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Sponsor / Company: sanofi-aventis	**Study Identifier:** NCT00956644
Drug substance(s): irbesartan/amlodipine	**Study code:** IRBAM_R_04220

Title of the study: **Efficacy and safety of irbesartan/amlodipine fixed combination therapy compared with amlodipine monotherapy in hypertensive patients uncontrolled on amlodipine 5 mg monotherapy. A prospective, randomized, open-label with blinded endpoint evaluation, multicentre, phase III study.**

Study period:

Date first patient enrolled: 21/Jul/2009

Date last patient completed: 26/Aug/2010

Phase of development: Phase III pivotal study for registration

Objectives:

The primary objective was to demonstrate that the antihypertensive efficacy of the fixed combination irbesartan/amlodipine 150/5 mg is superior to that of amlodipine 5 mg monotherapy in lowering SBP as assessed by home BP measurement (HBPM) after 5 weeks of treatment (W5).

The secondary objectives were the following:

- To compare the antihypertensive efficacy of the fixed combination irbesartan/amlodipine 150/5 mg with that of amlodipine 5 mg monotherapy after 5 weeks of treatment (W5) using the following criteria:
  - DBP assessed by HBPM
  - SBP and DBP assessed by Office Blood Pressure Measurements (OBPM)
  - Percentage of patients with SBP<135 mmHg and DBP<85 mmHg assessed by HBPM
  - Percentage of patients with SBP<140 mmHg and DBP<90 mmHg assessed by OBPM
- To compare the antihypertensive efficacy of the fixed combination therapy irbesartan/amlodipine 150/10 mg with that of amlodipine 10 mg monotherapy at the end of treatment (W10) using the following criteria:
  - SBP and DBP assessed by HBPM
  - SBP and DBP assessed by OBPM
  - Percentage of patients with SBP<135 mmHg and DBP<85 mmHg assessed by HBPM
  - Percentage of patients with SBP<140 mmHg and DBP<90 mmHg assessed by OBPM
- To examine in each treatment group the change from week 5 to week 10 in SBP and DBP assessed by HBPM and by OBPM

To determine the incidence and severity of adverse events

Methodology:

This was a multicenter, prospective randomised open-label, parallel group with blinded endpoint evaluation (PROBE) study.

All patients received amlodipine 5 mg during 7 to 10 days (Period A). After this period, patients with home SBP $\geq$ 135 mmHg were randomized using a central randomization procedure (1:1):

- Monotherapy treatment group: patients received amlodipine 5 mg from W0 to W5 (Period B), then amlodipine 10 mg from W5 to W10 (Period C),
- Fixed combination therapy treatment group: patients received fixed combination irbesartan/amlodipine 150/5 mg from W0 to W5 (Period B), then fixed combination irbesartan/amlodipine 150/10 mg from W5 to W10 (Period C).

Home BP measurements were performed by using for all patients the same validated automatic non invasive BP monitor according to a standard procedure. Office BP measurements were performed using for all the investigators the same validated automatic non invasive BP monitor. This allowed a standardization of BP measurements.

Number of patients: Planned: 244

Randomized: 290

Treated: 288

Evaluated:

	Fixed combination	Monotherapy	Total
Included patients			403
Safety population for period A			399
Randomized patients	147	143	290
Safety population for period B+C	145	143	288
ITT population	144	143	287
PP population	130	132	262

Diagnosis and criteria for inclusion:

Men and women ≥ 18 years, with established essential hypertension, treated with amlodipine 5 mg monotherapy for at least 4 weeks, with uncontrolled BP defined as mean SBP ≥ 145 mmHg assessed by OBPM.

Randomisation criteria: Mean SBP ≥ 135 mmHg assessed by HBPM, 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, creatinine clearance ≥ 30 ml/min.

Investigational product: fixed combination of irbesartan and amlodipine

Dose: irbesartan 150 mg/amlodipine 5 mg from W0 to W5, irbesartan 150 mg/amlodipine 10 mg from W5 to W10.

Administration: Treatment was administrated orally, once daily in the morning. The patient was instructed not to take the treatment prior to the office visit in order to measure residual blood pressure.

Duration of treatment: 11 weeks.

Duration of observation: 11 weeks.

Reference therapy: Monotherapy with amlodipine.

Dose: Amlodipine 5 mg from W0 to W5, amlodipine 10 mg from W5 to W10.

Administration: Treatment was administrated orally, once daily in the morning. The patient was instructed not to take the treatment prior to the office visit in order to measure residual blood pressure.

Criteria for evaluation:

Efficacy: The primary efficacy variable was the change in mean home SBP between V2 (W0) and V3 (W5).

The secondary efficacy variables were:

- The change in mean home DBP between V2 (W0) and V3 (W5),
- The change in mean home SBP and DBP between V2 (W0) and V4 (W10),
- The change in mean home SBP and DBP between V3 (W5) and V4 (W10),
- The proportion of subjects at V3 (W5), and at V4 (W10), with home SBP<135 mmHg AND home DBP<85 mmHg,
- The change in mean office SBP and DBP between V2 (W0) and V3 (W5).
- The change in mean office SBP and DBP between V2 (W0) and V4 (W10),
- The change in mean office SBP and DBP between V3 (W5) and V4 (W10),
- The proportion of subjects at V3 (W5), and at V4 (W10), with office SBP<140 mmHg AND office DBP<90 mmHg.

Safety:

- Treatment-emergent adverse events (TEAEs),reported or observed,
- Vital signs blood pressure, pulse rate),
- Laboratory tests (serum potassium, sodium and creatinine, creatinine clearance).

Statistical methods:

The type I error risk of the statistical tests was set at 5% (two-sided).

The primary efficacy variable, the change in mean home SBP between W0 and W5, was compared between treatment groups considering ITT population using an ANCOVA including mean home SBP at baseline (W0) as covariate and interaction treatment*baseline.

Secondary efficacy variables, change in mean home DBP and mean office SBP and DBP between W0 and W5, change in mean home and office SBP and DBP between W0 and W10, were analyzed using the same statistical method as the one used for the primary analysis of the primary efficacy variable.

Change in mean home and office SBP and DBP between W5 and W10 was analyzed using an ANCOVA including value at W0 as covariate and interaction treatment*baseline. BP control at W5 based on mean home SBP (mean home SBP < 135 mmHg) was added to the model (post hoc) in order to take into account the difference in terms of proportion of controlled patients at W5 between the 2 groups.

Proportions of responder patients based on HBPM and OBPM were compared between groups using a Chi-square test.

Safety variables were only described overall and per treatment group. No statistical test was performed.

Summary:

Efficacy results:

Primary criterion: Mean change from baseline to Week 5 in home SBP

On the ITT population, at baseline, the mean home SBP (±SD) was similar between groups: 148.5 (±10.3) mmHg in the Fixed combination therapy group and 149.2 (±9.7) mmHg in the Monotherapy group. At week 5, the mean home SBP (±SD) decreased to 135.9 (±11.6) mmHg in the Fixed combination therapy group and to 142.9 (±12.2) mmHg in the Monotherapy group.

The adjusted mean change (±SE) from baseline was -12.4 ±0.7 mmHg in the Fixed combination group compared to -6.3 ±0.7 mmHg in the Monotherapy group. The adjusted mean difference between groups (-6.2 mmHg) was statistically significant ($p<0.001$).Therefore the fixed combination irbesartan/amlodipine 150/5 mg was superior to amlodipine 5 mg monotherapy in lowering SBP as assessed by HBPM after 5 weeks of treatment.

Similar results were obtained on the PP population.

Secondary criteria:

Mean change from baseline to Week 5 in home DBP

On ITT population, at baseline, the mean home DBP (±SD) was similar between groups: 84.8 (±9.6) mmHg and 85.1(±8.8) mmHg in Fixed combination therapy and Monotherapy groups respectively.

Mean home DBP decreased from baseline to week 5 in both treatment groups. The adjusted mean change (SE) from baseline at week 5 was more important in the Fixed combination group: -5.6 ±0.5 mmHg compared to -3.0 ±0.5 mmHg in the Monotherapy group. The adjusted mean difference between groups was statistically significant ($p<0.001$).

Mean change from baseline to Week 5 in office BP

Results obtained with OBPM were consistent with those obtained with HBPM.

At baseline, mean office SBP (151.1 ±13.0 mmHg in Fixed combination group and 151.8 ±12.8 mmHg in Monotherapy group) and DBP (85.3 ±9.9 mmHg and 86.4 ±9.8 mmHg respectively) were slightly higher than mean home SBP and DBP and similar between groups. As for HBPM, the decrease from baseline to week 5 in SBP as well as in DBP was greater in the Fixed combination group and the adjusted mean difference between groups (-7.4 ±1.4 mmHg for Office SBP and – 2.6 ±0.9 mmHg for office DBP) was statistically significant.

Mean change from baseline to Week 10 in home BP

After forced titration, at week 10, the adjusted mean change from baseline in home SBP was still greater in the Fixed combination group: -18.1 ±0.7 mmHg compared to -13.5 ±0.7 mmHg in the Monotherapy group, with a statistically significant adjusted mean difference between groups (p<0.001).

In the same way, the adjusted mean change (±SE) from baseline at week 10 in home DBP was greater in the Fixed combination group: -9.4 ±0.5 mmHg compared to -6.2 ±0.5 mmHg in the Monotherapy group. The adjusted mean difference between groups was statistically significant (p<0.001).

Mean change from baseline to Week 10 in office BP

Results obtained with OBPM were similar to those obtained with HBPM.

All results on BP changes from baseline are summarized in the following table.

Adjusted mean changes in blood pressure from baseline (mmHg) – ITT population

	Fixed combination (N=144)	**Monotherapy (N=143)**		
BP in mmHg	Adjusted mean change from baseline (SE)	Adjusted mean change from baseline (SE)	Adjusted mean difference between groups (SE)	p-value
Week 5				
Home SBP (n= 141/139)	**-12.4 (0.7)**	**-6.3 (0.7)**	**-6.2 (1.0)**	**p<0.001**
Home DBP (n= 141/139)	-5.6 (0.5)	-3.0 (0.5)	-2.6 (0.7)	p<0.001
Office SBP (n= 143/143)	-10.8 (1.0)	-3.3 (1.0)	-7.4 (1.4)	p<0.001
Office DBP (n= 143/143)	-3.8 (0.6)	-1.2 (0.6)	-2.6 (0.9)	p=0.004
Week 10				
Home SBP (n= 132/131)	-18.1 (0.7)	-13.5 (0.7)	-4.5 (1.0)	p<0.001
Home DBP (n= 132/131)	-9.4 (0.5)	-6.2 (0.5)	-3.2 (0.7)	p<0.001
Office SBP (n= 134/136)	-18.4 (1.1)	-12.4 (1.1)	-6.0 (1.6)	p<0.001
Office DBP (n= 134/136)	-8.7 (0.6)	-5.6 (0.6)	-3.1 (0.9)	p<0.001

n= number of evaluable patients in Fixed combination group/number of evaluable patients in Monotherapy group

Response to treatment

At week 5, the proportion of controlled patients (mean home SBP < 135 mmHg) was significantly higher in the Fixed combination therapy group than in the Monotherapy group (54.6% vs. 25.9%, p<0.001). The proportion of responder patients to treatment (mean home SBP < 135 mmHg and mean home DBP < 85 mmHg) was also 2 fold higher in the Fixed combination therapy group than in the Monotherapy group (44.7% vs. 21.6%, p<0.001).

At week 10, the proportion of controlled patients increased to 69.7% in the Fixed combination group and 51.9% in the Monotherapy group and the difference between groups was still statistically significant (p=0.003). The proportion of responder patients to treatment was 67.4% among patients receiving the fixed combination and 44.3% among patients treated with monotherapy (p<0.001).

Response to treatment based on OBPM gave similar results to those based on HBPM.

These results are summarized in the following table.

Proportions of controlled patients and responder patients to treatment – ITT population

Response to treatment	Fixed combination (N=144)	Monotherapy (N=143)	p-value
According to HBPM			
Controlled patients (mean home SBP < 135 mmHg)			
Week 5 (n= 141/139)	54.6%	25.9%	p<0.001
Week 10 (n= 132/131)	69.7%	51.9%	p=0.003
Responder patients (mean home SBP < 135 mmHg and mean home DBP < 85 mmHg)			
Week 5 (n= 141/139)	44.7%	21.6%	p<0.001
Week 10 (n= 132/131)	67.4%	44.3%	p<0.001
According to OBPM			
Mean office SBP < 140 mmHg			
Week 5 (n= 144/143)	52.1%	28.7%	p<0.001
Week 10 (n= 135/136)	74.1%	55.1%	p=0.001
Mean office SBP < 140 mmHg and mean office DBP < 90 mmHg			
Week 5 (n= 144/143)	49.3%	25.9%	p<0.001
Week 10 (n= 135/136)	72.6%	52.9%	p<0.001

HBPM: home blood pressure measurements; OBPM: office blood pressure measurements
n= number of evaluable patients in Fixed combination group/number of evaluable patients in Monotherapy group

Changes in BP from week 5 to week 10

As the proportion of patients with controlled BP (mean home SBP < 135 mmHg) at W5 was unequal between the 2 groups, it appeared necessary to present the results on BP change from W5 to W10 according to BP control at W5.

Regarding SBP, a statistically significant decrease from week 5 to week 10 was observed for all subgroups of patients, with HBPM as well as with OBPM, and this decrease was more important in uncontrolled patients compared to controlled patients at week 5. The mean decrease in SBP from week 5 to week 10, measured at home or in the office, was similar in both treatment groups for uncontrolled patients, around 9 mmHg.

In controlled patients, decrease in mean home SBP from week 5 to week 10 was similar between treatment groups, between 2 and 3 mmHg. Results based on OBPM were different: decrease in mean office SBP was lower in the Fixed combination therapy group (-5.2 mmHg) than in the Monotherapy group (-7.9 mmHg).

Regarding DBP, a statistically significant decrease from week 5 to week 10 was observed for all subgroups of patients except for home measurements of controlled patients under monotherapy.

In uncontrolled patients, mean decrease in DBP from week 5 to week 10 was greater in the Fixed combination group with HBPM and OBPM. In controlled patients, mean change in DBP from week 5 to week 10 measured at home was close to 0 in the Monotherapy group and close to -3 mmHg in the Fixed combination group while this change was similar in both treatment groups with OBPM (-3.2 and -3.5 mmHg).

All these results are summarized in the following table.

Mean BP change from Week 5 to Week 10 (mmHg) according to control status at W5 – ITT population

	Fixed combination therapy		Monotherapy	
	Controlled patients (N=77)	Uncontrolled patients (N=64)	Controlled patients (N=36)	Uncontrolled patients (N=103)
Home SBP				
Week 5 Mean (SD)	127.6 (5.0)	146.0 (9.0)	129.3 (4.6)	147.7 (10.3)
Week 10 Mean (SD)	125.5 (9.4)	136.9 (10.4)	126.9 (6.7)	138.2 (9.9)
Change between W5 and W10 Mean (SD)	-2.2 (8.5)	-9.2 (7.3)	-2.5 (6.5)	-8.6 (6.8)
Home DBP				
Week 5 Mean (SD)	76.7 (8.0)	82.3 (8.9)	76.8 (7.6)	83.8 (9.4)
Week 10 Mean (SD)	74.0 (7.3)	77.2 (8.6)	76.7 (6.8)	79.5 (8.5)
Change between W5 and W10 Mean (SD)	-2.7 (5.1)	-5.0 (4.4)	-0.3 (6.4)	-3.7 (4.2)
Office SBP				
Week 5 Mean (SD)	135.4 (10.7)	146.8 (13.6)	137.3 (9.1)	152.2 (14.0)
Week 10 Mean (SD)	129.6 (13.8)	137.1 (14.0)	130.0 (11.3)	142.2 (13.4)
Change between W5 and W10 Mean (SD)	-5.2 (14.1)	-9.9 (12.9)	-7.9 (10.2)	-9.4 (12.8)
Office DBP				
Week 5 Mean (SD)	79.4 (9.0)	84.3 (11.0)	80.8 (8.6)	86.4 (9.3)
Week 10 Mean (SD)	76.0 (8.3)	78.1 (10.3)	78.3 (8.8)	81.6 (8.9)
Change between W5 and W10 Mean (SD)	-3.2 (8.5)	-6.1 (7.6)	-3.5 (7.8)	-4.4 (7.1)

For comparison of changes in BP from W5 to W10 between treatment groups, SBP control at W5 was added as covariate in the model of ANCOVA.

Adjusted mean changes from W5 to W10 in SBP showed similar decreases in the Fixed combination group (-6.3 mmHg) and in the Monotherapy group (-6.0 mmHg) with HBPM and a slightly more important decrease in the Monotherapy group with OBPM (-8.6 mmHg compared to -7.7 mmHg). The difference between groups was not statistically significant.

Adjusted mean change from W5 to W10 in home DBP showed a greater decrease in the Fixed combination group (-4.1 mmHg) than in the Monotherapy group (-2.4 mmHg), with a statistically significant adjusted mean difference between groups (p=0.008). Adjusted mean change from W5 to W10 in office DBP showed a slightly greater decrease in the Fixed combination group compared to Monotherapy group but the difference between groups was not statistically significant (p=0.345).

These results are summarized in the following table.

Adjusted mean changes in blood pressure between W5 and W10 (mmHg) – ITT population

BP in mmHg	Fixed combination	Monotherapy	Adjusted mean difference between groups (SE)	p-value
	Adjusted mean change (SE) from W5 to W10	Adjusted mean change (SE) from W5 to W10		
Home SBP (n= 132/129)	-6.3 (0.7)	-6.0 (0.7)	-0.3 (1.0)	p=0.730
Home DBP (n= 132/129)	-4.1 (0.4)	-2.4 (0.4)	-1.7 (0.6)	p=0.008
Office SBP (n=133/133)	-7.7 (1.2)	-8.6 (1.2)	0.9 (1.7)	p=0.592
Office DBP (n=133/133)	-4.9 (0.7)	-3.9 (0.7)	-0.9 (1.0)	p=0.345

ANCOVA linear model adjusted on value at baseline (W0) and control at W5
n= number of evaluable patients in Fixed combination group/number of evaluable patients in Monotherapy group

Safety results:

During period A, when all patients were receiving amlodipine 5 mg, 20 patients (5.0%) experienced at least one TEAE. The most frequently reported TEAEs were peripheral oedema (7 patients), headache (4 patients) and diarrhoea (2 patients).

During period B, overall 37 patients (12.8%) experienced at least one TEAE, with no difference between treatment groups. The most frequent adverse events in both treatment groups were reported in the SOC "Nervous system disorders", mainly headaches. Peripheral oedemas were reported mainly in the Monotherapy group (5 patients compared to one patient in the Fixed combination group).

During period C (forced titration), more patients experienced at least one TEAE: 46 patients (16.4%), the percentages being similar in both treatment groups. There was particularly an increase in peripheral oedemas (9 patients in the Monotherapy group and 7 patients in the Fixed combination group).

A total of 5, 14 and 34 TEAEs were considered as possibly related to the study product during period A, B and C respectively. The most frequent over the three periods was peripheral oedema, mostly associated to amlodipine. The number of peripheral oedemas and oedemas related to study product increased during forced titration with increased dosage of amlodipine (10 mg).

Other treatment-related TEAEs reported in both treatment groups, monotherapy as well as fixed combination therapy were vertigo, headache, dizziness and cough.

Treatment related TEAEs asthenia, paraesthesia, erectile dysfunction, hypotension, upper abdominal pain, constipation, hyperkalaemia, arthralgia and myalgia were reported only in the fixed combination group while face oedema and flushing were reported only in the Monotherapy group.

All these treatment related TEAEs had been previously reported with irbesartan or amlodipine.

There were no deaths reported during the study.

Only 2 SAEs were reported during the study in 2 patients receiving the fixed combination therapy: acute cholecystitis, not related to study product, during period B and hyperkalaemia, considered possibly related to study treatment, during period C.

Overall, 8 patients had to permanently discontinue the study treatment because of at least one TEAE: one patient during period A, 4 patients during period B and 3 patients during period C. For 4 patients in the Monotherapy group and 2 patients in the Fixed combination group, these AEs were considered related to study treatment.

Summary of treatment emergent adverse events occurring during the study

	Period A	Period B		Period C	
Number (%) of patients with at least one event	Total (N=399)	Fixed combination (N=145)	Monotherapy (N=143)	Fixed combination (N=139)	Monotherapy (N=141)
Any TEAEs	20 (5.0%)	20 (13.8%)	17 (11.9%)	22 (15.8%)	24 (17.0%)
TEAE possibly related to study product	5 (1.3%)	6 (4.1%)	7 (4.9%)	15 (10.8%)	15 (10.6%)
Any treatment emergent SAEs	-	1 (0.7%)	-	1 (0.7%)	-
SAE possibly related to study product	-	-	-	1 (0.7%)	-
TEAE leading to permanent discontinuation of study product	1 (0.3%)	1 (0.7%)	3 (2.1%)	2 (1.4%)	1 (0.7%)
TEAE possibly related to study product leading to permanent discontinuation of study product	-	-	3 (2.1%)	2 (1.4%)	1 (0.7%)

Regarding laboratory parameters, mean values of potassium and sodium were similar in both treatment groups and remained stable during the study. Mean creatinine value was similar in both treatment groups and showed a slight increase from baseline at W10. Mean creatinine clearance was similar in both treatment groups at baseline and slightly decreased at W10.

Between inclusion visit and randomization visit, mean decrease in Office SBP was -8.5 (±12.3) mmHg and mean decrease in office DBP was -3.3 (±8.3) mmHg. Between baseline and Week 5, there was a decrease in mean SBP and DBP, the decrease being more important in the fixed combination group. At week 10, mean decrease from baseline in Office SBP was -18.3 (±16.1) mmHg in the Fixed combination group and -12.5 (±13.0) mmHg in the Monotherapy group and mean decrease from baseline in Office DBP was -8.4 (±9.4) and -5.8 (±7.3) mmHg respectively. Mean heart rate remained stable during the study.

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