These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	Bristol-Myers Squibb & Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00264212
Generic drug name:	Irbesartan - Hydrochlorothiazide	**Study Code:**	R_8791
		Date:	17/12/2007

Title of the study:	A multicentre prospective randomized open-label 12-week study with blinded evaluation comparing the efficacy and safety of irbesartan and irbesartan-hydrochlorothiazide fixed combination with amlodipine and amlodipine plus hydrochlorothiazide in elderly patients with isolated systolic hypertension.
Investigator(s):	Chairman of the Steering Committee : Prof. P Deedwania, Chief, Cardiology Division, VACCHCS/UCSF, Fresno, Ca 93703, USA
Study center(s):	Chile (2 centers), China (8 centers), Indonesia (2 centers), Korea (4 centers), Mexico (3 centers), Philippines (2 centers), Taiwan (4 centers), Thailand (8 centers).
Publications (reference):	
Study period: Date first patient enrolled: 30/07/2004 Date last patient completed: 13/06/2006	**Phase of development:** IV
Objectives:	**The primary objective** of the study is to demonstrate that irbesartan (and/or irbesartan-hydrochlorothiazide fixed combination) is at least as effective as amlodipine (and/or amlodipine plus hydrochlorothiazide) in reducing the office seated systolic blood pressure in elderly patients with isolated systolic hypertension. **Secondary Objectives** - To demonstrate that irbesartan (and/or irbesartan-hydrochlorothiazide fixed combination) is at least as effective as amlodipine (and/or amlodipine plus hydrochlorothiazide) in reducing the pulse pressure - To compare the antihypertensive efficacy and tolerability of irbesartan and irbesartan- hydrochlorothiazide fixed combination therapy with amlodipine and amlodipine plus hydrochlorothiazide in treatment of isolated systolic hypertension.

Methodology:	- Multicentre, 2-parallel-arms, comparative, 12-week Phase IV study with PROBE (Prospective Randomised Open-label with Blinded Evaluation) design. - The patients were randomised to receive either irbesartan regimen or amlodipine regimen - The study was divided in 2 parts: Part I: 2-4 week wash-out (or single-blind placebo run-in) phase; Part II: open-label, 2-parallel arms, randomised comparative 12-week treatment phase with sequential dose-escalation and/or addition of hydrochlorothiazide.		
Number of patients: A total of 564 patients were included in the study.	Planned: 536 patients	Randomized: 392 randomised patients: 195 in the irbesartan and 197 in the amlodipine group.	Treated: 358 patients completed the study, 181 in the irbesartan group and 177 in the amlodipine group.
Evaluated:	Efficacy : The efficacy analysis was performed on the ITT (Intent To Treat) population including all patients who were randomised, took at least one dose of study medication and provided at least one post-baseline efficacy assessment : 380 patients, 191 in the irbesartan group and 189 in the amlodipine group	Safety: The safety analysis was performed in the APT (All Patients Treated) population including all patients who were randomised, took at least one dose of study medication : 392 patients, 195 in the irbesartan and 197 in the amlodipine group.	
Diagnosis and criteria for inclusion:	Inclusion criteria at screening - Outpatients of either sex - Aged 60 to 90 years inclusive [60-90] - Able to comply with the protocol - Having given their written informed consent of their own free will - With newly diagnosed and untreated OR previously diagnosed, treated and uncontrolled ISH defined as: Seated SBP >= 160 mmHg and <220 mmHg [160,220[and Seated DBP < 90 mmHg Inclusion criteria at randomisation - Having completed the 2-4 week wash-out/placebo run-in phase - Still eligible for BP: Seated SBP >=160 mmHg and <220 mmHg [160,220[and Seated DBP<90 mmHg		

Investigational product:	- 150 mg and 300 mg irbesartan: Aprovel® (Sanofi-Synthelabo) – 150 mg irbesartan-12.5 mg hydrochlorothiazide fixed combination and 300 mg irbesartan – 12.5 mg hydrochlorothiazide fixed combination	
Dose:	The starting dose was 150 mg irbesartan. In case of uncontrolled SBP (=140 mmHg) at week 4 and/or week 8, a sequential dose-escalation was allowed. At week 4: up-titration to: - 300 mg irbesartan or 150 mg irbesartan-12.5 mg hydrochlorothiazide fixed combination (depending on each country). At week 8: up-titration to: - 300 mg irbesartan-12.5 mg hydrochlorothiazide fixed combination if the patient was receiving 300 mg irbesartan or 150 mg irbesartan-12.5 mg hydrochlorothiazide fixed combination at week 4 OR - 300 mg irbesartan or 150 mg irbesartan-12.5 mg hydrochlorothiazide fixed combination (depending on each country) if the patient was receiving 150 mg irbesartan at week 4.	
Administration:	By the oral route once daily.	
Duration of treatment: 14-16 weeks (2-4 week run-in phase; 12 week treatment phase).		**Duration of observation:** 14-16 weeks
Reference therapy:	5 mg and 10 mg amlodipine: Norvasc® or Norvask® or Amlor® (Pfizer Inc.).	
Dose:	The starting dose was 5 mg amlodipine. In case of uncontrolled SBP (=140 mmHg) at week 4 and/or week 8, a sequential dose-escalation was allowed. At week 4: up-titration to: 10 mg amlodipine. At week 8: up-titration to: - 10 mg amlodipine + 12.5 mg hydrochlorothiazide if the patient was receiving 10 mg amlodipine at week 4 OR - 10 mg amlodipine if the patient receiving 5 mg amlodipine at week 4.	
Administration:	By the oral route once daily.	
Criteria for evaluation:		
Efficacy:	**Primary efficacy criteria:** Change from baseline in office seated SBP at week 12 or end of study (Dend). **Secondary efficacy criteria :** 1. Number of responders and normalized at 4, 8 and 12 weeks (or Dend); 2. Change from baseline in standing SBP and pulse pressure (SBP-DBP) at week 4, 8 and 12 (or Dend). **Other efficacy criteria**: Change from baseline in seated DBP, standing DBP and pulse rate at week 4, 8 and 12 (or Dend).	

Safety:	**<u>Safety criteria</u>:** - Change in standing SBP/DBP - Adverse events - Clinical laboratory - Vital signs - Physical examination - Treatment discontinuation
Statistical methods:	<u>Patients' characteristics:</u> Demographics and other baseline characteristics were presented by treatment group on the Intent-To-Treat (ITT) population. Quantitative variables were compared by using unpaired T-test or Mann-Whitney test and the qualitative variables by using a Fisher's exact test <u>Primary criterion</u>: The mean change from baseline in office seated SBP to week 12 (or end of study) were analyzed on the ITT population by using an Analysis of variance model (ANCOVA). The hypothesis of non-inferiority was tested by constructing a 95% confidence interval around the treatment differences in least square means from this model. <u>Secondary criteria</u>: The proportion of responders to treatment at W12 was compared between treatment groups on the Intent To treat (ITT) population. A two-sided 95% confidence interval was constructed around the relative risk of responding and Cochran-Mantel-Haenszel test was used to compare the 2 groups (proportion of responders to irbesartan at W12/proportion of responders to amlodipine at W12). The same analysis was done for the proportion of normalized patients. The change from baseline in seated SBP, standing SBP, seated DBP, standing DBP, pulse pressure and pulse rate to week 4, week 8 and week 12 was compared between treatment groups by using the same approach as for the primary analysis (ANCOVA). <u>Safety criteria</u> : the frequency of any treatment-emergent adverse event and of the treatment-emergent adverse events occurring in more than 2% of the patients were compared by using a Fisher's exact test

Summary:	A total of 564 patients were included in the study. 392 patients were randomised: 195 in the irbesartan group and 197 in the amlodipine group. Three hundred and fifty eight (358) patients completed the study, 181 in the irbesartan group and 177 in the amlodipine group. Most of the premature withdrawals were due to lost to follow up and adverse events A total of 380 patients were included in the ITT population. Around 70 percent of the patients were women and 30 percent were men in the two groups of treatment. Most of the patients were Asian (60%), the remaining patients were oriental (26%) or hispanic (13.%). Around half of the patients had a body mass index less than 25 kg/m² (52%), 28% of patients had a body mass index in [25,28] kg/m². The remaining patients had a body mass index greater than 28 kg/m² (21%) The patients were between 60 and 87 years old in the irbesartan group and between 59 and 88 years old with a mean age of 71.9 ± 6.3years and 72.2 ± 6.8 years in the irbesartan group and amlodipine group respectively. Seated SBP/DBP at randomization were 174.0±12.4/82.5±6.4 mmHg in the irbesartan group and 171.7±10.5/82.2±5.6 mmHg in the amlodipine group. Seated pulse rate was 72.5±15.5 beats/min in the irbesartan group and 71.5± 13.4 beats/min in the amlodipine group
Efficacy results: :	Irbesartan (and/or irbesartan–hydrochlorothiazide fixed combination) reduced the office seated systolic blood pressure and was at least as effective as amlodipine (and/or amlodipine plus hydrochlorothiazide) after 12 weeks of treatment. The adjusted difference betweens means was -0.5 mmHg [95% CI -3.36, 2.27]. The upper limit of the 95% confidence interval is below the pre-specified non-inferiority margin of 3 mmHg. The least square means and their 95% confidence interval were respectively equal to –30.39 [-32.65, -28.13] mmHg in the irbesartan group and –29.84 [-32.16, -27.52] mmHg in the amlodipine group. Non-adjusted means change from baseline to week 12 in seated SBP were -31.8±15.4 mmHg in the irbesartan group and -30.6±14 mmHg in the amlodipine group. The ANCOVA models showed that there was no significant difference between the irbesartan group and the amlodipine group in reducing the standing SBP, seated DBP, standing DBP, pulse pressure and standing pulse rate from baseline to week 12. Borderline significant difference (p=0.049) was observed between the irbesartan group and amlodipine group in favor of the irbesartan group in reducing the seated pulse rate from baseline to week 12 (least square means and 95% CI were respectively equal to –0.87 [-2.68, 0.93] beats/min and 1.28 [-0.59, 3.15] beats/min in the irbesartan and amlodipine groups). The proportion of patients who responded to treatment at the end of study was comparable between groups 82.7% in the irbesartan group and 79.0% in the amlodipine group. The normalization rate was also comparable between the two treatment groups 49.7% in the irbesartan group and 48.9% in the amlodipine group.

Safety results:	The safety data evaluation showed that both treatments were well tolerated. The frequency of treatment-emergent adverse events was 26.7% in the irbesartan group and 28.9% in the amlodipine group. The most commonly reported TEAEs were dizziness (4.1%), oedema peripheral (2.6%), upper respiratory tract infection NOS (2%), headache (2%), oedema NOS (1.5%) and palpitations (1.3%). The percentage of patients with treatment-emergent oedema NOS and oedema peripheral was significantly higher in the amlodipine group (respectively 3% and 5.1%) than in the irbesartan group (0% and 0%). A serious adverse event occurred in 3 patients before randomisation, in 6 patients in the irbesartan group (leading to withdrawal from treatment in 1 patient) and in 5 patients in the amlodipine group (leading to withdrawal from treatment in 4 patients). Withdrawal from the study following an adverse event occurred for 9 patients (2 in the irbesartan group and 7 in the amlodipine group). Treatment compliance was 87.0% in the irbesartan group and 81.6% in the amlodipine group.
Date of report:	23 October 2007