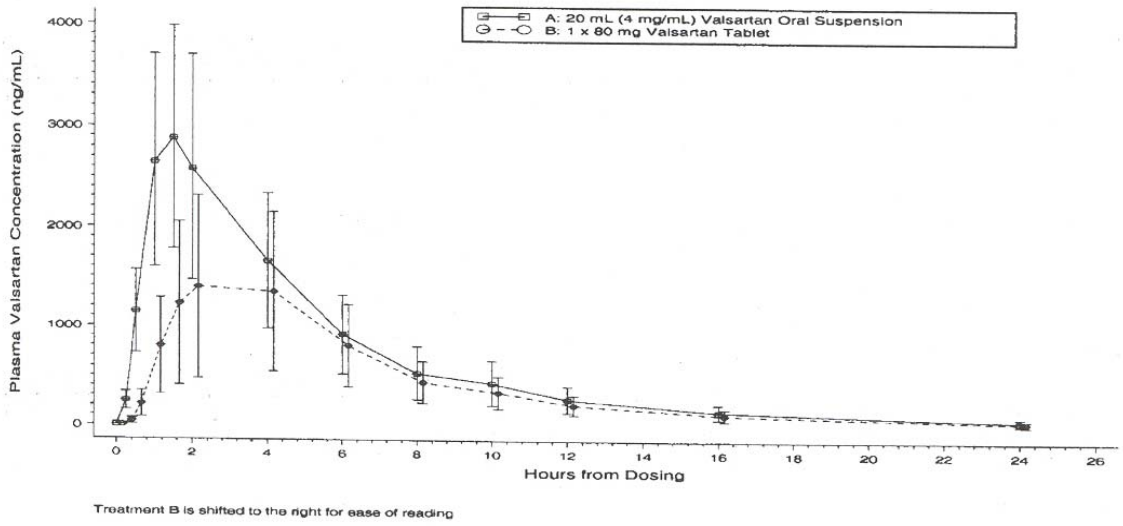
Tolerability

Two treatment emergent adverse events occurred in 2 subjects after administration of the valsartan oral suspension. One headache was moderate and occurred 1 h post-dose and was considered drug related by the investigator. The other headache was mild, occurred 15 h after drug administration and was considered unrelated to drug intake by the investigator. No serious adverse events or death occurred.

Pharmacokinetics

Plots of the mean plasma concentrations of valsartan after administration of the 20 mL (4mg/mL) oral suspension and 80 mg tablet are shown in the figure below:

Figure 8.1.3.1-1 Mean Plasma Valsartan Concentrations Versus Time



The plots indicate that the rate and extent of release of valsartan from the suspension is significantly greater than from the tablet.

The results of the arithmetic means, the geometric mean ratios and the 90% confidence intervals for the ratios of the treatments for Cmax, Tmax, AUC0-tlast, AUC0-inf, T1/2 and Kel listed in the table below confirm the visual impression from the plots:

Summary of the Pharmacokinetic Parameters of Plasma Valsartan for Treatments A and B

	--------- Plasma Valsartan ---------						
	Treatment A		Treatment B				
Pharmacokinetic Parameters	Arithmetic Mean	SD	Arithmetic Mean	SD	% Geometric Mean Ratio	p value	90% CI for True Ratio(A/B)
Cmax(ng/mL)	3128.0	1172.8	1764.3	960.07	192.8	0.0001	159.9- 232.5
Tmax(hr)	1.57	0.586	2.72	1.37	.	.	. - .
AUC(0-t)(ng*hr/mL)	16129	6287.3	10769	4933.8	158.0	0.0001	137.1- 182.2
AUC(0-inf)(ng*hr/mL)	16771	6605.1	11627	4985.3	155.7	0.0001	136.3- 178.0
T1/2(hr)	8.56	2.50	9.23	2.40	.	.	. - .
Kel(1/hr)	0.0865	0.0223	0.0805	0.0231	.	.	. - .

Treatment A = 20 mL (4 mg/mL) Valsartan Oral Suspension: test
Treatment B = 1 x 80 mg Valsartan Tablet: reference

Conclusions

The valsartan 20 mL (4mg/mL) oral suspension and 80 mg tablet are not bioequivalent. Cmax and AUC0-inf with the oral suspension is 1.93 and 1.56 times greater, respectively, than with the 80 mg tablet. Both treatments were tolerated well.

Comments

None

4.2 Study Report: VAL489J 2308 "An Open-Label, Single Dose, Two Period, Randomized Crossover Study to Determine the Relative Bioavailability of 80 mg Valsartan Pediatric Tablet (CSF) as Compared to a 80 mg Valsartan Marketed Tablet in Healthy Subjects"

Study Site and Investigator:

Objectives

The primary objective of this study was to determine the relative bioavailability of an 80 mg valsartan pediatric tablet (clinical service form, CSF) compared to an 80 mg valsartan marketed tablet final market image (FMI) in healthy subjects.

Investigational Drugs/Formulations

Valsartan pediatric (VAKL489A) 80 mg oral tablets (CSF), Lot No.:04-0110US, bulk number: AEUS/2004-0044

Valsartan marketed (VAL489A) 80 mg oral tablets (FMI), Lot No.:131J4422

Design

This study employed an open label, randomized, single dose, 2-period, crossover design. Twenty four subjects were randomly assigned to receive 1 of 2 treatments sequences. All subjects received a single 80 mg oral dose of valsartan pediatric tablet (CSF) (Treatment A) and a single 80 mg oral dose of valsartan marketed tablet (FMI) (Treatment B) under fasted conditions either as Treatment A followed by Treatment B or Treatment B followed by Treatment A during Periods 1 and 2. A seven day wash-out period was maintained between the Treatment periods.

Healthy male or female subjects in the age range between 18 and 45 years of age were eligible to participate in the study. Their good health was ascertained by medical history, physical examination, vital signs, ECG, and laboratory tests. Female subjects must not have been pregnant and must have been surgically sterilized at least 6 month before screening, using a double-barrier method of contraception, or be postmenopausal (defined as the absence of menstrual bleeding for 2 years before inclusion and confirmed by laboratory testing). Pregnancy tests were required of all women.
Participating subjects were confined to the study site for at least 12 h prior to dosing until 48 h after dosing. The subjects fasted for at least 10 h prior to dosing. The study drug was administered together with 240 mL of water.

Safety and Tolerability

Physical examination and hematology, chemistry and urinalysis was performed and vital signs, ECG, and adverse events recorded.

Pharmacokinetic Profiling

Blood samples for the determination of valsartan were collected at the following times: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h after dosing.

Bioassay

A HPLC/MS/MS method using turbo ion spray positive ion mode with an [redacted] was employed. The LLOQ of the method is 20 ng/mL. The concentration range of the linear calibration curve ranged between 20 ng/mL and 10000 ng/mL. The coefficients of determination of the linear fits of the calibration curve were ≥ 0.9938. The data were weighted by $1/Y^2$. The QC samples exhibited concentrations of 50.0 ng/mL, 4000 ng/mL and 8000 ng/mL. The inter-day accuracy of the QC samples ranged between -0.4% and -3.6% and the precision was ≤ 7.3%. The measurements of the plasma concentrations of valsartan were performed in the laboratories of the sponsor.

Pharmacokinetic Data Analysis

The following parameters were determined using non-compartmental methods: AUC0-tlast, AUC0-∞, Cmax, tmax, t1/2 and λ.

Statistical Evaluation

For assessment of bioavailability AUC0-tlast, AUC0-∞, and Cmax were compared between the 80 mg valsartan oral tablet (CSF) (test drug Treatment A) and the 80 mg valsartan marketed oral tablet (FMI) (reference drug-Treatment B). A linear mixed effect model on log transformed PK parameters, with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The ratio of treatment means on the original scale was estimated, along with 90% confidence interval, by the

antilog of the difference in least squares means on the log scale for AUC0-tlast, AUC0-∞ and Cmax.

Sample Size

An estimated intra-subject coefficient of variation of 25% obtained from Study VAL489A Study 604 was used to determine the sample size. With a sample size of 24 subjects, there was 80% power that the 90% confidence interval for the treatment ratios of mean AUC0-t, AUC0-∞ and Cmax would be contained in the bioequivalence range of 80% to 125% assuming the true formulation means were equal.

Results

Twenty-four subjects were enrolled and completed the study. The below table lists the demographics of the subjects:

Table 7-1 Summary of demographic information

	Treatment		
	Sequence 1 N = 12	Sequence 2 N = 12	Overall N = 24
Race (N [%])			
Caucasian	2 (16.7%)	2 (16.7%)	4 (16.7%)
Other	10 (83.3%)	10 (83.3%)	20 (83.3%)
Age (years)			
Mean	40.4	37.9	39.2
SD	9.51	6.49	8.06
Median	44.5	40.0	41.5
Minimum, Maximum	24, 50	25, 47	24, 50
Sex			
Male	4 (33.3%)	6 (50.0%)	10 (41.7%)
Female	8 (66.7%)	6 (50.0%)	14 (58.3%)
Body Frame			
Small	3 (25.0%)	3 (25.0%)	6 (25.0%)
Medium	6 (50.0%)	7 (58.3%)	13 (54.2%)
Large	3 (25.0%)	2 (16.7%)	5 (20.8%)
Weight (kg)			
Mean	70.4	72.6	71.5
SD	8.62	7.92	8.18
Minimum, Maximum	59.5, 87.4	57.7, 84.4	57.7, 87.4
Height (cm)			
Mean	162.4	168.2	165.3
SD	9.47	8.67	9.36
Median	160.5	169.0	164.5
Minimum, Maximum	148, 184	153, 179	148, 184
Elbow breadth (cm)			
Mean	6.6	6.6	6.6
SD	0.72	0.42	0.57
Median	6.6	6.8	6.7
Minimum, Maximum	5.6, 8.1	5.9, 7.1	5.6, 8.1

Source: Appendix 3, Table 2.2.2
Categorical data are presented as N (%).
Sequence 1 = Single 80-mg oral dose of valsartan pediatric tablet (CSF) (test drug) during Period 1 and a single 80-mg oral dose of valsartan marketed tablet (FMI) (reference drug) during Period 2.
Sequence 2 = Single 80-mg oral dose of valsartan marketed tablet (FMI) (reference drug) during Period 1 and a single 80-mg oral dose of valsartan pediatric tablet (CSF) (test drug) during Period 2.

Tolerability/Safety

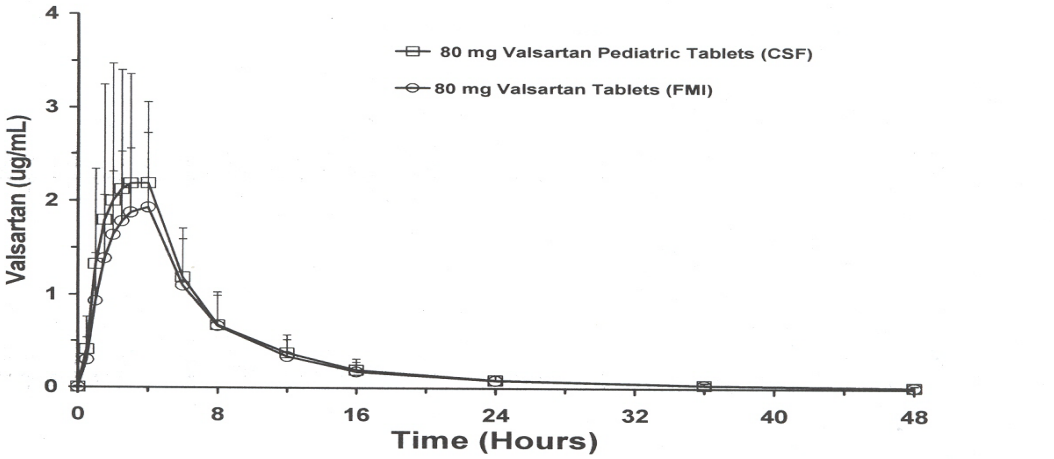
The treatments were tolerated well. One subject experienced a sore throat 25 h after receiving Treatment B. No serious adverse events or death occurred.

Pharmacokinetics

The estimates for AUC0-∞ and λz for subject 5106 were not included in the statistical analysis of the PK data, because the value for λz was unusually small in Treatment A. However, the corresponding Cmax and AUC0-tlast were inconspicuous and used in the statistical analysis.

The plasma concentration time profiles of valsartan following administration of the 80 mg valsartan pediatric tablet (CSF) and the 80 mg valsartan tablets (FMI) are shown in the plot below:

Figure 7-1 **Mean plasma valsartan concentration versus time profile following single-dose administration of 80-mg pediatric tablets (CSF) and 80-mg marketed tablets (FMI)**



It can be seen that the pediatric 80 mg tablets display slightly larger Cmax and AUC0-∞ values than the marketed 80 mg tablets.

The below two tables show the arithmetic means (SD) of AUC0-tlast, AUC0-∞, Cmax, tmax and t1/2 and the geometric means and 90% confidence intervals for the ratio of the geometric means:

Table 7-2 **Arithmetic mean plus or minus SD (CV%) pharmacokinetic parameters of valsartan following oral administration of 80-mg pediatric tablets (CSF) and 80-mg marketed tablets (FMI)**

Pharmacokinetic Parameter	Treatment A – test drug	Treatment B – reference drug
		(N = 24)
AUC_{0-t} (μg·h/mL)	17.04 ± 8.3 (48.5)	15.11 ± 5.4 (35.5)
$AUC_{0-\infty}$ (μg·h/mL)	17.46 ± 8.4 (48.1)	15.70 ± 5.4 (34.6)#
C_{max} (μg/mL)	2.6 ± 1.3 (50.3)	2.3 ± 0.7 (30.1)
$t_{1/2}$ (h)	8.26 ± 3.37 (40.8)	8.05 ± 3.24 (40.3)
t_{max} (h)*	3.17 (1.5, 6.0)	3.3 (1.5, 8.0)

Source: Appendix 4, Table 3, Appendix 4, Table 4 and Appendix 6, Table 6.1.1

* Median (minimum, maximum) values are presented.

\# N = 23

Treatment A = Single 80-mg oral dose of valsartan pediatric tablet (CSF).

Treatment B = Single 80-mg oral dose of valsartan marketed tablet (FMI).

Table 7-3 Assessment of relative bioavailability between 80-mg pediatric tablets (CSF) and 80-mg marketed tablets (FMI) for valsartan

Parameters	Treatment*	Geometric mean†	Ratio of geometric means†	90% CI for ratio†	*P* value†
AUC_{0-t} µg·h/mL (N=24)	A	15.4	1.09	(0.94, 1.28)	0.324
	B	14.1			
$AUC_{0-\infty}$ µg·h/mL (N=24)	A	15.8	1.08	(0.93, 1.26)	0.367
	B	14.6			
C_{max} µg/mL	A	2.3	1.06	(0.86, 1.31)	0.649
	B	2.2			

Source: Appendix 6, Table 6.1.1

* A = 80-mg pediatric tablet (test drug); B = 80-mg marketed tablet (reference drug)

† A mixed effect model analysis for the log-transformed values with treatment period and sequence as fixed effects and subject nested within sequence as a random effect.

The statistical evaluation of the data indicates that the geometric mean of Cmax and AUC with the 80 mg pediatric tablet is 1.06 and 1.08 times greater than with the commercial adult 80 mg tablet. The upper limits of the respective 90% confidence intervals for AUC0-tlast, AUC0-∞ and Cmax of the pediatric tablet with 1.28, 1.26 and 1.31 exceed the 1.25 margin, indicating that the pediatric tablet and the marketed tablet are bioinequivalent.

Conclusions

The bioavailability of the pediatric and the adult tablets are comparable, but are not equivalent. Both treatments were tolerated well.

Comments

None

4.3 Study Report: VAL489A 2304 " An Open Label, Single Dose, Two Period, Randomized Crossover Study To Determine the Relative Bioavailability of 4 x10 mg Valsartan Tablets (CSF) as Compared to a 40 mg Valsartan Tablet in Healthy Subjects"

Study Site and Investigator

Objectives

To determine the relative bioavailability of 4 x 10 mg valsartan tablets compared to 40 mg valsartan tablets in healthy volunteers

Investigational Drugs

4 x 10 mg valsartan tablets (CSF) Lot No.: H-05994
40 mg commercial valsartan tablets Lot No.: 001E6956

Design

This was an open-label, randomized, two-period, crossover study. Treatment A was a single dose of 4 x 10 mg valsartan tablets (test) and Treatment B was 1 x 40 mg valsartan tablet (reference). A wash-out period of 7 days was maintained between the two treatment periods. Twenty-four healthy subjects in the age between 18 and 45 years were to be enrolled in the study. Female subjects of childbearing potential were using or agreed to use double-barrier local contraception. The subjects were admitted to the study site on the evening of dosing days and domiciled for at least 24 h after dosing. The treatments were administered together with 180 ml water after a 10 h fast.

Tolerability and Safety

The health of the enrolled subjects was ascertained by medical history, physical examination, ECG, laboratory tests (hematology, clinical chemistry and urinalysis).

Pharmacokinetic Profiling

Blood samples for the determination of valsartan plasma concentrations were obtained at the following times: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 h post-dose.

Bioassay

A HPLC/MS/MS method using turbo ion spray positive ion mode with an [redacted] was employed. The LLOQ of the method is 2 ng/mL. The concentration range of the linear calibration curve ranged between 2 ng/mL and 5000 ng/mL. The coefficients of determination of the linear fits of the calibration curve were ≥ 0.9938. The data were weighted by $1/Y^2$. The QC samples exhibited concentrations of 4.0 ng/mL, 100 ng/mL and 4000 ng/mL. The inter-day accuracy of the QC samples ranged between -2% and 1% and the precision was ≤ 10.4%. The measurements of the plasma concentrations of valsartan were performed in the laboratories of the sponsor.

PK Data Analysis

The following parameters were determined: AUC0-t, AUC0-∞, Cmax, tmax, λz and t1/2. AUC0-tlast was determined by the linear trapezoidal rule. The other parameters were determined using non-compartmental standard methods.

Statistical Evaluation

The PK parameters AUC0-t, AUC0-∞ and Cmax were evaluated. For comparisons of means, parametric analyses were performed. A mixed effects model was fit to data

containing sequence, treatment, and period as fixed factors and subject within sequence as a random effect.
The 90% confidence limits for the difference between least squares means on the log scale were anti-logged to provide intervals for the ratios of the least squares means on the original scale.

Sample Size

Based on a previous bioequivalence study (VAL489Study 604), an estimated intra-subject CV of 0.25 was considered appropriate for sample size determination. Using this estimate and the normal approximation of the test statistic for the comparison between two means on the log–transformed scale, 24 subjects would provide approximately 80% power to have the 90% confidence intervals for the treatment ratios of mean AUC0-t, mean AUC0-∞, or mean Cmax to be contained entirely in the range 80%-125%, assuming the true ratio of the means of the formulations being 100%.

Results

Of the 24 subjects enrolled in the study 23 completed both treatments. Subject 05117 withdrew consent after Period 1. Mean weight and age of the subjects was 69 kg and 30 years, respectively.

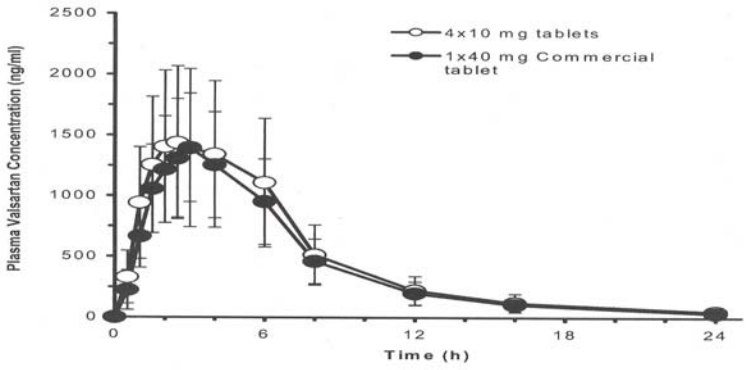
Tolerability and Safety

The two treatments were tolerated well. No serious adverse events of death were reported. Seven adverse events were recorded by 5 of 24 subjects. Six (6) of the adverse events were not suspected to be drug related by the investigator. Subject 5108 reported a headache which was suspected to be drug related by the investigator.

Pharmacokinetics

The mean plasma concentration time profiles of valsartan after administration of 4 x 10 mg tablets and 1 x 40 mg commercial tablet are shown below:

Figure 7-1 **Mean (±sd) plasma concentration vs time profiles of valsartan following single oral dose administration of 4x10 mg tablets of valsartan and 1x40 mg tablet of valsartan.**



The plots of the mean concentrations show that Cmax and AUC0-∞ after administration of 4 x10 mg tablets tend to be greater than after administration of the 40 mg commercial tablet.

Arithmetic means or medians of the bioavailability measures are shown in the below table:

Table 7-2 Summary of the pharmacokinetic parameters of valsartan after a single dose administration of 4x10 mg valsartan tablets vs 40 mg valsartan tablet (n=23, subject 5117 excluded due to drop out at period 2).

Treatment	Tmax (h) Median (min; max)	Cmax (ng/ml) Mean ± SD (CV%)	$AUC_{(0-t)}$ (ng.h/ml) Mean ± SD (CV%)	$AUC_{0-\infty}$ (ng.h/ml) Mean ± SD (CV%)
4x10 mg	2.5 (1.5; 6.0)	1766.5 ± 642.6 (36.4%)	11618.1 ± 4454.8 (38.3%)	11991.4 ± 4752.2 (39.6%)
40 mg	3.0 (1.07; 4.07)	1545.52 ± 426.4 (27.6%)	9925.3 ± 3104.8 (31.3%)	10227.7 ± 3309.9 (32.4%)

The geometric mean ratios and 90% confidence intervals are listed in the following two tables:

Table 7-3 Estimated ratios of means and 90% confidence intervals for AUC and C_{max} of valsartan (N=23)

PK parameter	Estimated ratio of means (4x10 mg / 40 mg)	90% confidence interval for the ratio
C_{max} (ng/mL)	1.08	(0.90, 1.29)
$AUC_{(0-t)}$ (ng.h/mL)	1.12	(0.96, 1.31)
$AUC_{(0-\infty)}$ (ng.h/mL)	1.12	(0.97, 1.31)

The results indicate that the bioavailability of the test 4 x 10 mg tablets and the reference 40 mg commercial tablet are comparable, but not equivalent. The geometric means of Cmax and AUC are 1.08 and 1.12 times greater, respectively, than with the commercial adult 40 mg tablet.

Conclusion

The bioavailability of valsartan from the test 4 x10 mg tablets and the reference 40 mg commercial tablets is comparable but not equivalent.

Comment

The plasma concentrations of valsartan should have been measured for more than 24 h in order to determine the true half-life of the terminal log linear disposition phase.

Overall Conclusion Regarding the Relative Bioavailability Studies

None of the test formulations was bioequivalent to the reference commercial adult tablets. The two solid test formulations, the pediatric 10 mg and 80 mg tablets, exhibited a marginally better bioavailability than the commercial adult 40 and 80 mg tablets. The third test formulation, the oral 4 mg/mL extemporaneous suspension, demonstrated a largely better bioavailability than the 80 mg adult tablet.

4.4 Study No. CVAL489A2305: A Multi-Center, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Valsartan Given as an Oral Suspension in Pediatric and Adolescent Subjects 2 Months to 16 Years of Age with Hypertension

Objectives

Primary

To determine the single-dose pharmacokinetics of valsartan given as an oral suspension

Secondary

To determine the safety and tolerability of a single oral dose of valsartan in 1-16 year old children with hypertension

Investigational Drugs/Formulations

Valsartan extemporaneous oral suspension 4 mg/mL (Lot No.: 054H8641 and 580003)

Design

This was a multi-center, open label, single dose study. Twenty six children in the age between 2 months and 16 years received a single dose of valsartan oral suspension 4 mg/mL given as a dose of 2 mg/kg (maximum dose of 80 mg**).** A total of 26 subjects, males or females, were to be enrolled in the study with 6 subjects per age group were to complete the study. Subjects were to be stratified by age using the following age groups: Group 1: 1 year to < 4 years, Group 2: 4 years to < 6 years, Group 3: 6 years to < 12 years and Group 4: 12 years to 16 years. Each study site could enroll up to a maximum of 3 subjects in any one age group. All subjects were to have hypertension defined as a systolic or diastolic blood pressure $\geq$ 95th percentile for age, sex, and height, measured on at least 2 separate occasions prior to dosing.

On the morning of the study, the subjects' intake of food and beverages were to have been restricted as follows:

For subjects < 2 years of age, at 2.5 h prior to dosing these subjects were given 90 mL (3 oz) of one of the following: Breast milk, formula, 2% milk, or a suitable milk substitute. Subjects were allowed to have 2 ounces of rice cereal and Pedilyte, if necessary. The intake of water was allowed throughout the study and was not restricted.

For subjects ≥ 2 years of age, the intake of solid foods and beverages (except water) was not allowed from 2 h prior to dosing until 2 h after dosing. Approximately 2.5 h prior to dosing subjects could have a light, low fat breakfast type meal, which may, for example, have included dry cereal with milk, oatmeal, farina, grits, toast, roll, bagel, etc. The intake of foods that had a high fat content such as fried eggs, bacon, sausage, ham etc, was prohibited. The intake of water was allowed throughout the study and was not restricted. The valsartan suspension was administered to the subjects between 0600 and 1200.

The scheduled study activities are shown in the table below:

Table 3-1 Evaluation and visit schedule

Evaluation	Screening Day -7 to –1 (Visit 1)	Dosing and PK sampling Day 1 (Visit 2)									Day 2	
		Pre-dose	0.5 hr	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr	24 hr	
Informed consent/assent	X											
Inclusion/exclusion criteria	X											
Concomitant medications	X											X [b]
Demographics/ medical history	X											
Physical examination	X											X [b]
Hepatitis screen	X											
Urine alcohol, drug & cotinine screen (subjects ≥6 yrs)	X	X										
Pregnancy test (post menarchal females only)	X [a]	X [a]										
Vital signs: BP, HR	X	X	X	X	X	X	X	X	X	X		X [b]
Body temperature	X	X										X [b]
Clinical laboratory tests (blood & urine)	X											X [b]
ECG	X				X							X [b]
Collect blood samples for PK evaluations (subjects 1 to <6 yrs)	X		X	X	X		X			X	X	
Collect blood samples for PK evaluations (subjects 6 to 16 yrs)		X	X	X	X	X	X	X	X	X	X	
Adverse event assessment		X	X	X	X	X	X	X	X	X		X [b]
Study completion												X

[a] Pregnancy test at screening performed using serum sample and pregnancy test at Visit 2 performed using urine sample; both pregnancy test results had to be negative prior to dosing with valsartan.

[b] To be done after 24-hour PK sample was collected.

Note: BP = blood pressure, HR = heart rate, hr = hour, yrs = years.

The inclusion and exclusion criteria were the following:

3.2.2 Inclusion and exclusion criteria

Inclusion criteria

Subjects meeting all of the following criteria were considered for admission into the study:

1. Female or male subject from 1 year to 16 years of age;
2. If post-menarchal female, serum pregnancy test result at screening was negative and urine pregnancy test result at Visit 2 (prior to receiving single-dose of oral valsartan) was negative;
3. Subject exhibited hypertension as defined by a sitting systolic or diastolic blood pressure measuring at or above the 95th percentile for age, gender, and height on at least two separate occasions at least one day apart (unless the subject was currently taking anti-hypertensive therapy) (see Protocol Section 7.1 – BP tables for children and Section 7.2 – Height tables);
4. Informed consent form (approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)) signed by the parent/legal guardian (plus approved pediatric assent signed by the subject if applicable);
5. Physical examination demonstrated no abnormalities that would make this study medically hazardous to the subject;
6. Subject (of the appropriate age) and/or parent/guardian was able to follow verbal and/or written instructions in the local language;
7. Subject demonstrated no clinically significant abnormalities or clinically noteworthy abnormal laboratory values (other than those relating to renal function);
8. Subject demonstrated no clinically significant ECG abnormalities other than those associated with left ventricular hypertrophy;
9. If subject ≥6 years of age, urine tests at screening and Visit 2 were negative for alcohol, drugs of abuse, and cotinine.

Exclusion criteria

Subjects meeting any of the following criteria were **not** to be included in the study:

1. Subject had any clinically significant unstable medical condition or chronic disease other than those associated with hypertension;
2. Subject who could not safely tolerate the temporary discontinuation of concomitant anti-hypertensive medications for 24 hours prior to valsartan dosing or whose blood pressure was not able to be controlled with only amlodipine or atenolol during the 24 hours prior to valsartan dosing.
3. Subject had experienced a significant clinical illness within 10 days prior to receiving the single-dose of study medication;
4. Subject tested positive at screening for the hepatitis B surface antigen or hepatitis C antibody, or had a history of a positive result for one of these tests;
5. Subject was known to have tested seropositive for the human immunodeficiency virus (HIV) or subject was concomitantly receiving anti-retroviral therapy;
6. Subject had a clinically significant abnormality of the hepatic system, or a history of malabsorption or previous gastrointestinal surgery that could effect drug absorption or metabolism;
7. Subject had a disorder or history of a condition that could interfere with drug absorption, distribution, metabolism, or excretion;
8. Subject had used any drug known or suspected to effect hepatic or renal clearance capacity within 30 days prior to start of study (this included drugs that are known to cause induction or inhibition of liver enzymes, see Protocol Section 7.5 for cytochrome P450 inducers and inhibitors);
9. Subject had any of the following clinical laboratory abnormalities:
   - AST/SGOT or ALT/SGPT >2 times the upper limit of the reference range;

- Total bilirubin or direct bilirubin >2 times the upper limit of the reference range;
- Creatinine clearance <40 ml/min/1.73m^2 (calculated using Modified Schwartz formula to estimate glomerular filtration rate (GFR), see Protocol Section 7.4 for formula)
- Hemoglobin <9 gm/dL;
- WBC count <3000/mm^3;
- Platelet count <100,000/mm^3;
- Serum potassium >upper limit of the reference range.

10. Subject had a known hypersensitivity to valsartan;
11. Subject had sustained a significant blood volume loss (>3% of calculated blood volume) in the past 30 days;
12. Subject had taken an investigational drug or participated in an investigational study within 30 days prior to study drug administration;
13. Subject consumed more than 180 mg of caffeine per day (see Protocol Section 7.3 – Caffeine content of beverages) and/or was unable/unwilling to refrain from ingesting caffeine or xanthine containing beverages from 24 hours prior to dosing through study completion.

Tolerability/Safety

The subjects' safety/tolerability was ascertained by monitoring adverse event, clinical vital signs, and ECG and by performing clinical laboratory evaluations.

Pharmacokinetic Profiling

Blood samples were collected for the determination of valsartan in plasma at the following times:
Children 2 months to < 6 years of age: pre-dose, 0.5, 1, 2, 4, 8, 12, and 24 h after dosing
Children 6 years to 16 years of age: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h after dosing

Bioassay

The plasma concentrations of valsartan were measured by a HPLC-MS/MS method using turbo ion spray positive ion mode. The method used an [redacted] procedure. The LLOQ of the method is 2.0 ng/mL. The range of the linear calibration curve is from 2.0 ng/mL to 5000 ng/mL. The coefficient of determination of the fits of the calibration curves to the data was ≥ 0.9925. The concentrations of the QC samples were 4.0 ng/mL 1000 ng/mL and 4000 ng/mL. The inter-day accuracy of the QC samples ranged between -7.8% and 2.3% and the precision was ≤ 8.7%.

PK Data Analysis

The following parameters were determined: AUC0-tlast, AUC0-tlast*(similar to AUC0-tlast, but using selected time points for estimation), AUC0-∞, Cmax, tmax, tlag, CL/F, λz and t1/2. The parameters were derived from non-compartmental methods using WinNonlin® Professional, version 3.1 or higher. AUC0-tlast was computed using the linear trapezoidal rule. λz was obtained from linear regressions of the natural log transformed concentration versus time data in the terminal phase (if estimable). A minimum of 3 points clearly visible in the terminal phase were required to calculate λz. All the parameters with the exception of tmax, tlag, λz and t1/2 were dose or body weight adjusted.

Statistical Evaluation

Descriptive statistics are reported by age group for the following dose unadjusted and dose adjusted (DA: adjusted to a dose of 2 mg/kg dose) valsartan parameters: AUC0-tlast, DA-AUC0-tlast, AUC0-tlast*, DA-AUC0-tlast*, AUC0-∞, DA-AUC0-∞, Cmax, DA-Cmax and body weight unadjusted and adjusted CL/F and body weight unadjusted t1/2. Regression analyses were performed to study the effect of age on the PK parameters DA-AUC0-tlast, DA-AUC0-tlast*, DA-AUC0-∞, DA-Cmax and body weight adjusted CL/F. The natural log-transformed parameter was the response variable (denoted as value in the model equation below), and age in years as continuous variable) was the predictor variable in accordance with Value = $\alpha + \beta \bullet AGE + \varepsilon$, where α is the intercept and β the slope of the straight line and ε is a random error. The point estimate and 90% confidence interval estimates of the slope and intercept and the p-vales for the test of the slope equal to zero were obtained for each parameter as well as the coefficient of determination of the linear fit.
The lack of fit of the regression model was also checked for quadratic curvature by including the term squared age variable to the above equation as follows:

$$Value = \alpha + \beta \bullet AGE + \gamma \bullet AGE^2 + \varepsilon$$

A test for $\gamma = 0$ was performed at 0.05 significance level. Non-rejection of this hypothesis ($P < 0.05$) showed the absence of a quadratic curvature.

Sample Size

The sample size of 6 subjects per age group was based on clinical judgment and common practices for pharmacokinetic studies in pediatric subjects, and was not based on statistical consideration.

Results

All 26 subjects enrolled completed the study. All subjects were included in the PK and tolerability/safety analyses.

The demographic characteristics of the study subjects by age group are shown in the table below:

Table 7-3 Demographic characteristics summary by age group

	Valsartan				
	1 year to <4 years (N = 6)	4 years to <6 years (N = 6)	6 years to <12 years (N = 7)	12 years to 16 years (N = 7)	Total (N = 26)
Age (year)					
Mean ± SD	2.3 (1.03)	4.2 (0.41)	8.1 (1.95)	13.6 (0.79)	7.3 (4.56)
Median	3.0	4.0	8.0	13.0	6.0
Sex – n (%)					
Male	4 (66.7)	3 (50.0)	2 (28.6)	4 (57.1)	13 (50.0)
Female	2 (33.3)	3 (50.0)	5 (71.4)	3 (42.9)	13 (50.0)
Race – n (%)					
Black	1 (16.7)	3 (50.0)	1 (14.3)	3 (42.9)	8 (30.8)
Caucasian	2 (33.3)	-	3 (42.9)	3 (42.9)	8 (30.8)
Oriental	-	-	-	-	-
Other	3 (50.0)	3 (50.0)	3 (42.9)	1 (14.3)	10 (38.5)
Weight (kg)					
Mean ± SD	15.1 (5.67)	20.5 (5.20)	42.0 (15.71)	92.0 (27.43)	44.3 (35.09)
Median	14.9	19.4	49.7	88.0	27.5
Height (cm)					
Mean ± SD	92.6 (13.34)	107.7 (4.76)	134.4 (14.08)	170.3 (12.62)	128.3 (32.22)
Median	96.8	108.3	140.0	166.0	116.8

N = number, SD = standard deviation.
Source: Appendix 3, Table 2.2.2.

A subject listing of relevant medical history and current medical conditions can be found in Appendix 3-Table 2.3.

The mean doses unadjusted and adjusted for body weight of the subjects in the 4 age groups are summarized in the following table:

Table 7-4 Demographic characteristics and dosing by age group

Group	Age [years]	Pts enrolled	Mean age	Mean body weight [kg]	Mean dose [mg]	Mean dose [mg/kg]
1	1-<4	6	2.3	15.1	30.5	2.0
2	4-<6	6	4.2	20.5	40.7	2.0
3	6-<12	7	8.1	42.0	68.4	1.6
4	12-16	7	13.6	92.0	80	0.9

It can be seen that the mean dose increased from about 30 mg in Group 1 (1- < 4 years of age) to 80 mg in Group 4 (12-16 years old). The weight normalized mean dose in Groups 1, 2, 3 and 4 was 2.0 mg/kg, 2.0 mg/kg, 1.6 mg/kg, and 0.9 mg/kg, respectively.

Tolerability/Safety

Changes in blood pressure were observed after administration of valsartan as follows:

Table 7-6 **Mean (plus minus SD) change from Day 1 pre-dose in systolic and diastolic blood pressure**

	SBP		DBP	
Day 1 pre-dose (hours)	**N**	**Mean (±SD)**	**N**	**Mean (±SD)**
0	25	113.0 (17.33)	25	69.7 (10.77)
Day 1 post-dose (hours)	**N**	**Mean change (±SD)**	**N**	**Mean change (±SD)**
0.5	25	-5.5 (18.90)	25	-5.9 (10.77)
1	25	-7.3 (13.05)	25	-6.8 (10.53)
2	25	-6.1 (12.71)	25	-8.5 (13.36)
3	24	-5.8 (15.84)	24	-8.7 (10.09)
4	25	-7.1 (15.95)	25	-10.0 (10.95)
6	24	-9.6 (17.43)	24	-9.2 (12.23)
8	24	-7.5 (15.02)	24	-6.5 (11.85)
12	25	-0.2 (16.02)	25	-4.8 (12.90)

DBP = diastolic blood pressure, N = number, SBP = systolic blood pressure, SD = standard deviation.
Source: Appendix 3-Table 3.4.3. (Note: Subject 0003/00303 missed baseline blood pressure reading/assessment)

The treatment was tolerated well by the subjects. There were no serious adverse events or death noted. Three of the subjects experienced an adverse event: ventricular hypertrophy in a 1 year old subject, injection site pain in an 8 year old subject and headache in a 14 year old subject. They were not suspected to be drug related.

Bioassay:

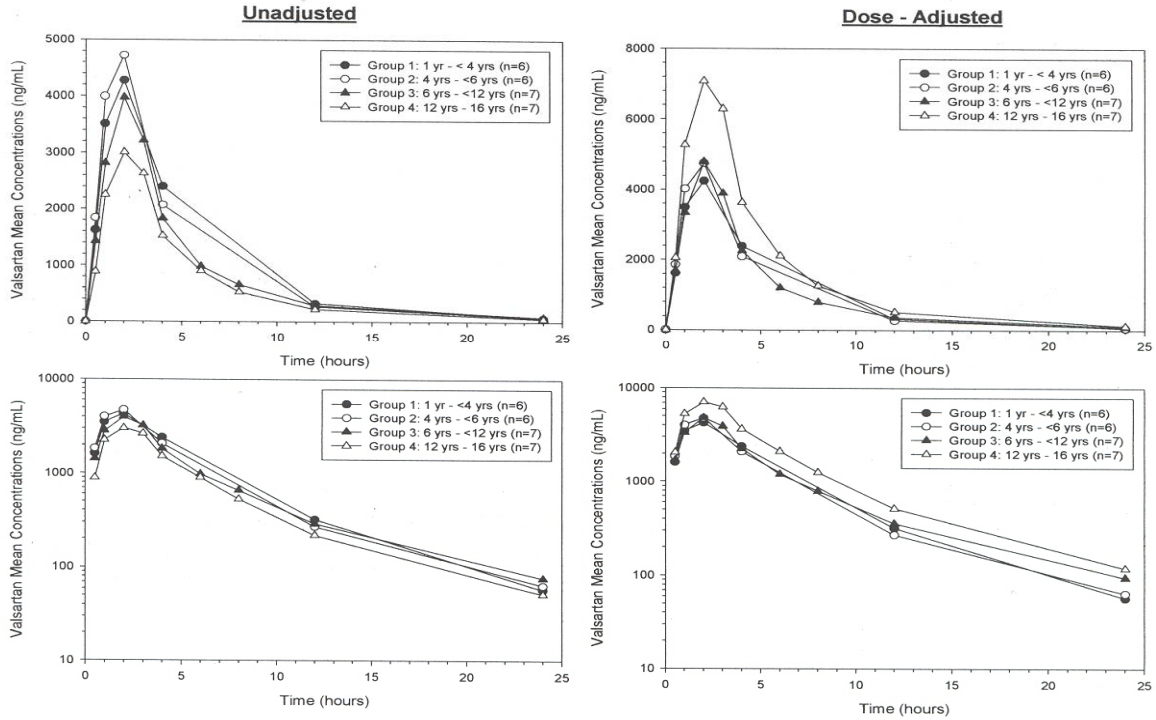
The plasma concentrations of valsartan were measured by an [redacted] procedure and analysis of the extract by HPLC-MS/MS using turbo ion spray positive ion mode. The calibration curve ranged between 2.0 ng/mL and 5000 ng/mL. The LLOQ was 2.0 ng/mL. QC samples were measured along samples with unknown concentrations of valsartan. The coefficient of determination of the linear function to the data was ≥ 0.9782. The data were weighted by $1/Y^2$. The QC samples had nominal concentrations of 4.0 ng/mL, 100 ng/mL and 4000 ng/mL. The inter-day accuracy of the QC samples ranged between 2.3% - (-)7.8 % and the precision was ≤ 8.7%.

Samples from subjects 02-0201, 02-0202, and 02-203 were thawed due to power interruption at the clinical site. The samples of the 3 subjects were in a 0 °C -15 °C environment for approximately 36 h. They were subsequently refrozen. In accordance with the results of the stability report ([redacted] Report 93027) valsartan does not degrade when exposed to room temperature for 72 h or during a freeze-thaw cycle.

Pharmacokinetics

Linear and semi-logarithmic plots of the arithmetic mean plasma concentrations of valsartan unadjusted and adjusted for dose are shown below:

Figure 7-1 **Linear and semi-log plots of mean unadjusted and dose-adjusted valsartan plasma concentration-time profiles by age group following single dosing with valsartan**



Note: Dose-adjusted concentrations are adjusted to a 2 mg/kg dose.
Source: Appendix 4, Table 1, and Appendix 4, Figure 1 and Appendix 4, Figure 2.

The dose unadjusted plasma concentrations time profiles indicate that the exposure to valsartan increases in the order Group 4 (adolescents), Group 3 (6-<12 years old), Group 2 (4 - < 6 years old) and Group 1 (1-< 4 years old). The plots of the dose adjusted arithmetic mean plasma concentrations indicate that the subjects in Group 4 (12-16 years of age) incur a slightly greater exposure to valsartan than the subjects of Groups 1-3 (1- < 12 years of age).

A summary of the dose unadjusted and dose adjusted mean Cmax and AUC, dose unadjusted tlag and t1/2 and body weight unadjusted and adjusted CL/F, are listed below:

Table 7-7 Summary of unadjusted and dose-adjusted valsartan pharmacokinetic parameters by age group

Pharmacokinetic Parameters	Arithmetic Mean (CV%) [Geometric Mean] Group 1: 1 year to <4 years (N = 6)	Group 2: 4 years to <6 years (N = 6)	Group 3: 6 years to <12 years (N = 7)	Group 4: 12 years to 16 years (N = 7)
Unadjusted				
C_{max} (ng/mL)	4307 (43) [3832]	4818 (39) [4500]	4254 (27) [4112]	3069 (41) [2835]
$AUC_{(0-t)}$ (ng*hr/mL)	25505 (43) [23203]	24500 (31) [23497]	19600 (36) [18447]	15560 (34) [14619]
$AUC_{(0-t)}$* (ng*hr/mL)	25505 (43) [23203]	24500 (31) [23497]	21414 (36) [20089]	16764 (39) [15564]
$AUC_{(0-\infty)}$ (ng*hr/mL)	25823 (43) [23517]	26800 (26) [26071]	20214 (36) [18994]	15944 (35) [14988]

Pharmacokinetic Parameters	Arithmetic Mean (CV%) [Geometric Mean] Group 1: 1 year to <4 years (N = 6)	Group 2: 4 years to <6 years (N = 6)	Group 3: 6 years to <12 years (N = 7)	Group 4: 12 years to 16 years (N = 7)
CL/F (L/hr)	1.50 (67) [1.23]	1.63 (21) [1.60]	3.80 (43) [3.45]	5.75 (45) [5.34]
$t_{1/2}$ (hr)	3.79 (10) [3.77]	3.95 (13) [3.92]	5.33 (12) [5.30]	4.97 (15) [4.92]
t_{max} (hr) [a]	2.00 (1.00, 2.02)	2.00 (1.00, 2.00)	2.00 (1.02, 3.00)	2.00 (1.00, 3.02)
Adjusted [b]				
DA-C_{max} (ng/mL)	4275 (43) [3796]	4848 (38) [4536]	5113 (30) [4882]	7214 (46) [6237]
DA-$AUC_{(0-t)}$ (ng*hr/mL)	25288 (42) [22983]	24667 (30) [23696]	23771 (40) [21919]	36806 (43) [32185]
DA-$AUC_{(0-t)}$* (ng*hr/mL)	25288 (42) [22983]	24667 (30) [23696]	26057 (42) [23856]	39703 (46) [34256]
DA-$AUC_{(0-\infty)}$ (ng*hr/mL)	25605 (42) [23294]	2700 (24) [26333]	24514 (40) [22544]	37667 (43) [32997]
CL/F (L/hr/kg)	0.097 (64) [0.086]	0.078 (26) [0.076]	0.098 (49) [0.089]	0.076 (94) [0.061]

N = number; DA = Dose-adjusted.
$AUC_{(0-t)}$* - $AUC_{(0-t)}$ which is calculated using only the time points that are common to all age groups.
[a] Median (min, max).
[b] C_{max} and AUC values are dose-adjusted to a 2 mg/kg dose. CL/F is adjusted to a unit body weight.
Source: Appendix 4-Table 2.

Table 1. Summary values of volume of distribution (Vd/F) by age group uncorrected and corrected for body weight.

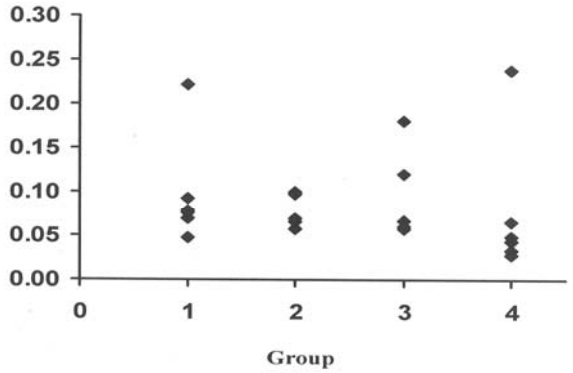
Pharmacokinetic Parameters	Arithmetic Mean ± SD (CV%) [Geometric Mean]			
	Group 1: 1 year to <4 years (N = 6)	Group 2: 4 years to <6 years (N = 6)[a]	Group 3: 6 years to <12 years (N = 7)	Group 4: 12 years to 16 years (N = 7)
Uncorrected				
Vd/F (L)	8.52 ± 6.40 (75.1%) [6.69]	9.22 ± 1.81 (19.6%) [9.08]	28.94 ± 12.27 (42.4%) [26.32]	41.56 ± 22.30 (53.7%) [37.93]
Corrected [b]				
Vd/F (L/Kg)	0.548 ± 0.412 (75%) [0.465]	0.436 ± 0.07 (16%) [0.432]	0.737 ± 0.334 (45.4%) [0.678]	0.571 ± 0.612 (107%) [0.429]

N = number; [a] For one subject, estimation of terminal half life was not possible. Thus, the summary parameters are for N=5 only; [b] is adjusted to a unit body weight.
Erratum: A reporting error was noticed in the derived Vd/F values for Group 3 and Group 4 in the CTD 2.7.2 document, Page 7, Table 2-2. The Vd/F values presented in this document are accurate and were generated from the source CL/F and elimination rate constant values. Please refer to the Appendix 4 of the study report for individual PK parameters.

Maximum plasma concentrations of valsartan are attained in all four groups 2 h after administration. The t1/2 of the terminal disposition phase in the four groups is comparable and ranges between 3.79 h and 5.33 h. The oral clearance increases with age from 1.50 L/h in Group 1 to 5.75 L/h in Group 4 indicating an age or body weight dependency. The oral volume of distribution increases with bodyweight and/or age as well. The coefficient of variation about Cmax and AUC ranges between 26% to 43% in the different age groups.

The dose adjusted arithmetic and geometric mean parameters Cmax and AUC0-∞ confirm that peak and average exposure to valsartan appears to be slightly greater in Group 4 (12- 16 year old subjects) than in the three younger 3 age groups, but the small number of subjects in the four age groups should be considered. The body weight unadjusted oral clearance of valsartan is greater in the adolescents than in the children in the age between 1- < 12 years. After adjusting oral clearance for body weight the CL/F values among the four age groups become more comparable as shown in the below figure:

Figure 7-2 **Body weight-adjusted clearance (Cl/F) of valsartan versus age**

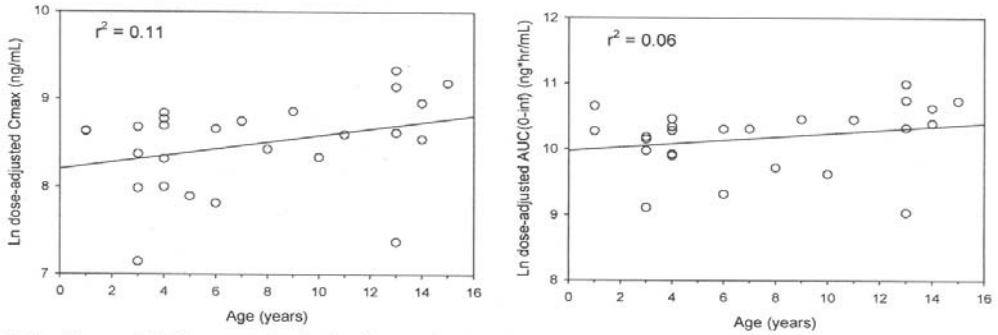


Results of regressions of valsartan parameters versus age showed that when C_{max} and AUC values were standardized to a uniform dose per unit body weight (i.e., 2 mg/kg), no significant age effect was observed ($p>0.05$, $r^2 \geq 0.11$; Figure 7-3, Appendix 6-Table 1, and Appendix 4-, Figure 9 to Appendix 4, Figure 12).

The geometric mean CL/F values (range: 0.06 -0.09 L/h/kg) and arithmetic mean CL/F values (range: 0.08-0.10 L/h/kg) are comparable in the 4 investigated pediatric age groups. There is considerable inter-subject variation. The report states that in adults receiving the suspension a mean value for CL/F of approximately 0.06 L/h/kg was obtained (Study CVA4892301). These results appear to provide a rationale for using a body weight normalized dose regimen for valsartan in the pediatric population. The body weight corrected oral volume of distribution is also comparable among the four age groups.

The figure below shows no important dependency for the natural log transformed and dose adjusted Cmax and AUC0-∞ on age.

Figure 7-3 **Linear regression plots of dose-adjusted valsartan C_{max} and $AUC_{(0-\infty)}$ versus age**



Note: C_{max} and $AUC_{(0-\infty)}$ are standardized to a valsartan dose of 2 mg/kg across all subjects.
Source: Appendix 3-Table 2.2.1, Appendix 4-Listing 2, and Appendix 6-Table 1.

Conclusions

The mean peak and average exposure to valsartan when normalized for dose appear not to be importantly different among the four pediatric age groups. The body weight adjusted oral clearance of valsartan after administration of a single dose of an extemporaneous suspension formulation in the four pediatric age groups ranges between 0.06-0.09 L/h/kg. The body weight adjusted clearance in adults receiving the same formulation of valsartan is 0.06 L/h/kg and comparable. These results provide a rationale for using body weight adjusted dose of valsartan in children.

Comments

1. The plasma concentrations of valsartan should have been measured for more than 24 h after administration in order to determine true half-life of the terminal log linear disposition phase.

2. There is a typographical error in table 7-7: The arithmetic mean of the dose adjusted mean AUC0-∞ is given as 2700 ng●h/mL.
   There is typographical error in Table 1.1: The dose of valsartan was normalized for body weight not age.

4.5 Bioanalytical Cross-Check between a HPLC and a LC/MS/MS Method for the Analysis of Valsartan in Human Plasma

The objective of the study was to cross-validate the LC/MS/MS method developed for the measurement of valsartan in plasma with a previously reported HPLC method with [redacted] detection. Six spiked QC samples and 14 actual samples obtained after administration of a 160 mg valsartan tablet daily for 7 days under fasting conditions from study CVAS489A2303 were used. All spiked QC samples at each level had to be within 15% of the theoretical concentration.

The individual and mean accuracy of valsartan in the spiked samples and the results of the actual samples when measured by the HPLC [redacted] method and the LC-MS/MS assay are shown in the two tables below:

Table 10-1 Individual and mean accuracy of valsartan in spiked samples (QCS)

Analytical method	Date of analysis	Nominal concentrations (µg/mL) 0.0300	1.00	7.50	Mean accuracy (%)	CV %
HPLC	20-Sep-02	[redacted]			**97.0**	**6.1**
LC/MS/MS	27-Feb-02	[redacted]			**104**	**5.6**

Table 10-2 Valsartan concentrations of human plasma samples analyzed with HPLC and LC/MS/MS

The comparison of the two bioanalytical methods was performed with 16 values of valsartan concentrations in actual plasma samples.

Study CVAS489A2303		Time (h)	HPLC Ref.	LC/MS/MS Test	Diff. Test-Ref.	% Diff.	Test/ref
SUBJECT 5112/A	Day 5	0	[redacted]				
	Day 6	0					
	Day 7	0					
		0.25					
		0.5					
		1					
		2					
		3					
		4					
		6					
		8					
		12					
		16					
		24					
N					14	14	14
Mean					0.10	7.6	1.08
SD					0.21	8.5	0.09
CV (%)							8.3

The data indicate that both assays exhibit the required accuracy in measuring the concentrations of the QC samples. The average % difference between LC (test) and HPLC (reference) in measuring the plasma concentrations of valsartan was 7.6 (8.5) %. The difference between the two methods with individual samples ranged between [redacted].

Conclusion

Plasma concentrations of valsartan measured by the HPLC and LC/MS/MS methods are comparable.

Comment

None

4.6. Publication Yamashiro W, Maeda K, Hirouchi M, Adachi Y, Hu Z, Sugiyama Y. Involvement of Transporters in the Hepatic Uptake and Biliary Excretion of Valsartan, a Selective Antagonist of the Angiotensin II AT1-Receptor, in Humans. Drug Metab Dispos 2006;34: 1247-1254

Valsartan is excreted in the bile. It is hydrophilic and has an anionic carboxyl group and could have difficulty in crossing plasma membranes. Therefore, anionic transporters could be involved in the hepatic transport of valsartan. OATP is involved in hepatic uptake and MDR1, MRP2 and BCRP are involved in hepatic efflux of organic anions.

This in vitro study examined the involvement and relative contribution of OATP1B1 and OATP1B3 to the hepatic uptake of valsartan using human cryopreserved hepatocytes and transporter expressing cells and identified the transporters responsible for the biliary excretion of valsartan using double transfectants and transporter expressing vesicles. The involvement of MRP2 in the pharmacokinetics of valsartan in vivo using Eisai hyperbilirubinenic (EHBR) rats, in which mrp2 is deficient was also investigated.

Materials and Methods

Materials and Methods

Materials. [^{3}H]Valsartan (80.9 Ci/mmol) and unlabeled valsartan were kindly donated by Novartis Pharma K.K. (Basel, Switzerland). [^{3}H]Estradiol-17β-glucuronide ($E_2$17βG) (45 Ci/mmol) and [^{3}H]estrone-3-sulfate (46 Ci/mmol) were purchased from PerkinElmer Life and Analytical Sciences (Boston, MA), and [^{3}H]cholecystokinin octapeptide (CCK-8) (77 Ci/mmol) was purchased from GE Healthcare Bio-Sciences (Buckinghamshire, UK). Unlabeled $E_2$17βG, estrone-3-sulfate, and CCK-8 were purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals were of analytical grade and commercially available.

Cell Culture. Transporter-expressing or vector-transfected HEK293 cells and MDCKII cells were grown in Dulbecco's modified Eagle's medium low glucose (Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum (Sigma, St. Louis, MO), 100 U/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml amphotericin B at 37°C with 5% CO_2 and 95% humidity. LLC-PK1 cells were cultured in Medium 199 (Invitrogen) supplemented with 10% fetal bovine serum (Sigma), 100 U/ml penicillin, and 100 μg/ml streptomycin.

Transport Study Using Human Cryopreserved Hepatocytes. This experiment was performed as described previously (Hirano et al., 2004). Cryopreserved human hepatocytes were purchased from In Vitro Technologies (Baltimore, MD) (lot 094 and OCF) and from the Research Institute for Liver Disease (Shanghai, China) (lot 03-013). Immediately before the study, the hepatocytes (1-ml suspension) were thawed at 37°C, then quickly suspended in 10 ml of ice-cold Krebs-Henseleit buffer and centrifuged (50*g*) for 2 min at 4°C, followed by removal of the supernatant. This procedure was repeated once more to remove cryopreservation buffer, and then the cells were resuspended in the same buffer to give a cell density of 1.0×10^6 viable cells/ml for the uptake study. The number of viable cells was determined by trypan blue staining. Before the uptake studies, the cell suspensions were prewarmed in an incubator at 37°C for 3 min. The uptake studies were initiated by adding an equal volume of buffer containing labeled and unlabeled substrates to the cell suspension. After incubation at 37°C for 0.5, 2, or 5 min, the reaction was terminated by separating the cells from the substrate solution. For this purpose, an aliquot of 80-μl incubation mixture was collected and placed in a centrifuge tube (450 μl) containing 50 μl of 2 N NaOH under a layer of 100 μl of oil (density, 1.015; a mixture of silicone oil and mineral oil; Sigma-Aldrich), and subsequently, the sample tube was centrifuged for 10 s using a tabletop centrifuge (10,000*g*; Beckman Microfuge E; Beckman Coulter, Inc.). During this process, hepatocytes passed through the oil layer into the alkaline solution. After an overnight incubation in alkali to dissolve the hepatocytes, the centrifuge tube was cut and each compartment was transferred to a scintillation vial. The compartment containing the dissolved cells was neutralized with 50 μl of 2 N HCl and mixed with scintillation cocktail, and the radioactivity was measured in a liquid scintillation counter.

Transcellular Transport Study Using Double Transfected Cells. The protocol has been described in detail previously (Matsushima et al., 2005). In brief, transfected MDCKII cells were seeded in a Transwell membrane insert (6.5-mm diameter, 0.4-μm pore size; Corning Costar, Cambridge, MA) at a density of 1.4×10^5 cells per well 96 h before the transport study. Among a series of cell lines we used in this experiment, human MDR1, MRP2, and OATP1B1 were stably transfected into MDCKII cells as shown previously (Evers et al., 1998; Matsushima et al., 2005). Human BCRP cDNA was transduced into MDCKII cells by the infection of recombinant adenovirus 48 h before the transport study. The cell culture medium was replaced with culture medium supplemented with 5 mM sodium butyrate 24 h before the transport assay. For uptake studies, cells were washed three times and preincubated with Krebs-Henseleit buffer. The experiment was initiated by replacing the medium at either the apical or the basal side of the cell layer with complete medium containing ^{3}H-labeled and unlabeled valsartan or $E_2$17βG (0.1 μM). The cells were incubated at 37°C and aliquots of medium were taken from each compartment at several time points. Radioactivity in 100 μl of medium was measured in a liquid scintillation counter after addition of 2 ml of scintillation

fluid. At the end of the experiments, the cells were washed three times with 1.5 ml of ice-cold Krebs-Henseleit buffer and solubilized in 500 μl of 0.2 N NaOH. After addition of 100 μl of 1 N HCl, 400-μl aliquots were transferred to scintillation vials. Then, 50-μl aliquots of cell lysate were used to determine protein concentrations by the method of Lowry et al. (1951) with bovine serum albumin as a standard.

Vesicle Transport Assay. The preparation procedure of the membrane vesicles expressing human MRP2 was described previously (Hirouchi et al., 2004). The transport medium (10 mM Tris, 250 mM sucrose, and 10 mM $MgCl_2$, pH 7.4) contained the labeled and unlabeled valsartan, 5 mM ATP, and an ATP-regenerating system (10 mM creatine phosphate and 100 μg/μl creatine phosphokinase). An aliquot of transport medium (15 μl) was mixed rapidly with the vesicle suspension (5 μg of protein in 5 μl). The transport reaction was stopped by the addition of 1 ml of ice-cold buffer containing 250 mM sucrose, 0.1 M NaCl, and 10 mM Tris-HCl buffer (pH 7.4). The stopped reaction mixture was passed through a 0.45-μm HA filter (Millipore Corp., Billerica, MA) and then washed twice with 5 ml of stop solution. The radioactivity retained on the filter was measured in a liquid scintillation counter after the addition of scintillation cocktail. Ligand uptake was normalized in terms of the amount of membrane protein.

In Vivo Pharmacokinetic Study. Male Sprague-Dawley (SD) rats and EHBRs (7–8 weeks old) were purchased from Nippon SLC (Shizuoka, Japan). All animals were maintained under standard conditions with a reverse dark-light cycle and were treated humanely. Food and water were available ad libitum. This study was carried out in accordance with the guidelines provided by the Institutional Animal Care Committee (Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan). SD rats and EHBRs were anesthetized by inhalation of diethyl ether. The abdomen was opened with a midline incision and the common bile duct was cannulated with a polyethylene tube (Becton Dickinson Primary Care Diagnostics, Sparks, MD). The phosphate-buffered saline containing [^{3}H]valsartan (8 μCi/ml) and unlabeled valsartan (1 mg/ml) was injected into a femoral vein (1 ml/kg body weight). Blood samples were collected from a femoral artery and bile samples were collected in preweighed tubes at designated times. The total radioactivity in plasma and bile samples was measured in a liquid scintillation counter.

Kinetic Analyses of Uptake Transporters. Ligand uptake was expressed as the uptake volume [μl/mg protein], given as the amount of radioactivity associated with the cells [dpm/mg protein] divided by its concentration in the incubation medium [dpm/μl]. Specific uptake was obtained by subtracting the uptake into vector-transfected cells from the uptake into cDNA-transfected cells. Kinetic parameters were obtained using the following equation:

$$v = \frac{V_{max} \cdot S}{K_m + S} + P_{dif} \cdot S \quad (1)$$

where v is the uptake velocity of the substrate (pmol/min/mg protein), S is the substrate concentration in the medium (μM), K_m is the Michaelis constant (μM), V_{max} is the maximum uptake rate (pmol/min/mg protein), and P_{dif} is the nonsaturable uptake clearance (μl/min/mg protein). Fitting was performed by the nonlinear least-squares method using a MULTI program (Yamaoka et al., 1981), and the Damping Gauss-Newton Method algorithm was used for curve fitting. The input data were weighted as the reciprocal of the observed values.

To determine the saturable hepatic uptake clearance in human hepatocytes, we first determined the hepatic uptake clearance ($CL_{(2\ min-0.5\ min)}$) (μl/min/10^6 cells) by calculating the slope of the uptake volume (V_d) (μl/10^6 cells) between 0.5 and 2 min (eq. 2). The saturable component of the hepatic uptake clearance (CL_{hep}) was determined by subtracting $CL_{(2\ min-0.5\ min)}$ in the presence of 100 μM substrate (excess) from that in the presence of 1 μM substrate (tracer quantity) (eq. 3).

$$CL_{(2\ min-0.5\ min)} = \frac{V_{d,2\ min} - V_{d,0.5\ min}}{2 - 0.5} \quad (2)$$

$$CL_{hep} = CL_{(2\ min-0.5\ min),tracer} - CL_{(2\ min-0.5\ min),excess} \quad (3)$$

where $CL_{(2\ min-0.5\ min),\ tracer}$ and $CL_{(2\ min-0.5\ min),\ excess}$ represent the $CL_{(2\ min-0.5\ min)}$ values estimated in the presence of 1 and 100 μM substrate, respectively.

Estimation of the Relative Contribution of Each Transporter to the Hepatic Uptake. This method for estimating the contribution of OATP1B1 and OATP1B3 to the overall hepatic uptake has been used previously (Hirano et al., 2004). In this analysis, estrone-3-sulfate and CCK-8 were chosen as transporter-selective substrates of OATP1B1 and OATP1B3, respectively. The ratio of the uptake clearance of the reference compounds in human hepatocytes to that in the expression system was calculated and defined as $R_{act,\ OATP1B1}$ and $R_{act,\ OATP1B3}$. The uptake clearance mediated by OATP1B1 and OATP1B3 in human hepatocytes was separately calculated by multiplying the uptake clearance of valsartan in transporter-expressing cells ($CL_{OATP1B1,\ test}$ and $CL_{OATP1B3,\ test}$) by $R_{act,\ OATP1B1}$ and $R_{act,\ OATP1B3}$, respectively, as described in the following equations:

$$R_{act,OATP1B1} = \frac{CL_{Hep,E_3S}}{CL_{OATP1B1,E_3S}} \quad (4)$$

$$R_{act,OATP1B3} = \frac{CL_{Hep,CCK\text{-}8}}{CL_{OATP1B3,CCK\text{-}8}} \quad (5)$$

$$CL_{hep,test,OATP1B1} = CL_{OATP1B1,test} \cdot R_{act,OATP1B1} \quad (6)$$

$$CL_{hep,test,OATP1B3} = CL_{OATP1B3,test} \cdot R_{act,OATP1B3} \quad (7)$$

Kinetic Analyses of Efflux Transporters. The basal-to-apical transcellular clearance (CL_{trans}) was calculated by dividing the steady-state efflux velocity for the transcellular transport (V_{apical}) by the ligand concentration in the incubation buffer on the basal side, whereas the efflux clearance across the apical membrane (PS_{apical}) in double transfected cells was obtained by dividing V_{apical} by the intracellular concentration of ligand at 120 min. In the vesicle transport assay, ATP-dependent transporter-specific uptake was calculated by subtracting the uptake in the presence of AMP from that in the presence of ATP. The saturation kinetics of CL_{trans}, PS_{apical}, and ATP-dependent uptake into vesicles were calculated using eq. 1 by the curve-fitting procedure described above.

Pharmacokinetic Analysis. The plasma concentration-time profile was fitted to a biexponential equation and the $AUC_{0-\infty}$ was estimated by integration up to infinity. The initial distribution volume (V_1) was calculated by dividing the dose by the initial plasma concentration estimated from the fitted biexponential equation. The plasma clearance (CL_p) was calculated as Dose/$AUC_{0-\infty}$. The biliary clearance (CL_{bile}) was calculated as the ratio of the cumulative excreted amount in bile over 120 min to the AUC over 120 min ($AUC_{0-120\ min}$).

Results

Uptake of Valsartan by OATP Transporter Expressing Cells

Valsartan is significantly taken up by OATP1B1 and OATP1B3 expressing HEK 293 cells compared with vector transfected cells as shown in the below Figure 1:

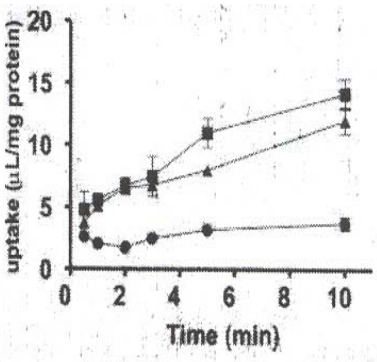


FIG. 1. Time profiles of the uptake of valsartan by OATP1B1- and OATP1B3-expressing HEK293 cells. Squares, triangles, and circles represent the uptake in OATP1B1- and OATP1B3-expressing cells and vector-control cells, respectively. Each point represents the mean ± S.E. (n = 3).

The process is time-dependent. The saturation kinetics of the valsartan uptake by OATP1B1 and OATP1B3-expressing cells and vector-transfected cells was evaluated for 5 min, over which time the uptake of valsartan remained linear. The Eadie-Hofstee plots are shown by Figure 2 and the kinetic parameters in Table 1:

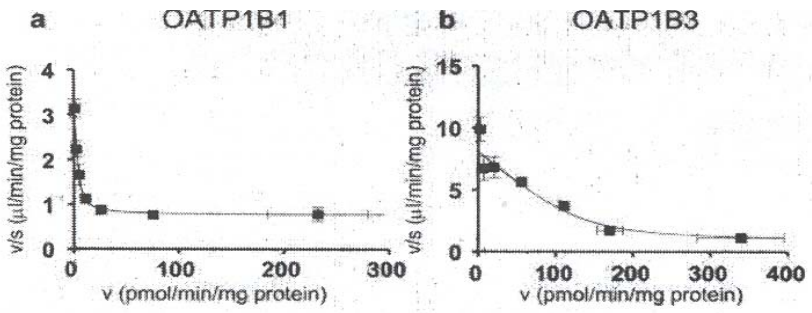


FIG. 2. Eadie-Hofstee plots of the uptake of valsartan by OATP1B1- and OATP1B3-expressing HEK293 cells. The concentration dependence of OATP1B1 (a)- and OATP1B3 (b)-mediated uptake of valsartan is shown as Eadie-Hofstee plots. The uptake of valsartan for 5 min was determined at various concentrations (0.1–300 μM). Each point represents the mean ± S.E. (n = 3).

TABLE 1

Kinetic parameters of the uptake of valsartan by OATP1B1- and OATP1B3-expressing HEK293 cells

Data shown in Fig. 2 were used to determine these parameters calculated by nonlinear regression analysis as described under *Materials and Methods*. Each parameter represents the mean ± computer-calculated S.D.

	K_m	V_{max}	P_{dif}
	µM	*pmol/min/mg protein*	*ml/min/mg protein*
OATP1B1	1.39 ± 0.24	3.85 ± 0.46	0.747 ± 0.022
OATP1B3	18.2 ± 5.9	135 ± 40	0.680 ± 0.223

There was not significant transport of valsartan by OATP2B1.

Uptake of Estrone-3 Sulfate, CCK-8, and Valsartan in Human Cryopreserved Hepatocytes

The uptake of Estrone-3-sulfate (E1S) a substrate of OATPB1B1, CCK-8, a substrate of OATP1B3 and valsartan by human hepatocytes is shown in Figure 3:

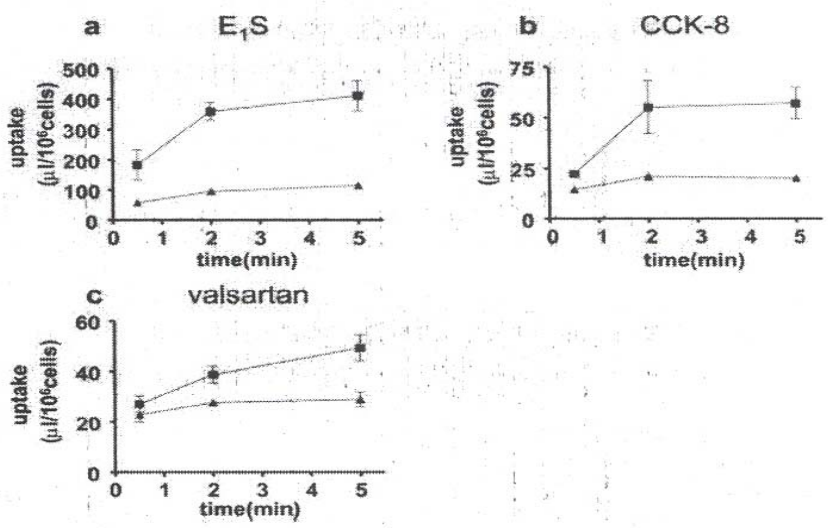


FIG. 3. Typical time profiles of the uptake of estrone-3-sulfate, CCK-8, and valsartan by human hepatocytes (lot OCF). The uptake of estrone-3-sulfate (a), CCK-8 (b), and valsartan (c) for 0.5, 2, and 5 min was determined at two concentrations (squares, 1 μM; triangles, 100 μM) at 37°C. Each point represents the mean ± S.E. (n = 3).

The uptake clearance of E1S, CCK-8 and valsartan are listed in Table 2 and the relative contributions of OATP1B1 and OATP1B3 in different batches of hepatocytes is shown in Table 3:

TABLE 2

Uptake clearance of reference compounds (E_1S and CCK-8) and valsartan in expression systems and human hepatocytes

	Transporter-Expressing Cells		Human Hepatocytes		
	$CL_{OATP1B1}$	$CL_{OATP1B3}$	OCF	094	03-013
	µl/min/mg protein		*µl/min/10^6 cells*		
E_1S	84.6		93.0	98.7	45.2
CCK-8		10.3	17.7	71.6	3.65
valsartan	1.56	0.96	3.55	17.1	6.15

TABLE 3

Contribution of OATP1B1 and OATP1B3 to the hepatic uptake of valsartan in each batch of human hepatocytes

In the column 'Estimated Clearance of Valsartan,' the lower row shows the percentage of OATP1B1- or OATP1B3-mediated uptake clearance relative to the sum of the estimated clearance mediated by OATP1B1 and OATP1B3. The details of this estimation are described under *Materials and Methods*.

Lot	Ratio of Uptake Clearance $CL_{-hep}/CL_{-transporter}$		Estimated Clearance of Valsartan	
	$R_{act,OATP1B1}$	$R_{act,OATP1B3}$	OATP1B1	OATP1B3
			µl/min/10^6 cells	
OCF	1.10	1.72	1.72	1.65
			51.0%	49.0%
094	1.17	6.95	1.83	6.67
			21.5%	78.5%
03–013	0.53	0.35	0.827	0.336
			71.1%	28.9%

Valsartan is less avidly taken up by OATP1B1 than E1S and also less avidly taken up by OAT1B3 than CKK-8. The results for valsartan vary dependent on the batch of hepatocytes used. The relative contribution of the uptake of valsartan by OATP1B1 and OATP1B3 varies also dependent on the batch of hepatocytes used.

Transcellular Transport of Valsartan across MDCKII Monolayers

The MDCKII monolayers express uptake and efflux transporters. No significant vectorial transport of valsartan was observed in single transfected cells expressing OATP1B1, MDR1, MRP2 and BCRP, and vector transfected control cells. However as shown in Figure 5 below the basal to apical transcellular transport of valsartan in OATP1B1/MRP2 double transfected cells is largest among the doubled transfected cells expressing OATP1B1/MRP2, OATP1B1/MDR1, and OATP1B1/BCRP:

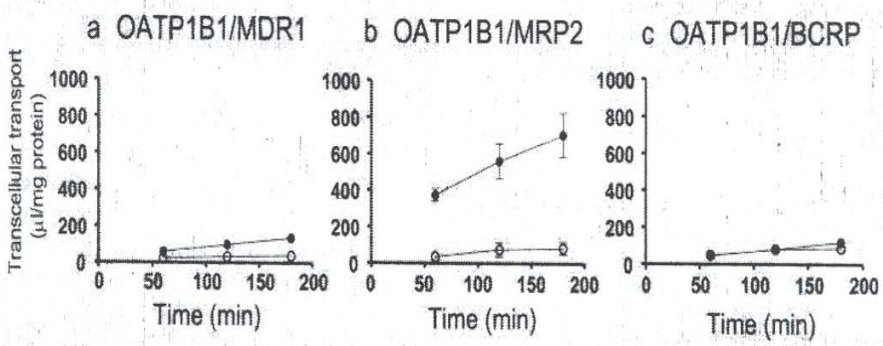


FIG. 5. Time profiles of the transcellular transport of valsartan across MDCKII monolayers expressing transporters. Transcellular transport of valsartan (0.1 μM) across MDCKII monolayers expressing OATP1B1/MDR1 (a), OATP1B1/MRP2 (b), and OATP1B1/BCRP (c) was observed. Open circles and closed circles represent the transcellular transport in the apical-to-basal and basal-to-apical directions, respectively. Each point represents the mean ± S.E. (n = 3).

The basal to apical transport of the control E2-17βG was 36, 8.9 and 6.1 time greater than that in the opposite direction.

ATP dependent Uptake of Valsartan in Human MRP2 Expressing Membrane Vesicles

To confirm that valsartan is a substrate of MRP2, the time dependent uptake of valsartan membrane vesicles prepared from MRP2-expressing LLC-PK1 cells was examined. As shown by Figure 7 valsartan is significantly and ATP dependently taken up into the membrane vesicles:

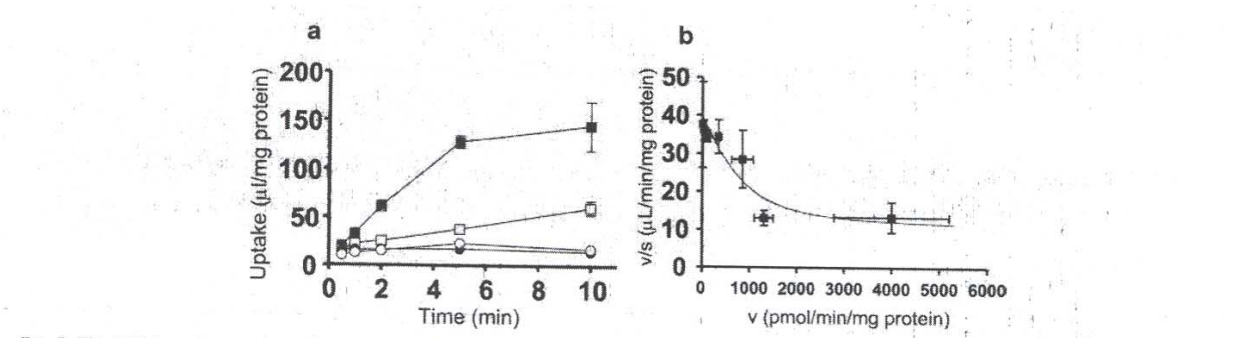


FIG. 7. The ATP-dependent transport of valsartan in MRP2-expressing LLC-PK1 cells. Time profiles for the uptake of valsartan were measured in isolated membrane vesicles prepared from LLC-PK1 cells expressing MRP2 (a). Membrane vesicles were incubated at 37°C with valsartan (0.1 μM) in the medium in the presence of ATP (closed symbols) or AMP (open symbols) for designated periods (0.5, 1, 2, 5, or 10 min). Squares and circles represent the uptake of membrane vesicles expressing MRP2 and control vesicles infected only with adenovirus containing tetracycline-responsive transcriptional activator, respectively. The concentration dependence of MRP2-mediated uptake of valsartan is shown as Eadie-Hofstee plots (b). The uptake of valsartan for 2 min was determined at various concentrations (0.3–300 μM). Each point represents the mean ± S.E. (n = 3).

The process is saturable.

Pharmacokinetics of Valsartan in Sprague-Dawley and EHBR Rats

The plasma concentrations of valsartan in the EHBR rats were significantly larger than in normal rats as shown in Figure 8a:

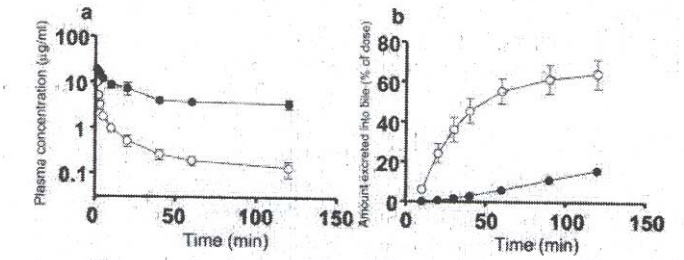


FIG. 8. Biliary elimination of valsartan in male SD rats and EHBRs. Rats were injected with valsartan (1 mg/kg body weight dissolved in phosphate-buffered saline) into a femoral vein after cannulation of the bile duct. The time profiles of the plasma concentration (a) and cumulative biliary excretion (b) of valsartan in SD rats (open circles) and EHBRs (closed circles) are shown. Each point represents the mean ± S.E. (n = 3).

Two hours after administration 70% of the total radioactivity injected was excreted into the bile in normal rats whereas only 15% was excreted by the EHBR rats. The AUC in EHBR rats was 17 times greater than in normal rats.

Conclusion

The data of the in vitro study suggest that valsartan is a substrate of OATP1B1 and OATP1B3 and MRP2. The in vivo study in EHBR rats deficient in mrp2 indicates that valsartan is a substrate of mrp2. The relevance of this finding is that drug interactions of valsartan and inhibitors of OATP including cyclosporine, rifampicin and other drugs could occur under clinical conditions. This potential liability should be noted in the labeling of valsartan.

Comments

1. mrp2 in rats and MRP2 in humans may not be orthologous.

5. BIOPHARMACEUTICS

Of the three tested clinical service formulations, the oral extemporaneous suspension and the pediatric 10 mg and 80 mg tablets, only the oral suspension is proposed for marketing in children in the age of 2- < 6 years old and adults who cannot swallow the tablet.

5.1. Valsartan 4 mg/mL Extemporaneous Suspension

Preparation and Composition of 4 mg/mL Oral Suspension of Valsartan

The commercially available Diovan 80 mg film coated tablets were used for the extemporaneous preparation of the oral suspension. The diluents used for the 4 mg/mL suspension are Ora-Plus oral suspending vehicle and Ora-Sweet SF oral syrup vehicle. These are commercially available vehicles from Paddock Laboratories, Inc., and contain compendial components. The composition of the Diovan® oral suspension is shown in the below table:

Table 2-1 Representative composition of Diovan 4 mg/mL suspension

Component	Quality
Diovan 80 mg tablets	8 tablets (640 mg of valsartan)
Ora-Plus oral suspending vehicle	80 mL
Ora-Sweet SF oral suspending vehicle	80 mL
Total volume of suspension	160 mL

The extemporaneous preparation of the 640 mg/160 mL (4mg/mL) suspension is as follows: 80 mL of Ora-Plus are added to the dispensing bottle containing eight 80 mg Diovan tablets. After shaking for at least 2 minutes, the suspension is allowed to stand for a minimum of one hour. Subsequently, the suspension is shaken for an additional one minute. Eighty (80) mL of Ora-Sweet SF is added to the bottle and the suspension is shaken for 10 seconds to disperse the ingredients.

6. REVIEW OF SPONSOR'S RESPONSES TO REVIEWER'S COMMENTS Submitted September 20, 2007

FDA Comment 1: Failure to consider impact of difference in relative bioavailability among pediatric clinical service formulations used in the clinical trials. Cmax (1.8 times) and AUC (1.4 times) were greater with the extemporaneous suspension administered to

children < 6 years of age than with the clinical service formulations administered to children ≥6 years of age.
Sponsor's Response: The sponsor's response does not address FDA Comment 1.

FDA Comment 2: Label does not consider impact of difference in relative bioavailability between the extemporaneous suspension and the commercial adult 40, 80 and 160 mg tablets (Cmax (1.9 times) and AUC (1.6 times) greater with the suspension than with the commercial adult tablets. The label does not state that the dose of the adult tablets should be increased by a factor of 1.6 to 1.9 when in a pre-school age child the extemporaneous suspension is changed to an adult tablet.

Sponsor's Response: The sponsor proposes to add the following statement to the CLINICAL PHARMACOLOGY section of the label: "The exposure (measured as AUC) of valsartan with the suspension formulation is 56% higher when compared to the tablet formulation in normal healthy adult volunteers." This Reviewer proposes that the label should state that "When the extemporaneous suspension is replaced by a tablet in a child the dose may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablets. "

FDA Comment 3: Failure to include in the label results from a published study (Yamashiro et al. 2006) showing evidence for valsartan to be a substrate of OATP and MRP2. Valsartan may be susceptible to interactions when co-administered with OATP inhibitors (e.g. rifampin, cyclosporine) or drugs interfering with the activity of MRP2 (e.g. ritonavir or probenecid).
Sponsor's Response: The sponsor believes that a label change is not required based on the following rationale:

- The absolute oral bioavailability of valsartan administered as solution is about 40%. The first-pass hepatic clearance is low and is lower than the hepatic blood flow.
- The mean estimated Km values observed in vitro studies are about 1.4, 18.2 and 27.5 µM with OATP1B1, 1B3 and MRP2, respectively, which are significantly higher than the free plasma concentrations of valsartan that are generally achieved with the maximum clinical dose of 320 mg about 1 µM.
- It has been shown that valsartan exhibits dose proportional and dose linear pharmacokinetics in the available clinical doses (20 to 320 mg) [CTD 2.7.1, VALIANT NDA 21-283, S-011].
- Pharmacokinetic drug interaction studies involving digoxin (OATP1B3 substrate) and simvastatin (OATP substrate) have shown that pharmacokinetics of valsartan were not affected to a significant extent [Protocol 39 (digoxin)*; Sunkara et al, 2007 (simvastatin)**]. *: this report was submitted with original NDA 20-665 submission of valsartan; ** Sunkara et al, 2007- Evaluation of a pharmacokinetic interaction between valsartan and simvastatin in healthy subjects, Curr Med Res Opin. 2007 Mar;23(3):631-40.
- Valsartan has been shown to be safe and effective in post-transplant patients who were on cyclosporine (Andres et al., 2006*). Cyclosporine is an inhibitor of MRP2 and OATPB1. *Efficacy and safety of valsartan, an angiotensin II receptor antagonist, in hypertension after renal transplantation: a randomized multicenter study, Transplant Proc. 2006 Oct;38(8):2419-23
- The current label of valsartan (Diovan) indicates that no dose adjustments are required with mild to moderate hepatic failure.

Among these arguments the most relevant is that valsartan was found to be safe and effective in patients who were on cyclosporine (Andres et al. submitted earlier).

This Reviewer believes that the findings by Yamashiro et al. should be mentioned in the labeling. The study by Andres et al. did not measure exposure to valsartan in the presence of cyclosporine. Even if cyclosporine were found not to increase exposure to valsartan extrapolations from one inhibitor to another should not be made. There is not enough experience with inhibitors of transporters.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 3, 2007
To:	Norman Stockbridge, MD Director, Division of Cardiovascular and Renal Products, HFD-110
Thru:	Linda Y. Kim-Jung, PharmD, Team Leader Denise P. Toyer, PharmD, Deputy Director Carol A. Holquist, R.Ph., Director Division of Medication Errors and Technical Support, HFD-420
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Errors and Technical Support, HFD-420
Subject:	DMETS Premarketing Labeling Review
Drug Name(s):	Diovan (Valsartan) Tablets 40 mg, 80 mg, 160 mg, and 320 mg
Application Type/Number:	NDA 21-283/S-024
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2007-1561

CONTENTS

EXECUTIVE SUMMARY

In review of the efficacy supplement for Diovan in the pediatric population one year of age and older, we noted the new indication of use provides for dosing that is not achievable from the currently marketed strengths of Diovan. To compensate, the sponsor proposed that healthcare providers compound an oral suspension from the available tablet strengths. The dosage range suggested in the Dosage and Administration sections will require the majority of patients to receive a compounded formula. Thus, errors may result in the preparaton of a superpotent or subpotent suspension. To avoid this type of error, the ideal solution would be to provide a commercially available oral suspension. We additionally noted areas in the Highlights of Prescribing Information--Dosage and Administration section, that need revision in order to minimize user error. See Section 6 for full recommendations.

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from the Division of Cardiovascular and Renal Products (HFD-110) for an evaluation of the Diovan insert labeling that provides for the treatment of hypertension in pediatric patients one year of age and older. Novartis submitted an efficacy supplement that provides for the use of Diovan in the pediatric population for the treatment of hypertension.

1.2 REGULATORY HISTORY

Diovan capsules were approved on December 23, 1996 and discontinued in 2002. Diovan tablets were approved on July 18, 2001 for the indication of the treatment of hypertension and heart failure in the adult population.

1.3 PRODUCT LABELING

Diovan is an Angiotensin II Receptor Blocker (ARB) indicated for the treatment of hypertension, heart failure (NYHA class II-IV), and for reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction in adults. The recommended starting dose for adults in the treatment of hypertension is 80 mg or 160 mg once daily, with a dosage range of 80 mg to 320 mg once daily. For the treatment of heart failure, the recommended starting dose is 40 mg twice daily. Up titration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient.

The recommended starting dose for the proposed indication of treatment of hypertension in pediatric patients is 1.3 mg/kg (up to 40 mg total). The dosage should be adjusted according to blood pressure response. Doses higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in pediatric patients 6 to 12 years of age. Doses higher than 80 mg have not been studied in children 1 to 5 years of age. Diovan is not recommended for treatment of infants below the age of 12 months or in pediatric patients with a glomerular filtration rate less than 30 mL/min/1.73 m^2, as no data are available.

The use of a suspension is recommended for children 1 to 5 years of age, patients who cannot swallow tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of Diovan. Directions for preparation of an oral suspension are proposed in the package insert labeling. Diovan is curently available as tablets in the following strengths: 40 mg (scored tablet), 80 mg, 160 mg, and 320 mg.

2 METHODS AND MATERIALS

The insert and patient package insert labeling submitted on May 29, 2007 was reviewed.

Additionally, since Diovan is a currently marketed drug product in the U.S., DMETS conducted a search of the FDA *Adverse Event Reporting System* (AERS) and the *Drug Quality Reporting System* (DQRS) for medication errors involving Diovan tablets.

2.1 AERS SELECTION OF CASES

AERS was searched using the MedDRA High Level Group Term "Medication Errors" and the Preferred Term "Pharmaceutical Product Complaint", the tradename "Diovan" and active ingredient "valsartan" for cases received through August 2007. The Preferred Terms "Intentional Overdose" and "Multiple Drug Overdose Intentional" were omitted.

2.2 DQRS SELECTION OF CASES

DMETS searched the Drug Quality Reporting System for all cases involving Diovan through August 2007 using the trade name "Diovan%" and established name "valsartan%".

3 RESULTS

Fourteen relevant cases (n=14) were identified from our searches; 8 cases from AERS and 6 cases from DQRS.

3.1 AERS

Twelve cases were returned from AERS. However, three cases involved look-alike concerns between Diovan 80 mg capsules and Effexor 37.5 mg capsules and one case involved look-alike concerns between Diovan 80 mg and 160 mg capsules. DMETS omitted these four cases because the Diovan capsules dosage form was discontinued in 2002. Thus, eight cases (n=8) remain. Six (n=6) of the eight cases describe wrong drug errors and two (n=2) cases describe a lack of readability of information on the silver foil unit-dose blister container labels. Five (n=5) of the wrong drug errors involved name confusion between Diovan/valsartan and either losartan (1), Darvon (2), or Zyban (2). The remaining wrong drug error case involved a dispensing error in which Diovan was prescribed but Diovan HCT was dispensed instead, in error. Causality was identified in two cases. In one of the Zyban cases, knowledge deficit was alluded to as the source of the error. In one of the Diovan/Darvon cases the reporter indicated that the two names look alike. The patient took the wrong drug in the Diovan HCT case and one of the Zyban cases. However, causality or outcome information was not provided. The remaining two cases concerned complaints about the lack of readability of the drug information imprinted on the silver foil unit-dose blister container labels in which Diovan tablets were packaged.

3.2 DQRS

Six cases (n=6) were identified in DQRS. One (n=1) case involved a wrong drug error and five (n=5) cases concerned complaints about the lack of readability of information on the silver foil unit-dose blister container labels in which Diovan tablets were packaged. The wrong drug error involved a dispensing error in which Diovan HCT was prescribed but Diovan was dispensed instead.

4 DISCUSSION

Following review of the labeling to include dosing instructions for pediatric patients, we are very concerned about the unavailability of a commercially produced oral formulation. The new

indication of use provides for dosing that may not be achievable from the currently marketed strengths of Diovan. To compensate, the sponsor proposes that healthcare providers compound an oral suspension from the available tablet strengths. Since the majority of pediatric doses will require a pharmacist to compound the formulation, this provides opportunity for errors that may result in the preparation of a superpotent or subpotent suspension. Errors may occur at any point in the compounding process such as: product selection (the wrong tablet strength may be selected for use in the compound), mathematical calculations (if the tablet strength recommended for use in the compound is not available, using a different tablet strength would require a calculation), preparation (if the tablets are not properly dissolved a homogeneous suspension will not be obtained and, therefore, the desired drug concentration will not be achieved), labeling (if not properly labeled by the pharmacist, errors in drug administration, storage, etc. may occur), and dispensing (a dosing administration device such as a cup or syringe with the proper markings will have to be obtained/purchased separately and omission of this step could result in drug administration errors). Furthermore, confusion may occur if pharmacists/pharmacy technicians are unaware that the insert includes a formula for preparation of the suspension (they may choose to make their own formula). These errors could be avoided if Diovan is made commercially available in an oral suspension.

Upon evaluation of the proposed insert labeling we identified potential failure points with the presentation of the dosing information and oral suspension preparation instructions and confusing pediatric dosing information in the Highlights of Prescribing Information—Dosage and Administration section of the insert labeling. The sponsor provides detailed directions for preparation of Diovan oral suspension using tablets. These directions for preparation are currently presented in a paragraph format, which may be more difficult to follow than a bulleted or numbered set of steps. When directions for use are not presented in a clear format, confusion may occur. Presenting this information in a numbered series may decrease confusion and increase the readability of these directions. Additionally, the directions state to "Shake the bottle well (at least 10 seconds) prior to dispensing the suspension." However, it is not clear from this statement whether the bottle should be shaken prior to each use. Furthermore, the directions include storage and handling guidance, however, this information is not repeated in the patient package insert where patients look for proper storage information.

In the Highlights of Prescribing Information, Dosage and Administration section, there is a chart that contains the dosing ranges in a condensed format. However, when using this chart it may not be clear to prescribers that there are limitations in dosing depending upon the patients' age unless they read the Full Prescribing Information--Dosage and Administration section. For example, the dose range for pediatric hypertension is stated as "1.3-2.7 mg/kg once daily (up to 40-160 mg total). However, it doesn't indicate that there is a maximum dose based on the pediatric patient's age range (i.e., 80 mg for patients 1 to 5 years of age and 160 mg for patients 6 to 16 years of age), see chart on page 4. This lack of clarity is misleading and increases the potential for improper dosing. Thus, additional information with regards to the dosing limitations must also be presented. DMETS also notes that the first dose specified (i.e., 40) in the dosage range specification for pediatric hypertension is not followed by its corresponding unit of measure (i.e., mg), and therefore may be confusing. The dose should consistently be followed by its unit of measure so as to avoid misinterpretation.

----------DOSAGE AND ADMINISTRATION----------

Indication	Starting dose	Dose Range	Target Maintenance Dose*
Adult Hypertension (2.1)	80 or 160 mg once daily	80-320 mg once daily	---
Pediatric Hypertension (2.1)	1.3 mg/kg once daily (up to 40 mg total)	1.3-2.7 mg/kg once daily (up to 40-160 mg total)	---
Heart Failure (2.2)	40 mg twice daily	40-160 twice daily	160 mg twice daily
Post-Myocardial Infarction (2.3)	20 mg twice daily	20-160 mg twice daily	160 mg twice daily

* as tolerated by patient

Our analysis of the postmarketing medication error cases identified wrong drug name confusion between Diovan/valsartan and Zyban, Darvon, or losartan and a dispensing error between Diovan and Diovan HCT. However, the last case reported with regards to wrong drug name confusion was received in 2002. Thus, the issue of confusion between Diovan/valsartan and Zyban, Darvon, Diovan HCT or losartan is not a safety concern at this time. Analysis of the medication error cases concerning the readability of information on the silver foil unit-dose blisters revealed that the sponsor has revised the silver foil unit-dose blisters. The currently used labels are easier to read. Thus, the readability of the silver foil unit-dose blisters is no longer a safety issue.

5 CONCLUSION

This application provides for a pediatric dosing for children one year of age and older. However, the current product is not formulated to deliver all of the dosages recommended in these age groups. As a result, DMETS anticipates compounding errors may result in the preparation of a superpotent or subpotent suspension. DMETS concludes that the sponsor should be required to provide a commercially available oral suspension that will allow for the safe and proper dosing of this product. Providing a commercially available suspension rather than relying on healthcare professionals to compound the product is a much higher leverage approach to minimizing the chances of errors in preparation, especially since the majority of pediatric patients will likely be using a dose that cannot be obtained from the commercially available tablets. Additionally, the proposed Diovan insert labeling currently lacks clarity in the Highlights of Prescribing Information--Dosage and Administration section and under the instructions for preparation for oral suspension and should be revised in order to minimize user error.

6 RECOMMENDATIONS

1. To avoid errors in preparation of the pediatric suspension, we recommend that the sponsor market a commercially available Diovan oral suspension. A commercial suspension will provide full labeling, better sterility, and a more stable product.

2. An educational campaign should be developed and implemented to educate healthcare professionals on the pediatric indication of use, and availablilty of a recipe for compounding the oral suspension (in lieu of a commercially available suspension).

3. Include a notation in or below the Dosage and Administration chart located in the Highlights of Prescribing Information section of the insert that states the maximum dose

recommended for the pediatric age groups as specified in the Full Prescribing--Dosage and Administration section of the insert labeling.

4. Include the unit of measure (e.g., 40 mg) in the oral dosage range statement and wherever the dose appears throughout the package insert.
5. DMETS recommends that the steps for preparaton of the suspension be numbered or bulleted and listed vertically in order to improve readability of the instructions.
6. If the bottle of prepared Diovan oral suspension needs to be shaken prior to each use, please state this in the directions for preparation of the oral suspension. Instructions that state which auxillary stickers (e.g., Shake well, Store in refrigerator, etc.) need to be placed on the label prior to dispensing would be helpful and is recommended.
7. Include information concerning storage and handling of the prepared oral suspension in the Patient Package Insert.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any correspondence to the sponsor pertaining to this issue. If you have further questions or need clarification, please contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

7 REFERENCES

1. Adverse Events Reporting System (AERS)

   AERS is a database application in CDER FDA that contains adverse event reports ofr approved ddrugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontenaous reporting system that captures reports from healthcare professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reorting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Drug Quality Reporting System (DQRS)

   Drug Quality Reporting System (DQRS) contains voluntarily reports of observed or suspected defects or quality problems with marketed drug products. The agency receives reports through the MedWatch Program. The Division of Compliance Risk Management and Surveillance evaluates and prioritizes drug quality reports in order to identify and follow-up on significant health hazards through assignment and review of investigative reports. Drug quality reports are also used to identify industry trends associated with pharmaceutical manufacturing, packaging, and labeling. The division shares the data with the U.S. Pharmacopeia to enhance compendial standards for drug products.

3. OSE Review 06-0164, Label and Labeling Review of Diovan HCT, dated March 26, 2006

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/s/

Loretta Holmes
12/3/2007 08:51:41 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
12/3/2007 08:57:45 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/3/2007 10:23:59 AM
DRUG SAFETY OFFICE REVIEWER

RHPM Overview - AP Action
NDA 21-283/S-024
Diovan (valsartan) Tablets,
40, 80, 160, and 320 mg

Sponsor:	Novartis Pharmaceuticals Corporation
Classification:	Priority
Submission Date:	May 29, 2007
Receipt Date:	May 29, 2007
User Fee Goal Date:	November 29, 2007

Background
This efficacy supplement provides for the use of Diovan (valsartan) Tablets for the treatment of hypertension in pediatric patients. Valsartan was initially approved under NDA 20-665 (Diovan Capsules) on December 23, 1996. Diovan Tablets was approved under NDA 21-283 on July 18, 2001. Clinical investigations of Diovan for the treatment of pediatric patients were conducted under IND 40,704.

This submission contains pediatric study reports in response to a Written Request (WR). This sNDA was subject to a 6-month priority review clock per Section 5 of the Best Pharmaceuticals for Children Act. The original WR was issued on December 19, 2000, and subsequently amended on November 25, 2002 and June 18, 2003. "Re-issue" letters were sent on July 3, 2002 and May 10, 2004. The submission contains an annotated WR. On August 8, 2007, a pediatric exclusivity determination meeting was held and pediatric exclusivity was granted.

This sNDA provides the efficacy and safety results for valsartan in hypertensive children 6-16 years of age. In support of approval, the sponsor has submitted chemistry, nonclinical pharmacology, clinical pharmacology, clinical, and statistical data.

Medical Review
In her 10/15/07 clinical review, Dr. Targum wrote the following:

Conclusions:
1. A treatment effect is supported by Phase 2 results from both clinical studies.
2. A dose-response is not demonstrated in A2307 (hypertensive children aged 1-5 years). It is not clear whether the lack of dose-response reflects the higher exposures seen with the extemporaneous suspension.
3. A dose-response is demonstrated in A2302 (hypertensive children aged 6-16 years); the data, when weight-adjusted on a mg/kg basis, does not fit a linear, log-linear, or Emax model.
4. Results for diastolic blood pressure are consistent with the results for systolic blood pressure and support a treatment effect.
5. Results by subgroup are consistent with the overall results.
6. In study A2307, marked rises in transaminases were seen in two patients at the end-ofstudy visit; a third patient was discontinued due to hepatitis and was subsequently hospitalized with fatal pneumonitis.
7. As noted, increases in BUN, creatinine, uric acid, and potassium are seen in the database.

Recommendation on Regulatory Action
It is recommended that valsartan be granted an "approvable" action.
Outstanding issues are:

1. Instructions for use: we would like to further understand how to dose, given the lack of dose-response in A2307 and the relatively flat (albeit with significant mean slope) change

from baseline in BP as a function of weight-adjusted valsartan dose.
2. Safety: Given the cases of transaminase elevations, the sponsor should demonstrate safety in the younger age group. From the current database, the reviewer cannot tell whether these transaminase elevations represent a hepatic safety issue in a vulnerable population, or whether these cases are related to an increase in valsartan exposure (with the extemporaneous suspension), or are related to some incidental concomitant condition.
3. Two deaths occurred in 1 year-old patients exposed to valsartan during the open-label phase; while these events might have been related to concomitant conditions, this reviewer is unable to rule out a drug effect.

Joint Medical/Statistical Review
In their 10/4/07 joint medical/statistical review, Drs. Targum, and Freidlin wrote the following:

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 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).

Clinical Pharmacology Review
In his 11/20/07 review, Dr. Hinderling wrote the following:

The review of the Clinical Pharmacology part of the submission indicated the following deficiencies:

1. Failure to consider impact of difference in relative bioavailability among the pediatric clinical service formulations used in the clinical trials

The sponsor states that “the protocol specified doses used in clinical studies 2302 (6-16 year old children) and 2307 (1- < 6 year old children) were selected on the basis of expected blood pressure response rather than plasma concentration levels of valsartan. Adult doses were scaled down to corresponding doses for the respective pediatric population based on the body surface area of adults vs. children.” In reality doses were scaled down in the basis of body weight in all four age groups, but the exposure to valsartan in the two younger age groups was 1.8 times (Cmax) and 1.4 times (AUC) greater than in the two older age groups. The bioavailability of valsartan with the extemporaneous suspension administered to the two younger age groups is significantly greater than with the pediatric

10 and 80 mg tablets given to the two older age groups. The significantly higher exposure of the 1- < 6 years old children in the clinical trial should be considered in comparing the dose-response relationship in trials 2302 and 2307.

2. Label does not consider impact of difference in relative bioavailability between the extemporaneous suspension and the commercial adult 40, 80, 160 and 320 mg tablets

The bioavailability of valsartan with the extemporaneous suspension is about 1.9 times (Cmax) and 1.6 times (AUC) greater than with the commercial adult 80 mg tablet. Similarly, the bioavailability of valsartan with the extemporaneous suspension is about 1.8 times (Cmax) and 1.4 times (AUC) greater than with the commercial adult 40 mg tablet. Despite the significant difference in relative bioavailability between the extemporaneous suspension and the adult tablets the label recommends the same doses corrected for body weight for 1-6 year old children and 6-16 year old children.
Also, the label does not state that the dose of the adult tablets should be increased by a factor of 1.6-1.9 when in a pre-school age child the extemporaneous suspension is changed to an adult tablet.

3. Failure to include in the label results from a published study showing evidence for valsartan to be a substrate of OATP and MRP2

A publication by Yamashiro et al., Drug Metab Dispos 2006;34:1247-1254, shows in vitro evidence for involvement of OATP1B1 and OATP1B3 in hepatic uptake and MRP2 in hepatic extrusion of valsartan. The authors showed further delayed elimination of valsartan using mrp2 deficient rats. The findings suggest that valsartan may be susceptible to interactions when co-administered with OATP inhibitors such as e.g. rifampicin or cyclosporine or drugs interfering with the activity of MRP2, such as e.g. ritonavir or probenecid. The label of valsartan should include the results from this study.

1.1 RECOMMENDATION

From a Clinical Pharmacology viewpoint the submission is acceptable. The sponsor is advised to resolve the above identified issues.

See his review in DFS for labeling recommendations.

Pharmacology review

In his 10/4/07 review, Dr. Jagadeesh recommended that the sNDA was "Approvable." See his review in DFS for labeling recommendations.

Chemistry review

In his 9/13/07 review, Dr. Raman wrote the following:

Comments: This efficacy supplement is submitted in response to Agency request to provide the efficacy and safety results for valsartan in hypertensive children 1-16 years of age. The drug product for pediatric patients will be prepared extemporaneously by suspending Diovan 80 mg tablets in Ora-Plus oral suspending vehicle and Ora-sweet SF syrup vehicle to a dose of 4 mg/mL. The current submission contains information regarding the suspension, the vehicle, and stability data under long-term and accelerated conditions and labeling information. Review of stability data support a 2.5 month shelf life for the Diovan 4 mg/mL oral suspension when stored in amber glass bottles with child resistant closure at 2-8°C. The application is subject of DMF (b) (4) review, which was reviewed by this reviewer (review # 1) on 8/29/07 and found adequate.

Conclusions and Recommendations: Adequate information has been provided in support of the proposed the 4 mg/mL oral suspension of marketed Diovan (valsartan) tablets prepared extemporaneously by suspending Diovan 80 mg tablets in Ora-Plus oral suspending vehicle and Ora-

Sweet SF syrup vehicle. The supplement is "**approved**" from CMC perspective. Please issue an approval letter.

Environmental Assessment
The sponsor states that this sNDA qualifies for a categorical exclusion from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement in accordance with 21 CFR Part 25.31(a). In his 9/13/07 review, Dr. Raman wrote that this was acceptable.

Division of Scientific Investigations
In her 11/21/07 Clinical Inspection Summary, Dr. Gershon wrote the following:

> **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**
> DSI recommends the data at this site are acceptable in support of this pediatric supplement. The deficiencies noted do not appear likely to affect the outcome of the study.
>
> **Note:** Observations noted above are based on the Form FDA 483, preliminary EIR and communications from field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.
>
> Follow-up action: none needed.

Safety Update
The sponsor submitted the 120-Day Safety Update on 9/20/07.

In her 11/29/07 memo, Dr. Targum wrote the following:

> Comment: The information in the safety update, as well as the teleconference today, do not preclude an approval action.

Pediatrics
A pediatric exclusivity determination meeting was held on August 8, 2007 and pediatric exclusivity was granted.

Labeling
The original submission contains proposed draft labeling for the package insert (PI), patient package insert (PPI) in PLR and SPL format. This proposed Diovan package insert is the first version to appear in PLR format. No changes were proposed to the carton/container labeling.

DDMAC provided comments on the proposed labeling in a review dated 11/18/07.

DSRCS provided comments on the proposed PPI in a review dated 11/20/07.

SEALD and MHT provided comments on the proposed labeling on 11/27/07.

A labeling discussion was held with the sponsor on 11/28/07.

Financial Dislosure
In her 11/29/07 memo, Dr. Targum wrote the following:

> A Financial Disclosure certification, dated April 30, 2007, was reviewed.
> No clinical investigators were full or part-time employees of the sponsor. Of studies, A2301,

A2302, A2304, A2305, A2307, and A2308, 98-100% of the investigators responded to requests for financial disclosure information. No disclosable financial interests were reported that would affect the conduct of the clinical studies.

User Fee
The user fee for this application was paid in full (User Fee ID# PD3007346).

CSO Summary
An approval (AP) letter on agreed-upon draft labeling will be drafted for Dr. Stockbridge's signature.

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
11-29-07

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/s/

Quynh Nguyen
11/29/2007 05:14:42 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 20, 2007
To:	Norman L. Stockbridge, M.D., Ph.D., Director Division of Cardio-Renal Products
Thru:	Toni Piazz-Hepp, Pharm. D., Deputy Director Division of Surveillance, Research and Communication Support
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Division of Surveillance, Research and Communication Support
Subject:	Review of Patient Labeling (Patient Package Insert)
Drug Name(s):	Diovan (valsartan) tablets (40 mg, 80 mg, 160 mg, 320 mg)
Application Type/Number:	NDA # 21-283
Submission Number:	S-024
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2007-1560

1 INTRODUCTION

Novartis Pharmaceuticals Corporation received initial approval for Diovan (valsartan) capsules under NDA 20-665 on December 23, 1996. The sponsor has since discontinued marketing the capsules under this NDA. Diovan (valsartan) tablets received original approval under NDA 21-283 on July 18, 2001. Diovan is an angiotensin II receptor blocker which is currently indicated:

- for treatment of hypertension
- for treatment of heart failure (NYHA class II-IV)
- to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.

The sponsor submitted a supplemental NDA, sNDA21-283/S-024 on May 29, 2007 in response to an FDA Written Request dated June 18, 2003. The purpose of the supplemental NDA is to provide the efficacy and safety data results for Diovan (valsartan) tablets in hypertensive children 1-16 years of age. The Professional Information (PI) has been converted to PLR with this submission.

DSRCS has been requested to review the Patient Labeling (Patient Package Insert) that is included as part of the supplemental NDA. The currently approved version of the Diovan (valsartan) tablets labeling, dated June 20, 2007, includes a Patient Package Insert.

2 MATERIAL REVIEWED

Professional Information and Patient Package Insert as revised by the review division on November 16, 2007.

3 DISCUSSION

See the attached document for our suggested revisions to the Diovan (valsartan) tablets PPI. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. Since there is already an approved PPI for this product, and the sponsor's proposed changes are primarily related to the new indication for treating hypertension in the pediatric population, we have focused our review in this area. We have ensured that the PPI is consistent with the PI and reflects the revision of the PI to PLR format, simplified the wording where possible and eliminated redundant information. These recommended revisions are consistent with current research to improve risk communication to a broad range of audiences, including those with lower levels of literacy.

Comments to the review division are ***bolded, underlined and italicized.***

4 CONCLUSIONS AND RECOMMENDATIONS

- A PPI for Diovan (valsartan) tablets is voluntary. All strengths of Diovan (valsartan) tablets are packaged in bottles and unit dose blister packages. Unless all Diovan product is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI. The sponsor should clarify how they intend to insure that the PPI is distributed to patients and parents/caregivers. This is important with the proposed pediatric indication since pharmacists may be mixing oral suspension for children. The PPI now includes information on administration and storage of Diovan as a suspension.

- See the attached document for our suggested revisions to the currently approved PPI. The proposed PPI revision submitted by the sponsor has a Flesch Kincaid grade level 6.9 and a Flesch Reading Ease score of 66.6. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8th grade reading level). The reading scores as submitted by the sponsor are acceptable. Our revised PPI has a Flesch Kincaid grade level of 7.4 and a Flesch Reading Ease score of 65.6. The increase in scores reflects the need to add information about the new pediatric indication.

- Under "What is the most important information I should know about Diovan?" for consistency we have boxed and modified the first paragraph to match the language in the approved Exforge PI and PPI. We recommend revising the language in PPIs for other products containing valsartan, for consistency.

- Information has been added to the PPI regarding administering and storing Diovan when mixed as a suspension for children who can not swallow tablets or the prescribed tablet strength is not available.

- It is unclear how the sponsor chose the most common side effects of Diovan used to treat people with high blood pressure. We made the list consistent with the PI.

- We are providing the review division with marked up and clean Word copies of our revisions to the PPI. We recommend using the clean copy as the working document.

Please let us know if you have any questions.

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/s/

Sharon Mills
11/20/2007 06:20:54 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
11/21/2007 09:06:23 AM
DRUG SAFETY OFFICE REVIEWER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 20, 2007

TO: Quynh M. Nguyen, Pharm.D.
Regulatory Health Project Manager
Shjeri Targum, Medical Officer (21-283/S-024)
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting-Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Sharon K. Gershon, Pharm.D., CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-283/S-024
Sponsor: Novartis

DRUG: Valsartan (Diovan)

CHEMICAL CLASSIFICATION: 1S

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: evaluate the dose-response of valsartan in sitting systolic blood pressure in children aged 6 to 16 with hypertension.

CONSULTATION REQUEST DATE: July 24, 2007

ACTION GOAL DATE: September 21, 2007

PDUFA DATE: November 29, 2007

I. BACKGROUND:

Valsartan is an angiotensin II receptor blocking agent (ARB), that has been shown to be effective in reducing systolic and diastolic blood pressure in adults, when used as once daily monotherapy, or in combination with hydrochlorthiazide. The purpose for this study was to obtain dosing information and data on safety and tolerability of valsartan in pediatric and adolescent patients with hypertesioin.

This study took place at 55 centers, in 9 countries (29 in the US, 10 in Brazil). A total of 228 patients completed Phase I and 206 patients completed phase 2, and 177 patients completed the Open Label phase of the study. Only one site in Brazil was selected to inspect. This site was selected because it appears to have the largest enrollment and the smallest p-value. It is likely that the significant results from this site will have affected the overall results of the study. Dr. Jose Pacheco Martins is not listed in the CDER COMIS database.

II. RESULTS :

Clinical Investigator	Number of Subjects	Inspection Dates	Protocol No.	Field Classification	EIR Receipt Date
Site #601 Dr. Jose Pacheco Martins (PI) Dr. Monica Pereira (sub-PI) Dr. Cleusa Santos (Sub-PI) Dr. Ana Carneiro (Sub-PI) Recife, Brazil	18	9/22-29/2007	VAL489A2302	VAI	pending

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

A. Protocol #: # VAL489A2302: "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," sponsored by Novartis Pharmaceuticals.

a. What was inspected? The inspection reviewed records from 18 subjects, including 2 screen failures and one subject that was discontinued. A total of 21 subjects were enrolled. The records included source documents (lab data, EKGs), case report forms and

concurrence of data listings for efficacy endpoints, adverse events, 100% of informed consent forms, concomitant medications and drug accountability records.

b. Limitations: There were no limitations to this inspection.

c. General Observations: A 2-item FDA 483 was issued for the following:

1) Version 2.3 of the informed consent form lacked important contact information for the following 3 of 21 subjects: 0601-00001, 0601-0002, and 0601-0003. The consent form was amended for 2 of the subjects 5 months later; one informed consent form was not amended. In his response letter, Dr. Pacheco states that the informed consent document for patient #0601-0003 was never amended because this patient was a screen failure;

2) Information provided in the source records was not accurately documented in the CRF. For example,

a) the concomitant medication list did not identify when and for how long a drug was used by the subject. In his response letter Dr. Pacheco stated that the concomitant medication CRF did not collect CM start/stop dates, and that this information was in the source documentation;

b) the IVRS information regarding dispensing of medications was not documented in the CRF on a consistent basis. For example, Subject #0601-001 lacked IVRS medication information on the Case Report Form for visits 6 through 14, and Subject #0601-0004 lacked IVRS medication information on the CRF for Visits 1, 6 thru 11, 13 and 14.
In his response letter, Dr. Pacheco states that the CRF was designed to collect the medication number information only at the randomization visit.

d. Assessment of Data Integrity: The deficiencies noted on the FDA-483 do not appear to affect the outcome of this study, and DSI recommends that data is acceptable in support of the NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

DSI recommends the data at this site are acceptable in support of this pediatric supplement. The deficiencies noted do not appear likely to affect the outcome of the study.

Note: Observations noted above are based on the Form FDA 483, preliminary EIR and communications from field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Follow-up action: none needed.

{See appended electronic signature page}

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting-Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Sharon Gershon
11/21/2007 12:40:51 PM
CSO

Tejashri Purohit-Sheth
11/21/2007 03:22:17 PM
MEDICAL OFFICER

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that valsartan be “approvable” for use in pediatric patients. Outstanding issues include: understanding how to dose in order to write appropriate instructions for use; and the sponsor providing convincing evidence of safety with regard to transaminase elevations seen in several cases in study A2307.

In addition, two deaths were seen in the open-label phase of the valsartan study in two 1 year-old patients (severe vomiting and diarrhea in one case with no other available data; in the other case, fatal pneumonitis with respiratory failure occurring 11 days after a hospitalization for pneumonitis and hepatitis with valsartan discontinued due to hepatitis).

The question of dosing arises from study A2307 (1-5 year olds), which showed a flat dose-response in the dose-ranging phase; and the results of weight-adjusted dosing in A2302 (6-16 year olds), which showed a high degree of variability, small effects, and do not appear to fit linear, log-linear, or Emax models.

If dosing and titration can be clarified, then the other outstanding issue involves cases of transaminase elevation in A2307; since similar cases were not seen in the older children, it would then be recommended that valsartan be approved in hypertensive patients aged 6-16 years old.
If approved, it is recommended that proposed labeling be amended to include appropriate efficacy and safety information.

1.2 Recommendation on Postmarketing Actions

None

1.2.1 Risk Management Activity

Appropriate information should be communicated to patients and physicians.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor conducted two clinical studies with nearly identical designs (Written Request Trial C). Study A2302 was the pivotal study conducted in hypertensive children aged 6-16 years. Study A2307 was a supportive study in hypertensive children aged 1-5 years. Per the Trial C design, each study incorporated a two-week double-blind dose-response phase (Phase 1), a two-week double-blind placebo-controlled randomized withdrawal phase (Phase 2), and a voluntary open-label extension.

1.3.2 Efficacy

In both studies, results of the randomized withdrawal phase showed a statistically significant different between pooled valsartan and placebo.
In study A2302, results of the two-week dose-ranging phase showed a negative slope of the mm Hg systolic blood pressure per unit increase in dose ratio that was significantly different from zero, supporting a dose-dependent decrease in systolic blood pressure. From additional analyses, these data, when weight-adjusted (mg/kg), showed slope analyses that were significantly different from zero when fit to a linear, linear model on log transformed weight-adjusted dose, and Emax models; however, the data did not "best fit" any of these models.
In study A2307, results of the two-week dose-ranging phase showed a flat dose-response with decreases from baseline in all dose groups (no placebo arm); the slope analyses was not significantly different from zero.

1.3.3 Safety

In A2307 (1-5 years), markedly elevated transaminases were seen at the end-of-study visit in two patients. A third patient subsequently discontinued the study due to hepatitis.

In the A2302 (6-16 years) open-label population, serum creatinine increased by 10% from baseline; in the A2307 open-label population, BUN increased by 15% from baseline. There were two discontinuations from the clinical studies due renal impairment (A2307) and increased creatinine (A2302), respectively.

Two deaths during (or after premature discontinuation from) open-label were noted in A2307. No deaths occurred in A2302.

1.3.4 Dosing Regimen and Administration

Study A2302 employed unapproved tablets. A2307 used an unapproved extemporaneous suspension. According to the clinical pharmacology reviewer, exposure of the 1-5 year old children receiving the extemporaneous suspension was higher than in adults receiving

the adult 80 mg tablet; the exposure of the 6-16 year old children receiving pediatric 10 and 80 mg tablets was comparable to adults receiving the adult tablet.
The dosing regimen in the two clinical studies is summarized in Figure 1-1, below.

Figure 1-1 Study Design, Study A2302 and Study A2307

Screening	Double-blind treatment			Open-Label
Screening Phase[a]	**Phase 1[b] (dose-response)**		**Phase 2[c] (placebo withdrawal)**	**Open Label[d]**
Day -7 to Day 0	**Day 0 to Day 14 Randomized 2:1:2 (L: M: H) dose**		**Days 14 – 28 Re-randomize**	**Weeks 4 to 52**
	Study A2302 (Ages 6 - 16 years)	**Study A2307 (Ages 1 – 5 years)**	**1:1 Ratio**	Based on trough blood pressure: 40mg, 80mg , 160mg or 160 +HCTZ 12.5 mg for children 6-16 years old. 20mg, 40 mg, 80mg, and 80mg +HCTZ 12.5 mg for children 1-5 years old
	Dose	**Dose**		
	Weight < 35 kg	Weight < 18 kg		
Placebo Wash-out	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d.	Low 5 mg o.d Medium 20 mg o.d. High 40 mg o.d.	Continue Phase 1 dose OR Switch to Placebo	
	Weight ≥ 35 kg	Weight ≥ 18 kg		
	Low 20 mg o.d. Medium 80 mg o.d. High 160 mg o.d.	Low 10 mg o.d. Medium 40 mg o.d. High 80 mg o.d		

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/s/

Norman Stockbridge

11/16/2007 09:14:37 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-283/S-024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-283 SUPPL # 024 HFD # 110

Trade Name Diovan Tablets

Generic Name valsartan

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known 11/29/07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE5

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-665 Diovan (valsartan) Capsules

NDA# 21-283 Diovan (valsartan) Tablets

NDA# 21-990 Exforge (amlodipine and valsartan) Tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study VAL489A2302 and Study VAL489A2307

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study VAL489A2302 and Study VAL489A2307

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 40,704	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 40,704	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Quynh Nguyen, Pharm.D.
Title: Regulatory Health Project Manager, Division of Cardiovascular and Renal Products
Date: 11/29/07

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Norman Stockbridge

11/29/2007 05:01:19 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-283 **Supplement Type (e.g. SE5): SE5** **Supplement Number: 024**

Stamp Date: 5/29/07 **PDUFA Goal Date: 5/29/07**

HFD 110 **Trade and generic names/dosage form: Diovan (valsartan) Tablets**

Applicant: Novartis Pharmaceuticals Corp. **Therapeutic Class: antihypertensive**

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

XX Yes. Please proceed to the next section.
☐ No. PREA does not apply. Skip to signature block.

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): Treatment of hypertension. This fixed dose combination is not indicated for initial therapy.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Treatment of hypertension in pediatric patients.

Is this an orphan indication?

☐ Yes. PREA does not apply. Skip to signature block.
XX No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.
XX No: Please check all that apply: ___Partial Waiver ___Deferred _X_Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- **☐ Products in this class for this indication have been studied/labeled for pediatric population**
- **☐ Disease/condition does not exist in children**
- **☐ Too few children with disease to study**
- **☐ There are safety concerns**
- **☐ Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments: The PK study 2305 enrolled patients 1-16 years old. Study A2302 enrolled patients 6-16 years old. Study A2307 enrolled patients aged 1-6 years (all were pre-pubertal). Please refer also to the Written Request.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: Quynh Nguyen, Pharm.D.

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-283/S-024
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 6-23-2005)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA 21-283/S-024
HFD-960/ Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 6-23-2005)

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/s/

Quynh Nguyen
8/14/2007 12:23:28 PM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21-283	BLA STN# NDA Supplement # 024	If NDA, Efficacy Supplement Type SE5	
Proprietary Name: Diovan Established Name: valsartan Dosage Form: Tablets		Applicant: Novartis Pharmaceuticals Corporation	
RPM: Quynh Nguyen, Pharm.D.		Division: DCRP	Phone # 301-796-0510

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (if different)	11/29/07
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ **(**iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	N/A
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Avalide, Cozaar, amlodipine besylate
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Included
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☐ DMETS ☒ DSRCS 11/20/07 ☒ DDMAC 11/18/07 ☒ SEALD 11/27/07 ☒ Other reviews MHT 11/27/07 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	NDA Filing Review 8/6/07; RHPM Overview (AP action) 11/29/07
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	N/A
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	9/13/07
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	9/13/07
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☒ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: N/A ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	11/4/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	10/4/07; 10/15/07; 10/19/07; 11/16/07; 11/19/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	11/29/07
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	11/29/07
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	11/21/07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☐ None 10/4/07
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 11/20/07; 11/20/07

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s Office of Regulatory Policy representative.

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/s/

Quynh Nguyen

11/29/2007 05:13:34 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-283/S-024

DISCIPLINE REVIEW LETTER

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy Price
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Price:

Please refer to your May 29, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) Tablets.

We also refer to your submission dated October 17, 2007.

Our review of the Clinical section of your submission is complete, and we have identified the following deficiencies:

We are concerned with the following cases of on-treatment transaminase elevations that were seen in the valsartan pediatric submission:

Study A2307 (N=90):

1. Patient #085-00003, hospitalized with pneumonitis and hepatitis (serology negative), with SGPT=542 U/L and SGOT=53 U/L on valsartan 80 mg QD on Study Day 198 (open-label); his valsartan dose was decreased to 20 mg QD and repeat liver enzymes showed an improvement in SGPT (43 U/L) and normal SGOT 9 days later. This patient was discontinued from study drug, but was readmitted 11 days later for pneumonitis, developed respiratory failure, and died.

2. Patient #080-00003, who had SGPT=339 U/L and SGOT=502 U/L on Study Day 393; Visit 15 (open-label end-of-study visit). Repeat transaminases 10 days later were normal.

3. Patient #061-00006, with a mildly elevated SGOT at screening (33 U/L; upper limit of normal = 25 U/L) and normal SGPT (15 U/L; upper limit of normal=25 U/L) developed an SGOT of 77 U/L and an SGPT of 23 U/L at the open-label end-of-study visit (Day 393; Visit 15). A repeat SGOT of 27 U/L and SGPT of 11 were obtained on Day 414.

Study A2302:

1. Patient #0608_00012, with elevated screening SGOT (48 U/L; upper limit of normal = 41 U/L) and SGPT (84 U/L; upper limit of normal = 30 U/L), developed SGOT =60 U/L and SGPT =111 U/L on Day 7 (Visit 3). This patient was discontinued due to a protocol violation (phase 1 exposure < 7 days) and we do not have repeat laboratory tests. This patient's actual exposure to study drug is unclear and we have requested the associated case report form.

2. Patient #0603_00004, with normal screening SGOT (15 U/L) and SGPT (14 U/L), completed Phases 1 and 2 and entered open-label, where he was discontinued after Visit 12 due to unsatisfactory therapeutic effect. His SGOT on Visit 12 (Visit Day 70 per electronic dataset) was 73 U/L (upper limit of normal = 41 U/L) and his SGPT was 100 U/L (upper limite of normal = 30 U/L); no repeat transaminases were seen in the electronic database.

We note a previous rise in transaminases (SGOT = 100 U/L; SGPT = 69 U/L) during an unscheduled visit prior to Visit 4 (Day 14); at Visit 4 (Day 14), the transaminases improved (SGOT = 52 U/L; SGPT = 44 U/L) but were above the upper limit of normal.

Thus, we are faced with several cases of "on-treatment" transaminase elevation, sometimes occurring at the last study visit (as in patients #080_00003, 061_00006, 0608_00012, and 0603_00004) in a small safety database. While the transaminase elevations might be explained by other factors, we are nonetheless concerned about a possible drug effect.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please contact:

Quynh Nguyen, Pharm.D.
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm

11/2/2007 09:51:59 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-283/S-024

Novartis Pharmaceuticals Corporation
Attention: Ms. Nancy A. Price
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Ms. Price:

Please refer to your May 29, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diovan (valsartan) 40, 80, 160, and 320 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on July 28, 2007 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call:

Quynh Nguyen, Pharm.D.
Regulatory Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge

8/10/2007 08:17:49 AM