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Safety and tolerability of azilsartan medoxomil in subjects with essential hypertension: a one-year, phase 3, open-label study

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Abstract

This 56-week phase 3, open-label, treat-to-target study, involving 2 consecutive, non-randomized cohorts, evaluated the safety and tolerability of azilsartan medoxomil (AZL-M) in essential hypertension (mean baseline blood pressure [BP] 152/100 mmHg). All subjects ($n = 669$) initiated AZL-M 40 mg QD, force-titrated to 80 mg QD at week 4, if tolerated. From week 8, subjects could receive additional medications, starting with chlorthalidone (CLD) 25 mg QD (Cohort 1) or hydrochlorothiazide (HCTZ) 12.5–25 mg QD (Cohort 2), if required, to reach BP targets. Adverse events (AEs) were reported in 75.9% of subjects overall in the two cohorts (73.8% Cohort 1, 78.5% Cohort 2). The most common AEs were dizziness (14.3%), headache (9.9%) and fatigue (7.2%). Transient serum creatinine elevations were more frequent with add-on CLD. Clinic systolic/diastolic BP (observed cases at week 56) decreased by 25.2/18.4 mmHg (Cohort 1) and 24.2/17.9 mmHg (Cohort 2). These results demonstrate that AZL-M is well tolerated over the long term and provides stable BP improvements when used in a treat-to-target BP approach with thiazide-type diuretics.

Keywords

Hypertension, angiotensin receptor blocker, diuretic, azilsartan, chlorthalidone, hydrochlorothiazide

History

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Introduction

Azilsartan medoxomil (AZL-M) is a potent angiotensin II receptor blocker (ARB) approved for the management of hypertension, alone or in combination with other antihypertensive agents (1–5). At its maximal dose (80 mg) AZL-M lowers blood pressure (BP) more effectively than the ARBs olmesartan and valsartan at their maximal approved doses without increasing adverse events (AEs) in a general hypertensive population with mild-to-moderate hypertension (6–8). Similarly, AZL-M (at a dose of either 40 or 80 mg) is more effective and better tolerated than the angiotensin-converting enzyme (ACE) inhibitor ramipril at a dose of 10 mg/day (9).

Most patients with hypertension require treatment with multiple antihypertensive agents in order to achieve BP targets (10–12). Co-administration of a renin-angiotensin system (RAS)-blocking agent with a diuretic is a common, effective, recommended approach to treating hypertension (12,13). Short-term randomized controlled trials investigating the use of AZL-M plus the thiazide diuretic hydrochlorothiazide (HCTZ; free combination) or the thiazide-like diuretic chlorthalidone (CLD; free or fixed-dose combination [FDC]) have shown these combinations to be safe, well tolerated and effective treatments for hypertension (14–16). The FDC of AZL-M with CLD appeared to be particularly effective at lowering systolic BP when compared with the free combination of AZL-M and HCTZ (14,17,18).

It is also important to consider the safety, tolerability and efficacy of AZL-M with or without thiazide-like diuretics over the longer term. The present study provides long-term (56-week) experience during use of AZL-M with addition of CLD or HCTZ as part of a typical titrate-to-target BP approach for patients with essential hypertension.

Patients and methods

Study design

This was a 56-week phase 3, open-label, multicenter study to evaluate the safety and tolerability of AZL-M in subjects with essential hypertension (ClinicalTrials.gov trial registration: NCT00695955). The study took place between June 2007 and May 2010 and included a 7-day screening period, a 56-week open-label period, and a 7-day post-treatment AE follow-up phone call. A total of 669 eligible subjects were enrolled in 1 of 2 sequential cohorts (screening began in 2007 for Cohort 1 and 2009 for Cohort 2) at 39 centers in the USA (both cohorts) and Latin America (Chile, Mexico; Cohort 1 only). The study was approved by institutional review boards or ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects gave written informed consent to participate in the study.

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All subjects initiated treatment with AZL-M 40 mg QD on day 1, which was added to existing treatments (a maximum of two other antihypertensive agents), if applicable; at week 4, AZL-M was force-titrated to 80 mg QD, if tolerated. Thereafter (week 8 onwards), subjects could have additional medications added, if needed, to reach BP targets (<140/90 mm Hg for non-diabetic subjects and <130/80 mmHg for diabetic subjects). In the first cohort (Cohort 1), investigators were instructed to give CLD 25 mg QD as the initial add-on agent for subjects who did not achieve target BP on AZL-M alone, followed by any other additional antihypertensive treatments (except other ARBs). In the second cohort (Cohort 2), HCTZ 12.5 mg QD was the initial add-on agent, followed by titration to 25 mg QD, then any other additional antihypertensive treatments (except other ARBs). If BP remained elevated (confirmed sitting mean DBP $\geq$ 115 mmHg or sitting mean SBP $\geq$ 185 mmHg), despite adherence to the treatment algorithm for study medication and additional antihypertensive agents, the investigator could consider discontinuation of the subject at any time.

Patient eligibility

Male or female subjects aged >18 years who were either treatment-naïve or currently receiving up to two antihypertensive agents were eligible for inclusion in the study. Subjects without diabetes or chronic kidney disease (CKD) were required to have DBP $\geq$ 95 mmHg and $\leq$119 mmHg at Screening (day −7 and enrollment visit); those with diabetes or CKD had to have DBP $\geq$ 85 mm Hg and $\leq$109 mm Hg. Subjects had to have clinical laboratory evaluations (including clinical chemistry, hematology and complete urinalysis) within the reference ranges for the testing laboratory evaluation, unless the results were deemed not clinically significant by the investigator. The main exclusion criteria were: SBP >185 mmHg; taking >2 antihypertensive agents; hypersensitivity to ARBs, thiazide-type diuretics, or sulfonamide-derived compounds; clinically relevant or hemodynamically unstable cardiovascular diseases within 6 months of enrollment; secondary hypertension of any etiology; known or suspected unilateral or bilateral renal artery stenosis; severe renal dysfunction or disease (creatinine clearance <30 ml/min/1.73 m^2) at Screening; uncontrolled diabetes mellitus with poor glucose control at Screening ($HbA_{1c} > 8.5\%$); alanine aminotransferase >2.5 times the upper limit of normal (ULN), active liver disease, or jaundice; and serum potassium level >ULN (per central laboratory reference ranges) at screening. If a subject was taking an ARB, it could be substituted with AZL-M.

Safety and efficacy assessments

Clinic BP measurements were taken at every visit ~24 h after the previous dose, and prior to dosing or blood collection. Either a standard mercury sphygmomanometer or a certified automated and calibrated BP device was used, as well as appropriate cuff size. In case the auscultation method was used, SBP and DBP were measured at Korotkoff Phase I and V, respectively. Every effort was made to standardize the conditions of clinic BP monitoring (19).

Safety and tolerability were assessed with treatment-emergent AE, laboratory results, and other safety variables (weight, vital signs, 12-lead ECGs). Any AEs were coded using the Medical Dictionary for Regulatory Activities, Version 11.1. AEs, including worsening of previous conditions, were recorded from the start of treatment through 14 or 30 days after the permanent discontinuation of the study medication for non-serious AEs and serious AEs, respectively. All abnormal clinically significant laboratory results at final visit were followed until resolution to baseline levels or stabilization.

Statistics

The primary objective of this study was to evaluate the safety and tolerability of treatment with AZL-M for up to 56 weeks in subjects with essential hypertension. The full analysis data set was used for efficacy and safety analysis, consisting of all subjects with at least 1 dose of study medication. For both safety and efficacy, data were summarized by treatment received (AZL-M only, AZL-M plus CLD or AZL-M plus HCTZ). Interpretation of these summary results should consider the differences in duration of exposure between treatments, as diuretics could only be added from week 8 onwards.

AEs and laboratory values were summarized descriptively and listed. The incidence of symptomatic hypotension was assessed as part of the AE review. Markedly abnormal laboratory values were also identified and summarized independently. Serum creatinine was evaluated as a laboratory parameter of special interest, and the frequency of elevations $\geq$50% (or $\geq$30%) from baseline and >ULN at $\geq$2 consecutive study visits was summarized.

Changes from Baseline for BP (DBP and SBP) were summarized using descriptive statistics. There was no formal statistical sample size justification for this study, although a target of ~650 subjects was set. All data are presented as mean ± SD, unless otherwise stated.

Results

Patient disposition and demographics

A total of 1039 subjects were screened and 669 subjects entered the treatment phase. Demographic and baseline characteristics were generally similar in the two cohorts, except that subjects in Cohort 1 were older (Table 1). The majority of subjects (64%) were aged 45–64 years, 11% were $\geq$65 years of age, and 15% had diabetes. Nearly two-thirds were white and approximately one-third were black/African American. During the study, ~60% of subjects required the addition of CLD (Cohort 1) or HCTZ (Cohort 2) to their AZL-M therapy (Table 1). Those requiring add-on diuretic therapy with CLD or HCTZ had higher mean SBP/DBP at baseline and a greater proportion were male and black/African American (Table 1). The mean duration of treatment was 315 days, and the majority of subjects (81%) received a minimum of 6 months treatment with AZL-M (70% received a minimum of 12 months of treatment).

Overall, 46% of subjects were taking at least one other BP-lowering medication that was ongoing at baseline

Table 1. Demographic and baseline characteristics.

Parameter	By cohort			By treatment		
	Cohort 1	Cohort 2	*p* value	AZL-M[a] (both cohorts)	AZL-M + CLD[b] (Cohort 1)	AZL-M + HCTZ[b] (Cohort 2)
N	362	307		269	216	184
Gender, *n* (%)			0.877			
Male	189 (52.2)	163 (53.1)		133 (49.4)	120 (55.6)	99 (53.8)
Female	173 (47.8)	144 (46.9)		136 (50.6)	96 (44.4)	85 (46.2)
Age, years (mean ± SD)	53.0 ± 10.4	50.1 ± 10.3	<0.001	51.0 ± 10.0	53.9 ± 10.7	49.9 ± 10.4
Race, *n* (%)[c]			0.931			
American Indian/Alaska Native	5 (1.4)	3 (1.0)		5 (1.9)	1 (0.5)	2 (1.1)
Asian	5 (1.4)	5 (1.6)		5 (1.9)	0	5 (2.7)
Black/African American	122 (33.7)	108 (35.2)		69 (25.7)	83 (38.4)	78 (42.4)
Native Hawaiian/Pacific Islander	3 (0.8)	3 (1.0)		4 (1.5)	1 (0.5)	1 (0.5)
White	228 (63.0)	189 (61.6)		187 (69.5)	131 (60.6)	99 (53.8)
Multiracial	1 (0.3)	1 (0.3)		1 (0.4)	0	1 (0.5)
BMI, kg/m^2 (mean ± SD)	33.3 ± 7.7	33.1 ± 7.2	0.755	33.2 ± 7.6	33.1 ± 7.7	33.2 ± 7.0
Baseline SBP, mmHg (mean ± SD)	151.2 ± 12.7	152.3 ± 13.0	0.253	147.4 ± 12.1	154.2 ± 11.9	155.0 ± 13.3
Baseline DBP, mmHg (mean ± SD)	99.4 ± 6.0	100.3 ± 6.8	0.099	98.6 ± 5.3	100.0 ± 6.5	101.4 ± 7.3

AZL-M, azilsartan medoxomil; BMI, body mass index; CLD, chlorthalidone; HCTZ, hydrochlorothiazide.
[a]Subjects who did not require additional treatment with CLD or HCTZ (Cohorts 1 and 2 combined).
[b]Subjects who required additional treatment with CLD (Cohort 1) or HCTZ (Cohort 2) after week 8.
[c]Subjects who indicated more than 1 race category were included in each category indicated and also in the multiracial category.

(irrespective of whether it was continued throughout the treatment period) – 27% were receiving agents acting on the RAS (most commonly lisinopril), 11% diuretics, 10% calcium channel blockers and 8% beta-blockers. After baseline, 127 subjects (19.0%) received additional BP-lowering medications other than study algorithm-driven AZL-M, CLD or HCTZ therapy. This included 8% of the subjects who received AZL-M alone (both cohorts combined), 30% of the subjects who received add-on CLD (Cohort 1) and 22% of the subjects who received add-on HCTZ (Cohort 2) (note that some of these additional medications were initiated outside of the study algorithm). Overall (both cohorts combined), 31% of subjects discontinued prematurely. In Cohort 1, 28% of subjects discontinued prematurely (37% receiving AZL-M alone and 22% requiring add-on CLD) (Figure 1A) and in Cohort 2, 34% discontinued prematurely (44% receiving AZL-M alone and 27% requiring add-on HCTZ) (Figure 1B). Over half of these were due to a combination of voluntary withdrawal or loss to follow-up (Figure 1).

Efficacy

At baseline, the mean clinic sitting SBP for all subjects with at least one post-baseline SBP measurement in either Cohort 1 or Cohort 2 was higher in subjects who later required add-on CLD (Cohort 1) or HCTZ (Cohort 2) to achieve target BP compared with subjects who received AZL-M alone (Table 1; Figure 2A and B). At week 8, the overall reduction in clinic SBP with AZL-M (before any add-on CLD or HCTZ) was smaller for subjects who later required add-on diuretic (Figure 2A and B) compared with subjects who continued to receive AZL-M alone. In both cohorts, the changes in clinic SBP observed at week 8 were maintained throughout the study for subjects who received AZL-M alone and did not require add-on diuretic to achieve BP control. Additional reductions in clinic SBP were observed after week 8 for subjects who subsequently received add-on CLD (Cohort 1) or HCTZ (Cohort 2).

By week 56 in Cohort 1, the overall change from baseline in clinic SBP (observed cases) was -25.2 ± 18.1 mmHg ($n = 259$; 21.1 ± 15.2 mmHg for subjects receiving AZL-M alone [$n = 93$] and -27.4 ± 19.2 mmHg for those requiring add-on CLD [$n = 166$]) (Figure 2A). In Cohort 2, the overall change from baseline in clinic SBP was -24.2 ± 16.0 mmHg ($n = 201$; -21.6 ± 14.2 for mmHg AZL-M alone [$n = 68$] and -25.6 ± 16.7 mmHg for add-on HCTZ [$n = 133$]) (Figure 2B).

By week 56 in Cohort 1, the overall change from baseline in clinic DBP (observed cases) was -18.4 ± 9.5 mmHg (-18.0 ± 8.8 mmHg for AZL-M alone and -18.6 ± 9.9 mmHg with add-on CLD) (Figure 3A). By week 56 in Cohort 2, the change from baseline in clinic DBP was -17.9 ± 10.9 mmHg (-17.9 ± 9.4 mmHg for subjects AZL-M alone and -18.0 ± 11.6 mmHg with add-on HCTZ) (Figure 3B).

Safety and tolerability

Overall incidences of AEs, serious AEs, and discontinuations due to AEs in the two cohorts are summarized in Table 2. Approximately 76% of subjects overall in the two cohorts experienced an AE. Within each cohort, more events were reported among subjects who received add-on therapy with CLD or HCTZ (Table 2). The most commonly reported AEs ($\geq$5% of subjects) in both cohorts combined, regardless of add-on diuretic therapy, were dizziness (14.3%), headache (9.9%), fatigue (7.2%), upper respiratory tract infection (6.7%) and urinary tract infection (5.7%). Among the AEs related to conditions associated with hypertension treatment in general and RAS blockade specifically (in addition to dizziness and headache noted earlier), hypotension, cough, peripheral edema, increased blood creatinine, and postural dizziness were all reported by $\geq$2 to <5% of all subjects. Gout and hyperuricemia were reported as AEs in 0.7 and 1.2% of subjects, respectively. Mean changes in vital signs were small and there were no notable changes in ECGs during the study.

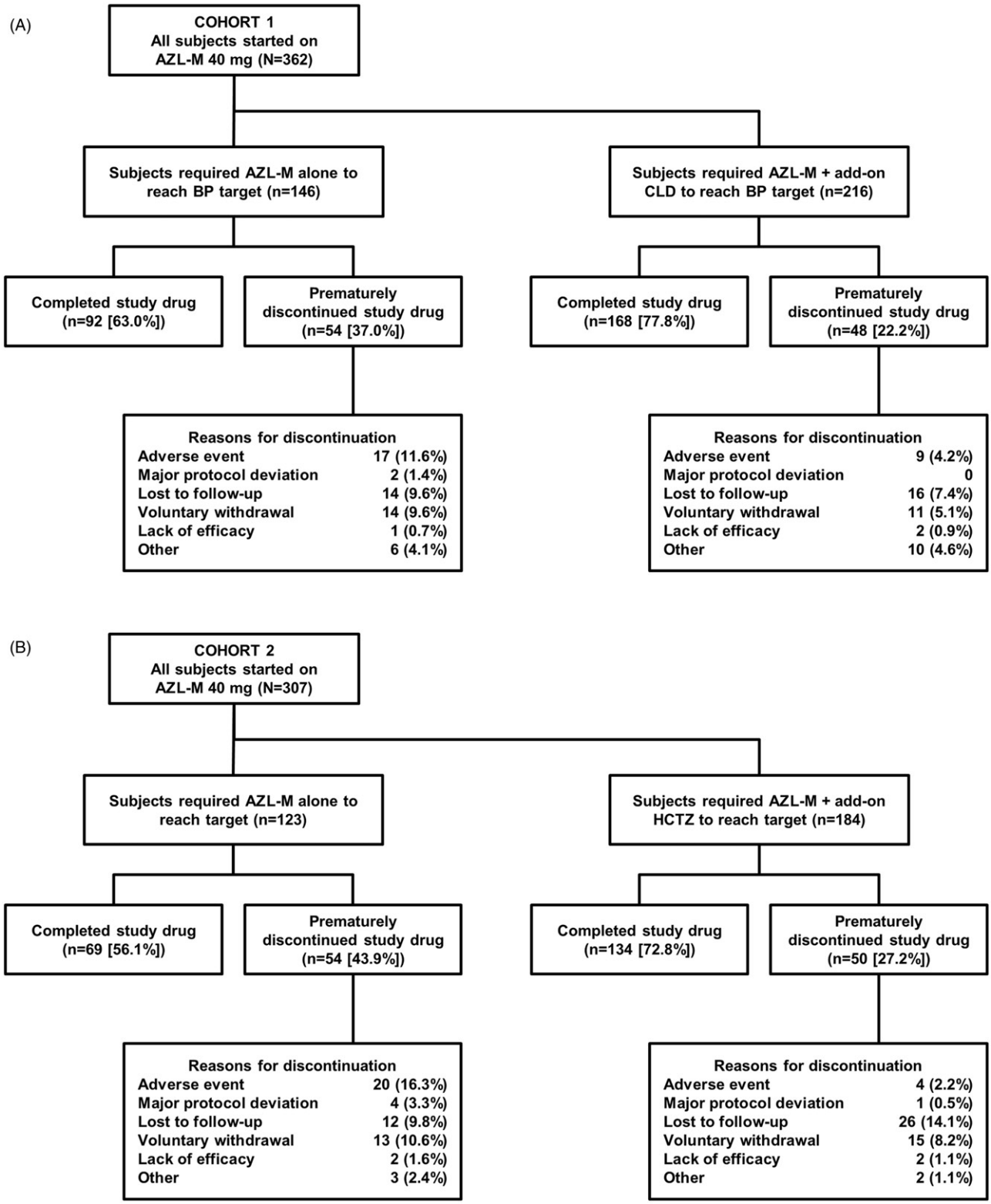

Figure 1. Subject disposition in Cohorts 1 (A) and 2 (B).

Overall, 62 subjects (9.3%) permanently or temporarily discontinued study drug due to the occurrence of at least one AE. Discontinuations for AEs were more common among subjects who received AZL-M without subsequent addition of CLD or HCTZ. However, it should be emphasized that discontinuations for poor tolerability typically occur early in clinical trials, and in the current trial all subjects were receiving AZL-M alone prior to week 8, the point when diuretics could be added. The AEs most frequently leading to discontinuation were fatigue (1.5% overall for both cohorts combined), dizziness (1.8%) and headache (1.0%). There were no discontinuations due to hypokalemia across the two cohorts and discontinuations due to increased creatinine were uncommon ($n = 2$ [0.3%]). Serious AEs were reported in 52 subjects (8%) overall and this was consistent across the two cohorts irrespective of therapy

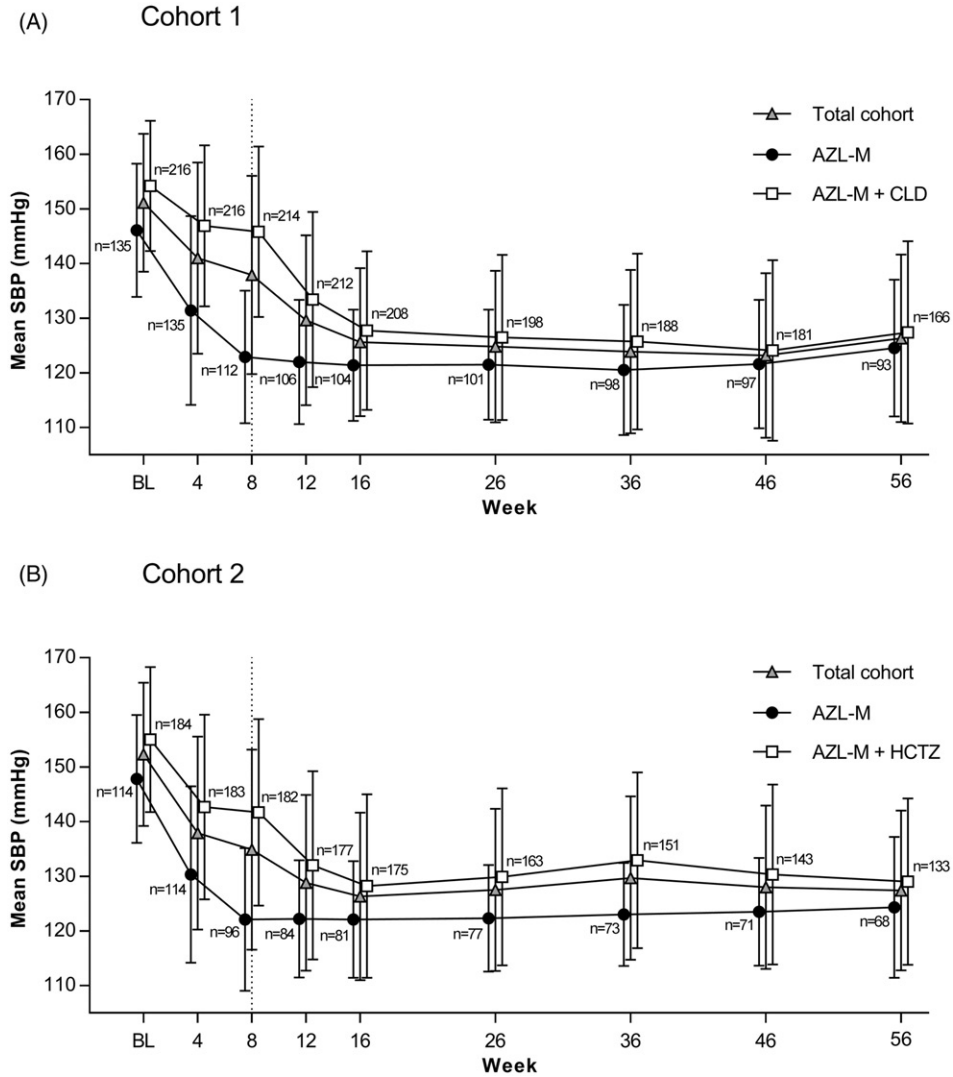

Figure 2. Mean sitting clinic SBP by study visit (observed cases). Data are mean ± SD. The dashed line at week 8 represents the first visit at which subjects in Cohort 1 could additionally have received CLD and subjects in Cohort 2 could additionally have received HCTZ.

received. Serious AEs reported by more than one subject included: chest pain ($n = 3$ subjects [0.4%]), coronary artery disease ($n = 2$ [0.3%]), small intestinal obstruction ($n = 2$ [0.3%]), road traffic accident ($n = 2$ [0.3%]), vasovagal syncope ($n = 2$ [0.3%]), asthma ($n = 2$ [0.3%]), pulmonary embolism ($n = 2$ [0.3%]), and hypotension ($n = 2$ [0.3%]). One additional subject had a serious AE of syncope. Serious AEs were reported as related to study drug in only four subjects. These included erythema multiforme major that occurred after 4 days on AZL-M 40 mg; vomiting, increased creatinine (195 µmol/l) and an episode of vasovagal syncope that occurred after 16 weeks while on AZL-M 80 mg plus CLD 25 mg; hypokalemia (3.4 mmol/l) that occurred after 10 weeks while on AZL-M 80 mg plus CLD 25 mg; and renal impairment that occurred after 46 weeks while on AZL-M 80 mg plus CLD 25 mg. All events resolved.

Laboratory evaluations

There were no notable mean changes in liver enzymes, bilirubin or creatine kinase (data not shown). Small mean increases in uric acid were greater among subjects who received add-on diuretic therapy (Table 3), although AEs of gout were infrequent ($n = 3$ [0.8%] with diuretics, $n = 2$ [0.7%] with no diuretics). Mean changes in potassium were negligible (Table 3), and no subjects had markedly abnormal values (<3.0 or >6.0 mmol/l), although non-serious AEs of hypokalemia were reported more frequently with add-on diuretic ($n = 13$ [3.3%]), and there was one serious AE of hypokalemia as indicated earlier.

Consecutive creatinine elevations ≥50% of baseline and >ULN were reported in 21 (3.2%) subjects overall, mostly in those who received add-on CLD ($n = 18$ [8.3%]) (Table 3). For all subjects with an elevated creatinine value at the final visit, the follow-up serum creatinine returned to within normal levels of the reference range, to baseline/screening values or to near baseline values (≤0.2 mg/dl [18 µmol/l] above baseline value). In general, subjects with serum creatinine elevations tended to have greater SBP reductions. For subjects without a creatinine elevation ≥30% from baseline and >ULN (both cohorts combined) at the final visit, SBP decreased from a mean of approximately 151 mmHg at baseline to ~130 mmHg at the final visit, but decreased from 156 to 118 mmHg in those with creatinine elevations. Mean changes in serum fasting glucose (Table 3),

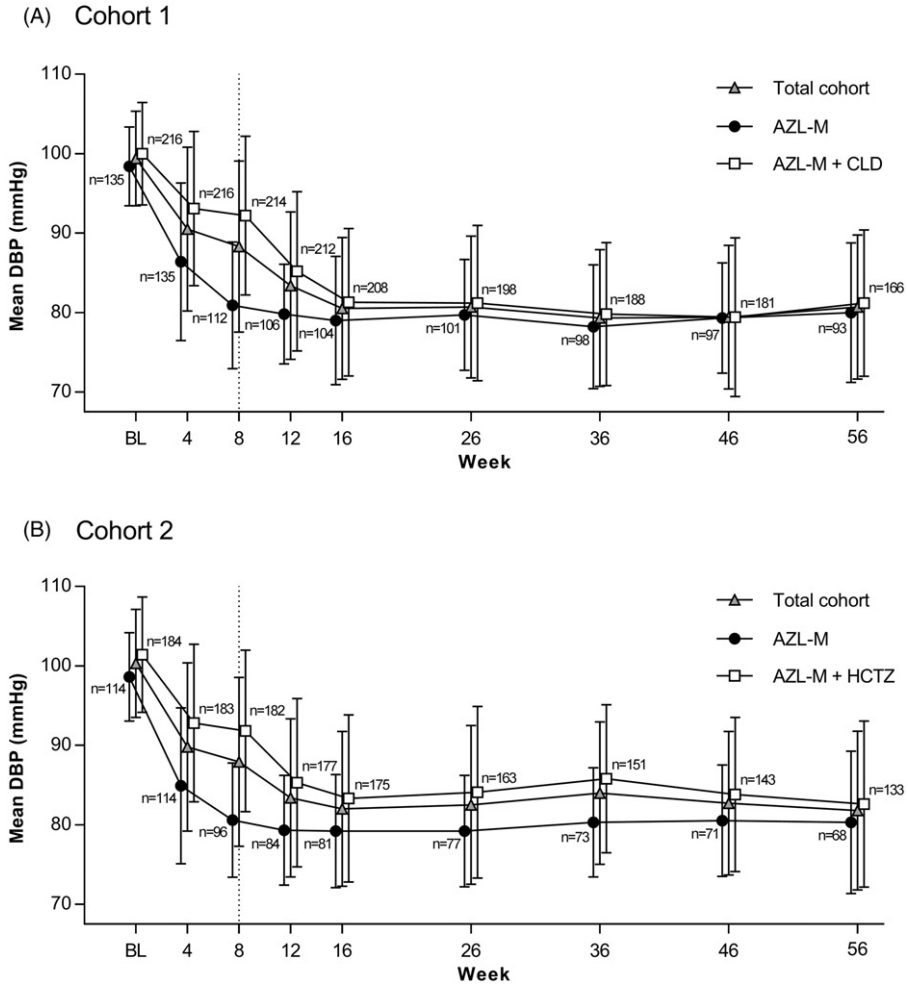

Figure 3. Mean sitting clinic DBP by study visit (observed cases). Data are mean ± SD. The dashed line at week 8 represents the first visit at which subjects in Cohort 1 could additionally have received CLD and subjects in Cohort 2 could additionally have received HCTZ.

Table 2. Overview of AEs.

	Number (%) of subjects with event				
Adverse event	AZL-M (Cohort 1) ($n = 146$)	AZL-M (Cohort 2) ($n = 123$)	AZL-M + CLD (Cohort 1) ($n = 216$)	AZL-M + HCTZ (Cohort 2) ($n = 184$)	Total (Both cohorts combined) ($n = 669$)
Death	1 (0.7)	0	0	0	1 (0.1)[a]
Serious AE	10 (6.8)	9 (7.3)	20 (9.3)	13 (7.1)	52 (7.8)
Any AE (≥1 event)	99 (67.8)	92 (74.8)	168 (77.8)	149 (81.0)	508 (75.9)
AE leading to discontinuation[b]	18 (12.3)	22 (17.9)	16 (7.4)	6 (3.3)	62 (9.3)
AE (preferred term) in ≥5% of all subjects					
Dizziness	21 (14.4)	22 (17.9)	31 (14.4)	22 (12.0)	96 (14.3)
Headache	18 (12.3)	10 (8.1)	20 (9.3)	18 (9.8)	66 (9.9)
Fatigue	18 (12.3)	8 (6.5)	14 (6.5)	8 (4.3)	48 (7.2)
Upper respiratory tract infection	8 (5.5)	7 (5.7)	17 (7.9)	13 (7.1)	45 (6.7)
Urinary tract infection	11 (7.5)	2 (1.6)	16 (7.4)	9 (4.9)	38 (5.7)

AZL-M, azilsartan medoxomil; CLD, chlorthalidone; HCTZ, hydrochlorothiazide.
[a]The subject reportedly committed suicide. According to the investigator, this was unrelated to study drug.
[b]AEs leading to temporary drug interruption or permanent discontinuation.

lipids and urinalysis parameters were small. Shifts from normal to high uric acid and from normal to low potassium were more common in subjects who received AZL-M +CLD than in those who received AZL-M alone. 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 subjects who also received CLD. However, the percentage of subjects with markedly reduced values was low (hematocrit <0.8 of baseline, 0.8% AZL-M, 3.7% AZL-M + CLD, 0% AZL-M + HCTZ; hemoglobin 3 g/dl decrease from baseline, 0.8, 2.3, 0.5%, respectively; RBC count <0.8 of baseline, 0.4, 1.9, 0.5%, respectively). One hematology-related AE (anemia) resulted in premature discontinuation.

Table 3. Key serum laboratory parameters (safety population).

Parameter	AZL-M (both cohorts combined) ($n = 269$)	AZL-M + CLD (Cohort 1) ($n = 216$)	AZL-M + HCTZ (Cohort 2) ($n = 184$)	Total (both cohorts combined) ($n = 669$)
Creatinine				
≥2 consecutive elevations (≥1.5 × BL and >ULN), n/N (%)	2/251 (0.8)	18/216 (8.3)	1/184 (0.5)	21/651 (3.2)
Potassium				
Baseline, mean ± SD (mmol/l)[a]	4.25 ± 0.42	4.11 ± 0.40	4.21 ± 0.41	4.19 ± 0.41
Change, mean ± SD (mmol/l)[a]	0.15 ± 0.48	−0.01 ± 0.48	−0.01 ± 0.43	0.05 ± 0.47
Shift from normal to low, n/N (%)[b]	4/233 (1.7)	25/204 (12.3)	5/175 (2.9)	34/612 (5.6)
Shift from normal to high, n/N (%)[c]	10/233 (4.3)	5/204 (2.5)	4/175 (2.3)	19/612 (3.1)
Sodium				
Baseline, mean ± SD (mmol/l)[a]	139.8 ± 2.3	139.7 ± 2.3	140.1 ± 2.2	139.8 ± 2.3
Change, mean ± SD (mmol/l)[a]	−0.8 ± 2.6	−0.9 ± 2.7	−0.5 ± 2.2	−0.7 ± 2.5
Shift from normal to low, n/N (%)[d]	5/245 (2.0)	6/212 (2.8)	2/183 (1.1)	13/640 (2.0)
Uric acid				
Baseline, mean ± SD (μmol/l)[e]	364.7 ± 87.1	354.9 ± 93.1	350.1 ± 90.6	357.3 ± 90.2
Change, mean ± SD (μmol/l)[e]	11.2 ± 56.9	61.2 ± 86.7	38.1 ± 71.9	35.5 ± 75.1
Shift from normal to high, n/N (%)[f]	23/210 (11.0)	49/189 (25.9)	23/167 (13.8)	95/566 (16.8)
Fasting serum glucose				
Baseline, mean ± SD (mmol/l)[g]	5.86 ± 1.42	6.01 ± 1.59	5.66 ± 1.17	5.85 ± 1.42
Change, mean ± SD (mmol/l)[g]	0.06 ± 1.40	0.36 ± 3.09	0.08 ± 1.32	0.17 ± 2.10
Shift from normal to high, n/N (%)[h]	9/225 (4.0)	11/192 (5.7)	8/175 (4.6)	28/592 (4.7)

AZL-M, azilsartan medoxomil; BL, baseline; CLD, chlorthalidone; HCTZ, hydrochlorothiazide; SD, standard deviation; ULN, upper limit of normal.
[a]For potassium and sodium, 1 mmol/l = 1 mEq/L.
[b]Definition of ''low'' (mmol/L): <3.6.
[b]Definition of ''high'' (mmol/l): >5.2.
[d]Definition of ''low'' (mmol/l): <132 (18–59 years), <135 (>59 years).
[e]To convert μmol/Ll to mg/dl, divide by 59.5.
[f]Definition of ''high'' (μmol/l): >521 (male), >379 (female).
[g]To convert mmol/l to mg/dl, multiply by 18.
[h]Definition of ''high'' (mmol/l): >7.8.

Discussion

The objective of this open-label study was to evaluate the safety and tolerability of treatment with AZL-M (with addition of CLD or HCTZ, if required) for up to 56 weeks in subjects with essential hypertension. Mean baseline BP was 152/100 mmHg, indicating that these subjects (half of whom were already receiving background antihypertensive medication) generally had both systolic and diastolic hypertension. Treatment with AZL-M alone or co-administered with CLD or HCTZ as part of a titrate-to-target-BP approach led to effective reductions in clinic BP, which were maintained for up to 56 weeks. Over one-third of subjects did not require any antihypertensive medication other than AZL-M 40–80 mg added to background therapy in order to achieve BP targets. Among subjects who did not achieve target with AZL-M administration alone over 8 weeks, the addition of CLD or HCTZ resulted in large incremental reductions in BP. Nevertheless, these subjects did not quite achieve the same absolute BP level as those who responded well to AZL-M alone (reflecting the higher baseline BP in initial non-responders).

Long-term (56 weeks) administration of AZL-M alone was well tolerated, with the most common AEs being dizziness, headache and fatigue. The safety profile was generally similar in those subjects who required add-on therapy with CLD or HCTZ in order to achieve target BP. However, it should be emphasized that any comparisons among subjects who received AZL-M alone or with add-on CLD or HCTZ are limited by the open-label design of the study, lack of randomization and control group, the treat-to-target approach, differences in enrollment time of the two cohorts, and variations in length of exposure to study drugs. Subjects within each cohort represented a single group of patients all undergoing the same treat-to-target strategy; however, those who required add-on diuretic therapy had more difficult to treat hypertension, which might relate to any number of hemodynamic, clinical and/or demographic factors. It should also be noted that up to week 8, no subjects were receiving add-on CLD or HCTZ, and any discontinuations in this period were classified as occurring in subjects who received AZL-M only, leading to a higher apparent discontinuation rate in patients who responded well to AZL-M. The overall percentage of subjects who discontinued due to AEs in the current study (9.3%) is consistent with other long-term, treat-to-target studies with ARBs, although comparisons are limited by differences in study design (20–23). For example, in a pooled analysis of five 12–24-month open-label extension studies of irbesartan therapy ± HCTZ ± other antihypertensive drugs, 9.1% of subjects discontinued due to AEs during the open-label extensions, in addition to 7.1% who discontinued in the initial 8–26-week double-blind phases of the trials (20).

Elevations of uric acid were more common in subjects who received add-on CLD or HCTZ. This is a well-characterized effect of thiazide-type agents (24), but AEs of gout were infrequent ($n = 3$ [0.8%]) in those on diuretics. Serum creatinine elevations were more common

in subjects who received add-on CLD or HCTZ, and this is consistent with previous studies investigating the combination of AZL-M plus CLD (14–16). Importantly, creatinine elevations were generally transient and reversible, either during treatment or after discontinuation of treatment, and were associated with relatively large BP reductions. Elevated creatinine is a mechanism-based effect that has been described previously in patients receiving agents that block the RAS, including ACE inhibitors and ARBs (25–28). Animal studies suggest that the more effective reduction in intraglomerular pressure provided by RAS inhibitors is associated with protection from renal injury (29). Furthermore, clinical studies suggest that there is a strong association between acute increases in serum creatinine after initiating RAS inhibitor therapy (or more aggressive combination therapy with RAS inhibitors and diuretics) and preservation of renal function over the longer term in subjects with chronic renal disease (25,27–29). Thus, patients with renal failure are the most likely to have increases in serum creatinine and these are the ones who will benefit most from greater BP reductions (30). This effect is caused by inhibition of angiotensin II-mediated vasoconstriction of efferent glomerular arterioles, resulting in decreased intraglomerular pressure, and thus a reversible acute decrease of glomerular filtration rate (25). The acute creatinine increases observed with RAS blockade may be exacerbated under certain conditions, such as hypovolemia associated with potent diuretic use, as in the present study (25).

In this study, subjects not achieving BP goals on AZL-M 80 mg were given add-on CLD 25 mg (the minimum commercially available dose of CLD in the USA). However, subsequent data have shown that AZL-M 40/25 mg provides similar BP-lowering efficacy to 80/25 mg and is better tolerated (15,16,31). Consequently, 40/25 mg is the maximum approved dose of FDC AZL-M/CLD in the USA (17,31). Furthermore, a 40/12.5 mg dose of FDC AZL-M/CLD is also available, as it was also shown to provide additional BP reductions compared with AZL-M 80 mg or CLD 25 mg monotherapy (17,31). AZL-M/CLD 40/12.5 mg is the current recommended starting FDC dose in subjects uncontrolled on AZL-M 80 mg monotherapy (17,31). In the current study, three of the four serious AEs considered related to study treatment by a reporter occurred in subjects on AZL-M/CLD 80/25 mg. Better tolerability might have been possible (without compromising additional BP lowering) if subjects uncontrolled on AZL-M 80 mg had been switched to AZL-M/CLD 40/12.5 mg in the first instance, with subsequent uptitration to 40/25 mg in cases where BP target was not achieved.

In conclusion, this study provides long-term experience during use of AZL-M alone or with either of two of the most commonly used diuretic agents (CLD and HCTZ) as part of a treat-to-target strategy in patients with essential hypertension. These results support the good long-term safety and tolerability profile of AZL-M in this setting and provide evidence for long-term stable BP improvements. The availability of FDCs, such as AZL-M with CLD (17,18), may facilitate this approach to therapy.

Declaration of interest

A.H. is a full-time employee of Takeda Pharmaceuticals International, Inc. (Deerfield, IL). E.L. and A.R. are full-time employees of Takeda Global Development Center Americas, Inc. (Deerfield, IL). B.B. was an employee of Takeda during the time of the study and is currently employed at AbbVie, Inc. (North Chicago, IL).

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