2017

Evaluation of the angiotensin II receptor blocker azilsartan medoxomil in African-American patients with hypertension

Wallace Johnson
University of Maryland

William B. White
University of Connecticut

Domenic Sica
Virginia Commonwealth University

See next page for additional authors

Received: 26 July 2016 | Revised: 9 November 2016 | Accepted: 30 December 2016

DOI: 10.1111/jch.12993

ORIGINAL PAPER

WILEY

Evaluation of the angiotensin II receptor blocker azilsartan medoxomil in African-American patients with hypertension

Wallace Johnson MD, FASH[1] | William B. White MD, FASH[2] | Domenic Sica MD, FASH[3] | George L. Bakris MD, FASH[4] | Michael A. Weber MD, FASH[5] | Alison Handley PhD[6] | Alfonso Perez MD[7,#] | Charlie Cao PhD[8] | Stuart Kupfer MD[7,#] | Elijah B. Saunders MD, FASH[1,†]

[1]University of Maryland School of Medicine, Baltimore, MD, USA

[2]Cardiology Center, University of Connecticut School of Medicine, Farmington, CT, USA

[3]Virginia Commonwealth University Health System, Richmond, VA, USA

[4]University of Chicago Medicine, Chicago, IL, USA

[5]SUNY Downstate College of Medicine, New York, NY, USA

[6]Takeda Pharmaceuticals International Inc., Deerfield, IL, USA

[7]Takeda Development Center Americas Inc., Deerfield, IL, USA

[8]Takeda Pharmaceuticals America, Inc.

Correspondence
Wallace Johnson, MD, University of Maryland School of Medicine, Baltimore, MD, USA.
Email: wjohnson@medicine.umaryland.edu

Funding information
Takeda Development Center Americas, Inc.

The efficacy and safety of azilsartan medoxomil (AZL-M) were evaluated in African-American patients with hypertension in a 6-week, double-blind, randomized, placebo-controlled trial, for which the primary end point was change from baseline in 24-hour mean systolic blood pressure (BP). There were 413 patients, with a mean age of 52 years, 57% women, and baseline 24-hour BP of 146/91 mm Hg. Treatment differences in 24-hour systolic BP between AZL-M 40 mg and placebo (−5.0 mm Hg; 95% confidence interval, −8.0 to −2.0) and AZL-M 80 mg and placebo (−7.8 mm Hg; 95% confidence interval, −10.7 to −4.9) were significant ($P \leq .001$ vs placebo for both comparisons). Changes in the clinic BPs were similar to the ambulatory BP results. Incidence rates of adverse events were comparable among the treatment groups, including those of a serious nature. In African-American patients with hypertension, AZL-M significantly reduced ambulatory and clinic BPs in a dose-dependent manner and was well tolerated.

1 | INTRODUCTION

Blocking the renin-angiotensin system (RAS) in the management of hypertension in African-American (AA) patients has had varying results for the treatment of hypertension. In fact, the modest effectiveness of angiotensin receptor blocker (ARB) and angiotensin-converting enzyme inhibitor (ACEI) monotherapy trials have led to the avoidance of these classes of therapies as an initial option in the treatment of hypertension in AAs.[1–3] In addition, there are proven racial variations in clinical phenotype and genetic characteristics, making stratification by race more than just a physiologic grouping in trials of cardiovascular medications. The AA population has a disproportionate burden of cardiovascular disease as well as a heterogeneous response to medications (intraracial variability).[4] Clinicians should not assume that all AAs are a homogenous entity with the same response to a particular class of antihypertensive medication, including ARBs. Potentially, ARBs could allow a significant number of AAs to reach their target blood pressure (BP) if effective and well-tolerated.

Azilsartan medoxomil (AZL-M) is a prodrug that is quickly hydrolyzed to the active moiety azilsartan (AZL), a potent and highly selective ARB with estimated bioavailability of 60% and elimination half-life

[#]These authors are former employees of Takeda who participated in the study at the time that it was conducted.

[†]Deceased. See tribute to Dr Saunders in Acknowledgment section of the article.

Clinical Trials.gov identifier: NCT00591253.

of approximately 11 hours.[5] Superior antihypertensive efficacy to valsartan and olmesartan has been demonstrated in three clinical trials[6–8]; this greater efficacy may be related to the more potent and persistent binding of AZL to the angiotensin II type 1 receptor relative to other ARBs.[9,10] From prior pivotal studies evaluating the safety and efficacy of AZL-M vs placebo and other ARBs,[6-8] a subgroup analysis in AA patients demonstrated significant reductions in 24-hour systolic BP (SBP) vs placebo.[11] The present trial was a dedicated study in AAs with stages 1 and 2 hypertension designed to evaluate both the efficacy and safety of AZL-M vs. placebo in this population. The primary end point was the change in 24-hour mean SBP, as determined by ambulatory BP monitoring (ABPM). Given the high prevalence of hypertension and the lower efficacy rates of ARBs in AA patients, as well as the underrepresentation of AAs in hypertension clinical trials, this study addressed an important medical need.

2 | METHODS

2.1 | Patients and study design

This was a 6-week, randomized, double-blind, multicenter, placebo-controlled study comparing the antihypertensive effects and safety and tolerability of AZL-M, 40 or 80 mg once daily, with placebo in AA patients with stages 1 or 2 systolic hypertension. The protocol conformed to the Declaration of Helsinki and regional regulatory guidelines, and the study was approved by regional institutional review boards (IRBs). Each patient signed an IRB-approved consent form before any study procedures were initiated. Eligible patients were randomized after participating in a 3- to 4-week washout of previous antihypertensive therapy that coincided with a 2-week single-blind, placebo run-in period.

At randomization, each patient was required to be 18 years or older, with a clinic SBP ≥150 and ≤180 mm Hg and a 24-hour mean SBP ≥130 and ≤170 mm Hg. Exclusion criteria included known or suspected secondary hypertension or severe diastolic hypertension (seated diastolic [DBP] >114 mm Hg); severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2); history of a major cardiovascular event in the previous 6 months; type 1 or poorly controlled type 2 diabetes mellitus (glycated hemoglobin >8%); poor compliance with study medication during the placebo run-in period; or hyperkalemia (serum potassium concentration>upper limit of normal for the reference laboratory). In addition, night-shift workers, pregnant or nursing women, and women of childbearing potential not using approved means of contraception were excluded from participation. Concomitant medications known to affect BP were not permitted; these medications were listed in the protocol and available to all study personnel.

Seated BP was measured in the clinic at baseline and at weeks 2, 4, and 6, and ABPM was performed at baseline and week 6. Clinic BP was measured in triplicate in the nondominant arm using an automated BP monitor (Omron HEM 705-CP, Lake Forest, IL, USA) after the patient was seated for 5 minutes. Every effort was made to ensure that the clinic BP readings were obtained approximately 24 hours after the last dose of study medication (ie, at trough) and before other procedures, including venipuncture. ABPM was performed with the Spacelabs 90207 device (Spacelabs, Inc., Issaquah, WA, USA), and was initiated in the morning immediately after dosing. The ABPM device measured BP every 15 minutes between 6 AM and 10 PM and every 20 minutes between 10 PM and 6 AM. To pass the minimum quality-control criteria, each ABPM recording must have: (1) been ≥24 hours in duration; (2) captured ≥80% of the possible readings; (3) had ≤2 nonconsecutive hours with <1 valid reading; and (4) had no consecutive hours with <1 valid reading. If these criteria were not met, the patient was asked to repeat the procedure within 5 days. If the repeated ABPM procedure also failed, the ABPM data were considered nonevaluable.

2.2 | Statistical analyses

The primary end point was change from baseline to week 6 in 24-hour mean SBP by ABPM, and the key secondary end point was change in trough sitting clinic SBP (referred to as clinic SBP). Changes in 24-hour mean DBP by ABPM and clinic DBP were also evaluated, as were the proportion of responders. The definition of response included achievement of: (1) clinic SBP <140 mm Hg and/or a reduction of ≥20 mm Hg from baseline; (2) clinic DBP <90 mm Hg and/or a reduction of ≥10 mm Hg from baseline; or both 1 and 2. Subgroup analyses of the primary and key secondary analyses were conducted by age, sex, body mass index, baseline 24-hour mean SBP, and estimated glomerular filtration rate.

The primary efficacy analysis was based on an analysis of covariance model that included treatment as a fixed effect and baseline 24-hour mean SBP by ABPM as a covariate, and utilized the last-observation-carried-forward principle. The intention-to-treat approach was used for the primary efficacy analysis for all randomized patients with at least one dose of study medication. A patient was included in the primary analysis only when there was both a baseline value and at least one postbaseline value. Similar statistical methods were used to analyze the other secondary efficacy end points that were continuous variables.

All statistical tests were two-sided and results were presented as treatment differences with 95% confidence intervals (CIs) and *P* values at the 5% significance level. Type 1 error was controlled for the primary analysis by using the principle of "closed" testing.[12] For the key secondary efficacy variable, the same statistical model and testing procedure used for the primary end point were used. Given the assumptions of a standard deviation of 13 mm Hg and a 20% dropout rate, the sample size of this study provided at least 90% power to detect a difference of 6 mm Hg between each of the AZL-M treatment groups and placebo for the primary end point.

Safety measures included adverse events, clinical laboratory results (including pregnancy testing), physical examination findings, and electrocardiographic data. All adverse events observed by the investigator or reported spontaneously by the patient were recorded and further characterized by the investigator as being nonserious or serious; whether the event led to discontinuation of treatment was also recorded. Safety laboratory parameters of interest that were measured

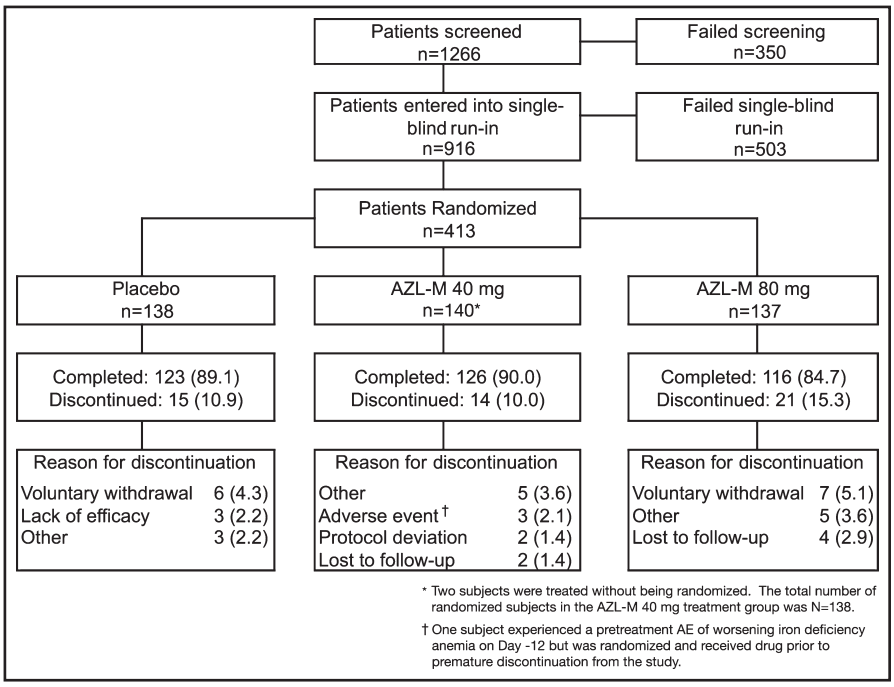

FIGURE 1 Patient disposition. Data are expressed as number (percentage). The most common reasons for permanent discontinuation from the study are listed. The category "other" includes discontinuations that were due to reasons other than an adverse event, lack of efficacy, voluntary withdrawal, lost to follow-up, protocol deviation, or pregnancy. Patients could have had more than one reason for discontinuation, but only the primary reason is presented here. AZL-M indicates azilsartan medoxomil

at each visit included renal and hepatic function tests and serum potassium levels. Blood samples were analyzed by a central laboratory (ICON Laboratories, Farmingdale, NY, USA).

3 | RESULTS

A total of 1266 patients were screened, and 916 patients were enrolled in the single-blind placebo run-in period at 74 principal investigators in the United States and Puerto Rico. Of these patients, 413 fully met the entry criteria and were randomly assigned to one of three treatment arms as follows: 138 patients to placebo, 138 patients to AZL-M 40 mg, and 137 patients to AZL-M 80 mg. A total of 365 of the 413 randomized patients completed 6 weeks of treatment as planned: 123 (89%) in the placebo arm, 126 (90%) in the AZL-M 40-mg arm, and 116 (85%) in the AZL-M 80-mg arm. Discontinuation rates were low; the most common reason for premature discontinuation was voluntary withdrawal (n=14, 3.4%) (Figure 1). There were no major differences in baseline characteristics among the three treatment groups (Table 1). The mean age was 52 years, and a greater percentage of the participants were women (57%). Mean baseline clinic BP was approximately 158/96 mm Hg and 24-hour mean BP was 146/91 mm Hg.

3.1 | Efficacy findings

The absolute changes from baseline on ambulatory BP after 6 weeks of therapy for all the treatments are shown in Figure 2. Significant dose-related reductions in 24-hour mean SBP were observed for AZL-M 40 and 80 mg. The treatment difference between AZL-M 40 mg and placebo for 24-hour mean SBP (−5.0 mm Hg; 95% CI, −8.0 to −2.0) and AZL-M 80 mg and placebo (−7.8 mm Hg; 95% CI, −10.7 to −4.9) were both statistically significant ($P \leq .001$ vs placebo for both comparisons). Changes in daytime and nighttime BP were similar and significantly greater with both doses of AZL-M vs placebo (Figure 2). Hourly SBPs with AZL-M 40 and 80 mg were both consistently lower than with placebo throughout the dosing interval (Figure 3).

The effect of each treatment on clinic BP at week 6, the key secondary end point, is shown in Figure 4. Placebo-subtracted decreases in the clinic SBP were −6.5 mm Hg with AZL-M 40 mg (95% CI, −10.2 to −2.8) and −6.5 mm Hg with AZL-M 80 mg (95% CI, −10.3 to −2.8), respectively, and were statistically significant ($P \leq .001$ vs placebo for both comparisons). A larger proportion of patients receiving AZL-M achieved a reduction of clinic SBP of <140 mm Hg and/or a reduction of ≥20 mm Hg (≈40%) compared with placebo (25%).

Changes in DBP, as measured by both ambulatory and clinic measurements, were statistically significantly greater with both doses of AZL-M vs placebo (Figures 2 and 4). Placebo-subtracted mean reductions in 24-hour DBP were −3.4 mm Hg (95% CI, −5.5 to −1.4) for AZL-M 40 mg and −5.8 mm Hg (95% CI, −7.8 to −3.8) for AZL-M 80 mg ($P \leq .001$ vs placebo for both comparisons). Placebo-subtracted mean reductions in clinic DBP were −3.1 mm Hg (95% CI, −5.2 to −1.0) for AZL 40 mg and −3.0 mm Hg (95% CI, −5.1 to −0.8) for AZL-M 80 mg ($P = .004$ and $P = .006$ vs placebo, respectively).

3.2 | Safety findings

Rates of treatment-emergent adverse events were comparable in the three treatment groups (Table 2). Treatment-emergent adverse events were generally mild to moderate in severity. The most common adverse events during the trial were headache, increased creatine phosphokinase, and urinary tract infection (Table 2). Four patients experienced serious adverse events, three in the AZL-M 40-mg group

Characteristic	Placebo n=138	AZL-M 40 mg n=138	AZL-M 80 mg n=137
Age, y	52±11	52±11	51±10
Male/female, %	44/57	44/57	42/58
Body mass index, kg/m^2	32.9±7.4	31.4±6.3	31.6±7.7
Diabetes, %[b]	13.8	12.3	9.4
Clinic BP, mm Hg	158/96±13/10	157/97±14/10	159/95±14/10
24-h mean BP, mm Hg	145/91±10/9	146/92±11/9	147/92±11/10
Daytime BP, mm Hg[c]	148/94±11/10	149/95±11/10	150/95±11/11
Nighttime BP, mm Hg[d]	137/82±13/11	138/83±14/11	139/84±13/12

[a]Data mean±standard deviation unless specified otherwise.
[b]Subjects (Ns) for this characteristic are from the safety analysis set which had 138, 137, 137 subjects for placebo, azilsartan medoxomil (AZL-M) 40 mg, and AZL-M 80 mg groups, respectively.
[c]Daytime interval is from 6 AM to 10 PM.
[d]Nighttime interval is from 12 AM to 6 AM.
Abbreviation: BP, blood pressure.

TABLE 1 Baseline Characteristics of Randomized Patients[a]

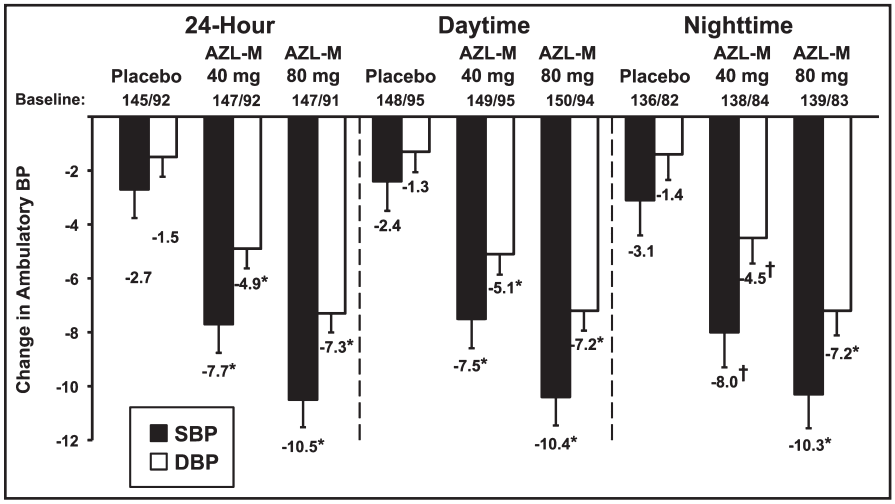

FIGURE 2 Change from baseline (mm Hg) in ambulatory systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 6. Data are least squares mean (±standard error). Sample sizes are 94, 94, and 101 for the placebo, azilsartan medoxomil (AZL-M) 40-mg, and AZL-M 80-mg groups, respectively, for each measure. *P≤0.001 vs placebo. †P<.05 vs placebo. BP indicates blood pressure

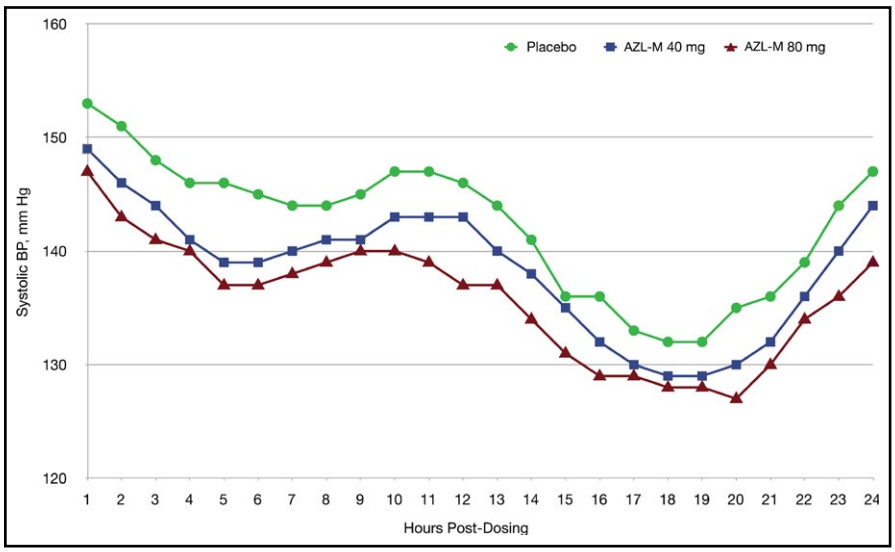

FIGURE 3 Hourly profiles of the 24-hour systolic blood pressure (BP) at week 6. Double-blind medication dosing was administered at hour 0. AZL-M indicates azilsartan medoxomil

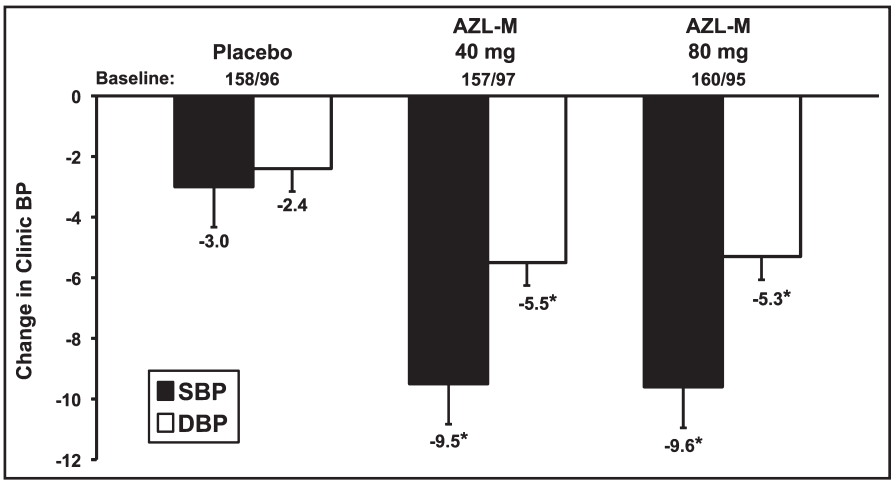

FIGURE 4 Change from baseline (mm Hg) in clinic systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 6. Data are least squares mean (±standard error). Sample sizes are 133, 134, and 130 for the placebo, azilsartan medoxomil (AZL-M) 40-mg, and AZL-M 80-mg groups, respectively, for each measure. *P<.01 vs placebo. BP indicates blood pressure

TABLE 2 Safety Findings During the Trial

AEs, No. (%)	Placebo n=138	AZL-M 40 mg n=137	AZL-M 80 mg n=137
Any AEs	49 (35.5)	50 (36.5)	45 (32.8)
AEs leading to discontinuation	1 (0.7)	3 (2.2)	2 (1.5)
Serious AEs	0	3 (2.2)	1 (0.7)
Deaths	0	0	0
Most frequently reported AEs			
Headache	3 (2.2)	6 (4.4)	9 (6.6)
Blood CK increased	6 (4.3)	4 (2.9)	3 (2.2)
Urinary tract infection	6 (4.3)	3 (2.2)	3 (2.2)
AEs of special interest			
Dizziness	1 (0.7)	4 (2.9)	3 (2.2)
Hyperkalemia[a]	0	0	1 (0.7)

Abbreviations: AEs, adverse events; AZL-M, azilsartan medoxomil; CK, creatine kinase.
[a]≥5.5 mmol/L.

(diabetic ketoacidosis, cerebral hemorrhage, and an exacerbation of asthma) and one in the AZL-M 80-mg treatment group (vomiting). There were no deaths in the trial.

There were no differences in mean changes in serum creatinine, potassium, or liver enzymes observed among the three treatment groups. No participant experienced serum potassium >6 mmol/L. One participant (0.7%) in the placebo treatment group and one participant in the 80-mg treatment group had an increase in serum creatinine ≥50% above baseline and above the upper limit of normal. There were no instances of a persistent increase in serum creatinine following discontinuation of study drug.

4 | DISCUSSION

The results of this trial demonstrate that AZL-M produced significant BP-lowering effects throughout the dosing interval in AA patients with hypertension and was well tolerated. The reductions in ambulatory and clinic BPs from baseline were highly significant and clinically important, showing greater dose-related reductions for 80 mg vs 40 mg in this patient population.

There has been a longstanding impression that RAS inhibitors are much less efficacious in AA patients with hypertension when compared with their white counterparts (which is clearly the case for a number of agents, including telmisartan, another fairly long-acting ARB). These impressions were based on the theory that the RAS is less active in AAs vs whites because of the tendency towards suppressed circulating renin activity in AAs[13,14] and the lesser average BP response in AA as compared with white hypertensive patients to ACEIs when used as monotherapy.[1,15-18] However, circulating renin levels are not fully suppressed in the majority of AAs.[19] Also, suppressed renin production and circulating renin levels from high sodium intake have been associated with higher levels of vascular angiotensin II production[20] and a greater activation of RAS in healthy AAs as compared with whites.[21] The excessive rates of target organ injury such as chronic kidney disease and proteinuria in hypertensive AAs have all been associated with RAS activation,[22] which supports the evidence from prior studies demonstrating that ACEIs and ARBs are effective antihypertensives for slowing the progression of kidney disease in patients with diabetic and nondiabetic chronic kidney disease.[23-27] The basis for the primary use of ACEIs in the AA population with hypertension

is well documented in the African American Study of Kidney Disease and Hypertension (AASK), which demonstrated superiority of ACEI over β-blocker and dihydropyridine calcium channel blocker therapy for slowing the rate of decline in the glomerular filtration rate in AA patients with moderate renal insufficiency and proteinuria.[28]

Trials comparing the efficacy of various ARBs in reducing CV outcomes of interest have consistently shown a disproportionately lower representation of AAs in those studies compared with their white counterparts.[1,22] Therefore, evidence-based recommendations regarding superiority or inferiority of ARBs vs ACEIs in managing hypertension or its related comorbidities are difficult to determine. Few studies have evaluated the efficacy of ARBs as monotherapy for the treatment of hypertension specifically in the AA population. One such study was the Association of Black Cardiologists (ABC) trial,[29] in which the efficacy of the RAS blocker candesartan was explored in AA patients with hypertension. In this study, small but significant reductions in clinic BP were observed vs placebo (−5/−2.5 mm Hg) after 8 weeks of treatment with candesartan. In fact, most of the evidence for efficacy and tolerability of RAS inhibition in AA patients has been derived from subgroup analyses.

At least two studies have compared the efficacy of different ARBs in black vs nonblack patients, in post hoc subgroup analyses. In one study, Giles and colleagues[30] compared the efficacy of olmesartan medoxomil, losartan potassium, and valsartan in black vs nonblack patients with hypertension, in a 12-week, placebo-controlled forced-titration (at 4 and 8 weeks) study. Significant reductions in SBP were observed by 2 weeks of treatment with all three ARBs in the nonblack patients versus placebo; however, significant reductions vs placebo were not observed in the black patients until 8 weeks of treatment (and titration to double the starting dose), and only with olmesartan treatment. These results show that clinically relevant BP reductions can be achieved with RAS blockade in black patients, but may require higher doses than their nonblack counterparts or more potent RAS agents and likely combination therapy.

White and coworkers[6–8,11] previously described the comparative BP-lowering efficacy and tolerability of AZL-M vs olmesartan and valsartan in black patient subgroups from three large, randomized trials of patients with stage 1 and 2 hypertension. AZL-M's efficacy was greater than olmesartan and valsartan at their highest clinically used doses after 6 to 8 weeks of treatment and was well tolerated in black patients with hypertension.[11] However, even though there were reasonable proportions of black patients in the individual pivotal trials comparing AZL-M to placebo,[6-8] the subgroup analyses were exploratory and the total number of patients on either dose of AZL-M was relatively low.[11] The results of this larger, dedicated study are consistent with the previous subgroup analyses and definitively demonstrate clinically meaningful reductions in clinic and 24-hour mean SBP of AZL-M in the AA population.[6–8,11]

5 | CONCLUSIONS

The results from our study demonstrate that an ARB with potent efficacy such as AZL-M was able to provide clinically meaningful reductions in ambulatory and clinic BP when used as monotherapy in AA patients. It is also noteworthy that use of AZL-M shows greater efficacy in AA patients when combined with other types of antihypertensives, particularly the long-acting diuretic chlorthalidone and the long-acting dihydropyridine calcium channel blocker amlodipine.[31–33] Race and/or ethnicity should not be a deterrent to clinicians for using ARBs as evidenced by our data. AZL-M can be considered as a potentially effective and well-tolerated monotherapy or in combination with other therapy for this often difficult to manage population.

DISCLOSURES

This study was sponsored by Takeda Development Center Americas, Inc., Deerfield, Illinois. W. Johnson receives funding from the Amarin Corporation and Amgen in the form of research support. W. White has served as the chair of the steering committee and of the Cardiovascular Endpoints Committee for the EXAMINE trial and the CARES trial, respectively, sponsored by Takeda Global Research and Development Center, Inc. D. Sica has had a research and/or consultant relationship with Takeda Pharmaceuticals and Merck. G. Bakris has received grant or research support from Medtronic and Relypsa and is a consultant for Takeda, AbbVie, Janssen, Eli Lilly, Astra Zeneca, Bayer, Merck, and the United States Food and Drug Administration. M. Weber is a consultant for Astellas, Boehringer Ingelheim, Daiichi Sankyo, Forest, Novartis, and Takeda. A. Handley is an employee of Takeda Pharmaceuticals International Inc. C. Cao is an employee of Takeda Pharmaceuticals America, Inc. S. Kupfer and A. Perez were employees of Takeda Development Center Americas, Inc. at the time of the study. E. Saunders was a consultant for Novartis, Takeda, and Daiichi Sankyo, and speaker for Forest, Arbor, and Novartis.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr Elijah B. Saunders for his significant contribution to this manuscript and pay tribute to his life and legacy as a true pioneer in clinical hypertension. Dr Saunders established the first Hypertension Division at the University of Maryland School of Medicine where he was professor and division head. Dr Saunders was among the first to recognize the high incidence of hypertension in the African-American population and the first to move hypertension screening from the healthcare setting to the community through the Baltimore barbershop blood pressure screening initiative. His interest in medical research for African-American patients led to the policy of including underserved populations in large clinical trials conducted in the United States and abroad. In April 2015, Dr Saunders passed away, leaving many family members, friends, and a host of medical professionals with a great sense of loss; however, his legacy as a father, husband, clinician, and researcher will inspire us all to strive to uphold and honor his dedication to science, medicine, and preserving human life. The authors would also like to acknowledge Ebenezer O. Oloyede, MD, and Jude Ediae, MD, for their contributions to this manuscript.

REFERENCES

1. Brewster LM, van Montfrans GA, Kleijnen J. Systematic review: antihypertensive drug therapy in black patients. *Ann Intern Med*. 2004;141:614–627.
2. Peck RN, Smart LR, Beier R, et al. Difference in blood pressure response to ACE-inhibitor monotherapy between black and white adults with arterial hypertension: a meta-analysis of 13 clinical trials. *BMC Nephrol*. 2013;14:201.
3. Abraham HMA, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. *Drug Saf*. 2015;38:33–54.
4. Yancy CW. Race-based therapeutics. *Curr Hypertens Rep*. 2008;10:276–285.
5. Edarbi (azilsartan medoxomil) complete prescribing information. http://edarbyclorrx.com/efficacy/#edarbi. Accessed February 21, 2017.
6. White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension*. 2011;57:413–420.
7. Bakris GL, Sica D, Weber MA, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. *J Clin Hypertens (Greenwich)*. 2011;13:81–88.
8. Sica D, White WB, Weber MA, et al. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)*. 2011;13:467–472.
9. Ojima M, Igata H, Tanaka M, et al. In vitro antagonistic properties of a new angiotensin type 1 receptor blocker, azilsartan, in receptor binding and function studies. *J Pharmacol Exp Ther*. 2011;336:801–808.
10. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. *Vasc Health Risk Manag*. 2012;8:133–143.
11. White WB, Weber MA, Sica D, et al. Azilsartan medoxomil vs olmesartan and valsartan: effects on ambulatory and clinic BP in hypertensive black patients. *J Hypertens*. 2012;30:e164–e164. Abstract 558.
12. Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika*. 1976;63:655–660.
13. Price DA, Fisher ND. The renin-angiotensin system in blacks: active, passive, or what? *Curr Hypertens Rep*. 2003;5:225–230.
14. Alderman MH, Cohen HW, Sealey JE, Laragh JH. Plasma renin activity levels in hypertensive persons: their wide range and lack of suppression in diabetic and in most elderly patients. *Am J Hypertens*. 2004;17:1–7.
15. Wright JT Jr, Dunn JK, Cutler JA, et al. Outcomes in hypertensive black and nonblack patients treated with chlorthalidone, amlodipine, and lisinopril. *JAMA*. 2005;293:1595–1608.
16. Mokwe E, Ohmit SE, Nasser SA, et al. Determinants of blood pressure response to quinapril in black and white hypertensive patients: the Quinapril Titration Interval Management Evaluation Trial. *Hypertension*. 2004;43:1202–1207.
17. Sehgal AR. Overlap between whites and blacks in response to antihypertensive drugs. *Hypertension*. 2004;43:566–572.
18. Saunders E, Weir MR, Kong BW, et al. A comparison of the efficacy and safety of a beta blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med*. 1990;150:1707–1713.
19. Chrysant SG, Danisa K, Kem DC, Dillard BL, Smith WJ, Frohlich ED. Racial differences in pressure, volume and renin interrelationships in essential hypertension. *Hypertension*. 1979;1:136–141.
20. Boddi M, Poggesi L, Coppo M, et al. Human vascular renin-angiotensin system and its functional changes in relation to different sodium intakes. *Hypertension*. 1998;31:836–842.
21. Price DA, Fisher ND, Osei SY, Lansang MC, Hollenberg NK. Renal perfusion and function in healthy African Americans. *Kidney Int*. 2001;59:1037–1043.
22. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in blacks. An update of the International Society of Hypertension consensus. *Hypertension*. 2010;56:780–800.
23. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421–2431.
24. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
25. de Zeeuw D, Ramjit D, Zhang Z, et al. Renal risk and renoprotection among ethnic groups with type 2 diabetic nephropathy: a post hoc analysis of RENAAL. *Kidney Int*. 2006;69:1675–1682.
26. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting–enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329:1456–1462.
27. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
28. Sica DA. The African American study of kidney disease and hypertension (AASK) trial: what more have we learned? *J Clin Hypertens (Greenwich)*. 2003;5:159–167.
29. Evaluation of candesartan cilexetil in black patients with systemic hypertension: the ABC trial. *Heart Dis*. 2000;2:392–399.
30. Giles TD, Oparil S, Wang A, Dubiel R. An evaluation of the efficacy of olmesartan medoxomil in black patients with hypertension. *J Am Soc Hypertens*. 2009;3:395–402.
31. Cushman WC, Bakris GL, White WB, et al. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. *Hypertension*. 2012;60:310–318.
32. Sica D, Bakris GL, White WB, et al. Blood pressure-lowering efficacy of the fixed-dose combination of azilsartan medoxomil and chlorthalidone: a factorial study. *J Clin Hypertens (Greenwich)*. 2012;14:284–292.
33. Weber MA, White WB, Sica D, et al. Effects of combining azilsartan medoxomil with amlodipine in patients with stage 2 hypertension. *Blood Press Monit*. 2014;19:90–97.

How to cite this article: Johnson W, White WB, Sica D, et al. Evaluation of the angiotensin II receptor blocker azilsartan medoxomil in African-American patients with hypertension. *J Clin Hypertens*. 2017;19:695-701. https://doi.org/10.1111/jch.12993