Safety, Tolerability, and Efficacy of Azilsartan Medoxomil With or Without Chlorthalidone During and After 8 Months of Treatment for Hypertension

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A phase 3, 26-week, open-label, titrate-to-target study (n=418) assessed the safety of azilsartan medoxomil (AZL-M) alone and with chlorthalidone (CLD), followed by a 6-week, double-blind, placebo-controlled reversal phase with change in clinic diastolic blood pressure (DBP) as the primary endpoint. Target blood pressure (BP) was <140/90 mm Hg (<130/80 mm Hg with diabetes/chronic kidney disease). AZL-M was initiated at 40 mg once a day (QD), force-titrated to 80 mg at week 4. CLD 25 mg QD could be added (weeks 8–22), if required, to reach target, followed by additional antihypertensives from week 12. At the end of the open-label phase, mean change in systolic BP (SBP)/DBP from baseline was −23/−16 mm Hg. The most common adverse events, irrespective of treatment, were dizziness (8.9%) and headache (7.2%). Serious AEs were reported in eight patients (1.9%). Consecutive creatinine elevations ≥50% with values exceeding the upper limit of normal (ULN) were reported in nine (2.2%) patients. All returned to below the 50% threshold; most also returned to below the ULN after drug discontinuation. Mean DBP was maintained through the reversal phase in patients receiving AZL-M, but increased with placebo (difference: −7.8 mm Hg, 95% confidence interval, −9.8 to −5.8; $P<.001$). AZL-M alone or with CLD showed good long-term safety and stable BP improvements in a titrate-to-target approach. BP improvements caused by AZL-M therapy were safely reversible upon AZL-M withdrawal. *J Clin Hypertens (Greenwich).* 2015; 17:183–192. © 2015 The Authors. *Journal of Clinical Hypertension* published by Wiley Periodicals, Inc.

Azilsartan medoxomil (AZL-M) 20 mg to 80 mg once daily (QD) is a potent angiotensin II receptor blocker (ARB) for the treatment of hypertension in adults, either alone or in combination with other antihypertensive agents.[1–4] It has a unique pharmacologic profile vs other agents in this class, including a slower angiotensin II type 1 receptor dissociation rate and improved receptor specificity.[5] In previous 6- to 8-week phase 3 studies, AZL-M 80 mg QD was statistically superior to placebo and two commonly prescribed ARBs—olmesartan medoxomil and valsartan at their maximal approved doses (40 mg/d and 320 mg/d, respectively)—in lowering both clinic and 24-hour mean blood pressure (BP) in a general hypertensive population with mild to moderate hypertension.[1,2,6–8] Based on data from three clinical trials, AZL-M 80 mg provided a 2.1 mm Hg to 3.5 mm Hg greater reduction in systolic BP (SBP) compared with olmesartan medoxomil 40 mg, and a 4.0 mm Hg to 5.4 mm Hg greater reduction compared with valsartan 320 mg.[6–8] This improved efficacy over olmesartan medoxomil and valsartan was observed without an increase in adverse events (AEs). Based on meta-analyses of clinical outcomes trials, BP differences of this magnitude may be of clinical significance, as they are associated with a reduced risk of cardiovascular disease, especially stroke.[9]

The available evidence suggests that at least 75% of hypertensive patients require combination therapy in order to achieve BP targets and at least 25% require triple therapy.[10,11] Coadministration of a renin-angiotensin system (RAS)–blocking agent with a diuretic agent, such as the thiazide-like diuretic chlorthalidone (CLD), is a recommended approach to treating hypertension.[12–15] A recently published study reported that a fixed-dose combination (FDC) of AZL-M plus CLD was more effective at lowering SBP than AZL-M coadministered with hydrochlorothiazide (HCTZ).[16] Furthermore, studies using the FDC of AZL-M and CLD showed that it provided substantially greater SBP reductions compared with the respective monotherapy components over 8 weeks, and the combination of AZL-M and CLD was associated with a reduced incidence of hypokalemia compared with CLD monotherapy.[17] The AZL-M/CLD FDC (force-titrated to a high dose of either 40/25 mg or 80/25 mg) also provided superior antihypertensive efficacy over 12 weeks compared with the maximum dose of the FDC olmesartan/HCTZ approved in the United States (40/25 mg).[18,19]

The phase 3, open-label, multicenter study reported here evaluated the safety and tolerability of AZL-M

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alone and in combination with CLD as part of a titrate-to-target BP approach for the longer duration of 26 weeks in patients with essential hypertension. The 26-week open-label treatment period was followed by a 6-week placebo-controlled, double-blind reversal phase to evaluate the durability of the antihypertensive effect and potential for rebound hypertension.

RESEARCH DESIGN AND METHODS

Patient Eligibility

The present study included male and female patients older than 18 years with essential hypertension. For inclusion, participants were required to have screening DBP values ≥95 mm Hg and ≤119 mm Hg (or ≥85 mm Hg and ≤109 mm Hg in those with diabetes mellitus or chronic kidney disease [CKD]) and clinical laboratory evaluations (including clinical chemistry, hematology, and complete urinalysis) within the reference ranges for the testing laboratory. The main exclusion criteria were SBP >185 mm Hg; current use of more than two antihypertensive agents; anticipated use of an ARB other than AZL-M; hypersensitivity to ARBs; clinically relevant or unstable cardiovascular diseases within 6 months of enrollment; secondary hypertension of any etiology; known or suspected unilateral or bilateral renal artery stenosis; severe renal dysfunction or disease (based on calculated creatinine clearance <30 mL/min/1.73 m^2) at screening; history of drug or alcohol abuse within the past 2 years; poorly controlled diabetes mellitus at screening (glycosylated hemoglobin >8.5%); alanine aminotransferase >2.5 times the upper limit of normal laboratory range (ULN), active liver disease, or jaundice; and serum potassium level greater than the ULN. Pregnant or lactating women were also excluded. Patients were not required to discontinue their antihypertensive medication(s) before entry into the open-label phase.

Study Design

This phase 3 study consisted of a 7-day screening phase; a 26-week open-label phase; a 6-week randomized, double-blind reversal phase; and a 7-day post-treatment AE follow-up phase (Figure 1). The study took place between June 2007 and May 2009. A total of 780 patients were screened at 51 sites in the United States, Mexico, and Argentina. The study was approved by the applicable institutional review boards or ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent to participate in the study.

For the 26-week, open-label phase, patients received an initial dose of AZL-M 40 mg QD. At week 4, the dose was force-titrated to 80 mg QD, and from week 8 to week 22, CLD 25 mg QD could be added to achieve target BP (defined as <140/90 mm Hg or <130/80 mm Hg for patients with diabetes mellitus or CKD). Additional antihypertensive treatment (except ARBs) could be added, if required, from week 12 to week 22. If the treatment algorithm for titration of study medication and additional antihypertensive agents was followed, patients could be discontinued if confirmed seated DBP was ≥115 mm Hg or seated SBP was ≥185 mm Hg. At week 26/end of open-label phase, patients were randomized into a 6-week, double-blind reversal phase in which they continued to receive AZL-M at their final dose level or were switched to placebo. Use of any other antihypertensive medications, including CLD, remained stable for the 4 weeks prior to randomization and during this 6-week phase. Study medication was taken with or without food, preferably in the morning.

Endpoints and Assessments

The primary efficacy endpoint was the change in trough clinic sitting DBP measured during the double-blind reversal phase (weeks 26–32). The secondary efficacy endpoint was the change in trough clinic sitting SBP for the same period. Trough clinic sitting DBP and SBP were summarized at scheduled time points using descriptive statistics. Efficacy analyses were based on the full analysis dataset (all randomized patients who received at least one dose of double-blind study medication).

Safety and tolerability were assessed based on systematic AE and serious AE (SAE) reporting and other specific safety parameters. Safety analyses were based on the safety analysis set (all enrolled patients who received at least one dose of study medication). During the 26-week open-label period, there were scheduled clinic visits at baseline and at weeks 4, 8, 12, 18, and 26. Scheduled visits during the reversal phase were at weeks 28, 30, and 32. At each clinic visit, vital signs, AEs, concomitant medications, and study medication compliance were recorded. At screening, baseline, and weeks 4, 8, 12, 18, 26, and 32, weight measurements, clinical laboratory tests, and serum pregnancy tests (in women) were performed. At screening and weeks 26 and 32 (or early termination), a complete physical examination and 12-lead electrocardiographic examination were performed.

Serum creatinine was evaluated as a laboratory parameter of special interest, with a focus on patients identified as having a creatinine elevation ≥50% from baseline and >ULN at any measurable time point (elevations ≥30% and >ULN at any time point were also recorded).

Statistical Analyses

Unless specified otherwise, separate data analyses were performed for the open-label phase and the double-blind reversal phase. Descriptive statistics were generated for continuous demographic and baseline variables for both treatment phases. Adverse events, clinical laboratory data, weight, vital signs, and other safety data were summarized descriptively in both phases.

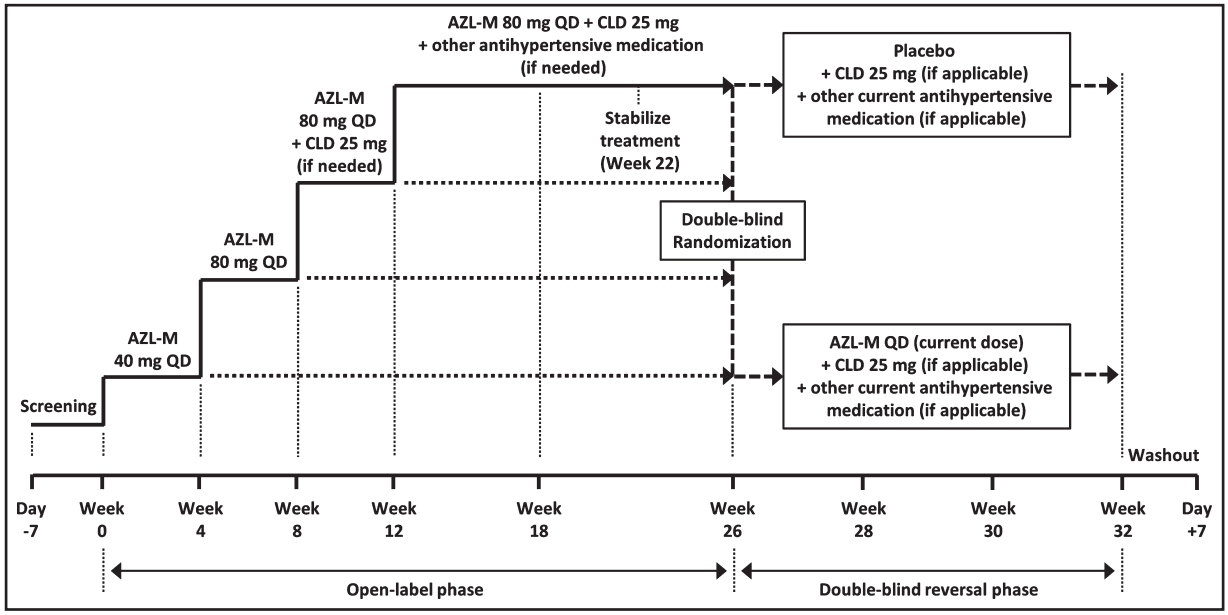

FIGURE 1. Study design for the open-label phase and double-blind reversal phase. AZL-M indicates azilsartan medoxomil; QD, once daily; CLD, chlorthalidone.

Open-label phase. Data from the open-label phase were summarized by treatment received as follows: (1) all patients, regardless of treatment received; (2) AZL-M (patients who never received CLD as part of the titrate-to-target regimen during the study); and (3) AZL-M plus CLD (patients who received CLD as part of the titrate-to-target regimen at some point during the study and, potentially, other non-ARB antihypertensive agents, as needed). These categories do not represent randomized groups, as treatment received was dependent on patient response. The BP-lowering efficacy in the open-label phase was analyzed by descriptive statistics only. Results are presented as mean±standard deviation unless otherwise specified.

Double-blind reversal phase. Analysis groups for the randomized, double-blind reversal phase were: (1) AZL-M (patients randomized to maintain their AZL-M treatment in addition to their current other antihypertensive medications, if applicable); and (2) placebo (patients randomized to switch from AZL-M to placebo in addition to their current other antihypertensive medications, if applicable). The treatment groups were compared using an analysis of covariance model with treatment as factor and baseline value (defined as the average of three trough sitting measurements at the double-blind randomization visit) as a covariate. A sample size of 140 patients per arm was calculated as sufficient to detect a difference of 3.5 mm Hg in mean change from baseline in DBP, based on a two-sample *t* test, at a 5% two-sided significance level, with a power of 90%, and an assumed standard deviation of 9 mm Hg. Approximately 400 patients were to be enrolled in this study to account for some dropouts. The last-observation-carried-forward procedure was used to handle missing assessments or early discontinuation during the double-blind treatment period.

RESULTS

Patient Disposition and Demographics

Open-label phase. A total of 780 patients were screened and 418 entered the open-label phase (Figure S1). The majority of patients were aged 45 to 64 years, 10% were 65 years or older, and 17% had diabetes. Demographic and baseline characteristics for the single cohort in the open-label phase are given in Table I. The study population also included a relatively high proportion of black patients (24%), and these patients tended to have a higher baseline DBP (Figure S2) and were younger (mean 47.8 vs 53.6 y for white patients), and a greater proportion were women (60% vs 47% for white patients). Overall, 40% of patients who entered the open-label phase were taking at least one other antihypertensive medication at baseline, and 24% of patients reported that they were receiving an angiotensin-converting enzyme (ACE) inhibitor (there were no recommendations against the use of dual RAS blockade at the time the study was performed).

A total of 354 patients (84.7%) were force-titrated from AZL-M 40 mg to 80 mg QD at week 4, in line with the study titration regimen (and if the 40-mg dose was deemed to be tolerable). Of the 64 patients (15.3%) who were not force-titrated, 30 discontinued prior to week 4 and 34 remained on 40 mg after week 4. Among the patients taking AZL-M 80 mg QD after week 4, 115 (27.5%) continued to receive AZL-M 80 mg QD alone,

TABLE I. Demographic and Baseline Characteristics

	Open-Label Phase (Baseline=Week 0)			Randomized, Double-Blind Reversal Phase (Baseline=Week 26)	
Parameter	Total Cohort	*AZL-M*[a]	*AZL-M+CLD*[b]	AZL-M	Placebo
No.	418	*179*	*239*	148	151
Sex, No. (%)					
Male	208 (49.8)	*83 (46.4)*	*125 (52.3)*	72 (48.6)	77 (51.0)
Female	210 (50.2)	*96 (53.6)*	*114 (47.7)*	76 (51.4)	74 (49.0)
Age, mean±SD, y	52.1±10.1	*50.4±10.2*	*53.3±10.0*	52.9±9.6	51.8±9.7
Race, No. (%)[c]					
American Indian/Alaska Native	32 (7.7)	*18 (10.1)*	*14 (5.9)*	10 (6.8)	9 (6.0)
Asian	4 (1.0)	*4 (2.2)*	*0*	1 (0.7)	2 (1.3)
Black/African American	99 (23.7)	*27 (15.1)*	*72 (30.1)*	30 (20.3)	38 (25.2)
White	287 (68.7)	*132 (73.7)*	*155 (64.9)*	107 (72.3)	104 (68.9)
Multiracial	4 (1.0)	*2 (1.1)*	*2 (0.8)*	0	2 (1.3)
BMI, mean±SD, kg/m^2	33.1±6.5	*33.2±6.7*	*33.0±6.3*	33.2±6.7	33.1±6.5
Baseline DBP, mean±SD, mm Hg	99.9±7.1	*98.2±7.3*	*101.2±6.6*	83.7±8.2	82.3±10.2
Baseline SBP, mean±SD, mm Hg	155.1±14.3	*150.8±14.8*	*158.3±13.0*	130.3±16.1	128.3±16.2

Abbreviations: AZL-M, azilsartan medoxomil; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation. Note that the individual columns in italics do not represent randomized groups and are part of a single cohort (ie, they are presented separately according to treatment received for clarity). [a]Patients who did not require additional treatment with chlorthalidone (CLD) during the open-label phase. [b]Patients who required additional treatment with CLD after week 8 during the open-label phase. [c]Patients who indicated more than 1 race category were included in each category indicated and also in the multiracial category.

217 (51.9%) subsequently received add-on CLD (without additional antihypertensive medication), and 22 (5.3%) received add-on CLD plus additional antihypertensive medication. Overall, 51 patients (12.2%) initiated antihypertensive medications other than AZL-M or CLD during the open-label phase (including medications that were initiated without adhering to the study titration regimen)—this included 6% of the patients who did not require add-on CLD and 17% of the patients who did require add-on CLD. The most common agents initiated after AZL-M or CLD were ACE inhibitors (5.3%), β-blockers, (3.3%), calcium channel blockers (2.9%), and diuretics/HCTZ (2.6%).

Patients who additionally received CLD in the open-label phase had a higher mean BP at baseline (158.3/101.2 mm Hg) compared with those who did not receive CLD (150.8/98.2 mm Hg) (Table I). Furthermore, patients who required CLD were slightly older and were more likely to be black. Approximately 73% of black patients required add-on CLD therapy compared with 54% of white patients. There was also a slight sex imbalance, with approximately 60% of men requiring add-on CLD therapy compared with 54% of women.

Of the 418 patients who enrolled in the open-label phase, 119 (28.5%) prematurely discontinued (Figure S1). The most frequent reasons for premature discontinuation from the open-label phase were voluntary withdrawal (8.9%), AE (6.5%), and loss to follow-up (5.7%). The mean duration of treatment during the open-label phase was 151.6 days, and 62% of the patients had at least 6 months of open-label AZL-M exposure.

Double-blind reversal phase. A total of 299 patients were randomized in the double-blind reversal phase: 148 stayed on AZL-M (at the final dose they received in the open-label phase) and 151 were switched from AZL-M to placebo. No major differences were observed between the randomized treatment groups in demographic and baseline characteristics (Table I). Of the 299 randomized patients, 17 (5.7%) discontinued prematurely from the double-blind reversal phase of the study (7.4% AZL-M, 4.0% placebo) (Figure S1). The most frequent reasons for premature discontinuation from the double-blind reversal phase were identical to the open-label phase of the study: voluntary withdrawal (2.3%), AE (1.3%), and loss to follow-up (1.0%).

Open-Label Phase—Efficacy

At open-label baseline, the mean trough clinic sitting DBP was 100.0 mm Hg (98.3 mm Hg in patients who received AZL-M alone and 101.2 mm Hg in patients who additionally received CLD). Clinic DBP decreased from open-label baseline to week 26 on average by 15.8 mm Hg (Figure. 2A). At open-label baseline, the mean trough clinic sitting SBP was 155.4 mm Hg (151.1 mm Hg in patients who received AZL-M alone and 158.3 mm Hg in patients who additionally received CLD). Clinic SBP decreased from open-label baseline to week 26 on average by 23.0 mm Hg (Figure 2B). At weeks 4 and 8, the decreases in clinic DBP and SBP were less in patients who later received AZL-M plus CLD compared with those who received AZL-M alone (Figures 2A and B). At weeks 12, 18, and 26, mean clinic DBP and SBP changes were similar between

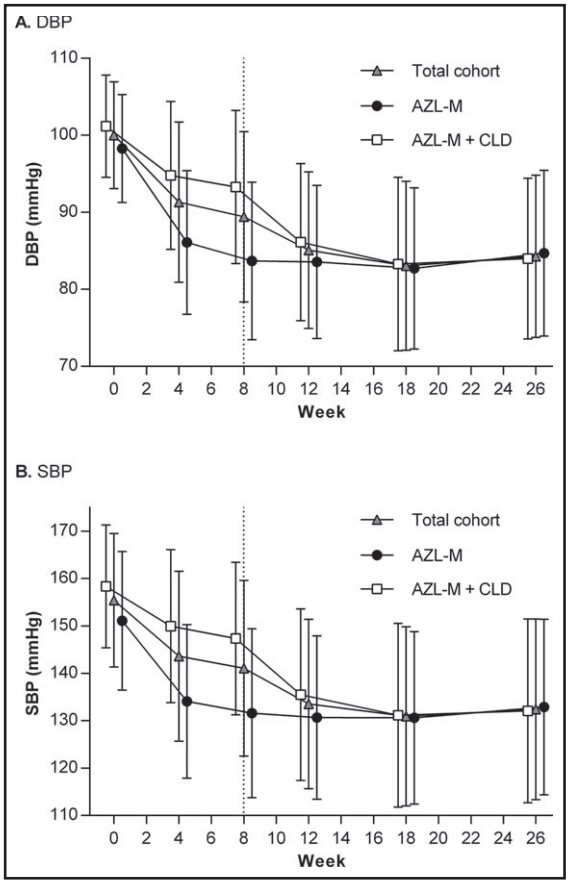

FIGURE 2. Mean trough clinic sitting diastolic blood pressure (DBP) (A) and systolic blood pressure (SBP) (B) by study visit (open-label phase; last observation carried forward). Note that the individual data lines do not represent randomized groups and are in a single cohort, but are presented separately according to treatment received for clarity. AZL-M indicates azilsartan medoxomil; CLD, chlorthalidone. Data are expressed as mean±standard deviation. The dashed line at week 8 represents the first visit at which patients could additionally have received CLD.

patients who received AZL-M alone and those who additionally received CLD (Figure 2A and 2B).

An analysis according to race for the open-label phase found no notable differences between black, white, and "other" patients in the magnitude of BP-lowering, although there were some differences in baseline values (Figure S2). At open-label baseline, the mean trough clinic sitting DBP in black patients was 102.5 mm Hg in patients who received AZL-M alone and 103.6 mm Hg in patients who additionally received CLD. This was higher than the baseline values seen in white patients (97.9 mm Hg and 100.3 mm Hg, respectively). In black patients, clinic DBP decreased from open-label baseline to week 26 on average by 12.7 mm Hg in patients who received AZL-M alone and 17.3 mm Hg in patients who additionally received CLD. In white patients, the corresponding values were similar at 13.8 mm Hg and 17.2 mm Hg. The corresponding SBP baseline values were 151.7 mm Hg and 157.0 mm Hg (black patients) and 151.3 mm Hg and 159.1 mm Hg (white patients), with week 26 decreases of 16.5 mm Hg and 25.6 mm Hg (black patients) and 18.6 mm Hg and 26.9 mm Hg (white patients).

Open-Label Phase—Safety and Tolerability

The overall incidences of AEs, SAEs, and discontinuations caused by AEs during the open-label phase are given in Table II. During the open-label phase, approximately half (54.1%) of patients overall experienced an AE and these were predominantly (>90%) mild to moderate in severity. The most commonly reported AEs overall were dizziness (8.9%) and headache (7.2%). Hypotension, cough, and increased blood creatine phosphokinase, although rare, were reported more frequently in patients who additionally received CLD. Hyperuricemia was reported as an AE in 1.0% of patients and there were no new cases of gout.

Overall, 29 patients (6.9%) permanently or temporarily discontinued study drug because of the occurrence of at least one AE, most commonly due to dizziness (n=6) and fatigue (n=5). There were no discontinuations related to AEs of hypokalemia or increased creatinine. Serious AEs were reported in eight patients (1.9%) during open-label treatment, although only one case (a patient reporting dehydration, dizziness, and hypotension) was judged to be related to study drug.

Analysis according to race found no differences in the overall incidences of AEs (black 57.6%, white 53.0%), SAEs (black 0.0%, white 2.4%), or discontinuations due to AEs (black 6.1%, white 7.0%). In black patients, overall AEs were more frequent in those who additionally received CLD (65.3% vs 37.0% for those not receiving CLD), whereas the frequency was approximately equal in white patients (56.8% vs 49.7%, respectively). The pattern of individual AEs was similar between black and white patients, with the exception of increased blood creatine phosphokinase, which was more frequent in black patients (8.1% vs 1.4% in white patients).

Laboratory evaluations. Mean values for liver function tests, calcium, and sodium remained relatively unchanged. Mean changes were small for potassium and serum fasting glucose (Table III) and all lipid parameters (data not shown). Shifts from normal at baseline to high at week 26/end of the open-label phase were observed for uric acid, and these were more common in patients who also received CLD (Table III). Shifts from normal at baseline to high were also reported for blood urea nitrogen (15.4% overall; 6.3% AZL-M; 20.0% AZL-M+CLD). A shift was observed from normal potassium at baseline to low at week 26 in 5.9% of patients overall (1.0% AZL-M; 8.4% AZL-M+CLD).

Consecutive serum creatinine elevations ≥50% and >ULN were reported in 9 (2.2%) patients in either the open-label (n=6 [1.4%]) or double-blind treatment phases (n=3 [1.0%]). Two cases occurred in patients

TABLE II. Overview of AEs in the Open-Label Phase (Safety Population)

AEs	Patients, No. (%) Total Cohort (N=418)	AZL-M[a] (n=179)	AZL-M+CLD[b] (n=239)
Death	0	*0*	*0*
Serious AE	8 (1.9)	*5 (2.8)*	*3 (1.3)*
Any AE	226 (54.1)	*96 (53.6)*	*130 (54.4)*
AE leading to discontinuation[c]	29 (6.9)	*14 (7.8)*	*15 (6.3)*
AE (preferred term) in ≥3% of all patients			
Dizziness	37 (8.9)	*16 (8.9)*	*21 (8.8)*
Headache	30 (7.2)	*13 (7.3)*	*17 (7.1)*
Fatigue	16 (3.8)	*6 (3.4)*	*10 (4.2)*
Urinary tract infection	16 (3.8)	*6 (3.4)*	*10 (4.2)*
Hypotension	15 (3.6)	*4 (2.2)*	*11 (4.6)*

Abbreviation: AZL-M, azilsartan medoxomil. Note that the individual columns in italics do not represent randomized groups and are part of a single cohort. [a]Patients who did not require additional treatment with chlorthalidone (CLD) during the open-label phase. [b]Patients who required additional treatment with CLD after week 8 during the open-label phase. [c]Adverse events (AEs) leading to temporary drug interruption or permanent discontinuation.

TABLE III. Key Serum Laboratory Parameters During the Open-Label Phase (Safety Population)

Parameter	Total Cohort (N=418)	AZL-M[a] (n=179)	AZL-M+CLD[b] (n=239)
Creatinine			
≥2 consecutive elevations (≥1.5× baseline and >ULN), n/N (%)	6/400 (1.5)[g]	*1/163 (0.6)[g]*	*5/237 (2.1)*
Potassium			
Baseline, mean±SD, mmol/L[c]	4.16±0.39	*4.19±0.38*	*4.14±0.40*
Change, mean±SD, mmol/L[c]	0.06±0.42	*0.21±0.36*	*−0.01±0.43*
Shift from normal to low, n/N, %[d]	17/288 (5.9)	*1/97 (1.0)*	*16/191 (8.4)*
Sodium			
Shift from normal to low, n/N (%)[d]	7/304 (2.3)	*1/101 (1.0)*	*6/203 (3.0)*
Uric acid			
Shift from normal to high, n/N (%)[e]	67/265 (25.3)	*11/88 (12.5)*	*56/177 (31.6)*
Fasting glucose			
Baseline, mean±SD, mmol/L[f]	5.86±1.31	*5.82±1.20*	*5.89±1.38*
Change, mean±SD, mmol/L[f]	0.35±1.30	*0.32±1.21*	*0.37±1.34*

Abbreviation: SD, standard deviation. Note that the individual columns in italics do not represent randomized groups and are part of a single cohort. [a]Patients who did not require additional treatment with chlorthalidone (CLD) during the open-label phase. [b]Patients who required additional treatment with CLD after week 8 during the open-label phase. [c]For potassium, 1 mmol/L=1 mEq/L. [d]Definitions of "low:" sodium (mmol/L) <132 (18–59 y), <135 (>59 y); potassium (mmol/L) <3.4. [e]Definitions of "high:" uric acid (μmol/L) >125 (18–50 y), >149 (>50 y). [f]To convert mmol/L to mg/dL, multiply by 18. [g]One additional patient had a creatinine elevation (≥1.5× baseline and greater than the upper limit of normal [ULN]) at the end of the open-label phase and a consecutive elevation at the start of the double-blind phase; the patient was receiving azilsartan medoxomil (AZL-M) 80 mg (without chlorthalidone [CLD]) and was randomized to the AZL-M group in the double-blind phase.

taking AZL-M alone and seven cases in patients taking AZL-M plus CLD. None of these cases remained >50% of the patient's baseline or screening value at the last visit, and most elevations also returned to ≤ULN. Patients with creatinine elevations tended to have greater reductions in SBP (from a mean 159 mm Hg at baseline to 120 mm Hg at week 26) than patients without creatinine elevations (from 155 *g* to 133 mm Hg).

There were no notable changes in urinalysis parameters, vital signs, and electrocardiographic findings. Mean changes in hematology parameters were small, although shifts from normal to low for hematocrit, hemoglobin, and red blood cell (RBC) count were more common in patients who also received CLD. However, the percentage of patients with markedly reduced values was low (hematocrit <0.8 of baseline, 1.3% AZL-M, 4.6% AZL-M+CLD; hemoglobin 3 g/dL decrease from

baseline, 1.3% AZL-M, 3.3% AZL-M+CLD; RBC count <0.8 of baseline, 1.3% AZL-M, 3.8% AZL-M+CLD).

Double-Blind Reversal Phase—Efficacy

At the double-blind phase baseline (week 26), the mean clinic DBP (primary efficacy variable) was similar in the AZL-M and placebo groups (83.5 mm Hg and 82.3 mm Hg, respectively). This DBP level was maintained to the final visit (week 32) in patients who received AZL-M (Figure 3A). In contrast, DBP increased among patients who received placebo, demonstrating a loss of efficacy after discontinuation of AZL-M (Figure 3A). The least-squares (LS) mean difference between AZL-M and placebo was −7.8 mm Hg (95% CI, −9.8 to −5.8; *P*<.001) at final visit. The LS mean difference between AZL-M and placebo was also statistically significant at each scheduled double-blind dosing visit. The DBP difference between AZL-M and placebo at the final visit did not vary appreciably according to race (black −7.5 mm Hg [n=64], white −7.7 mm Hg [n=206], other −11.0 mm Hg [n=22]).

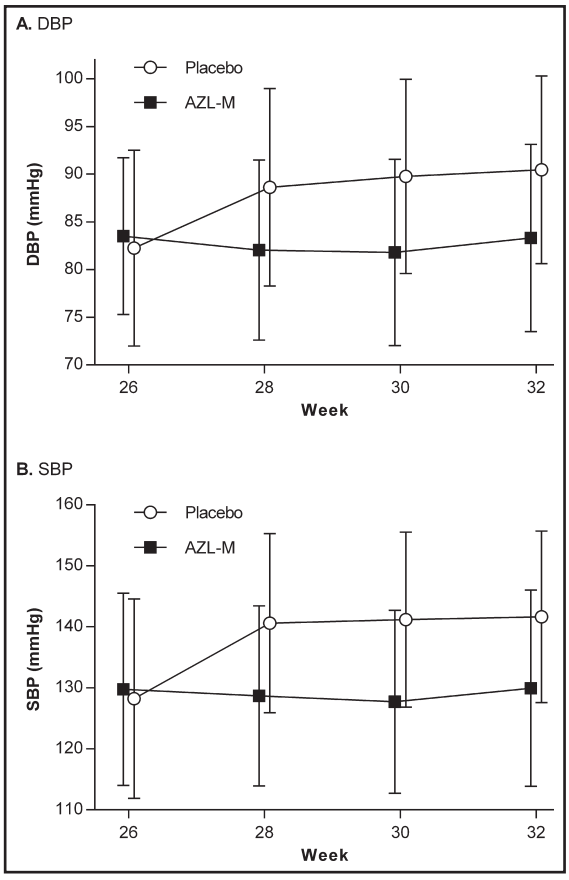

FIGURE 3. Mean trough clinic sitting diastolic blood pressure (DBP) (A) and systolic blood pressure (SBP) (B) by study visit (double-blind reversal phase; last observation carried forward). AZL-M indicates azilsartan medoxomil; CLD, chlorthalidone. Data are expressed as mean±standard deviation.

At the double-blind phase baseline (week 26), the mean clinic SBP was also similar in the AZL-M and placebo groups (129.8 mm Hg and 128.2 mm Hg, respectively). As with DBP, this SBP level was maintained from week 26 to week 32 in patients who received AZL-M, whereas it increased in patients receiving placebo (Figure 3B). The LS mean difference between AZL-M and placebo was −12.4 mm Hg (95% CI, −15.5 to −9.3; *P*<.001) at final visit, and the LS mean difference was statistically significant at each scheduled double-blind dosing visit. The SBP difference between AZL-M and placebo at the final visit was more variable than DBP when analyzed according to race (black −8.6 mm Hg [n=64], white −13.3 mm Hg [n=206], other −20.5 mm Hg [n=22]).

Double-Blind Reversal Phase—Safety and Tolerability

The overall incidences of AEs, serious AEs, and discontinuations due to AEs during the double-blind reversal phase are given in Table IV. Approximately one quarter of patients experienced an AE (28% in the AZL-M group and 25% in the placebo group) and most events (>90%) were mild to moderate in severity. Headache was the most frequently reported AE in placebo-treated patients (5.3% vs 3.4% with AZL-M); no AE was reported by ≥5.0% of patients in the AZL-M group. Only five patients (1.7%) permanently or temporarily discontinued study drug because of the occurrence of at least one AE (3 [2.0%] receiving AZL-M and 2 [1.3%] receiving placebo). One serious AE of hypertensive crisis was reported in a patient in the reversal phase 13 days after being randomized to placebo. The patient (a 44-year-old man with a history of obesity) was admitted to the hospital with headache and paresthesia of the left mid-face, which resolved the following day.

Laboratory evaluations. Consecutive creatinine elevations ≥50% and >ULN were reported in only two patients during the double-blind reversal phase (both in the AZL-M group [1.4%], excluding the one patient with a consecutive elevation that spanned both phases). In both patients, creatinine levels had returned to <50% above baseline and <ULN at follow-up. There were no notable differences in hematologic parameters (including hemoglobin) and urinalysis parameters, vital signs, and electrocardiographic findings between the two groups.

DISCUSSION

In the current study involving patients with mild to moderate essential hypertension, treatment with AZL-M, either alone or in combination with CLD 25 mg as part of a titrate-to-target approach, was safe and well tolerated and led to large reductions in clinic BP during the 26-week open-label phase (DBP −15.8 mm Hg and SBP −23.0 mm Hg). Approximately 43% of the cohort remained on AZL-M 40 mg or 80 mg monotherapy throughout the open-label phase, whereas 52% required

TABLE IV. Overview of AEs in the Double-Blind Reversal Phase (Safety Population)

	Patients With Event, No. (%)	
AEs	AZL-M (n=148)	Placebo (n=151)
Deaths	0	0
Serious AE	0	1 (0.7)
Any AE	42 (28.4)	38 (25.2)
AE leading to discontinuation[a]	3 (2.0)	2 (1.3)
AE (preferred term) in ≥2% of patients in either group		
Headache	5 (3.4)	8 (5.3)
Urinary tract infection	4 (2.7)	2 (1.3)
Hypokalemia	3 (2.0)	3 (2.0)
Pain in extremity	3 (2.0)	1 (0.7)
Back pain	3 (2.0)	0
Dizziness	3 (2.0)	3 (2.0)
Renal impairment	3 (2.0)	1 (0.7)
Chest pain	0	3 (2.0)
Nasopharyngitis	0	3 (2.0)

Abbreviation: AZL-M, azilsartan medoxomil. [a]Adverse events (AEs) leading to temporary drug interruption or permanent discontinuation.

addition of CLD alone and only 5% required addition of CLD plus further antihypertensive agents. The characteristics of patients who additionally received CLD in the current study are consistent with a population with more severe or resistant hypertension. Although comparisons between patients who received AZL-M alone and those who received add-on CLD in the open-label phase are limited by the open-label, uncontrolled design of the study, there was a pattern of large, stable BP reductions among patients who received AZL-M without subsequent addition of CLD, whereas patients who received CLD experienced, on average, a relatively attenuated response to AZL-M with large incremental BP reductions upon addition of CLD.

Notably, black patients also achieved absolute reductions in DBP and SBP of a similar magnitude, although more black patients required addition of CLD. Data from a factorial study investigating the AZL-M/CLD FDC suggest that black patients tend to have a lesser response to AZL-M (consistent with other RAS inhibitors) and a greater response to CLD, and these differences cancel each other out when AZL-M and CLD are used in combination.[17,20] That said, AZL-M appears to be one of the more effective ARBs in black patients. Pooled data from black patients in three ARB head-to-head comparator trials showed that the greater relative BP-lowering efficacy of AZL-M compared with olmesartan or valsartan previously reported in the general hypertensive population also occurs specifically in black patients.[6–8,21]

The withdrawal of AZL-M in patients randomized to placebo during the 6-week double-blind reversal phase provided the opportunity to evaluate the maintenance or reversal of the AZL-M–mediated BP reduction achieved during the prior 26 weeks of open-label treatment. After randomization, patients remaining on AZL-M maintained their improvements in BP, whereas those who switched to placebo showed a partial return towards baseline BP following withdrawal of AZL-M, which was observed as early as the second week of double-blind treatment (week 28). The mean change in SBP/DBP was statistically significant between the AZL-M and placebo treatment groups (0.59/0.14 mm Hg and 12.97/7.92 mm Hg, respectively; $P<.001$). The magnitude of the BP increase in the placebo group (after AZL-M withdrawal) is consistent with the magnitude of BP reductions attributable to AZL-M monotherapy seen in double-blind, placebo-controlled studies after initiation of treatment.[6-8] These results thus demonstrate the durability of the antihypertensive effect of AZL-M after longer-term treatment and that withdrawal of AZL-M yields BP increases that are within the anticipated range.

Treatment with AZL-M alone or in combination with CLD was well tolerated during the open-label and double-blind reversal phases of the study. In the open-label phase, the most commonly reported AEs were dizziness (8.9%) and headache (7.2%). In the double-blind reversal phase, the incidence of patients reporting AEs was similar between placebo-treated patients and those who maintained treatment with AZL-M, indicating that cessation of AZL-M treatment was well tolerated. Tolerability was similar in black patients, although there was a higher frequency of increased blood creatine phosphokinase compared with white patients. This result might be expected considering the known tendency for higher blood creatine phosphokinase in the black population, especially in young men, where median levels exceed the standard ULN.[22]

The elevation in serum creatinine observed in some patients in this study is consistent with the decrease in intraglomerular pressure and subsequent

acute reversible decrease in glomerular filtration rate (GFR) associated with RAS blockade, especially in the setting of potent diuresis and/or large BP decreases.[23–26] Thus, as expected, creatinine increases were seen primarily in patients receiving AZL-M in combination with the diuretic CLD, and these were generally the patients with higher baseline BP values and larger decreases in BP. Mostly, the serum creatinine elevations were transient (as exemplified by the low frequency of consecutive elevations) and reversible. These findings are consistent with previous studies involving AZL-M plus CLD.[16,17,19] Evidence from clinical studies with RAS inhibitors suggests that acute serum creatinine elevations are associated with long-term renal protection, in spite of short-term decreases in GFR, and thus appear to reflect a benefit of therapy rather than an AE.[23–28]

As might also be expected with diuretic therapy, elevations of uric acid were more common in patients who additionally received CLD to achieve target BP,[29,30] although it is notable that there were no AEs of gout. This occurs as a result of volume contraction and stimulation (by thiazide-type diuretics) of uric acid reabsorption in the kidney, and is generally thought to be an issue only in patients with a personal or family history of gout.[29] Similarly, hypokalemia was reported more frequently in patients who required addition of CLD. The hypokalemic effects of CLD and other diuretics are well characterized and evidence suggests that inhibition of RAS activity with agents such as AZL-M may counteract this effect.[17,28,29] For instance, in a recent 8-week, double-blind factorial study, mean changes in potassium were 0.08 mmol/L with AZL-M, −0.42 mmol/L with CLD, and −0.08 mmol/L with AZL-M/CLD.[17]

A wide range of diuretics are available, but CLD was chosen for use as add-on therapy in the current study because of its long half-life (~60 hours), high potency (~2 times that of HCTZ), and proven cardiovascular benefits based on several large outcomes trials.[31–33] The 25-mg dose of CLD was used as it was the only dose commercially available in the United States at the time. Notably, AZL-M and CLD are now available as a fixed-dose combination (40/12.5 mg and 40/25 mg) and this should provide a convenient option to facilitate such a strategy in clinical practice.[34] For patients not achieving BP goals on AZL-M 80 mg monotherapy, the recommended FDC AZL-M/CLD starting dose is 40/12.5 mg and the maximum dose is 40/25 mg.[18,35] Both of these doses have been shown to provide additional BP reductions compared with AZL-M 80 mg or CLD 25 mg monotherapy.[17–19,35] Furthermore, FDC AZL-M/CLD 40/25 mg has been shown to provide similar BP-lowering efficacy to 80/25 mg, but with better tolerability.[17,19,35] Thus, a better efficacy/safety profile might have been possible in the current study if the titration algorithm had been expanded to include the lower 12.5-mg dose option for CLD and utilized the 40-mg dose of AZL-M when the higher 25-mg dose of CLD was needed, as has been employed in other studies.[19]

CONCLUSIONS

These results demonstrate long-term stable improvements in BP with AZL-M used either alone or in combination with CLD as part of a titrate-to-target approach in patients with essential hypertension, irrespective of race. The strategy is associated with good long-term safety and tolerability. The BP improvements achieved with this strategy were maintained as long as AZL-M therapy was continued, and were safely reversible upon AZL-M withdrawal.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Patients disposition for (A) open-label phase and (B) double-blind reversal phase.

Figure S2. Mean trough clinic sitting diastolic blood pressure (DBP) and systolic blood pressure (SBP) according to race (black, white, other).