Comparison of the Novel Angiotensin II Receptor Blocker Azilsartan Medoxomil vs Valsartan by Ambulatory Blood Pressure Monitoring

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Azilsartan medoxomil (AZL-M) is a unique angiotensin II receptor blocker (ARB) under development for the treatment of hypertension. To compare this ARB with another in the class, the authors studied the effects of AZL-M and valsartan (VAL) in 984 patients with primary hypertension in a randomized, double-blind, multicenter study using ambulatory and clinic blood pressure (BP) measurements. The primary end point was change from baseline in 24-hour mean ambulatory systolic BP following 24 weeks of treatment. Hierarchical analysis testing for noninferiority was followed by superiority testing of AZL-M (80 mg then 40 mg) vs VAL. The mean age of participants was 58 years, 52% were men, and 15% were black. Baseline 24-hour mean systolic BP was similar (approximately 145.6 mm Hg) in each group. AZL-M 40 mg and 80 mg lowered 24-hour mean systolic BP (−14.9 mm Hg and −15.3 mm Hg, respectively) more than VAL 320 mg (−11.3 mm Hg; $P<.001$ for 40-mg and 80-mg comparisons vs VAL). Clinic systolic BP reductions were consistent with the ambulatory results (−14.9 mm Hg for AZL-M 40 mg and −16.9 mm Hg for AZL-M 80 mg vs −11.6 mm Hg for VAL; $P=.015$ and $P<.001$, respectively). The reductions in 24-hour mean and clinic diastolic BPs were also greater with both doses of AZL-M than with VAL ($P\leq.001$ for all comparisons). Small, reversible changes in serum creatinine occurred more often with AZL-M than with VAL; otherwise, safety and tolerability parameters were similar among the three groups. These data demonstrate that AZL-M across the effective dose range had superior efficacy to VAL at its maximal recommended dose without any meaningful increase in adverse events. These findings suggest that AZL-M could provide higher rates of hypertension control compared with other ARBs in the class. *J Clin Hypertens (Greenwich).* 2011;13:467–472. ©2011 Wiley Periodicals, Inc.

The effective lowering of blood pressure (BP) in patients with hypertension is essential to the lessening of cardiovascular events,[1,2] and various guideline-promulgating groups have advocated BP levels <140/90 mm Hg in patients without evidence of target-organ damage and <130/80 mm Hg in patients with either diabetes or heart or kidney disease.[3,4]

A variety of drug classes are available for the treatment of hypertension. Head-to-head studies have shown comparable BP reduction between and within various drug classes, including angiotensin-converting enzyme inhibitors, calcium channel blockers, and angiotensin II receptor blockers (ARBs).[5,6] What typically separates these drug classes has been their side-effect profile, with the popularity of ARBs, as such, relating to a tolerability profile similar to placebo.[7–12]

Azilsartan medoxomil (AZL-M) is a prodrug that is quickly hydrolyzed to the active moiety azilsartan, a potent and highly selective ARB with estimated bioavailability of 60% and elimination half-life of approximately 12 hours.[13] The major metabolite, M-II, is formed via CYP2C9 and has low affinity for the angiotensin type 1, or AT1, receptor. Based on dose-ranging studies and supporting pharmacokinetic data, the expected plateau of BP reduction for AZL-M in the majority of patients with hypertension is achieved at 40 mg or 80 mg once daily.[13]

The present study was designed to evaluate both the efficacy and safety of AZL-M across the effective dose range in comparison with the highest approved dose of valsartan (VAL; 320 mg once daily). The primary efficacy analysis of this study relied on between-drug differences in 24-hour mean systolic BP (SBP), as determined by ambulatory BP monitoring (ABPM) and, as such, substantially reduced the confounding of between-drug comparisons that often arises from office-based BP determinations.

METHODS

Study Design

This study was a 24-week randomized, double-blind, parallel-group, multicenter trial comparing the antihypertensive effects and safety and tolerability of AZL-M and VAL in patients with stage 1 or 2 hypertension (ClinicalTrials.gov trial registration: NCT00591578). Patients who qualified for the run-in period discontinued their previous antihypertensive medications 3 to 4 weeks prior to randomization and received single-blind placebo beginning at 2 weeks prior to randomization. There was no maximum number of drugs that

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a patient could be withdrawn from to enter the study. At screening, 702 of 982 (71.5%) of patients were taking antihypertensive medications. On average, the number of medications being taken prior to medication withdrawal was 1.6.

Patients who qualified for randomization were assigned in a double-blind manner and in 1:1:1 ratio into 3 groups: AZL-M 20 mg every day force-titrated to 40 mg every day after 2 weeks, AZL-M 20 mg every day force-titrated to 80 mg every day after 2 weeks, or valsartan 80 mg every day force-titrated to 320 mg every day after 2 weeks, with continued treatment for an additional 22 weeks. Randomization was stratified by race (ie, black or non-black).

Patients were evaluated for efficacy and safety end points every 2 to 4 weeks. Trough sitting office SBP and diastolic BP (DBP) were assessed at each visit. ABPM was performed for 24 hours on the day prior to randomization and before administration of the first dose of double-blind study medication. ABPM was subsequently conducted at the end of weeks 8 and 24.

Participants from 103 centers in the United States, Peru, Chile, and Mexico were enrolled in the trial. Before beginning the study, all patients were informed of the details of the study and signed consent forms approved by regional institutional review boards. Men and women aged 18 years or older with hypertension were included if their clinic SBP was $\geq$150 mm Hg and $\leq$180 mm Hg and 24-hour mean SBP was $\geq$130 mm Hg and $\leq$170 mm Hg.

Exclusion criteria included known or suspected secondary hypertension; severe diastolic hypertension (seated DBP >114 mm Hg); clinically significant renal dysfunction (estimated glomerular filtration rate <30 mL/min per 1.73 m^2); recent history (within 6 months) of major cardiovascular events; type 1 or poorly controlled type 2 diabetes mellitus (hemoglobin A_{1C} >8%); poor compliance with study medication (<70% or >130%) during the placebo run-in period; and hyperkalemia (serum potassium concentration >upper limit of normal). In addition, night-shift workers, pregnant or nursing women, and women of childbearing potential not using approved means of contraception were excluded from study participation. Concomitant medications known to affect BP were not permitted during the study.

Procedures

Clinic BP measurements were made in triplicate in the nondominant arm after the patient was seated for 5 minutes using a semiautomated digital BP recorder (Omron HEM 705-CP, Vernon Hills, IL). Every effort was made to ensure that the clinic BP readings were obtained approximately 24 hours after the last dose of study medication and prior to any procedures, including venipuncture. ABPM was performed with the Spacelabs 90207 monitor (Spacelabs, Inc, Issaquah, WA).

ABPM was initiated immediately after administration of study medication. BP was measured every 15 minutes between 6 AM and 10 PM and every 20 minutes between 10 PM and 6 AM. Minimum quality-control criteria included the following: (1) a monitoring period $\geq$24 hours in duration, (2) a minimum of 80% of the BP readings expected during the 24-hour period, (3) no more than 2 nonconsecutive hours with less than one valid BP reading, and (4) no consecutive hours with less than 1 valid BP reading. If these criteria were not met, the patient was asked to repeat the procedure within 5 days. If the repeat ABPM procedure failed to satisfy the quality-control criteria, the ABPM data were considered nonevaluable.

Blood samples were analyzed by a central laboratory (ICON Laboratories, Farmingdale, NY).

End Points

The primary efficacy end point was the change from baseline to week 24 in 24-hour mean SBP by ABPM. The key secondary efficacy end point was the change from baseline to week 24 in trough sitting clinic SBP. Other secondary end points included the change from baseline to week 24 in 24-hour mean DBP by ABPM and trough sitting clinic DBP.

Also evaluated was the proportion of patients who achieved a BP response, which was defined as follows: (1) clinic SBP <140 mm Hg and/or a reduction of $\geq$20 mm Hg from baseline, (2) clinic DBP <90 mm Hg and/or a reduction of $\geq$10 mm Hg from baseline, or both.

Statistical Analyses

Approximately 972 randomized patients (324 per AZL-M and VAL treatment group) were determined to be sufficient to achieve at least 90% power to detect a difference of 4.25 mm Hg between AZL-M and VAL for the primary end point of mean change from baseline in 24-hour mean SBP by ABPM, given the assumptions of a two-sided significance level of 5%, a standard deviation (SD) of 13 mm Hg, and a 30% dropout rate. This design provided at least 90% power for demonstrating noninferiority with a margin of 1.5 mm Hg between AZL-M and VAL on the primary end point.

The primary efficacy outcome was evaluated by applying an analysis of covariance (ANCOVA) for change from baseline to week 24 (or last treatment visit) for 24-hour mean SBP by ABPM. The model included treatment as a fixed effect and baseline 24-hour mean SBP by ABPM as a covariate. The main comparison involved AZL-M and VAL. In addition, AZL-M and VAL were compared in noninferiority analyses with a margin of 1.5 mm Hg, which was less than one third of the observed treatment difference between AZL-M and VAL. Type 1 error for the primary analysis was controlled by using a stepwise, hierarchal testing procedure. Testing for noninferiority was followed by superiority testing of AZL-M (80 mg then 40 mg) vs VAL.

A similar statistical model and stepwise procedures were used to analyze the key secondary efficacy end

point. Other secondary analyses used an ANCOVA model similar to the analyses used for the primary and key secondary efficacy variables but without the stepwise testing procedure.

All statistical tests were two-sided and results were presented with 95% confidence intervals (CIs) and *P* values at the 5% significance level. The efficacy analysis was based on the last observation carried forward. Subgroup analyses were conducted by age, sex, and race and by baseline body mass index, 24-hour mean SBP, and estimated glomerular filtration rate to evaluate for heterogeneity of the BP-lowering effects of AZL-M.

Safety Assessments

Safety variables included all adverse events, clinical laboratory data, physical examination findings including weight and vital signs, electrocardiographic data, and pregnancy evaluation. With regard to adverse events, all of the patients were queried at each visit with nonleading questions. Adverse events were characterized as nonserious or serious and as those resulting in discontinuation from the study. With regard to laboratory data, changes in renal function, liver enzymes, and serum potassium values were parameters of interest and were measured at all study time points. All clinically significant abnormal laboratory results present at the final visit were monitored until they returned to baseline or stabilized.

RESULTS

Patient Enrollment and Disposition

A total of 2603 patients were screened for the study, and 1970 patients were enrolled in the single-blind placebo run-in period. Of these 1970 patients, 984 fully met the entry criteria and were randomized. They were assigned to 1 of 3 treatment arms at final dose, as follows: 327 patients to AZL-M 40 mg, 329 patients to AZL-M 80 mg, and 328 patients to VAL 320 mg. A total of 742 of the 984 randomized patients completed the study as planned: 249 (76%) in the AZL-M 40-mg arm, 249 (76%) in the AZL-M 80-mg arm, and 244 (74%) in the VAL 320-mg arm. The most common reasons for premature discontinuation from the double-blind portion of the study were voluntary withdrawal (6.7%), adverse events (6.6%), and inadequate BP reduction (5.1%). All study patients were treatment naïve to AZL-M.

Baseline Characteristics of the Study Population

The baseline characteristics of all randomized patients in the 3 treatment arms are shown in Table I. For the entire patient population, the mean age was 58 years, with similar percentages of men and women, and patients were predominantly white (approximately 76%). The percentage of black patients was similar in each treatment group (approximately 15%). Across the treatment groups, the 24-hour mean and clinic SBP and DBP at baseline approximated 145.6/87.9 mm Hg and 157.2/91.2 mm Hg, respectively (Table I).

TABLE I. Characteristics of Randomized Patients at Baseline

Characteristic	AZL-M 40 mg (n=327)	AZL-M 80 mg (n=329)	VAL 320 mg (n=328)[a]
Mean±SD			
Age, y	57.8±12.1	56.8±10.7	58.1±10.9
Body mass index, kg/m^2	30.8±5.7	30.7±5.3	31.2±5.8
Clinic BP, mm Hg			
SBP	158.1±14.4	156.3±12.5	157.0±14.0
DBP	91.2±11.0	91.5±10.5	90.8±11.3
24-H mean BP, mm Hg			
SBP	146.0±9.8	145.2±9.5	145.5±10.2
DBP	87.7±9.3	88.4±9.2	87.5±9.4
No. (%)			
Sex			
Male	164 (50.2)	169 (51.4)	176 (53.7)
Female	163 (49.8)	160 (48.6)	152 (46.3)
Race			
White	247 (75.5)	256 (77.8)	251 (76.5)
Black	49 (15.0)	50 (15.2)	49 (14.9)
Native American	27 (8.3)	16 (4.9)	22 (6.7)
Asian	7 (2.1)	7 (2.1)	7 (2.1)

Abbreviations: AZL-M azilsartan medoxomil; BP, blood pressure DBP, diastolic BP; SBP, systolic BP; SD, standard deviation; VAL, valsartan. [a]For body mass index, n=326.

Changes in 24-Hour Mean SBP and Clinic SBP

The effects of the 3 treatments on 24-hour mean and clinic SBP are shown in Figure 1. All therapies lowered 24-hour mean SBP, with reductions ranging from −11.3 mm Hg for VAL 320 mg to −14.9 and −15.3 mm Hg for AZL-M 40 mg and 80 mg, respectively. Changes from baseline in 24-hour mean SBP were significantly greater with AZL-M 40 mg and 80 mg than with VAL 320 mg ($P<.001$ for both comparisons).

The timewise efficacy effects of each study treatment following 24 weeks of therapy are shown in Figure 2. AZL-M 40 mg and 80 mg lowered ambulatory SBP to a larger extent than VAL 320 mg at each hour. Mean decreases from baseline tended to be smaller during the 16- to 24-hour interval than during the 1- to 15-hour interval in all treatment groups.

The effect of treatments on clinic SBP from weeks 2 through 24 are shown in Figure 3. At baseline, mean clinic SBP was similar in all 3 treatment groups (Table I). At week 24, statistically significantly greater decreases in the change from baseline to week 24 in mean clinic SBP were observed for each of the AZL-M treatment groups (40 mg and 80 mg) compared with VAL 320 mg ($P=.015$ and $P<.001$, respectively), and the mean decrease was numerically greater with AZL-M 80 mg (−16.92 mm Hg) than with AZL-M 40 mg (−14.86 mm Hg).

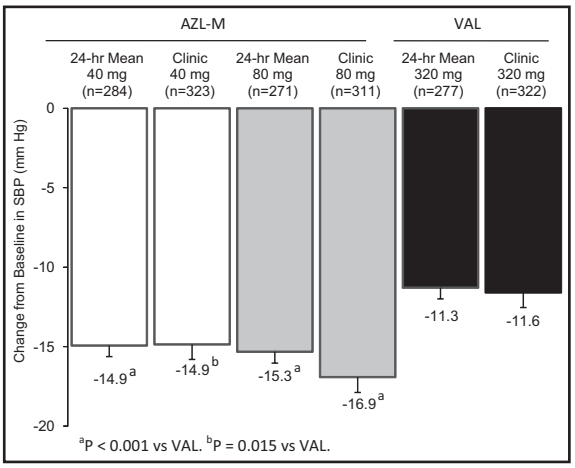

FIGURE 1. Change from baseline to week 24 in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring and clinic SBP (mm Hg). Data are least-squares mean ± standard error. AZL-M indicates azilsartan medoxomil; VAL, valsartan.

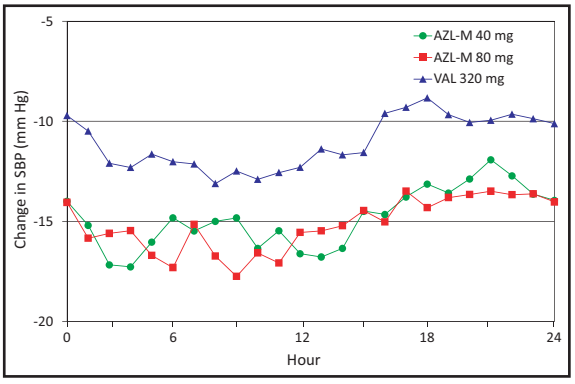

FIGURE 2. Changes from baseline in hourly systolic blood pressure (SBP) by ambulatory blood pressure monitoring according to treatment group at the final study visit. AZL-M indicates azilsartan medoxomil; VAL, valsartan.

Changes in Ambulatory and Clinic DBP

Overall changes in the ambulatory and clinic DBP were similar to findings for the changes in the SBP and are reported herein as treatment differences between AZL-M and VAL. Changes in both 24-hour and clinic DBP were significantly greater for AZL-M 40 mg and 80 mg than with VAL 320 mg. Relative to VAL 320 mg, mean reductions in 24-hour DBP were −2.16 (95% CI, −3.44 to −0.88) for AZL-M 40 mg and −2.69 (95% CI, −3.99 to −1.40) for AZL-M 80 mg ($P<.001$ vs VAL 320 mg for both comparisons). Relative to VAL 320 mg, mean reductions in clinic DBP were −2.52 mm Hg (95% CI, −4.06 to −0.98) for AZL 40 mg and −2.76 mm Hg (95% CI, −4.32 to −1.21) for AZL-M 80 mg ($P=.001$ and $P<.001$, respectively).

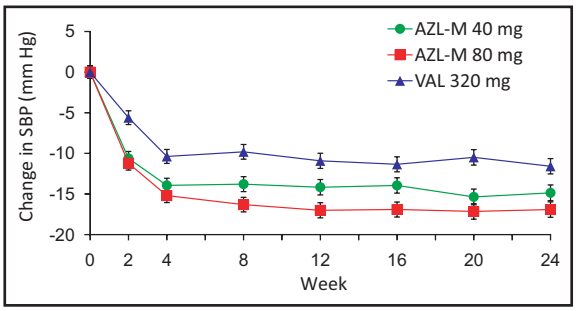

FIGURE 3. Changes from baseline in the mean (±standard error of the mean) trough clinic systolic blood pressure (SBP) by study visit. AZL-M indicates azilsartan medoxomil; VAL, valsartan.

Response Rates

The proportion of patients who achieved a reduction in clinic SBP to <140 mm Hg and/or a reduction of ≥20 mm Hg was significantly greater with AZL-M 40 mg (56%) and AZL-M 80 mg (59%) than with VAL 320 mg (47%; $P=.016$ and $P=.002$, respectively).

Findings According to Age, Sex, and Race

Consistent with the primary analysis, subgroup analyses revealed that each of the AZL-M treatment groups had a statistically significantly greater reduction in 24-hour mean SBP relative to VAL 320 mg for subgroups based on age, sex, and race. Similar reductions in 24-hour mean SBP were observed within each AZL-M treatment group based on sex ($P=.353$ for interaction) and age (younger than 65 or 65 and older; $P=.214$ for interaction). Smaller treatment effects were observed in black patients treated with either dose of AZL-M and VAL relative to non-black patients ($P=.071$ for interaction).

Safety

Of the 984 patients who were randomized to the study, 982 received at least one dose of study drug. Among these 982 patients, rates of treatment-emergent adverse events were similar in the AZL-M 40-mg (65.4%) and AZL-M 80-mg (65.3%) groups and somewhat lower in the VAL 320-mg group (59.2%). Treatment-emergent adverse events were mostly mild to moderate in severity. The most common adverse events during the trial were headache, dizziness, and urinary tract infection (Table II).

Twenty-one patients experienced serious adverse events, and these were distributed nearly equally among the 3 treatment groups. Two patients experienced sudden death, one each in the AZL-M 40-mg and VAL treatment groups.

Small mean changes in serum creatinine, potassium, and liver enzymes were observed in all groups; mean serum creatinine concentrations increased slightly more with AZL-M than with VAL. Only 1 patient (0.3%) each in the AZL-M 40-mg and 80-mg treatment groups had consecutive increases in serum creatinine ≥50%

TABLE II. Safety Findings by Treatment Group

Parameter	AZL-M 40 mg (n=327)	AZL-M 80 mg (n=329)	VAL 320 mg (n=326)
Total adverse events	214 (65.4)	215 (65.3)	193 (59.2)
Adverse events leading to discontinuation	23 (7.0)	27 (8.2)	20 (6.1)
Serious adverse events	8 (2.4)	5 (1.5)	8 (2.5)
Deaths	1 (0.3)	0	1 (0.3)
Treatment-emergent events in ≥3% of all patients			
Headache	33 (10.1)	29 (8.8)	28 (8.6)
Dizziness	27 (8.3)	29 (8.8)	15 (4.6)
Urinary tract infection	26 (8.0)	25 (7.6)	16 (4.9)
Fatigue	14 (4.3)	9 (2.7)	9 (2.8)
Nasopharyngitis	12 (3.7)	6 (1.8)	14 (4.3)
Arthralgias	8 (2.4)	10 (3.0)	12 (3.7)
↑ Blood CPK	8 (2.4)	13 (4.0)	8 (2.5)

Abbreviations: AZL-M, azilsartan medoxomil; CPK, creatine phosphokinase; VAL, valsartan. Data are number (percentage) of patients.

above baseline and above the upper limit of normal. No patient had a persistent increase in serum creatinine following discontinuation of study drug.

Hyperkalemia (serum potassium >6 mmol/L) occurred more often in the AZL-M 40-mg group (1.8%) than in the AZL-M 80-mg (0.3%) or VAL (0.6%) groups.

DISCUSSION

In this study, we compared the effects of AZL-M and VAL in a 24-week randomized double-blind trial using ambulatory and clinic BP measurements. The primary efficacy end point was a change in 24-hour mean SBP, which is often viewed as the gold standard for ascertainment of BP differences between drugs. AZL-M at a dose of 40 mg or 80 mg once daily showed greater efficacy than a 320-mg dose of VAL, the highest approved dose, on the basis of either ABPM or semiautomated in-clinic BP measurements. The significant BP reductions with AZL-M were well tolerated as to its adverse effects and study discontinuation rates. For these reasons, AZL-M should be a useful compound for the treatment of stage 1 hypertension, with its potent BP-lowering ability apt to be coupled with considerably better rates of hypertension control.

A distinctive facet of this trial was the use of the change in 24-hour mean SBP as the primary efficacy end point rather than the more traditional mean clinic SBP or DBP. Although mean 24-hour SBP has been shown to be an important correlate of cardiovascular morbidity in patients with hypertension,[14] it has not been used as the main efficacy end point in the clinical development of an antihypertensive agent. Showing differences in 24-hour SBP is a more demanding course of action than other approaches, particularly when comparative efficacy is being considered. In this particular study, in addition to the larger reductions in 24-hour mean ambulatory SBP the hourly reductions in SBP were consistently greater with either dose of AZL-M than with VAL.

In the majority of instances in which an intraclass comparison of antihypertensive drugs has been undertaken by using the highest approved doses, ambulatory and clinic BP findings have generally been similar among the agents.[5,15] The occasional exception to this observation relates to differing half-lives between the agents being compared, as observed when the ARBs candesartan, telmisartan, or irbesartan were compared with losartan.[16–18] Intraclass differences in BP lowering within the ARB class can go unrecognized with clinic BP readings and might be ascertained only with ABPM.[19] The finding that AZL-M lowered 24-hour SBP more than VAL suggests that there may be a measurable hierarchal response in the ARB class. This difference in BP-lowering response between AZL-M and VAL may be a function of the slowness with which AZL-M dissociates from the AT_1 receptor and AZL-M behaving as an inverse agonist; however, these in vitro determinations are yet to be corroborated in whole animal or human studies.[20]

The relatively large BP reductions with AZL-M were not accompanied by any significant increase in clinically related adverse events. The proportion of patients with adverse events and those who discontinued due to adverse events after receiving either dose of AZL-M were similar to VAL at the dose used in this study, which is the maximal dose approved for use in clinical practice. There was a greater likelihood of serum creatinine transiently increasing at any postbaseline visit, a finding not unexpected with the significant BP reduction seen with a potent ARB.[21,22] This finding is likely due to BP-related alterations in renal hemodynamics, as has been previously described in patients treated with either an angiotensin-converting enzyme inhibitor or an ARB who have a reduction in extracellular fluid volume.[23] Laboratory findings did not suggest any clinically relevant changes in potassium homeostasis with AZL-M or VAL. This is not an unexpected observation, since patients with severe renal disease and/or elevated serum potassium values were excluded from these studies.

CONCLUSIONS

AZL-M, a new ARB, had greater ambulatory and clinic BP-lowering effects than full-dose VAL and was well tolerated in patients with hypertension. BP control and response rates with this drug given at its highest dose were considerably greater (about 10% in absolute rate) than those seen with VAL. This is of particular importance in that, on average, only 50% of the hypertensive population in the United States attains goal BP. Although this study duration did not extend beyond 6 months of treatment, the tolerability of AZL-M would suggest that the long-term patient persistence on this therapy would be good and dropouts from adverse effects minimized.

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