

# Effects of combining azilsartan medoxomil with amlodipine in patients with stage 2 hypertension

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**Objective** The aim of the study was to measure the effects on blood pressure (BP) of the angiotensin receptor blocker azilsartan medoxomil, in 40 and 80 mg doses, combined with 5 mg of the calcium channel blocker amlodipine and to compare these effects with placebo plus amlodipine 5 mg.

**Methods** This was a randomized, controlled, double-blind study of 6 weeks' duration in 566 patients with stage 2 hypertension. The primary endpoint was 24-h systolic BP by ambulatory monitoring.

**Results** The mean age of the participants was 58 years; men and women were equally represented, and baseline 24-h BP (153–154/93 mmHg) and clinic BP (165–166/94–95 mmHg) were similar across the three treatment groups. After 6 weeks, 24-h BP decreased by 25/15 mmHg in both the azilsartan medoxomil/amlodipine 40/5 and 80/5 mg groups. These reductions were each greater than the 14/8 mmHg decrease with placebo plus amlodipine 5 mg ( $P \leq 0.001$  for both comparisons). All treatments were well tolerated, and adverse events did not increase with the azilsartan medoxomil doses. Edema or fluid retention was

less common in both combination groups (2.6 and 2.7%) than with placebo plus amlodipine (7.6%).

**Conclusion** Coadministration of azilsartan medoxomil with amlodipine was well tolerated and led to meaningful additional BP reductions compared with placebo plus amlodipine. *Blood Press Monit* 19:90–97 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Angiotensin receptor blockers are now used widely for treatment of hypertension. They have actions that provide cardiovascular, stroke and renal protection [1–4], and their blood pressure (BP)-lowering efficacy appears to cover the full age spectrum of hypertension [5,6]. However, achieving recommended goal BPs during antihypertensive treatment requires combination therapy in a large proportion of patients [7]. Most of the available fixed-dose two-drug combinations include a thiazide or a thiazide-like diuretic as one of the agents, a strategy that has been recommended by guidelines in the USA [7].

More recently, however, fixed combinations based on either ACE inhibitors or angiotensin receptor blockers have included the dihydropyridine calcium channel blocker amlodipine [8–12]. These amlodipine combinations have been shown to have BP-lowering efficacies similar to diuretic combinations. Among the reasons for

developing these newer combinations is that they avoid potential metabolic side effects of diuretic combinations and provide a therapeutic benefit for patients with such concomitant conditions as angina, for whom agents such as amlodipine would be indicated.

In addition, these newer combinations can offer some of the nonhemodynamic actions that might be associated with amlodipine [13,14]. In fact, in two major clinical outcomes trials where combinations of amlodipine with ACE inhibitors were compared with the combination of bendroflumethiazide with a  $\beta$ -blocker [15] or hydrochlorothiazide with an ACE inhibitor [16], the amlodipine combinations were associated with significantly lower cardiovascular event rates. The combination of blockers of the renin–angiotensin system with calcium channel blockers such as amlodipine has been recommended in the recent British guidelines on treating hypertension [17]. However, outcomes trials with combinations of amlodipine and angiotensin receptor blockers have not been conducted.

The angiotensin receptor blocker azilsartan medoxomil recently became available for treatment of hypertension and has been shown to be highly efficacious in reducing

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BP. This agent is a prodrug that is hydrolyzed to azilsartan, a powerful angiotensin receptor blocker with an elimination half-life of 12 h [18]. In a series of comparative studies, azilsartan medoxomil as a single agent was found to be more efficacious than other widely used angiotensin receptor blockers at their maximum approved doses [19,20]. These studies included comparisons with olmesartan, which itself appears to be one of the most efficacious agents in the class [21,22].

The present study was carried out as an initial exploration of the additional BP-lowering effects of azilsartan medoxomil combined with amlodipine. All patients in the trial received amlodipine 5 mg daily, the most widely used dose of this agent. Patients were randomized into three groups: those who received placebo plus amlodipine and those who received either 40 or 80 mg daily of azilsartan medoxomil plus amlodipine. We compared the antihypertensive effects of these therapeutic strategies using both ambulatory blood pressure monitoring (ABPM) and conventional clinic BP measurements, and also recorded adverse events.

## Methods

### Study design

This was a 6-week, randomized, double-blind, multicenter study designed to evaluate the antihypertensive efficacy and safety of the 40 and 80 mg doses of azilsartan medoxomil combined with 5 mg of the calcium channel blocker amlodipine, compared with placebo plus amlodipine 5 mg daily. The protocol conformed to the Declaration of Helsinki and regional regulatory guidelines and the study was approved by regional institutional review boards.

### Selection of participants

Each patient signed a board-approved consent form before any study procedures were initiated. To qualify for randomization, each patient was required to be at least 18 years of age, to participate in a 3–4-week washout of previous antihypertensive therapy (which incorporated a 2-week single-blind, placebo run-in period), and to have a postwashout 24-h systolic BP  $\geq 140$  and  $\leq 180$  mmHg and a clinic systolic BP  $\leq 160$  and  $\leq 190$  mmHg. Participants could also have had diastolic hypertension if it was not excessive (i.e.  $>119$  mmHg). Exclusion criteria included secondary hypertension; severe renal impairment (estimated glomerular filtration rate  $<30$  ml/min/1.73 m<sup>2</sup>); history of a major cardiovascular event in the previous 6 months; type 1 or poorly controlled type 2 diabetes mellitus (hemoglobin A1c  $>8\%$ ); a serum potassium concentration above the upper limit of normal; poor compliance with study medication during the placebo run-in period; and night-shift work. Pregnant or nursing women and women of childbearing potential not using approved means of contraception were also excluded, and use of medications known to affect BP was not allowed.

### Treatments

Participants were randomized to one of three treatment groups, including two combination groups and one monotherapy group. In the combination therapy arms, all participants received both active treatments as separate individual tablets (azilsartan medoxomil 40 mg + amlodipine 5 mg or azilsartan medoxomil 80 mg + amlodipine 5 mg), whereas the one-third of patients assigned to amlodipine 5 mg received matching placebo rather than active azilsartan medoxomil (i.e. placebo + amlodipine 5 mg).

### Assessments and measurements

ABPM was performed before randomization and at week 6 using a Spacelabs 90207 monitor (Spacelabs Inc., Issaquah, Washington, USA). The monitor was fitted in the morning immediately after dosing and programmed to measure BP every 15 min between 6 a.m. and 10 p.m. and every 20 min between 10 p.m. and 6 a.m. A successful ABPM recording must have been at least 24 h in duration, captured at least 80% of the possible readings, had 2 nonconsecutive hours or less with less than one valid reading, and had no consecutive hours with less than one valid reading. If these criteria were not fulfilled, the procedure could be repeated within 5 days. Clinic BP was recorded at baseline and weeks 2, 4, and 6 using an automated device (Omron HEM 705-CP, Lake Forest, Illinois, USA). Clinic measurements were obtained in triplicate (same arm at least 2 min apart)  $\sim 24$  h after the previous dose of study medication (i.e. at trough) after the patient had been seated for 5 min and before other procedures were initiated.

### Efficacy endpoints

Change from baseline to week 6 in 24-h systolic BP was the primary endpoint, and change in clinic systolic BP was the key secondary endpoint; changes in 24-h and clinic diastolic BP were also evaluated. Subgroup analyses were carried out by age, sex, race, BMI, and estimated glomerular filtration rate. The proportion of participants who achieved the BP target ( $<140/90$  mmHg) was also determined.

### Statistical analysis

The primary efficacy analysis was based on an analysis of covariance that included treatment as a factor and baseline 24-h systolic BP as a covariate. Missing data were handled using the last observation carried forward principle; type 1 error was controlled using 'closed' testing in which the pair-wise analyses between the individual treatment groups were carried out with no *P*-value adjustment only if the hypothesis 'all treatment groups are equal' was first rejected at the 0.05 level. Similar statistical methods were used to analyze the other secondary efficacy endpoints that were continuous variables. The proportion of participants who achieved clinic BP target was analyzed using a logistic model with

treatment as a fixed effect and baseline clinic BP as a covariate. Assuming an SD of 13 mmHg and a 15% dropout rate, the planned sample size of this study ( $N = 540$ , 180/group) provided at least 90% power to detect a difference of 5 mmHg between treatment groups for the primary endpoint.

### Evaluation of safety

Safety measures included adverse events, clinical laboratory results (including pregnancy testing), physical examination findings, and electrocardiographic data. All adverse events observed by the investigator or reported spontaneously by the patient were recorded and further characterized by the investigator as being nonserious or serious; whether or not the event led to discontinuation of treatment was also recorded. Safety laboratory parameters of interest that were measured at each visit included renal and hepatic function and serum potassium levels. Blood samples were analyzed by a central laboratory (ICON Laboratories, Farmingdale, New York, USA).

## Results

### Study participants

Patient disposition and demographics are shown in Fig. 1 and Table 1, respectively. A total of 1469 patients were enrolled in the single-blind placebo run-in period at 73 sites in the USA, Peru, Mexico, and Chile, and 566 eligible patients were assigned randomly to double-blind treatment ( $\approx 190$ /group). A total of 532 (94%) completed the study as planned. Overall, the most common reason for premature discontinuation was voluntary withdrawal ( $n = 13$ , 2.3%). Among randomized participants, the mean age was 58 years, with men and women equally represented; baseline 24-h BP (153–154/93 mmHg) and clinic BP (165–166/94–95 mmHg) were similar across groups. There were no major differences with respect to other demographic characteristics (Table 1).

### Changes in systolic blood pressure

BP changes after 6 weeks of randomized treatment are shown in Fig. 2. Decreases were observed in all treatment groups for the primary endpoint of 24-h systolic BP, with reductions of  $\sim 25$  mmHg in both the azilsartan medoxomil 40 mg + amlodipine 5 mg and the azilsartan medoxomil 80 mg + amlodipine 5 mg groups, which were statistically significantly greater than the 14 mmHg reduction observed with placebo + amlodipine 5 mg ( $P \leq 0.001$  for both comparisons). Reductions in other systolic ABPM parameters were consistent with the 24-h results; daytime and night-time reductions in the azilsartan medoxomil + amlodipine groups were  $\sim 25/16$  and  $23/14$  mmHg, respectively, whereas in the placebo + amlodipine 5 mg group, these parameters were reduced by  $14/8$  and  $13/8$  mmHg ( $P < 0.001$  for each comparison). The mean systolic BP values observed at each hour of the week 6 ambulatory recording are shown in Fig. 3.

For clinic systolic BP, significantly greater reductions of 26–27 mmHg were observed in the azilsartan medoxomil + amlodipine groups compared with 16 mmHg in the placebo + amlodipine group at week 6 ( $P < 0.001$  for each comparison; Fig. 2). Statistically significant reductions were also observed in favor of both azilsartan medoxomil + amlodipine groups at the other study visits, with near maximal effects achieved by the week 2 visit ( $-23$  mmHg in the azilsartan medoxomil + amlodipine groups and  $-14$  mmHg in the placebo + amlodipine group).

Subgroup analyses of the primary endpoint showed statistically significantly greater reductions in 24-h systolic BP in both azilsartan medoxomil + amlodipine groups relative to placebo + amlodipine irrespective of age ( $< 65$  and  $\geq 65$  years), sex, race (white, black, other), or BMI ( $< 30$  and  $\geq 30$  kg/m<sup>2</sup>) ( $P < 0.05$  for each comparison).

### Additional endpoints

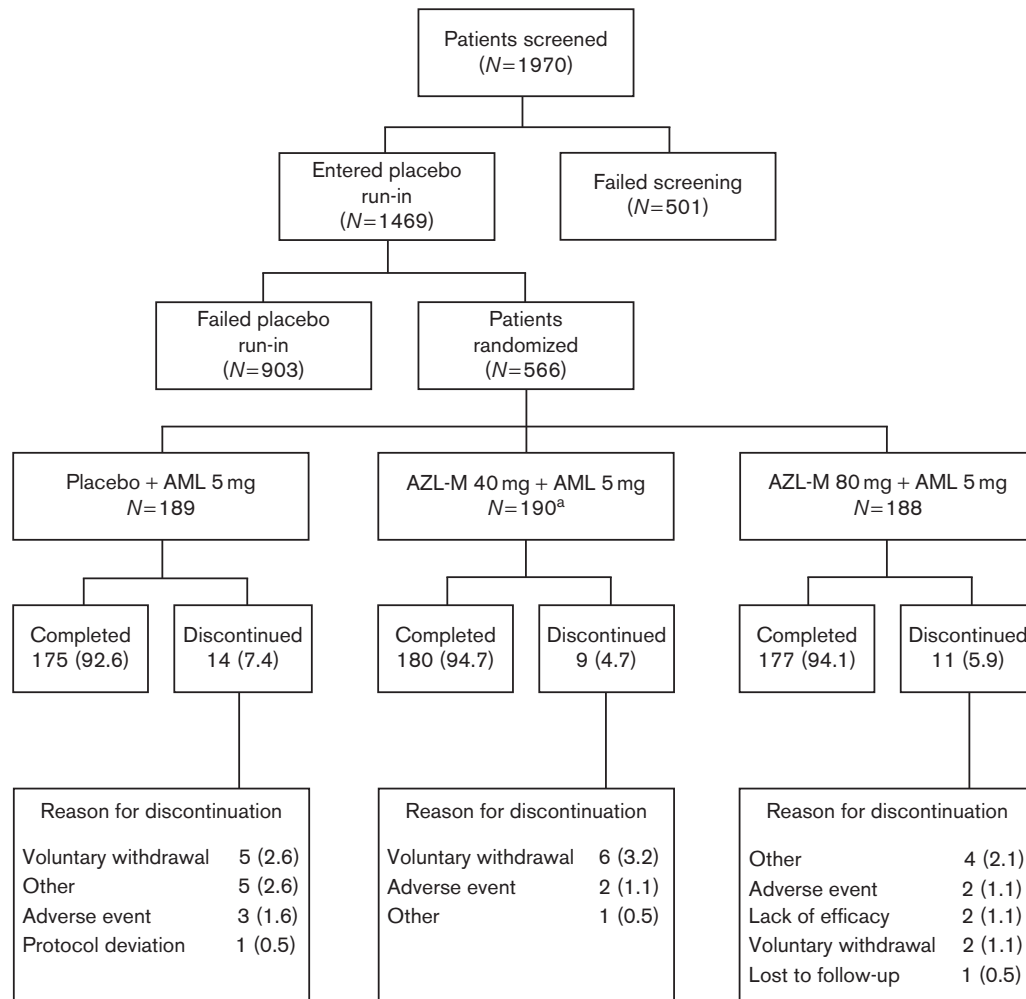
Changes in diastolic pressures, as measured by both ambulatory and clinic measurements, were consistently statistically significantly greater in both azilsartan medoxomil + amlodipine groups versus placebo + amlodipine. Reductions in 24-h diastolic BP were  $\sim 15$  mmHg with azilsartan medoxomil + amlodipine combination therapy and 8 mmHg with placebo + amlodipine, and reductions in clinic diastolic BP were 12–13 mmHg with combination therapy compared with 7 mmHg for placebo + amlodipine ( $P < 0.001$  for each comparison; Fig. 2). The proportions of patients whose individual reductions in clinic systolic and/or diastolic BP achieved the target were also significantly greater in both azilsartan medoxomil + amlodipine treatment groups compared with placebo + amlodipine (Fig. 4).

### Safety and tolerability

The safety findings are summarized in Table 2. At least one adverse event was reported by 253 (45%) participants across all treatment groups. The rate of adverse events was similar in the placebo + amlodipine 5 mg (47%) and azilsartan medoxomil 40 mg + amlodipine 5 mg (48%) groups, with a slightly lower rate in the azilsartan medoxomil 80 mg + amlodipine 5 mg group (40%). Edema was less common in both azilsartan medoxomil + amlodipine groups (3%) compared with placebo + amlodipine (7.6%). Diarrhea was reported most frequently in the azilsartan medoxomil 40 mg + amlodipine 5 mg group, but no cases were observed in the azilsartan medoxomil 80 mg + amlodipine 5 mg group. There were no deaths in the study. Four participants experienced serious adverse events (Table 2), with one event of syncope that was considered related to treatment (azilsartan medoxomil 40 mg + amlodipine 5 mg) and led to withdrawal of the patient.

In clinical laboratory tests, there were small mean increases in creatinine (0.4–2.2  $\mu\text{mol/l}$ ), potassium (0.11–0.13 mmol/l), and uric acid (2.7–8.5  $\mu\text{mol/l}$ ) in the azilsartan medoxomil +

Fig. 1



Patient disposition. Data are *n* (%). AML, amlodipine; AZL-M, azilsartan medoxomil; BP, blood pressure. The category 'other' includes discontinuations that were because of reasons other than an adverse event, lack of efficacy, voluntary withdrawal, loss to follow-up, or protocol deviation. <sup>a</sup>Includes one patient who was not randomized but received active study drug.

Table 1 Demographic characteristics of randomized patients

Characteristics	Placebo + AML 5 mg (N=189)	AZL-M 40 mg + AML 5 mg (N=189)	AZL-M 80 mg + AML 5 mg (N=188)
Age (mean±SD) (years)	59±11	58±11	58±12
Male/female (%)	50/50	48/52	55/45
BMI (mean±SD) (kg/m <sup>2</sup> )	30.0±5.4	30.8±6.2	30.3±5.5
Race (%) <sup>a</sup>			
American Indian <sup>b</sup>	22	19	20
Black or African American	16	15	16
White	59	60	58
BP (mean±SD) (mmHg)			
Clinic BP	166/94±13/12	166/95±12/12	165/95±14/13
24-h BP	154/93±10/11	153/93±9/10	154/93±11/11
Daytime BP	157/96±11/12	156/96±9/11	157/96±11/12
Night-time BP	144/83±13/11	142/83±14/11	144/84±14/12

AML, amlodipine; AZL-M, azilsartan medoxomil; BP, blood pressure; daytime BP, 6 a.m. to 10 p.m.; night-time BP, 12 a.m. to 6 a.m.

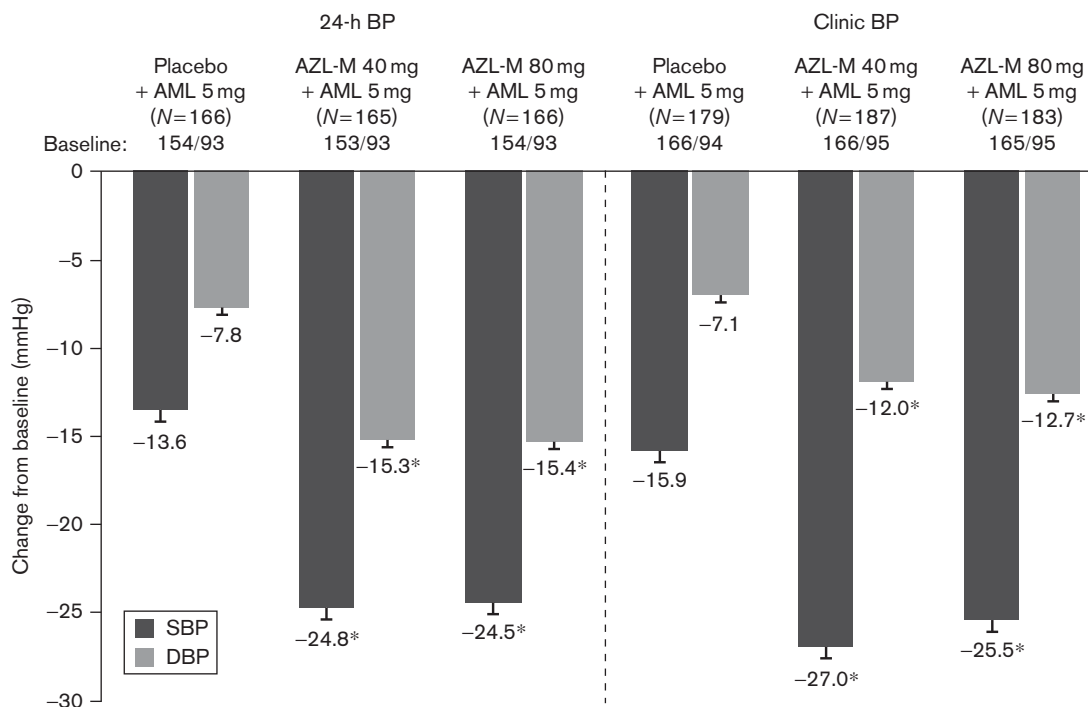
<sup>a</sup>More than one category may have been selected by patient; the three most commonly selected categories are listed.

<sup>b</sup>Predominantly selected by patients enrolled at Latin American sites.

amlodipine groups compared with slight decreases (−0.3, −1.0, −10.7 μmol/l, respectively) in the placebo + amlodipine group. However, no individual participant had a

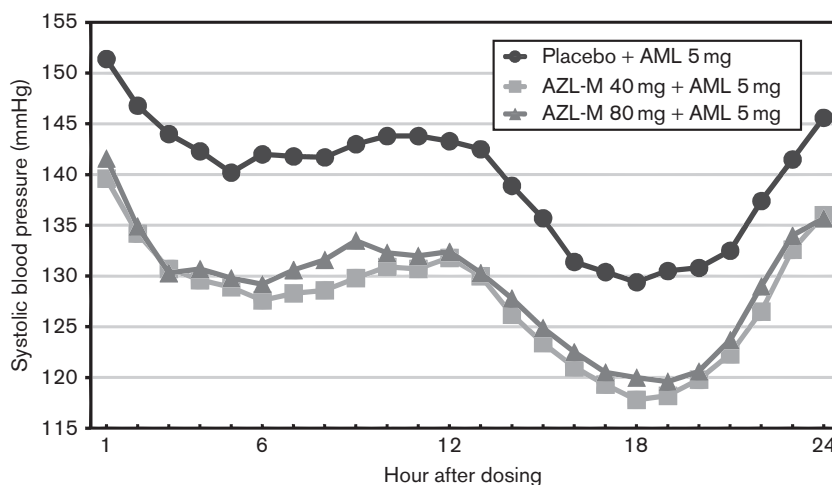
persistent serum creatinine elevation of at least 50% above baseline and above the upper limit of normal; hyperkalemia (serum potassium >6 mmol/l) was rare (one participant in

Fig. 2



Change from baseline in 24-h and clinic BP at week 6. AML, amlodipine; AZL-M, azilsartan medoxomil; BP, blood pressure. Data are least-squares mean ( $\pm$ SE). \* $P \leq 0.001$  vs. placebo + AML 5 mg.

Fig. 3



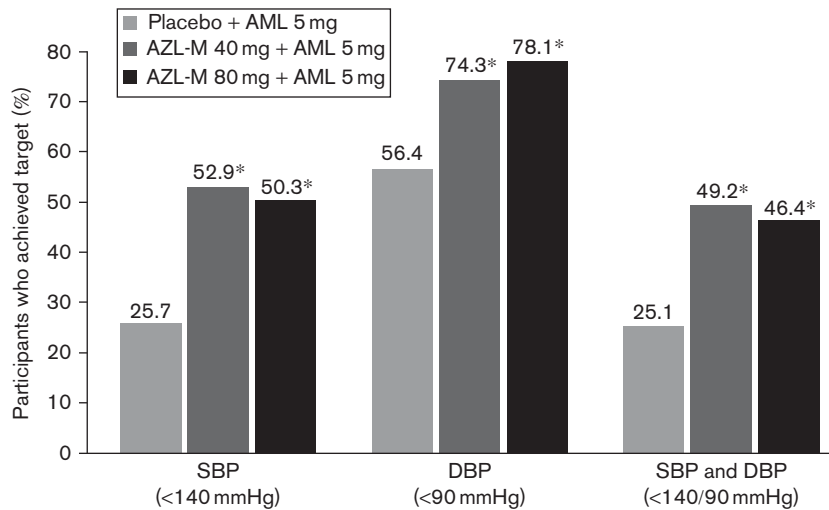
Ambulatory blood pressure at each hour after dosing at week 6. AML, amlodipine; AZL-M, azilsartan medoxomil.

each azilsartan medoxomil + amlodipine group); and there were few cases of gout (one patient with azilsartan medoxomil + amlodipine and one with placebo + amlodipine). There were no major differences for other clinical safety laboratory parameters (including hepatic transaminases, hematocrit, and hemoglobin) or ECGs.

### Discussion

The combinations of azilsartan medoxomil (40 or 80 mg daily) with amlodipine 5 mg produced similar 24-hour BP reductions of  $\sim 25/15$  mmHg in this study of patients with stage 2 hypertension. As there is generally little or no placebo effect with the use of ABPM, this result shows

Fig. 4



Percent of participants achieving the blood pressure target at week 6. AML, amlodipine; AZL-M, azilsartan medoxomil; DBP, diastolic blood pressure; SBP, systolic blood pressure. \* $P < 0.001$  vs. placebo + amlodipine.

Table 2 Safety findings

Parameters	Placebo + AML 5 mg (N=185)	AZL-M 40 mg + AML 5 mg (N=190)	AZL-M 80 mg + AML 5 mg (N=188)
Any adverse events	86 (46.5)	92 (48.4)	75 (39.9)
Adverse events leading to discontinuation	3 (1.6)	2 (1.1)	2 (1.1)
Serious adverse events	1 (0.5)	1 (0.5)	2 (1.1)
Most common adverse events			
Edema <sup>a</sup>	14 (7.6)	5 (2.6)	5 (2.7)
Headache	10 (5.4)	11 (5.8)	10 (5.3)
Dyslipidemia	7 (3.8)	9 (4.7)	7 (3.7)
Diarrhea	2 (1.1)	6 (3.2)	0
Other selected adverse events			
Dizziness	4 (2.2)	3 (1.6)	3 (1.6)
Hypotension	1 (0.5)	0	0
Syncope	0	1 (0.5)	0

Data are number of participants (%); includes all participants who received at least one dose of active treatment.

AML, amlodipine; AZL-M, azilsartan medoxomil

<sup>a</sup>Aggregate of three adverse event terms (edema, peripheral edema, and fluid retention).

the powerful efficacy of these combinations. Of note, the BP reductions with the combination treatments averaged 10/7 mmHg more than with amlodipine as a single agent. These comparative effects were similar in the daytime and night-time periods and were sustained across the full 24 h. There was no difference between the two azilsartan medoxomil doses in their effects on BP in this study.

The clinic BP measurements showed similar results for the combinations and single agent groups. With less than 140/90 mmHg as the criterion for BP control, 49 and 46% of patients receiving the 40 and 80 mg azilsartan medoxomil + amlodipine combinations achieved this target, compared with 25% for the placebo + amlodipine group. This degree of target achievement is a strong finding for this combination in the setting of stage 2 hypertension, particularly bearing in mind that the 5 mg dose of the amlodipine component used in this study is not the maximum dose of that drug.

These results are not surprising. Previous studies of combinations of amlodipine with angiotensin receptor blockers have reported strong antihypertensive effects when the 5 mg dose of amlodipine has been used [9–12]. Even though azilsartan medoxomil as monotherapy has been shown to be more effective than the angiotensin receptor blockers used in those previous combination studies [19,20], we cannot make any judgments on the relative efficacies of amlodipine/angiotensin receptor blocker combinations without carrying out direct head-to-head studies.

Azilsartan medoxomil has also been evaluated in combination with the thiazide-like diuretic chlorthalidone [23,24]. This diuretic is a powerful antihypertensive agent that also has shown outcomes benefits in clinical trials [25,26]. Its usual dose in contemporary medical practice has been 12.5 or 25 mg. When the lower dose of chlorthalidone was used in the combination studies with

azilsartan medoxomil, BP reductions were similar to those observed in the present study using the 5 mg dose of amlodipine in combination with azilsartan medoxomil [27]. As shown previously, the combination of the angiotensin receptor blockers with either amlodipine or a thiazide diuretic will likely provide effective therapy for patients with more difficult-to-control hypertension [28,29].

Although calcium channel blockers such as amlodipine are effective and generally well tolerated, they are more likely than other commonly used antihypertensive agents to cause peripheral edema. This effect may be because of these drugs causing a greater degree of arterial than venous dilation, an effect that can cause peripheral pooling. As blockers of the renin–angiotensin system work on both venous and arterial beds, their combination with such drugs as amlodipine can attenuate this unwanted effect.

The combination of an ACE inhibitor [8] or an angiotensin receptor blocker [9] with amlodipine has been associated with lower rates of peripheral edema than amlodipine alone, and a similar effect was observed in the present study when azilsartan medoxomil was combined with amlodipine, even though the treatment period was relatively short and the overall number of edema reports was low. The incidence of other adverse events was low and did not appear to differ between the combination therapies and the single agent. This tolerability has been shown previously in studies of angiotensin receptor blocker/amlodipine combinations [9] and has also been observed during long-term treatment with ACE inhibitor/amlodipine combinations [16].

This study was an initial exploratory trial to determine the potential value of azilsartan medoxomil/amlodipine combinations in treating hypertension. However, this experience was limited to only the 5 mg dose of amlodipine. Previous work with combination therapies has shown that 10 mg of amlodipine is meaningfully more powerful in reducing BP than 5 mg [30], and so it would be valuable to learn from a well-conducted clinical trial whether an even greater proportion of patients with stage 2 hypertension could have their BPs controlled with this higher dose. It has also been reported that the higher amlodipine dose is more likely to cause peripheral edema; thus, it would be important to confirm that azilsartan medoxomil could reduce the incidence or the severity of this effect.

Another limitation of this study is that we did not have a placebo-only group, even though the key observations of the BP effects of azilsartan medoxomil when added to amlodipine were compared with a control group in which placebo was added to amlodipine. In any case, it is accepted that ABPM usually prevents a placebo effect on BP; it is still useful to more accurately define the true effect of the active treatment. In addition, placebo

control can be important in understanding the incidence of adverse events.

### Conclusion

This study has shown that the combination of azilsartan medoxomil with amlodipine exerts a robust additional antihypertensive effect compared with placebo plus amlodipine. These data provide a strong justification for a multifactorial trial to help define which combinations of azilsartan medoxomil and amlodipine will provide optimal safety and efficacy in the treatment of hypertension.

### Acknowledgements

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### Conflicts of interest

Michael A. Weber is a member of the speakers' bureau and consultant for Boehringer-Ingelheim, Daiichi Sankyo, Forest, Novartis, and Takeda; William B. White has served as a paid safety consultant for the Takeda Global Research and Development Center; Domenic Sica has had a research and/or consultant relationship with Takeda Pharmaceuticals, Boehringer-Ingelheim, Novartis, and Merck; George L. Bakris has received a grant or research support from Takeda Pharmaceuticals and is a consultant for Takeda, Abbott, CVRx, Johnson & Johnson, Eli Lilly, Daiichi Sankyo, Medtronic, and Relypsa. He is a member of the speakers' bureau for Takeda; Charlie Cao and Andrew Roberts are employees of Takeda Global Development Center Americas, and Stuart Kupfer is an employee of Takeda Pharmaceuticals International.

### References

- Russell D, Stalhammar J, Bodegard J, Hasvold P, Thuresson M, Kjeldsen SE. Cardiovascular events in subgroups of patients during primary treatment of hypertension with candesartan or losartan. *J Clin Hypertens (Greenwich)* 2011; **13**:189–197.
- Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002; **359**:995–1003.
- Roy J, Shah NR, Wood GC, Townsend R, Hennessey S. Comparative effectiveness of angiotensin converting enzyme inhibitors and angiotensin receptor blockers for hypertension on clinical end points: a cohort study. *J Clin Hypertens (Greenwich)* 2012; **14**:407–414.
- Kjeldsen SE, Stalhammar J, Hasvold P, Bodegard J, Olsson U, Russell D. Effects of losartan vs candesartan in reducing cardiovascular events in the primary treatment of hypertension. *J Hum Hypertens* 2010; **24**:263–273.
- Wells T, Blumer J, Meyers KEC, Neto JPR, Meneses R, Litwin M, et al. Effectiveness and safety of valsartan in children aged 6 to 16 years with hypertension. *J Clin Hypertens (Greenwich)* 2011; **13**:357–365.
- Izzo JL, Weintraub HS, Duprez DA, Purkayastha D, Zappe D, Samuel R, Cushman WC. Treating systolic hypertension in the very elderly with valsartan-hydrochlorothiazide vs either monotherapy: ValVET primary results. *J Clin Hypertens (Greenwich)* 2011; **13**:722–730.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**:1206–1252.
- Frishman WH, Ram CV, McMahon FG, Chrysant SG, Graff A, Kupiec JW, Hsu H. Comparison of amlodipine and benazepril monotherapy to amlodipine plus benazepril in patients with systemic hypertension: a

- randomized, double-blind, placebo-controlled, parallel-group study. The Benazepril/Amlodipine Study Group. *J Clin Pharmacol* 1995; **35**: 1060–1066.
- 9 Ram CV. Antihypertensive efficacy of olmesartan medoxomil or valsartan in combination with amlodipine: a review of factorial-design studies. *Curr Med Res Opin* 2009; **25**:177–185.
  - 10 Weir MR, Hsueh W, Nesbitt SD, Littlejohn TJ, Graff A, Shojaae A, *et al.* A titrate-to-goal study of switching patients uncontrolled on antihypertensive monotherapy to fixed dose combinations of amlodipine and olmesartan medoxomil. *J Clin Hypertens (Greenwich)* 2011; **13**:404–412.
  - 11 Punzi H, Shojaae A, Wawerczak WF, Maa JF. Efficacy of amlodipine and olmesartan medoxomil in hypertensive patients with diabetes and obesity. *J Clin Hypertens (Greenwich)* 2011; **13**:422–430.
  - 12 Neutel JM, Mancia G, Black HR, Dahlof B, Defeo H, Ley L, Vinisio R. TEAMSTA Severe HTN Study Investigators. Single pill combination of telmisartan/amlodipine in patients with severe hypertension: results from the TEAMSTA severe HTN study. *J Clin Hypertens (Greenwich)* 2012; **14**:206–215.
  - 13 Lüscher TF, Wenzel RR, Moreau P, Takase H. Vascular protective effects of ACE inhibitors and calcium antagonists: theoretical basis for a combination therapy in hypertension and other cardiovascular diseases. *Cardiovasc Drugs Ther* 1995; **9 (Suppl 3)**:509–523.
  - 14 Neutel JM, Smith DH, Weber MA. Effect of antihypertensive monotherapy and combination therapy on arterial distensibility and left ventricular mass. *Am J Hypertens* 2004; **17**:37–42.
  - 15 Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al.* ASCOT Investigators. Prevention of cardiovascular events with antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005; **366**:895–906.
  - 16 Jamerson K, Weber MA, Bakris GL, Dahlöf B, Pitt B, Shi V. On behalf of the ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008; **359**:2417–2428.
  - 17 Krause T, Lovibond K, Caulfield M, McCormack T, Williams B. Guideline Development Group. Management of hypertension: summary of NICE guidance. *BMJ* 2011; **343**:d4891.
  - 18 Takeda Pharmaceuticals America Inc. *Edarbi (azilsartan medoxomil) package insert*. Deerfield, IL: Takeda Pharmaceuticals America Inc.; 2011.
  - 19 White WB, Weber MA, Sica D, Bakris GL, Perez A, Cao C, Kupfer S. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension* 2011; **57**:413–420.
  - 20 Bakris GL, Sica D, Weber M, White WB, Roberts A, Perez A, *et al.* The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. *J Clin Hypertens (Greenwich)* 2011; **13**:81–88.
  - 21 Ram CVS, Ramaswamy K, Qian C, Biskupiak J, Ryan A, Quah R, Russo PA. Blood pressure outcomes in patients receiving angiotensin II receptor blockers in primary care: a comparative effectiveness analysis from electronic medical record data. *J Clin Hypertens (Greenwich)* 2011; **13**:801–812.
  - 22 Ram CVS, Vasey J, Panjabi S, Qian C, Quah R. Comparative effectiveness analysis of amlodipine/renin angiotensin system blocker combinations. *J Clin Hypertens (Greenwich)* 2012; **14**:601–610.
  - 23 Sica D, White WB, Weber MA, Bakris GL, Perez A, Cao C, *et al.* Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)* 2011; **13**:467–472.
  - 24 Cushman WC, Bakris GL, White WB, Weber MA, Sica D, Roberts A, *et al.* Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. *Hypertension* 2012; **60**:310–318.
  - 25 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**:3255–3264.
  - 26 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**:2981–2997, [Errata in *JAMA* 2004; **291**: 2196, 2003; **289**:178].
  - 27 Sica D, Bakris L, White WB, Weber MA, Cushman WC, Huang P, *et al.* Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone: a factorial study. *J Clin Hypertens (Greenwich)* 2012; **14**:284–292.
  - 28 Izzo JL, Chrysant SG, Kereiakes DJ, Littlejohn T, Oparil S, Melino M, *et al.* 24-hour efficacy and safety of triple-combination therapy with olmesartan, amlodipine and hydrochlorothiazide: the TRINITY ambulatory blood pressure substudy. *J Clin Hypertens (Greenwich)* 2011; **13**:873–880.
  - 29 Kereiakes DJ, Chrysant SG, Izzo JL, Littlejohn T, Oparil S, Melino M, *et al.* Long-term efficacy and safety of triple combination therapy with olmesartan medoxomil and amlodipine besylate and hydrochlorothiazide for hypertension. *J Clin Hypertens (Greenwich)* 2012; **14**:149–157.
  - 30 Allemann Y, Fraile B, Lambert M, Barbier M, Ferber P, Izzo JL. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure after Single Therapy (EX-FAST) study. *J Clin Hypertens (Greenwich)* 2008; **10**:185–194.