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Sponsor/Company : sanofi-aventis **Drug substance :** IRBESARTAN / HYDROCHLOROTHIAZIDE	**Study Identifiers** : NCT00500604 **Study Code** : IRBEH_R_ 02584

Title of the Study:	A Comparative Study of the Efficacy of Irbesartan/ Hydrochlorothiazide 300/25 mg versus Valsartan/ Hydrochlorothiazide 160/25 mg Using Home Blood Pressure Monitoring in the Treatment of Mild to Moderate Hypertension. A Controlled, Randomised, Open-label, Multicentric, Phase IIIb/IV Study
Study Centers:	78
Date First Subject Enrolled: **Date Last Subject Completed:**	03 JUL 2007 18 JAN 2010
Phase of Development:	Phase IIIb/IV
Objectives:	**Primary:** To compare the antihypertensive efficacy of the combination Irbesartan/HCTZ 300/25 mg with the combination Valsartan/HCTZ 160/25 mg, using reduction in mean Systolic Blood Pressure (SBP) as primary efficacy criterion, as measured by Home Blood Pressure Monitoring (HBPM), after 24 weeks compared with baseline (W0), in hypertensive subjects insufficiently controlled by Hydrochlorothiazide (HCTZ) alone. **Secondary:** To compare the percentage of subjects with normalised Blood Pressure < 135/85 mmHg (measured by HBPM) at the end of the study (Week 24).
Methodology:	A prospective, controlled, randomised, open-label, multicenter, parallel group study with blinded endpoint evaluation.

Number of Subjects:	*Planned*	*Evaluated*	*Safety*
	1040	1056	1075

Inclusion Criteria:	**Age and Sex** 1) Men and women who are ≥ 18 and < 80 years of age **Target Population** 2) Established essential hypertension, untreated or treated but uncontrolled with treatment: Office Systolic Blood Pressure ≥ 160 mmHg for untreated subjects Office Systolic Blood Pressure ≥ 140 mmHg for subjects already treated with an antihypertensive drug. Previous antihypertensive therapy must have been implemented for a minimum of 4 weeks and must be either monotherapy or one of the following permitted combination drugs (or equivalent free dose combination):

	A. ACE inhibitor (Angiotensin Converting Enzyme) /calcium channel blocker B. Beta blocker/calcium channel blocker C. Beta blocker/low dose diuretic D. ACE inhibitor/low dose diuretic **Signed Written Informed Consent** 3) Signed written informed consent obtained
Exclusion Criteria:	**Target Disease Exceptions** 1) Systolic Blood Pressure ≥ 180 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 110 mmHg evaluated at doctor's office at Visit 1. **Medical History and Concurrent Diseases** 2) Known or suspected causes of secondary hypertension. 3) Subject with bilateral renal artery stenosis, renal artery stenosis in a solitary kidney; with a renal transplant or with only one functioning kidney. 4) Type 1 diabetes mellitus. 5) Significant cardiovascular, neurological, endocrinologic, renal, metabolic, or gastrointestinal disease, a malignancy or any other diseases ***considered by the Investigator*** to make participation in the study not in the best interest of the subject. **Related to Study Drugs** 6) Known hypersensitivity to diuretics or sulphonamides or history of angioedema or cough related to the administration of an angiotensin II receptor antagonist or any combination of the drugs used. 7) Known contraindications to any of the study drugs (see package inserts). **Prohibited Therapies and/or Medications** 8) Concomitant use of any other antihypertensive treatment. 9) Use of any of the investigational products for this study (Irbesartan, Irbesartan/Hydrochlorothiazide, Valsartan, Valsartan/Hydrochlorothiazide) within the 3 months prior to the study. **Other Exclusion Criteria** 10) Inability to obtain a valid HBPM recording i.e., obesity or arrhythmia. 11) Subject unable to understand the study procedures. 12) Administration of any other investigational drug in the last 30 days before enrolment and during the course of the study. 13) Prisoners or subjects who are compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical illness. 14) Pregnant or breast-feeding women 15) Women of childbearing potential not protected by effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy

Investigational Products: **Formulation(s):**	Irbesartan/Hydrochlorothiazide Hydrochlorothiazide (HCTZ): 25mg Co-Aprovel (Irbesartan/HCTZ): 150/12.5mg, 300/12.5mg Co-Diovan (Valsartan/HCTZ): 80/12.5mg, 160/12.5mg
Duration of Study:	**Enrollment period:** 21 months **Treatment period per subject:** 27-29 weeks **Total study duration:** Approximately 23 months
Criteria for Evaluation:	**Primary efficacy criterion:** Reduction in mean SBP between randomization (Week 0) and (Week 24), measured by HBPM. **Main secondary efficacy criterion:** Percentage of subjects with normalised BP < 135/85 mmHg (measured by HBPM) at Week 24. **Safety criteria:** Adverse events, vital signs and laboratory tests.
Statistical Methods:	**Main Analysis** The change of average SBP measured by HBPM between the initial state (at randomisation) and at the end of the study (W24) will be studied in a covariance analysis model of treatment factor, adjusted by SBP at randomisation. The treatment effect test will be a two-sided one with a Type-I error equal to 5%. Means and standard deviations by group will be described for the main criterion. SBP means at randomisation and at W24 with their standard deviations will also be described. Adjusted means by group with their standard errors will be given. Finally, an estimation of treatment effect, its standard error and its 95% confidence interval will be presented. This analysis will be carried out in the Intent To Treat (ITT) population. A sensitivity analysis will be made in the Per Protocol (PP) population according to the same model. **Tolerance** Adverse effects will be described by treatment groups in the Full Analysis Set (FAS) population. The number of subjects with at least one adverse event in each treatment group will be compared by a Fisher's exact test. **Sample Size Calculation** The COSIMA study compared Irbesartan/HCTZ and Valsartan/HCTZ combinations at lower doses (150/12.5 mg vs 80/12.5 mg) and showed an ITT treatment effect of 2.4 mmHg $\pm$ 0.9 mmHg after 8 weeks. From this result we have derived an assumption, that treatment effect difference between two groups would be 2.1mmHg $\pm$ 12 mmHg, when we consider different definitions on ITT population and conservative common standard deviation. A sample size of 520 in each group will have 80% power to detect a difference in means of 2.1mmHg assuming that the common standard deviation is 12mmHg using a two group t-test with a 0.05 two-sided significance level.

Summary:	This study was conducted in 78 centers in 14 countries. A total of 1056 subjects were randomized into the study (FAS Population) and were also analyzed for efficacy (ITT Population), with 535 subjects receiving Irbesartan/Hydrochlorothiazide and 521 receiving Valsartan/ Hydrochlorothiazide. 185 subjects were included in the Per Protocol (PP) Population by virtue of not causing any major protocol deviation during the study. The safety population included 1075 subjects. The age of ITT subjects ranged from 18 to 79 years. The average age of 535 subjects in the Irbesartan/HCTZ arm was 54.5 years, and that of 521 subjects in the Valsartan/HCTZ arm was 55 years. The Irbesartan/HCTZ arm included 281 (53%) male and 254 (47%) female subjects, while the Valsartan/HCTZ arm included 246 (47%) male and 275 (53%) female subjects. There were 324 (n=535; 60.6%) subjects in the Irbesartan/HCTZ arm and 331 (n=521; 63.5%) in the Valsartan/HCTZ arm who were on treatment for hypertension at the time of enrollment. The duration of hypertension in the Irbesartan/HCTZ arm ranged from 0.008 years to 38.081 years, with a mean duration of 6.21 years. The duration of hypertension in the Valsartan/HCTZ arm ranged from 0.003 years to 34.7 years, with a mean duration of 5.94 years.
Efficacy Results:	**Primary efficacy:** Comparison the average change in SBP by HBPM from Baseline (Week 0) to End of Study (Week 24) in the Efficacy Population (N=991) showed that the average change in SBP (SD) was 22.2 (13.2) mmHg in the Valsartan/HCTZ arm, and 22.7 (13.3) mmHg in the Irbesartan/HCTZ arm. Hence, Irbesartan/HCTZ was more effective in lowering SBP than Valsartan/HCTZ by an adjusted mean difference of 0.399 mmHg by Week 24 (95% CI; -1.917:1.119). The average change in SBP (HBPM) from Baseline to Week 24 in the Per Protocol analysis set (N=185) showed that the average change in SBP (SD) from Baseline to Week 24 was 25.2 (15) mmHg in the Valsartan/HCTZ arm, and 25.1 (12.7) mmHg in the Irbesartan/HCTZ arm. Hence, Valsartan/HCTZ was more effective in lowering SBP than Irbesartan/HCTZ by an adjusted mean difference of 0.180 mmHg by Week 24 (95% CI; -3.324:3.685). A comparison of average change in SBP from Baseline to Week 24 between ITT population and PP population shows that the average change in SBP from Baseline to Week 24 in the Valsartan/HCTZ arm was greater for the PP population (25.2 mmHg; n=94) as compared to the ITT population (22.2 mmHg; n=490). Similarly, in the Irbesartan/HCTZ arm, the average change in SBP from Baseline to Week 24 was greater for the PP population (25.1 mmHg; n=91) as compared to ITT population (22.7 mmHg; n=501). Although Valsartan/HCTZ displayed a greater SBP lowering effect in the PP population, the SBP lowering effect in the ITT population was more pronounced in the Irbesartan/HCTZ arm. **Efficacy evaluation at Week 16:** Comparison of mean change in SBP by HBPM between Week 0 and Week 16 showed that average change in SBP (SD) was 17.3 (12.42) mmHg in the Valsartan/HCTZ arm, and 18.56 (12.84) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering SBP than Valsartan/HCTZ by an adjusted mean difference of 1.139 mmHg by Week 16 (95% CI; -2.619:0.341). However, the mean change in SBP

	between the two treatment arms was not statistically significant (p=0.1314). Considering the morning SBP reduction by HBPM between Week 0 and Week 16, the average change in morning SBP (SD) from Baseline to Week 16 was 16.1 (12.9) mmHg in the Valsartan/HCTZ arm, and 17.8 (13.7) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering morning SBP than Valsartan/HCTZ by an adjusted mean difference of 1.401 mmHg by Week 16 (95% CI; -2.939:0.138). However, the mean change in morning SBP between the two treatment arms was not statistically significant (p=0.0743). The average change in evening SBP (SD) from Baseline to Week 16 was 18.1 (13.9) mmHg in the Valsartan/HCTZ arm, and 18.8 (13.9) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering evening SBP than Valsartan/HCTZ by an adjusted mean difference of 0.747 mmHg by Week 16 (95% CI; -2.335:0.841). However, the mean change in evening SBP between the two treatment arms was not statistically significant (p=0.3562). As far as the Diastolic Blood Pressure (DBP) was concerned, the average change in DBP from Baseline to Week 16 in the Efficacy Population (N=991) was 8.3 ± 7 mmHg in the Valsartan/HCTZ arm, and 8.8 ± 7.1 mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering DBP than Valsartan/HCTZ by an adjusted mean difference of 0.367 mmHg by Week 16 (95% CI; -1.173:0.44). However, the mean change in DBP between the two treatment arms was not statistically significant (p=0.3729). The average change in morning DBP (SD) from Baseline to Week 16 was 7.5 (7.1) mmHg in the Valsartan/HCTZ arm, and 8.5 (7.5) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering morning DBP than Valsartan/HCTZ by an adjusted mean difference of 0.756 mmHg by Week 16 [95% CI within limits (-1.592:0.081)]. However, the mean change in morning DBP between the two treatment arms was not statistically significant (p=0.0765). The average change in evening DBP (SD) from Baseline to Week 16 was 8.8 (8.4) mmHg in the Valsartan/HCTZ arm, and 8.9 (7.9) mmHg in the Irbesartan/HCTZ arm. Valsartan/HCTZ was more effective in lowering evening DBP than Irbesartan/HCTZ by an adjusted mean difference of 0.062 mmHg by Week 16 (95% CI; -0.85:0.975). However, the mean change in evening DBP between the two treatment arms was not statistically significant (p=0.8932). A comparison of subjects with normalized BP in the two groups at Week 16 (n=790) by HBPM showed that normalized BP was achieved in 192 (47.41%) subjects receiving Irbesartan/HCTZ (n=405) and 172 (44.68%) receiving Valsartan/HCTZ (n=385). The comparison of subjects with normalized BP between the two treatment arms was not statistically significant at Week 16 (p=0.3377). **Efficacy evaluation at Week 24:** The average change in morning SBP (SD) from Baseline to Week 24 was 20.8 (13.6) mmHg in the Valsartan/HCTZ arm, and 21.9 (14) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering morning SBP than Valsartan/HCTZ by an adjusted mean difference of 1.139 mmHg by Week 24 (95% CI; -2.338:0.775). However, the mean change in morning SBP between the two treatment arms was not statistically significant (p=0.3248). The average change in evening SBP (SD) from Baseline to Week 24 was 22.9 (14.5) mmHg in the Valsartan/HCTZ arm, and 22.7 (14.3) mmHg in the Irbesartan/HCTZ arm. Valsartan/HCTZ was more effective

	in lowering evening SBP than Irbesartan/HCTZ by an adjusted mean difference of 0.176 mmHg by Week 24 (95% CI; -1.444:1.796). However, the mean change in evening SBP between the two treatment arms was not statistically significant (p=0.8313). The average change in DBP (SD) from Baseline to Week 24 was 10.5 (7.6) mmHg in the Valsartan/HCTZ arm, and 11 (7.5) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering DBP than Valsartan/HCTZ by an adjusted mean difference of 0.219 mmHg by Week 24 (95% CI; -1.072:0.634). However, the mean change in DBP between the two treatment arms was not statistically significant (p=0.6151). The average change in morning DBP (SD) from Baseline to Week 24 was 9.7 (7.7) mmHg in the Valsartan/HCTZ arm, and 10.5 (7.7) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering morning DBP than Valsartan/HCTZ by an adjusted mean difference of 0.587 mmHg by Week 24 (95% CI; -1.461:0.286). However, the mean change in morning DBP between the two treatment arms was not statistically significant (p=0.1874). The average change in evening DBP (SD) from Baseline to Week 24 was 10.9 (8.8) mmHg in the Valsartan/HCTZ arm, and 10.9 (8.3) mmHg in the Irbesartan/HCTZ arm. Valsartan/HCTZ was more effective in lowering evening DBP than Irbesartan/HCTZ by an adjusted mean difference of 0.253 mmHg by Week 24 [95% CI within limits (-0.694:1.199)]. However, the mean change in evening DBP between the two treatment arms was not statistically significant (p=0.6003). A comparison of subjects with normalized BP in the two groups at Week 24 (n=644) by HPBM showed that 179 (53.59%) subjects receiving Irbesartan/HCTZ (n=334) and 148 (47.74%) receiving Valsartan/HCTZ (n=310) achieved normal BP by End of Study. The comparison of subjects with normalized BP between the two treatment arms was not statistically significant at Week 24 (p=0.0967). **Efficacy evaluation between Week 16 and Week 24:** A comparison between the mean SBP reduction as measured by Office Blood Pressure Monitoring (OBPM) at Week 16 and Week 24 from Week 0 showed that at Week 24, the average change in SBP (SD) from Baseline was 18.3 (15.7) mmHg in the Valsartan/HCTZ arm, and 21.8 (15.3) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering SBP than Valsartan/HCTZ by an adjusted mean difference of 2.662 mmHg by Week 24 (95% CI; -4.355:-0.968). The mean change in SBP between the two treatment arms was statistically significant (p=0.0021). In comparison, at Week 16, the average change in SBP (SD) from Baseline was 15.2 (14.1) mmHg in the Valsartan/HCTZ arm, and 16.7 (15) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering SBP than Valsartan/HCTZ by an adjusted mean difference of 0.907 mmHg by Week 16 (95% CI; -2.548:0.734). However, the mean change in SBP between the two treatment arms was not statistically significant (p=0.2785). Similarly, a comparison between the mean DBP reduction (OBPM) at Week 16 and Week 24 from Week 0 showed that at Week 24, the average change in DBP (SD) from Baseline was 7.7 (9.6) mmHg in the Valsartan/HCTZ arm, and 9.5 (9.4) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering DBP than Valsartan/HCTZ by an adjusted mean difference of 1.247 mmHg by Week 24 (95% CI; -2.251:0.243). The mean change in DBP between the two treatment arms was also statistically significant (p=0.0150). At Week 16, the average change in DBP (SD) from Baseline was 6.7 (8.8) mmHg

	in the Valsartan/HCTZ arm, and 7.5 (9.2) mmHg in the Irbesartan/HCTZ arm. Irbesartan/HCTZ was more effective in lowering DBP as compared to Valsartan/HCTZ by an adjusted mean difference of 0.253 mmHg by Week 16 (95% CI; -1.214:0.708). However, the mean change in DBP between the two treatment arms was not statistically significant (p=0.6057). A comparison of the percentage of subjects with normalized BP in the two groups at Week 16 and Week 24 by OBPM showed that at Week 16, 194 (47.9%) subjects in the Irbesartan/HCTZ arm (n=405) and 184 (47.8%) in the Valsartan/HCTZ arm (n=385) had normalized BP. The comparison of subjects with normalized BP between the two treatment arms was not statistically significant at Week 16 (p=0.6632). By Week 24, 179 (53.59%) subjects in the Irbesartan/HCTZ arm (n=334), and 146 (47.1%) in the Valsartan/HCTZ arm (n=310) achieved normalized BP. The comparison of subjects with normalized BP between the two treatment arms was statistically significant at Week 24 (p=0.0057).
Safety Results:	Out of 447 Adverse Events that occurred among 238 (43.8%) subjects in the Irbesartan/HCTZ arm (n=544), 110 (24.6%) AEs were related to the treatment. Out of 463 AEs that occurred among 226 (42.6%) subjects in the Valsartan/HCTZ arm (n=531), 83 (17.9%) AEs were related to the treatment with Valsartan/HCTZ. 5 severe AEs in Irbesartan/HCTZ arm and 2 severe AEs in Valsartan/HCTZ arm were related to the study drug. All of them were resolved without any sequelae, except for one severe AE each in both the arms, which were ongoing. 2 very severe AEs occurred in the Irbesartan/HCTZ arm and 1 very severe AE occurred in the Valsartan/HCTZ arm. None of the 3 very severe AEs reported in this study were considered related to the study drug.
Issue date:	31 July 2012