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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00950066
		Study Code:	IRBES_R_04320
Generic drug name:	Irbesartan + amlodipine	**Date:**	04 January 2011

Title of the study:	A Prospective, Randomized, Multi-national, Multi-center, Double-Blind, Placebo-Controlled, Six-arm, Parallel-group, Phase II (Factorial Design) Study to Evaluate the Safety and Efficacy of Two Fixed Dose Combinations of Irbesartan / Amlodipine *(150 mg/ 5 mg and 300 mg/ 5 mg)* and Monotherapy *(Amlodipine 5 mg, Irbesartan 150 mg and 300 mg)* after Eight Weeks of Treatment in Subjects with Uncomplicated Mild to Moderate Essential Hypertension (IRBES_R_04320).
Coordinating Investigator:	Pr Cheol-Ho Kim, Seoul National University, Bundang Hospital, Korea.
Study centers:	31 active centers: 20 in Korea, 7 in India and 4 in Philippines.
Publications (reference):	NA

Study period:	**Phase of development:**
Date first patient enrolled: 31-July-2009	Phase II
Date last patient completed: 28- January-2010	

Objectives:	Primary objective - To compare the extent of reduction of mean Seated Diastolic Blood Pressure (SeDBP) from baseline at the end of 8 weeks between each Fixed Dose Combination (FDC), its individual constituents administered as monotherapy and placebo. Secondary objectives *Efficacy objectives* • To compare the extent of reduction of mean Seated Systolic Blood Pressure (SeSBP) at the end of 8 weeks from baseline between each FDC, its individual constituents administered as monotherapy and placebo, • To compare the reduction of mean SeDBP and SeSBP at 4 weeks from baseline between each FDC, its

<table>
<tr><td></td><td>individual constituents administered as monotherapy and placebo,
• To compare treatment response rates (SeSBP < 140 mmHg and Se DBP < 90 mmHg) with the FDCs, monotherapies and placebo,*
• To assess the effectiveness of combination therapy relative to monotherapy by construction of a dose-response surface.*
*: these two secondary efficacy objectives were added in the statistical analysis plan, while they were only mentioned as additional analysis in the protocol
Safety objective
-To assess the safety and tolerability of the FDCs, the monotherapies and placebo.</td></tr>
<tr><td>Methodology:</td><td>This was a prospective randomized, multi-national, multi-center, double-blind, placebo-controlled six-arm, parallel-group, phase II, factorial study design.</td></tr>
<tr><td>Number of patients:</td><td>Planned: 240 | Randomized: 270 | Treated: 266</td></tr>
<tr><td>Evaluated:</td><td>
<table>
<tr><th></th><th>FDC 150/5 mg</th><th>FDC 300/5 mg</th><th>Amlodipine 5 mg</th><th>Irbesartan 150 mg</th><th>Irbesartan 300 mg</th><th>Placebo</th><th>Total</th></tr>
<tr><td>Washout Safety population (1)</td><td></td><td></td><td></td><td></td><td></td><td></td><td>80</td></tr>
<tr><td>Randomized patients</td><td>47</td><td>43</td><td>42</td><td>45</td><td>46</td><td>47</td><td>270</td></tr>
<tr><td>Safety population</td><td>47</td><td>42</td><td>40</td><td>45</td><td>45</td><td>47</td><td>266</td></tr>
<tr><td>mITT population</td><td>46</td><td>40</td><td>40</td><td>43</td><td>44</td><td>46</td><td>259</td></tr>
<tr><td>PP population</td><td>38</td><td>32</td><td>34</td><td>40</td><td>36</td><td>35</td><td>215</td></tr>
</table>
(1) Only for patients uncontrolled on anti-hypertensive monotherapy
</td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td>Patients (men and women aged ≥ 18 years) with uncomplicated mild to moderate essential hypertension (as per European Society of Cardiology Classification of Hypertension) were randomized if they were:
- Treatment naïve patients (newly diagnosed patients or patients currently only on lifestyle modification) with a mean SeDBP of 95 to 109 mmHg at screening and randomization visits,
- Patients uncontrolled on anti-hypertensive monotherapy with a mean SeDBP of 90 to 109 mmHg at screening visit and a mean SeDBP of 95 to 109 mmHg at randomization visit after a two-week single-blind placebo washout period.</td></tr>
<tr><td>Investigational products:
Dose:

Administration:</td><td>Combination Therapy:
• Irbesartan 150 mg / Amlodipine 5mg
• Irbesartan 300mg / Amlodipine 5mg
Monotherapy:
• Amlodipine 5mg
• Irbesartan 150mg
• Irbesartan 300mg

Oral administration once daily in the morning after breakfast between 7:00 a.m. and 10:00 a.m.
Washout Period (placebo run-in): 1 Capsule once daily.
Treatment period: 2 Tablets and 1 Capsule once daily.</td></tr>
</table>

		Treatment arm					
dose	form*	Placebo	amlodipine 5 mg	irbesartan 150 mg	irbesartan 300 mg	FDC 150/5 mg	FDC 300/5 mg
placebo	C	X			X		X
amlodipine 5 mg	C		X				
irbesartan 150 mg	C			X			
irbesartan 300 mg	T				X		
FDC 150/5 mg	C					X	
FDC 300/5 mg	T						X
Match Placebo FDC 300/5 mg	T	X	X	X	X	X	
Match placebo irbesartan 300 mg	T	X	X	X		X	X

*C: capsule; T: tablet

Duration of treatment: 8 weeks	**Duration of observation:** 8 weeks ±3 weeks for treatment naïve patients 10 weeks ±3 weeks for patients on previous antihypertensive treatment

Reference therapy:	Placebo
Dose:	Washout Period (placebo run-in for patients previously receiving antihypertensive therapy): 1 Capsule once daily. Treatment period: 2 Tablets and 1 Capsule once daily.
Administration:	Oral administration once daily in the morning after breakfast between 7:00 a.m. and 10:00 a.m.
Criteria for evaluation:	
Efficacy :	The primary efficacy variable was the change from baseline in mean SeDBP at the end of 8 weeks measured using a calibrated mercury sphygmomanometer. The secondary efficacy variables were: • the change from baseline in mean SeSBP at the end of 8 weeks measured using a calibrated mercury sphygmomanometer , • the change from baseline in mean SeDBP and SeSBP at 4 weeks measured using a calibrated sphygmomanometer, • the responder status after 4 and 8 weeks, • the dose-response surface of the change from baseline in mean SeDBP and mean SeSBP at the end of 8 weeks.
Safety:	The safety and tolerability of the FDCs, monotherapies and placebo were assessed by the incidence of clinical Adverse Events (AEs), including laboratory abnormalities.
Statistical methods:	The null hypothesis is "No difference between FDCs and their respective monotherapy components and placebo in the change from baseline in SeDBP at week 8". The superiority of FDC would be demonstrated in the following conditions: the superiority of FDC compared to the individual constituents which make up the combination product and to the placebo. The superiority of the individual components compared to the placebo was also evaluated. However, as this is a phase 2 dose ranging study, this study was primarily expected to demonstrate a dose response with FDC. The inter-group difference of these changes from baseline was compared between each FDC, its individual constituents administered as monotherapy and placebo with a repeated-measures analysis of variance using a mixed linear model with subject as a random effect, treatment group, baseline value, country, visit (V4 - Week 4 and V5 - Week 8) and the interaction between treatment groups and visit as

	fixed factors. Unstructured (UN) correlation structure was used by default. If this structure (UN) was not available (no result), the compound symmetry (CS) was used. To verify model adequacy, graphical diagnostics using residuals plots were performed. First, a plot was performed to check the normality of the residuals distribution. Then, another plot of residuals according to the predicted values was done. And finally, a last plot was performed to check outliers. If there was a strong violation of normal assumption, the non-parametric test (Wilcoxon rank-sum test) was also performed, as a sensitivity analysis, for each comparison at each time-point. The treatment response rates were compared with Cochran-Mantel-Haenszel test stratified by country for combinations versus both monotherapies. The analysis of the dose-response surface was conducted to estimate the treatment effect of the individual components of the FDC. This analysis was also used to identify a change pattern and the interaction conditions that can yield a "maximum" change. The SeDBP change from baseline at the end of 8 weeks was analyzed on PP and mITT populations by estimating the response surface as a function of Irbesartan and Amlodipine. Such an analysis yields a response surface with the following overall structure: $\text{SeDBP change} = \beta_0 + \beta_1 Dose_{Irbe} + \beta_2 Dose_{Amlo} + \beta_3 Dose_{Irbe}^2 + \beta_4 Dose_{Amlo}^2 + \beta_5 Dose_{Irbe} Dose_{Amlo} + \varepsilon$ Where $Dose_{Irbe}$: Magnitude of the Irbesartan dosage (0, 150 or 300mg) $Dose_{Amlo}$: Magnitude of the Amlodipine dosage (0, 5mg) ε: Error term due to model specifications Each efficacy and safety parameter was also described according to previous status: treatment naïve subject (newly diagnosed or subject currently only on lifestyle modification) or subject on anti-hypertensive monotherapy.
Summary:	The mITT population included 259 patients: 183 treatment naïve patients and 76 patients previously on anti-hypertensive monotherapy. The PP population included 215 patients: 152 treatment naïve patients and 63 patients previously on anti-hypertensive monotherapy. Demographic and other baseline characteristics were comparable between groups in the mITT population. The gender distribution was 56.0% of men and 44.0% of women. The mean (±SD) age was 49.8 (±10.2) years. SeDBP and SeSBP were comparable between groups at screening and at randomization. At randomization, the mean (±SD) SeDBP was 99.7 (±3.4) mmHg and the mean SeSBP was 152.6 (±11.9) mmHg. Demographic and other baseline characteristics were comparable between the mITT and PP populations. For the PP population, at randomization, the mean (±SD) SeDBP was 99.7 (±3.4) mmHg and the mean SeSBP was 152.5 (±11.6) mmHg.
Efficacy results:	**The primary criterion** was the reduction in SeDBP after 8 weeks of treatment. At week 8, mean SeDBP decreased in all groups. For each treatment group, the change from baseline in SeDBP at week 8 was statistically significant ($p<0.001$). The difference in adjusted mean change from baseline in SeDBP at week 8 between each monotherapy (irbesartan 300 mg, irbesartan 150 mg and amlodipine 5 mg) and placebo was statistically significant: $p<0.001$, $p=0.010$ and $p<0.001$ respectively. In the group receiving the placebo, an adjusted mean decrease of 8.6 mmHg was observed. The difference in adjusted mean change from baseline in SeDBP at week 8 was statistically significant between the groups receiving FDC 300/5 mg and FDC 150/5 mg and the group receiving placebo ($p<0.001$). In the group receiving FDC 150/5 mg, the adjusted mean reduction in SeDBP after 8 weeks of treatment was -19.3 mmHg, not statistically different from the adjusted mean reduction observed with amlodipine 5 mg (-16.4 mmHg, $p=0.150$), but significantly higher than the adjusted mean reduction observed with irbesartan 150 mg (-13.7 mmHg, $p=0.004$).

The adjusted mean reduction in SeDBP with FDC 300/5 mg was -18.1 mmHg, not significantly different from the adjusted mean reduction observed with irbesartan 300 mg (-18.4 mmHg) or the adjusted mean reduction observed with amlodipine 5 mg (-16.4 mmHg).

Therefore, the efficacy of both FDCs was demonstrated with respect to reduction in SeDBP. However, the superiority of the FDCs over monotherapies at the same doses in Se DBP change from baseline at week 8 was not demonstrated on the overall PP population in this Phase 2 study.

SeDBP Reduction from Baseline at Week 8 – PP population

SeDBP	n	Baseline	Week 8	Raw change (W8 – Baseline)	Within Group p-value*	Adjusted change (W8 – Baseline)	Difference at Week 8 (FDC - Mono)	Between Group p-value**
		Mean (SD)	Mean (SD)	Mean (SD)		Mean (SE)	μ [95% CI]	
FDC 300/5 mg	32	99.3 (3.3)	82.3 (8.1)	-17.1 (8.3)	<0.001	-18.1 (1.5)		
Irbesartan 300 mg	36	99.2 (2.9)	81.8 (9.7)	-17.4 (9.4)	<0.001	-18.4 (1.4)	0.30 [-3.75;4.36]	0.883
Amlodipine 5 mg	34	100.2 (3.8)	84.6 (9.4)	-15.6 (8.3)	<0.001	-16.4 (1.5)	-1.62 [-5.74;2.49]	0.438
Placebo	35	99.6 (3.3)	91.7 (7.9)	-7.9 (7.3)	<0.001	-8.6 (1.4)	-9.42 [-13.50;-5.34]	<0.001
FDC 150/5 mg	38	99.9 (3.6)	81.4 (10.5)	-18.5 (10.0)	<0.001	-19.3 (1.4)		
Irbesartan 150 mg	40	99.8 (3.5)	87.1 (9.5)	-12.7 (9.7)	<0.001	-13.7 (1.4)	-5.60 [-9.38;-1.82]	0.004
Amlodipine 5 mg	34	100.2 (3.8)	84.6 (9.4)	-15.6 (8.3)	<0.001	-16.4 (1.5)	-2.89 |-6.82;1.05]	0.150
Placebo	35	99.6 (3.3)	91.7 (7.9)	-7.9 (7.3)	<0.001	-8.6 (1.4)	-10.68 [-14.60;-6.77]	<0.001

*p-value of Student's t test
**p-value of Mixed ANCOVA linear model for repeated measures.

On the mITT population, the superiority of FDC 300/5 mg was not demonstrated in SeDBP change from baseline at week 8 but the superiority of FDC 150/5mg was demonstrated.

Secondary endpoints (PP population)

SeSBP at week 8

At baseline, the mean SeSBP was similar between groups. At week 8, the mean SeSBP decreased in all groups. For each treatment group, the change from baseline in SeSBP at week 8 was statistically significant (p<0.001).

In the group receiving the placebo, an adjusted mean reduction of 11.7 mmHg was observed.

The difference in adjusted mean change from baseline in SeSBP at week 8 between each monotherapy (irbesartan 300 mg, irbesartan 150 mg and amlodipine 5 mg) and placebo was statistically significant: p<0.001, p=0.002 and p=0.003 respectively

In the group receiving FDC 150/5 mg, the adjusted mean reduction in SeSBP after 8 weeks of treatment was -27.9 mmHg, significantly greater than the adjusted mean reduction observed with amlodipine 5 mg (-20.7 mmHg, p=0.015), and the adjusted mean reduction observed with irbesartan 150 mg (-20.9 mmHg, p=0.014). Therefore FDC 150/5 mg was superior to each component given in monotherapy at the same

dose in lowering SeSBP after 8 weeks of treatment.

The adjusted mean reduction in SeSBP was -27.0 mmHg with FDC 300/5 mg, not statistically significantly different from the adjusted mean reduction observed with irbesartan 300 mg (-23.9 mmHg) but significantly different from the adjusted mean reduction observed with amlodipine 5 mg (-20.7 mmHg, p=0.042).

SeSBP Reduction from Baseline at Week 8 – PP population

SeDBP	n	Baseline	Week 8	Raw change (W8 – Baseline)	Within Group p-value*	Adjusted change (W8 – Baseline)	Difference at Week 8 (FDC - Mono)	Between Group p-value**
		Mean (SD)	Mean (SD)	Mean (SD)		Mean (SE)	μ [95% CI]	
FDC 300/5 mg	32	151.4 (12.1)	125.7 (11.7)	-25.7 (15.8)	<0.001	-27.0 (2.2)		
Irbesartan 300 mg	36	152.4 (11.5)	129.1 (14.1)	-23.2 (16.8)	<0.001	-23. 9 (2.1)	-3.06 [-9.03;2.90]	0.312
Amlodipine 5 mg	34	152.1 (9.9)	132.1 (12.8)	-19.9 (13.0)	<0.001	-20.7 (2.2)	-6.29 [-12.34;-0.24]	0.042
Placebo	35	154.6 (12.9)	142.1 (13.1)	-12.5 (11.9)	<0.001	-11.7 (2.1)	-15.25 [-21.26;-9.23]	<0.001
FDC 150/5 mg	38	151.3 (12.7)	124.6 (13.2)	- 26.7 (16.8)	<0.001	-27.9 (2.1)		
Irbesartan 150 mg	40	153.0 (10.7)	132.4 (13.5)	-20.5 (13.0)	<0.001	-20.9 (2.0)	-7.01 [-12.59;-1.44]	0.014
Amlodipine 5 mg	34	152.1 (9.9)	132.1 (12.8)	-19.9 (13.0)	<0.001	-20.7 (2.2)	-7.20 [-12.99;-1.40]	0.015
Placebo	35	154.6 (12.9)	142.1 (13.1)	-12.5 (11.9)	<0.001	-11.7 (2.1)	-16.16 [-21.94;-10.37]	<0.001

*p-value of Student's t test
**p-value of Mixed ANCOVA linear model for repeated measures.

SeDBP and SeSBP at week 4

At week 4, the adjusted mean reduction in SeDBP and SeSBP obtained with FDC 150/5 was greater than the adjusted mean reduction obtained with each monotherapy and the differences were statistically significant.

With FDC 300/5 mg, the adjusted mean reduction in SeDBP was statistically superior to the adjusted mean reduction obtained with each monotherapy. For reduction in SeSBP, there was a significant difference between FDC 300/5 mg and amlodipine 5 mg (p=0.008) and a difference close to statistical significance with irbesartan 300 mg (p=0.055).

BP lowering effect was observed earlier in the groups receiving FDC compared to the groups receiving monotherapies.

Adjusted mean (SE) change in SeDBP and SeSBP from baseline– PP population

Adjusted Mean (SE) change from baseline	PP population (N=215)			
	SeDBP		SeSBP	
	At Week 4	At Week 8	At Week 4	At Week 8
FDC 300/5 mg	-18.5 (1.3)* †	-18.1 (1.5)	-27.6 (2.1)*	-27.0 (2.2)*
FDC 150/5 mg	-18.3 (1.2)* †	-19.3 (1.4) †	-26.5 (1.9)* †	-27.9 (2.1)* †
Irbesartan 300 mg	-13.4 (1.3)	-18.4 (1.4)	-22.2 (1.9)	-23.9 (2.1)
Irbesartan 150 mg	-12.8 (1.2)	-13.7 (1.4)	-16.7 (1.9)	-20.9 (2.0)
Amlodipine 5 mg	-13.8 (1.3)	-16.4 (1.5)	-20.1 (2.0)	-20.7 (2.2)
Placebo	-10.5 (1.3)	-8.6 (1.4)	-12.1 (2.0)	-11.7 (2.1)

* p<0.05 versus same dose amlodipine monotherapy;
† p<0.05 versus same dose irbesartan monotherapy.

Treatment response rate

At week 4, the treatment response rate was numerically higher in the groups receiving FDC (81.3 % in the group receiving FDC 300/5 mg and 78.9% in the group receiving FDC 150/5 mg) than in the groups receiving monotherapy or placebo: 61.1%, 52.9%, 45.0%, 34.3% for the patients in the groups receiving irbesartan 300 mg, amlodipine 5 mg, irbesartan 150 mg and placebo respectively.

At week 4, for FDC 300/5 mg, only the difference in treatment response rate with the group receiving amlodipine 5 mg was statistically significant (p=0.012). For FDC 150/5 mg, the difference in treatment response rate was statistically significant compared to the group receiving irbesartan 150 mg (p=0.002) and the group receiving amlodipine 5 mg (p=0.018).

At week 8, the rate of response was slightly lower in the groups receiving both FDCs compared to week 4 while the rate of response slightly increased for the groups receiving monotherapies. At week 8, there were no statistically significant differences in the rate of treatment responses between each FDC group and the groups receiving monotherapy at same doses.

A post-hoc analysis of treatment response rates with SBP < 130 mmHg and DBP < 80 mmHg was performed. At this more stringent threshold, the response rate with FDC was generally higher than that with monotherapy at the same doses, except with irbesartan 300mg at week 8. Response rates at week 8 were 34.4% (FDC 300/5 mg), 28.9% (FDC 150/5 mg), 36.1% (Irbesartan 300mg), 15.0% (Irbesartan 150mg), 14.7% (Amlodipine 5mg) and 2.9% (placebo).

Response rate– PP population

Response rate	PP population (N=215)			
	(SBP<140 mmHg and DBP<90 mmHg)		**(SBP<130 mmHg and DBP<80 mmHg)**	
	Week 4	Week 8	Week 4	Week 8
FDC 300/5 mg	81.3 %*	68.8%	28.1%	34.4%*
FDC 150/5 mg	78.9%* †	71.1%	31.6%†	28.9%
Irbesartan 300 mg	61.1%	72.2%	16.7%	36.1%
Irbesartan 150 mg	45.0%	55.0%	10.0%	15.0%
Amlodipine 5 mg	52.9%	61.8%	17.6%	14.7%
Placebo	34.3%	28.6%	0.0%	2.9%

***** p<0.05 versus same dose amlodipine monotherapy;
† p<0.05 versus same dose irbesartan monotherapy.

Dose response surface

Linear regression modelling on the dose-response surface for SeDBP was statistically significant: p = 0.013 for irbesartan and p < 0.001 for amlodipine. The modelled maximum change of SeDBP from baseline at week 8 was -17.9 mmHg, achieved with irbesartan and amlodipine dosage values of 203.4 mg and 5 mg respectively.

Linear regression modelling on the dose-response surface for SeSBP was statistically significant: p-value was 0.009 for irbesartan and 0.014 for amlodipine. The modelled maximum change of SeSBP from baseline at week 8 was -27.0 mmHg, achieved with irbesartan and amlodipine dosage values of 216.0 mg and 5 mg respectively.

Dose response – PP population

	PP population (N=215)	
	SeDBP	SeSBP
Theoretical maximum change at week 8 (mmHg)	-17.91	-26.97
Irbesartan dosage value (mg)	203.41	216.01
Amlodipine dosage value (mg)	5.00	5.00

Sub-group analysis: treatment naïve patients and patients previously on anti-hypertensive monotherapy.

Statistical analysis was performed on the sub-group of treatment naïve patients while only descriptive analysis was performed for patients previously on monotherapy considering the small number of patients from this sub-group in each treatment group (9 to 14 patients per group).

At week 8, the mean (±SD) reduction in SeDBP obtained with FDC 300/5 mg was -18.4 (8.5) mmHg in patients previously on anti-hypertensive monotherapy and -16.0 (8.2) mmHg in treatment naïve patients. With FDC 150/5 mg, the mean reduction was -17.3 (8.9) mmHg and -18.8 (10.4) mmHg respectively.

The results for treatment naïve patients were similar to those obtained for all patients in the PP population: the superiority of both FDC was not demonstrated in the change from baseline in SeDBP and only the superiority of FDC 150/5 mg was demonstrated in SeSBP change from baseline.

In the sub-group of patients previously on anti-hypertensive monotherapy, the reduction at week 8 in SeDBP with each FDC (300/5 mg and 150/5 mg) was numerically higher to the reduction obtained with each monotherapy at the same dose. This was also observed for reduction in SeSBP except with

irbesartan 150 mg.

The raw mean change in SeSBP from baseline was higher for treatment naïve patients than for patients on anti-hypertensive monotherapy for all treatment groups at week 4. At week 8, the same trend was observed, except for the group receiving irbesartan 150 mg.

Raw mean (SD) change in SeDBP from baseline according to previous status – PP population

Mean (SD) change from baseline in SeDBP	PP population			
	Treatment naïve patients (N= 152)		Patients on anti-hypertensive monotherapy (N=63)	
	At Week 4	At Week 8	At Week 4	At Week 8
FDC 300/5 mg	-16.4 (7.8)	-16.0 (8.2)	-19.0 (6.8)	-18.4 (8.5)
FDC 150/5 mg	-17.4 (8.3)	-18.8 (10.4)	-17.6 (6.8)	-17.3 (8.9)
Irbesartan 300 mg	-13.0 (6.7)	-19.6 (8.4)	-11.0 (8.4)	-11.6 (9.8)
Irbesartan 150 mg	-12.0 (7.3)	-12.8 (9.5)	-11.2 (5.5)	-12.6 (10.5)
Amlodipine 5 mg	-14.0 (7.8)	-16.5 (8.1)	-10.0 (8.8)	-13.0 (9.0)
Placebo	-9.4 (7.8)	-7.2 (6.6)	-10.7 (7.4)	-10.1 (9.1)

Raw mean (SD) change in SeSBP from baseline according to previous status – PP population

Mean (SD) change from baseline in SeSBP	PP population			
	Treatment naïve patients (N= 152)		Patients on anti-hypertensive monotherapy (N=63)	
	At Week 4	At Week 8	At Week 4	At Week 8
FDC 300/5 mg	-28.9 (16.1)	-28.4 (15.2)	-23.0 (11.7)	-22.2(16.4)
FDC 150/5 mg	-26.7 (14.2)	-28.1 (18.9)	-21.3 (4.4)	-22.3 (6.0)
Irbesartan 300 mg	-23.4 (15.4)	-26.5 (16.5)	-16.7 (14.0)	-14.7 (15.3)
Irbesartan 150 mg	-17.3 (12.0)	-19.9 (12.4)	-14.2 (13.0)	-22.0 (14.9)
Amlodipine 5 mg	-19.8 (15.1)	-20.4 (12.9)	-18.1 (11.3)	-18.7 (14.1)
Placebo	-15.2 (11.5)	-14.4 (9.7)	-6.1 (17.9)	-6.9 (16.2)

Regarding response rate, at week 4, patients previously on anti-hypertensive monotherapy had a better treatment response rate than treatment naïve patients for both FDC groups: 92.9% with FDC 300/5 mg and 88.9% with FDC 150/5 mg for patients on anti-hypertensive therapy compared to 72.2% and 75.9% respectively for treatment naïve patients.

For treatment naïve patients, at week 4, the difference of treatment response rate between the group receiving FDC 150/5 mg and the group receiving irbesartan 150 mg was statistically significant.

At week 8, for patients previously on anti-hypertensive monotherapy, treatment response rate was numerically higher than treatment response rates obtained with the monotherapies at the same doses: 71.4% with FDC 300/5 mg compared to 60.0% with irbesartan 300 mg and 55.6% with amlodipine 5 mg.

Response rate according to previous status – PP population

Response rate (SBP<140 mmHg and DBP<90 mmHg)	PP population			
	Treatment naïve patients (N= 152)		Patients on anti-hypertensive monotherapy (N=63)	
	Week 4	Week 8	Week 4	Week 8
FDC 300/5 mg	72.2%	66.7%	92.9%	71.4%
FDC 150/5 mg	75.9%†	72.4%	88.9%	66.7%
Irbesartan 300 mg	61.5%	76.9%	60.0%	60.0%
Irbesartan 150 mg	42.9%	53.6%	50.0%	58.3%
Amlodipine 5 mg	60.0%	64.0%	33.3%	55.6%
Placebo	30.8%	26.9%	44.4%	33.3%

† p<0.05 versus same dose irbesartan monotherapy.

For treatment naïve patients, linear regression modelling on the dose-response surface for SeDBP and SESBP was statistically significant. Analysis of dose response surface showed a modeled maximum change of SeDBP from baseline at week 8 of -17.9 mmHg, achieved with irbesartan and amlodipine dosage values of were 290.3 mg and 2.5 mg respectively. The modeled maximum change of SeSBP from baseline at week 8 was -27.5 mmHg, achieved with irbesartan and amlodipine dosage values of 292.7 mg and 2.5 mg respectively.

For patients on anti-hypertensive monotherapy, irbesartan and amlodipine dosage values were 271.9 mg and 5.0 mg respectively for a theoretical maximum change from baseline in SeDBP at week 8 of -18.4 mmHg. But the linear regression modelling on the dose-response surface was not statistically significant in this small subgroup (63 patients).

Dose response according to previous status - PP population

	Treatment naïve patients (N= 152)		Patients on anti-hypertensive monotherapy (N=63)	
	SeDBP	SeSBP	SeDBP	SeSBP
Theoretical maximum change at week 8 (mmHg)	-17.87	-27.52	-18.44	-25.99
Irbesartan dosage value (mg)	290.31	292.65	271.88	172.89
Amlodipine dosage value (mg)	2.50	2.50	5.00	5.00

Safety results:

Each of the study treatments was generally well tolerated, and there were no safety concerns identified during the course of this study.

Treatment Emergent Adverse Events (TEAES) were in line with the prescribing information of irbesartan and amlodipine.

A total of 73 patients (27.4%) experienced at least one TEAE during the double-blind treatment period. This percentage was similar for all treatment groups. Most TEAEs (63.2%) were of mild intensity and 91.5% of the TEAES were completely resolved at the end of the study.

The most frequent TEAEs were infections and infestations, at a slightly higher frequency in patients

	receiving irbesartan alone and placebo. Nervous system disorders were reported for nearly 7% of the patients, particularly dizziness and headache. Headache was only reported in the group receiving FDC 300/5 mg (4 patients) and in the placebo group (3 patients), all cases being of mild or moderate intensity. Dizziness was reported in all groups except FDC 150/5 mg, concerning only one patient in the groups receiving the monotherapies and 2 patients in the group receiving FDC 300/5 mg and in the placebo group. All cases were of mild intensity except one that was considered severe (in the group receiving irbesartan 300 mg). Gastrointestinal disorders were reported in all groups, with diarrhea (3 patients), upper abdominal pain (2 patients) and irritable bowel syndrome (2 patients). Adverse events were possibly related to the study medication for 17 patients (6.4%), two to four patients in each treatment group. They were essentially gastrointestinal disorders and nervous system disorders. Only one (dizziness in the group receiving irbesartan 300 mg) was graded of severe intensity and considered as a serious TEAE. Four of them led to permanent discontinuation of the study product: one (orthostatic hypertension) in the group receiving FDC 150/5 mg, two (headache and somnolence) in the group receiving FDC 300/5 mg and one (dizziness) in the group receiving irbesartan 300 mg. Four patients experienced one TEAE each that was considered serious: one case of accidental study drug overdose in the group receiving FDC 150/5 mg, one case of subarachnoid haemorrage in the group receiving irbesartan 150 mg, one case of dizziness and one case of infectious enteritis in the group receiving irbesartan 300 mg. Only the case of dizziness was considered related to the study drug (irbesartan 300 mg). Except the accidental overdose, all these SAEs led to permanent discontinuation of the study drug. No deaths were reported during the study. Laboratory parameters (haematology, serum chemistry) remained stable and mean values were similar between treatment groups. Urine analysis showed rare positive cases for glycosuria, proteinuria, Red Blood Cells/RBC and White Blood Cells/WBC. No safety concerns were identified in vital signs (pulse rate, Systolic Blood Pressure/SBP and Diastolic Blood Pressure/DBP), physical examination and ECG.
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