

## ORIGINAL ARTICLE

# The efficacy and long-term safety of a triple combination of 80 mg telmisartan, 5 mg amlodipine and 12.5 mg hydrochlorothiazide in Japanese patients with essential hypertension: a randomized, double-blind study with open-label extension

Jitsuo Higaki<sup>1</sup>, Issei Komuro<sup>2</sup>, Kosuke Shiki<sup>3</sup>, Hiroyuki Ugai<sup>3</sup>, Atsushi Taniguchi<sup>3</sup>, Hiroshi Ikeda<sup>3</sup>, Daisuke Kuroki<sup>3</sup>, Seichiro Nishimura<sup>3</sup> and Toshio Ogihara<sup>4</sup>

The aim of this study was to compare 80 mg telmisartan/5 mg amlodipine/12.5 mg hydrochlorothiazide (T80/A5/H12.5) with 80 mg telmisartan/12.5 mg hydrochlorothiazide (T80/H12.5) to determine their relative blood pressure (BP) lowering effects in essential hypertensive patients with inadequate control and to evaluate the long-term safety of T80/A5/H12.5 in a 52-week extension period. Patients ( $n=132$ ) were randomly assigned to receive double-blind treatment with T80/A5/H12.5 or T80/H12.5 for 8 weeks after a 6-week run-in-period of T80/H12.5. All 126 patients who completed the double-blind period entered the 52-week open-label extension and received T80/A5/H12.5. The adjusted mean changes from the reference baseline of the trough-seated systolic and diastolic BP (SBP/DBP) at week 8 were significantly larger in the T80/A5/H12.5 group ( $-10.6/-8.8$  mm Hg) than in the T80/H12.5 group ( $-2.3/-1.3$  mm Hg) ( $P<0.0001$ ). The BP-lowering effect of T80/A5/H12.5 was maintained over the 52-week extension period. The adverse events (AEs) during both treatment periods were generally mild. Drug-related AEs were reported in one patient in each group in the double-blind period and in five patients exposed to T80/A5/H12.5 in the double-blind and/or open-label extension period. T80/A5/H12.5 therapy was clinically and statistically superior to T80/H12.5 therapy for the reduction of BP in patients with essential hypertension uncontrolled with T80/H12.5, and its BP-lowering effect was maintained in the long term. T80/A5/H12.5 was generally well-tolerated.

*Hypertension Research* (2017) 40, 51–60; doi:10.1038/hr.2016.100; published online 1 September 2016

**Keywords:** amlodipine; combination therapy; hydrochlorothiazide; telmisartan

## INTRODUCTION

More than 43 million people in Japan are affected by hypertension. An estimated 60% of males and 45% of females aged >30 years have systolic blood pressure (SBP)  $\geq 140$  mm Hg or diastolic blood pressure (DBP)  $\geq 90$  mm Hg or take antihypertensive medications.<sup>1</sup> Furthermore, there are ~100 000 hypertension-related deaths per year in Japan.<sup>2</sup> Hypertension is associated with numerous life-threatening conditions, including stroke and myocardial infarction, and it is often these conditions that cause hypertension-related deaths. Thus, as the incidence of hypertension is expected to increase because the Japanese

population is aging,<sup>1</sup> it is imperative that more effective treatments are developed.

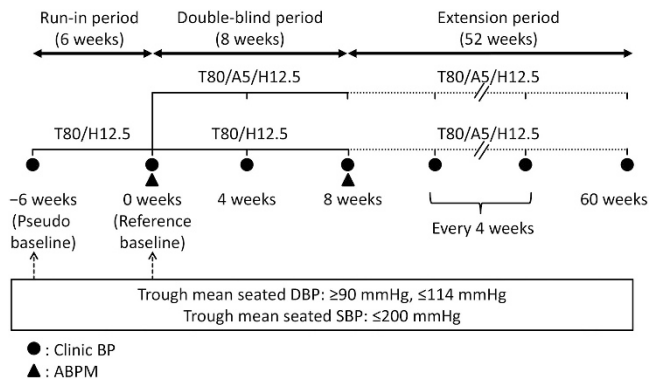
In the EPOCH-JAPAN study, high BP was associated with >50% of all deaths caused by stroke, coronary heart disease or cardiovascular disease.<sup>3</sup> Asian patients have a higher risk of stroke than of coronary artery disease compared with Western populations, and the association between clinic-measured BP and the risk of stroke is stronger in Asian patients than in Western patients.<sup>4,5</sup> It is estimated that an average 4 mm Hg reduction of SBP among Japanese patients would reduce the number of deaths from stroke in Japan by ~10 000 per year.<sup>1</sup>

<sup>1</sup>Department of Cardiology, Pulmonology, Hypertension & Nephrology, Ehime University Graduate School of Medicine, Ehime, Japan; <sup>2</sup>Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; <sup>3</sup>Medical Division, Nippon Boehringer Ingelheim Co. Ltd., Tokyo, Japan and <sup>4</sup>Morinomiya University of Medical Sciences, Osaka, Japan

Correspondence: Dr J Higaki, Department of Cardiology, Pulmonology Hypertension & Nephrology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan.

E-mail: jhigaki@m.ehime-u.ac.jp

Received 21 April 2016; revised 7 June 2016; accepted 12 June 2016; published online 1 September 2016



**Figure 1** Trial design. A, amlodipine; ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; H, hydrochlorothiazide; SBP, systolic blood pressure; T, telmisartan.

However, sufficient BP control (SBP/DBP < 140/90 mm Hg) is achieved in only ~30% of hypertensive men and 40% of hypertensive women receiving treatment for the disease.<sup>6,7</sup>

According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension,<sup>1</sup> first-line antihypertensive treatment should consist of a calcium channel blocker (CCB), angiotensin receptor blocker (ARB), angiotensin-converting enzyme (ACE) inhibitors, or a diuretic, in hypertensive patients without compelling indications. The use of two or three drugs in combination (from different classes) is often necessary to achieve the target BP. The recommended two-drug combinations are an ACE inhibitor+CCB, an ARB+CCB, an ACE inhibitor+diuretic, an ARB+diuretic or a CCB+diuretic. Patients not responding to a two-drug combination should be prescribed triple combination therapy. Furthermore, the guidelines and other studies show that the simplification of prescriptions using fixed-combination drugs can improve adherence.<sup>1,8,9</sup>

The fixed-dose combination of 80 mg telmisartan/12.5 mg hydrochlorothiazide effectively reduces BP and helps more patients achieve their target BP than monotherapy, with reductions in BP apparent as early as 1–4 weeks after starting treatment.<sup>10,11</sup> However, after treatment with T80/H12.5, some patients have persisting uncontrolled symptoms, and a triple-therapy regimen may be necessary. One such regimen is T80/H12.5 in combination with 5 mg amlodipine (T80/A5/H12.5). Because CCBs have strong BP-lowering effects, they decrease variability in SBP more than do other classes of drugs.<sup>12</sup>

The aim of this study was to determine the efficacy and safety of combined hypertension treatment with T80/A5/H12.5 compared with T80/H12.5 alone in patients with hypertension and to assess the long-term (52-week) safety of T80/A5/H12.5.

## METHODS

### Patients

Patients were enrolled between July 2013 and October 2013 and were either male or female outpatients aged  $\geq 20$  years with uncontrolled essential hypertension despite treatment with T80/H12.5 during a 6-week run-in period. The patients were also required to be taking two or three antihypertensive drugs at the time they provided informed consent, and to have a mean seated DBP  $\geq 90$  and  $\leq 114$  mm Hg and a mean seated SBP  $\leq 200$  mm Hg at week -6 (the pseudo baseline; at the beginning of the run-in period) and week 0 (the reference baseline; at the end of the 6-week run-in period). All patients had to be able to safely stop all current antihypertensive drugs (other than the study

medication) from -6 weeks through to the end of the trial without risk and had to provide informed consent.

The exclusion criteria included known or suspected secondary hypertension; current sustained ventricular tachycardia or other cardiac arrhythmia requiring medication; congestive heart failure (New York Heart Association functional class III–IV); a history of myocardial infarction, cardiac surgery or unstable angina within the previous 3 months; hypertrophic obstructive cardiomyopathy, aortic stenosis, or hemodynamically relevant stenosis of the aortic or mitral valve and a history of stroke or transient ischemic attack within the previous 6 months. Patients who had taken any investigational drugs within 28 days of signing the informed consent form were also excluded.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was granted by the institutional review boards at each center, and the documentation and conduct met the requirements and definitions of the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline for Good Clinical Practice ((GCP) ICH E6), 21 Code of Federal Regulations (CFR) 312.3, and of the participating country (Japan). All patients provided written informed consent, which they were free to withdraw at any time during the study.

### Study design

This was a multicenter, 8-week, randomized, double-blind, active-control, parallel-group comparative phase III clinical trial, followed by a 52-week open-label extension period (Figure 1). Before the double-blind period, all patients underwent a 6-week open-label run-in period in which they took the fixed-dose combination T80/H12.5 once daily. There was no washout period before the run-in period.

Interactive response technology was used for randomization and to ensure an appropriate supply of trial medication to the patients.

Patients who met the inclusion criteria and none of the exclusion criteria at the end of the 6-week T80/H12.5 run-in period were randomly assigned at a 1:1 ratio to the T80/A5/H12.5 group or to the control T80/H12.5 group in a double-blind manner using a permuted-block method with a block size of 4, stratified by site. All patients received T80/H12.5 once daily in combination with either 2  $\times$  2.5 mg over-encapsulated amlodipine tablets (T80/A5/H12.5 group) or 2  $\times$  2.5 mg over-encapsulated placebo tablets (T80/H12.5 group) in the double-blind treatment period, which lasted for 8 weeks (Figure 1).

In the 52-week extension period that directly followed the double-blind period, patients who had received T80/A5/H12.5 in the double-blind period continued their treatment, while patients who had received T80/H12.5 were switched to T80/A5/H12.5 (Figure 1). Therefore, all patients received T80/A5/H12.5 in the open-label extension period.

### Study endpoints

**Efficacy.** The primary endpoint was the reduction from the reference baseline in the mean trough-seated DBP after 8 weeks of the double-blind period. The key secondary endpoint was the reduction from the reference baseline in the mean trough-seated SBP after 8 weeks of the double-blind period.

The other secondary endpoints were:

- The proportion of patients with DBP < 90 mm Hg and SBP < 140 mm Hg for trough-seated BP after 8 weeks of the double-blind period and after 52 weeks of the extension period,
- The reduction from the reference baseline in the mean trough-seated DBP after 52 weeks of the extension period, and
- The reduction from the reference baseline in the mean trough-seated SBP after 52 weeks of the extension period.

Other endpoints measured in the study included:

- The seated DBP control rate at trough after 8 weeks of the double-blind period and after 52 weeks of the extension period,
- The seated SBP control rate at trough after 8 weeks of the double-blind period and after 52 weeks of the extension period,

- The seated DBP response rate at trough after 8 weeks of the double-blind period and after 52 weeks of the extension period from the reference baseline,
- The seated SBP response rate at trough after 8 weeks of the double-blind period and after 52 weeks of the extension period from the reference baseline, and
- The change from the reference baseline in the DBP and SBP hourly means over the 24-h dosing interval as measured by ambulatory BP monitoring (ABPM) after 8 weeks of the double-blind period.

### BP and heart rate measurements

All BP measurements were taken with a standard mercury sphygmomanometer, on the same arm, by the same operator where possible. BP and pulse rate were measured ~24 h ( $\pm 3$  h) after the last dose of the investigational product on the previous day (trough condition). Seated BP was calculated as the mean of three measurements.

Seated BP and the pulse rate were measured at the start and end of the 6-week run-in period, and every 4 weeks after the start of the double-blind treatment period until the end of the 52-week open-label extension period. Twenty-four-hour ABPM was performed at week 0 and week 8.

### Safety

Safety outcomes include adverse events (AEs) (including severe AEs and serious (S)AEs), and changes in BP and the pulse rate following position changes, the seated pulse rate, the pulse rate measured by ABPM, and general laboratory tests (blood biochemistry, hematology and urinalysis).

Safety for the 8-week double-blind treatment was based on all patients who took at least one dose of the study drug after randomization in the double-blind period. The safety data for long-term treatment were based on all patients who took at least one dose of T80/A5/H12.5 in the double-blind period or the extension period.

An AE was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition (whether deemed to be related to treatment or not) and were categorized as mild, moderate or severe. An SAE included any AE resulting in death, or that was immediately life-threatening, or resulted in persistent or significant disability/incapacity, or required prolonged patient hospitalization.

A potential causal relationship was determined by the investigators, and the reason for the decision on causality was recorded in the electronic case report form.

Changes in vital signs, electrocardiogram, physical examination and laboratory test results were to be recorded as an (S)AE in the electronic case report form if they were judged clinically relevant by the investigator. Changes in laboratory parameters were considered as having potential safety implications if they showed potentially clinically significant abnormalities post-baseline or represented shifts from normal baseline values during the double-blind or long-term extension period.

### Adherence

Adherence was assessed at each visit of the double-blind study period and the long-term extension period by asking patients how many of the scheduled tablets or capsules they had taken. The number of tablets or capsules taken was divided by the number scheduled and multiplied by 100 to obtain a percentage compliance rate.

### Positional hemodynamic changes

The changes in DBP, SBP and pulse rate during the change from a supine position to a standing position (at weeks 0, 8 and 60), changes in the seated pulse rate (every visit) and changes in the pulse rate measured by ABPM (at weeks 0 and 8) were not clinically relevant.

### Statistical analyses

The sample size of 130 patients in this trial was determined based on the following calculation. A sample size of 124 evaluable patients (62 per treatment

group) found to be adequate to demonstrate the superiority of the T80/A5/H12.5 group to the T80/H12.5 group with a two-sided significance level of 5% and 90% power, assuming a difference of seated DBP reduction between the T80/A5/H12.5 group and the T80/H12.5 group of 5.0 mm Hg and a s.d. of 8.5 mm Hg.

An analysis of covariance (ANCOVA) model was used to assess the treatment effects. The results are presented as the adjusted means, with treatment and center as fixed effects and the reference baseline as a linear covariate. The last observation carried forward (LOCF) approach was used to impute missing data. The ANCOVA model was used to analyze BP reductions 8 weeks after treatment with either T80/A5/H12.5 or T80/H12.5.

The test for the treatment effect (that is, the difference in the DBP reduction between treatment groups) was based on an F-statistic with the residual sum of squares from the model as the denominator. The treatment effect was estimated by the adjusted mean and its 95% confidence interval (CI).

Six analysis sets were defined for analyzing the trial data. Patients in non-compliance with GCP were excluded from all analysis sets. The treated set (TS) was defined as a collection of patients (i) randomly assigned to one of two treatment groups and (ii) taking at least one dose of either T80/A5/H12.5 or T80/H12.5 during the double-blind period. The full analysis set (FAS) was defined as those patients conforming to the intent-to-treat principle, who were (i) included in the TS and (ii) underwent measurements of seated DBP at the reference baseline and at one or more time points during the double-blind period. The per-protocol set (PPS) was defined as a collection of patients (i) included in the FAS and (ii) observing no important protocol violation that might affect the efficacy evaluation during the double-blind period. The ABPM set was defined as all patients (i) included in the TS; (ii) who underwent baseline and post-baseline ABPM measurements during the double-blind period, satisfying the successful monitoring criteria for ABPM measurement; and (iii) who did not meet the criterion of important violations for night-time workers. The TS for T80/A5/H12.5 (TS for T80/A5/H12.5) was defined as a collection of patients taking at least one dose of T80/A5/H12.5 during the double-blind period or the extension period. The FAS in the extension period (FASEX) was defined as all patients included in the FAS who took at least one dose of T80/A5/H12.5 in the extension period and whose seated DBP was measured at the reference baseline and at one or more time during the extension period.

The findings were verified using a sensitivity analysis with the PPS and using a mixed-effects model for repeated measures on the FAS without using the LOCF approach. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for the statistical analyses.

## RESULTS

### Patients

We enrolled 239 male and female Japanese patients in the study. Of these, 132 patients had uncontrolled BP despite treatment with T80/H12.5 during the run-in period (Figure 2). These patients had a mean seated DBP of 97.1 mm Hg and a mean seated SBP of 143.4 mm Hg at reference baseline. All patients had a seated DBP  $\geq 90$  mm Hg, and 61.4% of patients had a seated SBP  $\geq 140$  mm Hg at reference baseline. These baseline values were well-balanced between the treatment groups. Patients were randomly assigned to the study medication; 68 patients were assigned to receive T80/A5/H12.5, and 64 patients were assigned to receive T80/H12.5. The demographic and baseline characteristics were generally similar between the two treatment groups (Table 1). Most patients were male (78.8%), and most were aged  $< 65$  years (82.6%); the mean (s.d.) age was 55.2 (9.2) years. The severity of hypertension was classified as grade I or grade II in 94.7% of patients. In addition, 89.4% of the patients had at least one concomitant diagnosis other than hypertension. The most frequently reported diagnosis was metabolic and nutrition disorders (65.2%), which included hyperuricemia (32.6%), dyslipidemia (26.5%), hyperlipidemia (14.4%) and diabetes mellitus (11.4%). The second most frequently reported diagnosis was hepatobiliary disorders

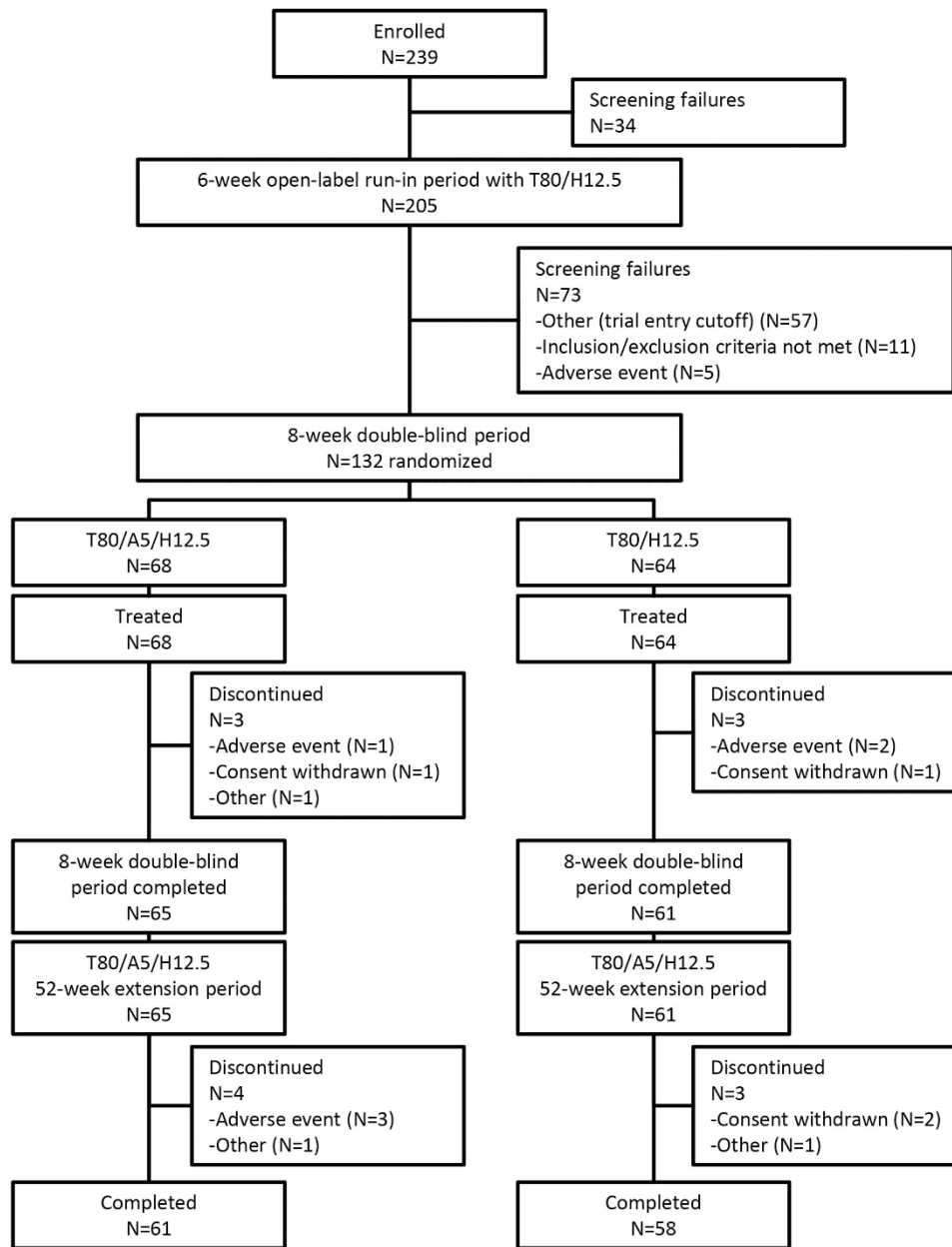


Figure 2 Patient dispositions.

(33.3%), which included hepatic steatosis (25.8%). Finally, gastrointestinal disorders (25.8%) included chronic gastritis and gastroesophageal reflux disease (both 10.6%).

Almost half of the patients were prescribed a combination of an ARB and a CCB (43.2%), followed by a combination of an ARB and a diuretic (32.6%), before enrollment.

#### Changes in the trough-seated DBP at week 8

The adjusted mean reduction in the trough-seated DBP at week 8 was 8.8 mm Hg in the T80/A5/H12.5 group and 1.3 mm Hg in the T80/H12.5 group (a difference of  $-7.5$  mm Hg; 95% CI:  $-9.7, -5.3$ ;  $P < 0.0001$ ) in the FAS, indicating the significant superiority of T80/A5/H12.5 over T80/H12.5 (ANCOVA analysis using LOCF). The sensitivity analysis in the PPS and mixed-effects model repeated

measures (MMRM) on the FAS were consistent with the primary analysis in the FAS. Figure 3a shows the adjusted mean changes in the trough-seated DBP from baseline to weeks 4 and 8 (MMRM analysis).

#### Changes in the trough-seated SBP at week 8

The adjusted mean reduction in the trough-seated SBP at week 8 was 10.6 mm Hg in the T80/A5/H12.5 group and 2.1 mm Hg in the T80/H12.5 group in the FAS (a difference of  $-8.6$  mm Hg; 95% CI:  $-12.7, -4.5$ ;  $P < 0.0001$ ) (ANCOVA analysis using LOCF). The sensitivity analysis in the PPS and MMRM on the FAS were consistent with the analysis in the FAS. Figure 3b shows the adjusted mean changes in the trough-seated SBP from baseline to weeks 4 and 8 (MMRM).

**Table 1 Demographic and baseline characteristics at week –6—treated set**

	T80/A5/H12.5	T80/H12.5	Total
N (%)	68 (100.0)	64 (100.0)	132 (100.0)
Male	55 (80.9)	49 (76.6)	104 (78.8)
Female	13 (19.1)	15 (23.4)	28 (21.2)
Age (years)			
Mean (s.d.)	56.1 (10.2)	54.4 (7.9)	55.2 (9.2)
Median (Min–Max)	56.0 (30–76)	54.5 (40–70)	55.0 (30–76)
Age categories (N (%))			
<65 years	53 (77.9)	56 (87.5)	109 (82.6)
≥65 years	15 (22.1)	8 (12.5)	23 (17.4)
Baseline BMI (kg m <sup>-2</sup> )			
Mean (s.d.)	26.87 (4.03)	26.82 (4.43)	26.85 (4.21)
Median (Min–Max)	26.46 (20.4–40.5)	26.32 (18.2–38.6)	26.42 (18.2–40.5)
BMI categories (N (%))			
<25 kg m <sup>-2</sup>	22 (32.4)	26 (40.6)	48 (36.4)
25 to <30 kg m <sup>-2</sup>	35 (51.5)	23 (35.9)	58 (43.9)
≥30 kg m <sup>-2</sup>	11 (16.2)	15 (23.4)	26 (19.7)
Abdominal obesity <sup>a</sup> (N (%))	56 (82.4)	43 (67.2)	99 (75.0)
Baseline blood pressure (mmHg)			
DBP mean (s.d.)	97.4 (6.3)	96.7 (5.6)	97.1 (5.9)
SBP mean (s.d.)	145.2 (13.9)	141.5 (10.3)	143.4 (12.4)
Duration of hypertension (N (%))			
≤1 year	10 (14.7)	9 (14.1)	19 (14.4)
>1–5 years	17 (25.0)	18 (28.1)	35 (26.5)
>5–10 years	23 (33.8)	19 (29.7)	42 (31.8)
>10 years	18 (26.5)	18 (28.1)	36 (27.3)
Hypertension severity <sup>b</sup> at baseline (N (%))			
Grade I	39 (57.4)	46 (71.9)	85 (64.4)
Grade II	25 (36.8)	15 (23.4)	40 (30.3)
Grade III	4 (5.9)	3 (4.7)	7 (5.3)
eGFR (ml min <sup>-1</sup> per 1.73 m <sup>2</sup> ) (N (%))			
≥90 (normal)	7 (10.3)	4 (6.3)	11 (8.3)
≥60 to <90 (mild)	46 (67.6)	48 (75.0)	94 (71.2)
≥30 to <60 (moderate)	15 (22.1)	12 (18.8)	27 (20.5)
<30 (severe)	0 (0.0)	0 (0.0)	0 (0.0)
Concomitant diagnoses (N (%))	62 (91.2)	56 (87.5)	118 (89.4)
Number of previous antihypertensives used (N (%))			
Two	58 (85.3)	56 (87.5)	114 (86.4)
Three	9 (13.2)	8 (12.5)	17 (12.9)
Previous antihypertensive therapies (N (%))			
Diuretics/Ca <sup>++</sup> antagonists	2 (2.9)	5 (7.8)	7 (5.3)
Diuretics/ARB	21 (30.9)	22 (34.4)	43 (32.6)
ACE – inhibitors/Ca <sup>++</sup> antagonists	4 (5.9)	2 (3.1)	6 (4.5)
Ca <sup>++</sup> antagonists/ARB	30 (44.1)	27 (42.2)	57 (43.2)
Ca <sup>++</sup> antagonists/other	1 (1.5)	0 (0.0)	1 (0.8)
Diuretics/Beta – blocking agents/ARB	1 (1.5)	0 (0.0)	1 (0.8)
Diuretics/Ca <sup>++</sup> antagonists/ARB	8 (11.8)	6 (9.4)	14 (10.6)
Beta – blocking agents/Ca <sup>++</sup> antagonists/ARB	0 (0.0)	1 (1.6)	1 (0.8)
Ca <sup>++</sup> antagonists/ARB/other	0 (0.0)	1 (1.6)	1 (0.8)

Abbreviations: ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

T80/A5/H12.5, patients randomized to telmisartan 80 mg/hydrochlorothiazide 12.5 mg+amlodipine 5 mg in the double-blind treatment period; T80/H12.5, patients randomized to telmisartan 80 mg/hydrochlorothiazide 12.5 mg+placebo in the double-blind treatment period.

<sup>a</sup>Abdominal obesity, baseline waist circumference >85 cm (male) and >90 cm (female).

<sup>b</sup>Hypertension severity: Grade I, seated SBP 140 to <160 mm Hg or seated DBP 90 to <100 mm Hg; Grade II, seated SBP 160 to <180 mm Hg or seated DBP 100 to <110 mm Hg; Grade III, seated SBP ≥180 mm Hg or seated DBP ≥110 mm Hg.

### Changes in the trough-seated DBP and SBP in the extension period

The changes in the trough-seated DBP and SBP (other secondary endpoints) during the 52-week extension period are shown in Figure 3c and Figure 3d, respectively. The BP-lowering effects observed at week 8 were maintained during the extension period.

### The proportion of patients with DBP <90 mm Hg and SBP <140 mm Hg at weeks 8 and 60

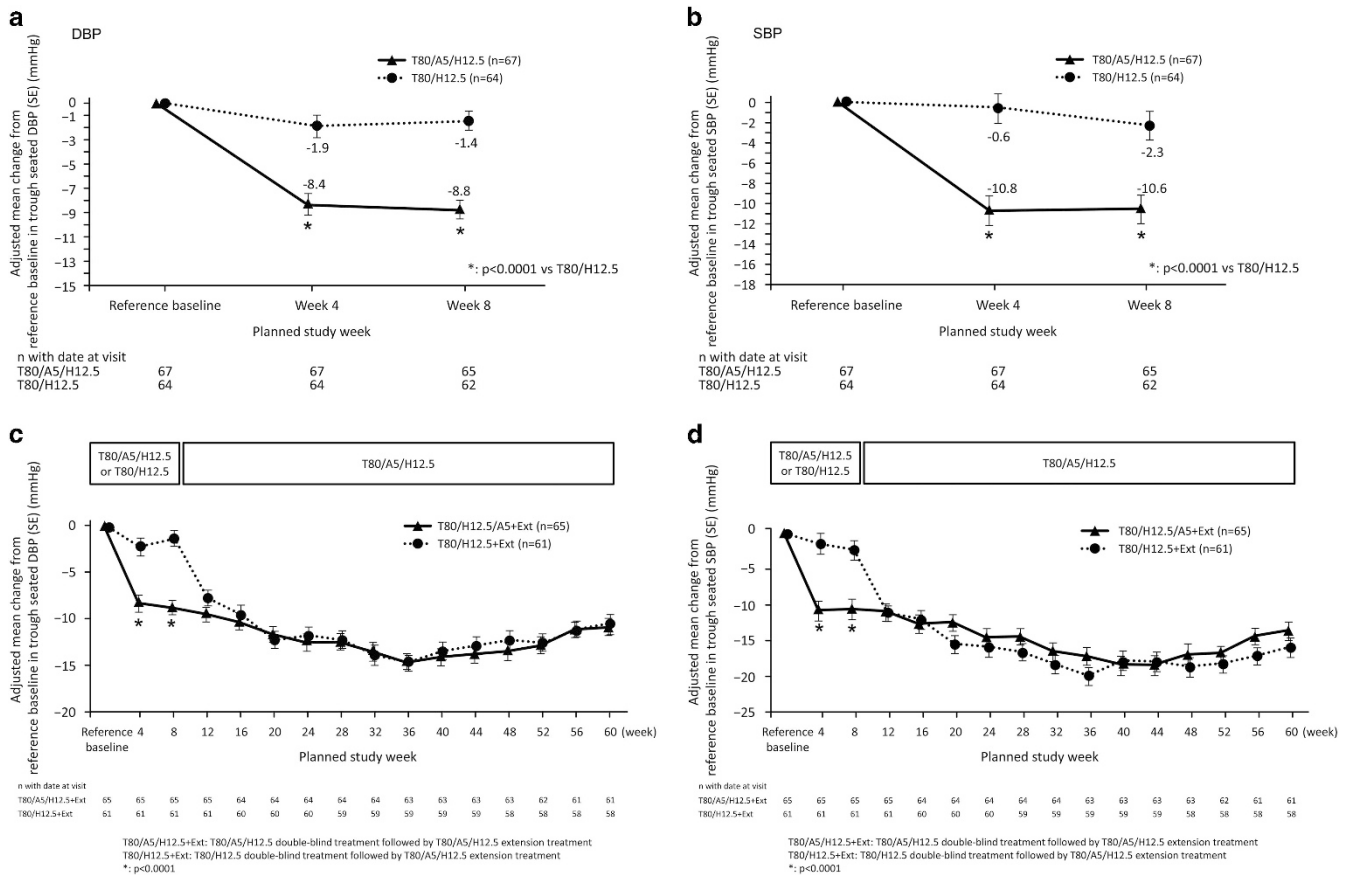
The percentage of patients who achieved a trough-seated DBP/SBP <90/140 mm Hg at week 8 of the double-blind period was 44.8%

(30 of 67 patients) in the T80/A5/H12.5 group and 21.9% (14 of 64 patients) in the T80/H12.5 group. At week 60, the percentage was 63.1% (41 of 65 patients) in the T80/A5/H12.5 group and 54.1% (33 of 61 patients) in the T80/H12.5 group (Table 2).

### The proportions of patients with a seated DBP <90 mm Hg and a seated SBP of <140 mm Hg at weeks 8 and 60

The proportions of patients in each group with a seated DBP <90 mm Hg or a seated SBP of <140 mm Hg at weeks 8 and 60 are shown in Table 2.





**Figure 3** The adjusted mean changes in the trough-seated diastolic blood pressure from baseline to weeks 4 and 8 of treatment in the FAS (a), in the trough-seated SBP from baseline to weeks 4 and 8 of treatment in the FAS (b), in the trough-seated diastolic blood pressure from baseline during the double-blind period and the open-label extension in the FASEX (c), and in the trough-seated systolic blood pressure from baseline during the double-blind period and the open-label extension in the FASEX (d). Findings were verified using a sensitivity analysis with the per-protocol set and using a mixed-effects model for repeated measures on the full analysis set with no imputation. T80/A5/H12.5, patients randomly assigned to 80 mg telmisartan/12.5 mg hydrochlorothiazide+5 mg amlodipine; T80/H12.5, patients randomly assigned to 80 mg telmisartan/12.5 mg hydrochlorothiazide+placebo. FAS, full analysis set; FASEX, full analysis set in the extension period; SBP, systolic blood pressure.

The proportions of patients in each group with a DBP reduction of  $\geq 10$  mm Hg or SBP reduction of  $\geq 20$  mm Hg at weeks 8 and 60 are also shown in Table 2.

The reductions in seated DBP and/or seated SBP observed at week 8 were maintained in the 52-week extension period.

#### Ambulatory BP changes at week 8

The adjusted mean change from baseline in DBP after 8 weeks of double-blind treatment as measured by the 24-h ABPM was  $-7.0$  mm Hg in the T80/A5/H12.5 group and  $-0.7$  mm Hg in the T80/H12.5 group in the ABPM set (a difference of  $-6.2$  mm Hg; 95% CI:  $-8.6, -3.8$ ;  $P < 0.0001$ ). The corresponding changes in SBP were  $-9.9$  and  $-1.3$  mm Hg (a difference of  $-8.6$  mm Hg; 95% CI:  $-13.0, -4.1$ ;  $P = 0.0002$ ).

#### Subgroup analyses

The primary endpoint (trough-seated DBP at week 8) and the key secondary endpoint (trough-seated SBP at week 8) were also analyzed in subgroups of patients divided by age ( $< 65, \geq 65$  years), sex (male, female), BMI ( $< 25, 25$  to  $< 30, \geq 30$  kg  $m^{-2}$ ), hypertension severity (Grade I, II, III) and hypertension duration ( $\leq 1, > 1$  to  $5, > 5$  to  $10,$

$> 10$  years) (Supplementary Tables 1 and 2). All subgroup analyses showed that the reductions in the trough-seated DBP and SBP at week 8 were greater in the T80/A5/H12.5 group than in the T80/H12.5 group, although the differences between treatments were small in some of the subgroups divided by hypertension duration and hypertension severity.

#### Safety

**Eight-week double-blind period.** The most common AEs reported in each group in the 8-week double-blind period are shown in Table 3. The proportion of patients who experienced AEs during this period was similar in both groups. No SAEs were reported in either group. Drug-related AEs were reported in one patient in each group (loss of consciousness in the T80/A5/H12.5 group and increased uric acid in the T80/H12.5 group). No deaths or other SAEs were reported during the double-blind period.

One AE was related to laboratory variables ( $\gamma$ -glutamyltransferase increase), which occurred in one (1.6%) patient in the T80/H12.5 group. One patient in the T80/H12.5 group in the double-blind period had increased uric acid that was considered treatment related.

**Table 2** Trough-seated blood pressure control and response rates after 8 and 60 weeks of treatment—full analysis set in the extension period

	T80/A5/H12.5		T80/H12.5 <sup>a</sup>	
	n	Achieved n (%)	n	Achieved n (%)
<i>BP control rates</i>				
DBP <90 mm Hg at week 8	65	36 (55.4)	61	16 (26.2)
DBP <90 mm Hg at week 60		43 (66.2)		34 (55.7)
SBP <140 mm Hg at week 8	42	23 (54.8)	34	11 (32.4)
SBP <140 mm Hg at week 60		27 (64.3)		26 (76.5)
<i>BP response rates</i>				
DBP <90 mm Hg or ≥10 mm Hg decrease from baseline at week 8	65	42 (64.6)	61	18 (29.5)
DBP <90 mm Hg or ≥10 mm Hg decrease from baseline at week 60		48 (73.8)		40 (65.6)
SBP <140 mm Hg or ≥20 mm Hg decrease from baseline at week 8	42	26 (61.9)	34	11 (32.4)
SBP <140 mm Hg or ≥20 mm Hg decrease from baseline at week 60		30 (71.4)		26 (76.5)
<i>DBP/SBP &lt; 90/140 mm Hg rates</i>				
SBP <140 mm Hg and DBP <90 mm Hg at week 8	65	30 (46.2)	61	13 (21.3)
SBP <140 mm Hg and DBP <90 mm Hg at week 60		41 (63.1)		33 (54.1)

Abbreviations: A5, amlodipine 5 mg; BP, blood pressure; DBP, diastolic blood pressure; H12.5, hydrochlorothiazide 12.5 mg; SBP, systolic blood pressure; T80, telmisartan 80 mg. Values are presented as n (%).

T80/A5/H12.5, patients who took T80/A5/H12.5 in the double-blind treatment period and in the extension period (weeks 8 and 60).

T80/H12.5, patients who took T80/H12.5 in the double-blind treatment period (week 8) and T80/A5/H12.5 in the extension period (week 60).

<sup>a</sup>Patients who took T80/H12.5 in the double-blind treatment period (week 8) and T80/A5/H12.5 in the extension period (week 60).

There were no other significant changes in laboratory variables in either treatment group (Supplementary Table 3a) in the double-blind treatment period. No AEs related to renal function or noteworthy shifts in renal function occurred during the double-blind period.

*Eight-week double-blind and/or 52-week open-label extension period.* AEs were experienced by 91/129 (70.5%) patients. Severe AEs were experienced by two (1.6%) patients, both of whom took T80/A5/H12.5 and T80/H12.5 in the double-blind period. Drug-related AEs were experienced by five patients who took T80/A5/H12.5 throughout the entire period of this study. Two patients (one in each treatment group) developed hyperuricemia. One patient who took T80/A5/H12.5 in the double-blind period was withdrawn from the trial after a fall resulting from dizziness, which may have been a result of a seasonal reduction in BP exacerbated by the study medication. There were no deaths.

There were no other significant changes in the laboratory variables in either treatment group (Supplementary Table 3b), and no AEs related to renal function or noteworthy shifts in renal function occurred.

*Adherence.* The overall compliance during the double-blind period and the entire period (double-blind period+extension period) was good in both treatment groups. A compliance rate of <80% occurred in one patient in the T80/A5/H12.5 group during the double-blind period. There was no patient with a compliance rate of <80% in either the T80/H12.5 group or the T80/A5/H12.5 group during the 52-week extension period.

*Positional hemodynamic changes and other safety parameters.* There were no clinically relevant changes from baseline in the pulse rate during treatment, or in DBP, SBP or the pulse rate due to position changes (from supine to standing), in either group, in either the double-blind or open-label extension periods (Supplementary Table 4).

## DISCUSSION

In this study, 8 weeks of treatment with T80/A5/H12.5 significantly reduced the trough-seated DBP and SBP compared with treatment with T80/H12.5, in patients with symptoms that were uncontrolled with T80/H12.5 in a run-in period. The T80/A5/H12.5 combination remained effective for the duration of the 52-week open-label extension period.

Varying combinations of CCBs, ARBs and diuretics have yielded similar results in other long-term studies. Balraj *et al.*<sup>13</sup> reported the results of a study in which patients with hypertension that was previously uncontrolled on two agents received 40 mg telmisartan, 5 mg amlodipine and 12.5 mg hydrochlorothiazide. The participants in their trial had a significantly reduced DBP and SBP compared with baseline levels after 30, 60 and 120 days of treatment.<sup>13,14</sup> In addition, as a result of the add-on effect of hydrochlorothiazide in a short-term study, Rakugi *et al.*<sup>15</sup> found that treatment with 50 mg losartan+12.5 mg hydrochlorothiazide +5 mg amlodipine for 8 weeks did not result in a significant difference in DBP reduction but did show a significant difference in SBP reduction compared with 50 mg losartan+5 mg amlodipine.

A greater proportion of patients in the T80/A5/H12.5 group achieved BP control or response than in the T80/H12.5 group, with more patients in the T80/A5/H12.5 group achieving a DBP of <90 mm Hg and/or an SBP of <140 mm Hg or a reduction in DBP of >10 mm Hg and/or SBP of >20 mm Hg (Table 2). The importance of the achievement of adequate BP control cannot be overestimated, given the marked relationship between high BP and stroke and other cardiovascular diseases.

ABPM is an accurate and useful measurement for the diagnosis and management of hypertension. ABPM data can contribute to the identification of early-morning hypertension and excessive BP variability, both of which are associated with cardiovascular events. In this study, the average 24-h SBP and DBP were significantly lower in the T80/A5/H12.5 group compared with the T80/H12.5 group after

**Table 3** Frequency of adverse events experienced by 2% or more of the patients in any one of the treatment group and all treatment-related adverse events during the 8-week double-blind trial (treated set) and long-term treatment period (treated set for T80/A5/H12.5)

	8-week double-blind period		8-week double-blind and/or open-label extension period	
	T80/A5/H12.5 (n = 68)	T80/H12.5 (n = 64)	T80/A5/H12.5 <sup>a</sup> (n = 68)	T80/H12.5 <sup>b</sup> (n = 61)
Any AE	17 (25.0)	19 (29.7)	52 (76.5)	39 (63.9)
SAEs	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)
Investigator-defined drug-related AEs	1 (1.5)	1 (1.6)	4 (5.9)	1 (1.6)
AEs leading to treatment discontinuation	0 (0.0)	2 (3.1)	3 (4.4)	0 (0.0)
<i>All AEs</i>				
Infections and infestations	11 (16.2)	10 (15.6)	38 (55.9)	29 (47.5)
Nasopharyngitis	6 (8.8)	6 (9.4)	25 (36.8)	16 (26.2)
Respiratory tract infection	3 (4.4)	1 (1.6)	4 (5.9)	2 (3.3)
Pharyngitis	1 (1.5)	0 (0.0)	2 (2.9)	3 (4.9)
Gastroenteritis	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)
Cystitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
<i>Helicobacter</i> infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Pneumonia	0 (0.0)	0 (0.0)	1 (1.5)	2 (3.3)
Bronchitis	0 (0.0)	1 (1.6)	2 (2.9)	1 (1.6)
Influenza	0 (0.0)	1 (1.6)	2 (2.9)	1 (1.6)
Upper respiratory tract infection	1 (1.5)	0 (0.0)	2 (2.9)	1 (1.6)
Metabolism and nutrition disorders	0 (0.0)	1 (1.6)	2 (2.9)	6 (9.8)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Nervous system disorders	3 (4.4)	1 (1.6)	6 (8.8)	5 (8.2)
Dizziness	0 (0.0)	0 (0.0)	2 (2.9)	1 (1.6)
Headache	2 (2.9)	0 (0.0)	2 (2.9)	1 (1.6)
Respiratory, thoracic and mediastinal disorders	2 (2.9)	2 (3.1)	13 (19.1)	5 (8.2)
Upper respiratory tract inflammation	2 (2.9)	1 (1.6)	6 (8.8)	1 (1.6)
Cough	0 (0.0)	0 (0.0)	2 (2.9)	1 (1.6)
Gastrointestinal disorders	1 (1.5)	1 (1.6)	11 (16.2)	14 (23.0)
Abdominal discomfort	1 (1.5)	0 (0.0)	2 (2.9)	3 (4.9)
Abdominal pain lower	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)
Constipation	1 (1.5)	0 (0.0)	3 (4.4)	2 (3.3)
Diarrhea	0 (0.0)	0 (0.0)	1 (1.5)	2 (3.3)
Gastroesophageal reflux disease	0 (0.0)	0 (0.0)	2 (2.9)	2 (3.3)
Large intestine polyp	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Dental caries	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)
Skin and s.c. tissue disorders	1 (1.5)	0 (0.0)	4 (5.9)	6 (9.8)
Eczema	0 (0.0)	0 (0.0)	2 (2.9)	3 (4.9)
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Musculoskeletal and connective tissue disorders	1 (1.5)	3 (4.7)	8 (11.8)	9 (14.8)
Back pain	0 (0.0)	2 (3.1)	1 (1.5)	3 (4.9)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Musculoskeletal pain	1 (1.5)	0 (0.0)	2 (2.9)	0 (0.0)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (1.6)	3 (4.4)	4 (6.6)
Chest pain	0 (0.0)	1 (1.6)	1 (1.5)	2 (3.3)
Injury, poisoning and procedural complications	3 (4.4)	0 (0.0)	11 (16.2)	2 (3.3)
Fall	1 (1.5)	0 (0.0)	4 (5.9)	0 (0.0)
<i>Treatment-related AEs</i>				
All treatment-related AEs	1 (1.5)	1 (1.6)	4 (5.9)	1 (1.6)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.6)
Hyperuricemia	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.6)
Nervous system disorders	1 (1.5)	0 (0.0)	2 (2.9)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Loss of consciousness	1 (1.5)	0 (0.0)	1 (1.5)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Orthostatic hypotension	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Investigations (laboratory data abnormalities)	0 (0.0)	1 (1.6)	1 (1.5)	0 (0.0)
Blood uric acid increased	0 (0.0)	1 (1.6)	1 (1.5)	0 (0.0)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Values are presented as n (%).

T80/A5/H12.5, patients randomized to telmisartan 80 mg/hydrochlorothiazide 12.5 mg+amlodipine 5 mg in the double-blind treatment period; T80/H12.5, patients randomized to telmisartan 80 mg/hydrochlorothiazide 12.5 mg+placebo in the double-blind treatment period.

<sup>a</sup>Includes AEs that occurred in both the double-blind period and the extension period (for a total of 60 weeks) during treatment with T80/A5/H12.5.

<sup>b</sup>Includes AEs that only occurred in the extension period during treatment with T80/A5/H12.5 (for 52 weeks).

8 weeks of double-blind treatment. T80/A5/H12.5, which contains longer-acting antihypertensives, may help to prevent cardiovascular morbidity and mortality.

Subgroup analyses in our study showed that the reductions in trough-seated DBP and SBP at week 8 were greater in the T80/A5/H12.5 group than in the T80/H12.5 group regardless of age, sex and BMI, but the differences between treatment groups were small in some

of the subgroups classified by hypertension duration and hypertension severity (Supplementary Tables 1 and 2).

Seasonal variations in BP are an important consideration in the long-term treatment of hypertension. BP is lower in summer and higher in winter, and treatment with a diuretic or doses of diuretic-containing antihypertensives sometimes requires an adjustment in the summer to avoid excessive BP lowering due to



dehydration.<sup>16</sup> In our study, no seasonal effect of hypotension was observed in the summer (32–40 weeks), and there was no need to change the treatment or adjust the dose for that reason. The only exception was one patient treated with T80/A5/H12.5 who was withdrawn in the open-label extension period after a fall resulting from dizziness that may have been a result of a seasonal reduction in BP exacerbated by the study medication. Therefore, treatment with T80/A5/H12.5 is considered safe without the need for dose adjustment in the summer.

The AEs reported over the entire 60-week period showed a good tolerability profile for T80/A5/H12.5. During the double-blind period, the majority of reported AEs were mild in intensity and no serious or severe AEs or deaths were reported. Most AEs reported during long-term treatment with T80/A5/H12.5 were also mild in intensity. AEs leading to the discontinuation of trial medication were reported for three (2.3%) patients.

The combination of T80/A5/H12.5 may also improve patient adherence. All 126 patients who completed the double-blind period were entered in the extension period and treated with T80/A5/H12.5, and there were few protocol violations. A previous study demonstrated that a fixed combination of valsartan/amlodipine/hydrochlorothiazide or olmesartan/amlodipine/hydrochlorothiazide improved adherence and persistence compared with the administration of each drug as individual tablets.<sup>17,18</sup>

### Strengths and limitations

The strengths of this study are its randomized, double-blind controlled design and a sufficient sample size to appropriately assess the efficacy and safety outcomes. The 52-week extension enabled further robust evaluations of safety and efficacy. The study was conducted in Japanese patients; therefore, extrapolation of the results to other treatment populations is limited. However, our results support those from other trials that were conducted in various ethnic groups. In addition, the small number of patients in each subgroup category means that our study was not sufficiently powered to make statistical comparisons between subgroups.

### CONCLUSIONS

This Phase III study indicates that T80/A5/H12.5 is more effective than T80/H12.5 in terms of reducing BP in patients with an inadequate response to T80/H12.5 and that this combination therapy is well-tolerated. The present results provide a new treatment option for patients with a relatively severe hypertensive condition. In addition, the results may support those of previous studies, indicating that fixed combinations of ARBs, CCBs and diuretics provide effective and well-tolerated long-term treatment for hypertension and can achieve BP control in a significant number of patients.

### CONFLICT OF INTEREST

JH has received consulting and lecture fees and/or research funding from Astellas Pharm, Nippon Boehringer Ingelheim, Mochida Pharm, Daiichi Sankyo, Sumitomo Dainippon Pharma, MSD K.K., Novartis Pharma K.K., Teijin Pharma Limited and Takeda Pharmaceutical. IK has received lecture fees, research funding and/or scholarship grants from Daiichi Sankyo, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Astellas Pharma, Teijin Pharma Limited, Sanofi K.K., Kowa Company, Bayel Yakuhin, TOA EIYO and Takeda Pharmaceutical. The remaining authors declare no conflict of interest. JH and IK were the medical experts and TO was the coordinating investigator of this study. KS, HU, AT, HI, DK and SN are employees of Nippon Boehringer Ingelheim.

### ACKNOWLEDGEMENTS

We would like to thank all of the investigators who contributed to this study, including the following Principal Investigators and their institutions: Hideki Makino, MD (Makino Clinic); Hiroshi Morinaga, MD (Morinaga Clinic); Masaya Kino, MD (Hokutsu General Hospital); Hikaru Ishii, MD (Shin-Nihonbashi Ishii Clinic); Yoshimasa Noguchi, MD (Noguchi Naika Clinic); Ryuji Yoshimura, MD (Yoshimura Internal Medicine); Hiroaki Yamamoto, MD (Gakkentoshi Clinic); Tadahiko Ogasawara, MD (Saikatsu Clinic); Kazuhiro Harada, MD (Kasaoka Daiichi Hospital); Hiroshi Kataoka, MD and Hidekazu Irie, MD (Hirakata Kohsai Hospital); Yo Kawamura, MD (Tokyo Daiya Building Clinic); Satoshi Kaneta, MD (Ono Clinic); Akiu Koh, MD (Koh Internal Medicine Clinic); Koji Okamoto, MD (Okamoto Clinic); Hiroya Tanaka, MD (Tanaka Clinic); Kousuke Mabuchi, MD (Kanda Clinic); and Arihiro Kiyosue, MD (Tokyo-Eki Center-building Clinic). The study drugs were developed by Nippon Boehringer Ingelheim. This study was supported by Nippon Boehringer Ingelheim. We thank Mami Mori of Nippon Boehringer Ingelheim for publication management and editorial support, and John Gibbins and Marion Barnett of Edanz Group for providing medical writing support. Clinical trial registration: NCT0191780. This study was funded by Nippon Boehringer Ingelheim.

- 1 Shimamoto K, Ando K, Fujita T, Hasebe N, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ishimitsu T, Ito M, Ito S, Itoh H, Iwao H, Kai H, Kario K, Kashiwara N, Kawano Y, Kim-Mitsuyama S, Kimura G, Kohara K, Komuro I, Kumagai H, Matsuura H, Miura K, Morishita R, Naruse M, Node K, Ohya Y, Rakugi H, Saito I, Saitoh S, Shimada K, Shimosawa T, Suzuki H, Tamura K, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Umemura S, Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253–390.
- 2 Ikeda N, Saito E, Kondo N, Inoue M, Ikeda S, Satoh T, Wada K, Stickley A, Katanoda K, Mizoue T, Noda M, Iso H, Fujino Y, Sobue T, Tsugane S, Naghavi M, Ezzati M, Shibuya K. What has made the population of Japan healthy? *Lancet* 2011; **378**: 1094–1105.
- 3 Fujiyoshi A, Ohkubo T, Miura K, Murakami Y, Nagasawa SY, Okamura T, Ueshima H, Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Blood pressure categories and long-term risk of cardiovascular disease according to age group in Japanese men and women. *Hypertens Res* 2012; **35**: 947–953.
- 4 Kario K. Proposal of a new strategy for ambulatory blood pressure profile-based management of resistant hypertension in the era of renal denervation. *Hypertens Res* 2013; **36**: 478–484.
- 5 Ueshima H, Sekikawa A, Miura K, Turin TC, Takahama N, Kita Y, Watanabe M, Kadota A, Okuda N, Kadowaki T, Nakamura Y, Okamura T. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation* 2008; **118**: 2702–2709.
- 6 Miura K. Comprehensive research business on strategies to prevent/treat cardiovascular disease/lifestyle-related diseases such as diabetes mellitus by a scientific grant/subsidy from the Ministry of Health, Labour and Welfare, 'Research on the start of follow-up of the subjects of the 2010 National Health and Nutrition Survey (NIPPON DATA2010) and continuation of NIPPON DATA80/90 follow-up', Comprehensive/project study reports in 2012. 2013 Ministry of Health, Labour and Welfare, Japan. (In Japanese).
- 7 Miura K, Nagai M, Ohkubo T. Epidemiology of hypertension in Japan. *Circ J* 2013; **77**: 2226–2231.
- 8 Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007; **120**: 713–719.
- 9 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.
- 10 Shiga Y, Miura S, Mitsutake R, Norimatsu K, Nagata I, Arimura T, Shimizu T, Mori J, Kuwano T, Uehara Y, Inoue A, Shirohata T, Fujisawa K, Matsunaga E, Saku K. Efficacy and safety of a single-pill fixed-dose combination of high-dose telmisartan/hydrochlorothiazide in patients with uncontrolled hypertension. *J Renin Angiotensin Aldosterone Syst* 2012; **13**: 394–400.
- 11 Bays H, Zhu D, Schumacher H. Single-pill combination of telmisartan and hydrochlorothiazide: studies and pooled analyses of earlier hypertension treatment. *High Blood Press Cardiovasc Prev* 2014; **21**: 119–126.
- 12 Webb AJ, Rothwell PM. Effect of dose and combination of antihypertensives on interindividual blood pressure variability: a systematic review. *Stroke* 2011; **42**: 2860–2865.
- 13 Balraj MS, Faruqui AA. Efficacy and safety of triple drug fixed-dose combination of telmisartan, amlodipine and hydrochlorothiazide in the management of hypertension. *Int J Res Med Sci* 2015; **3**: 1858–1862.
- 14 Maladkar M, Verma VK, Narsikar KA, Walinjkar RD, Patil WR, Saggau NJS, Kulkarni SP. Triple drug combination of telmisartan, amlodipine and hydrochlorothiazide in the treatment of essential hypertension. *Open J Intern Med* 2012; **2**: 67–71.

- 15 Rakugi H, Tsuchihashi T, Shimada K, Numaguchi H, Nishida C, Yamaguchi H, Shirakawa M, Azuma K, Fujita KP. Add-on effect of hydrochlorothiazide 12.5 mg in Japanese subjects with essential hypertension uncontrolled with losartan 50 mg and amlodipine 5 mg. *Hypertens Res* 2015; **38**: 329–335.
- 16 Shiga Y, Miura S, Adachi S, Suematsu Y, Sugihara M, Iwata A, Yahiro E, Nishikawa H, Ogawa M, Saku K. Visit-to-visit variability and seasonal variation in blood pressure with single-pill fixed-dose combinations of angiotensin II receptor blocker/calcium channel blocker and angiotensin II receptor blocker/diuretic in hypertensive patients. *J Clin Med Res* 2015; **7**: 802–806.
- 17 Machnicki G, Ong SH, Chen W, Wei ZJ, Kahler KH. Comparison of amlodipine/valsartan/hydrochlorothiazide single pill combination and free combination: adherence, persistence, health care utilization and costs. *Curr Med Res Opin* 2015; **23**: 1–29.
- 18 Mohan JC, Jain R, Chamle V, Bhargava A. Short Term Safety and Tolerability of a Fixed Dose Combination of Olmesartan, Amlodipine and Hydrochlorothiazide. *J Clin Diagn Res* 2015; **9**: OC10–OC13.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

© The Author(s) 2017

Supplementary Information accompanies the paper on Hypertension Research website (<http://www.nature.com/hr>)