Efficacy and Safety of the Angiotensin Receptor Blocker Valsartan in Children With Hypertension Aged 1 to 5 Years

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Abstract—The efficacy and safety of valsartan were studied in 90 children (mean age: 3.2 years; 60% male; 30% black) with systolic blood pressure (SBP) ≥95th percentile. Nineteen percent received valsartan in addition to previous antihypertensive therapy. Subjects were randomly assigned to low-, medium-, or high-dose valsartan for 2 weeks (phase 1) and then reassigned randomly to placebo or to remain on the same valsartan dose for 2 additional weeks (phase 2). After this, subjects were enrolled into a 52-week, open-label phase during which valsartan was dosed to achieve SBP <95th percentile. Statistically significant reductions in SBP and diastolic blood pressure of ≈8.5 mm Hg and 5.7 mm Hg, respectively, were observed at the end of phase 1 in all of the valsartan dose groups. SBP and diastolic blood pressure were also significantly lower during phase 2 in valsartan recipients compared with placebo recipients. SBP <95th percentile was achieved in 77.3% of subjects during the open-label phase. Adverse events were minor and occurred at similar frequencies in each of the 3 dose groups in phase 1 and at equal frequencies in the valsartan and placebo arms in phase 2. Serious adverse events and drug-related adverse events occurred infrequently during both the double-blind (2.2% and 5.6%, respectively) and open-label (14.8% and 6.8%, respectively) portions of the study. Valsartan treatment had no demonstrable negative effects on growth and development. In this study, the first trial of an antihypertensive agent conducted in children <6 years of age, valsartan effectively lowered SBP and diastolic blood pressure compared with placebo. (Hypertension. 2008;52:1-7.)

Key Words: children ■ kidney disease ■ hypertension ■ valsartan ■ angiotensin receptor blocker ■ clinical trial

Data regarding the efficacy and safety of antihypertensive medications in children have increased markedly over the past decade because of clinical trials conducted in response to incentives provided under the auspices of the Food and Drug Administration Modernization Act of 1997 and other legislative initiatives.1,2 To date, however, all of these studies have been conducted in children >6 years old, leaving a significant information deficit regarding the treatment of hypertension in younger children, most of whom have underlying kidney disease or other secondary causes of hypertension.3–5

Valsartan is an angiotensin II receptor blocker approved in adults for the treatment of hypertension, heart failure, and left ventricular failure or left ventricular dysfunction postmyocardial infarction.6 Its effects primarily result from selective blockade of the angiotensin type I receptor in vascular smooth muscle and adrenal gland.6,7 Valsartan effectively reduces systolic blood pressure (BP; SBP) and diastolic BP (DBP) in adults, both as monotherapy and in combination with other antihypertensive agents, displaying similar antihypertensive efficacy to other antihypertensive drug classes.7–10 Given its effects on angiotensin blockade, valsartan may also reduce proteinuria and have other beneficial effects in patients with underlying kidney disease.10 For these reasons, valsartan is an attractive drug for use in young children with hypertension.

This study was conducted to explore the efficacy of valsartan in reducing BP in children aged 1 to 5 years with hypertension. We also examined the safety and tolerability of both short- and long-term administration of valsartan in this population.

Methods

This was a double-blind, randomized, multicenter study sponsored by Novartis Pharmaceuticals and performed at 36 centers in 7

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countries (for list of investigators, please see the online data supplement available at http://hyper.ahajournals.org). Data collection and site monitoring were conducted by clinical research organizations in each country. Institutional review boards or ethics committees at each participating center reviewed and approved the study. Written informed consent was obtained from the parents or legal guardians of each subject before any study-related procedures were performed.

Entry Criteria

Children aged 1 to 5 years with seated SBP ≥95th percentile for age, gender, and height11 were eligible for enrollment. Patients could have either untreated hypertension or inadequately controlled hypertension on current treatment; in the latter group, valsartan was used as add-on therapy. Minimum patient weight was 8 kg, and the parent or guardian had to be able to follow written and/or verbal instructions in the local language.

Exclusion criteria included seated SBP ≥25% above the 95th percentile; physical abnormalities that would make the study medically hazardous to the subject; and any clinically significant laboratory, and safety assessments. Clinically significant unstable medical condition or chronic disease; positive serology for hepatitis B or C; positive test for HIV or use of antiretroviral therapy; known sensitivity to valsartan or other angiotensin II receptor blockers; or use of any investigational drug within 25% above the 95th percentile for age, weight, and continuing use of previous antihypertensive treatment; in the latter group, valsartan was used as add-on therapy. Minimum patient weight was 8 kg, and the parent or guardian had to be able to follow written and/or verbal instructions in the local language.

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Study Design, End Points, and Sample Size

This study consisted of a total of 4 phases using Food and Drug Administration trial design C (please see Figure S1). A 1-week single-blind placebo screening phase was followed by a 2-week, randomized, double-blind, dose-response phase (phase 1) during which patients were randomly assigned to low, medium, or high valsartan dose groups in a 2:1:2 ratio; dosing in each group varied with patient weight. Patients subsequently were reassigned randomly in a 1:1 ratio to either continue their phase 1 valsartan dose or to switch to placebo for ≤14 additional days (phase 2). Study visits were conducted weekly during phases 1 and 2.

The final phase was an optional 52-week, open-label treatment phase during which patients were treated with open-label valsartan to achieve a goal SBP of <95th percentile. Valsartan was started at 20 mg once daily and was then increased to 40 mg and then to 80 mg once daily to achieve the goal SBP. If subjects did not achieve this goal on valsartan alone, 12.5 mg of hydrochlorothiazide (HCTZ) could be added. Study visits occurred every 2 weeks for the first 8 weeks of the open-label phase and then every 8 to 10 weeks until the end of the study.

Primary efficacy variables were the change in mean seated SBP from baseline to the end of phase 1 and the change in mean seated SBP from the end of phase 1 to the end of phase 2. Secondary efficacy variables were change in mean seated SBP from baseline to the end of phase 2; change in mean seated DBP from baseline to the end of phase 1; change in mean seated DBP from the end of phase 1 to the end of phase 2; and change in mean seated DBP from baseline to the end of phase 2.

Sample size for this study was based on a requirement by the Food and Drug Administration that 25% of children enrolled in the sponsor’s pediatric valsartan program be ≥5 years of age. Given this, the goal for subject enrollment in this trial depended on the required enrollment in a separate study conducted in children 6 to 16 years of age.

BP Measurement

BP was measured in the right arm with a mercury column or aneroid sphygmomanometer, or an oscillometric BP device if a manual sphygmomanometer was not available, using a cuff of which the bladder length covered between 80% and 100% of the upper arm circumference.11 At each study visit, subjects rested in the seated position (or supine, depending on the age of the subject) for ≥5 minutes before 3 BP measurements were obtained. The mean of these readings was used as the subject’s BP for that visit.

Study Drug

Commercial valsartan 80-mg tablets, placebo tablets, and HCTZ 12.5-mg capsules were supplied to the participating sites by Novartis. An extemporaneous suspension of valsartan or placebo was prepared at each site by a designated research pharmacist (see Appendix). Parents were instructed to shake the bottle of suspension immediately before administration. If HCTZ was required in the open-label phase, subjects’ parents or legal guardians were instructed to open the HCTZ capsules and sprinkle the contents on applesauce or pudding for administration.

Safety Assessments and Adverse Event Monitoring

Laboratory evaluations, including blood chemistries, complete blood cell count, dipstick urinalysis, and ECGs, were obtained at the baseline visit, at the end of phases 1 and 2, and at weeks 26 and 52 of the open-label phase. Blood studies were performed at a central laboratory, and dipstick urinalyses were performed locally. ECGs were first read by the principal investigators and then reread by a central ECG reading laboratory (Children’s Hospital, Boston, Mass). A developmental assessment questionnaire (Child Development Inventory) was completed by the subjects’ parents or legal guardians at the baseline visit and at the end of the open-label phase.

Subjects could have been withdrawn from the study at any time after visit 2 if their mean seated SBP was ≥20% above the 95th percentile or for asymptomatic hypertension. Subjects could also have been withdrawn because of adverse events (AEs), clinically significant abnormal laboratory values, withdrawal of consent, or loss of follow-up. Individuals discontinued from phase 2 because of inadequately controlled BP could have been enrolled into the open-label phase as long as they were not also discontinued because of an AE. Those discontinued before completing all of the scheduled study visits were monitored for serious AEs (SAEs) for ≥4 weeks after discontinuation.

The occurrence of AEs was sought by nondirective questioning of the patient’s parent or guardian at each visit. Additional AE information was collected if volunteered at other times during the study or through physical examination, laboratory tests, or other assessments. All of the AEs were graded according to the following: severity, relationship to study drug, duration, and whether it constituted an SAE. An SAE was defined as an event that was fatal or life threatening, required prolonged hospitalization, was significantly or permanently disabling or incapacitating, or encompassed any other clinically significant event. All of the AEs and SAEs were reported to Novartis; however, SAEs occurring ≥4 weeks after study completion were only reported if the investigator suspected a relationship to the study drug.

Data Analysis

Continuous variables are presented as sample size, mean, SD, minimum, and maximum as appropriate. For categorical values, the number and percentage of subjects in each group are presented. Missing values were not imputed.

For phase 1, the slope of the dose-response curve for the change from baseline in mean seated SBP at the end of phase 1 was analyzed using an ANCOVA model with race, weight, and continuing use of antihypertensive treatment as factors and centered baseline mean seated SBP and dose ratio as covariates. The change in mean seated SBP from the end of phase 1 to the end of phase 2 was analyzed using an ANCOVA model with treatment (valsartan versus placebo), race, weight, and continuing use of previous antihypertensive treat-
ment as factors and centered visit 4 mean seated SBP as a covariate. For the open-label phase, data were summarized descriptively; no statistical analyses were performed.

All of the analyses were performed using SAS version 8.2 (SAS Institute Inc). All of the statistical tests were conducted against a 2-sided, alternative hypothesis, using a $P$ value of 0.05 to denote significance.

**Results**

**Study Subjects**

A total of 130 subjects were enrolled and entered into the screening phase, and 90 of these qualified for random assignment into phase 1 (Figure 1A). There were no differences in demographics, anthropometrics, or baseline BP between those who were enrolled and randomly assigned versus those who were enrolled but failed to meet the random assignment criteria (data not shown).

Baseline characteristics of subjects randomly assigned into phase 1 are displayed in Table 1. Because subjects were stratified by race (black versus nonblack), baseline weight ($<18$ versus $\geq18$ kg), and use or nonuse of concomitant antihypertensive therapy, the distributions across the 3 dose groups regarding these criteria were comparable. Baseline BPs were also comparable across dose groups (Table 1).

Eighty-eight randomly assigned subjects (97.8%) had $\geq1$ medical history abnormality or current medical condition at the time of study entry; the most frequently reported being renal and urinary disorders (63.3%), infections and infestations (46.7%), and congenital familial and genetic disorders (42.2%; includes many congenital renal, vascular, and urinary disorders). A total of 6.7% were classified as obese at study entry. Antihypertensive medications were taken by 71.1% of the randomly assigned population before the start of study medication, the most frequent being angiotensin-converting enzyme inhibitors (47.8%) and calcium channel blockers (28.9%); few patients were receiving angiotensin II receptor blockers (4.4%). No patient reported using valsartan before study entry.

A total of 87 subjects (97%) completed phase 1, of whom 83 (95%) went on to complete phase 2. Reasons for subjects exiting the study during phases 1 and 2 are indicated in Figure 1A. No subjects discontinued from either phase 1 or phase 2 because of AEs. Eighty-eight subjects entered the open-label phase, (including 1 of the subjects who discontinued from phase 1 because of an unsatisfactory therapeutic effect), of whom 82 (93%) completed this phase; those who did not complete this phase are indicated in Figure 1B.

**Effect on BP**

In phase 1, valsartan significantly lowered both SBP and DBP in all of the dose groups (SBP: low dose: $-8.4$ mm Hg; medium dose: $-8.3$ mm Hg; high dose: $-8.6$ mm Hg; DBP: low dose: $-5.5$ mm Hg; medium dose: $-6.4$ mm Hg; high
dose: −5.5 mm Hg; Figure 2). Similar reductions were seen in all of the subgroups (race: black versus nonblack; weight: <18 versus ≥18 kg; and use or nonuse of concomitant antihypertensive therapy at entry). For subject BPs at baseline and at the end of phases 1 and 2, please see the data supplement (Table S1).

From the end of phase 1 to the end of phase 2, subjects who remained on valsartan exhibited a mean reduction in seated SBP of −1.5 mm Hg, whereas placebo recipients had a mean increase in SBP of 1.5 mm Hg (Figure 2). The least-squares mean difference in the change in SBP between the pooled valsartan and placebo groups (−3.9 mm Hg) was significant (P = 0.02). Similarly, a mean decrease in seated DBP was observed in the valsartan group (−2.5 mm Hg), whereas an increase of 2.0 mm Hg was observed in the placebo group (Figure 2). The least-squares mean difference in the change in DBP between the 2 pooled groups (−3.7 mm Hg) was significant (P = 0.009).

During the open-label phase, 80 of 88 subjects (90.9%) remained on valsartan monotherapy (~38 at 20 mg, 24 at 40 mg, and 18 at 80 mg), whereas 8 (9.1%) were treated with valsartan plus HCTZ (6 at 80/12.5 mg and 2 at other combinations). By the end of this phase, 77.3% of subjects had achieved a mean seated SBP <95th percentile.

### Growth and Development

Growth parameters are summarized in Table 2. The Z scores for length/height for age and body mass index for age were calculated based on the World Health Organization Child Growth Standards for age <60 months and the 2000 Centers for Disease Control and Prevention growth charts for age ≥60 months as references. There was no significant change in length per height for age and body mass index for age Z scores from baseline to the end of the study. Mean head circumference increased during the study.

### Table 1. Baseline Characteristics by Dosage Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low (N=37)</th>
<th>Medium (N=18)</th>
<th>High (N=35)</th>
<th>Total (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>3.0 (1.3)</td>
<td>3.5 (1.4)</td>
<td>3.3 (1.3)</td>
<td>3.2 (1.3)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>18/19 (49/51)</td>
<td>11/7 (61/39)</td>
<td>25/10 (71/29)</td>
<td>54/36 (60/40)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White/black/other</td>
<td>13/12/12 (35/32/32)</td>
<td>8/6/4 (44/33/22)</td>
<td>16/9/10 (46/26/29)</td>
<td>37/27/26 (41/30/29)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>16.4 (6.02)</td>
<td>16.4 (5.41)</td>
<td>17.2 (7.74)</td>
<td>16.7 (6.58)</td>
</tr>
<tr>
<td>Weight group, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 kg/≥18 kg</td>
<td>24/13 (65/35)</td>
<td>12/6 (67/33)</td>
<td>22/13 (63/37)</td>
<td>58/32 (64/36)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>16.7 (2.9)</td>
<td>16.4 (1.9)</td>
<td>17.0 (3.4)</td>
<td>16.8 (2.9)</td>
</tr>
<tr>
<td>Continuing use of previous antihypertensive treatment, n (%)*</td>
<td>6 (16)</td>
<td>7 (22)</td>
<td>7 (20)</td>
<td>18 (20)</td>
</tr>
<tr>
<td>MSSBP, mm Hg</td>
<td>117.8 (6.9)</td>
<td>112.1 (8.6)</td>
<td>115.1 (6.3)</td>
<td>115.2 (7.2)</td>
</tr>
<tr>
<td>MSDBP, mm Hg</td>
<td>70.5 (8.5)</td>
<td>68.1 (8.6)</td>
<td>68.8 (7.6)</td>
<td>69.3 (8.2)</td>
</tr>
<tr>
<td>Pulse, bpm</td>
<td>104 (16)</td>
<td>104 (15)</td>
<td>101 (15)</td>
<td>103 (15)</td>
</tr>
</tbody>
</table>

*Antihypertensive treatment started before and continued after visit 2.

<table>
<thead>
<tr>
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</tr>
</tbody>
</table>

Data are expressed as means (SDs) except as otherwise noted. BMI indicates body mass index; MSSBP, mean seated systolic BP; MSDBP, mean seated diastolic BP. Data are from a randomly assigned population.

Figure 2. Change in mean sitting SBP and DBP: low dose: weight <18, ≥18 kg received 5 or 10 mg, respectively; medium dose: weight <18, ≥18 kg received 20 or 40 mg, respectively; high dose: weight <18, ≥18 kg received 40 or 80 mg, respectively; *Patients were randomly assigned to either continue their phase 1 valsartan dose or to switch to placebo for ≥2 weeks.
Table 2. Growth Parameters of Participants Who Completed the Open-Label Phase (N=88)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline, Mean (SD)</th>
<th>End of Study, Mean (SD)</th>
<th>Change From Baseline, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z score length/height for age*</td>
<td>–0.65 (1.75)</td>
<td>–0.63 (1.65)</td>
<td>0.02 (0.65)</td>
</tr>
<tr>
<td>Z score BMI for age*</td>
<td>0.49 (1.54)</td>
<td>0.42 (1.60)</td>
<td>–0.07 (1.06)</td>
</tr>
<tr>
<td>Head circumference, cm (N=77)†</td>
<td>49.6 (2.7)</td>
<td>50.8 (2.7)</td>
<td>1.2 (1.7)</td>
</tr>
</tbody>
</table>

*See text for details of Z score calculations. †Data show only subjects with both baseline and end-of-study values.

Mean scores on the developmental assessment questionnaire increased or improved for all of the assessments evaluated as follows: social development (+3.3 points), self-help (+3.7 points), gross motor (+2.2 points), fine motor (+3.1 points), expressive language (+5.1 points), language comprehension (+5.1 points), letters (+2.8 points), and numbers (+2.7 points). Review of the developmental questionnaire results revealed that the majority of subjects demonstrated results in the expected direction (ie, either an improvement or no change).

Safety
AEs (≥1) were reported by 29 subjects (32.2%) in phase 1, 39 subjects (44.8%) in phase 2, and 81 (92.0%) of those in the open-label phase. For AEs that occurred during phase 1, please see the data supplement (Table S2). No clear relationship was observed between the dose of valsartan and incidence of AEs in phase 1. No difference in AEs was seen for valsartan- and placebo-treated subjects in phase 2. Most of the AEs reported during the study were infection related (phase 1: 20.0%; phase 2: 25.3%; open label: 79.5%).

Two subjects (2.2%) experienced SAEs during double-blind treatment; 1 developed pneumonia, the other a urinary tract infection. Neither SAE was suspected to be study drug related, and although both subjects were hospitalized, neither was discontinued from the study. There were 27 SAEs affecting 13 subjects during the open-label phase. Most of these were infections; gastroenteritis (n=4) and diarrhea (n=2) were the most frequently reported. Ten subjects with SAEs were hospitalized, and 1 subject had an SAE that was suspected to be study drug related (hepatitis), which led to discontinuation from the study.

Three subjects (3.3%) had AEs that were suspected to be study drug-related during phase 1; these included pruritus and rash, decreased appetite, and blurred vision (affecting 1 subject each). During phase 2, 2 subjects in each group (2.3%) had AEs that were suspected to be study drug related. In the valsartan group, 1 subject experienced headache, and 1 experienced hypertriglyceridemia. In the placebo arm, 1 subject experienced hyperkalemia, and 1 experienced thrombocytopenia. During the open-label phase, 6 subjects (6.8%) had suspected study drug-related AEs: 5 in the valsartan-only group and 1 in the valsartan/HCTZ group. Hyperkalemia was the only suspected study drug-related AE that was reported for >1 subject, affecting 2 subjects in the valsartan group.

Neither subject had a potassium level of ≥5.5 mmol/L. Other AEs that were suspected to be study drug related (headache, hepatitis, malaise, thrombocytopenia, and edema) were experienced by 1 subject each.

No deaths occurred during the double-blind phase. There was 1 death, because of viral gastroenteritis, on day 83 of the open-label phase, and 1 subject died of pneumonia 11 days after discontinuing from open-label treatment. Neither death was judged to be related to study drug.

No clinically meaningful changes from baseline biochemistry values were observed during phase 1. Potassium ≥5.3 mmol/L increased from 5% of subjects at baseline to 15% at the end of the double-blind phase. Although 1 new case of hyperkalemia (potassium: ≥5.5 mmol/L) was reported at the end of the double-blind phase in a subject with congenital kidney disease, the changes in serum potassium were not thought to be clinically significant.

There were no clinically significant changes from baseline in the majority of biochemical parameters (serum creatinine, potassium, and blood urea nitrogen) during the open-label phase. However, 1 subject with nephrotic syndrome was discontinued during the open-label phase because of renal function impairment (elevation of blood urea nitrogen). There were 4 subjects with transient, isolated, elevation of liver enzymes during the open-label phase, none of whom had jaundice. All of the subjects with liver enzyme elevation were in regions of the world where viral hepatitis is endemic; indeed, hepatitis A was confirmed in 1 of these subjects, and viral hepatitis was suspected in 2 additional subjects. An independent panel of academic pediatric hepatologists that reviewed all of the trial data in a face-to-face meeting concluded that a causal relationship between the elevated liver enzymes and study drug could not be established in any of the 4 cases.

Discussion
This study is the first clinical trial of an antihypertensive agent conducted in children aged <6 years. The valsartan doses evaluated in this study generated clinically relevant and statistically significant decreases from baseline in both seated SBP and seated DBP during the 2-week dose-ranging portion of the trial (phase 1). The BP-lowering effect of valsartan was further confirmed by the reversal of BP reduction observed in the subjects who were reassigned randomly to placebo during the withdrawal phase (phase 2). In the open-label phase, >90% of subjects were maintained on valsartan alone, with only a small number of patients needing combination therapy; combination therapy with valsartan and HCTZ was effective in subjects who did not achieve BP control with valsartan alone. The efficacy of valsartan in this heterogeneous group of young hypertensive children suggests that it may be considered an appropriate antihypertensive medication for use in young patients, many of whom have renal disease.

The failure to demonstrate a linear dose response for valsartan during phase 1 could have occurred for several reasons. First and foremost among these was the relatively small sample size. A second possible explanation is that the dose range tested was too narrow: the valsartan doses used in the study ranged from 5 or 10 mg once daily to 40 or 80 mg...
daily, corresponding with a mean exposure range of 0.4 to 3.4 mg/kg daily. In contrast, the dose exposure tested in the pediatric losartan trial was wider, ~0.17 to 5.5 mg/kg daily. It is possible that these young children were uniquely sensitive to valsartan and that a lower starting dose might have facilitated demonstration of a dose-response effect.

The young age of the subjects enrolled in this study created unique problems during BP measurement, specifically, poor cooperation, which may have led to greater variability in BP than is typically seen in studies enrolling older children. Furthermore, 70% of participating centers only enrolled 1 or 2 subjects over a 2-year enrollment period, which may have impacted the quality of the data because of reduced familiarity with study procedures or variations in the technique of BP measurement. This, in turn, may have produced increased intercenter and intersubject variation.15,16

The increase in BP after placebo withdrawal (phase 2) was relatively small. This may have been the result of a persistent antihypertensive effect of valsartan beyond 2 weeks or a shortening of the placebo withdrawal period by the investigators for safety reasons as soon as any increase in BP was noted. In either event, the difference between groups at the end of phase 2 was significant, confirming the antihypertensive efficacy of valsartan.

All of the valsartan doses evaluated in this study were well tolerated. The overall incidence of study drug-related AEs was low, did not differ significantly for placebo- and valsartan-treated subjects, and did not appear to be dose dependent. The majority of AEs were mild or moderate and transient in nature, the most frequent being cough, fever, upper respiratory infection, and diarrhea. These AEs are typical illnesses experienced by children in this age group, and many of them have been observed in other clinical trials of antihypertensive medications conducted in older children.14,17–19 Of note, no subjects were discontinued from the study because of AEs during the double-blind phase, and only 3 subjects were discontinued because of AEs during the open-label extension. This phenomenon has been observed in other studies incorporating a prolonged open-label treatment phase19 and likely reflects the susceptibility of young children to common pediatric illnesses.

The incidence of SAEs was low during both the double-blind and open-label phases, affecting 2.2% and 14.8% of subjects, respectively. Many of these, including episodes of gastroenteritis and diarrhea, are common illnesses in children aged 1 to 5 years. Four cases of clinically significant increases in liver enzymes occurred during the open-label phase; however, no relationship to study drug could be determined in these subjects. One death secondary to gastroenteritis occurred during the open-label phase, which, although judged to be unrelated to study drug, highlights the risks of dehydration in children treated with antihypertensive drugs affecting the renin-angiotensin system and underscores the need for careful counseling and patient monitoring in children treated with such agents.

To date, the effects of treatment with antihypertensive medications on growth and development have not been systematically studied. For this reason, consensus organizations have emphasized that a definite need for drug treatment be established before antihypertensive medications are prescribed in children.11 We, therefore, assessed both growth and development of the young subjects in this trial. Valsartan did not appear to have adverse effects on linear growth or annual weight gain and did not affect progression of head circumference, a key indicator of brain growth in young children.20,21 Furthermore, because there was overall improvement in the areas assessed by the developmental questionnaire, it appears that valsartan had no clinically relevant impact on development over the 13 months of the study. Although longer periods of study are clearly necessary, these data should provide clinicians with some reassurance regarding the effects of antihypertensive medications on growth and development.

As would be expected in a trial of young children with hypertension, most subjects enrolled in this study had a history of ≥1 concurrent medical condition other than hypertension. Approximately 80% had renal and/or urinary abnormalities, including congenital kidney disease. This is consistent with previous studies demonstrating that the majority of hypertension in young children is of renal origin.7 Given the high frequency of renal disease in the present study population, the antihypertensive efficacy of valsartan demonstrated in this study suggests that this agent is worthy of further study in young children with kidney disease.

**Perspectives**

Hypertension is rare in young children, typically caused by underlying renal disease or other secondary causes. This study provides the first clinical trial results of an antihypertensive medication studied in hypertensive children aged <6 years. Valsartan, a selective angiotensin type 1 receptor blocker, produced significant reduction in SBP compared with placebo with a low rate of discontinuations because of AEs. Further study is warranted to more clearly delineate the role of valsartan in the management of young children with hypertension.

**Appendix**

**Compounding Instructions for the Extemporaneous Study Drug Suspensions**

Extemporaneous valsartan and placebo suspensions were prepared by placing 8 valsartan 80-mg tablets or 8 valsartan placebo tablets, respectively, in 80 mL of Ora-Plus suspending agent and shaking for a minimum of 2 minutes. The respective mixtures were then allowed to stand for 1 hour before the addition of 80 mL of Ora-Sweet SF vehicle. The resulting suspensions were shaken for 10 seconds and refrigerated until dispensed. Stability maintained for <2.5 months if they were kept refrigerated.6

**Acknowledgments**

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Disclosures

J.T.F. is a consultant to Novartis, a recipient of research funding from Novartis, and is presently participating in 4 trials sponsored by Novartis. K.E.C.M. has participated in other trials sponsored by Novartis and is presently participating in 4 trials sponsored by Novartis. J.P.N. has been involved in other clinical trials sponsored by Novartis. V.S., J.G., S.S-Y., and G.H. are all employees of Novartis Pharmaceuticals Corporation. The remaining authors report no conflicts.

References

Efficacy and Safety of the Angiotensin Receptor Blocker Valsartan in Children With Hypertension Aged 1 to 5 Years
for the Pediatric Valsartan Study Group

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EFFICACY AND SAFETY OF THE ANGIOTENSIN RECEPTOR BLOCKER VALSARTAN
IN CHILDREN WITH HYPERTENSION AGED ONE TO FIVE YEARS

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G Zilleruelo, Miami, United States
A Zurowska, Gdansk, Poland
Table S1A. Changes from baseline in mean SSBP and SDBP (mmHg) in Phase 1 by treatment group*

<table>
<thead>
<tr>
<th>Dosage Group</th>
<th>Low N = 37</th>
<th>Medium N = 18</th>
<th>High N = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP†</td>
<td>116.8 (6.9)</td>
<td>112.1 (8.6)</td>
<td>115.1 (6.33)</td>
</tr>
<tr>
<td>MSDBP†</td>
<td>70.5 (8.5)</td>
<td>68.1 (8.6)</td>
<td>68.8 (7.6)</td>
</tr>
<tr>
<td><strong>End of Phase 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>108 (11.0)</td>
<td>103.7 (7.4)</td>
<td>106.5 (8.7)</td>
</tr>
<tr>
<td>MSDBP</td>
<td>65.0 (7.8)</td>
<td>61.7 (7.6)</td>
<td>63.3 (6.8)</td>
</tr>
<tr>
<td><strong>Change from baseline to End of Phase 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>-8.4 (8.44)</td>
<td>-8.3 (7.63)</td>
<td>-8.6 (7.55)</td>
</tr>
<tr>
<td>MSDBP</td>
<td>-5.5 (6.06)</td>
<td>-6.4 (4.23)</td>
<td>-5.5 (8.47)</td>
</tr>
<tr>
<td><strong>p-value‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSDBP</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

*all data expressed as mean (standard deviation)

†MSSBP, mean seated systolic blood pressure; MSDBP, mean seated diastolic blood pressure

‡paired t-test of the null hypothesis of no change from baseline within each treatment group
Table S1B. Changes from end of Phase 1 to end of Phase 2 in MSSBP* and MSDBP* (mmHg) by pooled treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Valsartan N = 44</th>
<th>Placebo N = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End of Phase 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>106.5 (11.03)</td>
<td>106.7 (8.17)</td>
</tr>
<tr>
<td>MSDBP</td>
<td>64.2 (6.87)</td>
<td>63.3 (8.19)</td>
</tr>
<tr>
<td><strong>End of Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>105.0 (11.92)</td>
<td>108.5 (8.98)</td>
</tr>
<tr>
<td>MSDBP</td>
<td>61.7 (7.89)</td>
<td>65.3 (6.81)</td>
</tr>
<tr>
<td><strong>Change from end of Phase 1 to End of Phase 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔMSSBP</td>
<td>-1.5 (7.92)</td>
<td>1.5 (7.76)</td>
</tr>
<tr>
<td>ΔMSDBP</td>
<td>-2.5 (7.51)</td>
<td>2.0 (5.86)</td>
</tr>
<tr>
<td>p-value†, MSSBP</td>
<td>0.2135*</td>
<td>0.2273*</td>
</tr>
<tr>
<td>p-value†, MSDBP</td>
<td>0.0336*</td>
<td>0.0312*</td>
</tr>
<tr>
<td>Between-group p-value‡, MSSBP</td>
<td>0.0217*</td>
<td></td>
</tr>
<tr>
<td>Between-group p-value‡, MSDBP</td>
<td>0.0089*</td>
<td></td>
</tr>
</tbody>
</table>

*MSSBP, mean seated systolic blood pressure; MSDBP, mean seated diastolic blood pressure

†p-values are based on the paired t-test of the null hypothesis of no change from the end of Phase I within each treatment group.

‡p-value is from the ANCOVA model with treatment, race strata, weight strata and continuing use of prior antihypertensive treatment strata, and centered Visit 4 SDBP as a covariate.
Table S1C. Mean changes in SSBP and SDBP (mmHg) by double-blind treatment (Phases 1 & 2 combined)

<table>
<thead>
<tr>
<th>Treatment, Phase1/Phase2</th>
<th>Baseline</th>
<th>End of Phase 2</th>
<th>Change</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Low (n=19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP†</td>
<td>116.6</td>
<td>107.5</td>
<td>-9.1</td>
<td>0.0048</td>
</tr>
<tr>
<td>MSDBP†</td>
<td>72.3</td>
<td>63.3</td>
<td>-9.0</td>
<td>0.0012</td>
</tr>
<tr>
<td>Low/Placebo (n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>116.5</td>
<td>106.4</td>
<td>-10.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSDBP</td>
<td>68.0</td>
<td>64.7</td>
<td>-3.3</td>
<td>0.0260</td>
</tr>
<tr>
<td>Medium/Medium (n=8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>112.3</td>
<td>102.7</td>
<td>-9.6</td>
<td>0.0102</td>
</tr>
<tr>
<td>MSDBP</td>
<td>68.8</td>
<td>62.7</td>
<td>-6.1</td>
<td>0.0380</td>
</tr>
<tr>
<td>Medium/Placebo (n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>112.1</td>
<td>108.9</td>
<td>-3.2</td>
<td>0.0554</td>
</tr>
<tr>
<td>MSDBP</td>
<td>66.9</td>
<td>64.9</td>
<td>-1.9</td>
<td>0.3290</td>
</tr>
<tr>
<td>High/High (n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>116.3</td>
<td>103.3</td>
<td>-13.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MSDBP</td>
<td>69.4</td>
<td>59.5</td>
<td>-9.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High/Placebo (n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSSBP</td>
<td>114.1</td>
<td>110.9</td>
<td>-3.2</td>
<td>0.2337</td>
</tr>
<tr>
<td>MSDBP</td>
<td>68.4</td>
<td>67.3</td>
<td>-1.1</td>
<td>0.6378</td>
</tr>
</tbody>
</table>
*paired t-test of the mean change from baseline versus zero

†MSSBP, mean seated systolic blood pressure; MSDBP, mean seated diastolic blood pressure
Table S2. Number (%) of patients with adverse events (AEs) overall and by primary system organ class (≥3% for any group) in Phase 1.

<table>
<thead>
<tr>
<th>MedDRA category</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=37</td>
<td>N=18</td>
<td>N=35</td>
<td>N=90</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5 (13.5)</td>
<td>7 (38.9)</td>
<td>6 (17.1)</td>
<td>18 (20.0)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>3 (8.1)</td>
<td>1 (5.6)</td>
<td>4 (11.4)</td>
<td>8 (8.9)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>2 (5.4)</td>
<td>1 (5.6)</td>
<td>4 (11.4)</td>
<td>7 (7.8)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>2 (5.4)</td>
<td>1 (5.6)</td>
<td>1 (2.9)</td>
<td>4 (4.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (2.7)</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (2.7)</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (2.7)</td>
<td>1 (5.6)</td>
<td>1 (2.9)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>0 (0.0)</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0 (0.0)</td>
<td>2 (11.1)</td>
<td>0 (0.0)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Total</td>
<td>10 (27.0)</td>
<td>7 (38.9)</td>
<td>12 (34.3)</td>
<td>29 (32.2)</td>
</tr>
</tbody>
</table>
**Single-blind period**

**Screening phase**
- Placebo wash-out

**Placebo**

**Phase 1**
- 5 mg o.d. patients <18 kg
- 10 mg o.d. patients ≥18 kg
- 20 mg o.d. patients <18 kg
- 40 mg o.d. patients ≥18 kg
- 40 mg o.d. patients <18 kg
- 80 mg o.d. patients ≥18 kg

**Continue Phase 1 dose**
- 20 mg → 40 mg → 80 mg or
- 80 mg + 12.5 mg HCTZ o.d.

**Phase 2**
- 80 mg + 12.5 mg HCTZ o.d.
- 20 mg → 40 mg → 80 mg or
- 80 mg + 12.5 mg HCTZ o.d.

**Double-blind period**

**Day 0**
- 20 mg → 40 mg → 80 mg or
- 80 mg + 12.5 mg HCTZ o.d.

**Day 7**
- Continue Phase 1 dose

**Day 14**
- Continue Phase 1 dose

**Day 21**
- Continue Phase 1 dose

**Day 28**
- Continue Phase 1 dose

**Day 393**