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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00362258
		Study Code:	PM_L_0256
Generic drug name:	irbesartan	**Date:**	16 March 2011

Title of the study:	I PREVENT - Irbesartan In Hypertensive Diabetic Patients A Phase IV clinical trial Protocol number: PM_L_0256	
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STUDY CENTRE	The study was conducted in 54 centers located in Egypt	
Publications (reference):	Not Applicable	
Study period: Date first patient enrolled: 23-Feb-2006 Date last patient completed: 30-Sep-2008		**Phase of development:** IV

Objectives:	**Primary objective** Evaluation of blood pressure (BP) reduction to the targeted values (Systolic Blood Pressure/SBP ≤130 mmHg and Diastolic Blood Pressure/DBP ≤80 mmHg) in hypertensive type 2 diabetic patients treated with irbesartan. **Secondary objectives** Evaluation of efficacy of irbesartan in the reduction of microalbuminuria from baseline (if any at the inclusion visit) in hypertensive type 2 diabetic patients. Evaluation of safety of irbesartan in this population.		
Methodology:	This study was a multicenter, prospective, open, non-randomized, non-comparative Phase IV trial. All eligible patients were assigned a treatment schedule of Aprovel 150 mg once daily and assessed after 2 weeks (Week 2) for achievement of target BP (130/80 mmHg) and dose titration. The starting dose and the dose titration schedule can be modified according to the Investigator's judgment and based on patients' variabilities. If target BP was not achieved then the dose of Aprovel was doubled to 300 mg once daily and assessed after 2 additional weeks (Week 4). If target BP was still not achieved at the Week 4 assessment, CoAprovel 300/12.5 mg once daily was started and assessment performed at follow-up visits on Week 6, 12, 18 and 24. Whenever the BP target was achieved at a particular dose, that dose was maintained for the rest of the treatment period. For patients whose BP target were not achieved despite dose titration and required add-on therapy, this was considered as a treatment failure and the patient was removed from protocol treatment.		
Number of patients:	Planned: 1081	Enrolled: 797	Treated: 786 (11 patients did not show up after baseline visit)
Evaluated:	Efficacy: 626		Safety: 797
Diagnosis and criteria for inclusion:	Hypertensive patients aged between 30 and 75 years with Type 2 Diabetes; HbA1c >6% and ≤10% (with or without microalbuminuria); newly diagnosed hypertension with no treatment for hypertension ("treatment naïve"); patients receiving antihypertensives (maximum of two – one of which was a diuretic) and having achieved target BP, yet in the investigator's opinion would benefit more from switching to the study medication.		
Investigational product: Dose Administration	Aprovel and Co-Aprovel Aprovel 150 mg, Aprovel 300 mg and Co-Aprovel 300/12.5 mg Oral		
Duration of treatment: 6 months		**Duration of observation:** 6 months	
Reference therapy:	Not Applicable		
Criteria for evaluation:			
Efficacy	**Primary Efficacy Endpoints** 1. Percentage of patients reaching BP target (130/80 mmHg). 2. Percentage of patients controlled under CoAprovel 300/12.5 mg. **Secondary Efficacy Endpoints** Changes in albumin creatinine ratio (ACR) rate - Restoration of ACR rate in patients with normoalbuminuria (ACR rate <20 µg/min). - First detection of overt nephropathy (ACR rate >200 µg/min) in patients with microalbuminuria (ACR rate <200 µg/min), or at least 30% higher than at baseline on at least two consecutive occasions. (UAE rate as mentioned in the protocol is changed for ACR as per the real data captured)		

Safety	Occurrence of any side effect.
Analysis population	Intent to Treat population (ITT): It included all patients enrolled in the study and received at least one dose of study drug and had at least one assessment performed. Per protocol population (PP): It included the subset of the patients of ITT who satisfied the inclusion and exclusion criteria and had no major protocol violations. Those who did not achieve blood pressure target despite the dose titration and the patient who needed add on therapy were excluded from PP population as this was considered as treatment failure and the patient would go off protocol treatment. Safety analysis was performed on all subjects who were enrolled in the study.
Statistical methods:	Repeated Analysis of Covariance (ANCOVA) was used to compare the statistical significance of the differences between systolic and diastolic BP and ACR rate at baseline, Weeks 2, 4 and at different follow-up visits. An independent t-test was used for analyzing achievement of target BP for each treatment at different visits and the proportion of patients whose BP was controlled with different treatments was determined. The incidence rate of nephropathy for the follow-up period was determined and a univariate analysis with square of sample correlation coefficient and 95% confidence intervals were used to identify risk factors for the development of nephropathy. For risk factors with statistical significance of ≤5%, the Cox proportional hazards model was employed to identify independent risk factors. The Kaplan-Meier method was applied for different treatments to estimate cumulative probability for development of nephropathy. The frequency of adverse events associated with each treatment was determined. Descriptive demographic and baseline parameter statistics were calculated.
Summary:	A total of 797 patients were enrolled into the study and included in the safety analyses. The intent-to-treat population consisted of 707 patients as post-dose data was not available for 90 patients. The per-protocol population consisted of 626 patients as 51 patients had not met the eligibility criteria, 55 patients were excluded for having received other antihypertensive drugs during the study and 11 patients were excluded for not attending the baseline visit (patients could have had more than one reason for exclusion from analysis). A total of 187 patients discontinued from the study and 610 patients completed the study. The study consisted of 41.03% males and 56.59% females (gender details was missing for 19 [2.38%] patients) with a mean age of 53.84±8.36 years, a mean height of 167.26±9.01 cm and mean BMI of 31.34±5.43 kg/m2 (baseline information was missing for 11 patients). The baseline hematology values recorded for male and female were similar except for erythrocyte sedimentation rate (ESR) values which was 18.68±15.06 and 32.77±18.01 mm/hr in male and female patients, respectively. The mean rate of microalbuminuria excretion rate was 51.75±71.03 mg albumin per gm of creatinine. Mean SBP was 157.33±12.83 mmHg and DBP was 95.84±7.31 mmHg at baseline visit. At baseline 28.02%, 62.60%, 6.54% patients suffered from mild, moderate and severe grade hypertension, respectively. Remaining patients had optimal, normal or high normal BP. Patients had a mean diabetic history of 90.2 months of whom 79.59% were treated with oral hypoglycemic drugs.
Efficacy results:	**Mean Reduction in SBP (PP population with Last Observation Carried Forward [LOCF])** **Aprovel 150 mg:** Mean SBP at baseline was 154.25±12.07 mmHg. At week 24, the mean SBP was 124.51±11.25 mmHg indicating a statistically significant mean reduction of 26.63 mmHg (p=0.0035). The mean change in SBP from baseline (154.25±12.07 mmHg) to week 24 (124.51±11.25 mmHg) was statistically significant (p<0.0001). **Aprovel 300 mg:** Mean SBP at baseline was 158.61±10.62 mmHg. At week 24, the mean SBP was 130.26±12.28 mmHg indicating a mean reduction of 24.87 mmHg (p=0.0839). The mean change in SBP from baseline (158.61±10.62 mmHg) to week 24 (130.26±12.28 mmHg) was statistically significant (p<0.0001). **CoAprovel:** Mean SBP at baseline was 159.94±10.35 mmHg. At week 24 the mean SBP was 131.11±13.63 mmHg indicating a mean reduction of 29.53mmHg (p=0.5290). The mean change in SBP from baseline (159.94±10.35 mmHg) to week 24 (131.11±13.63 mmHg) was statistically significant (p<0.0001).

	Similar results were observed in the ITT population. **Mean Reduction in DBP (PP population with LOCF)** **Aprovel 150 mg:** Mean DBP at baseline was 94.60±6.81 mmHg. The mean DBP at week 24 was 78.99±6.86 mmHg indicating a statistically significant reduction of 13.89 mmHg (p<0.0001). The mean change in DBP from baseline (94.60±6.81 mmHg) to week 24 (78.99±6.86 mmHg) was statistically significant (p<0.0001). **Aprovel 300 mg:** Mean DBP at baseline was 97.94±6.05 mmHg. At week 12 the mean DBP was 81.56±9.18 indicating a statistically significant reduction in the mean DBP of 14.58 mmHg (p=0.0144). The Mean DBP at week 24 was 81.21±7.56 mmHg indicating a mean reduction of 14.91 mmHg (p=0.5337). The mean change in DBP from baseline (97.94±6.05 mmHg) to week 24 (81.21±7.56 mmHg) was statistically significant (p<0.0001). **CoAprovel:** Mean DBP at baseline was 97.55±6.57 mmHg. Mean DBP at week 24 was 81.64±7.50 mmHg indicating a mean reduction of 16.09 mmHg (p=0.2287). The mean change in DBP from baseline (97.55±6.57 mmHg) to week 24 (81.64±7.50 mmHg) was statistically significant (p<0.0001). Similar results were observed in the ITT population. *Please refer to Table 1: Comparison of mean SBP and DBP at different study intervals on different treatments with LOCF-PP population.* **Proportion of patients reaching BP target (PP population)** The number of subjects in the PP population with SBP≤130 mmHg at baseline were 20 (3.19%) in Aprovel 150 mg, 4 (0.64%) in Aprovel 300 mg and 2 (0.32%) in CoAprovel groups (n=626). At visits 2, 4, 6, 12, 18 and 24 the number of subjects reaching target SBP increased with maximum number at week 24. At week 24, there were 303/524 (57.82%) patients in Aprovel 150 mg, 95/524 (18.13%) in Aprovel 300 mg and 35/524 (6.68%) in CoAprovel group. There was a statistically significant (p<0.0001) increase in the number of patients attaining the SBP target value from baseline to week 24. Similar results were observed in the ITT population. The number of subjects in the PP population with DBP≤80 mmHg at baseline were 20 (3.19%) in Aprovel 150 mg, 6 (0.96%) in Aprovel 300 mg and 1 (0.16%) in CoAprovel groups (n=626). At visits 2, 4, 6, 12, 18 and 24 the number of subjects reaching target SBP increased with the maximum number at week 24. At week 24, there were 297/524 (56.68%) patients in Aprovel 150 mg, 93/524 (17.75%) in Aprovel 300 mg and 37/524 (7.06%) in CoAprovel groups reaching the BP target (p<0.0001). Similar results were observed in the ITT population. **Restoration of ACR rate (PP population)** At week 24, in Aprovel 150 mg group 92/151 patients, in Aprovel 300 mg group101/178 patients, and in CoAprovel group 118/195 patients achieved restoration of ACR <30 mg albumin/gm creatinine. These changes however failed to reach statistical significance at week 24 in both populations. **Development of Overt Nephropathy** Out of 626 patients who were available for the univariate analysis, only 11 patients had the instances of overt nephropathy in the study at week 24. None of the factor had a statistically significant correlation for development of overt nephropathy. In the multivariate analysis only HbA1c (Hazard ratio=1.41; p=0.0142) and Blood Urea Nitrogen (Hazard ratio=1.0315; p=0.0278) was a significant risk factor for the development of overt nephropathy.
Safety results:	The safety was analyzed on the safety population, using the data from all the enrolled patients. All safety endpoints were evaluated at scheduled visit and summarized using descriptive statistics for continuous variables and using frequencies and relative frequencies for categorical variables. All safety variables were analyzed in the 797 enrolled patients. A total of 178 adverse events

	(AEs) were reported from 104 patients reporting at least one treatment emergent AE. Seven patients were discontinued from the study due to AEs, 5 AEs were reported to be study drug related (3 possibly and 2 remotely) including 2 drug unrelated events. There were 5 severe and 14 moderate AEs and all other AEs were considered mild. Categorization of events according to the system organ class showed that central nervous system (41 patients) disorder was the most common class and headache was the most common AE (22 patients), 10 of them were deemed study drug related. There were 23 cardiac events, 21 musculoskeletal disorders and 21 complained of gastrointestinal symptoms. In the safety population, 5 patients suffered from SAEs: Cardiac arrest, two cerebrovascular strokes, vaginal hemorrhage and transient ischemic attack. All SAEs were unrelated to study drug. Two patients reportedly died of cardiac arrest and hemorrhagic stroke during the study. Overall tolerability of the study drug was assessed in 612 patients by physician and was reported to be excellent in 523 patients, good in 84 patients and fair in 5 patients. **Laboratory Evaluation**: The laboratory evaluation was performed for both haematology and biochemistry parameters in the study, and these evaluations were recorded only at baseline and at week 24. The percentage of the patients included in the section are calculated from the number of patients considered for this analysis. **Hematology:** Out of the 416 (54.95%) patients who had low hemoglobin values at baseline, 261 (45.79%) patients had low values and 36 (6.32%) patients had normal values at week 24. Out of 341 (45.05%) patients who had normal hemoglobin values at baseline, 67 (11.75%) patients had low values, 193 (33.86%) had normal values and 1 (0.18%) patient had high values at week 24. Out of the 29 (3.83%) patients who had low WBC values at baseline, 8 (1.40%) patients had low values, 10 (1.75%) patients had normal values and 1 (0.18%) patient had high values at week 24. Out of 663 (87.58%) patients who had normal WBC values at baseline, 6 (1.05%) patients had low values, 454 (79.65%) patients had normal and 27 (4.74%) patients had high values at week 24. Out of 65 (8.59%) patients who had high WBC values at Baseline, 2 (0.35%) patients had low values, 23 (4.04%) patients had normal values and 27 (4.74%) patients had high values at week 24. Out of the 224 (29.59%) patients who had low ESR values at baseline, 119 (20.88%) patients had low values, 11 (1.93%) patients had normal values and 38 (6.67%) patients had high values at week 24. Out of 29(3.83%) patients who had normal ESR values at baseline, 7 (1.23%) patients had low values, 3 (0.53%) patients had normal values and 9 (1.58%) patients had high values at week 24. Out of 504 (66.58%) patients who had high ESR values at baseline, 51 (8.95%) patient had low values, 11 (1.93%) patients had normal values and 309(54.21%) patients had high values at week 24. Out of the 13 (1.72%) patients who had low platelet values at baseline, 3(0.53%) patients had low values, 8(1.40%) patients had normal values and 1(0.18%) patient had high values at week 24. Out of 693 (91.55%) patients who had normal platelets values at baseline, 6(1.05%) patients had low values, 480 (84.21%) had normal values and 25 (4.39%) patients had high values at week 24. Out of 51 (6.74%) patients who had high platelets values at baseline, 16 (2.81%) patients had normal values and 19(3.33%) patients had high values at week 24. **Biochemistry** Out of the 2 (0.26%) patients who had low creatinine values at baseline, 2(0.35%) patients had normal values at week 24. Out of 722 (95.38%) patients who had normal creatinine values at baseline, 8 (1.40%) patients had low values, 512 (89.82%) patients had normal values and 16(2.81%) patients had high values at week 24. Out of 33 (4.36%) patients who had high creatinine values at baseline, 14 (2.46%) patients had normal values and 6 (1.05%) patients had high values at week 24. Out of the 3 (0.40%) patients who had low ASAT values at baseline, 1 (0.18%) patient had normal value and 1 (0.18%) patient had high values at week 24. Out of 659 (87.05%) patients who had normal ASAT values at baseline, 9 (1.58%) patients had low values, 456 (80.00%) patients had normal values and 16 (2.81%) patients had high values at week 24. Out of 95 (12.55%) patients who had high ASAT values at baseline, 2 (0.35%) patients had low values, 35 (6.14%) patients

	had normal values and 38 (6.67%) patients had high values at week 24. Out of the 5 (0.66%) patients who had low ALAT values at baseline, 1 (0.18%) patient had low value and 2 (0.35%) patients had high values at week 24. Out of 651 (86.00%) patients who had normal ALAT values at baseline, 8 (1.40%) patients had low values, 443 (77.72%) patients had normal values and 23 (4.04%) patients had high values at week 24. Out of 101 (13.34%) patients who had high ALAT values at baseline, 2 (0.35%) patients had low value, 45 (7.89%) patients had normal values and 34 (5.96%) patients had high values at week 24. Out of the 18 (2.38%) patients who had low serum potassium values at baseline, 1 (0.18%) patient had low value, 8 (1.40%) patients had normal values and 2 (0.35%) patients had high values at week 24. Out of 712 (94.06%) patients who had normal serum potassium values at baseline, 15 (2.63%) patients had low values, 496 (87.02%) patients had normal values and 19 (3.33%) patients had high values at week 24. Out of 27 (3.57%) patients who had high serum potassium values at baseline, 2 (0.35%) patients had low value, 13 (2.28%) patients had normal values and 4 (0.70%) patients had high values at week 24. As per the ADA classification, out of the 16 (2.11%) patients who had normal HbA1c values at baseline, 5 (0.88%) patients had normal value at week 24, 4 (0.70%) patients were pre-diabetic and 1(0.18%) patient was diabetic at week 24. Out of 77 (10.17%) patients who were pre-diabetic at baseline, 14 (2.46%) patients had normal values of HbA1c at week 24, 26 (4.56%) patients were pre-diabetic and 21 (3.68%) patients diabetic at week 24. Out of 648 (85.60%) patients who were diabetic at baseline, 26 (4.56%) had their HbA1c values normal at week 24, 56 (9.82%) were pre-diabetic and 380 (66.67%) were diabetic at week 24. Out of the 47(6.21%) patients who had low BUN values at baseline, 21(3.68%) patients had low, 16(2.81%) patients had normal values and 4(0.70%) patients had high values at week 24. Out of 591 (78.07%) patients who had normal BUN values at baseline, 28 (4.91%) patients had low values, 393(68.95%) patients had normal values and 19(3.33%) patients had high values at week 24. Out of 119 (15.72%) patients who had high BUN values at baseline, 7 (1.23%) patients had low values, 32 (5.61%) patients had normal values and 38 (6.67%) patients had high values at week 24. Blood and serum chemistry parameters showed improvement at week 24 compared to baseline. **Vital signs:** The mean heart rate reduced from 82.25±9.5bpm at baseline to 78.59±6.71 at 24 weeks. **Hypertension Grade (European Society of Cardiology Hypertension Guidelines 2009):** For 778 patients at baseline, the hypertension grade was recorded as optimal in 2, normal in 7, high-normal in 13, mild in 218, moderate in 487 and severe in 51 patients. Out of 613 patients at week 24, the hypertension grade was recorded as optimal in 54, normal in 258, high-normal in 181, mild in 98 and moderate in 21 patients. There were no patients with severe hypertension. BP value was missing for one patient at week 24.
Date of report	02-Dec-2010