Evaluation of the Efficacy and Tolerability of Fixed-Dose Combination Therapy of Azilsartan and Amlodipine Besylate in Japanese Patients With Grade I to II Essential Hypertension

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ABSTRACT

Background: Guidelines for the management of hypertension recommend using drugs with different mechanisms of action in antihypertensive regimens that include simple single-pill fixed-dose combination (FDC) products.

Objective: The objective of this study was to compare the efficacy and tolerability of the FDC of azilsartan (AZI) and amlodipine besylate (AML) with those of AZI monotherapy and AML monotherapy in Japanese patients with grade 1 to 2 essential hypertension.

Methods: This was a multicenter, randomized, double-blind, parallel-group study. After receiving placebo during a 4-week run-in period in a single-blind manner, patients were randomized to receive 1 of the following 5 treatments for 8 weeks: FDC containing AZI 20 mg and AML 5 mg (AZI/AML 20/5 mg), FDC containing AZI 20 mg and AML 2.5 mg (AZI/AML 20/2.5 mg), AZI 20 mg, AML 5 mg, or AML 2.5 mg once daily in a fasting or fed state. The primary end point was the change from baseline (week 0) in the seated trough diastolic blood pressure at week 8 (last observation carried forward [LOCF]), and the secondary end point was the change from baseline in the seated trough systolic blood pressure at week 8 (LOCF). Tolerability was assessed based on adverse events, vital signs, and physical examination findings.

Results: Of the 800 patients who provided informed consent, 603 were randomized to receive AZI/AML 20/5 mg (150 patients), AZI/AML 20/2.5 mg (151 patients), AZI 20 mg (151 patients), AML 5 mg (75 patients), or AML 2.5 mg (76 patients). The mean baseline systolic/diastolic blood pressure was 160.7/100.3 mm Hg. The mean change from baseline in seated blood pressure at week 8 (LOCF) was −35.3/−22.3 mm Hg in the AZI/AML 20/5 mg group and −31.4/−19.2 mm Hg in the AZI/AML 20/2.5 mg group, indicating a reduction significantly greater than that in corresponding monotherapy groups (−21.5/−13.9 mm Hg in the AZI 20 mg group, −26.4/−15.5 mm Hg in the AML 5 mg group, and −19.3/−11.6 mm Hg in the AML 2.5 mg group; $p < 0.0001$ for all contrast tests). No remarkable difference was found in the incidences of adverse events, vital signs, and physical examination findings among the treatment groups.

Conclusion: This study found that the FDC of AZI/AML 20/5 mg and 20/2.5 mg exhibited greater antihypertensive effects compared with each monotherapy. The FDC of AZI/AML had a similar safety profile to that of each monotherapy and was tolerable to Japanese patients with grade 1 to 2 essential hypertension.

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Key words: amlodipine besylate, azilsartan, essential hypertension, fixed-dose combination.

INTRODUCTION

The association between hypertension and morbidity or mortality from stroke, myocardial infarction (MI), and cardiovascular diseases has been well established.

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Meanwhile, the number of patients with hypertension is increasing with the changing lifestyles in Japan and the accelerated aging of the Japanese population. A survey conducted in 2009 (Japan Guideline Assessment Panel 2) indicated that blood pressure was not adequately controlled in 50% of patients receiving antihypertensive treatment.[1]

The 2009 Guidelines for the Management of Hypertension (Japanese guidelines for blood pressure control) recommend a combination of antihypertensive treatments when monotherapy is not sufficiently effective.[2] One of the treatments recommended by the guidelines, a combination therapy with an angiotensin II receptor blocker (ARB) and a calcium channel blocker (CCB), is a rational combination therapy from the aspects of both efficacy and safety because these 2 drug classes have different mechanisms of action and do not interfere with the efficacy of each other. The combination of an ARB and a CCB is thus one of the most commonly used treatment options in clinical practice, and several fixed-dose combinations (FDCs) of ARBs and CCBs have been approved recently in Japan, the United States, and Europe.

Azilsartan (AZI) is an ARB approved for the treatment of hypertension in Japan. A previously conducted study found that AZI (20 to 40 mg once daily) provided significantly greater reductions in both seated trough diastolic blood pressure (DBP) and seated trough systolic blood pressure (SBP) than did candesartan cilexetil (8 to 12 mg once daily), an existing ARB, in Japanese patients with grade 1 to 2 essential hypertension.[3] Amlodipine besylate (AML) is a long-acting CCB designed to correct the defects of dihydropyridine CCBs, including reflex sympathetic stimulation. It is the most commonly used CCB in Japan and is one of the most commonly used antihypertensive drugs. Its safety and efficacy have been well established.

Given the excellent clinical profiles of AZI and AML, a promising antihypertensive effect is expected from the combination therapy of the 2 drugs. An FDC of these 2 drugs will simplify prescriptions and improve patients' convenience and treatment adherence. A multicenter, randomized, double-blind, parallel-group study was conducted in Japanese patients with grade 1 to 2 essential hypertension to evaluate the efficacy and safety of an FDC of AZI/AML compared with those of AZI and AML monotherapies.

PATIENTS AND METHODS

Study Design

This study was a multicenter, randomized, double-blind, parallel-group study that consisted of a 4-week, single-blind, placebo, run-in period and an 8-week double-blind treatment period. Patients visited the medical centers on weeks −4, −2, 0, 2, 4, 6, and 8. Use of all antihypertensive drugs was stopped before starting the study, and all patients underwent a 4-week washout placebo period. At week 0, eligible patients were randomly assigned to one of the following treatment groups: FDC containing AZI 20 mg and AML 5 mg (AZI/AML 20/5 mg), FDC containing AZI 20 mg and AML 2.5 mg (AZI/AML 20/2.5 mg), AZI 20 mg monotherapy (AZI 20 mg), AML 5 mg monotherapy (AML 5 mg), or AML 2.5 mg monotherapy (AML 2.5 mg). Treatments were assigned at a ratio of 2:2:2:1:1 respectively, using the plasma renin activity (minimum to 0.4 ng/mL/h or 0.5 ng/mL/h to maximum) at week −2 as a randomization factor. Patients received study drugs in a blinded manner once daily in the morning at a fixed time either in a fasting or fed state. Throughout the study, the concomitant use of other antihypertensive drugs was prohibited.

Inclusion and Exclusion Criteria

Patients were eligible for study participation if they met all of the following main inclusion criteria: grade 1 to 2 essential hypertension, age of 20 years or older, ability to comprehend and sign the informed consent form, and having a seated SBP of ≥ 150 and < 180 mm Hg and a seated DBP of ≥ 95 and < 110 mm Hg at weeks −2 and 0 of the placebo run-in period. Patients were not eligible for study participation if they met any of the following main exclusion criteria: secondary or grade 3 hypertension, severe cardiovascular diseases, severe liver dysfunctions, severe renal insufficiency, hyperkalemia, and malignant tumors.

This study was approved by the institutional review board at each study center and was conducted in accordance with the ethical provisions outlined in the Declaration of Helsinki, the International Conference on Harmonisation, Harmonised Tripartite Guideline for Good Clinical Practice E6 (R1), and all applicable local laws and regulations.[4] All patients were required to provide written informed consent before the initiation of any study-related procedures.

Study Assessments

Vital signs and physical examination findings were monitored at every visit, and the severity of adverse events (AEs) and their association with study drugs were assessed by the investigator. Office-seated blood pressures were measured at least 3 times at 1- to 2-minute intervals after being seated for ≥5 minutes. Measurements were repeated until 2 consecutive stable measurements were obtained. The mean of the last 2 consecutive measurements was used for analysis. On the morning of blood pressure measurement, patients were not allowed to take the study drug. Measurements of blood pressures were taken in the morning approximately 24 hours after the last drug intake (acceptable range ±3 hours, ie, 21 to 27 hours after the last drug intake). Patients were prohibited from taking caffeine-containing foods or drinks or smoking within 30 minutes before the blood pressure measurement. Blood pressures were taken on the right arm (the left arm was used in case the measurement on the right arm was unfeasible for any reasons), and the measured arm was not changed throughout the study. Plasma renin activity was measured at week −2, and clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed at weeks −2, 0 (baseline), 2, and 8 after the patients had fasted for ≥10 hours. Both were measured by Mitsubishi Chemical Medicine Corporation (Tokyo, Japan).

Study End Points

The primary efficacy end point was the change from the end of the placebo run-in period (baseline [week 0]) in the seated trough DBP at the end of the double-blind treatment period (week 8, last observation carried forward [LOCF]). The secondary end points were the seated trough SBP (LOCF), the proportion of responders (patients who had a ≥20-mm Hg decrease in SBP and a ≥10-mm Hg decrease in DBP or who had an SBP of <130 mm Hg and a DBP of <85 mm Hg), the proportion of patients who achieved the target blood pressure (those who had a DBP of <85 mm Hg and an SBP of <130 mm Hg; the target blood pressure levels in the guidelines for the management of hypertension), and the seated trough DBP/SBP at each time point.

Safety variables included AEs, vital signs (supine and standing blood pressure and seated pulse rate), weight, resting 12-lead ECG results, and clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Statistical Analysis

The differences between the FDC and the monotherapy groups in the mean change of the seated trough DBP (changes from the baseline to week 8 [LOCF]) were assumed to be −8.0 mm Hg for AZI/AML 20/5 mg − AZI 20 mg, AZI/AML 20/5 mg − AML 5 mg, and AZI/AML 20/2.5 mg − AML 2.5 mg, and −4.0 mm Hg for AZI/AML 20/2.5 mg − AZI 20 mg, with a common SD of 10.0 mm Hg across the treatment groups. On the basis of these assumptions, the number of patients required to test the superiority of AZI/AML 20/5 mg and AZI/AML 20/2.5 mg to each of the single doses (AZI 20 mg and AML 2.5 mg), with at least a 0.90 simultaneous statistical power and a 2-sided significance level of 0.05, was determined to be 67 patients per group for AML 5 mg and AML 2.5 mg and 134 patients per group for AZI/AML 20/5 mg, AZI/AML 20/2.5 mg, and AZI 20 mg. Taking into account the patients without data available for the primary end point evaluation, this study planned to randomize the following numbers of patients: 71 patients per group for AML 5 mg and AML 2.5 mg and 142 patients per group for AZI/AML 20/5 mg, AZI/AML 20/2.5 mg, and AZI 20 mg.

The primary analysis was performed using the full analysis set (FAS). The FAS was defined as all patients who were randomized and received at least 1 dose of the study drug during the treatment period. For the primary end point, summary statistics were presented for each treatment group. The point estimate of the least-square (LS) mean and its 2-sided 95% CI for each treatment group were calculated using the ANOVA model. Contrast tests were performed using contrast coefficients assigned to each of the following treatment groups: AZI/AML 20/5 mg, AZI/AML 20/2.5 mg, AZI 20 mg, AML 5 mg, and AML 2.5 mg. Corresponding point estimates of the differences in the LS means between the treatment groups and their 2-sided 95% CIs were calculated. To confirm the superiority of the AZI/AML 20/5 mg treatment, contrast tests using contrast coefficients (1, 0, −1, 0, 0) and (1, 0, 0, −1, 0) were performed. Both contrast tests had to be statistically significant to declare the superiority of the AZI/AML 20/5 mg treatment to each monotherapy (AZI 20 mg or AML 5 mg). Similarly, contrast tests using contrast coefficients

(0, 1, −1, 0, 0) and (0, 1, 0, 0, −1) were performed to confirm the superiority of the AZI/AML 20/2.5 mg treatment. To declare the superiority of the AZI/AML 20/2.5 mg treatment to each monotherapy (AZI 20 mg or AML 2.5 mg), all 4 contrast tests needed to be statistically significant. As a secondary analysis, the point estimates of the differences in the LS means between the AZI/AML 20 /5 mg group and the AZI/AML 20/2.5 mg group and the 2-sided 95% CIs were calculated.

Secondary end points were also analyzed using the FAS. The same analysis as that performed on the primary end point was performed on SBP. The proportions of the responders and patients who achieved the target blood pressure were summarized at each time point by the treatment group. Safety end points were assessed using the safety analysis set, which was defined as all patients who received at least 1 dose of the study drug. For all statistical tests, the significance level was set at 0.05 (2-sided).

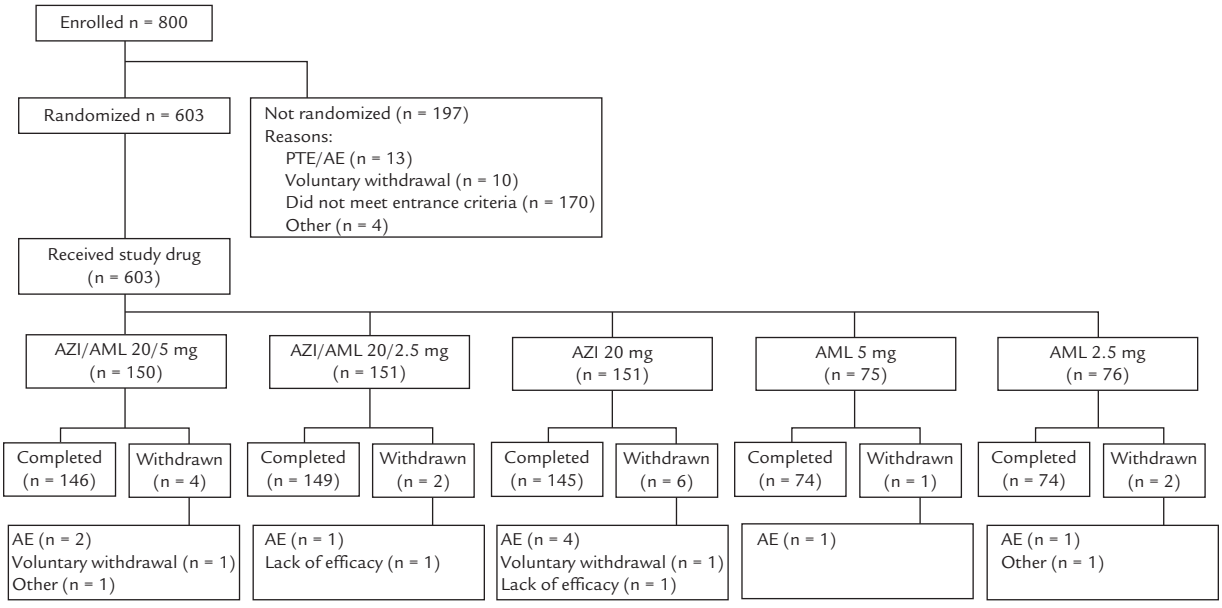
RESULTS

Patient Disposition and Baseline Characteristics

As summarized in Figure 1, a total of 800 patients provided informed consent. Of these, 603 were randomly allocated to the study treatments at 36 sites in Japan and received the study drug during the treatment period. The most common primary reason for allocation failure was "did not meet entrance criteria" in 170 patients. A total of 150 patients received AZI/AML 20/5 mg, 151 patients received AZI/AML 20/2.5 mg, 151 patients received AZI 20 mg, 75 patients received AML 5 mg, and 76 patients received AML 2.5 mg. Of these 603 patients, 588 completed the study treatment, and 15 withdrew prematurely. The baseline demographic and clinical characteristics in the FAS are summarized in Table I. The mean age of the patients ranged from 56.4 to 58.9 years across the treatment groups. Male patients accounted for 56.3% to 64.9% of patients across the treatment groups. The baseline mean seated SBP ranged from 160.2 to 161.1 mm Hg, and the mean seated DBP ranged from 99.9 to 101.0 mm Hg across the treatment groups. No remarkable differences in demographic characteristics were observed among the treatment groups.

Efficacy

Summary statistics for the primary efficacy end point (the change from baseline in the seated trough



AE = adverse event; AML = amlodipine besilate; AZI = azilsartan; n = number of patients; PTE = pre treatment event.

Figure 1. Flow diagram of enrolled patients.

Table I. Baseline demographic characteristics of the study patients (full analysis set).*

Treatment group	AZI/AML 20/5 mg (n = 150)	AZI/AML 20/2.5 mg (n = 151)	AZI 20 mg (n = 151)	AML 5 mg (n = 75)	AML 2.5 mg (n = 76)	Total (N = 603)
Age, mean (SD), y	57.6 (9.84)	57.4 (9.18)	58.5 (9.08)	58.9 (9.93)	56.4 (11.38)	57.8 (9.71)
Male sex	86 (57.3)	85 (56.3)	98 (64.9)	46 (61.3)	49 (64.5)	364 (60.4)
Weight, mean (SD), kg	68.95 (13.389)	68.29 (13.874)	69.52 (13.856)	67.23 (13.018)	70.40 (12.635)	68.90 (13.480)
BMI, mean (SD, kg/m^2)	25.91 (4.099)	25.80 (3.933)	25.92 (4.138)	25.37 (3.686)	25.99 (3.823)	25.82 (3.975)
DBP, mean (SD), mm Hg	100.3 (4.15)	99.9 (4.09)	100.4 (4.12)	100.0 (3.83)	101.0 (4.08)	100.3 (4.08)
SBP, mean (SD), mm Hg	160.7 (7.77)	161.1 (8.25)	160.2 (8.30)	161.1 (8.49)	160.3 (7.78)	160.7 (8.10)
Plasma renin activity, mean (SD), ng/mL/h	0.86 (0.729)	0.95 (1.196)	1.01 (1.015)	0.94 (1.044)	1.04 (0.994)	0.95 (1.003)
Complications	137 (91.3)	137 (90.7)	142 (94.0)	66 (88.0)	68 (89.5)	550 (91.2)
Cerebrovascular diseases	2 (1.3)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	3 (0.5)
Cardiovascular diseases	4 (2.7)	6 (4.0)	9 (6.0)	4 (5.3)	2 (2.6)	25 (4.1)
Renal dysfunction	4 (2.7)	2 (1.3)	1 (0.7)	2 (2.7)	1 (1.3)	10 (1.7)
Liver dysfunction	33 (22.0)	25 (16.6)	27 (17.9)	19 (25.3)	16 (21.1)	120 (19.9)
Diabetes mellitus	29 (19.3)	25 (16.6)	38 (25.2)	11 (14.7)	15 (19.7)	118 (19.6)
Dyslipidemia	89 (59.3)	92 (60.9)	84 (55.6)	43 (57.3)	42 (55.3)	350 (58.0)
History of antihypertensive medication	122 (81.3)	130 (86.1)	121 (80.1)	61 (81.3)	62 (81.6)	496 (82.3)
ARB	81 (54.0)	89 (58.9)	73 (48.3)	36 (48.0)	46 (60.5)	325 (53.9)
CCB	88 (58.7)	89 (58.9)	100 (66.2)	40 (53.3)	42 (55.3)	359 (59.5)
ACE inhibitor	6 (4.0)	2 (1.3)	4 (2.6)	3 (4.0)	1 (1.3)	16 (2.7)

ACE = angiotensin-converting enzyme; AML = amlodipine besylate; ARB = angiotensin receptor blocker; AZI = azilsartan; BMI = body mass index; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.
*Data are presented as number (percentage) of patients unless otherwise indicated.

DBP at week 8 [LOCF]) and the secondary efficacy end point (the change from baseline in the seated trough SBP at week 8 [LOCF]) are given in Table II. The mean change in the seated trough DBP at week 8 (LOCF) was −22.3 mm Hg in the AZI/AML 20/5 mg group, −19.2 mm Hg in the AZI/AML 20/2.5 mg group, −13.9 mm Hg in the AZI 20 mg group, −15.5 mm Hg in the AML 5 mg group, and −11.6 mm Hg in the AML 2.5 mg group. The mean change in the seated trough SBP at week 8 (LOCF) was −35.3 mm Hg in the AZI/AML 20/5 mg group, −31.4 mm Hg in the AZI/AML 20/2.5 mg group, −21.5 mm Hg in the AZI 20 mg group, −26.4 mm Hg in the AML 5 mg group, and −19.3 mm Hg in the AML 2.5 mg group. The results of the contrast tests confirmed the superiority of the AZI/AML 20/5 mg and 20/2.5 mg groups to each of the corresponding monotherapy groups in reducing the seated trough DBP at week 8 (LOCF) ($p < 0.0001$ for all 4 tests). In addition, the reduction in the seated trough DBP was significantly greater in the AZI/AML 20/5 mg group than in the AZI/AML 20/2.5 mg group ($p = 0.0014$). Similar results were obtained for the secondary end point where the change in the sitting trough SBP at week 8 (LOCF) was significantly greater in both the FDC groups than in each of the corresponding monotherapy groups ($p < 0.0001$ for all 4 tests) and significantly greater in the AZI/AML 20/5 mg group than in the AZI/AML 20/2.5 mg group ($p = 0.0044$).

The proportion of responders and patients who achieved the target blood pressure at week 8 (LOCF) are given in Table III. At week 8 (LOCF), the proportion of responders was 90.6% (135 of 149 patients) in the AZI/AML 20/5 mg group and 76.8% (116 of 151 patients) in the AZI/AML 20/2.5 mg group. As for the monotherapy groups, the proportion was 45.0% (68 of 151 patients) in the AZI 20 mg

Table II. Changes from baseline in seated DBP and SBP at week 8 (LOCF) (full analysis set).

	DBP, mm Hg					SBP, mm Hg				
	AZI/AML 20/5 mg	AZI/AML 20/2.5 mg	AZI 20 mg	AML 5 mg	AML 2.5 mg	AZI/AML 20/5 mg	AZI/AML 20/2.5 mg	AZI 20 mg	AML 5 mg	AML 2.5 mg
					Summary Statistics					
Values at baseline (week 0)										
No. of patients	150	151	151	75	76	150	151	151	75	76
Mean (SD)	100.3 (4.15)	99.9 (4.09)	100.4 (4.12)	100.0 (3.83)	101.0 (4.08)	160.7 (7.77)	161.1 (8.25)	160.2 (8.30)	161.1 (8.49)	160.3 (7.78)
Changes from baseline at week 8 (LOCF)										
No. of patients	149	151	151	75	76	149	151	151	75	76
Mean (SD)	−22.3 (8.47)	−19.2 (8.78)	−13.9 (8.47)	−15.5 (7.97)	−11.6 (7.38)	−35.3 (11.50)	−31.4 (13.26)	−21.5 (12.23)	−26.4 (10.07)	−19.3 (11.65)
					ANOVA					
LS means										
Estimate (SE)	−22.3 (0.69)	−19.2 (0.68)	−13.9 (0.68)	−15.5 (0.97)	−11.6 (0.96)	−35.3 (0.98)	−31.4 (0.98)	−21.5 (0.98)	−26.4 (1.39)	−19.3 (1.38)
Differences of LS means with 20 mg/5 mg (95% CI)		−3.1 (−4.99 to −1.19)	−8.4 (−10.31 to −6.52)	−6.7 (−9.06 to −4.41)			−4.0 (−6.69 to −1.24)	−13.9 (−16.58 to −11.14)	−8.9 (−12.25 to −5.58)	
P value		0.0014	<0.0001	<0.0001			0.0044	<0.0001	<0.0001	
Differences of LS means with 20 mg/2.5 mg (95% CI)			−5.3 (−7.21 to −3.43)		−7.6 (−9.95 to −5.33)			−9.9 (−12.61 to −7.18)		−12.1 (−15.42 to −8.78)
P value			<0.0001		<0.0001			<0.0001		<0.0001

AML = amlodipine besylate; AZI = azilsartan; DBP = diastolic blood pressure; LOCF = last observation carried forward; LS = least-squares; SBP = systolic blood pressure.

Table III. Proportion of responders and patients with well-controlled hypertension at week 8 (last observation carried forward) (full analysis set).

Treatment group	AZI/AML 20/5 mg (n = 149)	AZI/AML 20/2.5 mg (n = 151)	AZI 20 mg (n = 151)	AML 5 mg (n = 75)	AML 2.5 mg (n = 76)
Responders,* %	90.6	76.8	45.0	65.3	31.6
Patients who achieved the target blood pressure,† %	56.4	41.7	19.9	24.0	11.8

AML = amlodipine besylate; AZI = azilsartan.
*Patients who had ≥20 mm Hg decrease in systolic blood pressure and ≥10 mm Hg decrease in diastolic blood pressure or who had systolic blood pressure <130 mm Hg and diastolic blood pressure <85 mm Hg.
†Patients who had diastolic blood pressure <85 mm Hg and systolic blood pressure <130 mm Hg.

group, 65.3% (49 of 75 patients) in the AML 5 mg group, and 31.6% (24 of 76 patients) in the AML 2.5 mg group. The proportion of patients who achieved the target blood pressure was 56.4% (84 of 149 patients) in the AZI/AML 20/5 mg group and 41.7% (63 of 151 patients) in the AZI/AML 20/2.5 mg group. As for the monotherapy groups, the proportion was 19.9% (30 of 151 patients) in the AZI 20 mg group, 24.0% (18 of 75 patients) in the AML 5 mg group, and 11.8% (9 of 76 patients) in the AML 2.5 mg group.

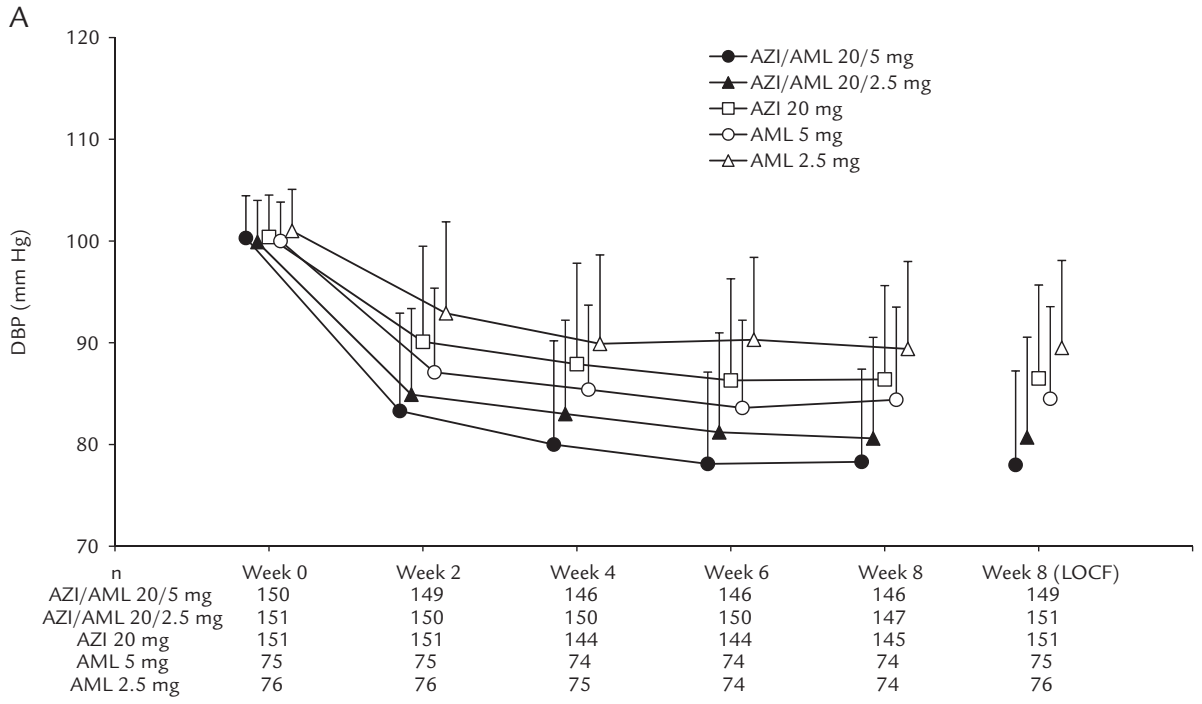
Time profiles of the mean plots of the seated trough DBP and SBP at each point for each treatment group are shown in Figure 2. The blood pressure levels decreased remarkably from baseline at week 2, and the decrease was maintained at a nearly constant level until week 8 (LOCF) in all the treatment groups. There was a greater decrease in the blood pressure level in the AZI/AML 20/5 mg and 20/2.5 mg groups than in each of the monotherapy groups at every time point.

Tolerability

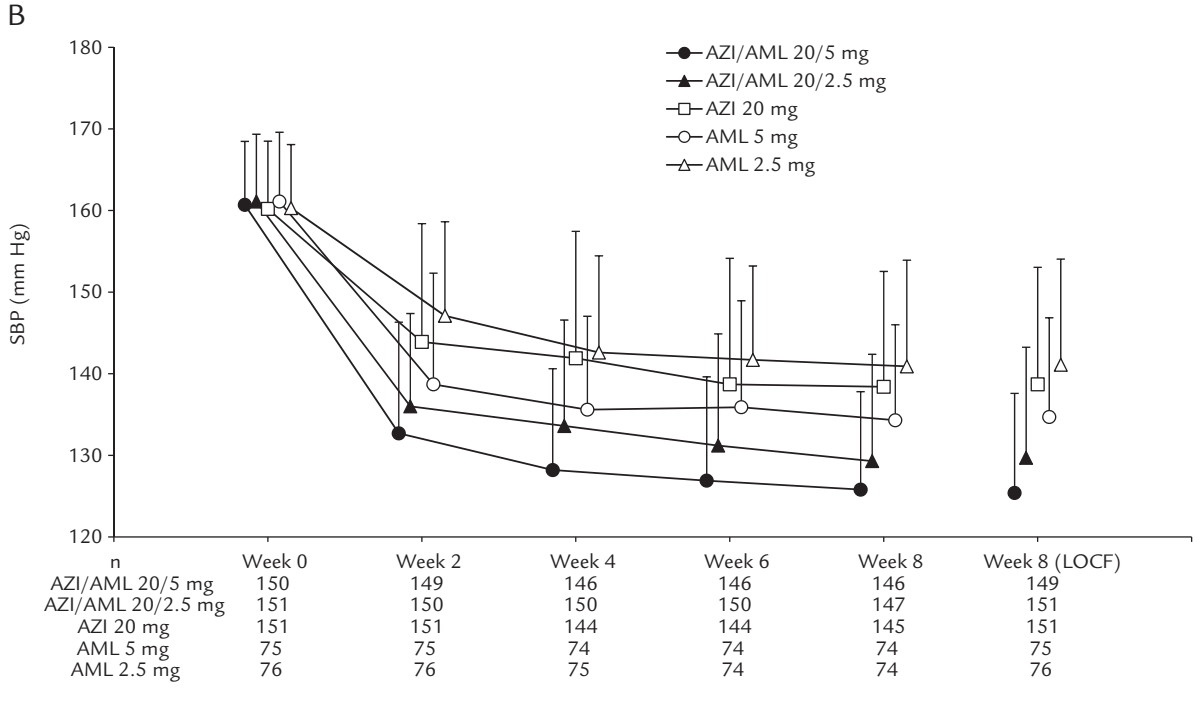
The incidence of overall AEs and the incidence of AEs occurring in ≥2% of patients in each treatment group (safety analysis set) are listed in Table IV. Common AEs that were reported in ≥2% of patients in the FDC of the AZI/AML groups were nasopharyngitis (8.0%) and dizziness (2.7%) in the AZI/AML 20/5 mg group and nasopharyngitis (12.6%), upper respiratory tract inflammation (4.6%), increased blood creatine phosphokinase level (3.3%), and influenza (2.0%) in the AZI/AML 20/2.5 mg group. These AEs were also reported in the monotherapy groups. No remarkable difference was found in the incidences of overall AEs among the treatment groups. Although no AEs related to the study drug were reported in the AML 5 mg group, no remarkable difference was found in the incidences of overall AEs related to the study drug among the other treatment groups. Most of the reported AEs were mild in intensity. Severe AEs were reported in 2 patients: stress cardiomyopathy in the AZI/AML 20/5 mg group and large intestine carcinoma in the AZI/AML 20/2.5 mg group. These severe AEs were considered by the investigator to be unrelated to the study drugs. Serious AEs were stress cardiomyopathy and thyroid neoplasm, each of which was reported in 1 patient in the AZI/AML 20/5 mg group; large intestine carcinoma, which was reported in 1 patient in the AZI/AML 20/2.5 mg group; and atrioventricular block complete and epistaxis, each of which was reported in 1 patient in the AZI 20 mg group. Atrioventricular block complete and epistaxis were considered to be related to the study drugs. No deaths were reported during the study. There were no remarkable findings of clinical concern with respect to the laboratory results, vital signs, weight, and 12-lead ECG findings. Overall, the FDC of AZI/AML was safe and well tolerated in patients with grade 1 to 2 essential hypertension in this study.

DISCUSSION

This study was conducted to evaluate the efficacy and tolerability of the FDC of AZI and AML compared with that of AZI or AML monotherapy in Japanese patients with grade 1 to 2 essential hypertension. The seated trough DBP and SBP at week 8 (LOCF) decreased from baseline in patients administered the FDC of AZI/AML



n	Week 0	Week 2	Week 4	Week 6	Week 8	Week 8 (LOCF)
AZI/AML 20/5 mg	150	149	146	146	146	149
AZI/AML 20/2.5 mg	151	150	150	150	147	151
AZI 20 mg	151	151	144	144	145	151
AML 5 mg	75	75	74	74	74	75
AML 2.5 mg	76	76	75	74	74	76



n	Week 0	Week 2	Week 4	Week 6	Week 8	Week 8 (LOCF)
AZI/AML 20/5 mg	150	149	146	146	146	149
AZI/AML 20/2.5 mg	151	150	150	150	147	151
AZI 20 mg	151	151	144	144	145	151
AML 5 mg	75	75	74	74	74	75
AML 2.5 mg	76	76	75	74	74	76

Figure 2. Time profiles of the mean plots of the seated trough diastolic blood pressure (A) and systolic blood pressure (B) at each point (full analysis set). Mean (SD) values are shown for each time point.

20/5 mg and the FDC of AZI/AML 20/2.5 mg. Moreover, all of the contrast tests consistently confirmed the superiority of AZI/AML 20/5 mg and AZI/AML 20/2.5 mg to each of the corresponding monotherapies in reducing the seated trough DBP and SBP at week 8 (LOCF). The reductions in DBP and SBP were also

Table IV. Incidence of overall AEs and incidence of AEs that occurred in ≥2% of patients in any treatment group (safety analysis set).*

Treatment group	AZI/AML 20/5 mg (n = 150)	AZI/AML 20/2.5 mg (n = 151)	AZI 20 mg (n = 151)	AML 5 mg (n = 75)	AML 2.5 mg (n = 76)
Overall AEs	51 (34.0)	68 (45.0)	61 (40.4)	29 (38.7)	24 (31.6)
Overall AEs related to the study drugs	8 (5.3)	14 (9.3)	13 (8.6)	0 (0.0)	6 (7.9)
Infections and infestations	16 (10.7)	27 (17.9)	17 (11.3)	12 (16.0)	9 (11.8)
Nasopharyngitis	12 (8.0)	19 (12.6)	11 (7.3)	10 (13.3)	6 (7.9)
Bronchitis	2 (1.3)	0 (0.0)	2 (1.3)	1 (1.3)	2 (2.6)
Influenza	0 (0.0)	3 (2.0)	0 (0.0)	1 (1.3)	0 (0.0)
Investigations	8 (5.3)	14 (9.3)	18 (11.9)	2 (2.7)	5 (6.6)
Increased blood creatine phosphokinase level	1 (0.7)	5 (3.3)	3 (2.0)	2 (2.7)	1 (1.3)
Increased blood uric acid level	1 (0.7)	1 (0.7)	2 (1.3)	0 (0.0)	2 (2.6)
Abnormal liver function test result	0 (0.0)	0 (0.0)	5 (3.3)	0 (0.0)	0 (0.0)
Increased blood triglyceride levels	0 (0.0)	1 (0.7)	3 (2.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	11 (7.3)	3 (2.0)	11 (7.3)	3 (4.0)	7 (9.2)
Back pain	1 (0.7)	2 (1.3)	4 (2.6)	3 (4.0)	0 (0.0)
Musculoskeletal stiffness	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	2 (2.6)
Nervous system disorders	5 (3.3)	5 (3.3)	9 (6.0)	2 (2.7)	2 (2.6)
Dizziness	4 (2.7)	1 (0.7)	2 (1.3)	1 (1.3)	0 (0.0)
Headache	0 (0.0)	2 (1.3)	4 (2.6)	0 (0.0)	2 (2.6)
Respiratory, thoracic and mediastinal disorders	3 (2.0)	9 (6.0)	6 (4.0)	5 (6.7)	0 (0.0)
Upper respiratory tract inflammation	2 (1.3)	7 (4.6)	4 (2.6)	3 (4.0)	0 (0.0)
Rhinitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.7)	0 (0.0)

AE= adverse event; AML = amlodipine besylate; AZI = azilsartan.
*Data are presented as number (percentage) of patients.

significantly greater in the AZI/AML 20/5 mg group than in the AZI/AML 20/2.5 mg group. In patients receiving multiple antihypertensive drugs, reducing the number of drugs with a simple single-pill FDC is thought to contribute to greater adherence, which in turn will help patients achieve their target blood pressure.[5–7] Results from this study suggest the FDC of AZI and AML could be a useful treatment option in the management of hypertension.

The target blood pressure in the guidelines for management of hypertension is <140/90 mm Hg in the United States and Europe.[8,9] In Japan, it is <130/85 mm Hg in young and middle-aged patients and <140/90 mm Hg in elderly patients.[2] The proportion of patients who achieved <130/85 mm Hg was 56.4% (84 of 149 patients) after treatment with AZI/AML 20/5 mg. Moreover, the proportion of patients who achieved a blood pressure <140/90 mm Hg was 80.5% (120 of 149 patients) after treatment with AZI/AML 20/5 mg. Because SBP is known to affect the risk of stroke and MI, the long-term incident stroke and MI risk of high blood pressure should be assessed mainly by SBP.[10–12] In the AZI/AML 20/5 mg group, the mean SBP decreased rapidly by ≥20 mm Hg from baseline at week 2, and the mean change from baseline at week 8 (LOCF) was −35.3 mm Hg in this study. Most of the patients who received AZI/AML 20/5 mg had a ≥20 mm Hg decrease or a value <140 mm Hg in the seated trough SBP at week 8 (LOCF) (143 of 149 patients [96%]). This study found that the AZI/AML 20/5 mg treatment resulted in a high achievement of target SBP; thus, it may be useful to use AZI/AML 20/5 mg in cases where a more strict SBP control is needed.

AZI is an ARB with a strong and long-acting antihypertensive effect. A previously conducted study found that once-daily administration of AZI produces a 24-hour sustained antihypertensive effect that is more potent than that of candesartan in Japanese patients with grade I to II essential hypertension.[3] On the other hand, AML is a long-acting CCB designed to correct the defects of dihydropyridine CCBs and produces a 24-hour sustained antihypertensive effect.[13,14] The mean blood pressure level during 24 hours, nocturnal blood pressure, and early morning

blood pressure have been reported to be more closely associated with hypertensive target organ damage and cardiovascular events than office-measured blood pressure.[15–17] The combination therapy of AZI and AML may provide additional clinical benefits to patients with hypertension in accordance with each of the excellent clinical profiles.

The principal limitations of the present study were that only patients with grade 1 to 2 essential hypertension (without cardiovascular disease or significant renal impairment) were eligible for enrollment and the relatively short treatment duration, which preclude its extrapolation to other categories of hypertensive patients and any definitive conclusions regarding its target organ-protective effects.

CONCLUSION

This study found that the FDC of AZI/AML 20/5 mg and 20/2.5 mg exhibited greater antihypertensive effects compared with each of the corresponding monotherapies. The FDC of AZI/AML had a similar safety profile to that of each monotherapy and was tolerable to Japanese patients with grade 1 to 2 essential hypertension.

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CONFLICTS OF INTEREST

H. Rakugi served as the medical expert for this study and received honoraria from Takeda Pharmaceutical Company Limited for the lectures he gave during the study period. E. Nakata, E. Sasaki, and T. Kagawa are employees of Takeda Pharmaceutical Company Limited. The study sponsor participated in all aspects of study conduct and manuscript development.

REFERENCES

1. Teramoto T, Fujita T. Japan Guideline Assessment Panel 2 (J-GAP2) [in Japanese]. *Prog Med*. 2010;30:1437–1449.
2. Ogihara T, Kikuchi K, Matsuoka H, et al. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res*. 2009;32:3–107.
3. Rakugi H, Enya K, Sugiura K, et al. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade I–II essential hypertension: a randomized, double-blind clinical study. *Hypertens Res*. 2012;35:552–558.
4. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/en/30publications/10policies/b3/. Accessed December 16, 2013.
5. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Health Syst Pharm*. 2007;64:1279–1283.

6. Schroeder K, Fahey T, Ebrahim S. How can we improve adherence to blood pressure-lowering medication in ambulatory care? systematic review of randomized controlled trials. *Arch Intern Med*. 2004;164:722–732.
7. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension*. 2010;55:399–407.
8. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
9. Task Force for the management of arterial hypertension of the European Society of Hypertension. 2013 ESH/ESC guidelines for the Management of Arterial Hypertension. *Blood Press*. 2013;22:193–278.
10. Miura K, Nakagawa H, Ohashi Y, et al. Four blood pressure indexes and the risk of stroke and myocardial infarction in Japanese men and women: a meta-analysis of 16 cohort studies. *Circulation*. 2009;119:1892–1898.
11. Lawes CM, Bennett DA, Parag V, et al. Blood pressure indices and cardiovascular disease in the Asia Pacific region: a pooled analysis. *Hypertension*. 2003;42:69–75.
12. Inoue R, Ohkubo T, Kikuya M, et al. Predicting stroke using 4 ambulatory blood pressure monitoring-derived blood pressure indices: the Ohasama Study. *Hypertension*. 2006;48:877–882.
13. Tomlinson B, Woo J, Thomas N, et al. Randomized, controlled, parallel-group comparison of ambulatory and clinic blood pressure responses to amlodipine or enalapril during and after treatment in adult Chinese patients with hypertension. *Clin Ther*. 2004;26:1292–1304.
14. Eguchi K, Kario K, Hoshide Y, et al. Comparison of valsartan and amlodipine on ambulatory and morning blood pressure in hypertensive patients. *Am J Hypertens*. 2004;17:112–117.
15. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA*. 1999;282:539–546.
16. Kikuya M, Ohkubo T, Asayama K, et al. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. *Hypertension*. 2005;45:240–245.
17. Asayama K, Ohkubo T, Kikuya M, et al. Prediction of stroke by home "morning" versus "evening" blood pressure values: the Ohasama study. *Hypertension*. 2006;48:737–743.

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