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ORIGINAL ARTICLE

Efficacy of olmesartan/amlodipine combination therapy in reducing ambulatory blood pressure in moderate-to-severe hypertensive patients not controlled by amlodipine alone

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This previously unpublished, preplanned analysis investigated the efficacy of the olmesartan/amlodipine combination at different doses on 24-h blood pressure (BP) control, as well as assessed trough estimation of trough-to-peak ratio (TPR) and smoothness index (SI). Ambulatory BP monitoring was performed in patients with moderate-to-severe hypertension whose BP was inadequately controlled after 8 weeks' treatment with amlodipine 5 mg. Patients were randomized to continue with amlodipine 5 mg or to receive olmesartan/amlodipine 10/5, 20/5 or 40/5 mg for 8 weeks (Period II). Patients not achieving BP control were uptitrated to a more powerful regimen for another 8 weeks (Period III). During Period II, each olmesartan/amlodipine combination reduced 24-h systolic and diastolic BP (SBP/DBP), as well as morning and early morning SBP/DBP, significantly more than amlodipine 5 mg ($P<0.001$ for all). TPRs were higher in each olmesartan/amlodipine group than with amlodipine 5 mg, and SI values showed dose-related increases; olmesartan/amlodipine 40/5 mg produced a significantly higher SI for SBP and DBP (1.55 and 1.33, respectively) than amlodipine 5 mg (0.96 and 0.77, respectively, $P<0.0001$ for each). During Period III, uptitrated patients showed further BP reductions, which were largest in those on olmesartan/amlodipine 40/10 mg. SI values increased in uptitrated patients and were highest with olmesartan/amlodipine 40/10 mg (SBP 1.62/DBP 1.41). The olmesartan/amlodipine combination effectively reduces BP over 24 h, including the morning hours, in a dose-related manner. Compared with amlodipine alone, the olmesartan/amlodipine combination has a better 24-h coverage (TPR) and a dose-related improvement in BP lowering homogeneity (SI).
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Keywords: ambulatory blood pressure monitoring; amlodipine; Olmesartan

INTRODUCTION

Clinical trials in hypertension have repeatedly shown that adequate blood pressure (BP) control is important for the prevention of cardiovascular morbidity and mortality.[1–3] However, most patients do not achieve target BP levels, and the majority of them require combination therapy with two or more drugs in order to obtain an adequate BP reduction.[1–5] The ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) study has shown that treatment with the combination of an angiotensin-converting enzyme inhibitor (ACE-I) and a calcium channel blocker (CCB) may not only be effective in achieving BP control and well tolerated, but may also reduce cardiovascular event rates to a larger extent than an ACE-I plus diuretic combination.[6] Single-pill combinations of CCBs and angiotensin II receptor blockers (ARBs) are now available and have been reported to be widely used, well tolerated and effective treatments for controlling BP.[7,8] One advantage of these combinations, as compared with a CCB and ACE-I, is that ARBs have been shown to be as effective as ACE-Is, but better tolerated.[9]

An adequate level of BP control throughout the 24-h dosing period is important in the treatment of hypertensive patients,[10] because BP levels evaluated by ambulatory BP monitoring (ABPM) have consistently been shown to provide valuable information on cardiovascular risk, independently from clinic BP levels.[1,2,11] In particular, BP assessed during the nighttime and in the morning is closely related to the rate of cardiovascular events, and its adequate control may be important in reducing the risk of such events.[1,12,13] Furthermore, studies have shown that BP variability is an important CV risk factor, which correlates with target organ damage in a manner that is independent of mean BP values.[14] Treatments that reduce BP

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in a smooth and consistent manner to give reduced variability over 24 h and effective BP control during the early morning period may thus provide optimal protection against the BP-related risk of cardiovascular complications.[14] The development of mathematical indices like the trough-to-peak ratio (TPR) and smoothness index (SI) has provided important insights into the ability of antihypertensive therapy to provide homogeneous BP reductions.[14,15] The reproducibility of the two indices has been demonstrated, with SI established as the more reproducible of the two measures.[16,17] As the SI has been shown in clinical studies to correlate with the regression of target organ damage,[17] long-acting agents that can provide smooth and sustained BP reduction may offer additional clinical benefits in this regard.

Recently a randomized, double-blind, parallel-group multicentre study was carried out in which the ARB olmesartan medoxomil was combined with the CCB amlodipine. The primary end point and several secondary end points in this study were based on changes in BP using measurements taken in a clinic setting and showed for example that more than 70% of patients who received the combination were able to achieve the target clinic BP.[18] The present paper reports the results of a prespecified and previously unreported secondary analysis of this study[18] in a subgroup of patients in whom ABPM was carried out. The aim of this ABPM analysis was to evaluate whether and by how much an olmesartan/amlodipine combination at different doses may control BP over 24 h, and whether it might achieve a smooth BP reduction over the day and night, as assessed by TPR and SI, in patients with moderate-to-severe hypertension not adequately controlled with amlodipine monotherapy.

METHODS

Study population

This study was a randomised, double-blind, parallel-group, multicentre trial conducted at 75 centers in Belgium, Finland, Italy, Germany, the Netherlands, the United Kingdom, Poland, Russia and the Ukraine. The trial was registered on the clinicaltrials.gov website as NCT00220233, and details of the methodology and primary results have been published previously.[18] In brief, male and female patients aged $\geqslant$18 years with moderate-to-severe hypertension were included: patients previously untreated or treated with drugs other than amlodipine 5 or 10 mg after the 1–2 week washout period had to fulfill the following criteria: seated DBP (SeDBP) $\geqslant$100 mm Hg, seated SBP (SeSBP) $\geqslant$160 mm Hg, 24-h DBP $\geqslant$84 mm Hg with $\geqslant$30% of daytime DBP $>$90 mm Hg; patients already taking amlodipine 5 mg or 10 mg had to fulfill the following criteria: moderate-to-severe hypertension before amlodipine therapy, SeDBP $\geqslant$90 mm Hg, SeSBP $\geqslant$140 mm Hg and 24-h DBP $\geqslant$80 mm Hg with $\geqslant$30% of daytime DBP $>$85 mm Hg while on continued treatment with amlodipine.

Key exclusion criteria[18] included secondary or malignant hypertension; mean SeDBP $>$115 mm Hg or mean SeSBP $>$200 mm Hg; nonresponsiveness to at least two conventional antihypertensive treatments; major co-morbidities including cardiovascular disease other than hypertension; contraindications to amlodipine or olmesartan medoxomil or other dihydropyridines or ARBs; and a history of poor efficacy on drugs from one of these classes.

Study design

The study consisted of three main treatment periods, each lasting 8 weeks (Figure 1). Eligible patients entered a period of open-label treatment during which they received amlodipine 5 mg once daily (Period I, weeks 0–8). At the end of open-label treatment, patients with a mean SeDBP $>$115 mm Hg or mean SeSBP $>$200 mm Hg were withdrawn from the study, and patients

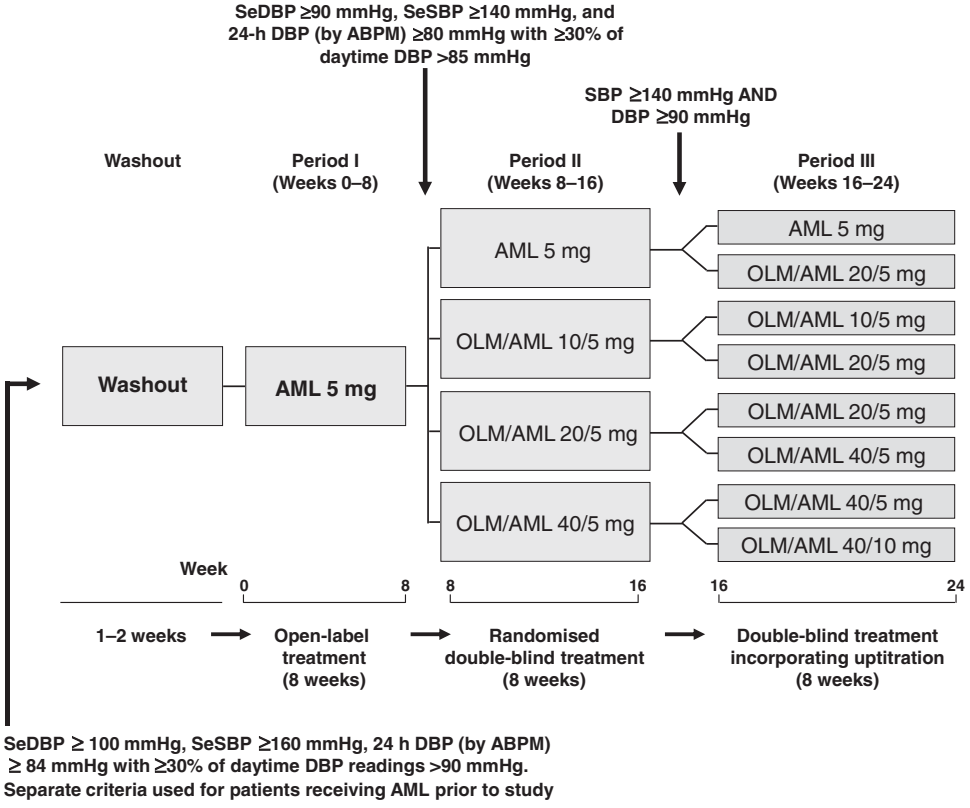

Figure 1 Study design.[18] AML, amlodipine; OLM, olmesartan medoxomil.

whose BP was not adequately controlled (mean SeDBP ⩾90 mm Hg and mean SeSBP ⩾140 mm Hg and a mean 24-h DBP ⩾80 mm Hg with ⩾30% of daytime readings >85 mm Hg) entered a period of double-blind treatment (Period II, weeks 8–16) in which they were randomised to continue with amlodipine 5 mg or to receive one of the following combinations: (i) olmesartan medoxomil/amlodipine 10/5 mg, (ii) olmesartan medoxomil/amlodipine 20/5 mg or (iii) olmesartan medoxomil/amlodipine 40/5 mg. This was followed by a further 8 weeks of double-blind treatment (Period III, weeks 16–24) during which patients who had achieved an adequate level of SeBP control (SBP <140 mm Hg and DBP <90 mm Hg) at the end of Period II (week 16) continued on the same double-blind treatment regimen from Period II, while those who did not meet the SeBP criteria for BP control underwent uptitration at week 16: patients on amlodipine 5 mg and olmesartan/amlodipine 10/5 mg went on to receive olmesartan medoxomil/amlodipine 20/5 mg; those on olmesartan/amlodipine 20/5 mg went on to receive olmesartan medoxomil/amlodipine 40/5 mg and those on olmesartan/amlodipine 40/5 mg were uptitrated to 40/10 mg (Figure 1). Patients were instructed to take their treatment at the same time each day (±2 h) between 0600 and 1100 hours. Investigators were aware that patients who did not achieve BP control in Period II received a higher dose combination in Period III, but the treatment regimen assignments remained double blind. Clinic visits were scheduled at the patient's normal dosing time so that trough BP measurements were obtained. Randomization to study treatments was based on a computer-generated randomization schedule using a block size of eight. Patients and investigators were blinded to treatment assignment throughout the study, and the randomization code was not revealed until after the database had been locked.

Measurements

Both clinic BP measurements and 24-h ABPM were performed at weeks 0, 8, 16 and 24. Clinic BP was measured using a mercury sphygmomanometer with the patient in a sitting position after having rested for 10 min. Three measurements were obtained at least 1 min apart, and their mean was used as the clinic BP value for that visit.

Twenty-four-h ABPM was performed using a validated device (TM-2430, A&D, Komaki, Japan). The recording was scheduled to start after study medication intake, which occurred between 0600 and 1100 hours, 24 h before the scheduled visit and was stopped during the visit. Automatic measurements were set at 15-min intervals from 0600 to 2159 hours (daytime) and at 30- min intervals from 2200 to 0559 hours (nighttime). During the recording, patients refrained from physical exertion and filled in a diary to provide information on their activity, sleeping phases and the time of medication intake. ABPM recordings were excluded from the analyses if the percentage of valid readings was below 70% or if the total number of valid readings was below 60.

Efficacy end points

Efficacy analyses were performed on the full analysis set (FAS): the subset of intent-to-treat (ITT) subjects in whom ABPM recordings of adequate quality were available at all time points (weeks 0, 8, 16 and 24). As reported previously, the primary efficacy end point of the study was the change in seated clinic DBP, measured using conventional sphygmomanometry, from the end of open-label amlodipine 5 mg treatment (week 8, defined as 'baseline') to the end of the 8-week, double-blind combination treatment period (week 16). Predefined secondary efficacy measures included the mean change from baseline (week 8) to weeks 16 and 24 in daytime, nighttime, and 24-h SBP

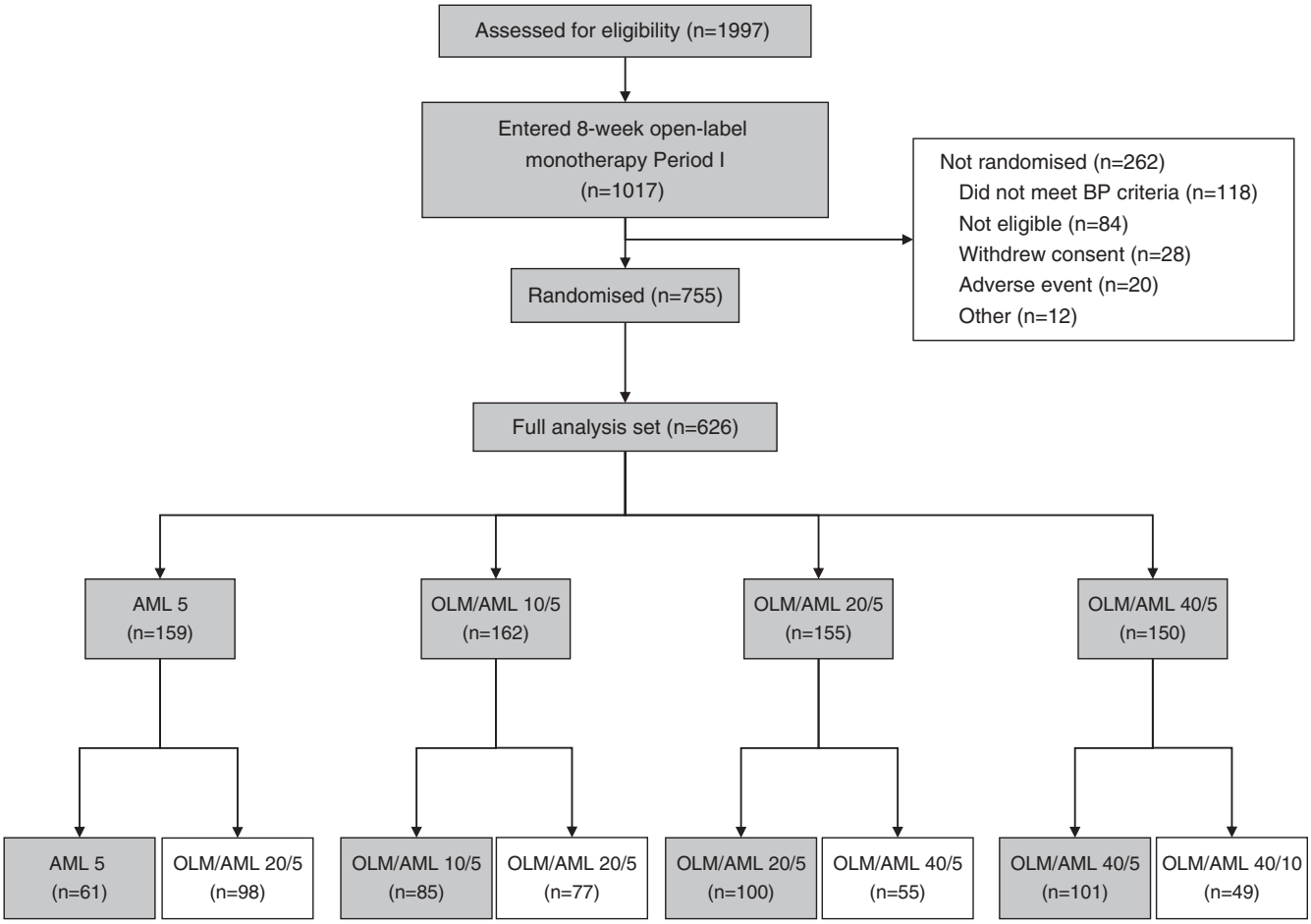

Figure 2 Disposition of patients in the ambulatory blood pressure monitoring (ABPM) analysis set through the study to week 24 (Periods I, II and III). AML, amlodipine; OLM, olmesartan medoxomil.

Table 1 Study population demographics and characteristics (mean and standard deviation) at week 0

	AML 5 mg	*OLM/AML 10/5 mg*	*OLM/AML 20/5 mg*	*OLM/AML 40/5 mg*	*All*
Parameter	n = *159*	n = *162*	n = *155*	n = *150*	n = *626*
Age (years)	55.9 (9.5)	56.2 (9.5)	55.3 (10.4)	55.6 (9.0)	55.8 (9.6)
Male (%)	62.3	64.2	70.3	56.0	63.3
BMI, $kg\,m^{-2}$	29.0 (3.7)	29.2 (3.7)	28.6 (4.0)	28.9 (3.9)	28.8 (3.8)
HR	72.8 (10.1)	72.4 (8.6)	72.4 (9.6)	72.5 (8.8)	72.5 (9.3)
Clinic BP					
SBP	166.2 (12.0)	164.5 (11.0)	164.4 (10.9)	163.2 (10.7)	164.6 (11.2)
DBP	102.1 (5.4)	101.9 (5.3)	101.7 (5.5)	102.0 (5.6)	101.9 (5.4)
Ambulatory BP					
24-h SBP	144.7	143.6	142.3	144.1	143.7
24-h DBP	89.7	89.7	89.3	89.9	89.6
Daytime SBP	150.5	148.9	148.0	150.2	149.4
Daytime DBP	94.3	94.3	94.2	94.9	94.4
Nighttime SBP	131.5	131.3	129.6	130.4	130.7
Nighttime DBP	79.2	78.9	78.5	78.5	78.8

Abbreviations: AML, amlodipine; BMI, body mass index; BP, blood pressure; DBP, diastolic BP; HR, heart rate; OLM, olmesartan; SBP, systolic BP.

and DBP, assessed by 24-h ABPM. Additional efficacy variables considered in the present analysis included assessment of early morning SBP and DBP (mean values between 0400 and 0700 hours); morning SBP and DBP (mean values between 0800 hours and noon); TPR and SI. TPR and SI were computed at weeks 16 and 24 in the subgroup of subjects not receiving any antihypertensive treatment at week 0 (subjects allowed to take amlodipine at week 0 were excluded). TPR for each visit was computed separately for SBP and DBP as the trough BP change from week 0 (when the subject was not on any antihypertensive treatment) divided by the peak BP change from week 0. Peak BP change was calculated by taking the average of the two consecutive largest hourly BP reductions in the time window between the 2nd and the 8th hour after drug intake. Trough BP change was calculated as the average of BP reductions in the 23rd and 24th hour after drug intake. TPR was computed for the entire population and for the subgroup of responders, that is, subjects with a SBP and DBP reduction at peak of at least 10 and 5 mm Hg, respectively. SI for any time point was calculated for SBP and DBP as the ratio between the mean of the hourly reductions in BP from week 0 to this time point, and the s.d. of these hourly reductions.

Sample size

Sample size was based on the primary outcome of the study (change in seated clinic DBP from week 8 to week 16) and was calculated to achieve a statistical power of 80% after adjusting for a dropout rate of 15%, assuming a difference of $\geqslant$3 mm Hg between the effects on seated DBP of olmesartan medoxomil/amlodipine combination treatment and amlodipine 5 mg after 8 weeks of treatment, a common s.d. of 7.5 mm Hg, and an overall type I error of 0.05, with adjustment for multiplicity. This required a total of 632 patients (158 per treatment group).

Methods of statistical analysis

All statistical ABPM efficacy analyses were preplanned and conducted on the ABPM analysis set consisting of the subset of 626 patients (the FAS) of the study, in whom ABPM recordings of adequate quality were available at all visits (weeks 0, 8, 16 and 24). Continuous parameters were characterized by means and s.d. at baseline (week 8) and at the end of study Periods II and III (weeks 16 and 24); changes in these parameters from baseline to the end of each study period were described in the same way. Categorical variables were described by absolute and relative frequencies. Most results were presented by treatment group in Period II (week 8 to week 16); some tables and figures were further stratified according to titration status in Period III. For relevant efficacy end points, comparisons between treatment groups were based on statistical least squares modeling, including the corresponding baseline value as a covariate in each model. Differences between treatments were estimated as baseline-adjusted differences and were tested as linear contrasts within the statistical model. Two-sided *P*-values were used and, without adjustment for multiplicity, compared with the alpha level of 0.05 in the sense of descriptive data analysis.

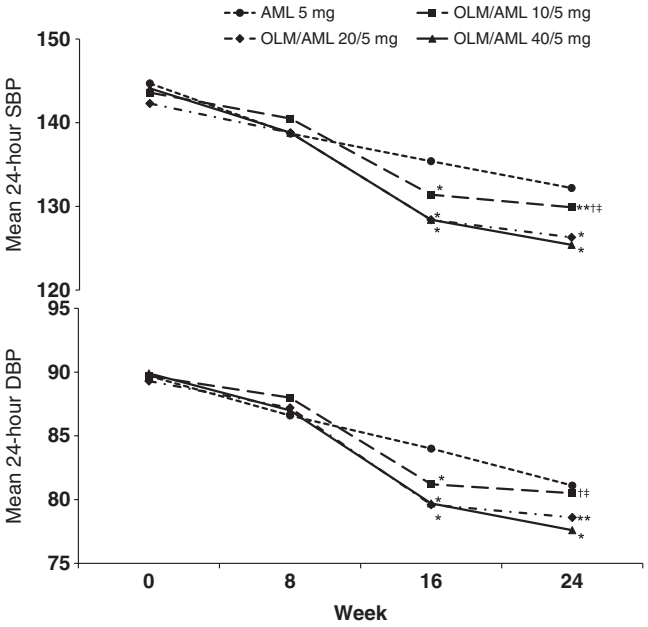

Figure 3 Mean 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) at study start and at the end of Periods I, II and III (Weeks 0, 8, 16 and 24, respectively). ΔSBP, Week 8–16: **P*<0.0001 (OLM/AML 10/5, 20/5 and 40/5 mg *vs.* AML 5 mg); Week 8–24 **P*<0.0001 (OLM/AML 20/5 and 40/5 mg *vs.* AML 5 mg), ***P*=0.0057 (OLM/AML 10/5 *vs.* AML 5 mg), †*P*=0.0193 (OLM/AML 10/5 *vs.* OLM/AML 20/5 mg) ‡*P*=0.0019 (OLM/AML 10/5 *vs.* OLM/AML 40/5 mg). ΔDBP, Week 8–16: **P*<0.0001 (OLM/AML 10/5, 20/5 and 40/5 mg *vs.* AML 5 mg); Week 8–24: **P*<0.0001 (OLM/AML 40/5 mg *vs.* AML 5 mg), ***P*=0.0002 (OLM/AML 20/5 mg *vs.* AML 5 mg), †*P*=0.0002 (OLM/AML 10/5 *vs.* OLM/AML 20/5 mg), ‡*P*=0.0008 (OLM/AML 10/5 *vs.* OLM/AML 40/5 mg).

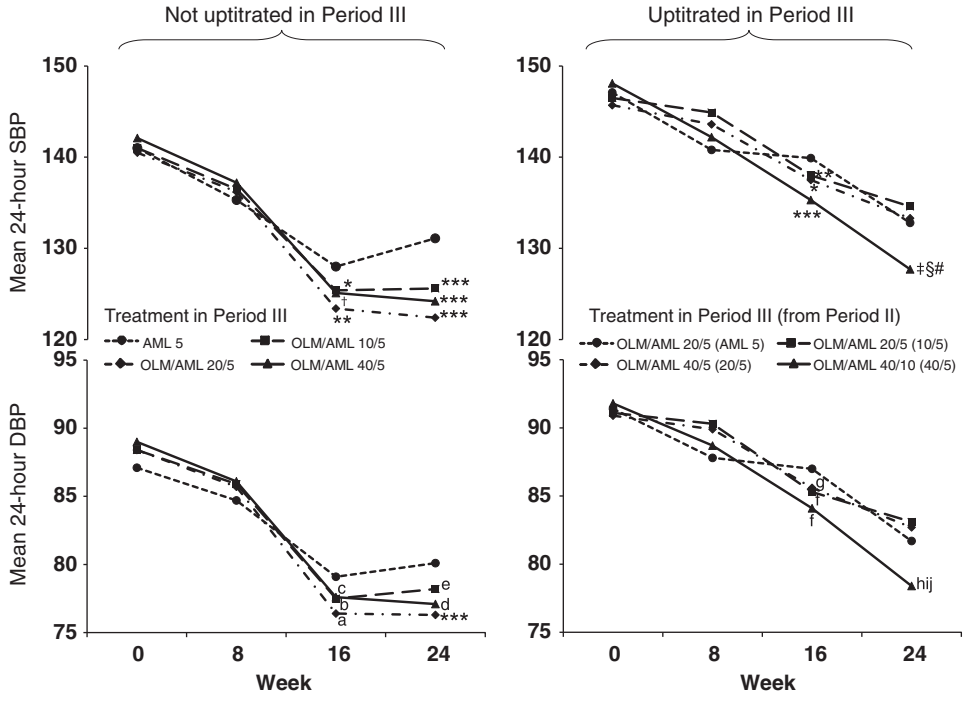

Figure 4 Mean 24-h systolic blood pressure (SBP) and diastolic blood pressure (DBP) at study start and at the end of Periods I, II and III (Weeks 0, 8, 16 and 24, respectively) in patients who were uptitrated during Period III, and in patients who were not uptitrated during Period III and who remained on the treatment that they received during Period II. ΔSBP in patients who were not uptitrated, Week 8–16: $^{*}P=0.0275$ (OLM/AML 10/5 *vs.* AML 5 mg), $^{**}P=0.0003$ (OLM/AML 20/5 *vs.* AML 5 mg), $^{\dagger}P=0.0057$ (OLM/AML 40/5 *vs.* AML 5 mg), Week 8–24: $^{***}P\leqslant0.0001$ (OLM/AML 10/5, 20/5 and 40/5 mg *vs.* AML 5 mg). ΔSBP in patients who were uptitrated, Week 8–16: $^{***}P<0.0001$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 20/5 mg [AML 5 in Period II]), $^{**}P=0.0007$ (OLM/AML 20/5 [10/5 in Period II] *vs.* 20/5 mg [AML 5 in Period II]), $^{*}P=0.0035$ (OLM/AML 40/5 [20/5 in Period II] *vs.* 20/5 mg [AML 5] in Period II) Week 8–24: $^{\ddagger}P=0.0032$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 20/5 mg [AML 5 in Period II]), $^{\S}P=0.0266$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 40/5 mg [20/5 in Period II]), $^{\#}P=0.0077$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 20/5 mg [10/5] in Period II). ΔDBP in patients who were not uptitrated, Week 8–16: $^{a}P=0.0011$ (OLM/AML 20/5 *vs.* AML 5 mg), $^{b}P=0.0305$ (OLM/AML 20/5 *vs.* AML 5 mg), $^{c}P=0.0272$ (OLM/AML 40/5 *vs.* AML 5 mg), Week 8–24: $^{***}P<0.0001$ (OLM/AML 20/5 *vs.* AML 5 mg), $^{d}P=0.0007$ (OLM/AML 40/5 *vs.* AML 5 mg), $^{e}P=0.0266$ (OLM/AML 10/5 *vs.* AML 5 mg). ΔDBP in patients who were uptitrated, Week 8–16: $^{f}P=0.0008$ (OLM/AML 40/10 [40/5 in Period II] and 20/5 [10/5 in Period II] *vs.* 20/5 mg [AML 5 in Period II]), $^{g}P=0.0115$ (OLM/AML 40/5 [20/5 in Period II] *vs.* 20/5 mg [AML 5] in Period II) Week 8–24: $^{h}P=0.0016$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 20/5 mg [AML 5 in Period II]), $^{i}P=0.0012$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 20/5 mg [10/5 in Period II]), $^{j}P=0.0038$ (OLM/AML 40/10 [40/5 in Period II] *vs.* 40/5 mg [20/5] in Period II).

RESULTS

Of 1997 patients screened, 1017 entered open-label treatment with amlodipine 5 mg (Period I), 755 were randomized to 8 weeks of double-blind treatment (Period II), and 746 patients received at least one dose of double-blind study medication during Period II and comprised the ITT population. Of these, 626 had good quality ABPM recordings at all study visits, including the last visit in Period III, and comprised the FAS in the present analysis. The flow of participants in the FAS through the study is shown in Figure 2. Demographics and baseline characteristics are detailed in Table 1.

The results with regard to the primary efficacy measure of the study, that is, change in seated clinic DBP at week 16 as well as to other measures of clinic BP obtained in the FAS did not differ importantly from those reported in the paper by Volpe *et al.*[18]

During treatment with open-label amlodipine 5 mg (Period I), significant reductions in 24-h, daytime and nighttime BP occurred. Subsequently, in patients who had not shown an adequate level of BP response during Period I, addition of olmesartan in Period II was associated with a significant decrease in ambulatory BP compared with subjects who were randomized to continue with amlodipine 5 mg alone. Patients treated with olmesartan/amlodipine 10/5, 20/5 and 40/5 mg showed adjusted mean reductions in 24-h SBP of 8.6, 10.6 and 10.6 mm Hg, respectively, compared with a reduction of 3.5 mm Hg in those who were randomized to continue on amlodipine 5 mg ($P<0.0001$ *vs.* each olmesartan/amlodipine combination). The same combination groups showed adjusted mean reductions in 24-h DBP of 6.5, 7.5 and 7.4 mm Hg, respectively, compared with a reduction of 2.8 mm Hg in patients who received amlodipine 5 mg ($P<0.0001$ *vs.* each olmesartan/amlodipine combination). The decreases in 24-h SBP and DBP were not significantly different between the different dosage combinations of olmesartan/amlodipine (Figure 3). In Period III, in patients who had seated clinic SBP and DBP under control and thus remained on the same therapeutic regimen as in Period II, 24-h BP remained generally unchanged compared with Period II, except for the amlodipine 5 mg group, in which there was a tendency for 24-h BP to increase (Figure 4). In patients who had clinic SBP and DBP levels above the target, treatment uptitration produced a further additional reduction in 24-h SBP/DBP of 7.1/5.3 mm Hg in patients uptitrated from amlodipine 5 mg to olmesartan/amlodipine 20/5 mg; of 4.2/2.9 mm Hg in patients uptitrated from olmesartan/amlodipine 20/5 mg to olmesartan/amlodipine 40/5 mg and of 7.6/5.7 mm Hg in patients uptitrated from olmesartan/amlodipine 40/5 mg to olmesartan/amlodipine 40/10 mg (Figure 4). The reductions in 24-h SBP/DBP seen in patients who were uptitrated to olmesartan/amlodipine 40/10 mg were significantly greater than those seen in each of the other groups

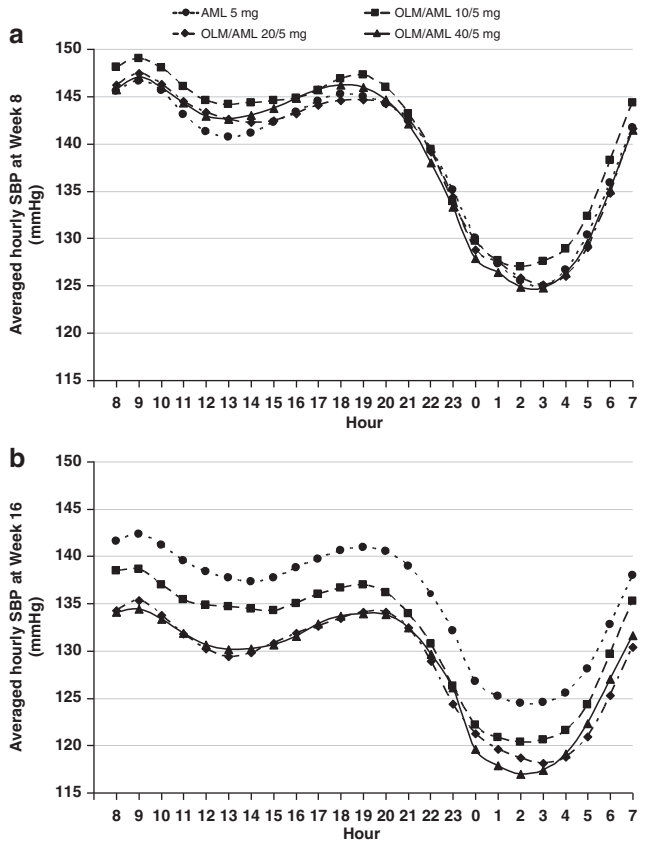

Figure 5 Twenty-four-hour ambulatory averaged hourly systolic blood pressure (SBP) profiles (mm Hg) at (**a**) the start of Period II (week 8) and (**b**) the start of Period III (week 16) before patients in the randomized groups received the first dose of double-blind treatment in the respective treatment period.

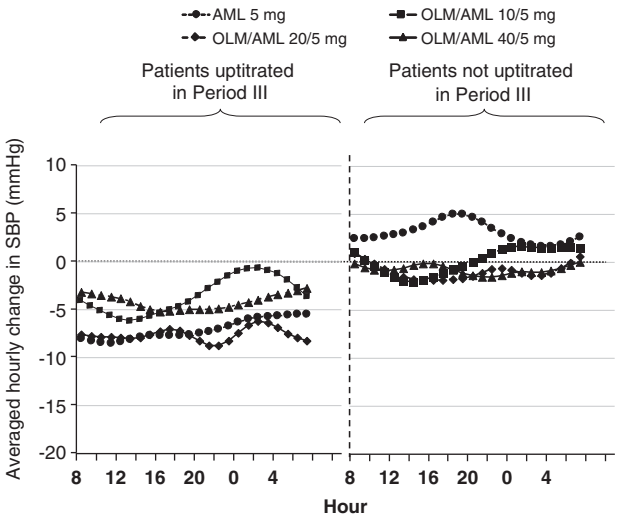

Figure 6 Profiles of averaged hourly changes in 24-h ambulatory systolic blood pressure (SBP) between the start and end of Period III (weeks 16 and 24) in patients who were uptitrated during Period III, and in patients who were not uptitrated and were maintained on the treatment that they were allocated to during Period II.

($P = 0.0266$ for changes in SBP; $P = 0.0038$ for changes in DBP). At the start of week 8, before patients received the first dose of double-blind therapy, the averaged hourly mean SBP profiles of the four treatment groups were similar (Figure 5). However, at week 16 (that is, the end of Period II), the averaged hourly SBP profile of patients who received amlodipine 5 mg was higher than that of those who were randomized to olmesartan/amlodipine combination therapy (Figure 5). The profile of averaged hourly changes in SBP over 24 h from the beginning to end of Period III further highlighted the differences between mean SBP reductions in patients who were uptitrated and those who remained on their Period II regimen (Figure 6). Data on the ABPM reductions in the early morning (0400–0700 hours) and morning (0800 hours to noon) during Period II are shown in Table 2. In all combination treatment groups, the reductions in both early morning and morning ambulatory BP were significantly larger than in the patients remaining on amlodipine. The reductions in morning BP were broadly comparable to the reductions in mean daytime values, whereas the reductions in early morning BP were similar to the reductions in nighttime BP values. Table 3 shows the week 16 TPR and mean SI values in the subgroup of subjects who were not already receiving antihypertensive therapy at week 0. At week 16, the SI values in the groups that received olmesartan/amlodipine combination therapy showed an increasing trend compared with patients who received amlodipine 5 mg, with the highest dose of olmesartan/amlodipine (40/5 mg) having the highest SI values ($P < 0.0001$ for combination groups *vs.* amlodipine 5 mg for both SBP and DBP SI values). Between week 16 and week 24, SI values decreased in patients treated with amlodipine 5 mg who were not uptitrated (Data not shown). In contrast, SI values increased in subjects who had their therapy uptitrated (Data not shown). At week 24, SI values were highest in patients who were uptitrated to olmesartan/amlodipine 40/10 mg (SBP SI: 1.62; DBP SI: 1.41). Within each combination treatment group, SI values were higher in patients who were uptitrated than in those who were not uptitrated

Safety

The safety and tolerability of olmesartan/amlodipine combination therapy in the primary analysis of this study have been previously reported and shown to be consistent with that of an ARB and a CCB.[18] The most frequently reported adverse events during double-blind treatment included peripheral edema, headache, dizziness and back pain, and the frequency of these events (3.5%, 3.4%, 2.7% and 2.6%, respectively) in the ABPM analysis set described here was consistent with those findings. Furthermore, only a single case of hypotension was reported as an adverse event in the patients who comprised the ABPM analysis set.

DISCUSSION

The assessment of BP changes by ABPM in a subgroup of patients was prespecified in the statistical plan for this study, but these findings were not described in the initial publication that focused on changes in primary and secondary end points based on BP measurements taken in a clinic setting.[18] The main finding of this preplanned analysis is that combination therapy with olmesartan/amlodipine is effective in smoothly reducing BP throughout 24-h in patients with moderate-to-severe hypertension whose BP was not adequately controlled with amlodipine 5 mg. The degree of 24-h BP reduction with this combination was proportional to the administered dose, with the largest reductions seen in patients who were treated with olmesartan/amlodipine 40/10 mg. This demonstration was clearly obtained thanks to the complex design of this study, which allowed to account for a possible confounding effect of time by considering the BP levels of patients whose treatment was not uptitrated.

Table 2 Morning (0800 hours to noon) and early morning (0400–0700 hours a.m.) blood pressure in the four study groups

	Morning				*Early morning*			
	AML 5 mg	*OLM/AML 10/5 mg*	*OLM/AML 20/5 mg*	*OLM/AML 40/5 mg*	*AML 5 mg*	*OLM/AML 10/5 mg*	*OLM/AML 20/5 mg*	*OLM/AML 40/5 mg*
SBP								
Week 8	145.3	147.9	146.2	145.9	130.8	132.8	129.6	130.2
Week 16	141.3	137.4	133.9	133.5	128.6	124.9	121.6	122.5
LSM change from W8 to W16	−3.99	−10.53	−12.24	−12.41	−2.19	−7.86	−8.07	−7.67
P-value for change *vs.* AML 5 mg		<0.0001	<0.0001	<0.0001		=0.0002	<0.0001	<0.0001
DBP								
Week 8	93.1	95.3	94.9	94.5	80.6	82.4	80.3	80.6
Week 16	90.4	87.5	85.7	85.8	79.0	76.6	74.6	75.1
LSM change from W8 to W16	−2.73	−7.79	−9.22	−8.67	−1.63	−5.77	−5.76	−5.50
P-value for change *vs.* AML 5 mg		<0.0001	<0.0001	<0.0001		=0.0006	<0.0001	<0.0001

Abbreviations: AML, amlodipine; BP, blood pressure; DBP, diastolic BP; LS: least squares; OLM, olmesartan; SBP, systolic BP.

Table 3 Trough to peak ratios (TPRs) and smoothness indexes (SIs) at week 16

Group	*SBP TPR*	*DBP TPR*	*SBP SI*	*DBP SI*
AML 5 mg	0.68	0.65	0.96	0.77
OLM/AML 10/5 mg	0.77	0.78	1.09	0.99
OLM/AML 20/5 mg	0.80	0.72	1.32	1.20
OLM/AML 40/5 mg	0.78	0.71	1.55	1.33

Abbreviations: AML, amlodipine; BP, blood pressure; DBP, diastolic BP; OLM, olmesartan; SBP, systolic BP; SI, smoothness index; TPR, trough to peak ratio.

Epidemiological studies indicate that a linear relationship exists between BP and the risk of cardiovascular disease, this being particularly the case when focusing on 24-h ambulatory BP. To obtain adequate BP reduction, in particular over the entire 24-h period, a combination of two or more antihypertensive drugs is required in most patients.[1–3,5,18] Combinations involving a CCB with a blocker of the renin–angiotensin–aldosterone system (RAAS), for example, an ARB or ACE-I, are among those recommended by the guidelines[19,20] and are becoming increasingly used in clinical practice. Their usefulness is based on a favorable pharmacodynamic profile (different mechanisms of antihypertensive action favor efficacy, while RAAS blockade counteracts edema formation caused by dihydropyridines), which translates into clinical benefits in terms of effectiveness in achieving BP control and tolerability.[21] Furthermore, as recently demonstrated in the ACCOMPLISH trial,[6] the combination of a RAAS blocker (the ACE-I benazepril) and amlodipine may reduce cardiovascular event rates to a larger extent than the same RAAS blocker combined with a diuretic (hydrochlorothiazide), despite similar achieved SBP and DBP levels (between group difference: 0.9 mm Hg for SBP and 1.1 mm Hg for DBP). The reasons for this difference in risk reduction are not understood at present, but several factors might have a role, including the adverse impact of thiazide diuretics on metabolic risk[22] or, as reported by one study, the lower efficacy of diuretics in suppressing the morning BP elevation.[23] It would be reasonable to expect similar benefits from an ARB/CCB combination, probably accompanied by better tolerability. This is because ARB treatment has equivalent efficacy in reducing BP and cardiovascular risk to that of an ACE-I, but its use is associated with significantly fewer adverse events, notably angioedema and cough as shown in the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) study.[9]

Our study made use of ABPM for assessing the antihypertensive efficacy of CCB-ARB combinations. This method is currently used in many studies on antihypertensive drugs for several reasons. First, a number of prognostic studies have shown that ambulatory BP may have superior prognostic value compared with clinic BP both in untreated and treated subjects.[24,25] Second, this method allows the assessment of BP control throughout the full 24-h period, also during clinically important subperiods, not easy to monitor with other available techniques, such as the nighttime and the morning hours. Third, it allows the duration and homogeneity of antihypertensive action to be assessed through the calculation of indices such as TPR and SI.[15]

One important aspect of our analysis is the assessment of the 24-h BP lowering coverage of the study treatments and the homogeneity of BP reduction occurring throughout the 24-h period. At the end of Period II, TPR exceeded 60% in all treatment groups and was higher (70–80%) in the combination arms, while SI values increased progressively from amlodipine monotherapy to the most powerful combination of olmesartan 40 mg with amlodipine 5 mg and was equal or higher than one for all combinations used in the study. The achievement of these high TPR and SI values confirm that all olmesartan/amlodipine combinations were characterized by good 24-h coverage and provided a smooth BP reduction throughout 24 h. This represents a further advantage because a smooth and sustained BP reduction may help counteract increased BP variability and the associated increased risk of organ damage and subsequent clinical events in hypertensive patients.[15,26,27] Indeed, it has been shown that higher SI values with antihypertensive treatment correlate with regression of left ventricular hypertrophy (SAMPLE study)[17] and reduction of intima-media thickness.[28]

In our study, the combination of amlodipine with the ARB olmesartan decreased not only 24-h BP levels but also early morning and morning BP levels. This finding is important in the light of previous reports suggesting that either morning blood pressure surge[13,29] or morning hypertension[30] may be an independent risk factor for cardiovascular events. As the methodology of morning surge assessment is far from being defined, we focused on assessing the average BP level in two subperiods of the morning hours that is, (1) early morning (0400–0700 hours), which in most subjects lies in the preawake period and is associated with a sympathetic activation

related to the higher frequency of Rapid Eye Movement (REM) sleep, and with an increased activity of several hormonal systems (including RAAS or cortisol secretion),[31] which might contribute to the increased rate of cardiovascular events observed in this period; (2) morning (0800 hours to noon) corresponding to the first hours of subjects daily activity and associated commonly with significant BP variations due to changes in posture and physical activity. In both these periods, BP reductions from baseline were comparable to those occurring in the overall nighttime (for early morning BP) or daytime (for morning BP). This suggests that the therapies applied in the study did not lose their efficacy in these critical periods even if these periods coincide with the terminal portion of the once daily dosing interval (where short acting drugs lose their antihypertensive activity) or with its beginning (where the full antihypertensive action of the morning dose has not developed yet). The nighttime BP dipping pattern is also an independent risk factor for cardiovascular events, an increased incidence of cardiovascular events being associated with reverse dippers compared with dippers.[32] However, analysis of the nighttime BP dipping pattern was beyond the scope of this study.

Tolerability is an important factor determining the adherence to and persistence of hypertensive treatment. Treatment with amlodipine, a dihydropyridine CCB, is frequently associated with adverse symptoms, that is, flushing, ankle edema, headache and palpitation, caused by drug-induced vasodilation.[33] Although these symptoms usually do not lead to major complications, their presence affects patients' quality of life and leads to a reduction in treatment adherence[34] and relatively high treatment discontinuation rates. In contrast, ARBs are the best-tolerated class of antihypertensive drugs and not only reduce BP without inducing a reflex increase in sympathetic nervous activity (and resulting tachycardia or palpitations)[35] but also, probably through inducing venous vasodilation, diminish the CCB-induced increase in hydrostatic pressure[36] and thereby reduce the frequency of edema.[8,37] This favorable safety profile of the CCB-ARB combination was clearly confirmed in our study where very few adverse events occurred even in subjects treated with the higher doses of both drugs. In particular, only one event of hypotension was reported as an adverse effect. This finding is probably not only related to the characteristics of the drug combinations used in the study, but also to the fact that only patients with both elevated clinic BP and ambulatory BP entered Period II, thus excluding subjects with white coat hypertension, in whom excessive BP lowering might occur.

A potential limitation of our study is that its duration did not allow us to demonstrate the long-term persistence of difference in efficacy between different antihypertensive regimens. However, it was previously shown that the combination of amlodipine and olmesartan maintained its antihypertensive efficacy over 44 weeks with no evidence of escape phenomenon.[38] Moreover, in the previous report of the present study it was shown that after an additional 8 weeks of follow-up, no significant changes in clinic BP occurred in patients controlled at week 16 and that those who were not controlled responded to another treatment uptitration with further clinic BP reduction.[18]

In conclusion, the combination of olmesartan medoxomil and amlodipine is safe and effective in achieving and maintaining good BP control over 24 h in patients with moderate-to-severe hypertension not controlled with amlodipine 5 mg monotherapy. In these patients, the combination of olmesartan and amlodipine not only reduced mean 24-h BP but also guaranteed a homogeneous distribution of BP reduction throughout the 24-h period, as shown by the increases in TPR and SI, which have been shown to be associated with reduced BP variability. This further highlights the potential advantages of introducing a combination therapy based on long-acting CCBs and ARBs in preventing hypertensive target organ damage and in reducing the risk of cardiovascular events.

CONFLICT OF INTEREST

Grzegorz Bilo and Gianfranco Parati have received lecture fees and honoraria for consultancy from Daiichi Sankyo Europe. Satoshi Hoshide has no disclosures to make. Winfried Koch provided statistical analysis and interpretation on behalf of Daiichi Sankyo GmbH.

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