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Sponsor / Company: Sanofi	**Study Identifiers:** NCT01625494, UTN U1111-1117-9116
Drug substance(s): irbesartan/amlodipine	**Study code:** IRBES_L_05887
Title of the study: A prospective open-label multicentre study of efficacy and safety of irbesartan/amlodipine 4 dose fixed combination therapy in hypertensive patients uncontrolled on irbesartan 150 mg or amlodipine 5 mg monotherapy	
Study center(s): The study was carried out in 8 Russian sites.	
Study period: Date first patient enrolled: 25/May/2012 Date last patient completed: 08/Jan/2013	
Phase of development: III	
Objectives: **Primary:** To assess the proportion of patients with controlled Office Blood Pressure Measurements (OBPM), defined as Systolic blood pressure (SBP) <140 mmHg and Diastolic blood pressure (DBP) <90 mmHg, at the end of the study **Secondary:** - To examine dynamics of antihypertensive effect of 4 dose fixed combination therapy with irbesartan/amlodipine on OBPM (SBP and DBP) over the time - To examine proportion of patients with controlled OBPM (SBP <140 mmHg and DBP <90 mmHg) taking 4 doses of fixed combination therapy in dynamics over the time - To determine the incidence and severity of adverse events (AEs).	
Methodology: Open-label comparative study on efficacy and safety of irbesartan/amlodipine 4 dose fixed combination therapy in hypertensive patients uncontrolled on irbesartan 150 mg or amlodipine 5 mg monotherapy. Both male and female patients with essential hypertension and uncontrolled SBP defined as ≥140 mmHg assessed by OBPM on at least 2 weeks irbesartan 150 mg or amlodipine 5 mg monotherapy have been selected. After selection, patients continued taking amlodipine 5 mg or irbesartan 150 mg monotherapy for the first 4 weeks. All patients in whom OBPM has been controlled (SBP <140 mmHg and DBP <90 mmHg) were withdrawn from further participation. Those patients with uncontrolled BP on monotherapy continued irbesartan/amlodipine 150/5 mg fixed combination intake for the next 4 weeks. Patients with uncontrolled BP continued irbesartan/amlodipine 150/10 mg or 300/5 mg intake for the next 4 weeks with possible further dose modification up to irbesartan/amlodipine 300/10 mg intake for the last 4 weeks of study participation, so doses were gradually to be escalated in accordance with the titration scheme until BP values are controlled. Patients with controlled OBPM continued treatment to the end of the study at the same dose.	

Number of patients:	Planned: 158
	Randomized: 158
	Treated: 149
Evaluated:	
	Efficacy: 149
	Safety: 158
	Pharmacokinetics: N/A

Diagnosis and criteria for inclusion:

- Men and women ≥18 years old
- Established essential hypertension
- Treated with irbesartan 150 mg or amlodipine 5 mg as monotherapy for at least 2 weeks
- With uncontrolled SBP defined as ≥140 mmHg assessed by OBPM
- Signed written informed consent obtained prior to inclusion to the study

Study treatments

Investigational medicinal product(s):

Irbesartan 150 mg

Amlodipine 5 mg

Irbesartan/Amlodipine 150/5 mg

Irbesartan/Amlodipine 300/5 mg

Irbesartan/Amlodipine 150/10 mg

Irbesartan/Amlodipine 300/10 mg

Formulation: N/A

Route(s) of administration: Oral

Dose regimen: once a day in the morning

Noninvestigational medicinal product(s) (if applicable): N/A

Formulation: N/A

Route(s) of administration: N/A

Dose regimen: N/A

Duration of treatment: 16 weeks

Duration of observation: 16 weeks

Criteria for evaluation:

Efficacy:

Primary efficacy criterion:

- Proportion of patients with controlled OBPM (SBP <140 mmHg and DBP <90 mmHg) at the end of the study.

Secondary efficacy criteria:

- Mean OBPM (SBP and DBP) changes between visits and by treatment group.

- Proportion of patients with controlled OBPM by visit and by treatment group.

OBPM have been measured at each visit. All investigators used the same validated automatic noninvasive BP monitor. Mean SBP and mean DBP have been calculated based on 2 from 3 available measurements.

Safety: Safety assessments were performed from the signing of informed consent form until Visit 5 and included monitoring of AEs, serious adverse events (SAEs), deaths, treatment discontinuations due to AEs, as well as control of laboratory safety parameters (creatinine, total bilirubin, serum ALT and AST) on Visit 1 (week 0) and Visit 5 (week 16).

Pharmacokinetics: N/A

Statistical methods:

To summarize the continuous variables, the number of patients, mean standard deviation, minimum, maximum values, and median were calculated. To summarize the categorical variables, number and % for each treatment were calculated.

Values of descriptive statistics are presented for:

- Demographic data and baseline characteristics for all patients and every treatment group.

- Safety values including AEs, laboratory values, mean office values of SBP, DBP and heart rate (HR).

For safety values, proportion of patients with simultaneous office SBP <140 mmHg and office DBP <90 mmHg for each treatment group.

The change in mean office SBP and DBP between visits were analyzed in each treatment group and summarized as continuous variables.

Proportions of patients having office SBP <140 mmHg, and office DBP <90 mmHg on Visit 3 (Week 8) and Visit 4 (Week 12) are also provided.

Summary: This Local randomized study was conducted to examine the efficacy and safety of irbesartan/amlodipine 4 dose fixed combination therapy. A total of 158 patients with uncontrolled arterial hypertension on irbesartan or amlodipine monotherapy were included.

Population characteristics: A total of 158 hypertensive patients were enrolled to the study, among which 119 were female (75.32%). At the enrollment of the study, SBP mean values were 154.51±8.02 mmHg (140.00 to 177.00 mmHg) and DBP mean values were 91.28±7.05 mmHg (60.00 to 108.00 mmHg). The average age was 57.61±10.12 years (31 to 88 years), while body mass index (BMI) was 29.38±4.97 kg/m^2 (19 to 49 kg/m^2). Among 158 patients, 78 patients (49.37%) were on irbesartan 150 mg monotherapy, and 80 (50.63%) were on amlodipine 5 mg monotherapy. A total of 63 patients (39.87%) were obese. BMI was <30 kg/m^2 in 92 patients (58.23%) and ≥30 kg/m^2 in 66 patients (41.77%). A total of 49 patients (31.01%) had dyslipidemia, and 21 (13.29%) had type 2 diabetes mellitus.

The following table provides cumulative statistical values for demographic and baseline characteristics of the test population:

Demographics and baseline characteristics:

		Amlodipine 5 mg (n = 80)	Irbesartan 150 mg (n = 78)	All patients (n = 158)
Age (years)	Mean	59.26	55.91	57.61
	SD	10.39	9.6	10.12
	Range	39-88	31-80	31-88
Sex (female)	n (%)	65 (54.62%)	54 (45.38%)	119 (100%)
Sex (male)	n (%)	15 (38.46%)	24 (61.54%)	39 (100%)
Weight (kg)	Mean	81.41	81.88	81.65
	SD	14.33	14.36	14.30
	Range	52.00-118.00	48.00-120.00	48.00-120.00
Height (cm)	Mean	165.83	167.76	166.78
	SD	7.3	8.32	7.86
	Range	150.00-186.00	152.00-195.00	150.00-195.00
BMI (kg/m^2)	Mean	29.61	29.16	29.38
	SD	4.78	5.17	4.97
	Range	20.00-41.00	19.00-49.00	19.00-49.00
SBP (mmHg)	Mean	155.30	153.71	154.51
	SD	7.37	8.61	8.02
	Range	140.00-174.00	140.00-177.00	140.00-177.00
DBP (mmHg)	Mean	92.74	89.78	91.28
	SD	6.58	7.25	7.05
	Range	60.00-108.00	62.00-102.00	60.00-108.00
HR (beats/min)	Mean	71.64	70.86	71.25
	SD	7.38	6.57	6.98
	Range	55.00-90.00	60.00-89.00	55.00-90.00

Among the 158 patients selected for study participation, 7 patients achieved controlled OBPM values at Visit 2, while 2 patients refused further participation in the study. On Visit 2, 149 patients with mean SBP 150.72±6.8 mmHg and DBP 88.96±7.26 mmHg were enrolled to the study and received irbesartan 150 mg/amlodipine 5 mg fixed combination therapy. At Visit 3, one patient (0.67%) was withdrawn from the study, while 65 (43.62%) achieved target BP values (SBP 130.31±7.34 mmHg; DBP 78,49±5,67 mmHg) and continued taking minimum irbesartan 150 mg/amlodipine 5 mg combination. A total of 83 (55.71 %) patients required dose increase: 42 (28.19%) patients with mean SBP 148.26±6.31 mmHg and DBP 89.33±6.46 mmHg received irbesartan 300 mg/amlodipine 5 mg combination therapy, and 41 (27.52%) with mean SBP 148.54±6.32 mmHg and DBP 86.54±8.31 mmHg received irbesartan 150 mg/amlodipine 10 mg. On Visit 4, 13 (8.73%) patients with mean SBP 146.92±5.44 mmHg and DBP 89.00±3.32 mmHg required the maximal combination of irbesartan 300 mg/amlodipine 10 mg. By Visit 5, 1 patient (0.67%) withdrew from the study, so 147 (98.66%) patients

completed the study, see table below. Among them were 64 (42.95%) patients taking irbesartan 150 mg/amlodipine 5 mg combination, 35 (23.49%) taking irbesartan 300 mg/amlodipine 5 mg, 35 (23.49%) taking irbesartan 150 mg/amlodipine 10 mg combination, and 13 (8.73%) taking irbesartan 300 mg/amlodipine 10 mg combination.

Distribution of patient treatment groups

	Therapy	Number of patients (n)	% Among enrolled patients (n=149)
Visit 2 (Week 4)	Irb 150/Aml 5	149	100%
Visit 3 (Week 8)	Withdrawn	1	0.67
	Irb 150/Aml 5	65	43.62
	Irb 150/Aml 10	41	27.52
	Irb 300/Aml 5	42	28.19
Study was continued		**148**	**99.33%**
Visit 4 (Week 12)	Irb 150/Aml 5	64	42.95
	Irb 150/Aml 10	36	24.16
	Irb 300/Aml 5	35	23.49
	Irb 300/Aml 10	13	8.73
Study was continued		**148**	**99.33%**
Visit 5 (Week 16)	Withdrawn	1	0.67
	Irb 150/Aml 5	64	42.95
	Irb 150/Aml 10	35	23.49
	Irb 300/Aml 5	35	23.49
	Irb 300/Aml 10	13	8.73
Study was completed		**147**	**98.66%**

Efficacy results: The primary objective of this study was to assess proportion of patients with SBP <140 mmHg and DBP <90 mmHg at the end of the study. Among 149 patients enrolled to combined therapy on Visit 2, 98.66% (n=147) patients completed the study. The proportion of patients with controlled OBPM values was progressively increased over time. A total of 43.62% (n=65) of patients reached controlled OBPM level on irbesartan 150 mg/amlodipine 5 mg at Visit 3. At Visit 4, the proportion of patients with controlled OBPM increased by two-fold to 86.58% (n=129): 63 patients from irbesartan 150 mg/amlodipine 5 mg group, 35 patients from irbesartan 150 mg/amlodipine 10 mg group, and 31 patients from irbesartan 300 mg/amlodipine 5 mg group. At Visit 5, the proportion of patients with controlled OBPM was 93.29% (n=139): 63 patients from irbesartan 150 mg/amlodipine 5 mg group, 33 patients from irbesartan 150 mg/amlodipine 10 mg group, 34 patients from irbesartan 300mg/amlodipine 5 mg group, and 9 patients from irbesartan 300 mg/amlodipine 10 mg group.

Proportion of patients with controlled OBPM over time

Therapy	Proportions of patients with controlled OBPM % (n)		
	Visit 3 (Week 8)	Visit 4 (Week 12)	Visit 5 (Week 16)
Irb 150/Aml 5	43.62% (n=65)	42.28% (n=63)	42.28% (n=63)
Irb 150/Aml 10		23.49% (n=35)	22.15% (n=33)
Irb 300/Aml 5		20.81 (n=31)	22.82% (n=34)
Irb 300/Aml 10			6.04% (n=9)
Total:	43.62% (n=65)	86.58% (n=129)	93.29% (n=139)

The more detailed efficacy analysis of the 4 irbesartan/amlodipine fixed dose combinations over time in various treatment groups showed that:

Among the 149 patients placed on irbesartan 150 mg/amlodipine 5 mg at Visit 2, 65 patients (43.62%) showed controlled OBPM at Visit 3 and 63 patients (42.28%) still had controlled OBPM at Visits 4 and 5. Among the 41 patients who received irbesartan 150 mg/amlodipine 10 mg at Visit 3 (Week 8), 35 patients (85.4%) showed controlled OBPM at Visit 4 (Week 12) and 33 patients still had controlled OBPM (80.5%) at the end of the study. Among the 42 patients who received irbesartan 300 mg/amlodipine 5 mg at Visit 3 (Week 8), 31 patients (73.8%) showed controlled OBPM at Visit 4 (Week 12) and 34 patients (81.0%) still had controlled OBPM at the end of the study. Among the 13 patients who received irbesartan 300 mg/amlodipine 10 mg at Visit 4 (Week 12), 9 patients (69.2%) showed controlled OBPM at Visit 5 (Week 16).

Proportion of patients with controlled OBPM over time in each treatment group

Therapy (n)	Proportions of patients with controlled OBPM (%)		
	Visit 3 (Week 8)	Visit 4 (Week 12)	Visit 5 (Week 16)
Irb 150/Aml 5 (n=149)	43.62% (n=65)	42.28% (n=63)	42.28% (n=63)
Irb 150/Aml 10 (n=41)		85.4% (n=35)	80.5% (n=33)
Irb 300/Aml 5 (n=142)		73.8% (n=31)	81.0% (n=34)
Irb 300/Aml 10 (n=13)			69.2% (n=9)
Total:	43.62% (n=65)	86.58% (n=129)	93.29% (n=139)

The treatment with minimal combination of irbesartan 150 mg/amlodipine 5 mg for 4 weeks in 43.62% of patients (n=65) resulted in significant decrease of mean SBP (10.38±10.79 mmHg; p<0.0001) and DBP (5.19±7.47 mmHg; p<0.0001) at Visit 3.

A total of 55.71% (n=83) of patients did not demonstrate significant decrease in BP values. In this group of patients, significant change in BP values was achieved at Visit 4 on irbesartan 150 mg/amlodipine 10 mg treatment (SBP decreased by 7.9±10.52 mmHg; p<0.0001 and DBP decreased by 6.30±7.46 mm Hg; p<0.0001) or on irbesartan 300 mg/amlodipine 5 mg treatment (SBP decreased by 13.5±8.38 mm Hg; p<0.0001 and DBP by 6.90±8.22 mmHg; p<0.0001). In 8.72% (n=13)

patients at Visit 4, mean BP values were still uncontrolled (SBP 146.92±5.44 mmHg, DBP 89.00±3.32 mmHg). Subsequent 4 week administration of maximal combination of irbesartan 300 mg/amlodipine 10 mg resulted in significant decrease in SBP by 9.92±5.94 mmHg; p<0.0001 and in DBP by 7.46±9.91 mmHg; p<0.0001 at Visit 5.

In all patients independent of study treatment, there was a significant decrease in mean BP values on each study visit. At Visit 5 in comparison with the start of combined therapy (Visit 2), mean decrease in SBP was 21.67±9.08 mmHg; p<0.0001; and in DBP 10.92±8.58 mmHg; p<0.0001.

Mean change in OBPM values over time in the treatment groups is shown in the tables below.

Mean OBPM values over time/treatment group

Therapy Irb/Aml	BP	Visit 2		Visit 3		Visit 4		Visit 5	
150/5	SBP	N= 149	150.72±6.8	N= 65	130.31±7.34	N= 64	128.17±6.46	N= 64	127.48±6.76
	DBP		88.96 ±7.26		78.49±5.67		77.95 ±5.86		76.81±6.52
150/10	SBP			N= 41	148.54±6.32	N= 35	127.94±8.05	N= 35	128.29±7.39
	DBP				86.54±8.31		79.09±8.51		78.63±7.12
300/5	SBP			N= 42	148.26±6.31	N= 35	132.23±6.97	N= 35	128.89±7.41
	DBP				89.33±6.46		81.34±6.82		77.89±6.62
300/10	SBP					N= 13	146.92±5.44	N= 13	137.00±9.14
	DBP						89.00±3.32		81.54±9.13

Mean change in OBPM over time/treatment group

Therapy Irb/Aml	Visit	N	SBP			DBP		
			Mean decrease mmHg	SD	p	Mean decrease mmHg	SD	p
150/5	2/3	149	10.38	10.79	**<0.0001**	5.19	7.47	**<0.0001**
	3/4	65	2.14	5.60	**0.003**			**-**
	4/5	64			**-**			**-**
150/10	3/4	40	17.90	10.52	**<0.0001**	6.30	7.46	**<0.0001**
	4/5	34			**-**			**-**
300/5	3/4	42	13.50	8.38	**<0.0001**	6.90	8.22	**<0.0001**
	4/5	35			**-**	3.46	5.85	**0.0013**
300/10	4/5	13	9.92	5.94	**<0.0001**	7.46	9.91	**0.02**
All groups	2/3	149	10.38	10.79	**<0.0001**	5.19	7.47	**<0.0001**
	3/4	147	9.67	10.54	**<0.0001**	3.93	7.55	**<0.0001**
	4/5	147	1.84	6.12	**0.0004**	2.01	5.99	**<0.0001**
	2/5	149	21.67	9.08	**<0.0001**	10.92	8.58	**<0.0001**

The proportion of patients with uncontrolled OBPM at Visit 5 was 5.37% (n=8). Some patients from groups irbesartan 150 mg/ amlodipine 5 mg, irbesartan 150 mg/amlodipine 10 mg, and irbesartan 300 mg/amlodipine 5 mg had showed optimal BP level at previous visit but demonstrated uncontrolled OBPM values on Visit 5: 1 patient from irbesartan 150 mg/amlodipine 5 mg group, 2 patients from irbesartan 150 mg/amlodipine 10 mg group, 1 patient from irbesartan 300mg/ amlodipine 5 mg group, and 4 patients from irbesartan 300 mg/amlodipine 10 mg group.

Safety results: Safety analysis was based on Investigator's Brochure on irbesartan/amlodipine, ed. 1 dated 14 Oct 2011 and included 158 patients. During the study no fatal SAEs were reported. Of the 158 patients included in the safety analysis, 35 AEs were reported in 31 patients (19.62%); 28 (17.72%) patients had 1 AE, 2 (1.26%) patients had 2 AEs, and 1 (0.63%) patient had 3 AEs. All AEs reported were consistent with the known safety profile of the fixed dose combination of irbesartan/amlodipine. The most frequently reported AE was inflammation of upper respiratory tract (51.43% [n=18]). The other AEs were neurological disorders (radiculopathy, dizziness; 17.14% [n=6]), cardiovascular disorders (increase of BP values, sinus tachycardia; 8.57% [n=3]), metabolic disorders (aggravation of diabetes mellitus or dyslipidemia; 11.43% [n=4]), gastrointestinal disorders (5.71% [n=2]), and general disorders (leg edema; 5.71% [n=2]).

Two (2) cases (5.71%) of leg edema occurring in 2 patients were categorized under general disorders and administrative site conditions and were assessed by investigators as possibly related to amlodipine intake. All other AEs were assessed by investigators as not related to study drug intake.

No patients were withdrawn from the study due to AEs.

No clinically significant changes in general health and laboratory values planned per protocol were reported.

Pharmacokinetic results: N/A

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