

A randomized titrate-to-target study comparing fixed-dose combinations of azilsartan medoxomil and chlorthalidone with olmesartan and hydrochlorothiazide in stage-2 systolic hypertension

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Background: Azilsartan medoxomil (AZL-M), an angiotensin II receptor blocker, has been developed in fixed-dose combinations (FDCs) with chlorthalidone (CTD).

Objective/methods: We compared FDCs of AZL-M/CTD 20/12.5 mg once daily titrated to 40/25 mg if needed or AZL-M/CTD 40/12.5 mg once daily titrated to 80/25 mg if needed with an olmesartan medoxomil (OLM)-hydrochlorothiazide (HCTZ) 20/12.5 mg FDC once daily titrated to 40/25 mg if needed in a randomized, double-blind, 8-week study of 1085 participants with clinic SBP 160–190 mmHg and DBP 119 mmHg or less. Titration to higher doses occurred at week 4 if BP was at least 140/90 mmHg ($\geq 130/80$ mmHg if diabetes or chronic kidney disease). The primary endpoint was change from baseline in clinic SBP; 24-h ambulatory BP monitoring was also measured.

Results: Greater reductions in clinic SBP from a baseline of 165 mmHg were observed ($P < 0.001$) in both AZL-M/CTD arms (-37.6 and -38.2 mmHg) versus OLM/HCTZ (-31.5 mmHg), despite greater dose titration in the OLM/HCTZ group. At 8 weeks, both AZL-M/CTD FDCs reduced 24-h SBP more than OLM/HCTZ (-26.4 and -27.9 versus -20.7 mmHg; both $P < 0.001$), and higher proportions in both AZL-M/CTD groups achieved target BP compared with the OLM/HCTZ group (69.4 and 68.9 versus 54.7%, both $P < 0.001$). Adverse events leading to drug discontinuation occurred in 6.2, 9.5, and 3.1% with the AZL-M/CTD lower and higher doses, and OLM/HCTZ, respectively.

Conclusion: This large, titration-to-target BP study demonstrated AZL-M/CTD FDCs to have superior antihypertensive efficacy compared with the maximum approved dose of OLM/HCTZ.

Keywords: angiotensin II receptor blocker, antihypertensive therapy, azilsartan medoxomil, chlorthalidone, fixed-dose combination, hypertension, thiazide-like diuretic

Abbreviations: ABPM, ambulatory blood pressure monitoring; ANCOVA, analysis of covariance; ARB, angiotensin II receptor blocker; AZL-M, azilsartan

medoxomil; AZL-M/CTD, azilsartan medoxomil/chlorthalidone; CKD, chronic kidney disease; CTD, chlorthalidone; eGFR, estimated glomerular filtration rate; FDC, fixed dose combination; HCTZ, hydrochlorothiazide; OLM, olmesartan medoxomil; OLM/HCTZ, olmesartan medoxomil/hydrochlorothiazide; SPRINT, Systolic Blood Pressure Intervention Trial; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal

INTRODUCTION

Hypertension is not controlled to recommended goals in approximately half of hypertensive patients in the United States [1], and in an even greater proportion of patients in most of the rest of the world [2]. Although it has been demonstrated that 70–80% BP control rates can be achieved in certain practice settings or clinical trials, half of the patients require three or more antihypertensive medications, and often are prescribed complex regimens to which adherence is difficult [3–5]. Also, many healthcare practitioners are uncertain what drugs/classes to combine. Therefore, the availability of simple, well tolerated, antihypertensive fixed-dose combinations (FDCs)

Journal of Hypertension 2018, 36:947–956

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*Andrew Roberts and Stuart Kupfer are no longer employees of Takeda, though they were, during the time the research was conducted.

Received 18 April 2017 **Revised** 8 September 2017 **Accepted** 11 November 2017

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DOI:10.1097/HJH.0000000000001647

that will control BP in a high proportion of hypertensive patients is likely to promote improved BP control rates.

Azilsartan medoxomil (AZL-M), a long-acting angiotensin II receptor blocker (ARB), has superior efficacy compared with both olmesartan (OLM) and valsartan at their maximum approved doses, without increasing adverse events [6–8]. Chlorthalidone (CTD) is a potent, long-acting thiazide-like diuretic that has demonstrated cardiovascular benefits in large, randomized, controlled clinical trials [9–15]. It is also more effective in lowering BP than the more commonly used thiazide diuretic, hydrochlorothiazide (HCTZ), both alone and in combination with AZL-M [16,17]. Coadministration of AZL-M and CTD has been demonstrated to be effective and well tolerated, and an FDC of these agents has been approved by multiple regulatory authorities.

Previously, we have reported the results of a large, active-comparator multicenter study of once-daily FDCs of AZL-M/CTD force-titrated to a high dose of either 40/25 or 80/25 mg compared with an FDC of the ARB OLM with the thiazide diuretic HCTZ force-titrated to 40/25 mg, its highest approved dose [18]. Although a forced-titration design provides the most accurate comparison of the anti-hypertensive efficacy between the drug doses and regimens being compared, it does not replicate the usual clinical practice of titrating medications to achieve a specified BP goal. A consequence of the forced-titration design is that the BPs achieved are often lower than would be necessary to reach BP goals and may exaggerate certain adverse effects by increasing the intensity of the regimen. Therefore, we conducted a large, randomized, active-controlled trial comparing the same dosage ranges for AZL-M/CTD FDC and OLM/HCTZ FDC as the forced-titration trial, but with a titration-to-goal protocol.

METHODS

Study design

This randomized, double-blind, parallel-group study, conducted from March 2009 to June 2010, enrolled patients with stage 2 systolic hypertension. The protocol conformed to the Declaration of Helsinki and regional regulatory guidelines, and the study was reviewed and approved by regional institutional review boards (IRB).

Before randomization, patients discontinued their previous antihypertensive medications for a 3-week to 4-week washout period, with all participants receiving single-blind placebo during the final 2 weeks of the washout. Subsequently, eligible patients were randomized (in a 1 : 1 : 1 ratio) using the Interactive Voice Response System (IVRS; United BioSource Corporation, San Francisco, California, USA) to one of three active treatments, which was stratified by race (i.e. black or nonblack). After randomization, patients received 8 weeks of double-blind treatment according to one of the following titration-to-target BP strategies: AZL-M/CTD 20/12.5 mg titrated if needed to 40/25 mg, AZL-M/CTD 40/12.5 mg titrated if needed to 80/25 mg, or OLM/HCTZ 20/12.5 mg titrated if needed to 40/25 mg. The study medication blind was maintained using IVRS. Patients who achieved target BP after 4 weeks of treatment continued with their initial dose for the remainder of the study, whereas patients

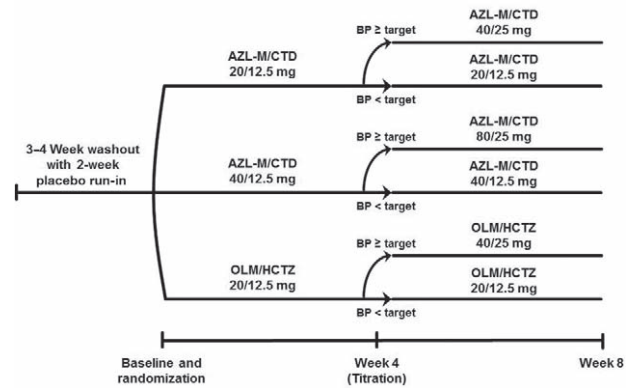


FIGURE 1 Treatments and titration schedule. AZL-M/CTD, azilsartan medoxomil/chlorthalidone; BP target, less than 140/90 mmHg or less than 130/80 mmHg for patients with chronic kidney disease or diabetes; OLM/HCTZ, olmesartan/hydrochlorothiazide.

who did not achieve target by week 4 had their dose up-titrated (Fig. 1). Target BP was less than 140/90 mmHg, or less than 130/80 mmHg for patients with diabetes or chronic kidney disease (CKD), based on the United States hypertension guidelines when the trial was designed and conducted [19].

Patients

Men and women with primary hypertension who were at least 18 years of age were recruited from 75 sites in the United States and 18 in Latin America (Argentina, Chile, and Mexico). Before participation began, each patient signed an IRB-approved informed consent form.

Participants were required to have a postwashout clinic, seated SBP at least 160 and 190 mmHg or less prior to randomization, whereas the following characteristics were exclusionary: secondary hypertension, including renal artery stenosis; DBP greater than 119 mmHg; estimated glomerular filtration rate (eGFR) less than 30 ml/min per 1.73 m², clinically relevant or unstable cardiovascular diseases within the previous 6 months; uncontrolled diabetes (hemoglobin A1c >8.0%); significant hepatic abnormalities; a potassium level above or below the normal range; a baseline ambulatory BP monitoring (ABPM) reading of insufficient quality; poor compliance during the placebo run-in period; or night-shift work. Additionally, pregnant or nursing women and women of childbearing potential not using medically approved means of contraception were excluded. Use of other antihypertensive agents or medications known to affect BP was not allowed, whereas potassium supplementation was not restricted.

BP and assessments

Clinic BP was measured at each scheduled visit (baseline and weeks 2, 4, 6, and 8) using the Greenlight 300 sphygmomanometer (Accoson, Harlow, United Kingdom) [20], which is a manual, mercury-free device with an indicator display to assist in applying a 2 mmHg per second deflation rate. Clinic BP measurements were obtained at trough, that is, approximately 24 h after the previous dose of study drug. At each visit, BP readings were initiated after the patient was seated for at least 5 min without talking and with back

supported; three readings were recorded at 2-min intervals. A single measurement was also obtained after the patient remained standing for 2 min to evaluate for orthostatic hypotension.

Ambulatory BP was recorded with a portable, automated device (Model 90207; Spacelabs, Inc, Issaquah, Washington, USA) [21] for 24 h before the first dose of active study drug, at week 4, and after the last dose at week 8. A final ABPM was attempted for participants who discontinued early if the patient received at least 4 weeks of treatment. During the ambulatory recording, BP was measured every 15 min between 0600 and 2200 h and every 20 min between 2200 and 0600 h. To pass quality criteria, the ABPM reading must have had a starting time of 8 a.m. \pm 2 h, spanned at least 24 h, had at least 80% of the expected BP readings with no more than two nonconsecutive hours in 24 h with less than one valid BP reading, and no consecutive hours with less than one valid BP reading. Unsuccessful baseline or week 8 readings could have been repeated once within 4–5 days of the original recording.

Safety assessments

Investigators evaluated participants for the presence of adverse events at each visit, and participants could report events spontaneously at any time. All events were categorized by the investigator as nonserious or serious and whether or not the event resulted in discontinuation of treatment. Other measures of safety included clinical laboratory tests, vital sign measurements, electrocardiograms, and physical examination findings. Key laboratory tests included those related to renal function (serum creatinine, blood urea nitrogen), electrolyte homeostasis (serum potassium, sodium, chloride, calcium, and magnesium), and metabolic function (serum uric acid, glucose, and fasting lipids). All serum creatinine elevations that were at least 30% above baseline and greater than the upper limit of normal (ULN) were recorded as an adverse event of special interest. Patients with creatinine values at least 50% above baseline and greater than ULN were to be considered for discontinuation if confirmed by a repeat test within 5–7 days.

Statistical analyses

The primary endpoint was change from baseline in trough, seated, clinic SBP at week 8. Changes in clinic DBP, 24-h mean SBP and DBP measured by ABPM, and other ABPM parameters, including trough mean BP (22–24 h postdose) were also assessed, as were the proportion of participants who achieved BP target. Assuming a two-sided significance level of 5%, SD of 14.5 mmHg, and 15% dropout rate, a sample size of 1110 randomized participants (370 per group) was determined as sufficient to achieve 90% power to detect a difference of 3.75 mmHg between the AZL-M/CTD groups and the OLM/HCTZ group for the primary endpoint of clinic SBP.

Statistical analysis of the primary endpoint utilized an analysis of covariance (ANCOVA) model with treatment as fixed effect and the baseline clinic SBP as covariate. All statistical tests were two-sided at the 5% significance level. In testing the primary endpoint, the type 1 error rate was controlled using a sequential testing procedure where the

sequence of statistical tests was performed only whenever the preceding test was statistically significant. Initially (step 1) noninferiority between AZL-M/CTD high dose (40/12.5–80/25 mg) and OLM/HCTZ would be concluded if the upper limit of the 95% confidence interval (CI) of the difference was 3.5 mmHg or less. Followed by (step 2) a two-sided test of superiority; next (step 3) a similar test of noninferiority between AZL-M/CTD low dose (20/12.5–40/25) and OLM/HCTZ and, lastly (step 4) a two-sided test of superiority would be performed. Secondary endpoints that were continuous variables were analyzed with a similar model. Analyses of the clinic BP measurements were based on the last observation carried forward method. A logistic model with treatment as fixed effect and baseline value as a covariate was used for the analyses of target BP achievement. Subgroup analyses were performed for each endpoint by age (<65, \geq 65 years), sex, race (black, white, other), baseline clinic SBP (<median, \geq median), BMI (<30, \geq 30 kg/m²), renal function [eGFR \geq 90 (normal), \geq 60 to <90 (stage 2 CKD), \geq 30 to <60 ml/min per 1.73 m² (stage 3 CKD)], and diabetes. For the above subgroups, posthoc analyses were performed on the primary endpoint and analysis by including the subgroup as a fixed effect to the ANCOVA along with the treatment subgroup interaction.

RESULTS

Patients

There were 3270 patients screened, and 2256 (69%) enrolled into the placebo run-in period. Of these patients, 1085 (48%) were found to be eligible and randomized to one of the three active treatments (356–372 per group). A total of 948 (87%) of the randomized patients completed the study as planned, with 85% ($n=317$) to 86% ($n=308$) completing treatment with AZL-M/CTD and 91% ($n=323$) completing treatment with OLM/HCTZ. The most common reasons for discontinuation were adverse events and voluntary withdrawal (Fig. 2).

There were no major differences between treatment groups with respect to demographics and baseline characteristics (Table 1). In the overall study population, mean age was 56 years, 48% of participants were women, 63% were white, and 27% were black. The baseline mean clinic BP was 165/96 mmHg; 17% of patients had diabetes per medical history and 9% of patients had CKD at screening (eGFR <60 ml/min per 1.73 m² or UACR >200 mg/g). Use of potassium supplementation was less than 2.5% in each group at baseline; a similar proportion of participants in the AZL-M/CTD 20/12.5–40/25 mg group and the OLM/HCTZ group initiated potassium supplementation during the study (1.3 and 1.1%, respectively), with a higher proportion of new potassium use in the AZL-M/CTD 40/12.5–80/25 mg group (2.2%).

Changes in clinic and ambulatory BP

Results for clinic and ambulatory BP are provided in Table 2. There were statistically significantly greater decreases in clinic SBP in both AZL-M/CTD groups than in the OLM/HCTZ group at week 4 after treatment with the initial doses, and significantly greater decreases in clinic SBP were maintained in both AZL-M/CTD groups at week 8

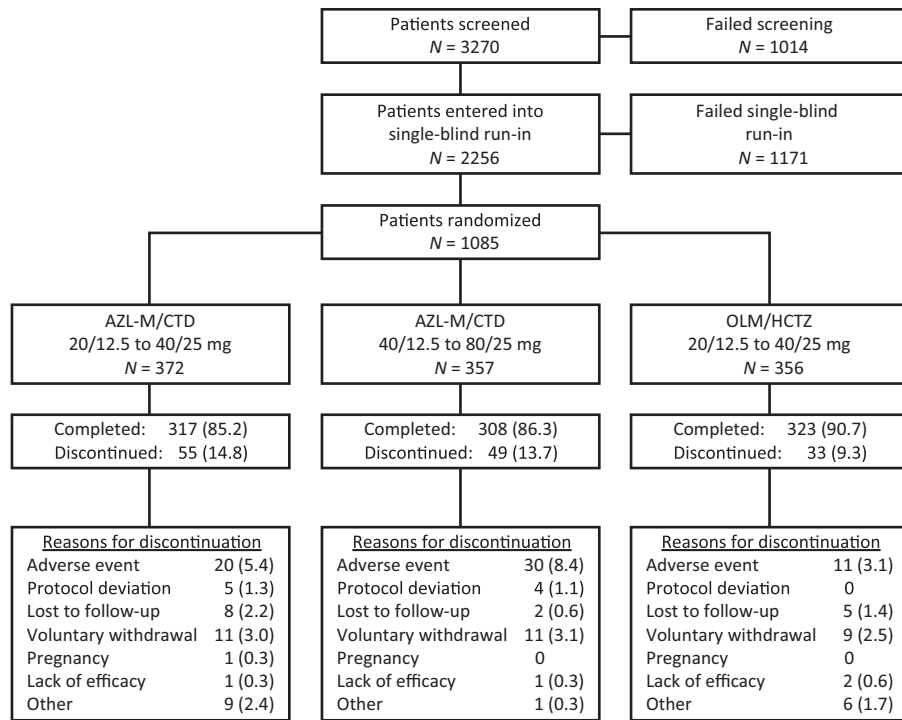


FIGURE 2 Patient disposition. Data are *n* (%). AZL-M/CTD, azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide. The three most common reasons for permanent discontinuation from the study are listed.

(the primary endpoint), despite proportionally more up-titration in the OLM/HCTZ group.

The SBP reductions observed at week 4 were -33.0 and -34.1 mmHg with AZL-M/CTD 20/12.5 and 40/12.5 mg, respectively, and -26.9 mmHg with OLM/HCTZ 20/

12.5 mg. On the basis of the BP assessments at the week 4 visit, approximately one-third of patients had their dose of AZL-M/CTD up-titrated (38% to 40/25 mg and 35% to 80/25 mg), whereas 52% of patients in the OLM/HCTZ group had their dose up-titrated to 40/25 mg (Table 3). Additional

TABLE 1. Demographic and baseline characteristics

Characteristic	AZL-M/CTD, 20/12.5–40/25 mg (N = 372)	AZL-M/CTD, 40/12.5–80/25 mg (N = 357)	OLM/HCTZ, 20/12.5–40/25 mg (N = 356)
Sex, <i>n</i> (%)			
Male	197 (53.0)	183 (51.3)	183 (51.4)
Female	175 (47.0)	174 (48.7)	173 (48.6)
Age, year, mean (SD)	55.5 (10.5)	56.7 (10.8)	55.7 (9.8)
Race, <i>n</i> (%) ^a			
American Indian or Alaska native	37 (9.9)	34 (9.5)	35 (9.8)
Asian	7 (1.9)	5 (1.4)	5 (1.4)
Black or African American	95 (25.5)	95 (26.6)	100 (28.1)
White	235 (63.2)	225 (63.0)	220 (61.8)
Diabetes, <i>n</i> (%)	58 (15.6)	59 (16.5)	71 (19.9)
CKD, <i>n</i> (%) ^b	25 (6.7)	41 (11.5)	66 (9.1)
eGFR, <i>n</i> (%)			
≥ 30 to < 60 ml/min per 1.73 m ²	26 (7.0)	25 (7.0)	25 (7.0)
≥ 60 to < 90 ml/min per 1.73 m ²	220 (59.1)	207 (58.0)	205 (57.6)
≥ 90 ml/min per 1.73 m ²	126 (33.9)	125 (35.0)	126 (35.4)
BMI, kg/m ² , mean (SD)	31.7 (5.9)	31.8 (6.4)	31.9 (6.1)
BP, mmHg, mean (SD)			
Clinic			
SBP/DBP	165.2 (11.1)/95.3 (10.5)	164.9 (10.1)/95.4 (10.0)	164.7 (10.4)/96.1 (10.4)
Hours 22–24 of the ambulatory BP study ^c			
SBP/DBP	151.9 (17.1)/91.7 (13.4)	150.7 (17.8)/90.6 (13.8)	151.1 (16.7)/91.0 (13.2)
24-h mean			
SBP/DBP	148.4 (15.0)/87.4 (12.0)	146.9 (14.7)/86.3 (12.2)	147.6 (14.8)/86.9 (11.9)

AZL-M/CTD, azilsartan medoxomil/chlorthalidone; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; OLM/HCTZ, olmesartan/hydrochlorothiazide.

^aPatients may have chosen more than one category for race.

^bDefined as eGFR less than 60 ml/min per 1.73 m² or UACR greater than 200 mg/g at screening.

^cMean of the last 2 h of the ambulatory BP recording.

TABLE 2. Change from baseline in clinic BP and trough and 24-h mean BP by ambulatory BP monitoring

	AZL-M/CTD, 20/12.5–40/25 mg	AZL-M/CTD, 40/12.5–80/25 mg	OLM/HCTZ, 20/12.5–40/25 mg	AZL-M/CTD, 20/12.5–40/25 mg	AZL-M/CTD, 40/12.5–80/25 mg	OLM-M/HCTZ, 20/12.5–40/25 mg
Clinic SBP, mmHg						
	N=363	N=350	N=353	N=363	N=350	N=353
Baseline	165.2±0.6	164.8±0.6	164.7±0.6	95.2±0.5	95.1±0.6	96.0±0.6
Change at week 4	-33.0±0.9*	-34.1±0.9*	-26.9±0.9	-13.6±0.5*	-14.2±0.5*	-10.4±0.5
Change at week 8	-37.6±0.8*	-38.2±0.9*	-31.5±0.8	-16.1±0.5*	-16.5±0.5*	-12.8±0.5
Difference at week 8 ^a	-6.1 (-8.4, -3.8)	-6.7 (-9.1, -4.4)	-	-3.3 (-4.6, -2.0)	-3.7 (-5.0, -2.4)	-
Trough SBP by ABPM (hours 22–24), mmHg						
	N=290	N=278	N=281	N=290	N=278	N=281
Baseline	152.0±1.0	151.1±1.0	151.2±1.0	91.9±0.8	91.2±0.8	90.9±0.8
Change at week 4	-22.4±1.0*	-23.6±0.9*	-17.4±1.0	-13.4±0.7**	-14.6±0.7*	-10.9±0.7
Change at week 8	-24.9±0.8*	-26.8±0.8*	-19.6±0.8	-14.6±0.6*	-15.9±0.6*	-12.0±0.6
Difference at week 8 ^a	-5.3 (-7.5, -3.0)	-7.2 (-9.4, -4.9)	-	-2.6 (-4.2, -1.1)	-3.9 (-5.4, -2.3)	-
24-h mean SBP by ABPM, mmHg						
	N=290	N=278	N=281	N=290	N=278	N=281
Baseline	148.4±0.9	147.6±0.9	147.9±0.9	87.6±0.7	86.9±0.7	86.7±0.7
Change at week 4	-24.1±0.8*	-24.4±0.8*	-18.4±0.8	-13.9±0.5*	-14.4±0.5*	-10.5±0.5
Change at week 8	-26.4±0.7*	-27.9±0.7*	-20.7±0.7	-15.1±0.5*	-16.4±0.5*	-12.0±0.5
Difference at week 8 ^a	-5.6 (-7.5, -3.7)	-7.2 (-9.1, -5.2)	-	-3.1 (-4.4, -1.9)	-4.4 (-5.6, -3.1)	-
Clinic DBP, mmHg						
Trough DBP by ABPM (hours 22–24), mmHg						
24-h mean DBP by ABPM, mmHg						

ABPM, ambulatory blood pressure monitoring; AZL-M/CTD, azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide. Baseline and change from baseline values are least squares mean ± SE. Sample sizes reflect participants who had both a baseline and final value.

* $P < 0.001$ versus OLM/HCTZ.

** $P = 0.008$ versus OLM/HCTZ.

^aLeast squares mean (95% CI) differences in change from baseline versus OLM/HCTZ at week 8.

TABLE 3. Titration and achievement of target BP

	AZL-M/CTD, 20/12.5–40/25 mg (N = 372)	AZL-M/CTD, 40/12.5–80/25 mg (N = 357)	OLM/HCTZ, 20/12.5–40/25 mg (N = 356)
Patients who received starting dose only ^a , %	61.6	65.3	48.3
Patients who were titrated to higher dose, %	38.4	34.7	51.7
Achievement of target BP ^b at week 8	N = 363	N = 350	N = 353
SBP, %	76.0 ^c	76.0 ^c	64.6
DBP, %	79.9 ^c	79.1 ^c	66.0
SBP and DBP, %	69.4 ^c	68.9 ^c	54.7

AZL-M/CTD, azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide.

^aIncludes patients who discontinued before the week 8 BP assessment.

^bLess than 140/90 mmHg (or <130/80 mmHg for patients with diabetes or CKD).

^c $P < 0.001$ versus olmesartan/hydrochlorothiazide.

decreases in clinic SBP were observed in all groups at week 8: -37.6 mmHg in the AZL-M/CTD 20/12.5–40/25 mg group, -38.2 mmHg in the AZL-M/CTD 40/12.5–80/25 mg group, and -31.5 mmHg in the OLM/HCTZ 20/12.5–40/25 mg group. The respective differences between treatments at the week 8 visit were -6.1 mmHg (95% CI -8.4 to -3.8) and -6.7 mmHg (95% CI -9.1 to -4.4) in favor of the AZL-M/CTD groups ($P < 0.001$ for each comparison). In addition, statistically significant reductions in clinic SBP were observed in favor of the AZL-M/CTD groups at the intermediate visits (i.e. weeks 2 and 6) and at each visit for clinic DBP.

As with the clinic data, there were also statistically significantly greater reductions in ambulatory BP in both of the AZL-M/CTD groups compared with OLM/HCTZ at weeks 4 and 8 (Table 2) ($P < 0.001$ for each comparison). A curve depicting the change from baseline at each hour of the 24-h recording at week 8 is provided in Fig. 3.

Consistent with the mean clinic BP data, the percentage of patients who achieved a target clinic SBP less than

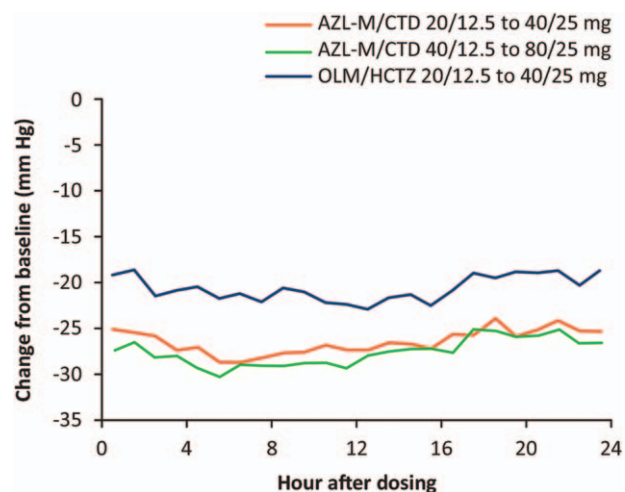


FIGURE 3 Change from baseline in SBP at each hour of the 24-h ABPM recording at week 8. Data are mean changes from baseline. ABPM, ambulatory blood pressure monitoring; AZL-M/CTD, azilsartan medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide.

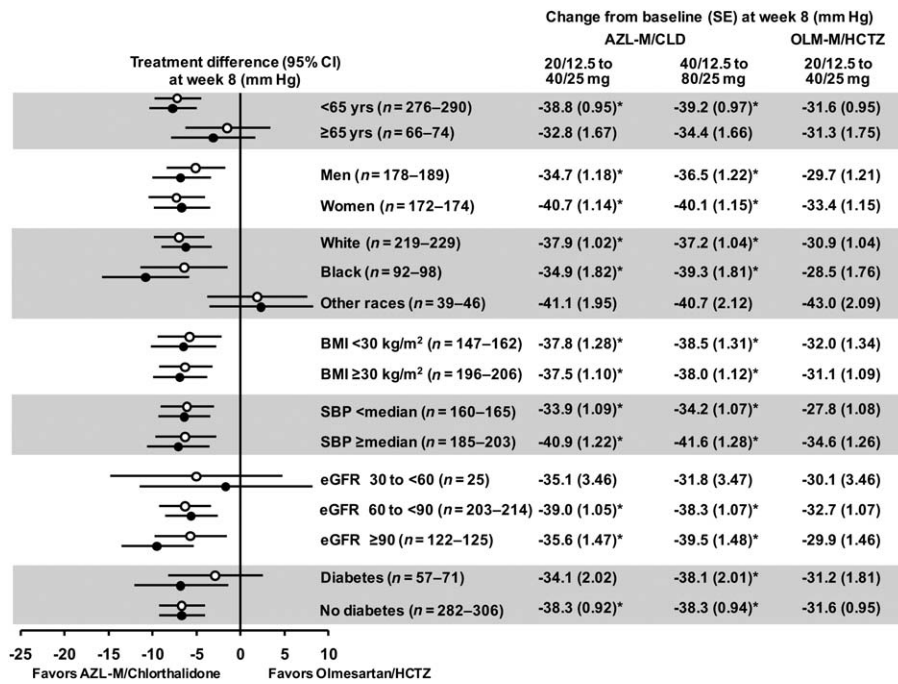


FIGURE 4 Subgroup analyses of clinic SBP by baseline characteristics. AZL-M/CTD, azilsartan-medoxomil/chlorthalidone; eGFR, estimated glomerular filtration rate; OLM/HCTZ, olmesartan/hydrochlorothiazide. Open circles (○) are treatment differences between AZL-M/CTD 20/12.5–40/25 mg and OLM/HCTZ. Closed circles (●) are the treatment differences between AZL-M/CTD 40/12.5–80/25 mg group and OLM/HCTZ. Baseline eGFR categories expressed as ml/min per 1.73 m². *P < 0.05 versus OLM/HCTZ.

140/90 mmHg (or <130/80 mmHg for patients with diabetes or CKD) was statistically significantly greater ($P < 0.001$) in both AZL-M/CTD groups (69.4 and 68.9%, respectively) compared with the OLM/HCTZ group (54.7%), even though more patients received the higher dose of the latter treatment (Table 3).

Significantly greater reductions in clinic SBP were observed in patients who received AZL-M/CTD relative to OLM/HCTZ in most subgroups (Fig. 4). There was no statistical evidence that response to any of the treatments differed by age, sex, baseline hypertension severity, BMI, renal function, or diabetes ($P > 0.10$). There was a significant treatment by race interaction, where clinic SBP reductions were similar across the three race categories (white, black, other) in both AZL-M/CTD groups, whereas participants constituting the ‘other’ race subgroup had a greater response to OLM/HCTZ than white or black participants, as shown in Fig. 4.

Safety and tolerability

The safety findings are summarized in Table 4. Although greater BP reductions were observed with AZL-M/CTD, the incidence of total adverse events was not substantially higher in the AZL-M/CTD 20/12.5–40/25 mg group (51.9%) than in the OLM/HCTZ group (48.0%), and only modestly higher in the AZL-M/CTD 40/12.5–80/25 mg group (55.7%). The most common adverse events were consistent with the BP-lowering effects of the drugs, including increases in serum creatinine and dizziness, with both occurring more frequently with AZL-M/CTD (Table 4). The percentage of participants who discontinued because of an adverse event in the AZL-M/CTD groups increased with dose (6–9.5%) and was higher than in the OLM/HCTZ

group (3%). Blood creatinine increase was the most common adverse event that led to discontinuation overall and was more frequent in the AZL-M/CTD 40/12.5–80/25 mg group (2.5%) compared with the AZL-M/CTD 20/12.5–40/25 mg (0.5%) and OLM/HCTZ 20/12.5–40/25 mg (0.6%) treatment groups. There were few reports of serious adverse events in any group.

Consecutive elevations of serum creatinine at least 50% above baseline and greater than ULN were infrequent in all groups ($\leq 1.1\%$). Additionally, these elevations were non-progressive and associated with relatively large BP reductions; serum creatinine elevations that led to withdrawal were based on laboratory findings only, not associated with clinical complications, and reversed after study drug discontinuation. Changes in other selected serum laboratory parameters were comparable across groups with the exception of greater uric acid increases in the AZL-M/CTD groups; however, reports of gout were infrequent (≤ 2 patients/group). There were more participants with low-sodium and low-potassium values observed with AZL-M/CTD 80/25 mg compared with the other two groups. There was no notable difference between groups with regard to shifts from normal to elevated fasting glucose levels.

DISCUSSION

This randomized, controlled, titration-to-BP-goal trial demonstrated superior antihypertensive efficacy for the two dose-titration options of AZL-M/CTD FDCs compared with the option of titration to the highest approved dose of OLM/HCTZ for both clinic and ABPM measurements. At 8 weeks, 20/12.5–40/25 mg and 40/12.5–80/25 mg

TABLE 4. Summary of safety and laboratory findings

	AZL-M/CTD, 20/12.5–40/25 mg	AZL-M/CTD, 40/12.5–80/25 mg	OLM/HCTZ, 20/12.5–40/25 mg
Adverse events, <i>n</i> (%)	<i>N</i> = 372	<i>N</i> = 357	<i>N</i> = 356
Participants with any adverse event	193 (51.9)	199 (55.7)	171 (48.0)
Most common adverse events			
Blood creatinine increased	36 (9.7)	45 (12.6)	25 (7.0)
Dizziness	25 (6.7)	24 (6.7)	20 (5.6)
Headache	14 (3.8)	14 (3.9)	18 (5.1)
Diarrhea	13 (3.5)	14 (3.9)	5 (1.4)
Fatigue	13 (3.5)	8 (2.2)	5 (1.4)
Nausea	7 (1.9)	8 (2.2)	11 (3.1)
Blood uric acid increased	11 (3.0)	4 (1.1)	2 (0.6)
Serious adverse events	4 (1.1)	8 (2.2)	6 (1.7)
Adverse events leading to discontinuation ^a	23 (6.2)	34 (9.5)	11 (3.1)
Blood creatinine increased	2 (0.5)	9 (2.5)	2 (0.6)
Hypotension	3 (0.8)	4 (1.1)	1 (0.3)
Dizziness	4 (1.1)	2 (0.6)	1 (0.3)
Serum laboratory parameters of interest ^b			
Creatinine			
Mean at baseline (mg/dl)	0.89	0.89	0.89
Mean change at final visit (mg/dl)	0.11	0.12	0.06
Participants (%) with at least two consecutive elevations ($\geq 1.5 \times$ baseline and $>ULN$)	1/364 (0.3)	4/352 (1.1)	4/354 (1.1)
Fasting glucose			
Mean at baseline (mg/dl)	104.5	102.8	104.9
Mean change at the final visit (mg/dl)	4.0	4.8	5.1
Participants (%) whose value shifted from less than 126 mg/dl to at least 126 mg/dl	23/329 (7.0)	25/316 (7.9)	29/313 (9.3)
Potassium			
Mean at baseline (mmol/l)	4.35	4.31	4.31
Mean change at the final visit (mmol/l)	−0.08	−0.05	−0.07
Participants (%) with low potassium (<3.4 mmol/l)	5/355 (1.4)	8/349 (2.3)	5/351 (1.4)
Sodium			
Participants (%) with low sodium (<130 mmol/l)	1/363 (0.3)	10/352 (2.8)	1/354 (0.3)
Uric acid			
Mean at baseline (mg/dl)	5.88	5.94	5.79
Mean change at the final visit (mg/dl)	1.28	1.39	0.88
Participants (%) with high uric acid (male >10.5 mg/dl; female >8.5 mg/dl)	44/353 (12.5)	57/349 (16.3)	22/347 (6.3)

AZL-M/CTD, azilsartan-medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide; ULN, upper limit of normal.

^aIncludes temporary interruption of study drug or permanent discontinuation from the study; the most common adverse events leading to discontinuation are shown.

^bOnly laboratory changes judged to be clinically significant by the investigator were reported as adverse events.

AZL-M/CTD reduced clinic SBP (6.1 and 6.7 mmHg, respectively) and trough ABPM SBP (5.6 and 7.2 mmHg, respectively) more than 20/12.5–40/25 mg OLM/HCTZ. In addition, 8-week SBP assessed by 24-h ABPM was reduced more with AZL-M/CTD than OLM/HCTZ throughout the 24-h dosing period. Reductions of clinic SBP were greater in both AZL-M/CTD groups compared with OLM/HCTZ across most subgroups examined, including black participants.

Although the previously reported forced-titration study of these same FDCs demonstrated greater absolute BP reductions and larger maximum differences with AZL-M/CTD compared with OLM/HCTZ [18], this titration-to-goal study reflects usual medical practice, wherein doses would only be increased if a patient has not achieved goal BP. In fact, 62 and 65% of the AZL-M/CTD participants reached goal on the initial dose, whereas only 48% of the OLM/HCTZ participants did so, leading to up-titration in only 38 and 35% of the AZL-M/CTD participants but 52% of the OLM/HCTZ participants. Despite the greater frequency of uptitration in the latter, only 55% of the OLM/HCTZ

participants reached goal BP, compared with 69% reaching goal BP in both AZL-M/CTD groups. Nearly 15% more participants on OLM/HCTZ (45 versus 31%) would have required additional antihypertensive drugs to achieve BP control.

Tolerability, reflected by discontinuation rates for adverse events, were relatively low ($<10\%$ in all three groups): lowest for OLM/HCTZ (3.1%), intermediate for the lower dose of AZL-M/CTD (6.2%), and moderately higher with the higher dose of AZL-M/CTD (9.5%). Many of the adverse events, particularly increases in creatinine, dizziness, hypotension, and electrolyte disturbances were, as expected, lower in this titration-to-goal trial than in our previously reported forced-titration trial, which used the same possible maximal doses. Overall adverse event rates were 12–20% lower (with nonoverlapping CIs; Table 5) and discontinuation rates for adverse effects were 3–5% lower in this titration-to-goal study than the forced-titration study. These comparisons suggest that drug intolerance would be low whenever these drugs are used in clinical practice in the usual titration-to-goal

TABLE 5. Comparison of overall adverse event rates (%; CI) in azilsartan medoxomil/chlorthalidone versus olmesartan/hydrochlorothiazide titration-to-target and forced titration studies

	Titration-to-target study	Forced titration study
AZL-M/CTD low dose	51.9 (46.7–57.1)	71.3 (66.3–75.9)
AZL-M/CTD high dose	55.7 (50.4–61.0)	70.7 (65.7–75.4)
OLM/HCTZ	48.0 (42.7–53.4)	60.2 (54.9–65.2)

AZL-M/CTD, azilsartan-medoxomil/chlorthalidone; OLM/HCTZ, olmesartan/hydrochlorothiazide.

manner and similar between AZL-M/CTD and OLM/HCTZ for the titration regimens that use 40/25 mg as the highest dose.

The present study was designed in accordance with previous hypertension guidelines [19], which endorsed lower BP targets than are currently recommended in the most recent hypertension 2013–2014 guidelines [22,23], especially for patients with diabetes mellitus or CKD, or for older patients. However, as recently demonstrated by the Systolic Blood Pressure Intervention Trial (SPRINT) [24], better outcomes, including reduced risk of major cardiovascular events and death, were observed among nondiabetic participants who were assigned to intensive BP control defined as target SBP less than 120 mmHg compared with the target of less than 140 mmHg. It is reasonable to expect that recommended BP goals may be adjusted accordingly in the future, both in the general hypertensive population, as well as for high-risk patients [25,26]. In the present study, AZL-M/CTD was shown to be an important option for treating patients to goal, and may often allow goal achievement without the need for more complex regimens in many patients.

Although previous studies have shown a high incidence of hypokalemia with CTD doses of 50–100 mg [27], it was infrequent (1–2%) with this AZL-M/CTD combination, and the frequency of hypokalemia with the highest approved dose of the AZL-M/CTD was no different than that of OLM/HCTZ despite CTD being a more potent diuretic. This finding may be related in part to the lower doses of CTD (12.5–25 mg/day) used in the combination and the potent attenuating effect of renin–angiotensin–aldosterone system inhibition associated with AZL-M, which was also seen in a previously conducted factorial study of the AZL-M CTD combination [28].

A number of trials have assessed the antihypertensive efficacy of an ARB–HCTZ combination, as almost all ARBs have been developed in combination with HCTZ. However, few have conducted titration-to-target studies in patients with stage 2 systolic hypertension. In a titration-to-target study of valsartan/HCTZ, which had a maximum dose of 320/25 mg, 384 men and women at least 70 years of age with systolic hypertension (mean sitting SBP 150–200 mmHg) were randomized (128 to the combination); mean baseline office SBP was 164 mmHg, similar to the 165 mmHg baseline SBP in the current trial [29]. However, SBP was reduced by 17 mmHg, which was less than the reductions that we observed with either dose of AZL-M/CTD (38 mmHg) or OLM/HCTZ (32 mmHg). In a study of

irbesartan/HCTZ in systolic hypertension [30], SBP was reduced 22 mmHg, although the entry SBP and mean baseline SBP (154 mmHg) were lower than the current study. In an open-label titration study of OLM/HCTZ in stage 2 systolic hypertension (SBP \geq 160 mmHg), the 40/25 mg dose reduced SBP 35 mmHg [31]. However, baseline SBP was higher (171 mmHg) than the current study and the design was different.

The greater efficacy of both doses of AZL-M/CTD over OLM/HCTZ may be from either the CTD compared with the HCTZ or the AZL-M compared with OLM, or both. AZL-M/CTD 40/12.5–25 mg/day was shown to reduce SBP 5.6 mmHg more ($P < 0.001$) than AZL-M/HCTZ, 40/12.5–25 mg/day in a randomized, double-blind, titration-to-target trial of patients with stage 2 systolic hypertension [17]. In a separate randomized, double-blind, forced-titration study, the maximum approved FDC dose of AZL-M/CTD 40/25 mg lowered SBP 5.3 mmHg ($P < 0.001$) more than the maximum approved FDC dose of OLM/HCTZ 40/25 mg [18]. In a meta-analysis, HCTZ 12.5–25 mg was reported to be less effective in reducing BP than full doses of other antihypertensive classes, although 50 mg was comparable with other classes [32]. However, we evaluated 12.5–25 mg/day of HCTZ in combination with OLM because this is the dose range available in the market for the OLM/HCTZ FDC and for all other currently marketed ARB–HCTZ FDCs. In addition, the greater efficacy of the AZL-M/CTD FDCs may be from the AZL-M component, as it has been shown to have greater antihypertensive efficacy than OLM alone or valsartan [6–8].

A limitation of the study is that this titration-to-target design may underestimate the differences between the regimens in BP reduction or adverse events, since a forced-titration design gives the most accurate reflection of true differences in the regimens being compared. However, titration-to-target is more consistent with usual clinical practice of titrating medications to achieve a specified BP goal and provides a better indication of the incidence and severity of adverse effects in clinical practice.

In conclusion, this large, 8-week, titration-to-target study comparing two ARB–diuretic FDCs demonstrated superior antihypertensive efficacy of two dose-titration options of AZL-M/CTD compared with the option of titrating to the maximum US Food and Drug Administration-approved dose of OLM/HCTZ. Only 38.4 and 34.7% of participants on the two dose levels of AZL-M/CTD were titrated to the higher doses at week 4, whereas 51.7% of participants on OLM/HCTZ were titrated to the higher level at week 4. Despite the higher proportion of titration in the OLM/HCTZ group, fewer patients achieved target BP at week 8 compared with the AZL-M/CTD groups (54.7 versus 69.4 and 68.9%, respectively). Tolerability was relatively similar for the lower dose of AZL-M/CTD and OLM/HCTZ FDC. There was a moderately higher adverse event discontinuation rate for the higher dose of AZL-M/CTD. Consistent with the comparable efficacy of the AZL-M/CTD 40/25 and 80/25 mg target doses, but better tolerability of the 40/25 mg target dose, the highest dose strength for the FDC proposed by the sponsor and approved by the US Food and Drug Administration is 40/25 mg.

The target dose of AZL-M/CTD 40/25 mg once daily provides a well tolerated and more effective treatment for stage 2 systolic hypertension than the target dose of OLM/HCTZ 40/25 mg and in practice may provide BP control to recommended target BP levels for a higher proportion of hypertensive patients than the other two-drug FDCs. For those hypertensive patients who require more medications to achieve their BP goal, the subsequent regimen will likely require fewer additional drugs.

ACKNOWLEDGEMENTS

Results from this study were presented at the American Society of Hypertension and the European Society of Hypertension Annual Meetings in 2011.

Clinicaltrial.gov identifier: NCT00846365

Conflicts of Interest

W.C.C. has received grant or research support from Lilly and a consulting fee from Takeda during the time of this study. He has been an unpaid consultant to Takeda since October, 2013. G.L.B. has received grant or research support from Bayer and is a consultant for Takeda, Abbvie, Janssen, Astra Zeneca, Bayer, Boehringer-Ingelheim, and Merck. He is a special government employee of the Food and Drug Administration and CMS. W.B.W. serves as a safety consultant for Takeda. M.A.W. is a member of the speakers bureau and consultant for Boehringer-Ingelheim, Daiichi Sankyo, Forest, Novartis, and Takeda; and D.S. has a research or consultant relationship with Takeda, Novartis, and Boehringer-Ingelheim; A.R. and S.K. were employees at Takeda during the time the research was conducted; E.L. is a full-time employee of Takeda. High-resolution and color figures for this manuscript were produced by Sam Schmitt of Extention Media Group, LLC and Blue Momentum, an Ashfield Company and were supported by Takeda Development Centers America, Inc. This study was sponsored by Takeda Development Center Americas, Inc. There was no payment by the sponsor to any non-Takeda authors for their work in analyzing data, writing, or editing of this article.

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Reviewer's Summary Evaluation

Reviewer 2

The main attraction of this paper is that it adds information about an effective fixed dose combination of blood

pressure lowering drugs—much needed for better control of hypertension worldwide.