I-COMBINE Study: Assessment of Efficacy and Safety Profile of Irbesartan/Amlodipine Fixed-Dose Combination Therapy Compared With Amlodipine Monotherapy in Hypertensive Patients Uncontrolled With Amlodipine 5 mg Monotherapy: A Multicenter, Phase III, Prospective, Randomized, Open-Label With Blinded–End Point Evaluation Study

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ABSTRACT

Background: Hypertension guidelines recommend the use of 2 agents with synergistic action when >1 agent is needed to achieve blood pressure goals. Newer antihypertensive treatment combinations include fixed-dose combinations of an angiotensin receptor blocker and a calcium channel blocker.

Objective: The I-COMBINE study aimed to determine whether the antihypertensive efficacy of the fixed-dose combination irbesartan 150 mg/amlodipine 5 mg (I150/A5) was superior to that of amlodipine 5 mg (A5) monotherapy in lowering home systolic blood pressure (HSBP) after 5 weeks' treatment.

Methods: The I-COMBINE study was a 10-week, multicenter, Phase III, prospective, randomized, parallel-group, open-label with blinded–endpoint study. The main inclusion criterion was essential uncontrolled hypertension (SBP ≥145 mm Hg at office, after at least 4 weeks of A5 monotherapy administered once daily). Patients continued to receive A5 for 7 to 10 days and were randomized to either monotherapy with A5 for 5 weeks then amlodipine 10 mg (A10) for the next 5 weeks or to a fixed-dose combination therapy (I150/A5 then I150/A10). Safety profile was assessed by recording adverse events reported by patients or observed by the investigator.

Results: Following enrollment, 290 patients were randomized to treatment, and 287 (mean [SD] age, 57.3 [11.2] years; 48% male) were included in the intention-to-treat analysis: 144 patients treated with I150/A5 then I150/A10, and 143 patients treated with A5 then A10. At randomization, mean HSBP was similar in both groups: 148.5 (10.3) mm Hg in the I150/A5 group and 149.2 (9.7) mm Hg in the A5 group. At week 5, the adjusted mean difference in HSBP between groups was −6.2 (1.0) mm Hg ($P < 0.001$). The proportion of controlled patients (mean home blood pressure <135 and 85 mm Hg) was significantly higher in the I150/A5 group than in the A5 group ($P < 0.001$). Treatment-emergent adverse events were experienced by 13.8% of I150/A5-treated patients and 11.9% of A5-treated patients during the first 5-week period, and by 15.8% of I150/A10-treated patients and 17.0% of A10-treated patients during the second 5-week period. Two serious adverse events were reported with the fixed-dose combination; both patients recovered.

Conclusions: Data from this adult population with essential hypertension suggest greater efficacy with the fixed-dose combination I150/A5 over A5 monotherapy in lowering SBP after 5 weeks. Both treatment regimens were well tolerated throughout the study. ClinicalTrials.gov identifier: NCT00956644. (*Clin Ther*. 2012;34: 1705–1719)

Key words: Home blood pressure monitoring, self blood pressure measurement, angiotensin II receptor antagonists, irbesartan/amlodipine.

INTRODUCTION

Effective interventions to lower blood pressure (BP) have been found to reduce the risk for cardiovascular events,[1–3] and systolic BP (SBP) may be a particularly

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more important target for treatment, as suggested by large-scale review of antihypertensive clinical trials in which reductions in SBP were directly correlated with a reduction in the risk for cardiovascular mortality.[4,5]

In most trials, a combination of 2 or more drugs was the most widely used treatment regimen to reduce BP effectively and to reach the predetermined goal.[1] Use of combination therapy with 2 agents having complementary mechanisms of action is reportedly more effective than monotherapy and may improve tolerability related to dose-dependent adverse effects and compliance by reducing treatment complexity.[1,6,7]

Treatment guidelines note that the combination of an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB) provide an effective option for patients with hypertension.[1] ARB/CCB combinations incorporate monotherapy components that act via complementary mechanisms[6] and therefore achieve greater sustained BP reductions than when the respective monocomponents are administered alone.[8–11] Benefits in tolerability, such as edema reduction, may also be gained when an ARB is added to a CCB.[12]

Irbesartan is a highly selective and potent ARB associated with clinically significant reductions in BP and a favorable tolerability profile.[13] Amlodipine is a long-acting dihydropyridine CCB that is effective for the treatment of hypertension.[14,15] Therefore, the combination therapy of irbesartan and amlodipine is expected to provide enhanced efficacy in patients whose disease is not adequately controlled by using amlodipine monotherapy alone. To the best of our knowledge, no clinical trial has investigated this hypothesis using irbesartan.

The current clinical trial (I-COMBINE) was a Phase III study conducted as part of the clinical development program for the registration of a new fixed-dose combination of irbesartan and amlodipine for the treatment of hypertension. We investigated whether the antihypertensive effect, as assessed by using home BP measurements (HBPM), of the fixed-dose combination therapy of irbesartan and amlodipine 150 mg/5 mg (I150/A5) was superior to that of amlodipine 5 mg (A5) alone in hypertensive patients whose condition was insufficiently controlled with A5 monotherapy.

PATIENTS AND METHODS

Patient Selection

This multicenter, parallel-group, prospective, randomized, open-label, blinded–end point study was conducted in 12 countries from July 2009 to August 2010. The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol also complied with the laws and regulations, as well as any applicable guidelines, of the 12 countries in which the study was conducted. It was submitted to independent ethics committees and institutional review boards for review and written approval. Written informed consent was obtained before the conduct of any study-related procedures.

Key inclusion criteria applied at screening included the following: men or women at least 18 years of age; established essential hypertension; treatment with A5 monotherapy for at least 4 weeks; and SBP ≥145 mm Hg assessed by using office BP measurements (OBPM) after 4 weeks. Key exclusion criteria at screening included: mean office SBP ≥180 mm Hg and/or mean diastolic BP (DBP) ≥110 mm Hg measured at visit 1; known or suspected causes of secondary hypertension; patients with bilateral artery stenosis, renal artery stenosis in a solitary kidney, renal transplant, or only 1 functioning kidney; known contraindications or hypersensitivity to either amlodipine or irbesartan or to the combination or history of angioedema related to the administration of an ARB or any combination of the drugs used; known type 1 diabetes; known severe hepatic cytolysis (alanine aminotransferase or aspartate aminotransferase level >5 times the upper limit of normal or history of hepatic encephalopathy, esophageal varices, or portacaval shunt); known severe renal failure (estimated glomerular filtration rate <30 mL/min determined by using the Cockroft and Gault formula[16]); concomitant use of any other antihypertensive treatment; administration of any other investigational drug within 30 days before inclusion; inability to obtain a valid automatic BP recording during the first period of measurement; presence of any severe medical or psychological condition which, in the opinion of the investigator, indicates that participation in the study is not in the best interest of the patient; and the presence of any other conditions (eg, geographical, social) that would restrict or limit the patient's participation for the duration of the study. Pregnant or breastfeeding women, as well as women of childbearing potential unable or unwilling to use an acceptable method to avoid pregnancy for the entire study period, were also excluded.

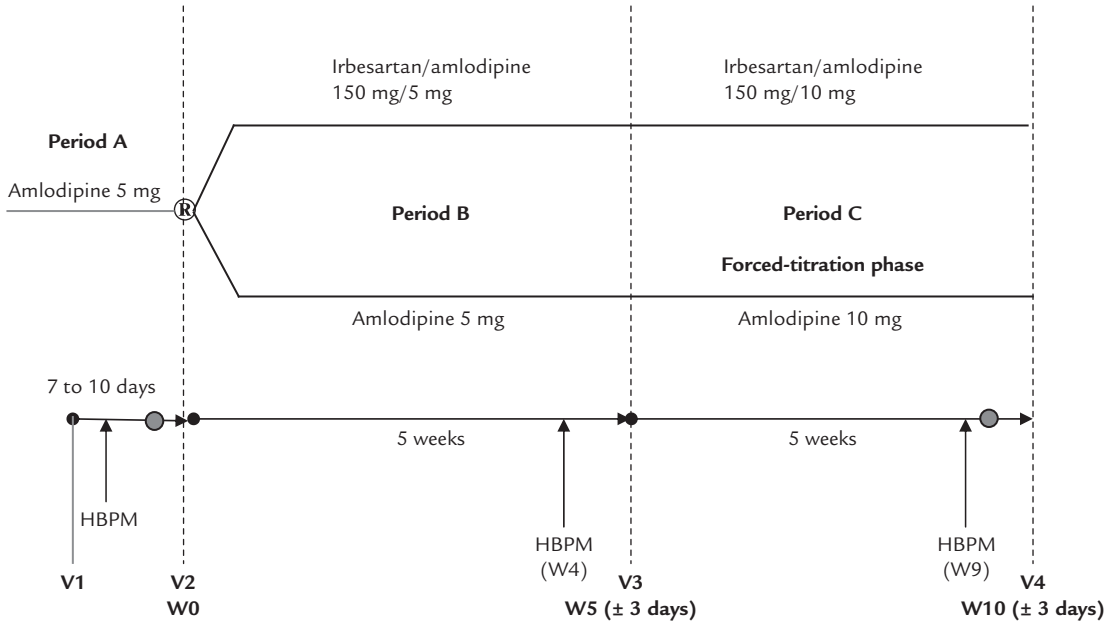

Figure 1. Study design. HBPM = home blood pressure measurement. V = visit; W = week.

Patients were randomized by using an interactive voice response system according to the following criteria: mean SBP ≥135 mm Hg assessed by using HBPM at the end of period A (treatment with A5 monotherapy for 7 to 10 days); good compliance with the HBPM protocol defined as at least 12 correct measurements performed over the last 6 days of the first period of measurements; and an estimated glomerular filtration rate ≥30 mL/min.

Study Design

The study design is displayed in Figure 1. This was a 10-week, multicenter, prospective, randomized open-label, parallel-group, Phase III study with a blinded–end point evaluation (HBPM).

Investigators were supplied with the following investigational products: A5 and amlodipine 10 mg (A10) and the fixed-dose combinations I150/A5 and irbesartan 150 mg/amlodipine 10 mg (I150/A10).

After at least 4 weeks of A5 monotherapy administered orally once a day, patients with a mean office SBP ≥145 mm Hg were given A5 at visit 1 for 7 to 10 days (period A) in an open-label fashion. The patient was instructed to begin the treatment on the day after the visit and to take 1 tablet once daily in the morning. No investigational product was to be taken on the morning of visit 2.

At visit 2 (W0), if randomization criteria were met, patients were randomized by using a central randomization procedure (1:1) either to A5 monotherapy or to the fixed-dose combination therapy I150/A5 for 5 weeks (period B). The investigator called the interactive voice response system center to obtain the treatment group of the patient. Patients were considered randomized after being assigned to a treatment group.

Patients took 1 tablet orally once a day from visit 2 for 5 weeks until visit 3.

At visit 3 (W5), patients treated with A5 monotherapy were provided with A10 monotherapy (forced titration). Patients treated with the I150/A5 fixed-dose combination were supplied with the I150/A10 fixed-dose combination (forced titration).

Patients took 1 tablet orally once a day from visit 3 for 5 weeks until visit 4 (period C). No investigational product was to be taken on the morning of visits 3 and 4.

Patients were not blinded to the treatment randomly assigned to them. However, BP measurements recorded through automatic BP monitoring were evaluated independently during data management, which supported an open-label treatment administration.

Patients were provided treatment and evaluations without charge. Physicians received honoraria for their

participation in this clinical study for entering patients' information (anonymized) into the study case-report forms.

Patients could withdraw from the study, before study completion if they decided to do so, at any time and irrespective of the reason, or they could be withdrawn at the investigator's discretion. Patients were assessed by using the procedure normally planned for the end-of-study visit. All study withdrawals had to be recorded by the investigator in the appropriate pages of the case-report form.

Outcome Measures

Home BP Measurements

All patients underwent a structured educational program during visit 1 to be able to self-manage BP measurements according to a standard procedure. At home, patients were asked to record the measurement time and results (SBP, DBP) in the diary cards and to staple all printouts in the diary cards. During the week before visits 2, 3, and 4, patients performed HBPM by using an automatic BP monitor (705CP-II, OMRON Healthcare Co., Ltd., Kyoto, Japan). BP measurements were recorded and evaluated independently during data management. The device used in this study had been previously validated according to the International Protocol of the European Society of Hypertension[17] and allowed a blinded evaluation of BP measurements.

Patients performed HBPM twice a day for 7 days according to a standard procedure: 2 seated measurements in the morning between 6:00 AM and 10:00 AM at 1-minute intervals, just before the study drug intake, and 2 measurements in the evening between 6:00 PM and 10:00 PM.

BP measurements began after a 5-minute rest in the seated position. The HBPM device allowed the patient to measure SBP and DBP over each 7-day sequence between visits. The patient recorded HBPM in the diary cards.

Office BP Measurements

OBPM had to be taken by using a validated automatic device (705CP-II) that was provided to the investigator at the beginning of the study. All OBPM had to be performed with the same device throughout the study at each visit. Because OBPM were made at trough, all visits had to be scheduled in the morning, preferably between 7:00 AM and 11:00 AM.

The same arm was used to measure BP at subsequent visits. All measurements had to be made in a seated position after a 5-minute rest. Three measurements were taken at least 1 minute apart and recorded in the case-report form.

Efficacy and Safety Variables

Primary Efficacy Variable

The primary efficacy variable was the change in mean home SBP between visit 2 (W0) and visit 3 (W5). Mean home SBP was based on the measurements made by the patient for the last 6 days of each measurement period and was calculated as the average of all available measurements from a maximum of 24 measurements (4 measurements per day for 6 days). This average was computed only if a minimum of 12 correct measurements were recorded over the last 6 days of each period of measurement.

Secondary Efficacy Variables

The secondary efficacy variables were: (1) the change in mean home DBP between visit 2 (W0) and visit 3 (W5); (2) the change in mean home SBP and DBP between visit 2 (W0) and visit 4 (W10); (3) the change in mean home SBP and DBP between visit 3 (W5) and visit 4 (W10); (4) the change in mean office SBP and DBP between visit 2 (W0) and visit 3 (W5); (5) the change in mean office SBP and DBP between visit 2 (W0) and visit 4 (W10); (6) the change in mean office SBP and DBP between visit 3 (W5) and visit 4 (W10); (7) the proportion of patients having reached mean home SBP $<$135 mm Hg at visit 3 (W5) and at visit 4 (W10); (8) the proportion of home-controlled patients (home SBP $<$135 mm Hg and home DBP $<$85 mm Hg) at visit 3 (W5) and at visit 4 (W10); (9) the proportion of patients having reached mean office SBP $<$140 mm Hg at visit 3 (W5) and at visit 4 (W10); and (10) the proportion of office-controlled patients (office SBP $<$140 mm Hg and office DBP$<$90 mm Hg) at visit 3 (W5) and at visit 4 (W10).

Mean home DBP was calculated as described for home SBP. Mean office SBP and mean office DBP were calculated on the basis of the number of available measurements (of 3), provided that at least 1 measurement was available.

Compliance with treatment was evaluated by pill counts based on empty blister packs at each visit. Good compliance was defined as compliance between 80% and 120%.

Safety Variables

The safety profile of the study drug was assessed by using the following parameters: treatment-emergent adverse events (TEAEs), reported by the patient or observed by the investigator, and collected on a specific dedicated page in the case-report form; vital signs; and laboratory tests.

Serious AEs (SAEs) and nonserious AEs were recorded after written informed consent was received. TEAEs were defined as AEs that developed or worsened during the on-treatment period (time from the first dose of A5 given at the inclusion visit up to the end of the study).

Vital signs (mean office SBP, DBP, and heart rate) were assessed at each visit. Laboratory parameters including serum potassium, sodium, creatinine, and creatinine clearance had to be performed at least 3 days before visits

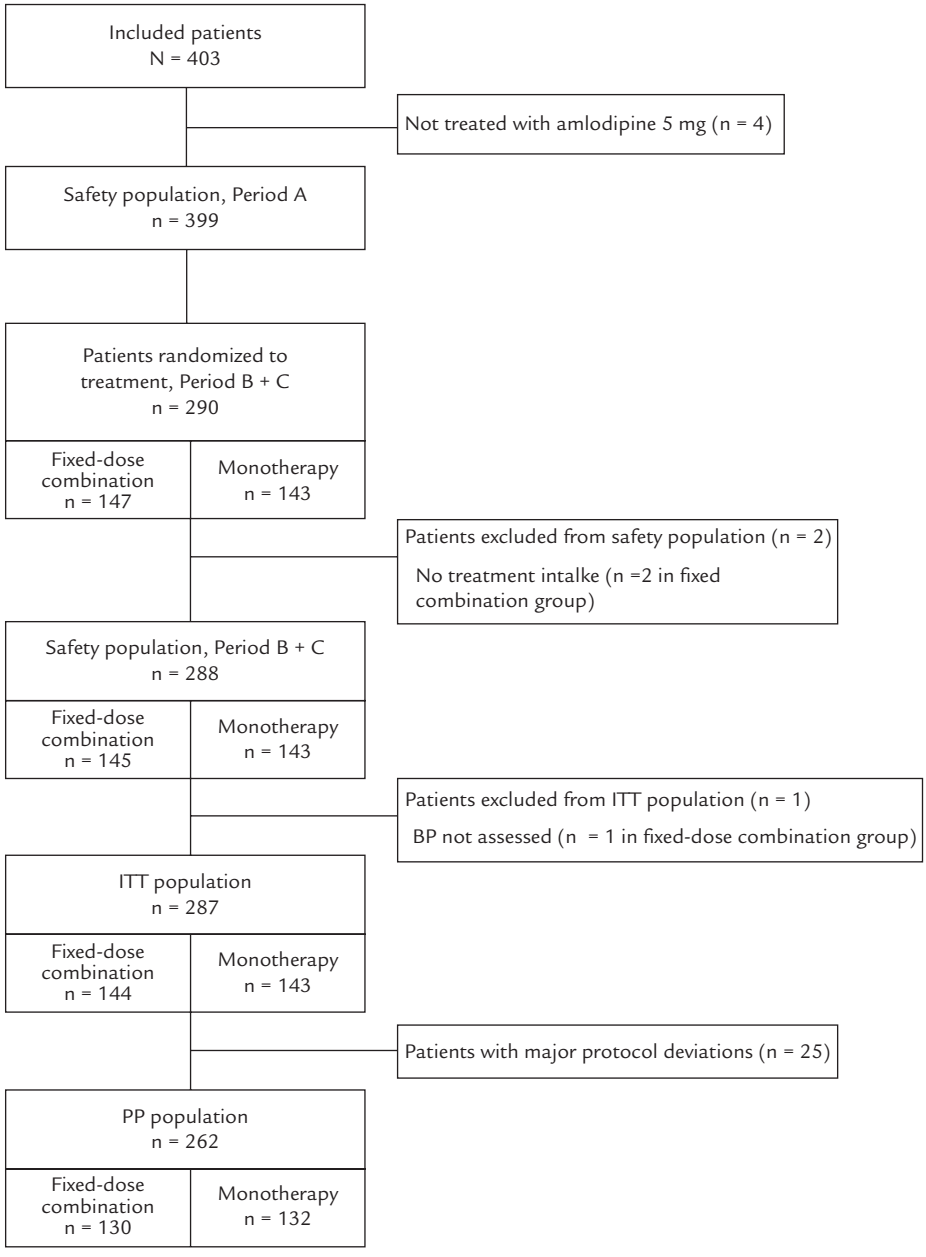

Figure 2. Study flowchart. ITT = intention-to-treat; BP = blood pressure; PP = per protocol.

2 and 4. The tests were performed by local laboratories, and the investigators were requested to record each value and the normal range values in the case-report form.

Statistical Analysis

All statistical analyses were performed by using SAS version 9.1 (SAS Institute, Inc, Cary, North Carolina). The type I error risk of the statistical tests was set at 5% (2-sided).

Estimation of sample size was conducted by using the results of the studies[9,10] evaluating the additional BP-lowering effect of the combination of A5 and an ARB over A5 monotherapy. To detect a treatment effect difference between the 2 treatment groups at W5 of 5 mm Hg with a 90% power, a total of 406 patients were to be enrolled in the study to take into account that ~40% of patients would present with an invalid or normal HBPM at randomization with an attrition rate of 15%.

Analysis of Primary Efficacy Variable

The primary efficacy analysis was conducted on the intention-to-treat (ITT) population, defined as all ran-

Table I. Demographic characteristics and medical history: intention-to-treat population.

Characteristic	Fixed-Dose Combination (n = 144)	Monotherapy (n = 143)	Total (N = 287)
Age, y			
Mean (SD)	58.1 (11.0)	56.4 (11.4)	57.3 (11.2)
Range	32.0–88.0	19.0–79.0	19.0–88.0
Sex, no. (%)			
Male	69 (47.9)	69 (48.3)	138 (48.1)
Female	75 (52.1)	74 (51.7)	149 (51.9)
Height, cm			
Mean (SD)	163.4 (9.6)	164.1 (10.1)	163.7 (9.8)
Range	144.0–186.0	143.0–190.0	143.0–190.0
Weight, kg			
Mean (SD)	81.2 (16.3)	80.1 (15.0)	80.6 (15.7)
Range	50.0–170.0	48.0–148.0	48.0–170.0
Home SBP at randomization, mm Hg			
Mean (SD)	148.5 (10.3)	149.2 (9.7)	148.8 (10.0)
Range	132.8–180.5	131.3–179.3	131.3–180.5
Home DBP at randomization, mm Hg			
Mean (SD)	84.8 (9.6)	85.1 (8.8)	85.0 (9.2)
Range	58.0–105.7	56.3–109.0	56.3–109.0
BMI, kg/m^2			
Mean (SD)	30.4 (5.1)	29.7 (4.5)	30.0 (4.8)
Range	19.5–51.3	20.2–46.1	19.5–51.3
BMI status $\geq$30 kg/m^2, no. (%)	66 (45.8)	54 (37.8)	120 (41.8%)
Dyslipidemia, no. (%)	47 (32.6)	42 (29.4)	89 (31.0)
Current smoking, no. (%)	27 (18.8)	20 (14.0)	47 (16.4)
Type 2 diabetes, no. (%)	22 (15.3)	22 (15.4)	44 (15.3)
Any cardiovascular history, no. (%)	8 (5.6)	11 (7.7)	19 (6.6)

SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index.

Table II. Blood pressure (BP) values at week 5 and changes from baseline: intention-to-treat population.

Parameter	Home BP				Office BP			
	BP at Week 5 Mean (SD)	Change From Baseline Mean (SE)*	Difference Between Groups*	*P*	BP at Week 5 Mean (SD)	Change From Baseline Mean (SE)*	Difference Between Groups*	*P*
SBP, mm Hg								
Fixed-dose combination	135.9 (11.6)	–12.4 (0.7)	–6.2 (1.0)	<0.001	140.6 (13.2)	–10.8 (1.0)	–7.4 (1.4)	<0.001
Monotherapy	142.9 (12.2)	–6.3 (0.7)			148.4 (14.6)	–3.3 (1.0)		
DBP, mm Hg								
Fixed-dose combination	79.2 (8.8)	–5.6 (0.5)	–2.6 (0.7)	<0.001	81.7 (10.1)	–3.8 (0.6)	–2.6 (0.9)	0.004
Monotherapy	82.0 (9.4)	–3.0 (0.5)			85.0 (9.3)	–1.2 (0.6)		

SBP = systolic BP; DBP = diastolic BP.
*Adjusted.

domized patients who had taken the study drug during the randomized treatment period at least once and had at least 1 BP measurement (home or office) assessed at baseline and when receiving treatment (ie, at W5 and/or W10). The primary efficacy variable (change in mean home SBP between visit 2 [W0] and visit 3 [W5]) was compared between treatment groups using ANCOVA, with mean home SBP at baseline (W0) as the covariate.

Analyses of Secondary Efficacy Variables

Secondary efficacy variables were analyzed by using the same statistical methods described for the primary variable, with baseline values (W0) as covariates. The proportions of patients at W5 and W10 having reached mean home SBP <135 mm Hg, as well as patients having reached mean office SBP <140 mm Hg and those with controlled BP either at home (SBP <135 mm Hg and DBP <85 mm Hg) or at office (SBP <140 mm Hg and DBP <90 mm Hg), were compared between groups by using the χ^2 test.

Analyses of the Safety Profile

Two safety populations were defined according to the treatment period assessed. The safety population for period A consisted of patients treated with at least 1 dose of A5 during this period; this population was used to assess the safety profile during treatment period A. The safety population for period B + C consisted of patients treated with at least 1 dose of study drug during the randomized treatment period regardless of whether they were randomized. This population was used to assess the safety profile during treatment periods B and C. The safety population included 1 patient (in the fixed-dose combination group) who was excluded from the ITT population.

AEs were coded by using the Medical Dictionary for Regulatory Activities (version 12.0). TEAEs were presented separately according to the treatment period (period A, then periods B and C) based on the start date of the AE. Safety variables were described for the overall population and per treatment group; no statistical analyses were performed.

RESULTS

Study Patients

As shown in **Figure 2**, a total of 403 patients were included and 290 patients were randomized to treatment: 147 in the fixed-dose combination group and 143 in the monotherapy group. The ITT population

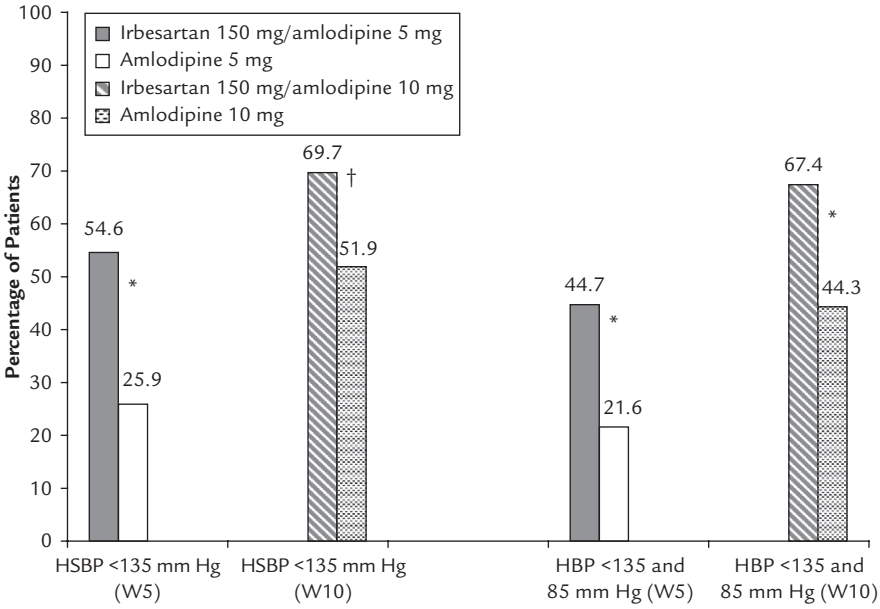

Figure 3. Percentage of patients having reached home systolic blood pressure (HSBP) <135 mm Hg and controlled patients (having reached home BP [HBP] <135 and 85 mm Hg) at weeks 5 (W5) and 10 (W10). *$P < 0.001$; †$P = 0.003$.

included 287 patients: 144 in the fixed-dose combination group and 143 in the monotherapy group. Demographic characteristics of the ITT population are presented in Table I. Forty-eight percent of patients were male and 52% were female. The most frequently reported specific medical history was dyslipidemia (32.6% of patients in the fixed-dose combination group and 29.4% of patients in the monotherapy group). Finally, 6.6% of the patients reported a history of any cardiovascular disease (5.6% in the fixed-dose combination group and 7.7% in the monotherapy group).

Efficacy

Primary Efficacy Variable

Mean HBPM values at W5 and changes from baseline are shown in Table II. Compared with baseline, fixed-dose combination therapy produced a significantly greater reduction in mean (SE) home SBP than monotherapy at W5 (primary end point, ITT analysis): –12.4 (0.7) versus –6.3 (0.7) mm Hg (adjusted mean difference [SE] between groups, –6.2 [1.0] mm Hg; $P < 0.001$).

Secondary Efficacy Variables

Comparable results were seen for mean home DBP and mean office SBP and DBP from baseline at W5 (Table II). Proportion of patients having reached mean home SBP <135 mm Hg and controlled patients at home at W5 are reported in Figure 3. Percentages of patients having reached mean office SBP <140 mm Hg and controlled patients at W5 are summarized in Figure 4.

Comparable results were seen for mean home SBP and DBP and mean office BP from baseline at W10 (Table III). Percentage of patients having reached mean home SBP <135 mm Hg and controlled patients at W10 are reported in Figure 3.

Percentage of patients having reached mean office SBP <140 mm Hg and controlled patients at W10 are summarized in Figure 4.

Compliance With Treatment

Mean (SD) compliance at W5 was comparable between groups (101.1% [10.5%] in the I150/A5 group and 99.6% [5.6%] in the A5 group). A total of 280 patients (97.2%) had good compliance (ie, between 80% and 120%): 140 patients (96.6%) in the fixed-dose combination group and 140 patients (97.9%) in the monotherapy group.

Mean compliance at W10 was also comparable between groups: 102.8% (11.2%) in the I150/A10 group and 99.8% (6.6%) in the A10 group. A total of 255

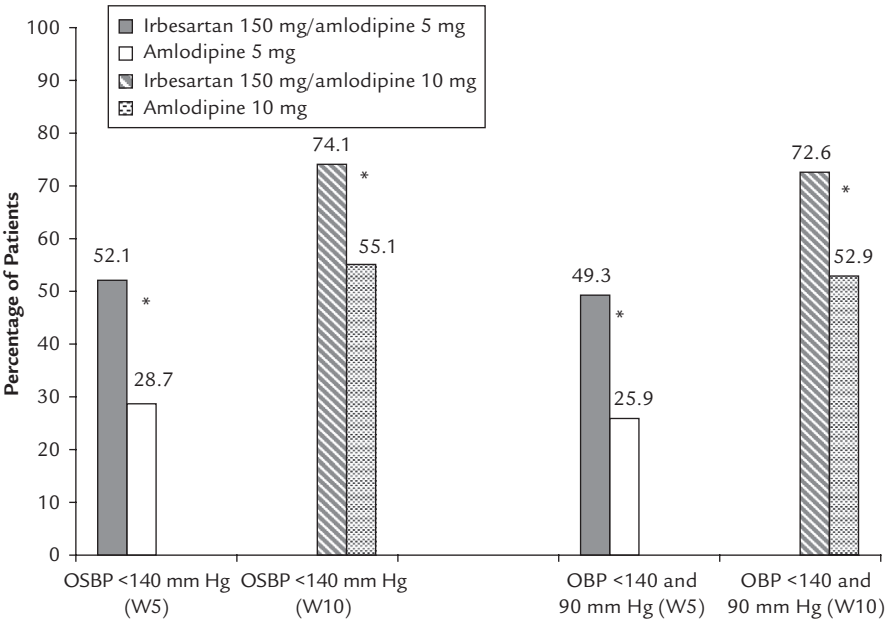

Figure 4. Percentage of patients having reached office systolic blood pressure (HSBP) <140 mm Hg and controlled patients (having reached office BP [OBP] <140 and 90 mm Hg) at weeks 5 and 10. *$P < 0.001$.

patients (93.8%) had good compliance (ie, between 80% and 120%): 121 patients (89.0%) in the fixed-dose combination group and 134 patients (98.5%) in the monotherapy group).

Safety Profile

TEAEs were experienced by 20 (5.0%) of 399 patients during period A, 37 patients during period B (20 [13.8%] of 145 patients treated with the fixed-dose combination and 17 [11.9%] of 143 patients treated with monotherapy), and 46 patients during period C (22 [15.8%] of 139 patients treated with the fixed-dose combination and 24 [17.0%] of 141 patients treated with monotherapy) (**Table IV**). Most TEAEs were of mild or moderate intensity, and only few were considered severe (6 during period B and 3 during period C). There were 1 non–drug-related serious TEAE (cholecystitis acute) during period B (I150/A5 group) and 1 drug-related serious TEAE (hyperkalemia) during period C (I150/A10 group). Both patients recovered. The event of cholecystitis led to study discontinuation. No deaths were reported.

Overall, 8 patients had to permanently discontinue treatment because of at least 1 TEAE. During period A, there was 1 TEAE leading to the discontinuation of 1 patient. During period B, there were 7 TEAEs leading to treatment discontinuation (3 TEAEs in the I150/A5 group and 4 in the A5 group) in 4 patients and 5 TEAEs leading to treatment discontinuation (4 in the I150/A10 group and 1 in the A10 group) in 3 patients during period C.

The most frequent TEAE leading to treatment discontinuation over the periods of treatment was peripheral edema. All 3 events were reported with amlodipine monotherapy.

Mean values for potassium and sodium were similar in both treatment groups (~4.2 mmol/L for potassium and ~140 mmol/L for sodium) at baseline and W10. The mean change in potassium and sodium was close to 0 (**Table V**). Mean (SD) creatinine values at baseline were similar in the fixed-dose combination (75.8 [22.4] μmol/L) and monotherapy (74.4 [18.2] μmol/L) groups. At W10, mean (SD) creatinine values increased slightly from baseline in both treatment groups: 2.7 (12.4) μmol/L and 1.8 (14.4) μmol/L for fixed-dose combination therapy and monotherapy, respectively.

Mean (SD) creatinine clearance was similar in both treatment groups at baseline (~84 mL/min) and slightly decreased at W10. The mean decrease was –3.3 (16.0) mL/min in the fixed-dose combination group and –1.5 (15.1) mL/min in the monotherapy group.

Table III. Blood pressure (BP) values at week 10 and changes from baseline: intention-to-treat population.

Parameter	Home BP				Office BP			
	BP at Week 10 Mean (SD)	Change From Baseline Mean (SE)*	Difference Between Groups*	*P*	BP at Week 10 Mean (SD)	Change From Baseline Mean (SE)*	Difference Between Groups*	*P*
SBP, mm Hg								
Fixed-dose combination therapy	148.5 (10.3)	–18.1 (0.7)	–4.5	<0.001	151.1 (13.0)	–18.4 (1.1)	–6.0	<0.001
Monotherapy	149.2 (9.7)	–13.5 (0.7)			151.8 (12.8)	–12.4 (1.1)		
DBP, mm Hg								
Fixed-dose combination therapy	84.8 (9.6)	–9.4 (0.5)	–3.2	<0.001	85.3 (9.9)	–8.7 (0.6)	–3.1 (0.9)	<0.001
Monotherapy	85.1 (8.8)	–6.2 (0.5)			86.4 (9.8)	–5.6 (0.6)		

SBP = systolic BP; DBP = diastolic BP.
*Adjusted.

Regarding vital signs, there was a decrease in mean SBP and DBP between baseline and W10. The decrease was larger in the fixed-dose combination group. At W10, the mean decrease from baseline in office SBP was –18.3 (16.1) mm Hg in the fixed-dose combination group and –12.5 (13.0) mm Hg in the monotherapy group. The mean decrease from baseline in office DBP in the 2 groups was –8.4 (9.4) and –5.8 (7.3) mm Hg, respectively. Mean heart rate remained stable throughout the study.

DISCUSSION

This was the first study to assess the antihypertensive efficacy and safety profiles of fixed-dose combination therapy with irbesartan, an ARB, and amlodipine, a dihydropyridine CCB, on BP. Fixed-dose combination therapy with I150/A5 or I150/A10 resulted in increased BP-lowering response and a favorable safety profile compared with amlodipine monotherapy.

SBP was lowered to a greater extent after 5 weeks of treatment with I150/A5 than after 5 weeks of monotherapy with A5, with a higher proportion of patients attaining mean home SBP <135 mm Hg and mean office SBP <140 mm Hg. Achieving the target BP level also is important in preventing the cardiovascular morbidity and mortality associated with hypertension. A recent meta-analysis[5] found that lowering SBP by 10 mm Hg or DBP by 5 mm Hg using any of the main classes of BP-lowering drugs reduced coronary heart disease events (fatal and nonfatal) by approximately one quarter and stroke by about one third, regardless of the presence of vascular disease and the BP values before starting treatment, with no increase in nonvascular mortality. Heart failure was also reduced by approximately one quarter. Although not assessed, the decreases in SBP and DBP that we observed with I150/A5 or I150/A10 suggest a potentially positive impact on cardiovascular outcomes, making these new fixed-dose therapies valuable additions to the treatment armamentarium for hypertension. This is in line with the latest recommended BP treatment strategies of the National Institute of Health and Clinical Excellence (NICE).[11]

Both fixed-dose combination therapies (I150/A5 or I150/A10) were relatively well tolerated in our study population compared with the use of amlodipine monotherapy (A5 or A10). During the combined period B and C, fewer patients in the I150/A5 or I150/A10 groups had to permanently discontinue

Table IV. Description of treatment-emergent adverse events (TEAEs) by System Organ Class and Preferred Term during study periods A, B, and C (safety population).

	Period A	Period B		Period C	
TEAE	Amlodipine 5 mg (n = 399)	Fixed-Dose Combination 150 mg/5 mg (n = 145)	Monotherapy Amlodipine 5 mg (n = 143)	Fixed-Dose Combination 150 mg/10 mg (n = 139)	Monotherapy Amlodipine 10 mg (n = 141)
Patients with at least 1 TEAE, no. (%)	20 (5.0)	20 (13.8)	17 (11.9)	22 (15.8)	24 (17.0)
Patients with at least 1 drug-related TEAE, no. (%)	5 (1.3)	6 (4.1)	7 (4.9)	15 (10.8)	15 (10.6)
Total no. of TEAEs	23	25	24	27	30
Patients with serious TEAEs, no. (%)	—	1 (0.7)	—	1 (0.7)	—
Patients with drug-related serious TEAEs, no. (%)	—	—	—	1 (0.7)	—
No. of TEAEs leading to permanent treatment discontinuation (NAE/NP [%])	1/1 (0.3)	3/1 (0.7)	4/3 (2.1)	4/2 (1.4)	1/1 (0.7)
General disorders and administration site conditions	1/1 (0.3)	—	2/2 (1.4)	1/1 (0.7)	1/1 (0.7)
Peripheral edema	—	—	2/2 (1.4)	—	1/1 (0.7)
Asthenia	—	—	—	1/1 (0.7)	
Chest pain	1/1 (0.3)	—	—	—	—
Hepatobiliary disorders	—	2/1 (0.7)	—	—	—
Cholecystitis acute	—	1/1 (0.7)	—	—	—
Hepatic cirrhosis	—	1/1 (0.7)	—	—	—
Renal and urinary disorders	—	1/1 (0.7)	—	—	—
Renal cyst	—	1/1 (0.7)	—	—	—
Nervous system disorders	—	—	1/1 (0.7)	—	—
Headache	—	—	1/1 (0.7)	—	—
Respiratory, thoracic, and mediastinal disorders	—	—	1/1 (0.7)	—	—
Cough	—	—	1/1 (0.7)	—	—
Vascular disorders	—	—	—	1/1 (0.7)	—
Hypotension	—	—	—	1/1 (0.7)	—
Musculoskeletal and connective tissue disorders	—	—	—	2/1 (0.7)	—
Arthralgia	—	—	—	1/1 (0.7)	—
Myalgia	—	—	—	1/1 (0.7)	—

NAE = number of AEs; NP (%) = number and percentage of patients with at least 1 AE.

Table V. Serum chemistry summary: safety population, period B + C.

Variable	Baseline		Week 10		Change From Baseline at Week 10	
	Fixed-Dose Combination (n = 145)	Monotherapy (n = 143)	Fixed-Dose Combination (n = 145)	Monotherapy (n = 143)	Fixed-Dose Combination (n = 145)	Monotherapy (n = 143)
Potassium, mmol/L						
n	143	143	130	128	130	128
Mean (SD)	4.2 (0.5)	4.3 (0.5)	4.3 (0.4)	4.2 (0.5)	0.1 (0.5)	–0.1 (0.5)
Median	4.2	4.3	4.3	4.2	0.2	–0.1
Range	3.0 to 5.7	3.2 to 6.0	2.9 to 5.8	3.1 to 5.4	–1.1 to 1.7	–1.3 to 1.9
Sodium, mmol/L						
n	143	142	130	126	130	126
Mean (SD)	140.5 (3.0)	140.5 (2.8)	140.0 (2.8)	140.3 (2.7)	–0.4 (3.0)	–0.01 (3.3)
Median	140.1	140.7	140.0	140.0	–0.6	0.0
Range	128.7 to 148.0	133.0 to 150.0	131.0 to 146.0	132.2 to 146.0	–8.0 to 12.7	–10.8 to 9.1
Creatinine, μmol/L						
n	145	143	132	128	132	128
Mean (SD)	75.8 (22.4)	74.4 (18.2)	78.9 (23.1)	76.4 (20.4)	2.7 (12.4)	1.8 (14.4)
Median	72.0	70.8	74.3	73.5	0.9	0.0
Range	30.1 to 177.9	31.0 to 127.4	35.4 to 207.1	34.5 to 177.0	–40.2 to 54.0	–30.1 to 79.7
Creatinine clearance, mL/min						
n	145	143	132	128	132	128
Mean (SD)	83.9 (32.3)	84.1 (27.8)	79.7 (29.2)	82.7 (29.2)	–3.3 (16.0)	–1.5 (15.1)
Median	79.4	82.7	75.5	79.8	–1.2	0. 0
Range	24.6 to 192.7	31.0 to 170.3	21.1 to 168.4	27.1 to 169.0	–81.5 to 44.5	–80.4 to 55.2

study treatment because of related TEAEs compared with the A5 or A10 groups. Edema, which was reported more often with amlodipine monotherapy in this study, was also reported as 1 of the most frequent TEAEs in other studies assessing the antihypertensive efficacy of combination therapy with amlodipine and an ARB.[10,18–23]

There have been other studies evaluating the antihypertensive efficacy of amlodipine with an ARB other than irbesartan.[10,18–23] A meta-analysis of these studies[24] concluded that combining BP-lowering drugs from different classes is ~5 times more effective than doubling the dose of 1 drug.

The fixed-dose combination of irbesartan and amlodipine is intended to be used as a single daily oral tablet. International guidelines[1] suggest that drugs which exert their antihypertensive effect over 24 hours with a once-a-day administration may be preferred because a simple treatment schedule favors adherence. Better treatment adherence is associated with better efficacy; it has been shown that nonadherent patients tend to have higher BP than adherent patients.[25] Moreover, the multiple dose strengths of a fixed-dose combination of irbesartan and amlodipine (daily dose of amlodipine 5 or 10 mg and irbesartan 150 mg in a single daily administration) allows for greater flexibility in upward and downward titrations of treatment according to a patient's response in terms of efficacy or safety profile, an option that may not be afforded by some fixed-dose combinations.

The study did have some limitations. It was relatively short in duration (10 weeks of treatment) and thus had limited ability to predict long-term effectiveness or tolerability. The results of this study apply to the population studied (adults with essential hypertension and treated with A5 monotherapy for at least 4 weeks) and may not be extrapolated to other populations with different characteristics.

Although the study was an open-label design, which could have been a limiting factor, it was performed by using independent evaluation of BP measurements during data management. This allowed a blinded evaluation of BP measurements and supported open-label treatment administration.

CONCLUSIONS

Data from this population of adult patients with essential hypertension suggest greater efficacy with the fixed-dose combination I150/A5 over A5 alone in lowering SBP after 5 weeks of treatment. Both treatment regimens were well tolerated throughout the study.

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CONFLICTS OF INTEREST

Dr. Bobrie received payment from the sponsor of the study, Sanofi. Dr Bobrie worked as a consultant in the I-COMBINE study, for which he provided support in interpretation of the results.

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