INTRODUCTION

Hypertension is one of the most important cardiovascular risk factors and its prevalence is still high (Europe 44.2%, North America 27.6%).

However, despite the availability of numerous pharmacological treatments and guidance for beneficial lifestyle modification, hypertension remains inadequately controlled: In EUROASPIRE III, only about one-third of patients continue to maintain control successfully.

Although there are many effective antihypertensive drugs available today, most are associated with dose-limiting side effects that preclude their use at the higher doses that may be necessary for optimal BP reduction. For example, angiotensin-converting enzyme (ACE) inhibitors are very effective at lowering BP by inhibition of the renin–angiotensin–aldosterone system (RAAS); however, these agents are often associated with significant cough and more rarely with angioedema. To achieve better BP control and to improve patient adherence with the treatment, it is necessary to prescribe more potent, yet well-tolerated antihypertensive agents. As a class, angiotensin II receptor blockers (ARBs) have similar or greater efficacy compared with other classes of hypertensive agents but are much more tolerable. The epidemiological data demonstrate that in spite of the available potent drugs, there is still a need for compounds with improved efficacy for the treatment of hypertension.

Azilsartan medoxomil (AZL-M) is a prodrug that is rapidly hydrolyzed in the gastrointestinal tract during absorption to azilsartan, which has high affinity for the angiotensin II type 1 receptor. Azilsartan has an estimated bioavailability of 60%, which is not affected by food, and an elimination half-life of approximately 11 h. No drug interactions have been observed in studies of AZL-M or azilsartan.

The present study was designed to compare the efficacy, safety and tolerability of once-daily (QD) AZL-M 40 and 80 mg with QD ramipril (RAM) 10 mg, the most commonly used dose strength and the highest dose approved in Europe.

MATERIALS AND METHODS

Ethical consideration

This study was performed in accordance with the principles of International Conference on Harmonisation/Good Clinical Practice, the Declaration of Helsinki, the current CPMP ‘Notes for Guidance on Clinical Investigation of Medical Products in the Treatment of Hypertension’ and all national and country-specific legal requirements. The study protocol was approved by all relevant ethics committees before enrollment of patients. The patient’s written informed consent was required before the start of study-related procedures. Patients currently taking antihypertensive drugs had to be willing to discontinue these drugs at screening. The study is registered at ClinicalTrials.gov with the registry number NCT00760214.
Study design
This phase 3 study was a randomised, double-blind, multicenter trial
designed to evaluate the efficacy and safety of QD AZL-M 40 and 80 mg,
compared with QD RAM 10 mg, in patients with stage 1 or 2 hypertension
after 24 weeks of treatment. Qualifying subjects underwent a 3- to 4-week
wash-out period of their former antihypertensive drugs, which coincided
with a 2-week single-blind placebo run-in period, 24 weeks of double-blind
treatment. Eligible subjects were randomised in a double-blind manner to one
of the three treatment groups: AZL-M 20 mg QD force-titrated to 40 mg QD
after 2 weeks, AZL-M 20 mg QD force-titrated to 80 mg QD after 2 weeks, or
RAM 2.5 mg QD force-titrated to 10 mg QD after 2 weeks, with continued treatment for an additional 22
weeks. Patients were evaluated for efficacy and safety endpoints at baseline
and at weeks 2, 4, 8, 12, 16, 20 and 24 after randomisation. Trough, seated, clinic systolic and diastolic blood pressure (SBP and DBP)
were assessed at each visit. Ambulatory blood pressure monitoring (ABPM)
was performed at baseline and at the end of week 24. Data at the 1-week
follow-up were generated by telephone call.

Patients
Men and women ≥18 years of age with hypertension were included if their
clinic SBP was between 150 and 180 mm Hg inclusive at randomisation and
their clinical laboratory profile was not considered clinically significant.
Exclusion criteria included clinic SBP >180 mm Hg or DBP >114 mm Hg at
randomisation; secondary hypertension; severe renal disease (estimated
glomerular filtration rate <30 ml min⁻¹ per 1.73 m²); recent history (within
6 months) of a major cardiovascular event or intervention; significant
conduction defects; aortic valve stenosis; use of antihypertensive
medications or other concomitant medications known to affect BP;
recent history (within 30 years) of diabetes mellitus; hyperkalemia (serum potassium > upper limit of normal, 5.5 mmol l⁻¹); and
night shift work. Pregnant or nursing women and woman of child-
bearing potential not using approved means of contraception were also
excluded.

Procedures
Clinic BP measurements were made in triplicate in the nondominant arm
after the patient was seated for 5 min using a semiautomated digital BP
recorder (Omron HEM 705-CP, Vernon Hills, IL, USA). Every effort was made
to ensure that the clinic BP readings were obtained approximately 24 h
after the last dose of study medication and before any procedures, including
venipuncture.

ABPM was performed on day 1 before randomisation and at the end of
week 24, using the Spacelabs Medical Model 90207 (Spacelabs
Healthcare, Issaquah WA, USA). During the treatment period, ABPM was
initiated immediately after administration of study medication; BP was
measured every 15 min during the day (beginning between 0600 and
2200 hours) and every 20 min during the night (between 2200 and
0600 hours).16-18 Quality criteria used for an acceptable ambulatory BP
recording included (a) monitoring period ≥24 h in duration, (b) minimum
of 80% of the BP readings expected during the 24-hour period, (c) no more
than two non-consecutive hours with less than one valid BP reading, and
(d) no consecutive hours with less than one valid BP reading.

Safety assessments included physical examination findings, vital signs
and weight, adverse events, clinical laboratory tests and electrocardio-
graphic data. Laboratory parameters were analyzed at a central laboratory.
Tolerability and safety were assessed by recording adverse events at all
visits. An adverse event was defined as the development of an undesirable
condition or a deterioration of a pre-existing medical condition. A serious adverse event was an adverse event that resulted in death, was
jeopardised the patient or required medical intervention.

Statistical methods
The primary endpoint was the change from baseline to week 24 in trough
systolic and diastolic blood pressures. The analysis of covariance model
was used to model change from baseline to week 24 for clinic SBP. The model
included treatment as a fixed effect and baseline clinic SBP as covariate;
mean treatment effects and treatment differences (including P-values and
two-sided 95% confidence intervals) were obtained from the framework
of the analysis of covariance model. The type 1 error of 0.05 was
controlled using a sequential stepwise procedure that required meeting
the statistical objective of each step in order to advance to the next step
with a non-inferiority margin of 1.5 mm Hg; step (1) test for noninferiority
TAK-491 80 mg vs RAM; step (2) test of significance TAK-491 80 mg vs RAM;
step (3) test for noninferiority TAK-491 40 mg vs RAM; and step (4) test of
significance TAK-491 40 mg vs RAM. Similar inferential statistical methods
were applied to the secondary endpoints. Secondary endpoints included
change from baseline to week 24 in trough, seated, clinic DBP, measures
of ambulatory BP, and BP response rates (defined as the proportion of
subjects who achieved (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)). Safety parameters were
summarized using descriptive statistics.

All randomised subjects were included in the analysis of the primary and
secondary endpoints (intent to treat), provided subjects had both a
baseline and at least 1 post-baseline value. Missing data for the primary
and secondary endpoints were handled using last observation carried
forward methodology.

A sample size of 270 subjects per group was determined to have at least
90% power to detect a difference of 4.75 mm Hg between the AZL-M and
RAM groups by a two-sample t-test of the mean change from baseline
in SBP, with a 0.05 two-sided significance level, assuming a 14.5 mm Hg
s.d. and a 20% dropout rate.

RESULTS

Patients
A total of 1229 patients were screened at 106 sites in Europe and
Russia, and 1089 patients entered the single-blind period. Of these
1089 patients, 884 met the entry criteria and were randomised to
1 of 3 treatment arms: 295 patients to AZL-M 40 mg, 294 patients
to AZL-M 80 mg and 295 patients to RAM 10 mg. A total of 784 of
the 884 randomised patients completed the 24 weeks of treatment
with double-blind study medication: 265(89.8%) in the
AZL-M 40 mg group, 264 (89.8%) in the AZL-M 80 mg group
and 255 (86.1%) in the RAM group. The demographics and the
baseline characteristics of study population are given in Table 1.
There was no significant difference in any parameters. Nearly half
of the subjects were male. The mean age was 56.9 ± 11.1 years,
and mean body mass index was 29.5 ± 4.7 kg m⁻². All but four
subjects were Caucasian.

Mean baseline clinic and ambulatory measures of SBP and DBP
were similar in the three groups (Table 1). Medical history did not
differ among the groups. Type 2 diabetes mellitus was reported for
7.5–12.6% of the subjects, and 11.1% of the subjects among

Table 1. Demographics and baseline characteristics

| Characteristics          | AZL-M 40 | AZL-M 80 | RAM 10 |
|-------------------------|----------|----------|--------|
| Number                   | 295      | 294      | 295    |
| Male (%)                 | 53.9     | 53.7     | 49.5   |
| Age (years)              | 56.9 ± 11.5 | 56.8 ± 11.3 | 56.8 ± 10.5 |
| BMI (kg m⁻²)             | 29.6 ± 4.8 | 29.5 ± 4.7 | 29.5 ± 4.6 |
| Clinic SBP (mm Hg)       | 160.7 ± 7.3 | 161.4 ± 7.7 | 161.2 ± 8.5 |
| Clinic DBP (mm Hg)       | 94.7 ± 9.5 | 95.6 ± 8.7 | 94.5 ± 8.9 |
| ABPM 24 h mean SBP (mm Hg)| 140.7 ± 1.0 | 139.5 ± 1.0 | 141.0 ± 1.0 |
| ABPM 24 h mean DBP (mm Hg)| 146.4 ± 1.2 | 142.3 ± 1.3 | 143.4 ± 1.6 |
| ABPM mean daytime SBP (mm Hg)| 89.2 ± 9.6 | 88.0 ± 10.0 | 88.8 ± 10.1 |
| ABPM mean daytime DBP (mm Hg)| 128.9 ± 14.7 | 126.4 ± 14.4 | 128.0 ± 12.8 |
| ABPM mean nighttime SBP (mm Hg)| 75.5 ± 11.1 | 74.0 ± 9.9 | 74.9 ± 10.7 |

Abbreviations: ABPM, ambulatory blood pressure monitoring; AZL-M, azilsartan medoxomil; BMI, body mass index; DBP, diastolic blood pressure; RAM, ramipril; SBP, systolic blood pressure. No statistically significant differences.
achieved a reduction in clinic BP to
and RAM groups were highly significant ($P$ 0.001). The proportion of subjects achieving SBP and DBP response rates
were significantly greater for the AZL-M 40 and 80 mg treatment groups ($P$ <0.001). More subjects achieved a reduction in clinic BP to <140/90 mm Hg and/or a reduction in BP ≥20/10 mm Hg at week 24 following treatment with AZL-M compared with RAM (54.0% and 53.6% for AZL-M 40 and 80 mg vs 33.8% with RAM 10 mg, respectively; $P$ <0.001).

### Table 2. Baseline blood pressure and changes in clinic and ABPM of SBP/DBP after 24 weeks of treatment

| Table 2. Baseline blood pressure and changes in clinic and ABPM of SBP/DBP after 24 weeks of treatment |
| LS mean (s.e.) | AZL-M 40 | AZL-M 80 | RAM 10 |
|----------------|---------|---------|--------|
| **Baseline clinic BP** |         |         |        |
| SBP | 160.9 ± 0.5 | 94.8 ± 0.5 | 161.5 ± 0.5 |
| DBP | −20.6 ± 0.9 | −10.2 ± 0.6 | −21.2 ± 0.9 |
| **Baseline 24-h mean ABPM** |         |         |        |
| SBP | 140.7 ± 1.0 | 86.4 ± 0.8 | 139.5 ± 1.0 |
| DBP | −12.7 ± 1.0 | −8.0 ± 0.7 | −12.3 ± 1.0 |
| **Change from BL to week 24** |         |         |        |
| Mean daytime (0600–2200 hours) | −12.6 ± 1.0 | −8.2 ± 0.7 | −12.4 ± 1.0 |
| Mean nighttime (0000–0600 hours) | −12.8 ± 1.1 | −7.4 ± 0.8 | −12.7 ± 1.1 |
| Mean trough (22–24h) | −15.6 ± 1.2 | −10.2 ± 0.9 | −14.9 ± 1.2 |

Abbreviations: ABPM, ambulatory blood pressure monitoring; AZL-M, azilsartan medoxomil; BL, baseline; DBP, diastolic blood pressure; LS, least squares; RAM, ramipril; SBP, systolic blood pressure. AZL-M vs RAM: $P$ < 0.05 for all comparisons.

Clinic BP
After 24 weeks of treatment, trough, sitting, clinic SBP decreased significantly in all the groups (Table 2). The changes from baseline were significantly greater for the AZL-M 40 and 80 mg treatment groups (−20.6 ± 0.95 and −21.2 ± 0.95 mm Hg, respectively) than for RAM 10 mg (−12.2 ± 0.95 mm Hg) (Table 2). The differences between the AZL-M-treated subjects and the RAM-treated subjects were −8.4 mm Hg for AZL-M 40 and −9.0 mm Hg for AZL-M 80 ($P$ <0.001 for both comparisons). Change in trough, sitting, DBP was −10.2 ± 0.55 mm Hg in the AZL-M 40 mg group, −10.5 ± 0.55 mm Hg in the AZL-M 80 mg and −4.9 ± 0.56 mm Hg in the RAM 10 mg group (Table 2). The differences in DBP between the AZL-M and the RAM-treated subjects were −5.3 mm Hg for AZL-M 40 and −5.7 mm Hg for AZL-M 80, respectively (both $P$ <0.001). The majority of the reduction in SBP and DBP was achieved by week 4 after only 2 weeks at the highest dose in each treatment arm and remained nearly unchanged through the end of treatment at week 24 (Figure 1).

Ambulatory BP
Table 2 also summarizes the baseline and change from baseline to week 24 in ambulatory measures of SBP and DBP. AZL-M 40 and 80 mg reduced ambulatory SBP and DBP significantly more than RAM for all ABPM time intervals evaluated, including 24-hour mean, mean daytime, mean nighttime and mean trough pressure. The hourly reductions in ambulatory measures of SBP at (a) baseline and (b) final visit/week 24 are displayed in Figure 2. AZL-M 40 and 80 mg lowered ambulatory SBP to a greater extent than RAM 10 mg at every hour of the 24-h dosing interval.

Response rates
The proportion of subjects achieving SBP and DBP response criteria is shown in Table 3. The differences between the AZL-M and RAM groups were highly significant ($P$ <0.001). More subjects achieved a reduction in clinic BP to <140/90 mm Hg and/or a reduction in BP ≥20/10 mm Hg at week 24 following treatment with AZL-M compared with RAM (54.0% and 53.6% for AZL-M 40 and 80 mg vs 33.8% with RAM 10 mg, respectively; $P$ <0.001).

Subgroup analyses
Consistent with the overall population, subgroup analyses for the baseline clinical covariates of age, gender, body mass index, clinic SBP and estimated glomerular filtration rate demonstrated statistically significantly or numerically greater BP reduction following treatment with AZL-M 40 or 80 mg compared with RAM (Figure 3).
Adverse events leading to discontinuation were less frequent with AZL-M 40 and 80 mg (2.4% and 3.1%) than with RAM (4.8%). There were no deaths in any of the treatment groups.

Clinically significant increases in serum potassium, sodium and uric acid were observed more often during treatment with the AZL-M 40 and 80 mg as compared with RAM, respectively: potassium >6.0 mmol l⁻¹, 2.8, 3.8 vs 1.7%; sodium >150 mmol l⁻¹, 2.8, 2.1 vs 1.0%; and uric acid >506 μmol l⁻¹ female or >625 μmol l⁻¹ male, 4.1, 3.5 vs 0.7%. The frequency of consecutive creatinine elevations ≥30% from baseline and greater than the upper limit of normal was low in all the groups: 0.7% and 0.3% for AZL-M 40 and 80 mg, respectively, and none for RAM 10 mg. No subjects had consecutive increases in serum creatinine ≥50% above baseline and above the upper limit of normal or persistent increases in serum creatinine following discontinuation of study drug.

**DISCUSSION**

In antihypertensive treatment, the efficacy and safety of renin-angiotensin system blockade by ACE inhibitors or ARBs is well established. Drugs that inhibit the biological activity of angiotensin II elicit potent BP reductions, are highly protective against end organ damage and may have beneficial metabolic effects, such as delaying the onset of type 2 diabetes.19–21 In clinical studies like the HOPE or the LIFE study, treatment with an ACE inhibitor or an ARB significantly reduced the risk for cardiovascular death, myocardial infarction or stroke, as well as the incidence of new onset diabetes.22–26 The ONTARGET study demonstrated that, in high-risk patients with cardiovascular disease or diabetes, an ARB strategy (telmisartan) was equivalent to an ACE inhibitor strategy (RAM) for the reduction in major cardiovascular events and was better tolerated with lower incidence of cough and angioedema.27,28 The excellent tolerability of the ARB class translates into high patient adherence relative to other antihypertensive drug classes.29,30 Nevertheless, to optimize antihypertensive therapy, more effective drugs that do not sacrifice tolerability are needed. AZL-M is a new ARB with superior efficacy within the ARB class31–33 and characterized by placebo-like tolerability. In the current study, AZL-M was compared with RAM on its blood-pressure-lowering efficacy and its safety and tolerability. RAM was selected as the active comparator owing to its well-established efficacy in treating hypertension and reducing cardiovascular risk and target organ damage, in addition to its well-described safety profile, and the 10 mg dose was evaluated because it is the most commonly used and highest approved dose in Europe.

In the three treatment groups investigated, patients with uncomplicated, stage 1 and 2 hypertension were identical in baseline characteristics and comparable with usual hypertensive patients with respect to age, body weight and accompanying diseases. Both doses of AZL-M were superior to RAM in reducing trough, clinic and ambulatory SBP and DBP, although there were no apparent differences between the 40 and the 80 mg doses. This greater BP efficacy translated into greater reductions in progression rates among subjects treated with AZL-M. Larger BP reductions were consistently observed among patients who received AZL-M relative to RAM in each subgroup examined.

The study also served to evaluate the safety and tolerability of AZL-M at doses within the expected therapeutic range, over a treatment period of 6 months and in comparison with the well-characterized antihypertensive agent RAM. The safety profile of AZL-M observed in this study was comparable with that of RAM with less cough and slightly more dizziness and hypotension among patients treated with AZL-M, the latter likely related to the greater BP reductions achieved with AZL-M relative to RAM. Twice as many subjects (n = 14, 4.8%) in the RAM group compared with the AZL-M 40 mg group (n = 7, 2.4%) discontinued study
medication owing to adverse events, although the absolute incidence was low. Persistent elevations in serum creatinine were uncommon.

In conclusion, the results from this study demonstrate that AZL-M at doses of 40 and 80 mg QD was significantly superior to RAM 10 mg QD in reducing clinic and ambulatory SBP and DBP. A plateau in BP reduction was reached after 4 weeks of treatment and was maintained throughout the 24 weeks of treatment, illustrating the durability of the BP effects of AZL-M. The better efficacy in BP reduction was consistent with the higher responder rates observed for AZL-M compared with RAM. The overall safety profile of AZL-M 40 and 80 mg observed in this study was similar to that of RAM, with fewer discontinuations due to adverse events. The favorable efficacy and safety profile of AZL-M may translate into better persistence during chronic therapy and more patients achieving BP control.

What is known about this topic
In spite of well-established antihypertensive agents, only a small portion of patients with hypertension permanently reach blood pressure targets. Thus, more potent and well-tolerated antihypertensive agents are still needed.

Angiotensin II type 1 (AT-1) receptor blockers are accepted as very effective antihypertensive drugs with adverse event profiles similar to placebo. Antihypertensive potency of AT-1 receptor blockers was proven to be similar to that of other antihypertensive agents.

What this study adds
The AT-1 receptor antagonist azilsartan medoxomil is a newly developed, potent antihypertensive compound with constant blood pressure-lowering effect over 24 h. The effect was still preserved after a treatment period of 24 weeks.

In the tested doses of 40 mg day$^{-1}$ and 80 mg day$^{-1}$, azilsartan medoxomil lowered blood pressure much more effectively and resulted in greater achievement of target blood pressure than the angiotensin-converting enzyme inhibitor ramipril at its highest approved dose (10 mg day$^{-1}$). The tolerability of azilsartan medoxomil was better than that of ramipril.

CONFLICT OF INTEREST
This study was sponsored by Takeda Global Research and Development Center. There was no payment by the sponsor to any authors for their work in analyzing data or writing or editing of this article. The principal investigator was GL, Park-Klinikum, Bad Krozingen, Germany. GB has a consultant relationship with Takeda Pharma Germany and is a member of the speakers’ bureau for Takeda Pharma Germany, Merck Pharma, Germany, Merck, Sharp and Dohme, Boehringer Ingelheim, Daiichi Sankyo and AstraZeneca. DS has had a research and/or consultant relationship with Takeda Pharmaceuticals, Boehringer-Ingelheim, Novartis and Merck. GLB has received

### Table 4. Adverse events reported in ≥2% of the subjects in any treatment group

| Adverse event                      | AZL-M 40 | AZL-M 80 | RAM 10 |
|------------------------------------|----------|----------|--------|
| N = 294                            | N = 293  | N = 293  |
| Any adverse event                 | 112 (38.1) | 128 (43.7) | 113 (38.6) |
| Related to study drug*             | 37 (12.6) | 39 (13.3) | 41 (14.0) |
| Leading to discontinuation#        | 7 (2.4) | 9 (3.1) | 14 (4.8) |
| Serious adverse event              | 8 (2.7) | 12 (4.1) | 6 (2.0) |
| Deaths                             | 0 | 0 | 0 |
| Events in ≥2% of subjects          |          |          |        |
| Nasopharyngitis                    | 19 (6.5) | 13 (4.4) | 17 (5.8) |
| Headache                           | 12 (4.1) | 10 (3.4) | 14 (4.8) |
| Cough                              | 3 (1.0) | 4 (1.4) | 24 (8.2) |
| Increase in blood creatine kinase  | 6 (2.0) | 9 (3.1) | 4 (1.4) |
| Dizziness                          | 8 (2.7) | 7 (2.4) | 4 (1.4) |
| Back pain                          | 5 (1.7) | 11 (3.8) | 2 (0.7) |
| Contusion                          | 7 (2.4) | 4 (1.4) | 1 (0.3) |
| Hypotension                        | 4 (1.4) | 6 (2.0) | 2 (0.7) |
| Increase in γ-glutamyl transferase | 7 (2.4) | 1 (0.3) | 3 (1.0) |

Abbreviations: AZL-M, azilsartan medoxomil; RAM, ramipril. Data are n (%).

*Definitely, probably, or possibly related, as attributed by the investigator.

#Might include temporary drug interruption or permanent discontinuation and includes all subjects who discontinued the study drug at least once.

Figure 3. Open circles are seated, clinic SBP treatment differences between the group that received AZL-M 40 mg and the RAM group. Closed circles are the treatment differences between the AZL-M 80 mg group and the RAM group. The median clinic SBP at baseline was 160.3 mm Hg. Baseline estimated glomerular filtration rate (eGFR) categories expressed as ml min$^{-1}$ per 1.73 m$^2$. *P<0.05 vs RAM. BMI, body mass index.
grant or research support from Forest Labs, Medtronic and Relypsa is a consultant for Takeda, Abbott, CVRx, Johnson & Johnson, Eli Lilly and Daichi Sankyo. He is a member of the speakers’ bureau for Takeda. WBW has served as a paid safety consultant for Takeda Global Research and Development Center. MAW is a member of the speakers’ bureau and consultant for Boehringer-Ingelheim, Daichi Sankyo, Forest, Novartis and Takeda; and AP, CC, AH and SK are full-time employees of Takeda Global Research and Development Center (Deerfield, IL, USA).

ACKNOWLEDGEMENTS

This study was sponsored by Takeda Global Research and Development Center, IL, USA. There was no payment by the sponsor to any authors for their work in analyzing data or writing or editing of this article.

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