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A phase 3 double-blind randomized (CONSORT-compliant) study of azilsartan medoxomil compared to valsartan in Chinese patients with essential hypertension

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Abstract

Background: Azilsartan medoxomil (AZL-M), an angiotensin II receptor blocker, has a well-characterized efficacy and safety profile in patients with hypertension. AZL-M is approved for use in over 40 countries globally; however, it is not yet approved in China. Therefore, a phase 3 registration study to assess the efficacy (antihypertensive effect), safety, and tolerability of AZL-M compared with valsartan in Chinese patients with essential hypertension was undertaken.

Methods: This multicenter, double-blind, randomized, 8-week phase 3 study compared AZL-M with valsartan in Chinese patients aged ≥18 years with essential hypertension. Endpoints included change from baseline to week 8 in trough sitting clinic systolic blood pressure (scSBP) and ambulatory blood pressure monitoring parameters.

Results: Overall, 612 patients (mean age, 57.1 years; 57.5% male) were randomized to AZL-M 80 mg (n = 209), AZL-M 40 mg (n = 199), or valsartan 160 mg (n = 204). Baseline mean scSBP was similar in all groups (157.9–158.5 mm Hg). The mean reduction in trough scSBP from baseline to week 8 was significantly greater with AZL-M 80 mg than with valsartan (−24.2 vs −20.6 mm Hg; $P = .010$), and noninferior with AZL-M 40 mg versus valsartan (−22.5 vs −20.6 mm Hg; $P = .184$). Mean reduction in 24-hour mean systolic blood pressure (n = 257) was significantly greater with both AZL-M 80 mg (−17.0 mm Hg; $P < .001$) and AZL-M 40 mg (−14.7 mm Hg; $P = .014$) than with valsartan (−9.4 mm Hg). Treatment-emergent adverse events had similar incidence (52.8%–56.5%) across the treatment groups and were generally mild or moderate. Dizziness was the most frequent treatment-related treatment-emergent adverse events (AZL-M 80 mg, 1.9%; AZL-M 40 mg, 1.5%; valsartan, 1.0%). The safety and tolerability of AZL-M were comparable with valsartan.

Conclusions: AZL-M was noninferior to valsartan at the 40-mg dose and superior to valsartan at the 80-mg dose in reducing trough scSBP, and showed acceptable safety—consistent with the AZL-M safety profile in other populations—in Chinese adults with hypertension.

Trial Registration number: NCT02480764

Abbreviations: ABPM = ambulatory blood pressure monitoring, AE = adverse event, ANCOVA = analysis of covariance, ARB = angiotensin type II receptor blocker, AZL-M = azilsartan medoxomil, CI = confidence interval, DBP = diastolic blood pressure, ECG = electrocardiogram, LS = least squares, OR = odds ratio, QD = once daily, SAE = serious adverse event, SBP = systolic blood

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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pressure, scDBP = sitting clinic diastolic blood pressure, scSBP = sitting clinic systolic blood pressure, TEAE = treatment-emergent adverse event.

Keywords: angiotensin II receptor blockers, azilsartan medoxomil, essential hypertension, randomized controlled trial, valsartan

1. Introduction

Hypertension is a global health issue affecting 40% of the adult population worldwide and is a leading cause of death related to cardiovascular disease and stroke.[1–3] China represents 20% of the world population, and the prevalence of hypertension has been rapidly increasing within the past 30 years.[4,5] Approximately 25% of Chinese adults overall and up to 40% of Chinese adults aged ≥45 years have hypertension; however, approximately half of these patients are unaware of their condition.[6,7] Of the patients aware of their condition, approximately 80% receive antihypertensive medication, though <10% of patients have their hypertension controlled.[8,9]

Current guidelines in China recommend a blood pressure control target of <140/90 mm Hg (<130/80 mm Hg for patients with diabetes, coronary heart disease, or renal disease, and <150/90 mm Hg for patients ≥65 years).[10] Recently updated guidelines in the United States define stage 1 hypertension as blood pressure of 130 to 139/80 to 89 mm Hg and recommend pharmacologic treatment for high-risk patients.[11] If these guidelines were adopted in China, 55% of adults aged 45 to 75 years would be classified as hypertensive, further increasing the number of under- or untreated patients.[12]

Chinese hypertension guidelines recommend 5 classes of antihypertensive drugs, including calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin type II receptor blockers (ARBs), diuretics, and beta-blockers.[10] ARBs, such as olmesartan medoxomil (Benicar, Daiichi Sankyo, Tokyo, Japan) and valsartan (Diovan, Novartis, Basel, Switzerland), are widely used for the treatment of hypertension globally, have well-established safety profiles, and are better tolerated than other antihypertensive drugs, including ACE inhibitors.[13–15] Currently, 7 ARBs are approved in China, including valsartan, olmesartan medoxomil, and losartan (Cozaar, Merck, Kenilworth, NJ). Valsartan was the ARB market leader in China from 2011 to 2017.[16] and its highest approved dose in China is 160 mg.[17]

Azilsartan medoxomil (AZL-M [Edarbi], Takeda, Tokyo, Japan), a pro-drug that is rapidly hydrolyzed to the active moiety, azilsartan, is a highly potent, long-acting ARB. AZL-M has approval in over 40 countries globally, including Korea, Taiwan, Thailand, Malaysia, Singapore, and the Philippines, as well as Hong Kong, for the treatment of hypertension, either alone or in combination with other antihypertensive agents. Phase 3 studies, including the pivotal global study,[18] have demonstrated that AZL-M at a dose of 40 or 80 mg once daily (QD) is an effective and safe treatment for hypertension.[18–20]

While the efficacy of AZL-M compared with placebo has been established in previous studies in the United States, Mexico, Argentina, Peru, Chile, Guatemala, Puerto Rico, Europe, Russia, and South Korea,[18,19,21–23] and global studies have also compared AZL-M with valsartan,[19–21] the current ARB market leader in China,[24] this was the first phase 3 registration study to assess the efficacy (antihypertensive effect), safety, and tolerability of AZL-M compared with valsartan in Chinese patients with essential hypertension. The design of this study was closely modeled upon previous studies comparing AZL-M with valsartan[19–21] as well as the global pivotal study[18] that supported approval of AZL-M in Europe, North America, Latin America, the Middle East, and Asia.

2. Methods

2.1. Materials and data availability

This multicenter, randomized, parallel-group, double-blind, 8-week phase 3 study to evaluate the efficacy and safety of AZL-M 40 or 80 mg QD in comparison with valsartan in adult patients with essential hypertension was conducted at 30 study sites in China. Placebo was not included as a comparator in this study, as the efficacy of AZL-M has been established globally.[18,19,23] This study was registered with ClinicalTrials.gov (NCT02480764) on June 24, 2015. The institutional review board at each study site was responsible for approval of the clinical study in accordance with ethical principles and conducted under the Guidelines of the Declaration of Helsinki, the regulations and guidelines of the International Conference on Harmonisation, the Harmonised Tripartite Guideline for Good Clinical Practice, and all applicable local regulations. All patients provided written informed consent prior to screening. The data that support the findings of this study are available from Takeda Pharmaceutical Company or the corresponding author upon reasonable request.

2.2. Study design

After initial screening, eligible patients participated in a single-blind placebo run-in period for 2 weeks prior to treatment with study drug (Fig. 1). Patients who had not received antihypertensive treatment within 28 days of start of study treatment entered the 2-week (days −14–−1) run-in period following verification that they met all entry criteria. Patients who had received antihypertensive agents within 28 days of start of study treatment also participated in a 3-week (days −21–−1) or, for patients treated with amlodipine or chlorthalidone, 4-week (days −28–−1) washout.

On day 1, all patients who qualified for the study after the placebo run-in were randomized (via an interactive Web Response System and Interactive Voice Response System accessible by randomization personnel) 1:1:1 to receive AZL-M 80 mg QD, AZL-M 40 mg QD, or valsartan 160 mg QD for 8 weeks. The blinding of the study drug was maintained throughout the study and was not broken unless information concerning the study drug was essential for medical treatment. Randomization information was stored in a secured area, accessible only by authorized personnel.

2.3. Key inclusion criteria

Adult (aged ≥18 years) male or female patients with mean sitting clinic systolic blood pressure (scSBP) of 150 to 180 mm Hg on day 1 of the study (before randomization) were eligible.

2.4. Key exclusion criteria

Patients were excluded if they had post-placebo run-in sitting clinic diastolic blood pressure (scDBP) >110 mm Hg at baseline

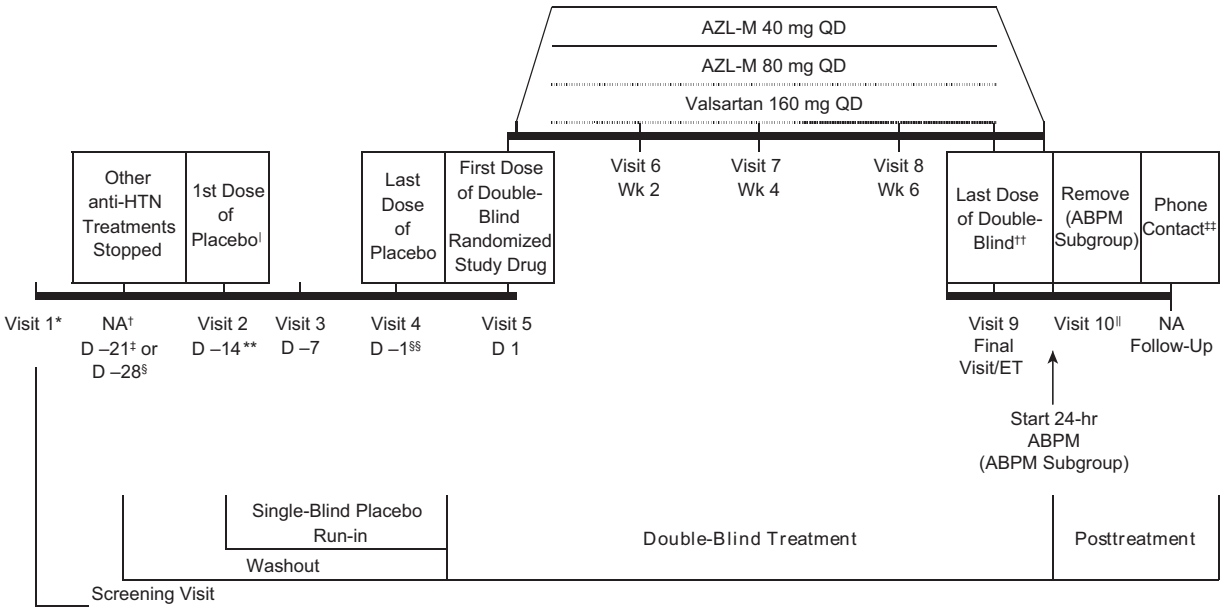

Figure 1. Study design. *The screening visit was scheduled before the washout/run-in period so that laboratory tests results were reviewed and patient eligibility confirmed before other treatments were stopped or placebo was initiated. †Patients were notified by telephone to begin the washout period. ‡Patients taking previous antihypertensive agents were required to participate in a 3-week washout/run-in period (days −21–−1). §If the subject's previous antihypertensive treatment included amlodipine or chlorthalidone, the washout was extended to 4 weeks (days −28–−1). ‖The first dose of placebo was taken at the clinic on day −14 (visit 2). **Patients who had not received antihypertensive treatment within 28 days before screening were entered into the run-in period as soon as all inclusion and exclusion criteria, including laboratory results, were verified. ††The last dose of double-blind treatment was the day of week 8/final clinic visit or ET (visit 9); patients in the ABPM subgroup started 24-hour ABPM measurement. ‡‡The follow-up telephone contact was made approximately 14 days after the last dose. §§Visit 4 applied to ABPM subgroup patients only, who started 24-hour ABPM measurement. ‖‖Visit 10 applied to ABPM subgroup patients only. ABPM = ambulatory blood pressure monitoring. AZL-M = azilsartan medoxomil, D = day, ET = early termination, N/A = not applicable, QD = once daily.

or secondary hypertension of any etiology. Patients were excluded if they had known or suspected unilateral or bilateral renal artery stenosis; history of a major cardiovascular event; poorly controlled diabetes (hemoglobin A1c >8.5%); estimated glomerular filtration rate <30 mL/min/1.73 m^2; alanine aminotransferase level >2.5 × the upper limit of normal (ULN); hyperkalemia (defined as serum potassium >ULN per the central laboratory); a history of hypersensitivity or allergies to AZL-M, any of its excipients, or other angiotensin II receptor blockers; or continued use of medication that had a blood pressure effect. All patients with contraindications of AZL-M (including pregnant or nursing women) were excluded.

2.5. Blood pressure measurement

For measurements of trough scSBP and scDBP, patients were assessed using the same semiautomated blood pressure device (Omron HEM-907 [Omron Corporation, Minato-ku, Tokyo, Japan], provided by the sponsor) on the patient's dominant arm for serial blood pressure measurements (3 seated measurements taken ≥2 minutes apart after cuff deflation). A subset of patients at selected sites underwent 24-hour ambulatory blood pressure monitoring (ABPM) twice during the study: at baseline and at week 8 after the last dose of the double-blind treatment.

Blood pressure was measured using an appropriately sized cuff (with the cuff bladder encircling at least 80% of the arm) applied at the upper dominant arm at heart level. Blood pressure measurements were taken approximately 24 hours after the previous dose of study drug and prior to dosing or blood collection on the day of clinic visits at day 1 (baseline) and at weeks 2, 4, 6, and 8.

Patients were excluded from the ABPM subgroup if they worked from 11 PM to 7 AM or had an upper arm circumference <24 or >42 cm. Patients were instructed to withhold their dose of study drug in the morning when an ABPM recording was scheduled to begin, and that day's dose of study drug was administered in the clinic at 8 AM (±2 hours). The 24-hour ABPM reading was started immediately after in-clinic dosing.

2.6. Efficacy and safety endpoints

The primary efficacy endpoint was the change from baseline to week 8 in trough scSBP. Secondary efficacy endpoints included change from baseline to week 8 in trough scDBP and the percentage of patients who achieved responder criteria at week 8 (defined as scDBP <90 mm Hg and/or reduction of ≥10 mm Hg from baseline and/or scSBP <140 mm Hg and/or reduction of ≥20 mmHg from baseline). Change from baseline to week 8 in ABPM parameters included 24-hour mean systolic blood pressure (SBP) and diastolic blood pressure (DBP), trough (22–24 hours after dosing) SBP and DBP, mean daytime (6 AM–10 PM) SBP and DBP, mean nighttime (12–6 AM) SBP and DBP, and mean SBP and DBP at 0 to 12 hours after dosing.

Safety was evaluated by incidence of adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG) findings, and laboratory assessments.

2.7. Collection and reporting of AEs

AEs (i.e., signs and symptoms) were collected and evaluated throughout the study. Investigators asked general questions to patients during prespecified visits, or patients could self-report

AEs throughout the study. AEs were assessed for seriousness, severity and relatedness by the investigator and documented in an electronic case report form. AEs were coded using the Medical Dictionary for Regulatory Activities.

2.8. Statistical analysis

A sample size of 200 patients per treatment group (N = 600), assuming a standard deviation of 17 mm Hg and a 10% dropout rate, was determined sufficient to achieve ≥90% power to detect a difference of 6 mm Hg between AZL-M and valsartan by a 2-sample *t* test on the mean change from baseline to week 8 in mean scSBP with an alpha of 0.05. This sample size also provided ≥90% power for demonstrating noninferiority with a margin of 1.5 mm Hg between AZL-M and valsartan.

The primary efficacy analysis was performed using the full (intent-to-treat) analysis set, which consisted of all randomized patients who received ≥1 dose of double-blind study drug. The safety analysis set consisted of all patients who received at least 1 dose of double-blind study drug. The primary efficacy endpoint was analyzed using an analysis of covariance (ANCOVA) model, with treatment group as a fixed effect and baseline scSBP as a continuous covariate. Estimates of treatment least squares (LS) mean, differences in LS means between AZL-M treatment groups and valsartan, *P* value, and 2-sided 95% confidence intervals (CIs) for the treatment difference were determined from the framework of the ANCOVA model. For the primary analysis, the overall type 1 error rate of 0.05 was controlled using sequential testing.

Sequential testing of the primary analysis was a 4-step process. A test for noninferiority of AZL-M 80 mg to valsartan 160 mg was performed using a noninferiority margin of 1.5 mm Hg. If the upper limit of the 2-sided 95% CI of the treatment difference (AZL-M vs valsartan) was ≤1.5, a test for noninferiority of AZL-M 40 mg to valsartan 160 mg was performed using a noninferiority margin of 1.5 mm Hg. If the upper limit of the 2-sided 95% CI of the treatment difference (AZL-M vs valsartan) was ≤1.5, a test for significant difference between AZL-M 80 mg and valsartan 160 mg was performed with a 5% threshold. If *P* was ≤.05, a test for significant difference between AZL-M 40 mg and valsartan 160 mg was performed with a 5% threshold.

Change from baseline in trough scDBP at week 8 was analyzed using the ANCOVA model described for the primary endpoint, excluding the sequential testing. Change from baseline to week 8 in 24-hour mean SBP by ABPM was analyzed using an ANCOVA model with treatment as a fixed effect and baseline 24-hour mean SBP by ABPM as a covariate. Similar analyses were performed for the other ABPM parameters.

Frequency of treatment-emergent AEs (TEAEs) were summarized by treatment group. Shifts in laboratory test and ECG parameters from baseline versus each postbaseline visit were also summarized. No inferential statistical analyses were performed.

3. Results

3.1. Patient disposition

Patient recruitment commenced on August 27, 2015, the last dose of study drug was administered on September 22, 2017, and the last patient visit occurred on October 13, 2017.

Of 1258 patients screened, 612 who met the study criteria were randomized into the double-blind period to treatment with AZL-M 80 mg (n = 209), AZL-M 40 mg (n = 199), or valsartan 160 mg (n = 204; Fig. 2). A total of 52 patients prematurely discontinued: 11 of 204 (5.5%) in the AZL-M 40-mg group, 20 of 204 (9.6%) in the AZL-M 80-mg group, and 21 of 204 (10.3%) in the valsartan 160-mg group. Common reasons for discontinuation of study drug included voluntary withdrawal (3.4%, 21 of 612), pretreatment events/AEs (2.1%, 13 of 612), and major protocol deviations (1.3%, 8 of 612).

The ABPM subset included 257 of the 612 randomized subjects: 95 in the AZL-M 80-mg group, 84 in the AZL-M 40-mg group, and 78 in the valsartan 160-mg group. The majority (91.4%, 235 of 257) of patients in the ABPM subset completed 8 weeks of treatment with double-blind study drug and all planned study visits. Twenty-two patients discontinued study visits prematurely.

3.2. Demographic and baseline characteristics

Patient demographic and baseline characteristics, including age, sex, body mass index, and comorbid diseases, were similar across administration arms (Table 1). There was no meaningful difference between treatment groups for scSBP or scDBP at baseline. Demographic and baseline characteristics within the ABPM subset were also generally similar across the 3 treatment groups (Table SDC1, Supplemental Digital Content, http://links.lww.com/MD/E623).

3.3. Changes in scSBP and scDBP

The overall treatment group effect was statistically significant for changes in both the primary endpoint, scSBP (*P* = .038), and the secondary efficacy endpoint, scDBP (*P* = .011), from baseline to week 8. For the primary endpoint, there was a significantly greater reduction in scSBP in the AZL-M 80-mg group than in the valsartan 160-mg group (LS mean difference, −3.69 mm Hg [95% CI, −6.50–−0.87]; *P* = .010) and a numerically greater reduction in scSBP in the AZL-M 40-mg group than in the valsartan group (LS mean difference, −1.93 mm Hg [95% CI, −4.78–0.92]; *P* = .184; Fig. 3). For the secondary efficacy endpoint, there was a significantly greater reduction in scDBP in the AZL-M 80-mg group than in the valsartan 160-mg group (LS mean difference, −2.82 mm Hg [95% CI, −4.66–−0.99]; *P* = .003) and a numerically greater reduction in scDBP in the AZL-M 40-mg group than in the valsartan group (LS mean difference, −1.46 mm Hg [95% CI, −3.32–0.40]; *P* = .123; Fig. 3).

At weeks 2, 4, and 6, there was a statistically significant treatment effect for both AZL-M 40 mg and AZL-M 80 mg compared with valsartan 160 mg in change from baseline in both trough scSBP and scDBP (*P* < .05; Fig. 4).

3.4. Response rates

The percentage of patients at week 8 who achieved the scSBP target (<140 mm Hg and/or a reduction of ≥20 mm Hg), the scDBP target (<90 mm Hg and/or a reduction of ≥10 mm Hg), or both targets was similar in the AZL-M 80-mg group (scSBP: 68.9%; scDBP: 81.6%; both: 67.0%), the AZL-M 40-mg group (scSBP: 67.0%; scDBP: 81.2%; both: 62.9%), and the valsartan 160-mg group (scSBP: 69.0%; scDBP: 79.7%; both: 64.5%; Fig. SDC2, http://links.lww.com/MD/E625, Supplemental Digital Content). At week 4, there was a statistically significant difference in the percentage of patients achieving the SBP target with AZL-M 80 mg compared with valsartan 160 mg (70.9% vs 56.9%, *P* < .01). There was also a statistically significant difference in the

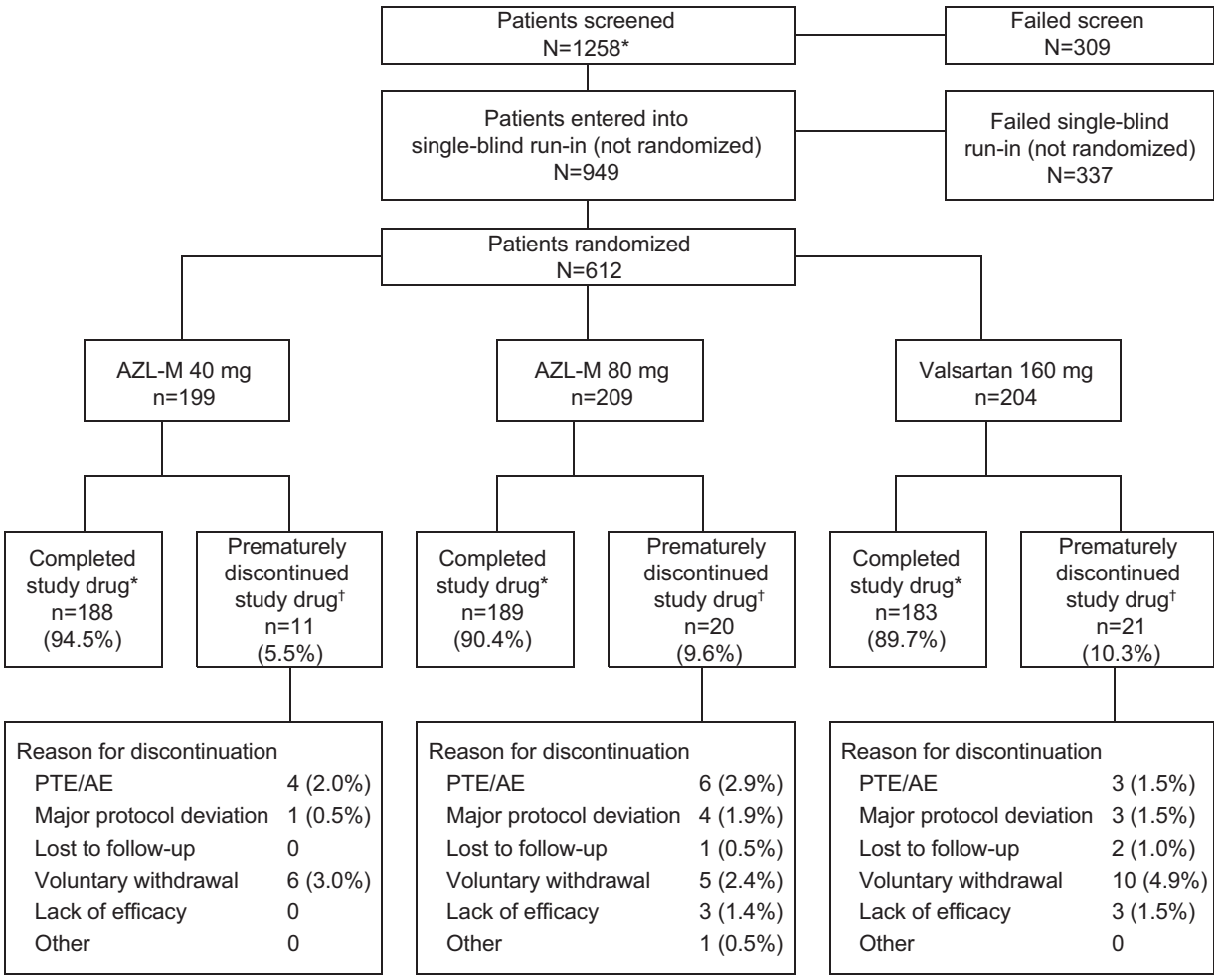

Figure 2. Consort flow diagram. *Patients who completed the study were the total number randomized per treatment group minus those who discontinued. †Patients could have had more than 1 reason for discontinuation; only the primary reason is presented. AE = adverse event, AZL-M = azilsartan medoxomil, PTE = pretreatment event.

percentage of patients achieving the DBP target with AZL-M 80 mg compared with valsartan 160 mg at both week 2 (77.3% vs 65.6%, $P < .05$) and week 4 (82.0% vs 67.5%, $P = .001$) as well as with AZL-M 40 mg compared with valsartan 160 mg at week 4 (79.2% vs 67.5%, $P < .05$) and week 6 (84.3% vs 73.6%, $P < .05$). A statistically significant overall treatment effect ($P < .05$) was observed in the percentage of subjects achieving these joint response criteria at weeks 2, 4, and 6 (with no adjustment for the multiple comparisons).

At week 8, among the 3 treatment groups, an overall statistically significant difference was observed for patients achieving target scSBP < 130 mm Hg ($P = .013$) and scDBP <80 mm Hg ($P = .013$; Fig. SDC3, Supplemental Digital Content, http://links.lww.com/MD/E626). A total of 28.4% of patients in the valsartan group achieved scSBP <130 mm Hg compared with 42.7% of patients in the AZL-M 80-mg group (odds ratio [OR] = 1.9 [95% CI, 1.24–2.95]; $P = .003$) and 37.6% of patients in the AZL-M 40-mg group (OR = 1.5 [95% CI, 1.0–2.3]; $P = .077$). Similarly, 37.1% of patients in the valsartan group achieved the scDBP <80 mm Hg target compared with 51.9% of patients in the AZL-M 80-mg group (OR = 2.0 [95% CI, 1.26–3.22]; $P = .003$) and 45.2% of patients in the AZL-M 40-mg group (OR = 1.4 [95% CI, 0.9–2.3]; $P = .137$). In addition, 21.8%, 28.9%, and 33.0% of patients achieved the joint scSBP/scDBP target in the valsartan 160 mg, AZL-M 40 mg, and AZL-M 80-mg groups, respectively ($P = .051$).

3.5. Changes in ABPM, SBP, and DBP

Relative to valsartan 160 mg, clinically meaningful and significantly greater reductions in SBP and DBP at week 8 from baseline were observed in patients treated with AZL-M 40 mg and 80 mg in the ABPM subset, including the 24-hour, daytime (6 AM–10 PM), 0 to 12 hours postdose, and trough (22–24 hours) assessments, and significantly greater reductions in SBP and DBP at week 8 from baseline were also observed in patients treated with AZL-M 80 mg in the ABPM subset in the nighttime (12–6 AM) assessments (Table SDC4, Supplemental Digital Content, http://links.lww.com/MD/E624).

At week 8, hourly average values from 0 to 24 hours (8 AM –7 AM) for ABPM SBP and DBP were lower in both AZL-M groups than in the valsartan 160-mg group (Fig. 5).

Table 1

Patient demographics and baseline characteristics.

Parameter	AZL-M 40 mg (n = 199)	AZL-M 80 mg (n = 209)	Valsartan 160 mg (n = 204)
Age, mean (SD), yr*	57.4 (9.5)	57.0 (9.9)	56.8 (9.5)
Sex, n (%)			
Male	107 (53.8)	115 (55.0)	130 (63.7)
Female	92 (46.2)	94 (45.0)	74 (36.3)
Race, n (%)			
Asian (Chinese)	199 (100.0)	209 (100.0)	204 (100.0)
Height, mean (SD), cm	164.3 (8.9)	164.2 (8.8)	165.3 (7.7)
Weight, mean (SD), kg†	71.8 (14.0)	71.6 (11.9)	72.8 (12.9)
BMI, mean (SD), kg/m^2‡	26.4 (3.8)	26.5 (3.4)	26.5 (3.4)
eGFR, mean (SD), mL/min/1.73 m^2	109.5 (26.3)	110.45 (28.8)	108.0 (29.2)
Diabetes status, n (%)			
Diabetes mellitus	8 (4.0)	8 (3.8)	14 (6.9)
Type 2 diabetes mellitus	14 (7.0)	20 (9.6)	14 (6.9)
Concomitant medication, n (%)§			
Medication continued into double-blind treatment period	53 (26.6)	54 (25.8)	48 (23.5)
Initiated use during double-blind treatment period	128 (64.3)	148 (70.8)	138 (67.6)
Smoking classification, n (%)			
Never smoked	151 (75.9)	147 (70.3)	136 (66.7)
Ex-smoker	9 (4.5)	11 (5.3)	13 (6.4)
Current smoker	39 (19.6)	51 (24.4)	55 (27.0)
scSBP, mean (SD), mm Hg	157.9 (6.7)	158.2 (7.4)	158.5 (7.4)
scDBP, mean (SD), mm Hg	91.8 (9.8)	91.4 (10.6)	92.0 (10.5)

AZL-M = azilsartan medoxomil, BMI = body mass index, eGFR = estimated glomerular filtration rate, scDBP = sitting clinic diastolic blood pressure, scSBP = sitting clinic systolic blood pressure, SD = standard deviation.

* Age at date of signing informed consent form.

† Weight was measured before the first dose of double-blind study drug.

‡ BMI was calculated from the weight taken before the first dose of study drug and height taken at screening.

§ No clinically meaningful differences were observed between treatment groups in the percentages of patients taking concomitant medications.

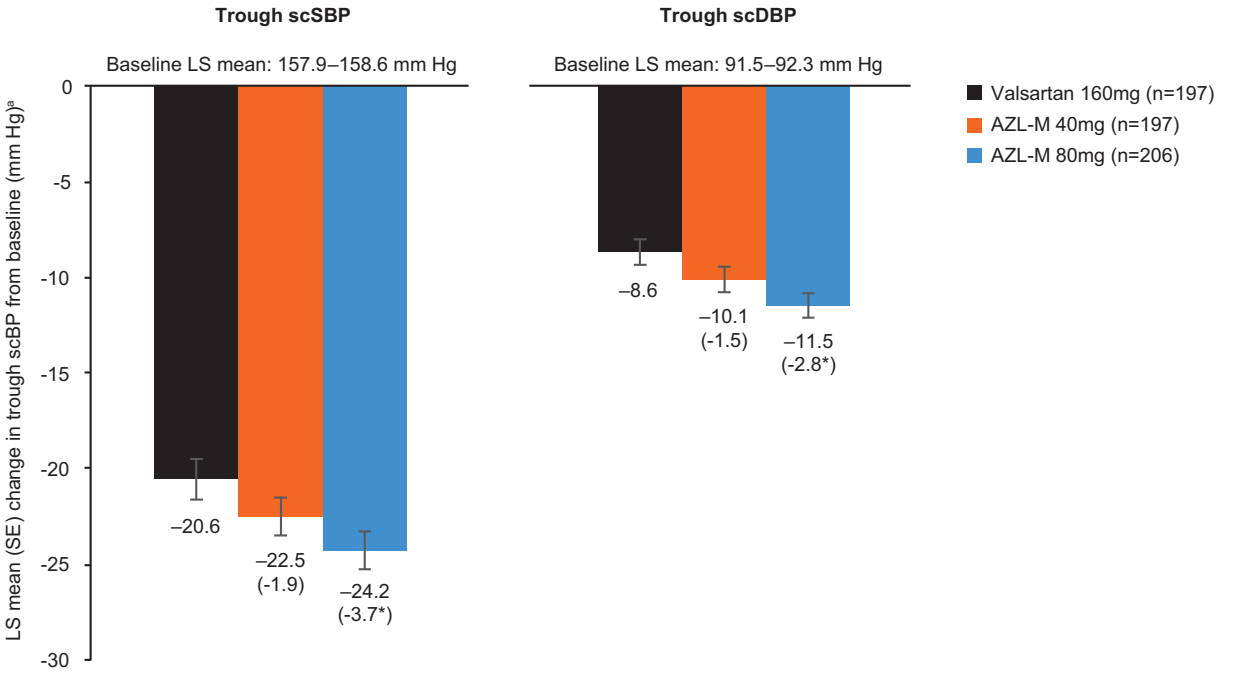

Figure 3. Least squares mean (standard error) change from baseline to week 8 in trough sitting clinic systolic blood pressure and sitting clinic diastolic blood pressure (full analysis set, last observation carried forward). *Indicates $P \leq .01$ compared with valsartan 160 mg. †Values in parentheses are the least squares mean difference between azilsartan medoxomil and valsartan. FAS = full analysis set, LOCF = last observation carried forward, LS = least squares, scDBP = sitting clinic diastolic blood pressure, scSBP = sitting clinic systolic blood pressure, SE = standard error.

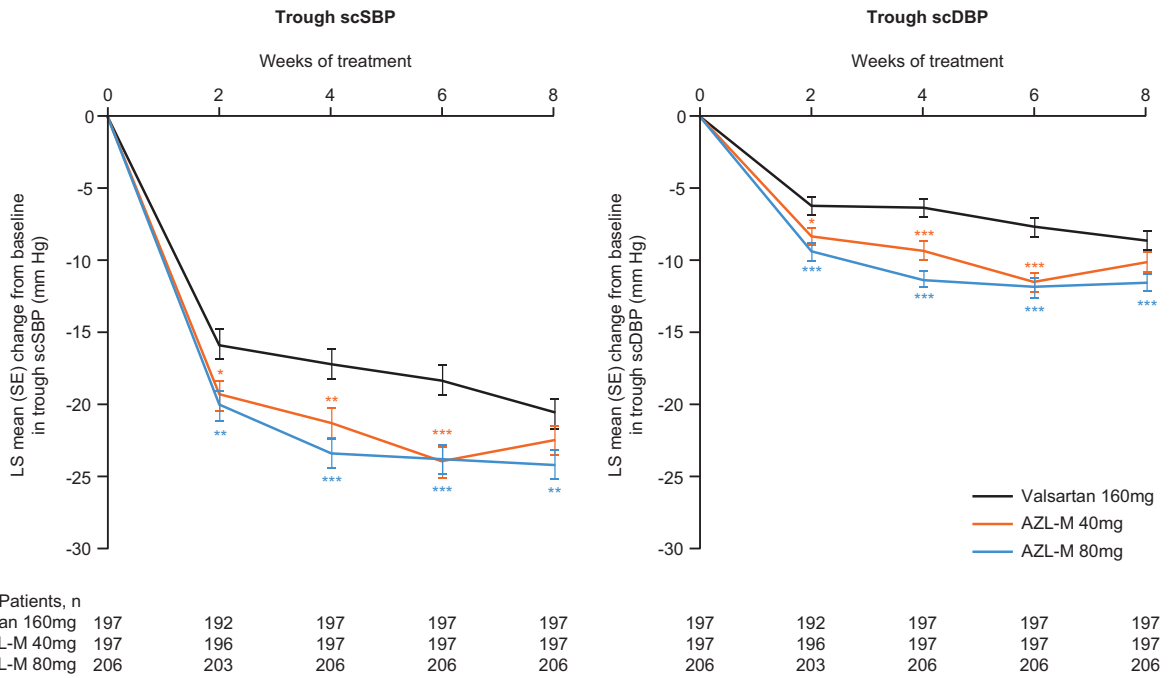

Figure 4. Change from baseline in trough sitting clinic systolic blood pressure and sitting clinic diastolic blood pressure at weeks 2, 4, 6, and 8 (full analysis set, last observation carried forward). $^{*}P < .05$. $^{**}P \leq .01$. $^{***}P \leq .001$. FAS = full analysis set, LOCF = last observation carried forward, scDBP = sitting clinic diastolic blood pressure, scSBP = sitting clinic blood pressure.

3.6. Other subgroup analysis

Evidence of significantly greater treatment effect with AZL-M than with valsartan was observed in subgroups defined by baseline scSBP and scDBP, age, sex, and body mass index after 8 weeks of treatment (Figs. SDC5A–E, Supplemental Digital Content, http://links.lww.com/MD/E627, http://links.lww.com/MD/E628).

Significantly greater reductions in 24-hour mean ABPM SBP and DBP with AZL-M than with valsartan were also observed in ABPM baseline SBP, and baseline DBP, and age subgroups (Figs. SDC6A–C, Supplemental Digital Content, http://links.lww.com/MD/E629).

3.7. Safety and tolerability

In the safety analysis set, 336 of 612 patients (54.9%) had at least 1 TEAE during the 8 weeks of treatment, and the percentage of patients with TEAEs was similar in the AZL-M 80 mg (56.5%, 118 of 209), AZL-M 40 mg (52.8%, 105 of 199), and valsartan 160 mg (55.4%, 113 of 204) groups (Table 2). TEAEs were considered mild in severity in the majority of these patients (89.6%, 301 of 336). Twelve of 336 patients (3.6%) had at least 1 severe TEAE: 3 of 199 (1.5%) in the AZL-M 40-mg group, 4 of 209 (1.9%) in the AZL-M 80-mg group, and 5 of 204 (2.5%) in the valsartan 160-mg group. Hyperlipidemia (7.2%) and upper respiratory tract infection (6.0%) were the most frequently reported TEAEs overall. TEAEs in ≥2% of patients in any treatment group are reported in Table 3.

Twelve of 612 patients (2.0%) discontinued study drug because of a TEAE; 6 of 209 (2.9%) in the AZL-M 80-mg group, 4 of 199 (2.0%) in the AZL-M 40-mg group, and 2 of 204 (1.0%) in the valsartan 160-mg group. Overall, 65 of 612 patients (10.6%) had a TEAE that was considered related to study drug. Dizziness was the most frequent treatment-related TEAE, reported in 9 of 612 patients (1.5%; Table 3).

Serious AEs (SAEs), defined as any untoward medical occurrence that is life-threatening, requires hospitalization, or results in death, occurred in 15 of 612 patients (2.5%): 7 in the AZL-M 80-mg group, 2 in the AZL-M 40-mg group, and 6 in the valsartan 160-mg group. Hypertension was the only treatment-related SAE (one patient in each treatment group). No other SAE was considered treatment related. One patient in the AZL-M 40-mg group had a fatal subarachnoid hemorrhage that was not considered related to the study drug. No clinically meaningful differences were observed between treatment groups in laboratory parameters (including hepatic transaminases, potassium, lipids, and creatinine; Table 4) or vital signs and 12-lead ECG results.

4. Discussion

This was the first phase 3 study conducted in China of AZL-M in patients with essential hypertension and, as such, it the first phase 3 study to establish the efficacy and safety of AZL-M—which is not yet approved for use in China—in this population. As the efficacy of AZL-M has been established and antihypertensive treatments have been approved in China, valsartan was used as a comparator instead of placebo in this study. The primary objective of the study was met, and the majority (62.2%) of patients in all groups achieved the target response. Both AZL-M 40 mg and AZL-M 80 mg had noninferior efficacy in reducing scSBP compared with valsartan 160 mg (the maximum dose of valsartan indicated, per product labeling in China). In addition, patients in the AZL-M 80-mg group had significantly greater reductions in scSBP than the valsartan group. Therefore, AZL-M 80 mg was considered superior to valsartan 160 mg for the treatment of hypertension in Chinese patients. These

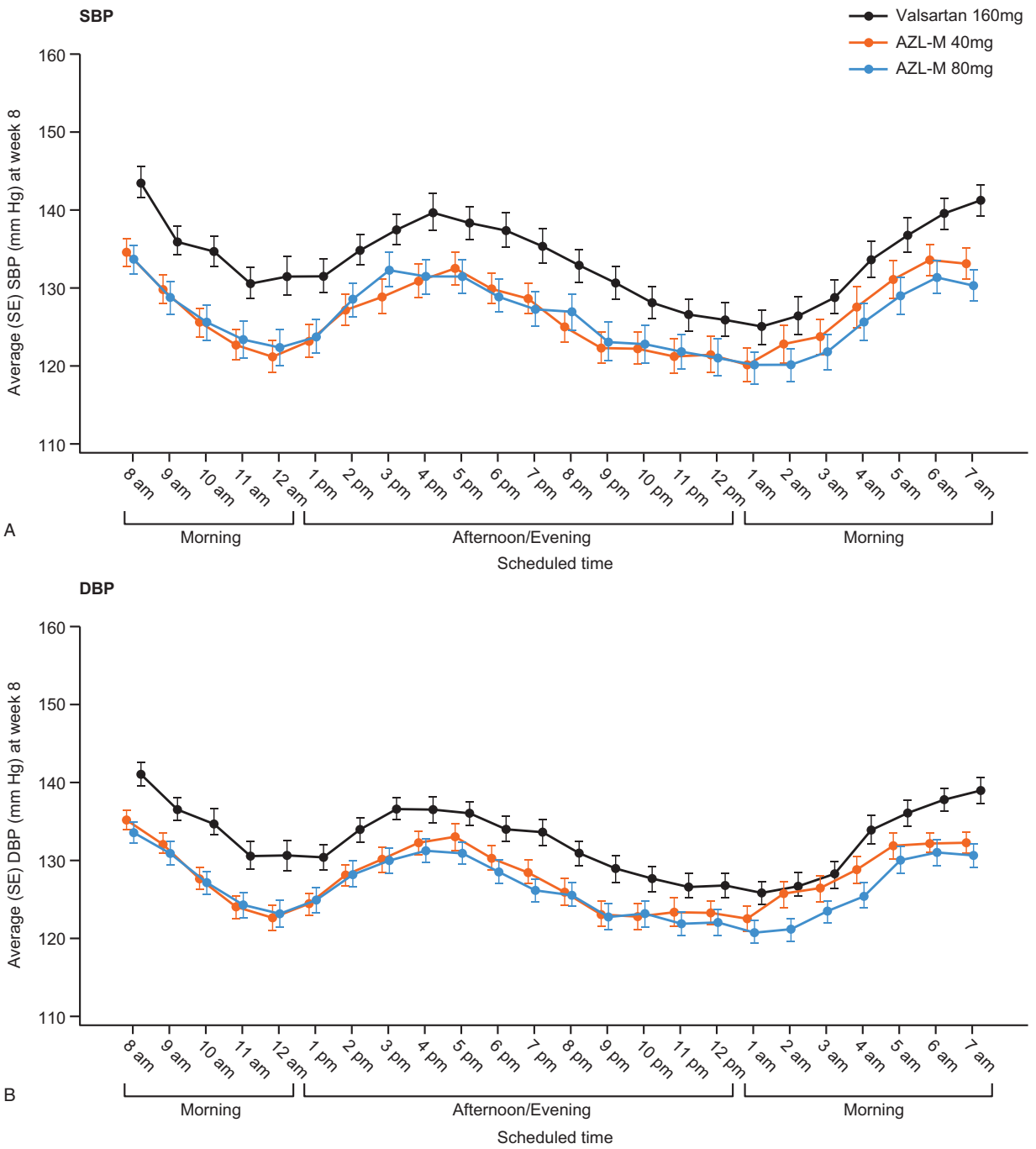

Figure 5. Hourly systolic blood pressure (A) and diastolic blood pressure (B) ambulatory blood pressure monitoring data at week 8. ABPM = ambulatory blood pressure monitoring, AZL-M = azilsartan medoxomil, DBP = diastolic blood pressure, LS = least squares, SBP = systolic blood pressure, SE = standard error.

results are consistent with previous phase 3 studies conducted in Western populations of AZL-M, which showed that AZL-M 80 mg was more effective than valsartan 320 mg in reducing SBP.[19,21]

Hypertension is a global health concern; however, awareness and control of blood pressure is insufficient in many Asian countries. and more clinical studies are needed.[25,26] In a recent placebo-controlled phase 3 study in Korea, AZL-M showed clinically meaningful and statistically significant reductions in blood pressure at 40- and 80-mg doses.[23] In the current study, AZL-M 80 mg showed superior efficacy to valsartan 160 mg in reducing scSBP and scDBP following 8 weeks of treatment. At earlier study visits (weeks 2, 4, and 6), AZL-M yielded significantly greater decreases in scSBP and scDBP than valsartan 160 mg. In the ABPM subset, both AZL-M 80 and 40 mg reduced 24-hour SBP and DBP by significantly more than valsartan. ABPM is less prone than clinic blood pressure measurements to "white-coat hypertension" and is a better measure of estimated hypertension control.[27,28] ABPM parameters may be clinically more predictive of cardiovascular outcome than clinic measurements, and 24-hour SBP has been demonstrated to be the best predictor of cardiovascular risk.[29–31]

Table 2

Overview of treatment-emergent adverse events.

	AZL-M 40 mg (n = 199)		AZL-M 80 mg (n = 209)		Valsartan 160 mg (n = 204)		Total (N = 612)	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Total TEAEs	193	105 (52.8)	236	118 (56.5)	221	113 (55.4)	650	336 (54.9)
Related to study drug	31	23 (11.6)	31	24 (11.5)	22	18 (8.8)	84	65 (10.6)
Not related to study drug	162	82 (41.2)	205	94 (45.0)	199	95 (46.6)	566	271 (44.3)
TEAE severity								
Mild	183	97 (48.7)	217	105 (50.2)	199	99 (48.5)	599	301 (49.2)
Moderate	7	5 (2.5)	15	9 (4.3)	17	9 (4.4)	39	23 (3.8)
Severe	3	3 (1.5)	4	4 (1.9)	5	5 (2.5)	12	12 (2.0)
TEAEs leading to discontinuation		4 (2.0)		6 (2.9)		2 (1.0)		12 (2.0)
SAEs	2	2 (1.0)	7	7 (3.3)	6	6 (2.9)	15	15 (2.5)
Deaths		1 (0.5)		0		0		1 (0.2)

AZL-M = azilsartan medoxomil, SAE = serious adverse event, TEAE = treatment-emergent adverse event.

Table 3

Most common (≥2% of patients) treatment-emergent adverse events and treatment-related treatment-emergent adverse events (≥1% of patients).

	AZL-M 40 mg (n = 199)	AZL-M 80 mg (n = 209)	Valsartan (n = 204)	Total (N = 612)
Any TEAE (in ≥2% of patients)				
Hyperlipidemia	14 (7.0)	14 (6.7)	16 (7.8)	44 (7.2)
Upper respiratory tract infection	10 (5.0)	13 (6.2)	14 (6.9)	37 (6.0)
Albuminuria	11 (5.5)	10 (4.8)	6 (2.9)	27 (4.4)
Hyperuricemia	8 (4.0)	11 (5.3)	8 (3.9)	27 (4.4)
Urinary tract infection	7 (3.5)	7 (3.3)	4 (2.0)	18 (2.9)
Protein urine present	2 (1.0)	7 (3.3)	6 (2.9)	15 (2.5)
Dizziness	4 (2.0)	7 (3.3)	3 (1.5)	14 (2.3)
Hematuria	5 (2.5)	4 (1.9)	5 (2.5)	14 (2.3)
Renal impairment	3 (1.5)	5 (2.4)	6 (2.9)	14 (2.3)
Carotid arteriosclerosis	5 (2.5)	6 (2.9)	2 (1.0)	13 (2.1)
Diarrhea	4 (2.0)	5 (2.4)	4 (2.0)	13 (2.1)
Hypertriglyceridemia	2 (1.0)	6 (2.9)	4 (2.0)	12 (2.0)
Urine albumin/creatinine ratio increased	3 (1.5)	4 (1.9)	5 (2.5)	12 (2.0)
Albumin urine present	2 (1.0)	3 (1.4)	6 (2.9)	11 (1.8)
Cough	4 (2.0)	5 (2.4)	1 (0.5)	10 (1.6)
Blood creatinine phosphokinase increased	5 (2.5)	1 (0.5)	3 (1.5)	9 (1.5)
Blood triglycerides increased	4 (2.0)	3 (1.4)	2 (1.0)	9 (1.5)
Headache	1 (1.0)	1 (0.5)	5 (2.5)	8 (1.3)
Blood glucose increased	1 (0.5)	2 (1.0)	4 (2.0)	7 (1.1)
TEAEs related to study drug (in ≥1% of patients), n (%)				
Dizziness	3 (1.5)	4 (1.9)	2 (1.0)	9 (1.5)
Albuminuria	4 (2.0)	3 (1.4)	0	7 (1.1)
Hyperlipidemia	1 (0.5)	2 (1.0)	2 (1.0)	5 (0.8)
Hypotension	1 (0.5)	3 (1.4)	0	4 (0.7)
Blood creatinine phosphokinase increased	2 (1.0)	0	1 (0.5)	3 (0.5)
Gamma-glutamyltransferase increased	1 (0.5)	0	2 (1.0)	3 (0.5)
Headache	1 (0.5)	0	2 (1.0)	3 (0.5)
Hyperkalemia	1 (0.5)	2 (1.0)	0	3 (0.5)
Hyperuricemia	1 (0.5)	2 (1.0)	0	3 (0.5)
Hypertension	0	2 (1.0)	1 (0.5)	3 (0.5)
Blood potassium increased	0	0	2 (1.0)	2 (0.3)
Endocrine disorder	2 (1.0)	0	0	2 (0.3)
Hepatic function abnormal	0	2 (1.0)	0	2 (0.3)
Renal impairment	2 (1.0)	0	0	2 (0.3)

AZL-M = azilsartan medoxomil, TEAE = treatment-emergent adverse event.

Table 4

Serum chemistry changes from baseline to final visit (safety analysis set).

	AZL-M, 40 mg N = 199		AZL-M, 80 mg N = 209		Valsartan 160 mg N = 204	
Serum chemistry test	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Albumin (g/L)						
Baseline	199	45.6 (2.30)	209	45.8 (2.55)	204	45.8 (2.41)
Final visit	195	45.5 (2.14)	204	45.4 (2.45)	197	45.6 (2.42)
Change	195	−0.2 (2.16)	204	−0.3 (2.23)	197	−0.2 (2.38)
ALT (U/L)						
Baseline	199	22.7 (15.02)	209	21.7 (11.50)	204	21.3 (11.27)
Final visit	195	22.3 (12.04)	204	22.5 (13.09)	197	22.3 (11.53)
Change	195	−0.6 (11.37)	204	0.8 (8.73)	197	0.9 (9.13)
AST (U/L)						
Baseline	199	22.2 (9.82)	209	21.4 (7.71)	204	21.5 (12.44)
Final visit	195	21.7 (7.62)	204	21.5 (8.47)	197	21.3 (5.91)
Change	195	−0.5 (9.04)	204	0.2 (5.25)	197	−0.2 (12.09)
Alkaline phosphatase (U/L)						
Baseline	199	77.1 (19.81)	209	76.5 (20.01)	204	77.3 (20.22)
Final visit	195	75.3 (18.51)	204	74.8 (18.37)	197	75.8 (19.30)
Change	195	−1.2 (8.38)	204	−1.5 (9.77)	197	−1.1 (9.14)
Total bilirubin (μmol/L)						
Baseline	199	10.268 (5.1533)	209	10.930 (4.8486)	204	11.114 (5.3000)
Final visit	195	9.705 (4.9978)	204	10.060 (4.4908)	197	10.176 (4.6533)
Change	195	−0.517 (3.5889)	204	−0.792 (4.0010)	197	−0.965 (3.8092)
Creatinine kinase (U/L)						
Baseline	199	109.0 (57.18)	209	114.4 (69.53)	204	192.4 (1156.45)
Final visit	195	112.5 (86.49)	204	118.1 (82.01)	197	121.9 (76.28)
Change	197	3.5 (80.63)	204	3.7 (60.23)	197	−73.1 (1164.89)
Creatinine (μmol/L)						
Baseline	199	61.3 (15.68)	209	62.0 (18.10)	204	64.6 (17.70)
Final visit	195	62.1 (18.35)	204	62.6 (17.43)	197	65.3 (18.57)
Change	195	0.6 (9.04)	204	0.9 (7.90)	197	0.5 (8.64)
Glucose (mmol/L)						
Baseline	199	5.35 (0.798)	209	5.64 (1.676)	204	5.62 (1.599)
Final visit	195	5.55 (1.018)	204	5.70 (1.484)	197	5.65 (1.216)
Change	195	0.19 (0.799)	204	0.06 (1.081)	197	0.02 (1.185)
Potassium (mmol/L)						
Baseline	199	4.16 (0.352)	209	4.18 (0.325)	204	4.18 (0.343)
Final visit	195	4.26 (0.367)	204	4.24 (0.375)	197	4.21 (0.353)
Change	195	0.09 (0.363)	204	0.05 (0.353)	197	0.03 (0.383)
Sodium (mmol/L)						
Baseline	199	141.6 (1.74)	209	141.2 (1.90)	204	141.4 (1.88)
Final visit	195	141.3 (1.90)	204	141.3 (1.99)	197	141.0 (1.95)
Change	195	−0.2 (1.95)	204	0.0 (1.95)	197	−0.4 (2.03)
Uric acid (μmol/L)						
Baseline	199	353.6 (82.84)	209	349.3 (89.52)	204	365.1 (98.65)
Final visit	195	365.4 (86.16)	204	362.7 (97.10)	197	374.4 (102.82)
Change	195	10.8 (59.55)	204	14.4 (55.87)	197	9.6 (58.72)
Total cholesterol (mmol/L)						
Baseline	199	4.896 (0.9165)	209	4.910 (0.9032)	204	4.899 (0.9494)
Final visit	195	4.834 (0.9454)	202	4.837 (0.9444)	194	4.870 (0.9552)
Change	195	−0.059 (0.5890)	202	−0.070 (0.5583)	194	−0.005 (0.7106)
HDL (mmol/L)						
Baseline	199	1.298 (0.3443)	209	1.259 (0.3240)	204	1.249 (0.3522)
Final visit	195	1.265 (0.3534)	202	1.229 (0.3335)	194	1.210 (0.3274)
Change	195	−0.032 (0.1883)	202	−0.029 (0.2194)	194	−0.028 (0.2082)
LDL (mmol/L)						
Baseline	199	2.765 (0.8044)	209	2.801 (0.8033)	204	2.776 (0.8611)
Final visit	195	2.662 (0.8073)	202	2.709 (0.8025)	194	2.710 (0.7647)
Change	195	−0.098 (0.5433)	202	−0.088 (0.5437)	194	−0.047 (0.5863)
Triglycerides (mmol/L)						
Baseline	199	1.863 (1.1052)	209	1.875 (0.8584)	204	1.994 (1.0694)
Final visit	195	2.131 (1.6635)	202	2.044 (1.2895)	194	2.214 (1.7216)
Change	195	0.257 (1.4532)	202	0.173 (1.0977)	194	0.203 (1.4551)

ALT = alanine transaminase, AST = aspartate transaminase, AZL-M = azilsartan medoxomil, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SD = standard deviation.

The proportion of responders at week 8 were similar across the treatment groups for the response criteria for scSBP (<140 mm Hg and/or reduction of ≥20 mm Hg), scDBP (<90 mm Hg and/or reduction of ≥10 mm Hg), and the joint target (scSBP <140 mm Hg and scDBP <90 mm Hg). However, a larger percentage of patients achieved the target response at weeks 4 and 6 with AZL-M than with valsartan 160 mg.

Current Chinese clinical guidelines recommend a target blood pressure of 140/80 mm Hg; however, the recently updated American College of Cardiology/American Heart Association (ACC/AHA) guidelines define stage 1 hypertension as SBP between 130 to 139 or DBP between 80 to 89.[10,11]

If the updated American College of Cardiology/American Heart Association guidelines are adopted in China, the percentage of population in China classified as having hypertension and in need of pharmacologic treatment will increase substantially.[12] In the current study, a statistically significantly higher percentage of patients at week 8 achieved scSBP <130 mm Hg or scDBP <80 mm Hg in the AZL-M 80-mg group compared with the valsartan 160-mg group.

The present study confirms that AZL-M demonstrates a consistent safety profile in Chinese patients with hypertension, similar to other populations around the world.[18,19] There was a low incidence of SAEs and a low rate of discontinuations due to TEAEs. The most frequent TEAE (hyperlipidemia) is often comorbid with hypertension,[32] and the most frequent treatment-related TEAE (dizziness) is a common adverse reaction with ARBs.[33] There were no clinically meaningful trends in any treatment group with respect to laboratory parameters, including high-density lipoprotein cholesterol, total cholesterol, and triglycerides. There were also no clinically meaningful changes in serum potassium levels, which is consistent with findings in Korean patients who were treated with AZL-M 40 and AZL-M 80 mg.[23]

The study has several limitations. Only a subgroup of patients were evaluated with ABPM; however, AZL-M groups demonstrated significantly greater reductions in both 24-hour mean ABPM SBP and DBP compared with the valsartan 160-mg group, regardless of age, baseline SBP, or baseline DBP. Only a small number of patients were aged ≥65 years (n = 127, 20.8%), but a similar treatment effect among the 3 groups was observed in elderly patients. Only patients with mild to moderate hypertension (scSBP 150–189 mm Hg) were eligible for enrollment, and the relatively short treatment duration precludes extrapolation of the results to a broader categories of hypertension or conclusive statements about the long-term treatment effect of ACL-M.

5. Conclusions

This was the first phase 3 study to establish the efficacy and safety of AZL-M in a Chinese population. AZL-M demonstrated clinically meaningful reductions in blood pressure in Chinese patients with essential hypertension, with noninferior efficacy at the 40-mg dose level and superior efficacy at the 80-mg dose level compared with valsartan 160 mg, and showed acceptable safety —consistent with the AZL-M safety profile in other populations.

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Author contributions

Administrative support: Michie Hisada, Jingtao Wu, Wei Zhou, and Changsheng Ma.
Collection and assembly of data: All authors collected the data; the data was assembled by Michie Hisada, Jingtao Wu, and Wei Zhou.
Conception and design: Changsheng Ma, Takeda.
Data analysis and interpretation: Michie Hisada (safety) and Takeda Development Center performed statistical analysis of the data; all authors interpreted the data.
Final approval of manuscript: all authors.
Manuscript writing: all authors.
Provision of study materials or patients: Jiahui Wu, Xin Du, Qiang Lv, Zhanquan Li, Zeqi Zheng, Yong Xia, Chengchun Tang, Zhuhua Yao, Jun Zhang, Mingzhi Long, and Changsheng Ma provided patients; study materials were provided by Takeda Development Center Americas, Inc., Deerfield, IL, USA, and Takeda Development Center Asia, Pte. Ltd., Shanghai, China.

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