I-ADD Study: Assessment of Efficacy and Safety Profile of Irbesartan/Amlodipine Fixed-Dose Combination Therapy Compared With Irbesartan Monotherapy in Hypertensive Patients Uncontrolled With Irbesartan 150 mg Monotherapy: A Multicenter, Phase III, Prospective, Randomized, Open-Label With Blinded–End Point Evaluation Study

Guillaume Bobrie, MD, for the I-ADD Study Investigators*

Department of Hypertension Hôpital Européen Georges Pompidou, Paris, France

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-ADD study aimed to demonstrate whether the antihypertensive efficacy of fixed-dose combination irbesartan 300 mg/amlodipine 5 mg (I300/A5) was superior to that of irbesartan (I300) monotherapy in lowering home systolic blood pressure after 10 weeks' treatment.

Methods: The I-ADD study was a 10-week, multicenter, Phase III, prospective, randomized, parallel-group, open-label with blinded–end point study. The main inclusion criterion was essential uncontrolled hypertension (systolic blood pressure ≥145 mm Hg at office after at least 4 weeks of irbesartan 150 mg [I150] monotherapy administered once daily). Patients continued to receive I150 for 7 to 10 days and were randomized to either monotherapy with I150 for 5 weeks then I300 for the next 5 weeks, or to a fixed-dose combination therapy (I150/A5, then I300/A5). Safety profile was assessed by recording adverse events reported by patients or observed by the investigator.

Results: Following enrollment, 325 patients were randomized to treatment, and 320 (mean [SD] age, 56.7 [11.4] years; 41% male) were included in the intention-to-treat analysis: 155 patients treated with I150/A5 then I300/A5, and 165 patients treated with I150 then I300. At randomization, mean home systolic blood pressure was similar in both groups: 152.7 (11.8) mm Hg in the I150/A5 group and 150.4 (10.1) mm Hg in the I150 group. At week 10, the adjusted mean difference in home systolic blood pressure between groups was −8.8 (1.1) mm Hg ($P < 0.001$). The percentage of controlled patients (mean home blood pressure <135 and 85 mm Hg) was nearly 2-fold higher in the I300/A5 group versus the I300 group ($P < 0.001$). Treatment-emergent adverse events were experienced by 10.5% of I300/A5-treated patients and 6.6% of I300-treated patients during the second 5-week period. Three serious adverse events were reported; 2 with monotherapy (1 with I150 and 1 with I300) and 1 with fixed-dose combination I300/A5. All patients affected by serious adverse events made a full recovery.

Conclusions: These 10-week data from this patient population suggest a greater antihypertensive efficacy of the fixed-dose combination I300/A5 over I300 alone in lowering systolic blood pressure. Both treatments were well tolerated throughout the study. ClinicalTrials.gov identifier: NCT00957554. (*Clin Ther*. 2012;34: 1720–1734)

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 cardiovascu-

*Members of the I-ADD Study Investigators are listed in the Acknowledgments.

Accepted for publication July 5, 2012.
http://dx.doi.org/10.1016/j.clinthera.2012.07.001
0149-2918/$ - see front matter

lar events, [1–4] and systolic BP (SBP) may be a particularly more important target for treatment, as suggested by large-scale review of antihypertensive clinical trials in which reductions of 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 reach the predetermined goal.[1] Use of combination therapy with 2 agents having complementary mechanisms of action has been reported to be more effective than monotherapy and may improve tolerability related to dose-dependent adverse effects, as well as 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) is 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] Tolerability benefits such as reduction in edema 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 in the treatment of hypertension.[14,15] Therefore, the combination therapy of irbesartan and amlodipine is expected to provide enhanced efficacy in patients whose condition is not adequately controlled with irbesartan monotherapy alone. To the best of our knowledge, no clinical trial has investigated this hypothesis with irbesartan.

I-ADD 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 blood pressure measurements (HBPM), of the fixed-dose combination therapy of irbesartan 300 mg and amlodipine 5 mg (I300/A5) was superior to that of irbesartan 300 mg (I300) alone in hypertensive patients whose condition was insufficiently controlled with I300 monotherapy.

PATIENTS AND METHODS

Patient Selection

This multicenter, parallel-group, prospective, randomized, open-label, blinded–end point study was conducted in 10 countries from July 2009 to September 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 10 countries where 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.

The patient inclusion and exclusion criteria applied were the same as those reported in the I-COMBINE study.[16]

Patients were randomized to treatment 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 irbesartan 150 mg [I150] monotherapy for 7–10 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 (HBPM).

Investigators were supplied with the following investigational products: I150, I300, and a fixed-dose combination of irbesartan 150 mg/amlodipine 5 mg (I150/A5) and I300/A5.

After at least 4 weeks of I150 monotherapy administered orally once a day, patients with a mean office SBP ≥145 mm Hg were administered I150 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 to treatment using a central randomization procedure (1:1), either to I150 monotherapy or the fixed-dose combination therapy

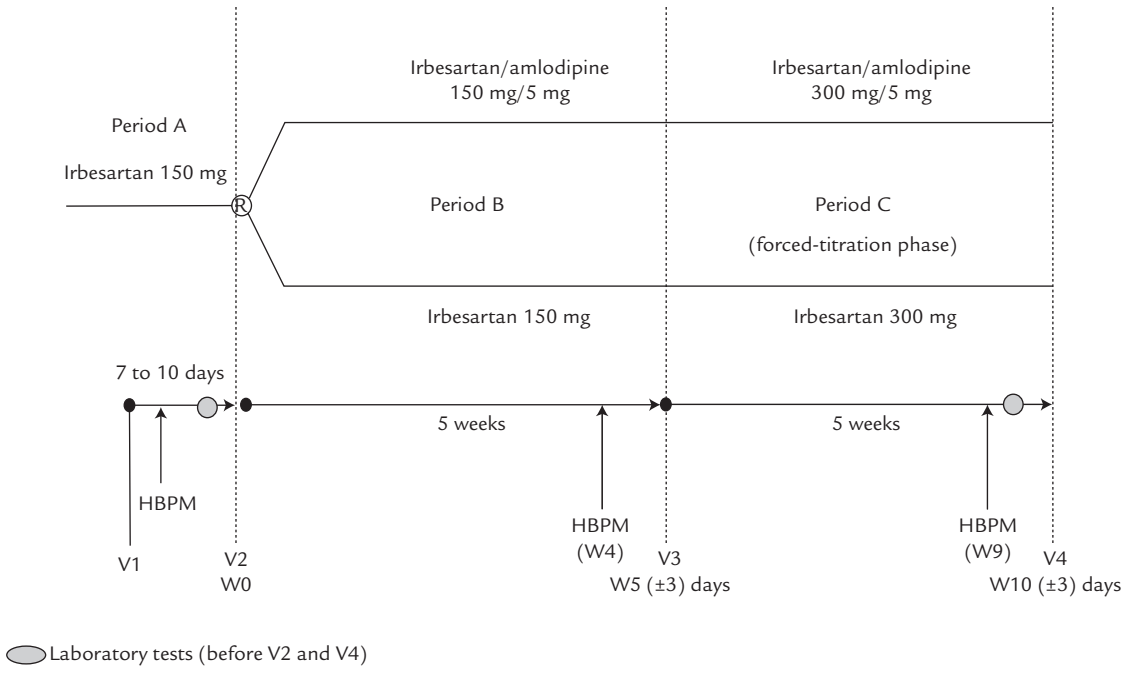

Figure 1. Study design. HBPM = home blood pressure measurements; V = visit; W = week.

I150/A5 for 5 weeks (period B). The investigator called the interactive voice response system center to determine the patient's treatment group. Patients were considered randomized after being assigned to a treatment group.

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

At visit 3 (W5), patients treated with I150 monotherapy were provided with I300 monotherapy (forced titration). Patients treated with the I150/A5 fixed-dose combination were supplied with the I300/A5 fixed-dose combination (forced titration).

Patients took 1 tablet 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 an automatic BP monitor were evaluated independently during data management, which supported an open-label treatment administration.

Patients were treated and evaluated without charge. Physicians received honoraria for their participation in this registration clinical study for entering patients' information (anonymized) into the study case-report forms.

If they decided to do so, patients could withdraw from the study, at any time and for any 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.

Outcomes 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 and 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). Blood pressure measurements were recorded and evaluated independently during data management. The device used in this study had been previously validated according to the International Pro-

tocol 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.

Office BP Measurements

Office BP measurements (OBPM) had to be taken using a validated automatic device (705CP-II) that was provided to the investigator at the beginning of the study. All office BP measurements had to be performed with the same device throughout the study at each visit. Because these measurements 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 4 (W10). 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 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 as follows: the change in mean home DBP between visit 2 (W0) and visit 4 (W10); the change in mean home SBP and DBP between visit 2 (W0) and visit 3 (W5); the change in mean home SBP and DBP between visit 3 (W5) and visit 4 (W10); the change in mean office SBP and DBP between visit 2 (W0) and visit 4 (W10); the change in mean office SBP and DBP between visit 2 (W0) and visit 3 (W5); the change in mean office SBP and DBP between visit 3 (W5) and visit 4 (W10); the proportion of patients having reached mean home SBP <135 mm Hg at visit 3 (W5) and at visit 4 (W10); 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); the proportion of patients having reached mean office SBP <140 mm Hg at visit 3 (W5) and at visit 4 (W10); and 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 (out of 3), provided that at least 1 measurement was available.

Compliance with treatment was evaluated by pill counts in the 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: (1) treatment-emergent adverse events (TEAEs), reported by the patient or observed by the investigator, which were collected on a specific dedicated page in the case-report form; (2) vital signs; and (3) laboratory tests.

Serious AEs and nonserious AEs were recorded after written informed consent was given. TEAEs were defined as AEs that developed or worsened during the on-treatment period (time from the first dose of I150 mg given at 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 included serum potassium, sodium, and creatinine. Creatinine clearance had to be performed at least 3 days before visits 2 and 4. The tests were performed by local laboratories, and the investigators recorded 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 done by using the results of the studies[9,10] evaluating the additional BP-

lowering effect of the combination of A5 and an ARB over an ARB alone. To detect a treatment effect difference between the 2 treatment groups at W10 of 5 mm Hg with a 90% power, a total of 406 patients were to be enrolled in the study to account for the fact that ~40% of patients would present with an invalid or normal HBPM at randomization with an attrition rate of 15%.

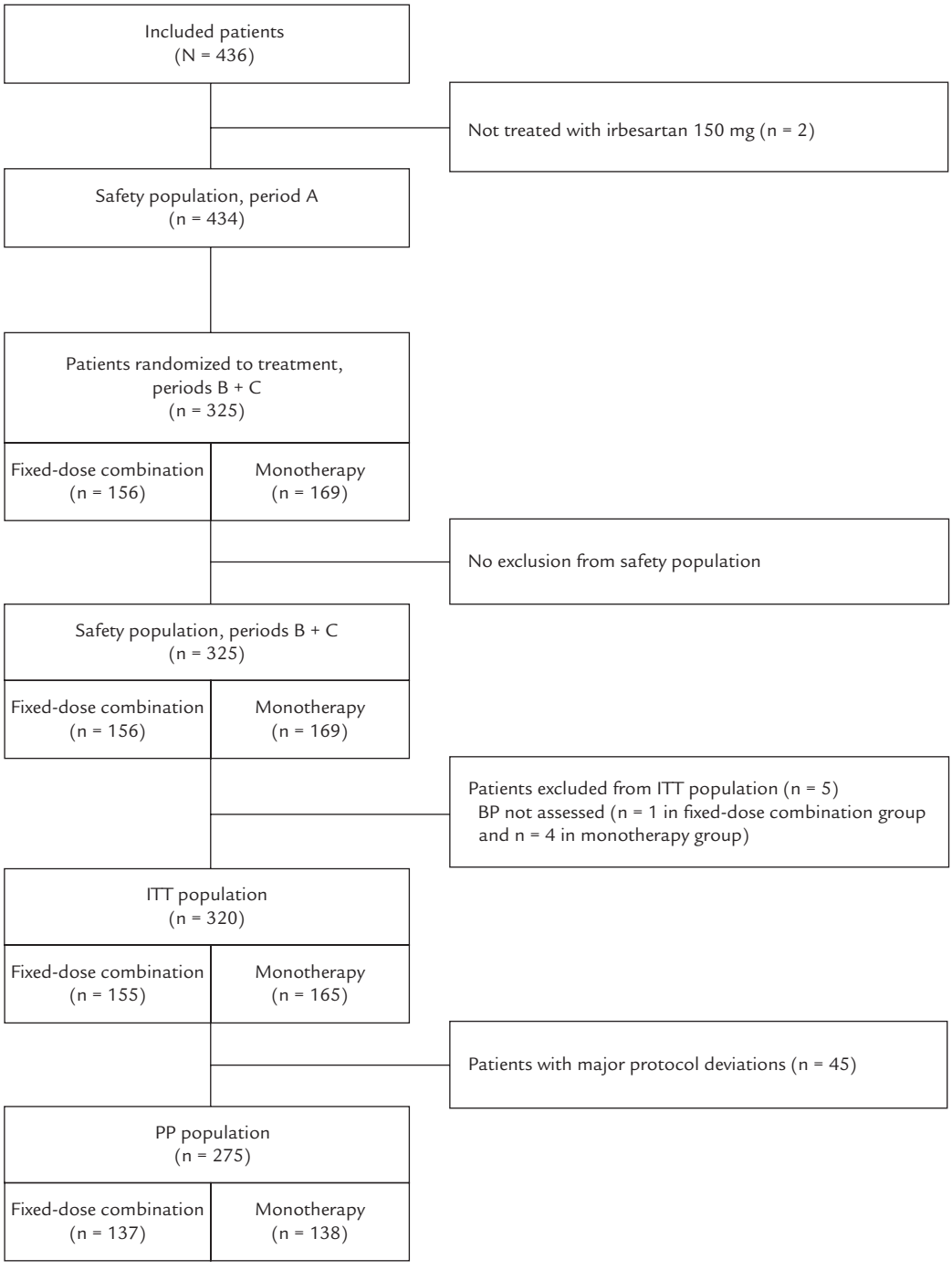

Figure 2. Study flow chart. BP = blood pressure; ITT = intention-to-treat; PP = per protocol.

Analysis of Primary Efficacy Variable

The primary efficacy analysis was performed on the intention-to-treat population, defined as all randomized patients who had taken the study drug during the randomized treatment period at least once and who had at least 1 BP measurement (home or office) assessed at baseline and when receiving treatment (ie, at W5 and/or W10). The primary end point (change in mean home SBP between visit 2 [W0] and visit 4 [W10]) was compared between treatment groups by using an 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 method described for the primary variable, with the baseline value (W0) as covariate. The proportions of patients at W5 and W10 having reached mean home SBP <135 mm Hg (home), of patients having reached mean office SBP <140 mm Hg (office), and those with controlled BP either at home (SBP <135 mm Hg and DBP <85 mm Hg) or office (SBP <140 mm Hg and DBP <90 mm Hg) were compared between groups by using χ^2 test.

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

Characteristic	Fixed-Dose Combination (n = 155)	Monotherapy (n = 165)	Total (N = 320)
Age, y			
Mean (SD)	56.0 (11.5)	57.4 (11.3)	56.7 (11.4)
Range	22.0–83.0	30.0–81.0	22.0–83.0
Sex, no. (%)			
Male	62 (40.0)	70 (42.4)	132 (41.3)
Female	93 (60.0)	95 (57.6)	188 (58.8)
Height, cm			
Mean (SD)	163.4 (9.8)	162.5 (9.8)	162.9 (9.8)
Range	142.0–189.0	141.0–194.0	141.0–194.0
Weight, kg			
Mean (SD)	79.1 (16.4)	78.4 (14.2)	78.7 (15.3)
Range	48.0–146.0	47.0–149.0	47.0–149.0
Home SBP at randomization, mm Hg			
Mean (SD)	152.7 (11.8)	150.4 (10.1)	151.5 (11.0)
Range	135.4–178.9	134.2–178.3	134.2–178.9
Home DBP at randomization, mm Hg			
Mean (SD)	86.6 (10.0)	86.0 (10.4)	86.3 (10.2)
Range	54.2–111.0	51.3–109.9	51.3–111.0
BMI, kg/m^2			
Mean (SD)	29.6 (5.1)	29.7 (4.6)	29.6 (4.9)
Range	18.6–48.9	19.1–46.5	18.6–48.9
BMI status ≥30 kg/m^2, no. (%)	69 (44.5)	66 (40.0)	135 (42.2)
Dyslipidemia, no. (%)	27 (17.4)	36 (21.8)	63 (19.7)
Current smoking, no. (%)	14 (9.0)	12 (7.3)	26 (8.1)
Type 2 diabetes, no. (%)	29 (18.7)	36 (21.8)	65 (20.3)
Any cardiovascular history, no. (%)	9 (5.8)	10 (6.1)	19 (5.9)

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

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 I150 during period A to assess the safety profile during this period. The safety population for periods 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.

Adverse events 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 436 patients were included and 325 patients were randomized to treatment: 156 in the fixed-dose combination group and 169 in the monotherapy group. The intention-to-treat population included 320 patients: 155 in the fixed-dose combination group and 165 in the monotherapy group.

Demographic characteristics of the patient population are presented in Table I. In the intention-to-treat population, 41% of patients were male and 59% were female. The most frequently reported medical history was type 2 diabetes (18.7% of patients in the fixed-dose combination group and 21.8% of patients in the monotherapy group) and dyslipidemia (17.4% of patients in the fixed-dose combination group and 21.8% of patients in the monotherapy group). Only 5.9% of patients reported a history of any cardiovascular disease (5.8% in the fixed-dose combination group and 6.1% in the monotherapy group).

Efficacy

Primary Efficacy Variable

Mean HBP values at W10 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 W10 (primary end point, intention-to-treat analysis): –18.7 (0.8)

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

	Home BP				Office BP			
Parameter	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	133.6 (10.9)	−18.7 (0.8)	−8.8	<0.001	136.1 (14.9)	−17.9 (1.2)	−9.5	<0.001
Monotherapy	140.7 (13.7)	−9.9 (0.8)			145.1 (15.7)	−8.4 (1.1)		
DBP, mm Hg								
Fixed-dose combination	77.9 (8.4)	−8.6 (0.5)	−4.7	<0.001	79.8 (9.7)	−7.7 (0.7)	−4.2	<0.001
Monotherapy	81.9 (10.6)	−3.9 (0.5)			84.1 (11.8)	−3.5 (0.7)		

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

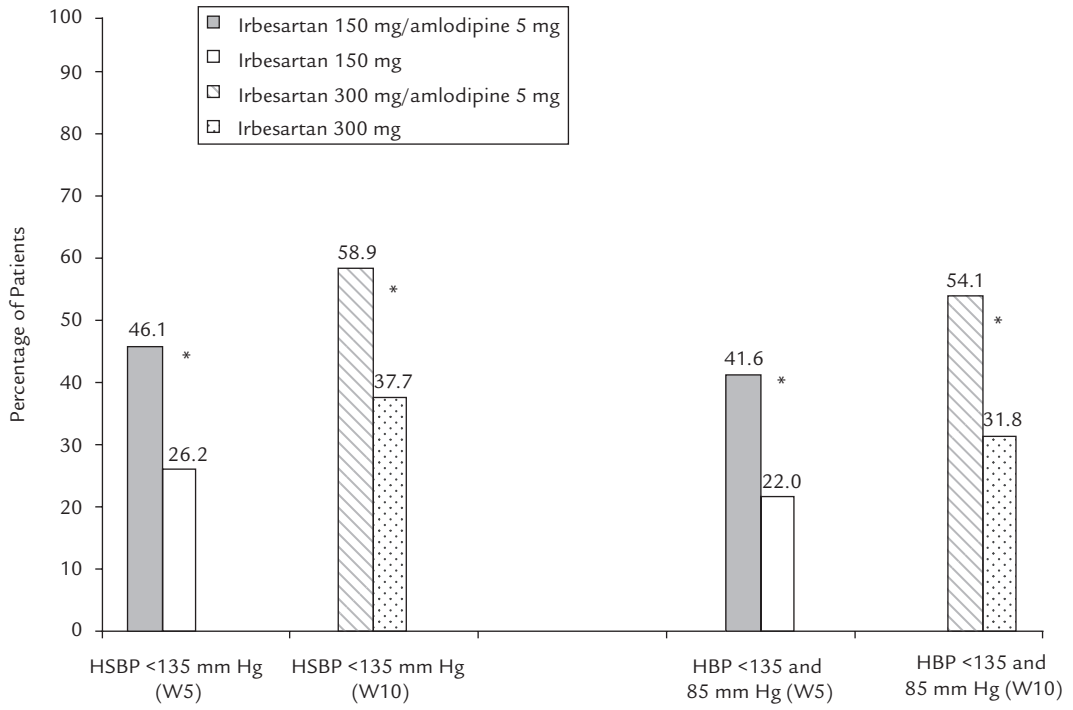

Figure 3. Percentage of patients having reached home systolic blood pressure (HSBP) <135 mm Hg and controlled patients (having reached home BP [HBP] <135 and 85 mm Hg) at weeks 5 (W5) and 10 (W10). *$P < 0.001$, χ^2 test.

versus –9.9 (0.8) mm Hg (adjusted mean difference between groups, –8.8 [1.1] mm Hg; $P < 0.001$).

Secondary Efficacy Variables

Comparable results were seen for changes in mean home DBP and mean office SBP and DBP from baseline at W10 (Table II). The proportions of patients having reached mean home SBP <135 mm Hg and controlled patients at home at W10 are shown in Figure 3. The percentages of patients having reached mean office SBP <140 mm Hg and controlled patients at W10 are summarized in Figure 4.

Comparable results were seen for changes in mean home SBP and DBP and mean office BP from baseline at W5 (Table III). The percentages of patients having reached mean home SBP <135 mm Hg and controlled patients at W5 are shown in Figure 3.

Percentages of patients having reached mean office SBP <140 mm Hg and controlled patients at W5 are summarized in Figure 4.

Compliance With Treatment

Mean (SD) compliance at W10 was comparable between groups (102.2% [17.6%] in the I300/A5 group and 100.5% [8.0%] in the I300 group). A total of 302 patients (96.8%) had good compliance (between 80% and 100%): 144 (96.6%) patients in the fixed-dose combination group and 158 (96.9%) patients in the monotherapy group. Mean compliance at W5 was also comparable between groups: 100.7% (6.5%) in the I150/A5 group and 99.6% (4.6%) in the I150 group. A total of 315 patients (98.1%) had good compliance (between 80% and 100%): 151 (97.4%) patients in the fixed-dose combination group and 164 (98.8%) patients in the monotherapy group.

Safety Profile

TEAEs were experienced by 21 (4.8%) of 434 patients during period A, 32 patients during period B (17 [10.9%] of 156 patients treated with the fixed-dose combination and 15 [8.9%] of 169 patients treated with monotherapy), and 27 patients during period C (16 [10.5%] of 152 patients treated with the fixed-dose combination and 11 [6.6%] of 166 patients treated with monotherapy) (Table IV).

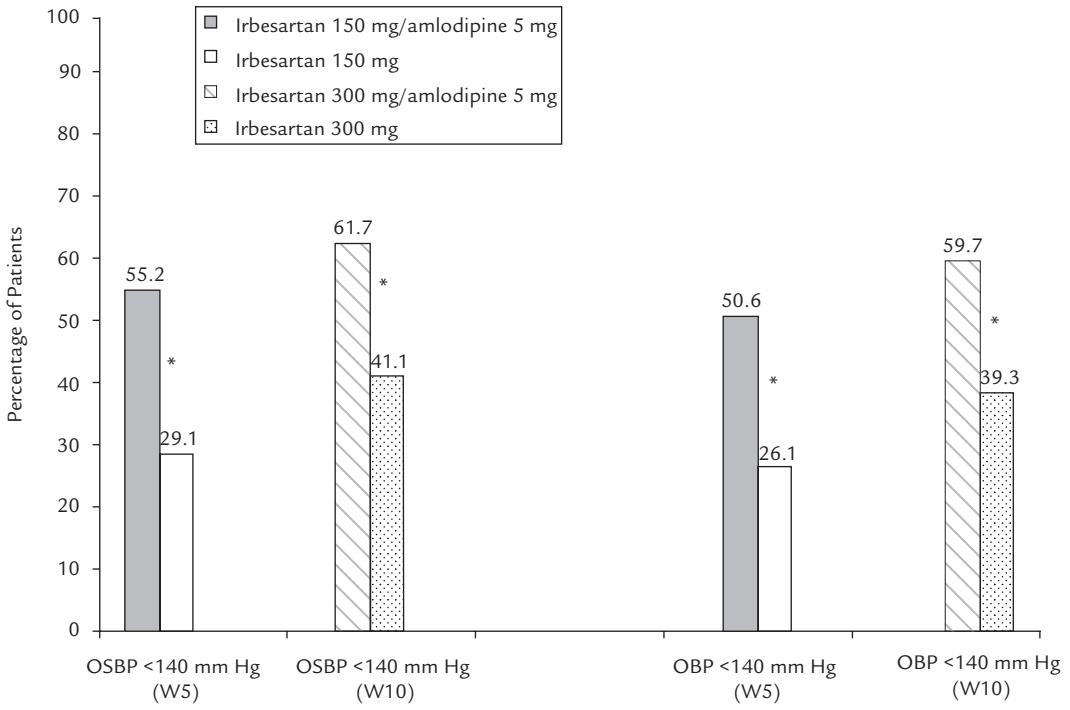

Figure 4. Percentage of patients having reached office systolic blood pressure (OSBP) <140 mm Hg and controlled patients (having reached office BP <140 and 90 mm Hg) at weeks 5 (W5) and 10 (W10). *$P <$ 0.001, χ^2 test.

Most TEAEs were of mild or moderate intensity; only a few were considered to be severe (3 during period A and 1 [monotherapy group] during period C). There was 1 serious TEAE (fall) during period A and 2 serious TEAEs (colon cancer and acute myocardial infarction) during period C (1 in each group). These serious TEAEs were considered by the investigator to be treatment related. The event of fall and acute myocardial infarction led to study discontinuation. All patients made a full recovery. No deaths were reported.

Overall, 7 patients had to permanently discontinue study treatment because of at least 1 TEAE. During period A, there were 4 TEAEs leading to treatment discontinuation in 2 patients. During period B, there were 3 TEAEs leading to treatment discontinuation in 3 patients (all in the I150/A5 group), and 2 TEAEs leading to treatment discontinuation in 2 patients from the I300 group during period C (**Table IV**).

The most frequent TEAEs leading to treatment discontinuation were peripheral edema and edema (3 events) reported in 3 patients treated with I150/A5 during period B. They were considered to be associated with amlodipine at the beginning of study treatment. No TEAEs related to edema leading to treatment discontinuation were observed in the I300/A5 group during period C. A list of complete TEAEs with frequencies of patients having at least 1 TEAE is given in the **Supplemental Table** (available in the online version at doi: http://10.1016/j.clinthera.2012.07.001).

Mean values of 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, and 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 (78.6 [21.7] μmol/L) and monotherapy (78.6 [19.2] μmol/L) groups. At W10, creatinine values remained stable from baseline in the fixed-dose combination group (0.14 [14.52] μmol/L) and slightly decreased in the monotherapy group (–2.45 [13.65] μmol/L).

Mean creatinine clearance was comparable in both treatment groups at baseline (81.4 [30.5] mL/min in the fixed-dose combination group and 78.8 [30.0] mL/min in the monotherapy group). At W10, the mean

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

	Home BP				Office BP			
Parameter	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	136.8 (12.1)	−15.4 (0.8)	−9.8	<0.001	139.3 (14.2)	−14.7 (1.0)	−9.6	<0.001
Monotherapy	144.8 (13.6)	−5.6 (0.8)			148.0 (14.6)	−5.1 (1.0)		
DBP, mm Hg								
Fixed-dose combination	79.1 (9.8)	−7.4 (0.5)	−5.0	<0.001	80.4 (10.6)	−7.3 (0.7)	−4.9	<0.001
Monotherapy	83.6 (10.5)	−2.4 (0.5)			85.2 (11.2)	−2.4 (0.6)		

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

(SD) change was 0.4 (15.1) mL/min in the fixed-dose combination group and 3.08 (14.2) mL/min in the monotherapy group.

Regarding vital signs, between baseline and W10, there was an overall decrease in mean SBP and DBP. 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 –8.1 (15.4) mm Hg in the monotherapy group. The mean decrease from baseline in office DBP was –7.5 (11.5) mm Hg in the fixed-dose combination group and –3.6 (9.0) mm Hg in the monotherapy group. Mean heart rate remained stable throughout the study.

DISCUSSION

In this study, treatment with the fixed-dose combination of I150/A5 or I300/A10 resulted in a better BP response than with irbesartan monotherapy, with a similar safety profile. After 10 weeks of study treatment, the reduction in SBP was greater (adjusted mean difference between groups, –8.8 mm Hg) with fixed-dose combination therapy (I150/A5 for 5 weeks, then I300/A5 for 5 additional weeks) than with monotherapy (I150 for 5 weeks, then I300 for 5 additional weeks), with higher proportions of patients attaining mean home SBP <135 mm Hg (58.9% vs 37.7%) and mean office SBP <140 mm Hg (61.7% vs 41.1%). Achieving a target BP level is important in preventing the cardiovascular morbidity and mortality associated with hypertension. A recent meta-analysis 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 fatal and nonfatal coronary heart disease events by about one quarter and stroke by about one third, with no increase in nonvascular mortality.[4] Heart failure was also reduced by about one quarter. The findings of this meta-analysis were unrelated to the presence or absence of vascular disease or to BP values before starting treatment. Although not assessed, the decreases in SBP and DBP that we observed with I150/A5 or I300/A5 suggest a potential positive impact on cardiovascular outcomes, making these new fixed-dose combination therapies a valuable addition to the treatment armamentarium for hypertension. This finding 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 and I300/A5) were relatively well tolerated in our study population. Edema and peripheral edema were the only TEAEs reported in the fixed-dose combination

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.

Parameter	Period A	Period B		Period C	
	Irbesartan 150 mg (n = 434)	Fixed-Dose Combination 150 mg/5 mg (n = 156)	Monotherapy Irbesartan 150 mg (n = 169)	Fixed-Dose Combination 300 mg/5 mg (n = 152)	Monotherapy Irbesartan 300 mg (n = 166)
Patients with at least 1 TEAE, no. (%)	21 (4.8)	17 (10.9)	15 (8.9)	16 (10.5)	11 (6.6)
Patients with at least 1 drug-related TEAE, no. (%)	5 (1.2)	9 (5.8)	2 (1.2)	7 (4.6)	1 (0.6)
Total no. of TEAEs	24	21	16	17	12
Patients with serious TEAEs, no. (%)	1 (0.2)	—	—	1 (0.7)	1 (0.6)
Patients with serious drug–related TEAEs, no. (%)	—	—	—	—	—
No. of TEAEs leading to permanent treatment discontinuation, NAE/NP (%)	4/2 (0.5)	3/3 (1.9)	—	—	2/2 (1.2)
General disorders and administration site conditions	1/1 (0.2)	3/3 (1.9)	—	—	—
Edema, peripheral	—	2/2 (1.3)	—	—	—
Edema	—	1/1 (0.6)	—	—	—
Fatigue	1/1 (0.2)	—	—	—	—
Nervous system disorders	1/1 (0.2)	—	—	—	—
Dizziness	1/1 (0.2)	—	—	—	—
Injury, poisoning and procedural complications	2/1 (0.2)	—	—	—	1/1 (0.6)
Fall	1/1 (0.2)	—	—	—	—
Upper limb fracture	1/1 (0.2)	—	—	—	—
Muscle strain	—	—	—	—	1/1 (0.6)
Cardiac disorders	—	—	—	—	1/1 (0.6)
Acute myocardial infarction	—	—	—	—	1/1 (0.6)

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

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

Parameter	Baseline		Week 10		Change From Baseline to Week 10	
	Fixed-Dose Combination (n = 156)	Monotherapy (n = 169)	Fixed-Dose Combination 300mg/5mg (n = 156)	Monotherapy Irbesartan 300mg (n = 169)	Fixed-Dose Combination 300mg/5mg (n = 156)	Monotherapy Irbesartan 300mg (n = 169)
Potassium, mmol/L						
n	153	168	146	158	143	157
Mean (SD)	4.2 (0.5)	4.2 (0.4)	4.2 (0.4)	4.3 (0.4)	−0.01 (0.38)	0.01 (0.38)
Median	4.3	4.3	4.2	4.2	0.00	0.00
Range	3.1 to 5.7	3.2 to 5.3	3.1 to 6.4	3.1 to 5.3	−1.33 to 0.90	−1.20 to 0.84
Sodium, mmol/L						
n	152	166	145	157	141	154
Mean (SD)	140.0 (3.0)	139.8 (3.1)	140.4 (3.0)	140.0 (2.9)	0.21 (2.82)	0.02 (2.93)
Median	140.0	140.0	140.0	140.0	0.00	0.00
Range	133.0 to 149.0	130.0 to 147.8	134.0 to 150.0	134.0 to 152.1	−9.00 to 8.00	−10.00 to 10.48
Creatinine, μmol/L						
n	154	167	146	157	144	155
Mean (SD)	78.6 (21.7)	78.6 (19.2)	79.1 (25.4)	76.6 (20.8)	0.14 (14.52)	−2.45 (13.65)
Median	78.8	77.9	73.7	74.0	0.00	−0.89
Range	44.8 to 202.7	39.8 to 159.3	44.2 to 269.0	31.9 to 177.0	−35.40 to 66.37	−40.71 to 47.70
Creatinine clearance, mL/min						
n	154	167	146	157	144	155
Mean (SD)	81.4 (30.5)	78.8 (30.0)	81.5 (31.2)	81.1 (30.7)	0.40 (15.10)	3.08 (14.19)
Median	80.1	73.0	81.7	74.9	0.00	1.00
Range	22.7 to 206.8	26.3 to 212.2	17.1 to 177.2	22.8 to 208.0	−48.45 to 56.57	−50.40 to 48.34

group. These events were considered to be associated with amlodipine. Edema has been reported as one of the most frequent TEAEs in previous studies assessing the antihypertensive efficacy of combination therapy with amlodipine and an ARB.[10,18–23]

There have been other studies assessing the antihypertensive efficacy of amlodipine with ARBs in addition to irbesartan.[10,19–24] A meta-analysis of these studies reported that combining BP-lowering drugs from different classes is ~5 times more effective than doubling the dose of 1 drug.[24]

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 once-a-day administration may be preferred because a simple treatment schedule favors adherence. Better treatment adherence is likely to be associated with better efficacy; nonadherent patients have been reported to have higher BP than adherent patients.[25] Moreover, the multiple dose strengths of the fixed-dose combination of irbesartan and amlodipine (daily dose of I150 or I300 and A5 in a single daily administration) allow for greater flexibility in upward and downward titrations of treatment according to patients' response in terms of efficacy or safety. This treatment option may not be available with some fixed-dose combinations.

This study did have some limitations. It was relatively short in duration (10 weeks of treatment) and thus has limited ability to predict long-term effectiveness and tolerability. The results of this study apply to the population studied (adults with essential hypertension and treated with I150 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 evaluations of BP measurements during data management. This allowed a blinded evaluation of BP measurements and supported an open-label treatment administration.

CONCLUSIONS

The results of the current study conducted in a population of adult patients with essential hypertension suggest a greater antihypertensive efficacy of the fixed-dose combination (I150/A5 for 5 weeks, then I300/A5 for 5 additional weeks) compared with irbesartan alone (I150 for 5 weeks, then I300 for 5 additional weeks) in terms of lowering SBP after 10 weeks of treatment. Both treatments were well tolerated throughout the study.

ACKNOWLEDGMENTS

Sanofi France was the sole sponsor of the I-ADD study and the supplier of the investigational products.

Nathalie Genès, MD, Véronique Daclin, MD, and Agnès Mourier, PhD, of Sanofi, and Sanofi study manager, Laurence Mondesir, contributed equally to the preparation and conduction of the I-ADD study. Data entry, data management, and statistical analysis were performed by the personnel in the contract research organization LINCOLN, Boulogne-Billancourt, France. Nadine Friese, PhD, and Riphed Jaziri, PhD, assisted Dr. Bobrie in the preparation of the manuscript including editing, coordinating revisions, checking content and language, formatting, referencing, and preparing tables and figures.

The I-ADD study principal investigators were as follows: Algeria: Adghar Djamila, Centre national de médecine sportive; Agrane Khadidja, Polyclinique; Chettih Leila, Centre national de médecine sportive; Djouadi Nadia, private office; Brazil: de Almeida Fernando Antonio, Hospital Santa Lucinda; de Rosa Eduardo Maffini, Universidade de Caxias do Sul; Mota Gomes Marco Antonio, Clinicor; Tarcísio Freire Antonio, Santa Casa de Belo Horizonte; Colombia: Elias Maria, Cardiolab; Manzur Fernando, Centro de Diagnostico Cardiologico; Miguel Urina, Fundacion BIOS; Guatemala: Alonzo Omar, Hospital General San Juan de Dios; Arango Juan Luis, UNICAR; Guzman Ismael, Hospital Roosevelt; Sánchez Vicente, Hospital General de Enfermedad Común IGSS; Wyss Fernando, UNICAR; Mexico: Rodríguez Briones Ignacio, Unidad de Cardiología y Medicina Interna; Barrera Bustillos Manuel de los Reyes, Clinica de Merida; Cardona Muñoz Ernesto Germán, Unidad de Investigación Cardiovascular CUCS Universidad de Guadalajara; Calvillo Jorge Carrillo, Hospital Central Dr. Ignacio Morones Prieto; Ficker García Guillermo Adrián, CONDOMEDICs; Meaney Martínez Alejandra, Servicio Médico Integral Escuela Superior de Medicina del Instituto Politecnico Nacional; Vargas Flores Armando Rafael, private office; Morocco: Azzouzi Laila, Cardiology Department, Ibn Rochd Hospital, Casablanca; Cherti Mohamed, Cardiology department, Cardio B, Suissi Maternity, Avicenne Hospital, Rabat; Chraibi Said, Abdelmoumen center, Casablanca; Hamani Ahmed, Cardiology Department, Mohamed V

Military Hospital, Rabat; Srairi Marouane, 16 Bd Abdeltif Benkaddour, Résidence de triangle d'or, 20050 Racine, Casablanca; Saudi Arabia: Kinsara Abdulhalim Jami, National Guard Hospital, King AbdulAziz Medical City, Jeddah; United Arab Emirates: Binbrek Azan Salim, Rashid Hospital, Dubai; Wael Abdulrahman Almahmeed, Sheikh Khalifa Medical City, Abudhabi; Tunisia: Ali ben Khalfallah, Hopital Régional Menzel Bourguiba; Drissa Habiba, Hopital La Rabta Tunis; Gamra Habib, Hopital Fattouma Bourguiba Monastir; Jridi Gouider, Hopital Farhat Hached Sousse; Kachboura Salem, Hopital Abderrahmane Mami Ariana; Lotfi Slimane, Hopital Habib Thameur Tunis; Mokdad Ayari, Centre Medical El Farabi; Sondos Kraïem, Hopital Habib Thameur Tunis; Zouari Soraya, Hopital des FSI La Marsa; and Venezuela: Vergara Gloria, University of Zulia (LUZ) Maracaibo.

CONFLICT OF INTEREST

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

SUPPLEMENTAL MATERIAL

A supplemental table accompanying this article can be found in the online version at doi: http://10.1016/j.clinthera.2012.07.001.

REFERENCES

1. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.
2. Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003; 362:1527–1535.
3. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998; 317:703–713.
4. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009;338:b1665.
5. Wang JG, Staessen JA, Franklin SS, et al. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. *Hypertension*. 2005;45:907–913.
6. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. *Drugs*. 2002; 62:443–462.
7. Weber MA. Creating a combination antihypertensive regimen: what does the research show? *J Clin Hypertens*. 2003;5(Suppl 3):12–20.
8. Morgan T, Anderson A. A comparison of candesartan, felodipine, and their combination in the treatment of elderly patients with systolic hypertension. *Am J Hypertens*. 2002;15:544–549.
9. Allemann Y, Fraile B, Lambert M, et al. Efficacy of the combination of amlodipine and valsartan in patients with hypertension uncontrolled with previous monotherapy: the Exforge in Failure after Single Therapy (EX-FAST) study. *J Clin Hypertens*. 2008;10:185–194.
10. Chrysant SG, Melino M, Karki S, et al. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther*. 2008;30:587–604.
11. NICE. Hypertension: The clinical management of primary hypertension in adults. CG127/NICE Guidelines. *National Clinical Guideline Centre*. August 2011.
12. Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens*. 2007;21:220–224.
13. Croom KF, Curran MP, Goa KL, Perry CM. Irbesartan: a review of its use in hypertension and in the management of diabetic nephropathy. *Drugs*. 2004;64:999–1028.
14. Haria M, Wagstaff AJ. Amlodipine. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs*. 1995;50:560–586.
15. Epstein BJ, Vogel K, Palmer BF. Dihydropyridine calcium channel antagonists in the management of hypertension. *Drugs*. 2007;67:1309–1327.
16. Bobrie G. for the I-COMBINE Study Investigators. 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-babel with blinded-end point evaluation study. *Clin Ther*. 2012;34:1698–1712.
17. O'Brien E, Pickering T, Asmar R, et al. Working Group on Blood Pressure Monitoring of the European Society of Hypertension International Protocol for validation of blood pressure measuring devices in adults. *Blood Press Monit*. 2002;7:3–17.
18. Smith TR, Philipp T, Vaisse B. Amlodipine and valsartan combined and as monotherapy in stage 2, elderly, and

black hypertensive patients: subgroup analyses of 2 randomized, placebo-controlled studies. *J Clin Hypertens*. 2007;9:355–364.
19. Philipp T, Smith TR, Glazer R. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther*. 2007;29:563–580.
20. Flack JM, Calhoun DA, Satlin L, et al. Efficacy and safety of initial combination therapy with amlodipine/valsartan compared with amlodipine monotherapy in black patients with stage 2 hypertension: the EX-STAND study. *J Hum Hypertens*. 2009;23:479–489.
21. Fogari R, Zoppi A, Mugellini A, et al. Efficacy and safety of two treatment combinations of hypertension in very elderly patients. *Arch Gerontol Geriatr*. 2009;48:401–405.
22. Calhoun DA, Lacourcière Y, Chiang YT, Glazer RD. Triple antihypertensive therapy with amlodipine, valsartan, and hydrochlorothiazide: a randomized clinical trial. *Hypertension*. 2009;54:32–39.
23. Oparil S, Giles T, Ofili EO, et al. Moderate versus intensive treatment of hypertension with amlodipine/valsartan for patients uncontrolled on angiotensin receptor blocker monotherapy. *J Hypertens*. 2011;29:161–170.
24. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
25. Pimenta E, Oparil S. Fixed combinations in the management of hypertension: patient perspectives and rationale for development and utility of the olmesartan-amlodipine combination. *Vasc Health Risk Manag*. 2008;4:653–664.

Address correspondence to: Guillaume Bobrie, MD, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75908 Paris Cedex 15, France. E-mail: guillaume.bobrie@egp.aphp.fr

Supplemental Table. List of all treatment-emergent adverse events (TEAEs) and frequencies of patients affected during study periods A, B, and C: safety population.

	Period A		Period B				Period C			
	Irbesartan 150 mg (n = 434)		Fixed-Dose Combination 150 mg/5 mg (n = 156)		Monotherapy Irbesartan 150 mg (n = 169)		Fixed-Dose Combination 300 mg/5 mg (n = 152)		Monotherapy Irbesartan 300 mg (n = 166)	
System Organ Class Preferred Term	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs
Total	21 (4.8)	24	17 (10.9)	21	15 (8.9)	16	16 (10.5)	17	11 (6.6)	12
Cardiac disorders	1 (0.2)	1	–	–	–	–	1 (0.7)	1	1 (0.6)	1
Acute myocardial infarction	–	–	–	–	–	–	–	–	1 (0.6)	1
Chest pain	1 (0.2)	1	–	–	–	–	–	–	–	–
Sinus bradycardia	–	–	–	–	–	–	1 (0.7)	1	–	–
Ear and labyrinth disorders	–	–	–	–	1 (0.6)	1	–	–	–	–
Tinnitus	–	–	–	–	1 (0.6)	1	–	–	–	–
Eye disorders	1 (0.2)	2	–	–	1 (0.6)	1	–	–	–	–
Eye pruritus	–	–	–	–	1 (0.6)	1	–	–	–	–
Glaucoma	1 (0.2)	2	–	–	–	–	–	–	–	–
Gastrointestinal disorders	2 (0.5)	2	2 (1.3)	2	1 (0.6)	1	–	–	1 (0.6)	1
Abdominal pain	–	–	–	–	–	–	–	–	1 (0.6)	1
Diarrhea	1 (0.2)	1	–	–	–	–	–	–	–	–
Gastric disorder	1 (0.2)	1	–	–	–	–	–	–	–	–
Gastritis	–	–	–	–	1 (0.6)	1	–	–	–	–
Nausea	–	–	2 (1.3)	2	–	–	–	–	–	–
General disorders and administration site conditions	1 (0.2)	1	7 (4.5)	7	2 (1.2)	2	2 (1.3)	2	1 (0.6)	1
Fatigue	1 (0.2)	1	–	–	–	–	–	–	1 (0.6)	1
Edema	–	–	1 (0.6)	1	–	–	1 (0.7)	1	–	–
Edema, peripheral	–	–	5 (3.2)	5	1 (0.6)	1	1 (0.7)	1	–	–
Pyrexia	–	–	1 (0.6)	1	1 (0.6)	1	–	–	–	–
Immune system disorders	–	–	1 (0.6)	1	–	–	–	–	–	–
Food allergy	–	–	1 (0.6)	1	–	–	–	–	–	–

(continued)

Supplemental Table (continued).

System Organ Class Preferred Term	Period A		Period B				Period C			
	Irbesartan 150 mg (n = 434)		Fixed-Dose Combination 150 mg/5 mg (n = 156)		Monotherapy Irbesartan 150 mg (n = 169)		Fixed-Dose Combination 300 mg/5 mg (n = 152)		Monotherapy Irbesartan 300 mg (n = 166)	
	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs
Infections and infestations	4 (0.9)	4	4 (2.6)	4	3 (1.8)	3	4 (2.6)	4	2 (1.2)	2
Acute sinusitis	–	–	–	–	–	–	1 (0.7)	1	–	–
Bronchitis	–	–	–	–	1 (0.6)	1	–	–	–	–
Dengue fever	–	–	–	–	1 (0.6)	1	–	–	–	–
Enteritis infectious	1 (0.2)	1	–	–	–	–	–	–	–	–
Folliculitis	–	–	–	–	–	–	1 (0.7)	1	–	–
Helicobacter pylori gastritis	1 (0.2)	1	–	–	–	–	–	–	–	–
Influenza	–	–	1 (0.6)	1	–	–	1 (0.7)	1	1 (0.6)	1
Nasopharyngitis	–	–	–	–	1 (0.6)	1	–	–	–	–
Pharyngotonsillitis	1 (0.2)	1	–	–	–	–	–	–	–	–
Tooth infection	–	–	1 (0.6)	1	–	–	–	–	–	–
Upper respiratory tract infection	–	–	–	–	–	–	1 (0.7)	1	–	–
Urinary tract infection	1 (0.2)	1	–	–	–	–	–	–	1 (0.6)	1
Viral upper respiratory tract infection	–	–	2 (1.3)	2	–	–	–	–	–	–
Injury poisoning and procedural complication	2 (0.5)	3	–	–	–	–	1 (0.7)	1	1 (0.6)	1
Fall	1 (0.2)	1	–	–	–	–	–	–	–	–
Muscle strain	–	–	–	–	–	–	–	–	1 (0.6)	1
Overdose	–	–	–	–	–	–	1 (0.7)	1	–	–
Posttraumatic pain	1 (0.2)	1	–	–	–	–	–	–	–	–
Upper limb fracture	1 (0.2)	1	–	–	–	–	–	–	–	–
Metabolism and nutrition disorders	–	–	–	–	–	–	–	–	1 (0.6)	1
Hypoglycemia	–	–	–	–	–	–	–	–	1 (0.6)	1
Musculoskeletal and connective tissue disorders	–	–	1 (0.6)	1	2 (1.2)	2	2 (1.3)	2	–	–
Arthralgia	–	–	–	–	–	–	1 (0.7)	1	–	–
Back pain	–	–	–	–	–	–	1 (0.7)	1	–	–
Intervertebral disc protrusion	–	–	–	–	1 (0.6)	1	–	–	–	–
Joint stiffness	–	–	1 (0.6)	1	–	–	–	–	–	–
Pain in extremity	–	–	–	–	1 (0.6)	1	–	–	–	–

(continued)

Supplemental Table (continued).

System Organ Class Preferred Term	Period A: Irbesartan 150 mg (n = 434)		Period B: Fixed-Dose Combination 150 mg/5 mg (n = 156)		Period B: Monotherapy Irbesartan 150 mg (n = 169)		Period C: Fixed-Dose Combination 300 mg/5 mg (n = 152)		Period C: Monotherapy Irbesartan 300 mg (n = 166)	
	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs	No. (%) of Patients	No. of TEAEs
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)	–	–	–	–	–	–	1 (0.7)	1	–	–
Colon cancer	–	–	–	–	–	–	1 (0.7)	1	–	–
Nervous system disorders	11 (2.5)	11	5 (3.2)	5	4 (2.4)	4	2 (1.3)	2	3 (1.8)	4
Dizziness	3 (0.7)	3	2 (1.3)	2	–	–	1 (0.7)	1	1 (0.6)	1
Headache	7 (1.6)	7	2 (1.3)	2	3 (1.8)	3	1 (0.7)	1	2 (1.2)	2
Neuropathy, peripheral	–	–	–	–	1 (0.6)	1	–	–	–	–
Paraesthesia	–	–	1 (0.6)	1	–	–	–	–	–	–
Sciatica	1 (0.2)	1	–	–	–	–	–	–	–	–
Transient ischemic attack	–	–	–	–	–	–	–	–	1 (0.6)	1
Psychiatric disorders	–	–	–	–	–	–	1 (0.7)	1	–	–
Depression	–	–	–	–	–	–	1 (0.7)	1	–	–
Renal and urinary disorders	–	–	–	–	–	–	2 (1.3)	2	1 (0.6)	1
Azotemia	–	–	–	–	–	–	1 (0.7)	1	–	–
Hypercreatinemia	–	–	–	–	–	–	1 (0.7)	1	1 (0.6)	1
Respiratory, thoracic, and mediastinal disorders	–	–	1 (0.6)	1	–	–	1 (0.7)	1	–	–
Cough	–	–	1 (0.6)	1	–	–	–	–	–	–
Productive cough	–	–	–	–	–	–	1 (0.7)	1	–	–
Skin and subcutaneous tissue disorders	–	–	–	–	1 (0.6)	1	–	–	–	–
Alopecia	–	–	–	–	1 (0.6)	1	–	–	–	–
Vascular disorders	–	–	–	–	1 (0.6)	1	–	–	–	–
Phlebitis	–	–	–	–	1 (0.6)	1	–	–	–	–

TEAEs = treatment-emergent adverse events.