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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00708344
		Study Code:	IRBEH_R_02931
Generic drug name:	Irbesartan/Hydrochlorothiazide	**Date:**	08 July 2010

Title of the study:	Efficacy and safety of irbesartan/hydrochlorothiazide combination: A comparison of active and usual titration regimen in the treatment of hypertensive patients insufficiently controlled by monotherapy
Coordinating investigator(s):	NA
Study center(s):	89 centers Trial location: Argentina, Brazil, Colombia, Ecuador, Mexico, Peru, Venezuela Algeria, Egypt, Morocco, Tunisia, Lebanon, Saudi Arabia, United Arab Emirates
Publications (reference):	NA
Study period: Date first patient/subject enrolled: 16-Jun-2008 *Date of first signed informed consent* Date last patient/subject completed: 10-Jul-2009 *Date of last patient last visit*	**Phase of development:** IIIb/IV

Objectives:	**Primary objective:**
	To compare the antihypertensive efficacy of the combination irbesartan/hydrochlorothiazide (HCTZ) using either a usual or an active elective titration regimen.
	The main efficacy criteria was the change in mean SBP, measured at doctor's office with an automatic device, after a 10-week treatment period in hypertensive patients insufficiently controlled by monotherapy.
	Secondary objectives:
	- To compare the antihypertensive efficacy of the active titration vs usual titration of the combination irbesartan/HCTZ after a 10-week treatment period
	  ○ Differences in mean DBP
	  ○ Percentage of controlled patients
	  • BP < 140/90 mmHg for all patients
	  • BP < 140/90 mmHg in non diabetics and
	  • BP < 130/80 mmHg in diabetics
	- To compare the antihypertensive efficacy of the active titration vs usual titration of the combination irbesartan/HCTZ after a 6-week treatment period
	  ○ Differences in mean SBP and mean DBP
	  ○ Percentage of controlled patients

	• BP < 140/90 mmHg for all patients • BP < 140/90 mmHg in non diabetics and • BP < 130/80 mmHg in diabetics - To compare the antihypertensive efficacy of the combination irbesartan/HCTZ between V1 (W0) and V4 (W10) in obese patients (BMI > 30 kg/m2) vs non obese patients (BMI ≤ 30 kg/m2) using the following criteria : o Differences in mean SBP and DBP o Percentage of controlled patients (BP<140/90 mmHg) - To compare the antihypertensive efficacy of the combination irbesartan/HCTZ between V1 (W0) and V4 (week 10) in type 2 diabetic patients vs non diabetic patients using the following criteria : o Differences in mean SBP and mean DBP o Percentage of controlled patients (BP < 140/90 mmHg in non diabetics and BP < 130/80 mmHg in diabetics) - To determine the incidence and severity of adverse events		
Methodology:	10-week, prospective, comparative, randomised, open-label, international, multicentre, parallel group study		
Number of patients:	Planned: 658	Randomized: 832	Treated: 804
Evaluated:	795	Safety: 804	
Diagnosis and criteria for inclusion:	**Inclusion criteria:** - Male or female outpatient who are ≥ 18 years old - Established essential hypertension treated for at least 4 weeks by one antihypertensive drug alone (Fixed-dose combination does not represent monotherapy) - With uncontrolled Blood Pressure (BP) defined as: o SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg in non diabetic patients o SBP ≥ 150 mmHg and/or DBP ≥ 90 mmHg in diabetic patients - Signed written Informed Consent obtained prior to study entry **Exclusion criteria :** - SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg at V1 - Known or suspected causes of secondary hypertension - Patient with bilateral renal artery stenosis, renal artery stenosis in a solitary kidney; history of renal transplant or only has one functioning kidney - Associated cardiovascular conditions that prevent the patient from stopping the current antihypertensive drug (e.g.: Betablocker for angina, ACE-inhibitors for heart failure, etc…). - 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 - Known contraindications to the study drugs: o Severe renal dysfunction (creatinine clearance <30ml/min) o Known hypokaliemia (< 3 mmol/L) , known hypercalcemia o Severe hepatic impairment, biliary cirrhosis, cholestasis - Inability to obtain a valid automatic BP measurement recording - Administration of any other investigational drug within 30 days prior to study entry and		

<table>
<tr><td></td><td>during the course of the study
- Presence of any severe medical or psychological condition that, in the opinion of the investigator, indicate that participation in the study is not in the best interest of the subject
- Presence of any other conditions (e.g. geographic, social, etc) that would restrict or limit the subject participation for the duration of the study
- Pregnant or breast-feeding women
- Women of childbearing potential not protected by effective contraceptive method of birth control</td></tr>
<tr><td>Investigational product:
Dose:

Administration:</td><td>Irbesartan/Hydrochlorothiazide - Active titration regimen
Period W0-W2
irbesartan/HCTZ 150/12.5 mg: 1 tablet once daily in the morning for 2 weeks

Period W2-W6
- Patients with controlled BP (group 2.1):
irbesartan/HCTZ 150/12.5 mg 1 tablet once daily in the morning for 4 weeks
- Patients with uncontrolled BP (group 2.2):
irbesartan/HCTZ 300/25 mg 1 tablet once daily in the morning for 4 weeks

Period W6-W10
- Patients of group 2.2 : irbesartan/HCTZ 300/25 mg
1 tablet once daily in the morning for 4 weeks
- Patients of group 2.1
o with controlled BP (group 2.1.1):
irbesartan/HCTZ 150/12.5 mg 1 tablet once daily in the morning for 4 weeks
o with uncontrolled BP (group 2.1.2):
irbesartan/HCTZ 300/25 mg 1 tablet once daily in the morning for 4 weeks
Oral</td></tr>
<tr><td colspan="2">Duration of treatment: 10 weeks | Duration of observation: 10 weeks</td></tr>
<tr><td>Reference therapy:
Dose:

Administration:</td><td>Irbesartan/Hydrochlorothiazide - Usual titration regimen
Period W0-W2
irbesartan/HCTZ 150/12.5 mg: 1 tablet once daily in the morning for 2 weeks

Period W2-W6
irbesartan/HCTZ 150/12.5 mg: 1 tablet once daily in the morning for 4 weeks

Period W6-W10
- Patients with controlled BP (group 1.1):
irbesartan/HCTZ 150/12.5 mg 1 tablet once daily in the morning for 4 weeks
- Patients with uncontrolled BP (group 1.2):
irbesartan/HCTZ 300/25 mg 1 tablet once daily in the morning for 4 weeks
Oral</td></tr>
</table>

Criteria for evaluation:	
Efficacy/Pharmacodynamics:	**Primary efficacy criterion:** - Change in mean SBP between V1 (W0) and V4 (W10) **Secondary efficacy criteria:** - Change in mean DBP between the baseline (W0) end W10 - Change in mean SBP and mean DBP between the baseline and W6 - BP control defined according to the following definitions - Non diabetic patients: SBP<140 mmHg and DBP<90 mmHg - Diabetic patients: SBP<130 mmHg and DBP<80 mmHg - All patients: SBP<140 mmHg and DBP<90 mmHg
Safety:	Adverse events, vital signs and laboratory tests [serum electrolytes (kaliemia, natremia), serum creatinine, creatinine clearance]
Statistical methods:	Main Analysis The change of average SBP measured by an automatic device between V1 (W0), at randomisation) and at V4 (W10, end of the study) was studied in a covariance analysis model of treatment factor, adjusted by SBP at randomisation. The treatment effect test was two-sided with a Type-I error equal to 5%. Means and standard deviations by group were described for the main criterion. SBP means at randomisation and at W10 with their standard deviations were also described. Adjusted means by group with their standard errors were given. Finally, an estimation of treatment effect, its standard error and its 95% confidence interval were presented. This analysis was carried out in the ITT population. A sensitivity analysis was made in the PP population according to the same model. Tolerance Adverse effects were described by treatment groups in the full analysis set (FAS) population. The number of patients with at least one adverse event in each treatment group was compared by a Fisher's exact test. Sample Size Calculation A 3mm Hg difference in mean SBP assessed by an automatic device between the 2 groups after 10 weeks was considered as the smallest difference to be clinically relevant. A sample size of 296 in each group had 80% power to detect a difference in means of 3 mmHg assuming that the common standard deviation was 13 mmHg using a two group t-test with a 0.050 two-sided significance level. To take into account an attrition rate of 10%, 658 (329 patients per group) should have been randomised.
Summary:	In total, 833 patients were included by 89 centres and randomised in 2 treatment groups: 418 patients were allocated to usual titration arm and 414 patients were allocated to active titration arm (1 patient was not randomized, because he was included after IVRS has been shut down). Among these 833 patients, 100 patients (12.0%) withdrew prematurely from study (because of an adverse event for 34 patients).Fifty seven patients (6.8%) presented a protocol deviation at inclusion and 236 patients (28.3%) presented a protocol deviation during the study. The main deviation during study was: Time interval between V3 and V4 not included in [24 ; 32] days (99 patients). Overall, among the 833 patients included in the study, 38 (4.6%) were excluded from the ITT population (13 patients in the usual titration group, 24 in the active titration group). Among the 795 patients of the ITT population, 225 (28.3%) were excluded from the PP population (111 patients in the usual titration group, 114 in the active titration group). Analysis were conducted on the ITT and the PP population.

Efficacy results:	The primary criterion of the trial was to compare the antihypertensive efficacy of the combination irbesartan/hydrochlorothiazide using either a usual or an active elective titration regimen. The main efficacy criterion was the change in mean SBP, measured at doctor's office with an automatic device, after a 10-week treatment period in hypertensive patients insufficiently controlled by monotherapy. In ITT population, the mean decrease of SBP, after a 10-week treatment period, was 31.0 mmHg in the usual titration group and 29.5 mmHg in the active titration group. The difference between the 2 groups was not significant (p=0.14, ANCOVA model, including the treatment group, the SBP at W0, the pulse pressure at W0 in class and the region). In the same way in ITT population, the mean decrease of DBP, after a 10-week treatment period, was 14.5 mmHg in the usual titration group and a decrease of 14.1 mmHg in the active titration group. The difference between the 2 groups was also not significant (p=0.83, ANCOVA model, including the treatment group, the DBP at W0, the pulse pressure at W0 in class and the region). Globally, the proportion of controlled patients, defined as patients with SPB <140 mmHg and DBP < 90 mmHg, or defined as SPB < 140 mmHg and DBP < 90 mmHg for non diabetic patients and SPB < 130 mmHg and DBP < 80mmHg for diabetic patients, at W10 was not significantly different in the 2 groups (the proportion of controlled patients (SPB <140 mmHg and DBP <90 mmHg) was 70.9% in the usual titration group and 66.2% in the active titration group; the proportion of controlled patients, taking into account the diabetic disease was 64.0% in the usual titration group and 57.7% in the active titration group). Similar results were observed in the PP population (the proportion of controlled patients (SPB <140 mmHg and DBP <90 mmHg) was 69.7% in the usual titration group and 65.2% in the active titration group; the proportion of controlled patients, taking into account the diabetic disease was 63.3% in the usual titration group and 58.0% in the active titration group). It is important to underline that in spite of the randomisation, the patients of active titration arm presented slightly more severity criteria than the usual titration arm (median age: 77.0 vs 75.0 years old, % male: 43.1% vs 37.5%, % type 2 diabetes: 24.4% vs 20.5%). These small but notable differences may have an impact on the mean decrease of SBP/DBP and on the proportion of controlled patients. All in all, the impact of active titration was not significant at W10. The results of the Actual study confirmed the efficacy of the irbesartan/HCTZ combination therapy, previously demonstrated in various trials, in patients failing on antihypertensive monotherapy and as initial therapy in patients with moderate or severe hypertension, as well as in observational studies. However, an accurate comparison of the results of the Actual study with the results of others studies appears difficult because of the differences in terms of BP characteristics at baseline, treatment doses and treatment exposure. Nevertheless, it seems important to highlight that the mean decrease in SBP/DBP at W10 in the Actual study (-31.0/-14.5 mmHg in the usual titration group and -29.5/-14.1 mmHg in the active titration group) is higher than the mean decrease in SBP/DBP described in studies led with fixed dose of irbesartan/HCTZ in patients failing on antihypertensive monotherapy: in these studies, the mean decrease in SBP/DBP ranged from -13.0/-9.5 mmHg (8 weeks 150/12.5 mg irbesartan/HCTZ treatment) to -25.2/-14.7 mmHg (12 weeks 300/25 mg irbesartan/ HCTZ treatment). Furthermore, in ITT population, the mean decrease of SBP and of DBP was significantly higher between W0 and W6 in the active titration in the usual titration group (28.8 mmHg vs 26.3 mmHg for SBP, p<0.05, and 13.4 mmHg vs 11.7 mmHg for DBP, p<0.001) (ANCOVA model, including the treatment group, the SBP at W0, the pulse pressure at W0 in class and the region). The proportion of controlled patients (defined as patients with SPB <140 mmHg and DBP <90 mmHg) at W6 was significantly higher in the active titration group than in the usual titration group (65.4% vs 56.5%). The proportion of controlled patients, taking into account the diabetic disease (non diabetic patients: SPB < 140 mmHg and DBP < 90 mmHg, diabetic patients: SPB < 130 mmHg and DBP < 80mmHg) at W6 was higher in the active titration group but not significantly different (51.4% in the usual titration group vs 54.9%

	active titration group). Similar results were observed in the PP population. These results suggest that the active titration enables an earlier BP decrease and BP control, even though the final BP decrease and BP control are comparable with the usual titration. This hypothesis might be supported by the comparison with the BP decrease in studies led with fixed dose of irbesartan/HCTZ: titration in itself may have a impact on the efficacy of the antihypertensive treatment. Besides, several studies have shown that higher rates of treatment intensification are associated with improved BP control or conversely, that lack of timely medication intensification contributed more to poor BP control than low medication adherence. Moreover, Julius et al. underlined the importance of a rapid BP control, in severe patients but also for patients with mild to moderate hypertension, given that moderate differences in BP even over a relatively short period of time (12 weeks) can result in significant changes in cardiovascular outcome (Julius S, Kjeldsen SE, Brunner HR, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet. 2004;363:2022-2031).
Safety results:	During this study, 177 patients experienced at least one TEAE. Among these patients, 57 patients experienced at least one TEAE possibly related to the study drug (respectively 31 patients in the usual titration group and 26 patients in the active titration group). The TEAEs possibly related to the study drug were consistent with the expected adverse event previously reported with the Investigational Product. A total of 13 patients experienced serious adverse events (3 patients in the usual titration group and 10 patients in the active titration group), no death were reported. The global rate of SAEs in the Actual study (1.6%) was similar to the one described in previous studies (1% in the INCLUSIVE study).
Date of report:	10-May-2010