A Double-Blind, Dose-Response Study of the Efficacy and Safety of Olmesartan Medoxomil in Children and Adolescents with Hypertension

Lydie Hazan, Oscar A. Hernández Rodriguez, As’ad E. Bhorat, Koichi Miyazaki, Ben Tao, Reinilde Heyrman, for the Assessment of Efficacy and Safety of Olmesartan in Pediatric Hypertension (AESOP) Study Group

Abstract—The current study investigated the efficacy and safety of olmesartan medoxomil in children with hypertension, defined as systolic blood pressure measured at or above the 95th percentile (90th percentile for patients with diabetes, glomerular kidney disease, or family history of hypertension) for age, gender, and height while off any antihypertensive medication. The active treatment phase was conducted in 2 periods, with 2 cohorts in each period (cohort A, 62% white; cohort B, 100% Black). In period 1, patients stratified by weight received low-dose (2.5 or 5 mg) or high-dose (20 or 40 mg) olmesartan medoxomil daily for 3 weeks. In period 2, patients maintained their olmesartan medoxomil dose or initiated placebo washout for an additional 2 weeks. Period 1 efficacy results showed a dose-dependent, statistically significant reduction in seated trough systolic and diastolic blood pressure for both cohorts, with mean blood pressure reductions numerically smaller in cohort B than in cohort A. The olmesartan medoxomil dose response remained statistically significant when adjusted for body weight. In period 2, blood pressure control decreased in those patients switching to placebo, whereas patients continuing to receive olmesartan medoxomil therapy maintained consistent blood pressure reduction. Adverse events were generally mild and unrelated to study medication. Olmesartan medoxomil was safe and efficacious in children with hypertension, resulting in significant blood pressure reductions. (Hypertension. 2010;55:1323-1330.)

Key Words: adolescent ■ angiotensin receptor blocker ■ children ■ hypertension ■ olmesartan medoxomil ■ safety

Hypertension is an increasingly recognized disease in children and adolescents, yet it often remains undiagnosed and untreated.¹⁻⁴ Contributory factors include genetic background and increased childhood obesity, with a long-term health risk of potentially devastating consequences, including target organ damage.²⁻³ The genetic component of hypertension is exemplified by a comparatively greater rise in blood pressure (BP) through adolescence for children of parents with hypertension compared with those of parents with normotension.⁵

Considering the long-term impact of hypertension on quality of life, morbidity, and mortality, controlling BP to recommended levels is imperative in children. A major consequence of untreated pediatric hypertension is the development of left ventricular hypertrophy, which has been reported in more than 40% of children with hypertension.⁶ However, the current management of pediatric hypertension is inadequate. As recently highlighted by the Chronic Kidney Disease in Children study, 37% of children with chronic kidney disease were diagnosed with elevated BP, and yet 39% of these were not receiving antihypertensive medication.⁴ The goal of treatment in pediatric hypertension is to reduce BP below the 95th percentile for age, gender, and height or below the 90th percentile for those patients with comorbidity.¹ Lifestyle modifications, including a low-sodium diet, increased exercise, and weight loss, often fail to achieve recommended BP goals. Consequently, achieving and maintaining BP levels within the clinically established limits may require pharmacological intervention.

Olmesartan medoxomil (OM) is an orally acting angiotensin II receptor blocker (ARB) approved for the treatment of hypertension in adults, with once-daily (OD) administration. OM-based therapy manages hypertension across a range of patient types, produces significant BP reductions, enables patients to achieve recommended BP goals, and has a safety profile similar to placebo.⁷ In response to a written request from the United States Food and Drug Administration, the current study evaluated the efficacy, safety, and dose-response relationship of OM administration in children and adolescents 6 to 16 years of age of any race with hypertension, as well as in an all-Black pediatric cohort.
Methods

Written informed consent and pediatric assent were obtained before study-specific procedures were performed. The study was conducted in compliance with ethical committee review and in accordance with ethical principles having their origin in the Declaration of Helsinki, the International Conference on Harmonisation E6 Guideline for Good Clinical Practices, and the Guidelines for Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations.

BP Measurement

The efficacy variables evaluated in this study were seated cuff systolic BP (SeSBP) and seated cuff diastolic BP (SeDBP). Trough BP was measured at each visit before administration of study medication. If possible, measurements were performed by the same medical personnel for each reading using a validated electronic BP measuring instrument; if that was not appropriate, a standard clinical sphygmomanometer was used (see Supplemental Table I, available online at http://hyper.ahajournals.org). At each visit, 3 BP measurements were taken at least 1 minute apart with the patient seated, and the results were averaged.

Patient Selection

Males and females aged 6 to 16 years, inclusive, undergoing treatment for hypertension, or who had hypertension, were considered for enrollment. A body weight ≥20 kg was required. Hypertension was defined as SeSBP measured at or above the 95th percentile (90th percentile for patients with diabetes, glomerular kidney disease, or a family history of hypertension) for age, gender, and height while off any antihypertensive medication.1 Patients were required to have a creatinine clearance (calculated using a Modified Schwartz equation to estimate glomerular filtration rate) that was >25 mL/min per 1.73 m² for inclusion. All sexually active females of childbearing potential were required to have negative results on serum pregnancy tests within 72 hours before receiving OM and been practicing an acceptable method of birth control. Exclusion criteria encompassed the presence of any clinically significant medical condition or chronic disease, a known hypersensitivity to OM or its excipients, or other ARBs or angiotensin-converting enzyme inhibitors. Patients with malignant hypertension or with SeSBP or SeDBP >2 standard deviations above the 99th percentile for the patient’s age, gender, and height were also excluded.

Study Design

This was a randomized, multicenter, double-blind, parallel-group, prospective dose-ranging study in patients 6 to 16 years of age with primary or secondary hypertension (see Supplemental Table II for blinding protocol). Although participants could not be older than 16 years of age at the time of giving informed consent, some patients could be 17 years of age at the end of the study. Initially, a total of 422 patients were screened at 61 sites. All patients participated in a screening/washout period that lasted a maximum of 14 days and were assigned a screening number in the order that they entered the study at the screening visit (see Supplemental Table II for determination of sample size and method of assigning screening numbers).

The active treatment phase of the study was conducted in 2 periods. Period 1 was a double-blind, dose-ranging study in which patients were randomly assigned to low-dose or high-dose OM for a 3-week active treatment period. Period 2 was a subsequent 2-week, placebo-controlled, withdrawal study during which patients either continued receiving OM or were administered placebo. Patients were enrolled in 1 of 2 cohorts based on race: cohort A comprised patients representing various races, of whom approximately 15% were Black, and cohort B was an all-Black patient population. When a minimum of 28 Black patients were randomly assigned to cohort A, enrollment in cohort B was begun.

Treatment compliance was monitored by assessing the relative volume of drug suspension in the bottle at each visit. Patients were instructed to return unused medication at each visit. Patient compliance was documented on the patient’s case report form.

Drug Preparation

The pharmacist prepared the OM (Benicar, Daiichi Sankyo, Inc, Parsippany, NJ) liquid suspensions on site or within a reasonable distance from the study site. The suspension was prepared by adding OM in a vehicle containing water, Ora-Plus, and Ora-Sweet at concentrations of 0.5 and 4.0 mg/mL (see Supplemental Table III). Matching placebo suspensions were prepared similarly from placebo tablets. To maintain the double-blind conditions, an independent, unblinded pharmacist prepared the suspension for each patient; therefore, neither the patient nor the investigator knew the treatment being administered. Placebo and OM suspensions (both high dose and low dose) were identical in appearance and taste.

Period 1: Double-Blind, Dose-Ranging Treatment Period

The primary purpose of period 1 was to define the dose response of OM in children with hypertension (see Supplemental Figure I). The initial screening consisted of a physical examination and medical history. If SeSBP at the screening visit met the criteria for the definition of hypertension for that individual’s age, gender, and height, the patient was randomly assigned to treatment sequences carried out through the remainder of the trial. If the patient was taking antihypertensive medication, these drugs were discontinued at this time.

On study Day 1, eligible patients were stratified initially into 2 weight categories; half of the patients in both weight categories took low-dose OM and half took high-dose OM. For patients weighing >20 kg and <35 kg, low-dose OM was 2.5 mg OD and high-dose OM was 20 mg OD. For patients weighing ≥35 kg, low-dose OM was 5.0 mg OD and high-dose OM was 40 mg OD. Follow-up BP measurements were scheduled on a weekly basis. On the morning of the BP measurement, the patient was advised not to take the study drug until after the office visit.

Period 2: Double-Blind, Placebo-Controlled Withdrawal Period

Following the 21-day, double-blind treatment period 1, patients underwent in a blinded manner either a randomized washout period to placebo or continuation of their current active treatment for up to 14 days. Selection of patients to be switched to placebo or to continue on the same dose of OM was based on the original randomization scheme, and BP was monitored at least weekly. OM or matching placebo was delivered as a compounded suspension to be taken by mouth at the same time each day.

Monitoring of Adverse Events

Safety was assessed throughout the study and included monitoring of adverse events, concomitant medications, routine laboratory safety tests, and physical examination findings.

Statistical Analysis

The intention-to-treat population, using the last-observation-carried-forward method, was used to test the primary hypothesis. The intention-to-treat population for the dose-ranging study (period 1) was defined as all patients who took at least 1 dose of study medication and had a documented baseline SeSBP and at least 1 SeSBP measurement after taking study medication. For period 2, the intention-to-treat population was defined as all patients who finished period 1 with a final SeSBP or SeDBP measurement, took study medication during period 2, and had an SeSBP or SeDBP measurement at the end of period 2.

The primary objective for the data analysis in period 1 was to assess the dose response in SeSBP or in SeDBP. The change in BP from baseline to the end of period 1 was analyzed for cohorts A and B using a linear regression model with OM dose or weight-adjusted...
OM dose as the independent variable. The null hypothesis of zero slope for dose on the change in BP was tested.

A secondary analysis was performed comparing OM to placebo for period 2. For these results, an analysis of covariance was performed using period 2 baseline BP as a covariate and treatment and country as factors. Changes in BP (SeSBP and SeDBP) from the period 2 baseline to the end of period 2 were indicated by a 95% confidence interval for the differences between least-squares means.

Results

Patient Characteristics

The study was a multicenter, international study conducted between April 2005 and September 2008. A total of 422 patients were screened at 61 sites, and 302 were randomly assigned to the 2 cohorts (cohort A: N=190; cohort B: N=112). On final enrollment, cohort A was 62% white, 18% Black, 10% Asian, and 14% other races (patients could check more than 1 race), and cohort B was 100% Black.

Demographic characteristics are shown in Table 1. For cohort A (n=190), 95 patients were randomly assigned to each of the OM dose groups, and for cohort B (n=112), 56 patients were randomly assigned to each of the OM dose groups (see Figures 1 and 2 for patient disposition).

Period 1: Dose-Response Effects

The primary efficacy analyses were based on the changes from baseline in trough SeSBP and SeDBP to the end of period 1 in cohorts A and B. Mean changes in SeSBP/SeDBP from the study baseline to the end of period 1 were −7.8/−5.5 mm Hg and −12.6/−9.5 mm Hg for low and high OM doses, respectively, in cohort A, and −4.7/−3.5 mm Hg and −10.7/−7.6 mm Hg for low and high OM doses, respectively, in cohort B (Figure 3). Reductions in SeSBP/SeDBP were consistently greater in the high-dose OM group than in the low-dose OM group. At all visits for both groups, the mean SeSBP/SeDBP reductions were numerically smaller in cohort B than in cohort A.

When analyzed by linear regression, a statistically significant OM dose response was observed for SeSBP and SeDBP in cohort A (P=0.0008 and 0.0026, respectively), cohort B (P=0.0032 and 0.0125, respectively), and the combined cohorts A+B (P<0.0001 for systolic BP [SBP] and diastolic BP [DBP]). When adjusted for baseline body weight, a statistically significant OM dose response was also observed for SeSBP and SeDBP in cohort A (P<0.0001 for SBP and DBP), cohort B (P=0.0265 and 0.0084, respectively), and cohorts A+B (P<0.0001 for SBP and DBP) (Figure 4).

Period 2: Randomized Withdrawal to OM or Placebo

Thirteen patients from period 1 did not enter period 2, resulting in a total of 182 patients in cohort A and 107 patients in cohort B for this randomized withdrawal phase. Three patients in each cohort who entered period 2 withdrew before study completion. In cohort A, all 3 patients were in the placebo group, with 1 each withdrawing because of an adverse event, protocol violation, or other reason. In cohort B, 1 each withdrew because of SeSBP/SeDBP criteria, at the patient’s request, or for another reason. BP changes were analyzed from period 2 baseline (end of period 1) through the end of period 2 (last observation carried forward). For cohort A, the mean increase in SeSBP was 0.43 mm Hg for subjects on OM and 4.9 mm Hg for subjects receiving placebo. The results from the analysis of covariance for the change in SeSBP for cohort A showed a statistically significant difference between OM and placebo of −3.6 mm Hg (P=0.0093). This statistically significant effect of OM was also observed for cohorts A+B (−3.16 mm Hg; P=0.0029). Results for SeDBP showed a similar OM treatment benefit. For cohort B, the mean SeSBP increase (1.4 mm Hg) for subjects on OM was numerically less than for subjects on placebo (3.8 mm Hg). However, this difference was not statistically significant. Results for SeDBP showed a pattern similar to that for SeSBP (Table 2; Figure 5).

Safety

Period 1: Treatment-Emergent Adverse Events

During period 1, the percentage of patients experiencing a treatment-emergent adverse event (TEAE) within each cohort

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort A (N=190)</th>
<th>Cohort B (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>12.2 (2.97)</td>
<td>12.5 (2.64)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>13.0 (6.0 to 17.0)</td>
<td>13.0 (6.0 to 16.0)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>154.2 (18.76)</td>
<td>155.2 (16.08)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>73.4 (38.51)</td>
<td>67.2 (33.25)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>118 (62.1)</td>
<td>1 (0.9)*</td>
</tr>
<tr>
<td>Black/African heritage</td>
<td>35 (18.4)</td>
<td>112 (100.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hawaiian</td>
<td>1 (0.5)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (13.2)</td>
<td>1 (0.9)*</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>122 (64.2)</td>
<td>57 (50.9)</td>
</tr>
<tr>
<td>Female</td>
<td>128 (67.4)</td>
<td>97 (86.6)</td>
</tr>
<tr>
<td>Family hypertension, n (%)</td>
<td>112 (58.9)</td>
<td>76 (67.9)</td>
</tr>
<tr>
<td>Baseline SeSBP, mm Hg, mean (SD)</td>
<td>129.3 (8.70)</td>
<td>131.2 (9.40)</td>
</tr>
<tr>
<td>Baseline SeDBP, mm Hg, mean (SD)</td>
<td>77.2 (8.16)</td>
<td>79.3 (8.09)</td>
</tr>
</tbody>
</table>

*All subjects in this cohort were Black; however, 2 were of mixed race, and subjects could be self-identified by more than one race.
was similar for the low- and high-dose OM groups. The majority of TEAEs were mild or moderate in intensity. A greater percentage of patients in cohort A (OM: low dose, 43.2%; high dose, 47.4%) reported having at least 1 TEAE compared with cohort B (OM: low dose, 33.9%; high dose, 28.6%). The most frequently occurring TEAEs in cohort A were headache (7.4%) and pharyngolaryngeal pain (6.3%) in the low-dose OM group and headache (14.7%) and dizziness (9.5%) in the high-dose OM group. The most frequently occurring TEAEs in cohort B were headache (5.4%) in the low-dose OM group and headache (8.9%) and toothache (3.6%) in the high-dose OM group. Two patients discontinued treatment because of TEAEs in the low-dose OM group in cohort A (1 because of moderate hypertension and 1 because of moderate hypoesthesia); the discontinuation due to hypoesthesia was considered to be possibly related to active therapy. There were no discontinuations resulting from TEAEs in cohort B.

The majority of TEAEs for both cohorts were determined to be not related to active therapy. Drug-related TEAEs were those events judged by the investigator to be possibly, probably, or definitely related to active therapy. Drug-related TEAEs in cohort A included headache (n=5), dizziness (n=4), tachycardia (n=1), diarrhea (n=1), hypoesthesia (n=1), and insomnia (n=1). In cohort B, only 1 patient in the high-dose OM group had a drug-related TEAE (headache), and there were no drug-related TEAEs in the low-dose OM group.

**Period 2: TEAEs**

During period 2, 35.5% of patients (n=33) in the OM group and 30.3% of patients (n=27) in the placebo group in cohort A experienced at least 1 TEAE, whereas 13.2% (n=7) and 14.8% of the patients (n=8), respectively, in cohort B experienced at least 1 TEAE. The majority of TEAEs were mild or moderate in intensity. Headache was the most common TEAE in OM groups for cohorts A and B. Drug-related TEAEs included hyperkalemia, headache, and dizziness in the OM group for cohort A. In cohort B, 1 patient in the OM group had 2 drug-related TEAEs, ie, renal impairment and moderate hypotension. The only discontinuation from the study due to a TEAE was reported for 1 patient in the cohort A placebo group who experienced severely elevated BP and moderate dizziness considered possibly related to treatment. Hematology, serum chemistry, and urinalysis values did not change substantially from baseline during the
study, and no trends or clinically relevant changes were noted.

**Discussion**

The goal of this study was to determine the safety and efficacy of OM in pediatric patients with hypertension. The study results demonstrated that both low and high doses of OM were effective in reducing BP in pediatric patients regardless of race; however, as has previously been shown with other ARB dose-ranging studies in children, the low doses used in this study resulted in BP lowering similar to placebo. Mean reductions in SeSBP and SeDBP were numerically greater in cohort A (predominantly non-Black patients) compared with cohort B (Black patients). A reduced responsiveness to modulators of the renin-angiotensin-aldosterone system in Black adults is well recognized and has been observed in a prior pediatric trial. For example, Menon et al showed that the angiotensin-converting enzyme inhibitor fosinopril had to be administered at higher doses on average in Black children to achieve similar SBP reductions and control versus non-Black children.

The primary efficacy end point of a change from baseline in trough SeSBP and SeDBP to the end of period 1 indicated a statistically significant OM dose response for all cohorts, and the use of a weight-adjusted analysis allowed for only 2 doses to be studied. From the regression analysis for the effect of weight-adjusted dose on the change in BP, using the SeSBP data in cohort A as an example, the slope of the regression line was estimated to be $-9.0 \text{ mm Hg per unit increase in dose (mg/kg)}$ after 3 weeks of treatment. Based on the dose-response relationship, an increase in dose by 0.3 mg/kg would result in an estimated additional SeSBP reduction of 2.7 mm Hg. The OM trial design, therefore, successfully incorporated only 2 fixed doses of the drug to achieve the primary efficacy end point, while concomitantly allowing for a body weight-adjusted dosing regimen. In contrast, candesartan failed to achieve the primary objective of detecting a significant slope for reduction in BP in pediatric patients because, in part, the highest doses tested did not produce additional BP lowering.

BP was also monitored during a placebo withdrawal period wherein one-half of the patients continued to receive OM. For cohort A, patients who had switched to placebo demonstrated...
a statistically significant increase in BP during the withdrawal period compared with those patients who continued to receive OM. Patients in the OM treatment group maintained their lower BP levels until the end of period 2, further establishing the antihypertensive efficacy of OM therapy. In contrast, no statistically significant treatment effect was demonstrated during period 2 for cohort B. Although, as mentioned above, Black adults can show a reduced responsiveness to renin-angiotensin-aldosterone system–blocking agents, and therefore this reduced effect might potentially occur in Black children as well, the lack of a significant effect during period 2 in cohort B was not an unexpected result because the population size was too small to show statistically significant differences. Increases in mean SeSBP and SeDBP were observed for cohort B in both the placebo and OM therapy groups, although greater increases were observed in the placebo group.

The results of this study support previous clinical trials establishing the efficacy of ARBs in the treatment of pediatric hypertension.9,12–15 OM exhibited BP-lowering efficacy in patients of different racial backgrounds and in a separate cohort comprising all Black patients. OM therapy was well tolerated at all doses in this study, and the most common TEAEs were headache and dizziness. However, the short-term duration of drug exposure precludes making any definitive conclusions regarding long-term, drug-related TEAEs. One limitation of this study was the short duration of active treatment compared with that typically used with adults. A longer period of exposure may have resulted in greater reductions in BP, as has been observed in adult hypertension trials with ARBs. In addition, although the results are not presented as placebo-subtracted values as usually done for adults, the clinical design is similar to that previously reported for determining the efficacy of losartan in children.
with hypertension. Finally, the low dose evaluated in this study demonstrated BP lowering similar to placebo based on the effects observed during the placebo-controlled withdrawal period, suggesting that higher doses may be required in clinical practice.

**Perspectives**

Hypertension in pediatric patients is an increasing societal problem. A proper therapeutic approach is required to prevent long-term consequences of untreated hypertension, including the specific assessment of antihypertensive drug efficacy in children. The current study accounted for the limitations in performing clinical trials in a pediatric population and demonstrated in a scientifically sound manner the efficacy and benefit of OM in children and adolescents of different races experiencing elevated BP or hypertension. The predominantly non-Black pediatric patient cohort did have numerically greater BP reductions compared with the Black pediatric patient cohort. This finding is consistent with efficacy

**Table 2. Blood Pressure Changes During Period 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>BP at Start of Period 2, Mean (SD)</th>
<th>BP Change During Period 2, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>88</td>
<td>118.0 (13.25)</td>
<td>4.93 (9.62)</td>
</tr>
<tr>
<td>SeSBP</td>
<td></td>
<td>69.1 (10.23)</td>
<td>4.43 (10.15)</td>
</tr>
<tr>
<td>SeDBP</td>
<td></td>
<td>120.4 (12.49)</td>
<td>0.43 (9.46)</td>
</tr>
<tr>
<td>OM</td>
<td>93</td>
<td>70.1 (10.34)</td>
<td>0.24 (8.12)</td>
</tr>
<tr>
<td><strong>Cohort B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>53</td>
<td>123.8 (11.81)</td>
<td>3.79 (10.02)</td>
</tr>
<tr>
<td>SeSBP</td>
<td></td>
<td>73.7 (10.18)</td>
<td>3.25 (8.74)</td>
</tr>
<tr>
<td>SeDBP</td>
<td></td>
<td>123.4 (12.86)</td>
<td>1.37 (9.50)</td>
</tr>
</tbody>
</table>

Patients either maintained the dose of OM from period 1 or received matching placebo.
results observed in the adult Black population and is most likely attributable to a reduced responsiveness to renin-angiotensin-aldosterone system–blocking agents. The availability of OM for the treatment of hypertension in pediatric patients is expected to expand the therapeutic arsenal for physicians and allow more patients to be treated.

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Disclosures

Dr Hazan’s group, Impact Clinical Trials, received payment from Daiichi Sankyo, Inc, to conduct this study. Dr Hazan holds shares in Pfizer. Koichi Miyazaki, Ben Tao, and Dr Reinilde Heyrman are employees of Daiichi Sankyo Pharma Development.

References

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A DOUBLE-BLIND, DOSE-RESPONSE STUDY OF THE EFFICACY AND SAFETY OF OLMESARTAN MEDOXOMIL IN CHILDREN AND ADOLESCENTS WITH HYPERTENSION

Lydie Hazan, MD; Oscar A. Hernández Rodríguez, MD; As’ad E. Bhorat, MD; Koichi Miyazaki, MS; Ben Tao, MS; Reinilde Heyrman, MD, for the Assessment of Efficacy and Safety of Olmesartan in Pediatric hypertension (AESOP) Study Group

Supplemental Material

Table S1: Blood Pressure Cuff Size Based on Age of Child or Adolescent Patient

Table S2: Procedures for Blinding of Treatment Identities, Determination of Sample Size, and Assigning Patients to Treatment Groups

Table S3: Procedure for Compounding Olmesartan Medoxomil Suspensions

Figure S1: Study Design

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<table>
<thead>
<tr>
<th>Cuff Name</th>
<th>Bladder Width (cm)</th>
<th>Bladder length (cm)</th>
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</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>2.5-4.0</td>
<td>5.0-9.0</td>
</tr>
<tr>
<td>Infant</td>
<td>4.0-6.0</td>
<td>11.5-18.0</td>
</tr>
<tr>
<td>Child</td>
<td>7.5-9.0</td>
<td>17.0-19.0</td>
</tr>
<tr>
<td>Adult</td>
<td>11.5-13.0</td>
<td>22.0-26.0</td>
</tr>
<tr>
<td>Large arm</td>
<td>14.0-15.0</td>
<td>30.5-33.0</td>
</tr>
<tr>
<td>Thigh</td>
<td>18.0-19.0</td>
<td>36.0-38.0</td>
</tr>
</tbody>
</table>
Table S2. Procedures for Blinding of Treatment Identities, Determination of Sample Size, and Assigning Patients to Treatment Groups

Blinding Protocol

1. In order to maintain the double-blind conditions, patients and investigators were blinded to the treatment being administered. An independent, unblinded pharmacist compounded each suspension based on the dose required for each patient for a period according to the randomization schedule.

2. Only the pharmacist in charge of compounding study medication had access to the randomization schedule.

3. The treatment disclosure was not provided to the Sponsor/CRO clinical team except for the unblinded monitors. The unblinded monitors had access to the randomization schedule in order to confirm the correct treatment had been chosen in accordance with the randomization schedule and to verify the drug accountability log.

4. The schedule/codes were not revealed to personnel involved in assaying the laboratory samples or to anyone involved in data review, cleaning, and analysis.

Sample Size Determination

1. Sample size calculation was based on an assumed treatment effect in Cohort A. For the primary analysis, using a dose ratio of 1:8 and assuming a 0.41 mmHg drop in SeSBP per dose unit increase, a total of 129 patients was required to have 80% power to test the null hypothesis of slope = 0 with a two-sided type I error of 5%.

2. In case the primary analysis did not demonstrate a dose-response during Period 1 and a Period 2 ANCOVA was needed, the following assumptions were made in the sample size calculations: the difference between the OM-treated and the OM-
withdrawn placebo group would be 4 mmHg in ScSBP at the end of Period 2 with a standard deviation of 12 mmHg, 80% power, and 2-sided alpha of 0.05. Based on these assumptions, 143 patients per group were required. In effect, the sample size requirement was 286 patients, which is consistent with the combined number of patients in Cohort A and Cohort B (n = 280).

3. The number of patients planned for Cohort B was based on FDA request. Cohort B was planned as an all Black cohort of 100 Black patients.

**Method of Assigning Subjects to Treatment Groups**

1. All patients were assigned a screening number in the order that they entered the study at the screening visit. After completion of screening and washout procedures, eligible patients were randomly assigned to treatment sequences on Day 1 of Period 1.

2. An algorithm was used to ensure the proper allocation of patients to Cohorts A and B and to balance the treatment assignments within Cohort A. In addition, after a minimum of 28 Black patients were randomized into Cohort A, Black patients were then allocated into Cohort B.

3. The randomizing of patients was accomplished centrally using an Interactive Voice Recognition System. The randomization schedule was prepared by ClinPro, Inc. (Bound Brook, NJ) and patients were randomized to treatment sequences as shown in the Methods section.
Table S3. Procedure for Compounding Olmesartan Medoxomil Suspensions

Table: Formulation Table

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benicar® 20 mg tablet</td>
<td>5 tablets</td>
<td>40 tablets</td>
</tr>
<tr>
<td></td>
<td>0.5 mg/mL Suspension</td>
<td>4.0 mg/mL Suspension</td>
</tr>
<tr>
<td>Ora-Sweet®</td>
<td>100 mL</td>
<td>100 mL</td>
</tr>
<tr>
<td>Ora-Plus®</td>
<td>50 mL</td>
<td>50 mL</td>
</tr>
<tr>
<td>Purified Water</td>
<td>50 mL</td>
<td>50 mL</td>
</tr>
</tbody>
</table>

Volumetric Method

Add 50 mL of purified water to five Benicar® 20 mg tablets (0.5 mg/mL)

Add 50 mL of purified water to forty Benicar® 20 mg tablets (4 mg/mL)

Let stand for 5 minutes, shake for 1 min x 4 times, standing for 1 minute

Add 100 mL of Ora-Sweet® and 50 mL of Ora-Plus®, shake for 1 minute
Figure Legend:

Figure S1. Study Design.