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Sponsor / Company: sanofi-aventis	**Study Identifier:** NCT00957554
Drug substance(s): Irbesartan and Amlodipine	**Study code:** IRBAM_R_04219

Title of the study: **Efficacy and safety of irbesartan/amlodipine fixed combination therapy compared with irbesartan monotherapy in hypertensive patients uncontrolled on irbesartan 150 mg monotherapy. A prospective, randomized, open-label with blinded endpoint evaluation, multicenter, phase III study.**

Study period:

Date first patient enrolled: 28/Jul/2009

Date last patient completed: 19/Sep/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 300/5 mg is superior to that of irbesartan 300 mg monotherapy in lowering SBP as assessed by home blood pressure measurement (HBPM) after 10 weeks of treatment (W10).

The secondary objectives were the following:

- To compare the antihypertensive efficacy of the fixed combination irbesartan/amlodipine 300/5 mg with that of irbesartan 300 mg monotherapy after 10 weeks of treatment (W10) 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 150/5 mg with that of irbesartan 150 mg monotherapy after 5 weeks of treatment (W5) 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 irbesartan 150 mg during 7 to 10 days (Period A). After this period, patients with home SBP $\geq$ 135 mmHg were randomized using a central randomisation procedure (1:1):

- Monotherapy treatment group: patients received irbesartan 150 mg from W0 to W5 (Period B), then irbesartan 300 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 300/5 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: 325

Treated: 325

Evaluated:

	Fixed combination	Monotherapy	Total
Included patients			436
Safety population for period A			434
Randomized patients	156	169	325
Safety population for period B+C	156	169	325
ITT population	155	165	320
PP population	137	138	275

Diagnosis and criteria for inclusion:

Men and women ≥ 18 years, with established essential hypertension, treated with irbesartan 150 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 300 mg/amlodipine 5 mg from W5 to W10.

Administration: Treatment was administered 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 irbesartan.

Dose: Irbesartan 150 mg from W0 to W5, irbesartan 300 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 V4 (W10).

The secondary efficacy variables were:

- The change in mean home DBP between V2 (W0) and V4 (W10),
- The change in mean home SBP and DBP between V2 (W0) and V3 (W5),
- 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 V4 (W10).
- The change in mean office SBP and DBP between V2 (W0) and V3 (W5),
- 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 W10, 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 W10, change in mean home and office SBP and DBP between W0 and W5, 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 responders based on HBPM (home SBP<135 mmHg AND home DBP<85 mmHg) and OBPM (office SBP<140 mmHg AND office DBP<90 mmHg) 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 10 in home SBP

On the ITT population, at baseline, the mean home SBP (±SD) was similar between groups: 152.7 (±11.8) mmHg in the Fixed combination therapy group and 150.4 (±10.1) mmHg in the Monotherapy group. At week 10, after forced titration in both groups, the mean home SBP (±SD) decreased to 133.6 (±10.9) mmHg in the Fixed combination therapy group and to 140.7 (±13.7) mmHg in the Monotherapy group.

The adjusted mean change (±SE) from baseline was -18.7 ±0.8 mmHg in the Fixed combination therapy group compared to -9.9 ±0.8 mmHg in the Monotherapy group. The adjusted mean difference between groups (-8.8 mmHg) was statistically significant (p<0.001).Therefore the fixed combination irbesartan/amlodipine 300/5 mg was superior to irbesartan 300 mg monotherapy in lowering SBP as assessed by HBPM after 10 weeks of treatment.

Similar results were obtained on the PP population.

Secondary criteria:

Mean change from baseline to Week 10 in home DBP

On ITT population, at baseline, the mean home DBP (±SD) was similar between groups: 86.6 (±10.0) mmHg and 86.0 (±10.4) mmHg in Fixed combination therapy and Monotherapy groups respectively.

Mean home DBP decreased from baseline to week 10 in both treatment groups. The adjusted mean change (±SE) from baseline at week 10 was more important in the Fixed combination therapy group: -8.6 ±0.5 mmHg compared to -3.9 ±0.5 mmHg in the Monotherapy group. The adjusted mean difference between groups (-4.7 mmHg) was statistically significant ($p<0.001$).

Mean change from baseline to Week 10 in office BP

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

At baseline, mean office SBP was slightly higher than mean home SBP and similar between groups: 154.2 (±13.9) mmHg in the Fixed combination therapy group and 152.9 (±12.5) mmHg in the Monotherapy group. This was also the case for mean office DBP: 87.5 (±11.4) mmHg and 87.8 (±11.0) mmHg respectively.

As for home SBP, the decrease from baseline to week 10 in office SBP was greater in the Fixed combination group (-17.9 ±1.2 mmHg) than in the Monotherapy group (-8.4 ±1.1 mmHg) and the adjusted mean difference between groups (-9.5 mmHg) was statistically significant ($p<0.001$).

The same was observed for office DBP with an adjusted mean change (±SE) from baseline to week 10 of -7.7 ±0.7 mmHg in the Fixed combination group and -3.5 ±0.7 mmHg in the Monotherapy group and an adjusted mean difference between groups (-4.2 mmHg) statistically significant ($p<0.001$).

Mean change from baseline to Week 5 in home BP

At week 5, the adjusted mean change (±SE) from baseline in home SBP was also greater in the Fixed combination therapy group: -15.4 ±0.8 mmHg compared to -5.6 ±0.8 mmHg in the Monotherapy group, with a statistically significant adjusted mean difference between groups (-9.8 mmHg, $p<0.001$).

In the same way, the adjusted mean change (±SE) from baseline at week 5 in home DBP was greater in the Fixed combination therapy group: -7.4 ±0.5 mmHg compared to -2.4 ±0.5 mmHg in the Monotherapy group. The adjusted mean difference between groups was statistically significant (-5.0 mmHg, $p<0.001$).

Mean change from baseline to Week 5 in office BP

Results obtained with OBPM were similar to those obtained with HBPM with an adjusted mean difference between groups of -9.6 mmHg for SBP and -4.9 mmHg for DBP, both being statistically significant ($p<0.001$).

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

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

BP in mmHg	Fixed combination (N=155)	Monotherapy (N=165)		
	Adjusted mean change from baseline (SE)	Adjusted mean change from baseline (SE)	Adjusted mean difference between groups (SE)	p-value
Week 10				
Home SBP (n= 146/153)	**-18.7 (0.8)**	**-9.9 (0.8)**	**-8.8 (1.1)**	**p<0.001**
Home DBP (n= 146/153)	-8.6 (0.5)	-3.9 (0.5)	-4.7 (0.7)	p<0.001
Office SBP (n= 149/162)	-17.9 (1.2)	-8.4 (1.1)	-9.5 (1.6)	p<0.001
Office DBP (n= 149/162)	-7.7 (0.7)	-3.5 (0.7)	-4.2 (1.0)	p<0.001
Week 5				
Home SBP (n= 153/163)	-15.4 (0.8)	-5.6 (0.8)	-9.8 (1.1)	p<0.001
Home DBP (n= 153/163)	-7.4 (0.5)	-2.4 (0.5)	-5.0 (0.7)	p<0.001
Office SBP (n=154/164)	-14.7 (1.0)	-5.1 (1.0)	-9.6 (1.4)	p<0.001
Office DBP (n= 154/164)	-7.3 (0.7)	-2.4 (0.6)	-4.9 (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 (46.1% versus 26.2%, p<0.001). The proportion of responder patients to treatment (mean home SBP < 135 mmHg and mean home DBP < 85 mmHg) was almost 2 fold higher in the Fixed combination therapy group than in the Monotherapy group (41.6% versus 22.0%, p<0.001).

At week 10, after forced titration in both groups, the proportion of controlled patients increased to 58.9% in the Fixed combination group and 37.7% in the Monotherapy group and the difference between groups was still statistically significant (p<0.001). The proportion of responder patients to treatment was 54.1% among patients receiving the fixed combination and 31.8% among patients treated with monotherapy (p<0.001).

Response to treatment based on OBPM gave slightly higher percentages than 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=155)	Monotherapy (N=165)	p-value
According to HBPM			
Controlled patients (mean home SBP < 135 mmHg)			
Week 5 (n= 154/164)	46.1%	26.2%	p<0.001
Week 10 (n= 146/154)	58.9%	37.7%	p<0.001
Responder patients (mean home SBP < 135 mmHg and mean home DBP < 85 mmHg)			
Week 5 (n= 154/164)	41.6%	22.0%	p<0.001
Week 10 (n= 146/154)	54.1%	31.8%	p<0.001
According to OBPM			
Mean office SBP < 140 mmHg			
Week 5 (n= 154/165)	55.2%	29.1%	p<0.001
Week 10 (n= 149/163)	61.7%	41.1%	p<0.001
Mean office SBP < 140 mmHg and mean office DBP < 90 mmHg			
Week 5 (n= 154/165)	50.6%	26.1%	p<0.001
Week 10 (n= 149/163)	59.7%	39.3%	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 only in uncontrolled patients, with HBPM as well as with OBPM.

In uncontrolled patients at W5 (mean home SBP ≥ 135 mmHg), forced titration led to a further decrease in mean home SBP from week 5 to week 10, of similar magnitude (5.5 mmHg) in both treatment groups. Although a similar decrease in mean office SBP was observed in the Fixed combination therapy group, the decrease observed from W5 to W10 in the Monotherapy group was slightly lower (-3.4 mmHg). In controlled patients, mean home SBP remained stable in both groups from week 5 to week 10 (mean decrease of only -0.7 mmHg in the Fixed combination group and -0.1 mmHg in the Monotherapy group). Regarding OBPM, the decrease in mean office SBP was slightly lower in the Fixed combination therapy group (-1.2 mmHg) than in the Monotherapy group (-2.6 mmHg).

Regarding DBP, a statistically significant decrease in mean home DBP was observed with forced titration from week 5 to week 10 only in uncontrolled patients. When measured in the office, this DBP decrease was not statistically significant.

In uncontrolled patients, mean decrease in DBP from week 5 to week 10 was similar between groups (2 mmHg with HBPM and 0.6 mmHg with OBPM). In controlled patients, the mean decrease in DBP between week 5 and week 10 was very small regarding both HBPM and OBPM (mean decrease of -0.7 mmHg and -1.0 mmHg in the Fixed combination group and -0.2 mmHg and -2.0 mmHg in the Monotherapy group, respectively).

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=71)	Uncontrolled patients (N=83)	Controlled patients (N=43)	Uncontrolled patients (N=121)
Home SBP				
Week 5 Mean (SD)	126.8 (5.6)	145.4 (9.2)	129.5 (5.5)	150.3 (11.2)
Week 10 Mean (SD)	126.1 (7.3)	139.8 (9.5)	129.5 (8.8)	145.1 (12.8)
Change between W5 and W10 Mean (SD)	-0.7 (5.6)	-5.9 (8.4)	-0.1 (7.3)	-5.3 (9.0)
Home DBP				
Week 5 Mean (SD)	76.5 (7.1)	81.3 (11.2)	77.1 (7.2)	85.9 (10.5)
Week 10 Mean (SD)	76.1 (6.6)	79.4 (9.3)	76.9 (7.6)	83.9 (11.0)
Change between W5 and W10 Mean (SD)	-0.7 (4.7)	-2.1 (5.5)	-0.2 (5.7)	-1.7 (5.9)
Office SBP				
Week 5 Mean (SD)	130.7 (11.7)	146.7 (12.0)	138.4 (12.5)	151.5 (13.8)
Week 10 Mean (SD)	130.2 (13.5)	140.9 (14.4)	135.8 (12.0)	148.3 (15.6)
Change between W5 and W10 Mean (SD)	-1.2 (12.9)	-5.7 (15.4)	-2.6 (12.4)	-3.4 (14.2)
Office DBP				
Week 5 Mean (SD)	79.4 (9.7)	81.1 (11.3)	82.9 (9.3)	86.0 (11.7)
Week 10 Mean (SD)	78.9 (8.9)	80.4 (10.3)	80.9 (9.5)	85.2 (12.4)
Change between W5 and W10 Mean (SD)	-1.0 (8.0)	-0.5 (8.7)	-2.0 (9.9)	-0.8 (9.3)

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 change from W5 to W10 in home SBP showed a similar decrease in the Fixed combination group (-4.1mm Hg) and the Monotherapy group (-3.3 mmHg), the difference between groups was not statistically significant (p=0.396). Similar results were obtained with office SBP.

Adjusted mean changes from W5 to W10 in home DBP showed similar slight decreases in the Fixed combination group (-1.5 mmHg) and in the Monotherapy group (-1.2 mmHg). The difference between groups was not statistically significant (p=0.573). When measured in the office, adjusted mean decrease in DBP from W5 to W10 was similar in the Monotherapy group (-1.3 mmHg) and lower in the Fixed combination therapy group (-0.7 mmHg), with no statistically significant difference between groups (p=0.574).

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: Adjusted mean change (SE) from W5 to W10	Monotherapy: Adjusted mean change (SE) from W5 to W10	Adjusted mean difference between groups (SE)	p-value
Home SBP (n= 145/153)	-4.1 (0.7)	-3.3 (0.7)	-0.8 (1.0)	p=0.396
Home DBP (n= 145/153)	-1.5 (0.5)	-1.2 (0.5)	-0.4 (0.7)	p=0.573
Office SBP (n=147/161)	-3.9 (1.2)	-3.1 (1.1)	-0.8 (1.7)	p=0.621
Office DBP (n=147/161)	-0.7 (0.7)	-1.3 (0.7)	0.6 (1.0)	p=0.574

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 irbesartan 150 mg, 21 patients (4.8%) experienced at least one TEAE. The most frequently reported TEAEs were headache (7 patients) and dizziness (3 patients).

During period B, overall 32 patients (9.8%) experienced at least one TEAE (17 patients (10.9%) in the Fixed combination group and 15 patients (8.9%) in the Monotherapy group). 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 Fixed combination group (5 patients compared to one patient in the Monotherapy group).

During period C (forced titration), 27 patients (8.5%) experienced at least one TEAE (16 patients (10.5%) in the Fixed combination group versus 11 patients (6.6%) in the Monotherapy group). The most frequent AEs were reported in the SOC "Infections and infestations" (4 patients in the Fixed combination group versus 2 patients in the Monotherapy group) and "Nervous system disorders" (2 patients versus 3 patients respectively).

A total of 6, 13 and 9 TEAEs were considered as possibly related to the study product during period A, B and C respectively. The most frequent TEAEs, possibly related to the study product over the three periods, were peripheral oedemas (all of them in the Fixed combination group), headaches and dizziness in both groups.

Treatment related TEAEs hypercreatininemia, azotemia, joint stiffness, nausea and sinus bradycardia were reported only in the Fixed combination group while alopecia was 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 3 SAEs were reported during the study; one during period A: upper limb fracture in a patient receiving irbesartan 150 mg, two during period C: colon cancer in a patient receiving the fixed combination irbesartan/amlodipine 300/5 mg and acute myocardial infarction in a patient receiving the monotherapy irbesartan 300 mg. None of these SAEs was considered related to study product.

Overall, 7 patients had to permanently discontinue the study treatment because of at least one TEAE: 2 patients during period A, 3 patients during period B in the Fixed combination group and 2 patients during period C in the Monotherapy group. TEAEs leading to permanent discontinuation during period A and B were considered related to study treatment (except one in period A).

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=434)	Fixed combination (N=156)	Monotherapy (N=169)	Fixed combination (N=152)	Monotherapy (N=166)
Any TEAEs	21 (4.8%)	17 (10.9%)	15 (8.9%)	16 (10.5%)	11 (6.6%)
TEAE possibly related to study product	5 (1.2%)	9 (5.8%)	2 (1.2%)	7 (4.6%)	1 (0.6%)
Any treatment emergent SAEs	1 (0.2%)	-	-	1 (0.7%)	1 (0.6%)
SAE possibly related to study product	-	-	-	-	-
TEAE leading to permanent discontinuation of study product	2 (0.5%)	3 (1.9%)	-	-	2 (1.2%)
TEAE possibly related to study product leading to permanent discontinuation of study product	2 (0.5%)	3 (1.9%)	-	-	-

Regarding laboratory parameters, mean values of potassium, sodium, creatinine and creatinine clearance were similar in both treatment groups and remained stable during the study.

Between inclusion visit and randomization visit, mean decrease in office SBP was -7.8 (±14.4) mmHg and mean decrease in office DBP was -3.1 (±9.3) 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 -8.1 (±15.4) mmHg in the Monotherapy group and mean decrease from baseline in office DBP was -7.5 (±11.5) and -3.6 (±9.0) mmHg respectively.

Mean heart rate remained stable during the study.

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