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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00335673
		Study Code:	IRBES_L_00165
Generic drug name:	irbesartan irbesartan/hydrochlorothiazide	**Date:**	17 March 2011

Title of the study:	Irbesartan in Mild to Moderate Hypertensive Patients Protocol number: IRBES_L_00165		
Investigator(s):	200 investigators/centers were planned for the study as per protocol design. 205 sites were opened while 156 sites were active.		
Study center(s):	The study was conducted in 156 centers all over Egypt		
Publications (reference):	NA		
Study period: Date first patient enrolled: 06-Feb-2006 Date last patient completed: 28-Nov-2006		**Phase of development:** IV	
Objectives:	**Primary objective:** To evaluate control rate of Blood Pressure (BP) ≤ 140/90 mm Hg in non-diabetic patients, and ≤ 130/80 mm Hg in diabetic patients. **Secondary objectives:** Percentage of patients achieving blood pressure control according to their profile (naïve, switch, patient history, etc…) at the end of the trial.		
Methodology:	Multi-center, prospective, open, non-randomized, non-comparative Phase IV clinical trial. All patients started on Aprovel® 150mg. If after 3 weeks, the target blood pressure was not achieved, the dose was doubled to 300mg. If after another 3 weeks the target blood pressure was still not achieved, Co-Aprovel® (300/12.5mg) was started. Whenever the target blood pressure was achieved, the dose was maintained for the remainder of the treatment period. The starting dose and the dose titration schedule were modified according to the Investigator's judgment and patients' BP variability. During follow up visits, if the target blood pressure was not achieved despite the dose titration, adjuvant therapy was documented in the Case Report Form (start date, generic and trade name of the added product, dose, ongoing or stopped….).		
Number of patients:	Planned: 1771	Randomized: NA	Enrolled: 1630

Evaluated:	Efficacy : Intent to Treat: 1582 Per protocol: 1555	Safety: 1630	
Diagnosis and criteria for inclusion:	Newly diagnosed "naïve" patients with documented mild to moderate hypertension, aged 30 to 75 years; Patient who was on antihypertensive therapy (maximum of two agents - one of them is a diuretic) and who in the investigator's opinion would benefit more by switching to the study medication. These patients underwent a wash out period for at least 7 days prior to enrollment.		
Investigational product: Formulation: Dose: Administration:	Irbesartan/Irbesartan hydrochlorothiazide Aprovel® (150 & 300mg) & Co-Aprovel® (300/12.5mg hydrochlorothiazide). One tablet/day. Oral		
Duration of treatment: 3 months		**Duration of observation:** 3 months	
Reference therapy:	NA		
Criteria for evaluation:			
Efficacy:	**Primary Efficacy Endpoints** 1. Proportion of enrolled patients reaching a blood pressure target "(≤ 140/90 mm Hg) in non-diabetic patients and (≤ 130/80 mm Hg) in diabetic patients" at 3 months study period. 2. The mean overall reduction and mean percent reduction in systolic and diastolic blood pressure levels compared to baseline levels: From the data available at the end of the 3-month study period. **Secondary Efficacy Endpoints** 1. The proportion of patients controlled (reaching target blood pressure) on Aprovel® (150 mg and 300 mg) and Co-Aprovel®. . 2. The mean reduction and percent reduction in systolic / diastolic blood pressure in patient subgroups according to Aprovel® prescription (Patients on Aprovel® 150mg only, patients on Aprovel® 300mg only and patients on Co-Aprovel® 300/12.5mg). 3. Percentage of patients achieving blood pressure control according to their profile (naïve, switch, gender, age groups) at the end of the trial. 4. Physician's overall assessment of efficacy: From the data available at the end of the 3-month study period.		
Safety:	**Primary Safety Endpoints** Reporting of any adverse drug reactions: The type, date and time of onset, intensity and relationship to the trial treatment of all the symptoms observed by the investigator, and/or those subjective symptoms reported by the patient in response to a general enquiry from the investigator at subsequent study visits**.** **Secondary Safety Endpoints** Physician's overall assessment of tolerability: At the end of the 3-month study period.		

Statistical methods:	Descriptive statistics were performed. For quantitative variables mean, range and standard deviation were calculated with 95% CI. For qualitative variables, rate and proportions were also calculated. For normal distribution of the quantitative data, paired t-test and repeated measures analysis were performed. For non-parametric distribution for paired data, Wilcoxon signed rank test was used. Chi square test was applied to qualitative data.
Summary:	**Population Characteristics of study patients** A total of 1630 patients with mild to moderate hypertension were enrolled into the study and included in the safety analyses. Out of 1630 patients, 1582 patients constituted the intent to treat (ITT) population as post-dose data was not available for 48 patients. The per protocol population (PP) consisted of 1555 patients as 19 patients were excluded from the study, for receiving other anti-hypertensive drugs and 8 patients were excluded for having severe hypertension at baseline. The total number of patients that completed the study in (ITT) population was 1452 and in (PP) population was 1425. The total number of patients who discontinued from the study was 178 (10.9%) patients. The main reasons for discontinuation were as follows: lost to follow up 120 (7.4%), patients were withdrawn upon their request 25 (1.5%) patients, other deviation from protocol 16 (1.0%) patients, 13 (0.8%) patients due to adverse experiences, 2 (0.1%) died during the study and 2 (0.1%) due to other reasons. The analysis of the demographic characteristics of the study population showed that the mean value of age (years) was 51.9 ± 9.8. The study consisted of 50.1% females and 47.7% males with missed data for 2.2% of population. The mean weight (kg) was 87.68 ± 14.86 while the mean height (cm) was 167.55 ± 8.6; accordingly the mean value of BMI (kg/m^2) was 31.38 ± 5.73. **Baseline Hematology:** The mean hemoglobin was 13.91 ± 1.67 g/dl, while the mean WBC count was 7.45 ± 3.52 10^9/l and the mean platelet count was 278.11 ± 79.26 10^9/l. The average ESR was 23.06 ± 17.1 mms. **Baseline Biochemistry:** The mean serum creatinine was 0.922 ± 0.264 mg/dl, while the mean ASAT (SGOT) was 24.48 ± 11.96 U/l and the mean ALAT (SGPT) was 27.08 ± 15.90 U/l. The mean serum potassium was 4.398 ± 0.489 mmol/l and the average BUN was 15.33 ± 6.47 mg/dl. The mean HbA1c was 6.52 ± 1.48 %. **Baseline Vital Signs:** The mean Systolic Blood Pressure (SBP) was 160.10 ± 11.4 mmHg and the mean DBP was 98.97 ± 5.99 mmHg. Average seated HR was 82.05 beats/min ± 8.64 beats/min. Hypertension grading was identified as normal for 5 (0.32%), high-normal for 15 (0.94%), mild for 525 (32.91%), moderate for 1042 (65.33%) and severe for 8 (0.5%) patients. **Diabetes History**: Out of the enrolled 1630 patients, 342 (21%) patients were diabetic and 1288 (79%) were non-diabetic. The mean duration of diabetes was 90.04 ± 74.02 months.

Efficacy results:	**Proportion of enrolled patients reaching a blood pressure target (≤ 140/90 mm Hg) in non-diabetic patients and (≤ 130/80 mm Hg) in diabetic patients" at 3 months study period:** By the end of the three months trial period (week 12), the percentage of overall ITT population who were treated by whatever form of Aprovel® and reached the target blood pressure was 91.18% with better blood pressure control for non-diabetic patients; 96.04 % response rate for non-diabetics compared to 71.71% for diabetics. The percentage of ITT population treated by Aprovel® 150 mg and that reached the target blood pressure was 82.7% for diabetic patients and 99.0% for non-diabetic patients. The percentage of patients reaching the target blood pressure on Aprovel® 300 was 76.0% for diabetics and 96.6% non-diabetics. While, the percentage of patients reaching the target blood pressure on Co-Aprovel® 300/12.5 was 55.4% for diabetics and 86.8% for non-diabetics. (p value < 0.001) Similar results were obtained for PP population. Analysis of the percentages of patients achieving blood pressure control according to gender revealed no statistically significant differences between male and female diabetic patients at different concentrations of the drug intake. Similar results were also shown in non-diabetic patients. (p value > 0.005) No statistically significant difference were obtained in naïve patients or switched to Aprovel® therapy patients who achieved blood pressure control. (p value > 0.005) There was no significant difference between age groups and achievement of the target blood pressure control among diabetic patients. While among non-diabetics, there was a significant difference only among those administered Co-Aprovel® 300/12.5, as those in the age group 30 to 49 years experienced better control than the other age groups. (p value > 0.005) **The mean overall effect of Aprovel® therapy** Among the ITT population, the mean Systolic BP at baseline was 159.76 ± 9.64 mmHg and reduced to a mean of 127.45 ± 8.14 mmHg at week 12.. The mean reduction from baseline at week 12 was 32.31 mmHg (20.22%) (p-value < 0.001).. Similar results were observed for PP population. Likewise, among the ITT population, the mean Diastolic BP at baseline was 98.6 ± 5.25 mmHg, and reduced to a mean of 80.65 ± 4.52 mmHg at week 12. The mean reduction from baseline at week 12 was 17.95 mmHg (18.2%) (p-value < 0.001). Similar results were observed for PP population. **Mean Reduction and mean percent reduction in SBP:** ***Aprovel® 150 mg:*** Among the ITT population, the mean value of SBP at baseline was 157.09 ± 10.16 mmHg decreasing significantly (P < 0.001) in each follow up visit to reach 123.93 ± 7.53 mmHg at week 12. The mean reduction in SBP from baseline to week 3 and week 12 was 26.83 mmHg (17.08%) and 33.16 mmHg (21.11%) respectively. Very similar results were obtained when SBP was analyzed for PP population who received the same concentration of Aprovel®; SBP was reduced by 33.22 mm Hg (21.15%) from baseline to week 12. ***Aprovel® 300 mg:*** Among the ITT population, the mean value of SBP at baseline was 161.19 ± 9.57 mmHg decreasing significantly (P < 0.001) in each follow up visit to reach 128.10 ± 7.98 mmHg at week 12. The mean reduction in SBP from baseline to week 3 and week 12 was 14.95 mmHg (9.27%) and 33.09 mmHg (20.53%) respectively. Very similar results were obtained when SBP was analyzed for PP

	population who received the same concentration of Aprovel®; SBP was reduced by 33.15 mm Hg (20.57%) from baseline to week 12. ***Co-Aprovel® 300 mg/12.5 mg Hydrochlorothiazide (HCTZ)*:** Among the ITT population, the mean value of SBP at baseline was 163.77 ± 8.68 mmHg decreasing significantly (P < 0.001) in each follow up visit to reach 134.14 ± 9.56 mmHg at week 12. The mean reduction in SBP from baseline to week 3 and week 12 was 11.59 mmHg (7.08%) and 29.63 mmHg (18.09%) respectively. Very similar results were obtained when SBP was analyzed for PP population who received the same concentration of Aprovel®; SBP was reduced by 29.57 mm Hg (18.07%) from baseline to week 12. **Mean Reduction and mean percent reduction in Diastolic Blood Pressure (DBP):** ***Aprovel® 150 mg*:** Among the ITT population, the mean value of DBP at baseline was 98.04 ± 5.10 mmHg decreasing significantly (P < 0.001) in each follow up visit to reach 79.43 ± 4.33 mmHg at week 12. The mean reduction in DBP from baseline to week 3 and week 12 was 15.62 mmHg (15.93) and 18.61 mmHg (18.98%) respectively. Very similar results were obtained when DBP was analyzed for PP population who received the same concentration of Aprovel®; DBP was reduced by 18.62 mm Hg (18.99%) from baseline to week 12. ***Aprovel® 300 mg:*** Among the ITT population, the mean value of DBP at baseline was 98.97 ± 5.59 mmHg decreasing significantly (P < 0.001) in each follow up visit to reach 80.55 ± 4.05 mmHg at week 12. The mean reduction in DBP from baseline to week 3 and week 12 was 8.60 mmHg (8.69%) and 18.42 mmHg (18.61%) respectively. Very similar results were obtained when DBP was analyzed for PP population who received the same concentration of Aprovel®; DBP was reduced by 18.41 mm Hg (18.60%) from baseline to week 12. ***Co-Aprovel® 300 mg/12.5 mg HCTZ*:** Among the ITT population, the mean value of DBP at baseline was 99.38 ± 5.22 mmHg decreasing significantly (P < 0.001) in each follow up visit to reach 83.31 ± 5.39 mmHg at week 12. The mean reduction in DBP from baseline to week 3 and week 12 was 6.25 mmHg (6.29%) and 16.07 mmHg (16.17%) respectively. Very similar results were obtained when DBP was analyzed for PP population who received the same concentration of Aprovel®; DBP was reduced by 16.07 mm Hg (16.18%) from baseline to week 12. **Evaluation of the overall efficacy:** Among the ITT population, analysis of the overall efficacy of Aprovel® 150 mg showed that 93.2% (562) of patients experienced reduction in their blood pressure while 0.66% (4 patients) experienced no change. Failure was not reported for any of the patients. For the ITT population who had taken Aprovel® 300 mg, 95.3% (405) of patients experienced reduction in their blood pressures while only 1 patient experienced no change and 1 patient with reported failure. 92.7% (393 patients) on Co-Aprovel® 300/12.5 experienced reduction in blood pressure while 9 patients experienced no change and 1 patient with reported failure. Similar results were observed for the PP population.

Safety results:	Adverse events whether observed by the investigator or reported by the patient were analyzed according to the type, date and time of onset, intensity and relationship to the study medication. The safety was analyzed on the safety population, using the data from all the enrolled patients. Out of 1630 patients, 56 (3.44%) patients reported adverse events at visit 2, 31 (1.9%) patients at visit 3, 0.92% percent at visit 4 and 0.61% at visit 5. The number of patients with adverse events through out study period was 112 (6.87%). Dizziness was the most common reported adverse event, being reported by 15 patients at visit 2 constituting 19% of 79 adverse events reported at visit 2 while the total frequencies of dizziness throughout the study was 25 (17.2%) of 145 adverse events reported. Headache and GIT disturbances were the second most common adverse events after dizziness; each was reported 16 times (11.0%) throughout the study period. Four patients had reported serious adverse events, all were males. There were 2 deaths, one patient (43 years old) died from PE, 6h after renal surgery and the other patient (75 years old) from a cerebro-vascular event. The other 2 SAEs reported were myocardial infarction (recovered without any sequelae and study medication was not changed) and recent angina with hospitalization (outcome not known as the patient was lost to follow up and study medication discontinued). All SAEs were not related to the study medication. Only 13 patients discontinued the study due to adverse events (9 patients at visit 2 and 4 patients at visit 3). Dose reduction or dose change was reported for 13 patients due to adverse events while for the rest of the patients with adverse events no further actions were required. Regarding the causality relation to study medication, the analysis revealed that about 48% of adverse events were not related to the study medication while 9.7%, 31% and 11% of adverse events were identified as remotely, possibly and probably related to the study medication respectively. The overall tolerability of Aprovel® was assessed as excellent by 87.7 % of physicians and 85.2% of patients.. Only 7.3% of physicians and 9.1% of patients considered the drug of good tolerability. Further analysis of the overall tolerability according to the different concentrations of Aprovel® revealed that for Aprovel® 150 mg group, Aprovel® 300 mg group and for Co-Aprovel® 300/12.5, the physicians considered it as excellent with percentages of 89.6%, 87.5% and 85.1% respectively. Similar results were obtained for patients' assessment of the overall tolerability according to the medication concentrations. There was a significant reduction in the heart rate among the study population. The average heart rate at the baseline was 82.05 ± 8.64 decreasing significantly throughout the study period to reach a mean of 77.6 ± 5.9 at week 12 with a p value <0.001. The mean values of hematological tests (hemoglobin, WBC, ESR, Platelets) before treatment were very close to the corresponding values after treatment although there were statistically significant differences in hemoglobin, WBC and platelets due to the large sample size of the study. It is clear that there is no clinical importance to these trivial differences in hematological parameters. Similar results were observed for

	blood chemistry, the mean values of creatinine, ASAT, ALAT, serum potassium, HbA1c% and BUN before and after treatment were very close and there were no clinically significant differences although there were statistically significant differences in some tests e.g. ALAT, serum potassium, HbA1c% as these values showed trivial declines by the end of study period.
Date of report:	14-Dec-2010