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ORIGINAL RESEARCH

Efficacy/Safety of Olmesartan Medoxomil Versus Losartan Potassium in Naïve Versus Previously Treated Subjects with Hypertension

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ABSTRACT

Introduction: A predefined exploratory analysis of a prospective, randomized, double-blind, forced-titration study of olmesartan medoxomil (OM) versus losartan potassium (LOS) in subjects with hypertension not previously or previously treated with antihypertensive medication is reported.

Methods: The study included a 3–4-week placebo run-in and an 8-week active treatment period: OM (weeks 1–4, OM 20 mg; weeks 5–8, OM 40 mg); placebo + OM (weeks 1–2, placebo; weeks 3–4, OM 20 mg; weeks 5–8, OM 40 mg); and LOS (weeks 1–4, LOS 50 mg; weeks 5–8, LOS 100 mg). Analyses focused on comparison of OM and placebo + OM combined versus LOS. Efficacy endpoints were mean change from baseline in seated cuff diastolic blood pressure (SeDBP) at week 8 (primary); seated cuff systolic blood pressure (SeSBP) at weeks 4 and 8, and SeDBP at week 4 (secondary), and BP target achievement (tertiary).

Results: The randomized population (n = 941) had a mean ± SD age of 51.9 ± 9.7 years, 54.5% were male, and 20.1% were naïve to antihypertensive medication. For treatment-naïve subjects, baseline seated BP (SeBP) (±SD) was 157.4 (±10.9)/101.8 (±4.3) mmHg with OM and 156.3 (±10.8)/101.1 (±3.9) mmHg with LOS, while non-naïve subjects had 158.4 (±10.2)/100.9 (±4.0) mmHg with OM and 158.8 (±10.1)/101.3 (±4.2) mmHg with LOS. OM monotherapy produced significantly greater changes in least-squares mean (±SE) SeDBP compared with LOS in both treatment-naïve (–9.7 [1.0] vs. –6.6 [1.0] mmHg; P = 0.0232 vs. LOS) and non-naïve subjects (–9.6 [0.5] vs. –7.3 [0.5] mmHg; P = 0.0013 vs. LOS). A significantly greater proportion of patients achieved the SeBP goal of <140/90 mmHg with OM compared

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with LOS in treatment-naïve (34.1% vs. 19.0%, respectively; $P = 0.0109$) and non-naïve subjects (31.0% vs. 19.6%; $P = 0.0008$).

Conclusion: Overall, OM monotherapy resulted in significantly greater SeBP reductions and greater SeBP goal achievement than LOS, irrespective of previous medication use. Both OM and LOS therapy were well tolerated.

Keywords: Ambulatory blood pressure; Blood pressure goal; Hypertension; Losartan potassium; Olmesartan medoxomil; Treatment naïve; Tolerability

INTRODUCTION

Although blood pressure (BP) control rates have improved in recent years, data from the National Health and Nutrition Examination Survey from 2007 to 2008 estimated that only 50.1% of subjects with hypertension achieve BP control while on antihypertensive medication [1]. Many individuals with hypertension will require ≥2 antihypertensive medications to achieve their BP goals [2]; however, monotherapy may be effective in some subjects, particularly in those with mild BP elevation without additional cardiovascular risk factors [3, 4]. Consequently, when choosing an antihypertensive agent as monotherapy, it is important to select a drug that provides the greatest opportunity for BP goal achievement while maintaining good tolerability.

Angiotensin receptor blockers (ARBs) are highly effective in reducing BP [5, 6], demonstrate placebo-like tolerability [5, 7], and some have shown benefits beyond BP lowering in reducing cardiovascular events [8]. Although all ARBs share the same mechanism of action, their pharmacokinetic and pharmacodynamic profiles vary [9]. Olmesartan medoxomil (OM) displays a high degree of binding insurmountability for the angiotensin II receptor type 1 (AT_1) receptor [10], whereas losartan potassium (LOS) displays completely surmountable antagonism for the AT_1 receptor [11]. This may help explain differences in BP lowering between ARBs, such as OM, compared with older ARBs, such as LOS [12].

OM produces potent, long-acting reductions in systolic BP (SBP) and diastolic BP (DBP) when administered alone or in combination with other agents across a range of subject types [13, 14]. Moreover, OM has a low potential for drug–drug interactions [15]. The comparative antihypertensive efficacy and safety of OM as monotherapy to other ARBs, including LOS, has been demonstrated in several large, published, randomized clinical monotherapy trials [5, 16]. OM 20–40 mg once daily was shown as more effective in lowering BP compared with LOS 50–100 mg once daily.

A recently published 8-week, phase 4, prospective, double-blind, active-comparator, multicenter, forced-titration study evaluated the efficacy and safety of once-daily maximum doses of OM and LOS monotherapy in subjects with stage 1 or 2 hypertension (ClinicalTrials.gov identifier: NCT00949884) [17]. Results of this study confirmed the greater efficacy of OM compared with LOS in reducing seated cuff BP (SeBP) and achieving SeBP goals, with a similar tolerability profile. This suggests that OM may be used as an effective and safe initial monotherapy to which other antihypertensives may be added for a multistep treatment algorithm. Here, the authors report findings of a prespecified exploratory subgroup analysis from this study evaluating treatment-naïve versus previously treated subjects with hypertension receiving once-daily maximum doses of OM or LOS.

MATERIALS AND METHODS

Study Design and Treatment

This was a prespecified exploratory subgroup analysis of previously treated (non-naïve) and

treatment-naïve (naïve) subjects from the above-mentioned prospective, randomized, controlled, double-blind, forced-titration study. Full details of the study design, methodology, and inclusion/exclusion criteria have been published previously [17]. "Non-naïve" was defined as subjects with hypertension who had been weaned off their current antihypertensive therapy (i.e., discontinued antihypertensive medication usage for at least 24 hours before being switched to placebo for the 3–4-week placebo run-in period), while "naïve" described subjects with hypertension who had never been treated with antihypertensive medications.

Subjects aged >18 and <100 years with mean seated cuff DBP (SeDBP) of >95 and <115 mmHg, and mean seated cuff SBP (SeSBP) of <180 mmHg were randomized in an 8:1:9 ratio to receive once-daily OM, placebo + OM, and LOS. Doses were as follows: OM: OM 20 mg for 4 weeks, followed by OM 40 mg for 4 weeks; placebo + OM: placebo for 2 weeks, followed by OM 20 mg for 2 weeks, and OM 40 mg for 4 weeks; and LOS: LOS 50 mg for 4 weeks, followed by LOS 100 mg for 4 weeks.

Study protocol and consent forms were reviewed and approved by the institutional review boards for each participating center. Each participant provided written informed consent at the screening visit. The study was conducted under the guidance of an institutional review board committee for each study center and in accordance with the principles of the Declaration of Helsinki.

Assessments

SeBP was assessed before treatment administration at baseline, and at weeks 4 and 8. BP was measured with a validated automatic BP monitoring device (Omron Corporation, Kyoto, Japan) on the nondominant arm. At prespecified sites, subjects also underwent 24-hour ambulatory BP monitoring (ABPM) using a SpaceLabs model 90207 automated device (SpaceLabs Healthcare, Ltd., Issaquah, WA, USA) at baseline, and at weeks 4 and 8. Safety variables were evaluated throughout the placebo run-in and active treatment periods by monitoring adverse events, changes in vital signs, routine laboratory tests, and physical findings. Complete medical histories and routine laboratory safety tests were performed at screening and at week 8.

Endpoints

The primary efficacy variable was the mean change from baseline in trough SeDBP at week 8. Secondary variables included the change from baseline in mean trough SeDBP at week 4, change from baseline in mean trough SeSBP at weeks 4 and 8, and tertiary variables included the proportion of subjects achieving the BP goal of <140/90 mmHg at weeks 4 and 8 (used irrespective of metabolic status as the vast majority of subjects in the study did not have diabetes mellitus), and the occurrence of treatment-emergent adverse events (TEAEs) during the study.

In a subgroup of subjects who had their ABPM assessed, the following endpoints were also used: change from baseline in mean 24-hour ambulatory SBP and DBP at weeks 4 and 8, and the proportion of subjects achieving the mean 24-hour ambulatory BP target of <130/80 mmHg at weeks 4 and 8.

Statistical Methods

A full description of the statistical analyses used in this study has been published previously [17]. The efficacy cohort was defined as all subjects receiving at least one dose of study medication, and who had a baseline assessment and at least one post-baseline efficacy assessment. The safety cohort was defined as all subjects who received at least one dose of randomized study medication.

An analysis of covariance model was used for the primary efficacy analysis (including

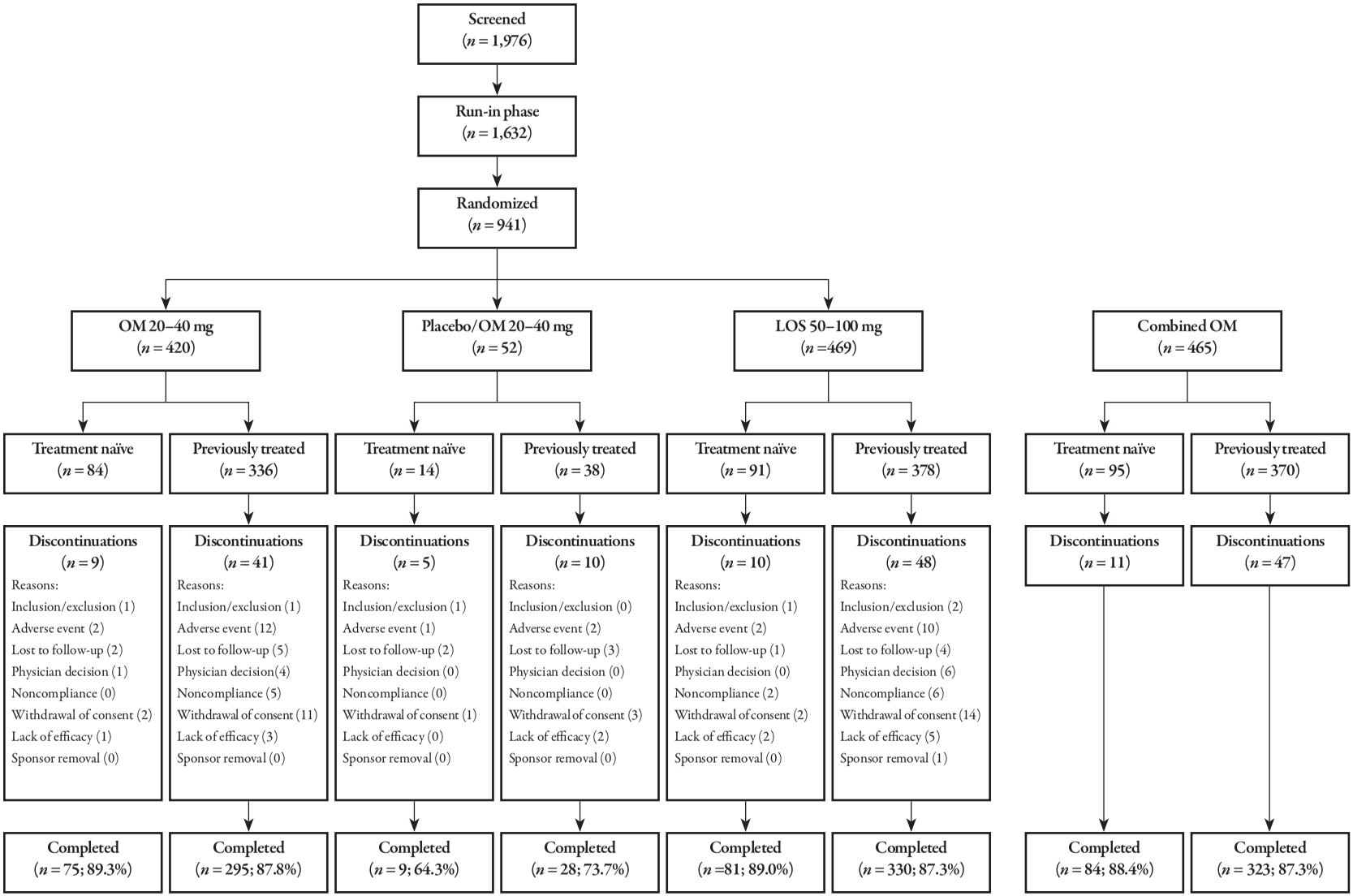

Fig. 1 Subject disposition. *LOS* losartan potassium, *OM* olmesartan medoxomil

treatment as a fixed effect and the baseline mean SeDBP value as a covariate). Superiority was concluded if the two-sided *P* value was <0.05. All changes from baseline BP were summarized and analyzed by a one-sample paired *t* test. The last (post-baseline) observation carried forward (LOCF) method was used to handle missing efficacy values for each treatment period.

Because the efficacy of OM was expected to be near maximum after 2 weeks of treatment, subjects originally randomized to receive OM and placebo + OM were combined to represent the OM group for week 4 and week 8 analyses. The proportions of subjects achieving BP goals were summarized and analyzed using a normal approximation to the binomial distribution.

RESULTS

Subject Disposition and Baseline Characteristics

Subject disposition during the study has been previously published [17]. Of 941 subjects enrolled and randomized, 934 received at least one dose of study medication (safety cohort) and 850 comprised

Table 1 Demographics and baseline characteristics in the randomized (*n* = 941) and safety (*n* = 934) populations

Characteristic	Naïve			Non-naïve		
	OM (*n* = 95)[a]	LOS (*n* = 91)[a]	Total (*n* = 189)[b]	OM (*n* = 370)[a]	LOS (*n* = 378)[a]	Total (*n* = 752)[b]
Age (years), mean ± SD	48.6 ± 10.46	49.3 ± 8.88	49.0 ± 9.66	52.5 ± 9.43	52.8 ± 9.85	52.7 ± 9.63
Age ≥65 years, *n* (%)	5 (5.3)	4 (4.4)	9 (4.8)	31 (8.4)	42 (11.1)	73 (9.7)
Male, *n* (%)	61 (64.2)	51 (56.0)	115 (60.8)	189 (51.1)	207 (54.8)	398 (52.9)
Race, *n* (%)						
Caucasian	65 (68.4)	62 (68.1)	129 (68.3)	236 (63.8)	242 (64.0)	481 (64.0)
Black	25 (26.3)	27 (29.7)	53 (28.0)	108 (29.2)	106 (28.0)	214 (28.5)
Other	5 (5.3)	2 (2.2)	7 (3.7)	26 (7.0)	30 (8.0)	57 (7.6)
BMI, kg/m^2, mean ± SD	32.85 ± 5.96	31.76 ± 6.30	32.25 ± 6.12	32.45 ± 6.43	32.41 ± 6.70	32.45 ± 6.57
BMI ≥30 kg/m^2, *n* (%)	59 (62.1)	50 (54.9)	110 (58.2)	225 (60.8)	221 (58.5)	449 (59.7)
Stage 1 hypertension, *n* (%)	25 (26.3)	25 (27.5)	52 (27.5)	116 (31.4)	109 (28.8)	225 (29.9)
Stage 2 hypertension, *n* (%)	70 (73.7)	66 (72.5)	137 (72.5)	254 (68.6)	269 (71.2)	527 (70.1)
Type 2 diabetes mellitus, *n* (%)	2 (2.1)	3 (3.3)	5 (2.6)	44 (11.9)	54 (14.3)	100 (13.3)
Metabolic syndrome, *n* (%)	36 (37.9)	32 (35.2)	70 (37.0)	152 (41.1)	150 (39.7)	306 (40.7)
SeBP, mmHg, mean ± SD						
SeSBP	157.4 ± 10.89	156.3 ± 10.75	156.8 ± 10.79	158.4 ± 10.22	158.8 ± 10.06	158.6 ± 10.14
SeDBP	101.8 ± 4.26	101.1 ± 3.94	101.4 ± 4.10	100.9 ± 3.96	101.3 ± 4.19	101.1 ± 4.09
24-hour ambulatory BP, *n*	21	22	43	102	101	203
SBP, mmHg, mean ± SD	139.4 ± 11.81	139.0 ± 14.51	139.2 ± 13.10	140.5 ± 13.85	143.4 ± 13.09	142.0 ± 13.52
DBP, mmHg, mean ± SD	87.6 ± 7.94	89.9 ± 10.36	88.8 ± 9.22	86.8 ± 8.66	89.0 ± 9.58	87.9 ± 9.17

BMI body mass index, *BP* blood pressure, *DBP* diastolic BP, *LOS* losartan potassium, *OM* olmesartan medoxomil, *SBP* systolic BP, *SeBP* seated cuff BP, *SeDBP* seated cuff DBP, *SeSBP* seated cuff SBP

[a] Randomized population

[b] Safety cohort (subjects who received at least one dose of study medication)

the efficacy cohort. Of the 941 randomized subjects, 752 were non-naïve (370 receiving OM and 378 receiving LOS) and 189 were naïve (95 receiving OM and 91 receiving LOS) (Fig. 1). A total of 246 of 941 subjects underwent ABPM [17], which was comprised of 203 non-naïve subjects (101 receiving LOS and 102 receiving OM) and 43 naïve subjects (22 receiving LOS and 21 receiving OM).

Demographic and baseline characteristics of naive and non-naïve subjects were similar (Table 1), except that the naïve cohort was younger (49.0 vs. 52.7 years, respectively) and less likely to have type 2 diabetes at enrollment (2.6% vs. 13.3%). Overall, the mean (±SD) age of the randomized population was 51.9 ± 9.7 years, 54.5% were male, and 20.1% were naïve to antihypertensive medication.

Efficacy

Seated Cuff Blood Pressure Reductions From Baseline

At week 8, the change from baseline in least-squares (LS) mean SeDBP (LOCF), the primary efficacy endpoint, was significantly greater with OM

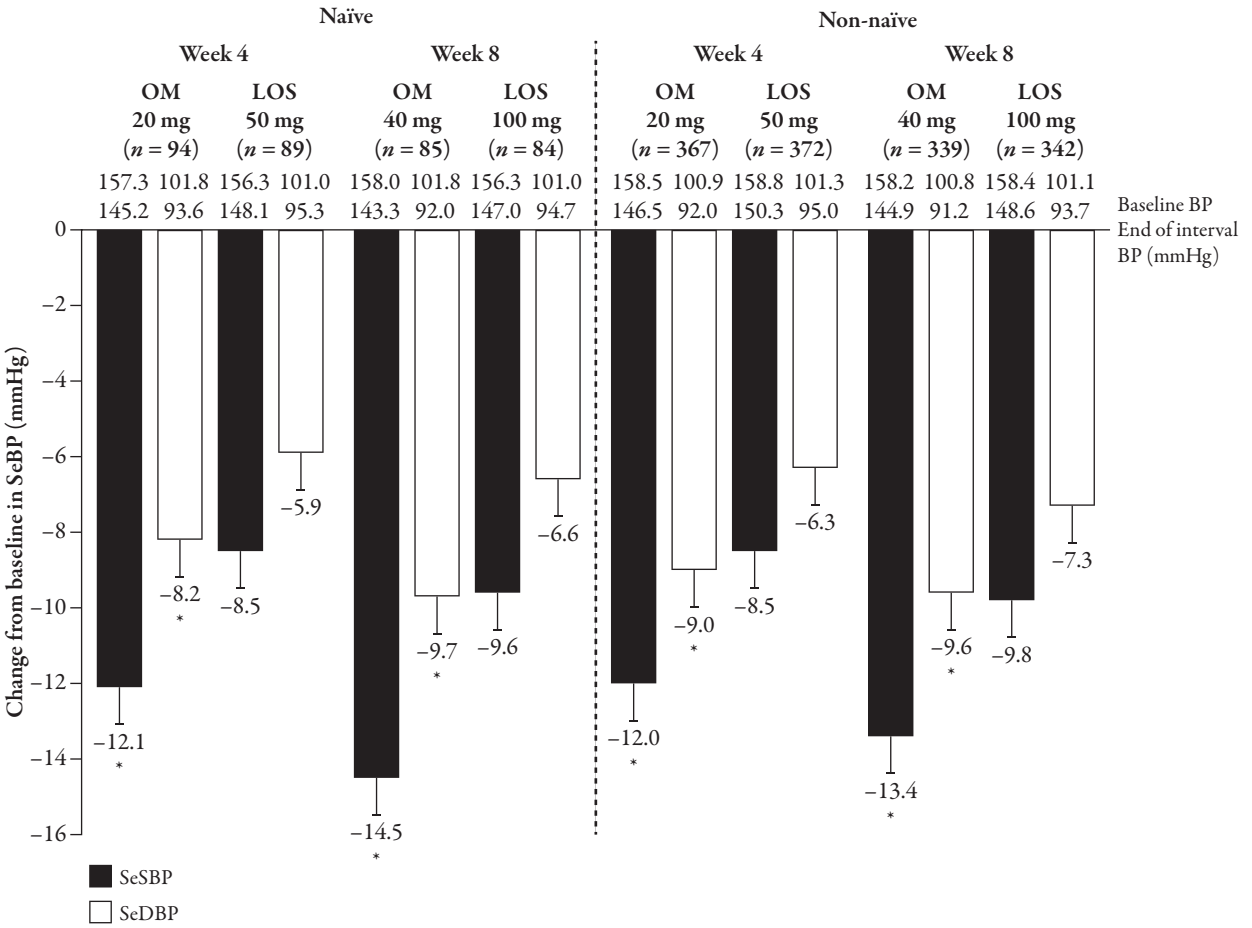

Fig. 2 LS mean (±SE of the mean) change from baseline in SeDBP (primary endpoint) and SeSBP at week 4 (OM 20 mg, LOS 50 mg) and week 8 (OM 40 mg, LOS 100 mg) in treatment-naïve (naïve) and previously treated (non-naïve) subjects, with LOCF. LS mean treatment difference reported in the narrative. * $P < 0.05$ for OM versus LOS. OM = combined OM and placebo + OM groups; weeks 4 and 8 LOCF analysis. *BP* blood pressure, *LOCF* last observation carried forward, *LOS* losartan potassium, *LS* least squares, *OM* olmesartan medoxomil, *SeBP* seated cuff blood pressure, *SeDBP* seated cuff diastolic blood pressure, *SeSBP* seated cuff systolic blood pressure

compared with LOS for both naïve and non-naïve subjects (Fig. 2). The mean treatment difference (±SE) between OM and LOS in SeDBP was –3.1 (±1.35; $P = 0.0232$ vs. LOS) in naïve subjects and –2.3 (±0.71; $P = 0.0013$ vs. LOS) in non-naïve subjects. A similar trend in significantly greater reductions from baseline with OM compared with LOS was observed at week 4 for SeDBP in naïve subjects (LS mean treatment difference: –2.3 [±1.10]; $P = 0.0337$ vs. LOS) and in non-naïve subjects (–2.7 [±0.67]; $P < 0.0001$ vs. LOS).

Similarly, both naïve and non-naïve subjects in the OM group had significantly greater mean reductions from baseline in SeSBP at week 4 compared with LOS (Fig. 2). The change in LS mean (±SE) SeSBP (LOCF) in naïve subjects was –12.1 (±1.2) versus –8.5 (±1.3) mmHg, respectively ($P = 0.0379$ vs. LOS), and –12.0 (±0.7) versus –8.5 (±0.7) mmHg ($P = 0.0006$ vs. LOS) in non-naïve subjects. At week 8, naïve and non-naïve subjects receiving OM had significantly greater mean SeSBP changes from baseline compared with those treated with LOS (–14.5 [±1.5] vs. –9.6 [±1.5] mmHg, respectively; $P = 0.0178$ vs. LOS, and –13.4 [±0.8] vs. –9.8 [±0.8] mmHg; $P = 0.0016$ vs. LOS).

Attainment of Seated Cuff Blood Pressure Goals

A significantly greater proportion of naïve subjects receiving OM achieved the SeBP goal of <140/90 mmHg LOCF at week 4 compared with LOS ($P = 0.0079$ vs. LOS) and at week 8 ($P = 0.0109$ vs. LOS) (Fig. 3). In addition, a significantly greater proportion of non-naïve subjects receiving OM achieved the SeBP goal of <140/90 mmHg at week 4 ($P = 0.0002$ vs. LOS) and at week 8 ($P = 0.0008$ vs. LOS). SeBP

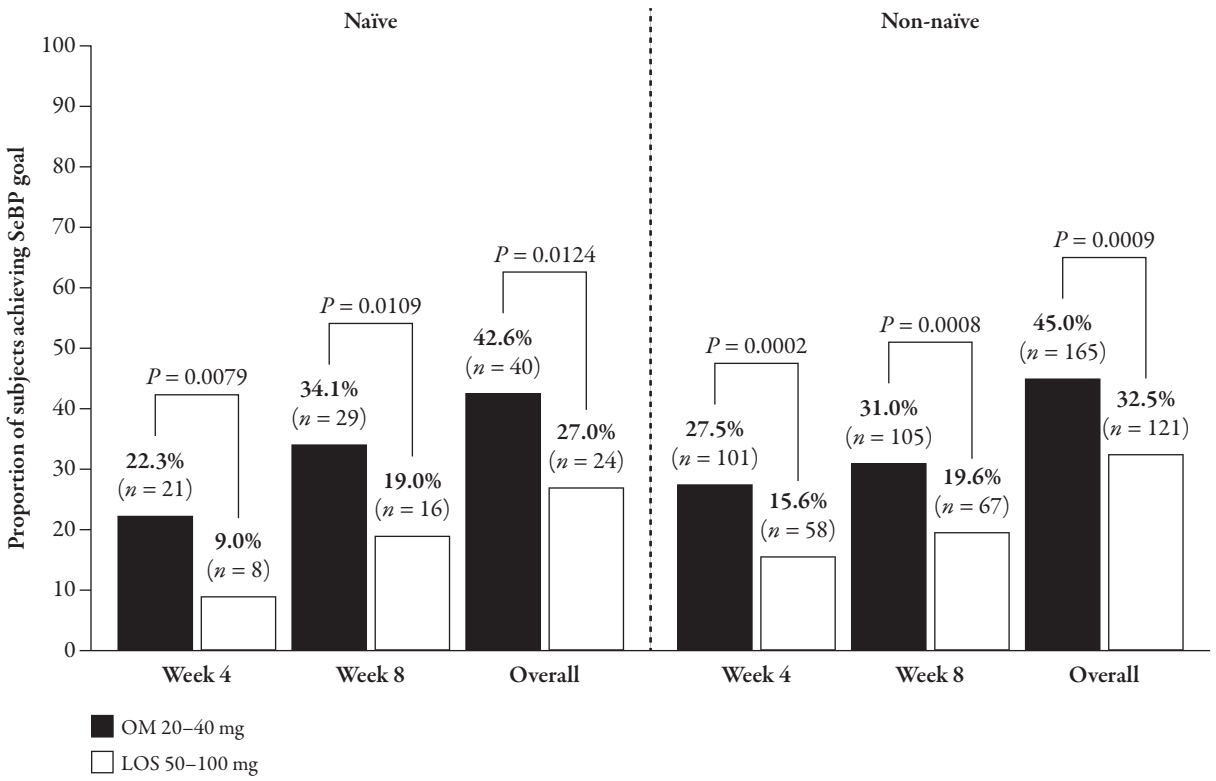

Fig. 3 Proportions of treatment-naïve (naïve) and previously treated (non-naïve) subjects achieving combined SeBP goal of <140/90 mmHg at weeks 4 and 8. *LOS* losartan potassium, *OM* olmesartan medoxomil, *SeBP* seated cuff blood pressure

goal achievement over the entire randomized treatment phase was higher for OM than for LOS in both naïve (42.6% vs. 27.0%, respectively) and non-naïve subjects (45.0% vs. 32.5%).

Twenty-Four Hour Ambulatory Blood Pressure Reductions From Baseline

In the population of subjects who underwent ABPM, the LS mean changes from baseline in 24-hour ambulatory BP were greater with OM compared with LOS at week 4 and week 8 in both naïve and non-naïve subjects. At week 4, the change from baseline in LS mean ambulatory BP (±SE) in naïve subjects was –7.8 (±1.9)/–5.8 (±1.2) mmHg for OM, and –4.0 (±1.9)/–2.7 (±1.2) mmHg for LOS. Although greater with OM, the LS mean treatment difference of –3.7 (±2.81)/–2.9 (±1.89) mmHg was not statistically significant for SBP ($P = 0.1904$ vs. LOS) or DBP ($P = 0.1268$ vs. LOS). In non-naïve subjects, the LS mean (±SE) change in ambulatory BP was –7.2 (±1.2)/–4.6 (±0.8) mmHg for OM, and –6.3 (±1.2)/–3.9 (±0.8) mmHg for LOS. The LS mean treatment difference of –0.9 (±1.69)/–0.8 (±1.12) mmHg was not statistically significant for SBP ($P = 0.6015$ vs. LOS) or DBP ($P = 0.4992$ vs. LOS).

At week 8, the change in LS mean ambulatory BP in naïve subjects was numerically greater for OM compared with LOS (Fig. 4); however, the LS mean treatment difference of –4.5 (±3.25)/–5.4

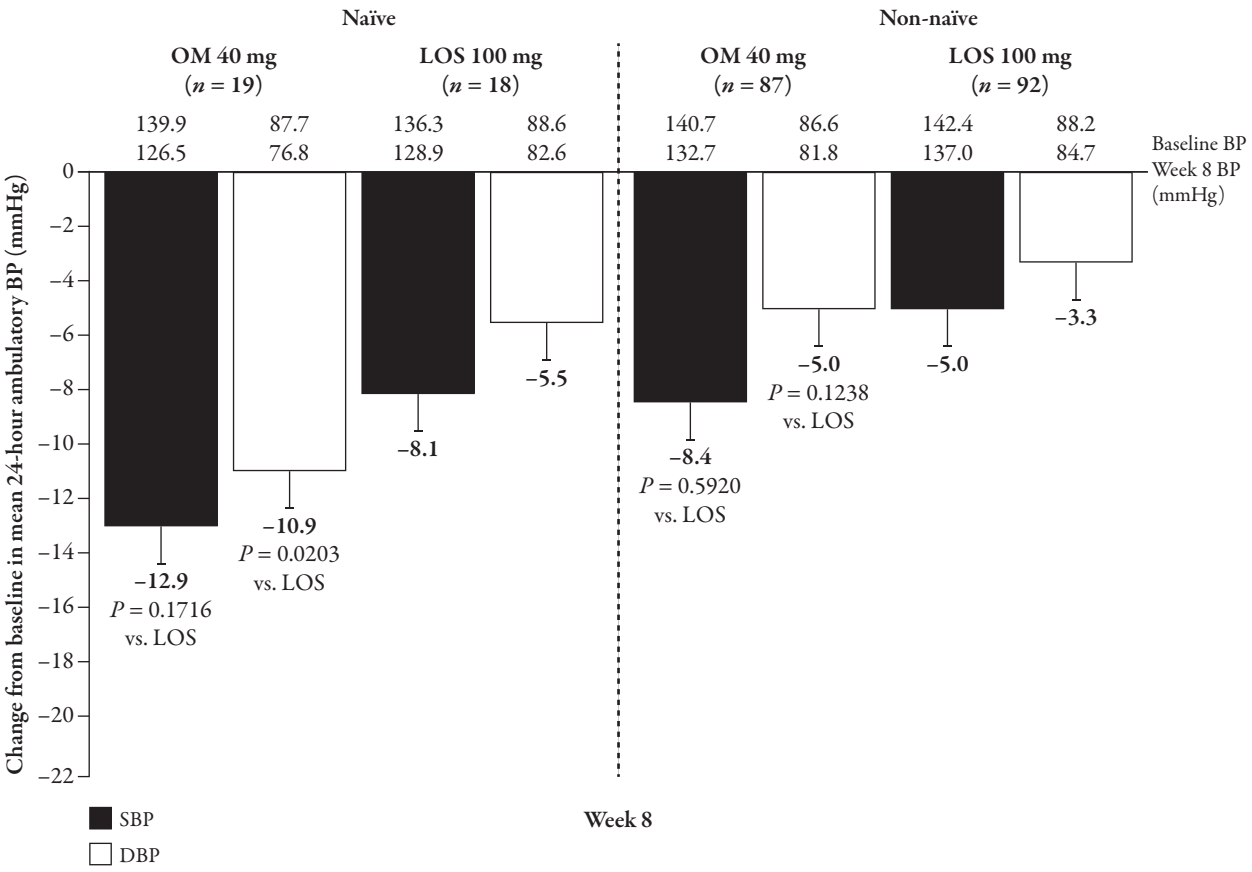

Fig. 4 LS mean (±SE) change from baseline in 24-hour ambulatory SBP and DBP at week 8 in treatment-naïve (naïve) and previously treated (non-naïve) subjects. OM = combined OM and placebo + OM groups; week 8 last observation carried forward analysis. LS mean treatment difference reported in the narrative. *BP* blood pressure, *DBP* diastolic blood pressure, *LOS* losartan potassium, *LS* least squares, *OM* olmesartan medoxomil, *SBP* systolic blood pressure

(±2.21) mmHg was not statistically significant for SBP (P = 0.1716 vs. LOS) but was statistically significant for DBP (P = 0.0203 vs. LOS). In non-naïve subjects, the change in LS mean ambulatory BP was also greater for OM compared with LOS; however, the LS mean treatment difference of –3.3 (±1.68)/–1.7 (±1.11) was not statistically significant for SBP (P = 0.0529 vs. LOS) or DBP (P = 0.1238 vs. LOS).

Attainment of Ambulatory Blood Pressure Targets

Overall, a greater percentage of naïve and non-naïve subjects achieved the mean 24-hour ambulatory BP target of <130/80 mmHg with OM treatment compared with LOS at weeks 4 and 8, although the differences were not statistically significant (Fig. 5). At week 4, the proportion of subjects who achieved the mean 24-hour ambulatory BP target was 28.6% (n = 6) versus 10.0% (n = 2) in naïve subjects (P = 0.1567 vs. LOS) and 30.9% (n = 30) vs. 21.4% (n = 21) in non-naïve subjects (P = 0.2932 vs. LOS). At week 8, the proportion of subjects who achieved the mean 24-hour ambulatory BP target was 57.9% versus 38.9% in naïve subjects (P = 0.0935 vs. LOS) and 29.9% versus 22.8% in non-naïve subjects (P = 0.4008). Ambulatory BP target achievement at any time during randomized treatment was also greater for OM compared with LOS in naïve (57.1% [n = 12] vs. 31.8% [n = 7]; P = 0.0563) and non-naïve subjects (39.2% [n = 40] vs. 27.7% [n = 28]; P = 0.1949).

Safety and Tolerability

TEAEs occurred in 30.5% of naïve and 31.4% of non-naïve subjects in the OM group, and in 33.0% of naïve and 31.2% of non-naïve

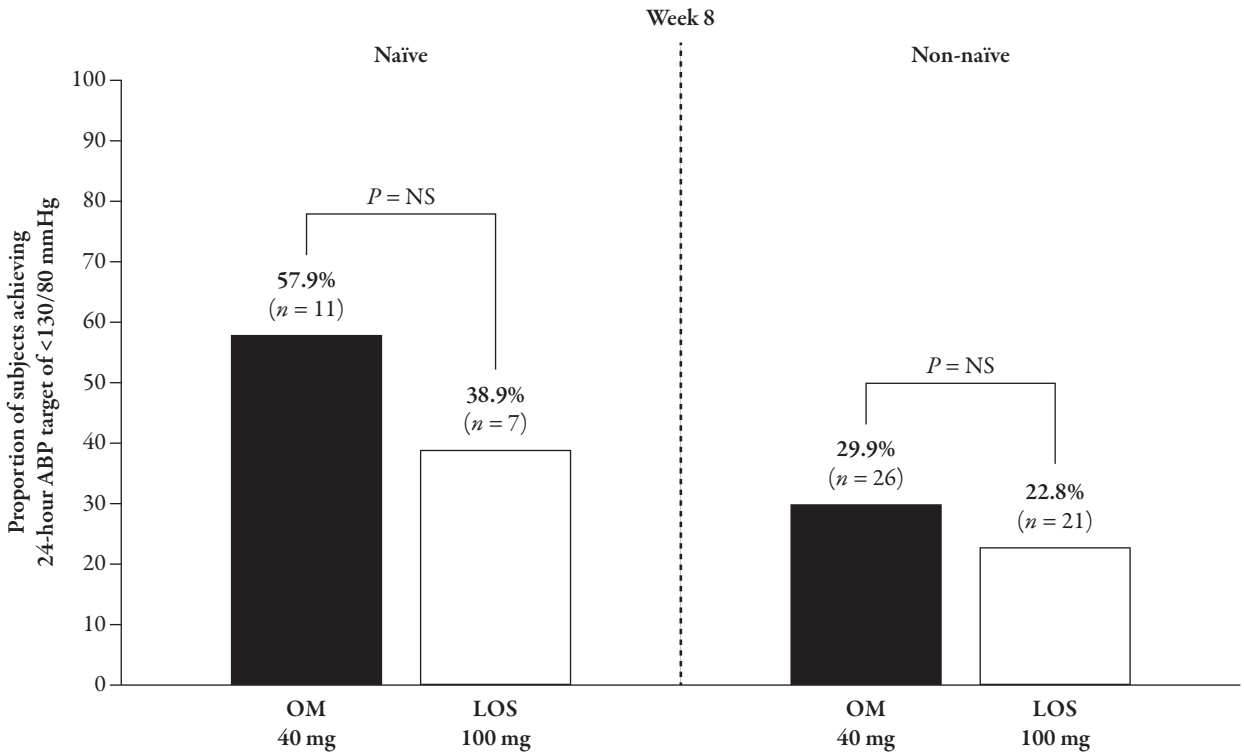

Fig. 5 Proportion of treatment-naïve (naïve) and previously treated (non-naïve) subjects achieving 24-hour ABP target of <130/80 mmHg at week 8. *ABP* ambulatory blood pressure, *LOS* losartan potassium, *NS* not statistically significant, *OM* olmesartan medoxomil

subjects in the LOS group (Table 2). Most were mild to moderate in severity. TEAEs observed in at least 2% of subjects in any group are shown in Table 2.

TEAEs led to discontinuation in 2.1% and 3.5% of naïve and non-naïve subjects receiving OM, respectively, and in 2.2% and 2.1% of naïve and non-naïve subjects receiving LOS (Table 2). No serious TEAEs were reported with OM treatment, whereas two naïve subjects (2.2%) and two non-naïve subjects (0.5%) in the LOS groups reported serious TEAEs; however,

Table 2 Number (%) of subjects experiencing TEAEs during 8 weeks of treatment with OM or LOS in the safety cohort ($n = 934$)

Adverse event, *n* (%)	Naïve		Non-naïve	
	OM ($n = 95$)	LOS ($n = 91$)	OM ($n = 370$)	LOS ($n = 378$)
Any TEAE	29 (30.5)	30 (33.0)	116 (31.4)	118 (31.2)
Severity of TEAEs				
Mild	15 (15.8)	17 (18.7)	57 (15.4)	60 (15.9)
Moderate	12 (12.6)	12 (13.2)	53 (14.3)	52 (13.8)
Severe	2 (2.1)	1 (1.1)	6 (1.6)	6 (1.6)
Any drug-related TEAE	8 (8.4)	3 (3.3)	23 (6.2)	23 (6.1)
Any TEAEs leading to discontinuations	2 (2.1)	2 (2.2)	13 (3.5)	8 (2.1)
Any discontinuations due to a drug-related TEAE	0 (0.0)	0 (0.0)	5 (1.4)	6 (1.6)
Any SAE	0 (0.0)	2 (2.2)	0 (0.0)	2 (0.5)
Any serious TEAE	0 (0.0)	2 (2.2)	0 (0.0)	2 (0.5)
Any drug-related serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse event leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Specific TEAEs reported in >2% of subjects in either treatment arm				
Headache	4 (4.2)	3 (3.3)	17 (4.6)	21 (5.6)
Dizziness	0 (0.0)	0 (0.0)	8 (2.2)	6 (1.6)
Insomnia	0 (0.0)	2 (2.2)	1 (0.3)	2 (0.5)
Nausea	1 (1.1)	1 (1.1)	7 (1.9)	8 (2.1)
Constipation	2 (2.1)	0 (0.0)	3 (0.8)	4 (1.1)
Nasopharyngitis	1 (1.1)	4 (4.4)	7 (1.9)	9 (2.4)
Upper respiratory tract infection	2 (2.1)	1 (1.1)	3 (0.8)	9 (2.4)
Viral gastroenteritis	2 (2.1)	0 (0.0)	0 (0.0)	1 (0.3)
Blood sodium increased	2 (2.1)	2 (2.2)	0 (0.0)	0 (0.0)
GGT increased	2 (2.1)	0 (0.0)	2 (0.5)	0 (0.0)
Hypertriglyceridemia	0 (0.0)	2 (2.2)	1 (0.3)	0 (0.0)
Cough	1 (1.1)	2 (2.2)	2 (0.5)	2 (0.5)
Oropharyngeal pain	0 (0.0)	2 (2.2)	0 (0.0)	2 (0.5)

GGT gamma-glutamyltransferase, *LOS* losartan potassium, *OM* olmesartan medoxomil, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

none were deemed drug related (Table 2). No subjects had adverse events resulting in death. Drug-related TEAEs occurred in 8.4% of naïve and 6.2% of non-naïve subjects, in the OM group, and in 3.3% of naïve and 6.1% of non-naïve subjects in the LOS group.

DISCUSSION

This subgroup analysis indicated that statistically significantly greater mean SeBP reductions from baseline were achieved in both naïve and non-naïve subjects receiving OM 40 mg daily compared with those treated with LOS 100 mg daily. In addition, a significantly greater proportion of subjects achieved the SeBP goal of <140/90 mmHg at week 8 LOCF with OM compared with LOS and at any time during the randomized treatment phase, irrespective of previous antihypertensive medication use. Although the differences between OM and LOS did not reach statistical significance, a higher proportion of subjects receiving OM achieved the ABPM target of <130/80 mmHg at week 4, week 8, and at any time point in the randomized treatment phase. Tolerability was similar in both groups, and most adverse events were mild to moderate.

These findings support those from previous studies that compared the efficacy and safety of OM versus LOS in subjects with essential hypertension. Oparil et al. showed that OM (n = 147) produced significantly greater changes in SeDBP (–11.5 vs. –8.2 mmHg; $P < 0.0005$) through 8 weeks and SeSBP at week 2 (–13.0 vs. –8.9 mmHg; $P \leq 0.005$) compared with LOS (n = 150) in a randomized, double-blind study of subjects with essential hypertension [16]. It should be noted that although both the present study and the Oparil et al. study had the same primary endpoint, the entry criteria for the Oparil et al. study differed from the present study in that for subjects to be randomized to treatment they had to have an average SeDBP of ≥100 and ≤115 mmHg, and a mean daytime ambulatory DBP of ≥90 and <120 mmHg as measured by ABPM. In the present study, subjects needed to have a mean SeDBP of ≥95 and ≤115 mmHg and mean SeSBP of ≤180 mmHg. Another important difference between the study methodologies is that Oparil et al. only evaluated the starting doses of OM (20 mg) and LOS (50 mg), whereas the present study evaluated both the starting and maximum OM- and LOS-approved doses. A secondary data analysis from that study showed that the change in mean 24-hour ambulatory BP was significantly greater with OM compared with LOS (–12.5/–8.5 mmHg vs. –9.0/–6.2 mmHg; $P < 0.01$) [18]; a finding that contrasts with the ABPM results in this secondary analysis where only mean 24-hour DBP was significantly greater for OM in naïve subjects (–10.9 vs. –5.5 mmHg; $P = 0.0203$).

In a randomized, double-blind, multicenter study of 287 Chinese subjects with mild-to-moderate essential hypertension comparing OM 20 mg daily versus LOS 50 mg daily, Zhu et al. [19] showed that OM provided significantly greater changes in SeDBP (–12.9 vs. –11.0 mmHg; $P = 0.035$) with similar overall tolerability. Significantly greater reductions in SeBP and BP goal achievement (BP <140/90 mmHg) with maximally titrated doses of OM (40 mg daily) compared with LOS (100 mg daily) were reported at week 8 in a 12-week randomized, double-blind, placebo-controlled study in 696 subjects with primary hypertension [5]. The change in BP was –15.2/–12.9 mmHg versus –10.9/–9.4 mmHg ($P < 0.001$), and BP goal achievement was 39.7% versus 19.8% ($P < 0.001$). By week 12, there was no significant difference in SeBP reduction or goal achievement between patients receiving OM 40 mg daily and LOS 50 mg twice daily.

Data from this subanalysis also support those from a subgroup analysis of previously treated and treatment-naïve subjects with hypertension receiving OM-based combination therapy. The BP-lowering effect was similar regardless of previous antihypertensive use [20]. The BP goal achievement of <140/90 mmHg in the Oparil et al. study was slightly higher at the maximum OM 40 mg dose (i.e., 37.7% for naïve and 35.5% for non-naïve subjects versus the 34.1% and 31.0%, respectively) observed in this secondary analysis. However, there were some notable differences between the study designs. In the Oparil et al. study, subjects in the OM 40 mg treatment group were initially given OM 40 mg and then remained on this dose for the entire 8 weeks of the study, whereas subjects in the present study were initiated on OM 20 mg and then uptitrated to 40 mg.

ABPM is considered one possible determinant of an antihypertensive agent's efficacy [21, 22] and, although there are no strict guidelines for target ABPM, the American Heart Association recommends a 24-hour BP target of <130/80 mmHg [23]. ABPM studies have shown that there are differences between ARBs with regard to their duration of action, with some ARBs demonstrating decreased efficacy during the last 4–6 hours of the dosing interval [18, 24]. Therefore, agents that provide 24-hour BP control when taken once daily should be the most efficacious approach to the treatment of subjects with hypertension [21]. Although most subjects with hypertension will require ≥2 antihypertensive medications to achieve BP control [2], the present study shows that a significant proportion of subjects were able to achieve clinically meaningful BP control in addition to significant SeBP reduction with monotherapy.

At maximum once-daily doses, OM enabled a greater proportion of subjects to achieve both their SeBP goal and 24-hour ambulatory BP target compared with LOS, while maintaining a similar tolerability profile, regardless of previous antihypertensive medication use. This finding suggests that OM may be used as an efficacious, well-tolerated, once-daily initial monotherapy to which other antihypertensives may be added for a multistep treatment algorithm. Taken together, these characteristics demonstrated by OM may also translate into a well-accepted and adopted therapy by subjects with hypertension, with the potential to increase adherence to their treatment regimen.

To assess whether any known pathophysiology differences might exist between treatment-naïve and non-naïve subjects that could affect treatment efficacy a literature search was conducted to further explore this issue. However, no studies were found that investigated such differences between naïve and non-naïve subjects and, therefore, this might be an interesting area for further research.

Limitations of the previously published parent study were that a LOS 50 mg twice-daily arm was not evaluated. Twice-daily dosing could potentially provide better 24-hour BP coverage; however, it can be argued that an agent providing 24-hour BP control with a single dose and no additional side effects may increase adherence with the prescribed medication, which could translate into improved BP-lowering efficacy. In addition, LOS is typically administered once daily in clinical practice, so the current study may be more indicative of a real-world setting. Another limitation is that ABPM was not an inclusion criterion and was only measured in a nonrandomized subgroup [17]. However, the similarity of subject demographics between the ABPM subgroup and the randomized population at baseline suggests the results of this substudy are unbiased.

CONCLUSION

Treatment with OM at the maximum recommended dose of 40 mg daily resulted in statistically significantly greater reductions in SeBP than treatment with LOS at the maximum dose of 100 mg daily. Moreover, a greater proportion of subjects achieved their SeBP target of <140/90 mmHg and ambulatory 24-hour BP goal of <130/80 mmHg, regardless of whether they were previously treated with antihypertensives or were treatment-naive and newly diagnosed with hypertension. The greater efficacy of OM treatment was achieved with tolerability similar to that of LOS.

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