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Sponsor/company:	Bristol-Myers Squibb and Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00561964
		Study Code:	L_9079
Generic drug name:	Irbesartan	**Date:**	22 Nov 2007

Title of the study:	Randomized, Double-blind, Multicenter, Placebo-control study of the efficacy and safety of Irbesartan on albuminuria in hypertensive Chinese patients with type II Diabetes Mellitus
Investigator(s):	- The PLA hospital Prof. Pan - Beijing China-Japan friendship hospital Prof. Yang - Beijing Xie-He hospital Prof. Xiang - The first hospital of Peking university Prof. Gao - Shanghai Rui-Jin hospital Prof. Ning - The Second hospital of Guang-Zhou university Prof. Chen - The First hospital of Guang-Zhou university Prof. Weng - The general hospital of Tian-Jin medical university Prof. Feng
Study center(s):	- The PLA hospital - Beijing China-Japan friendship hospital - Beijing Xie-He hospital - The first hospital of Peking university - Shanghai Rui-Jin hospital - The Second hospital of Guang-Zhou university - The First hospital of Guang-Zhou university - The general hospital of Tian-Jin medical university

Publications (reference):	1. Mathiesen ER, Hommel E, Hansen HP, Smidt UM, Parving H-H. Randomised controlled trial of long term efficacy of captopril on preservation of kidney function in normotensive patients with insulin dependent diabetes and microalbuminuria. BMJ 1999;319:24-5. 2. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-9. 3. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? Ann Intern Med 2001;134:370 4. Parving H-H. Initiation and progression of diabetic nephropathy. N Engl J Med 1996;335:1682-3. 5. Garcia-Donaire JA, Segura J, and Ruilope LM: An update of irbesartan and renin-angiotensin system blockade in diabetic nephropahy. Expert Opin. Pharmacother. 2005;6 (9):1587~1596 6. Rossing K, Schjoedt KJ, Jensen BR, Boomsma F, and Parving H-H: Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. Kidney Internaional 2005;68:1190~1198 7. Parving H-H, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, and Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001; 345: 870-878 8. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Julia B. Lewis JB, Ritz E, Atkins RC, Rohde R, and Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med. 2001: 345: 851-860 9. Agardh C-D, Garcia-Puig J, Charbonnel B, Angelkort B, Barnett AH. Greater reduction of urinary albumin excretion in hypertensive type II diabetic patients with incipient nephropathy by lisinopril than by nifedipine. J Hum Hypertens 1996;10:185-92. 10. De Jong PE, Navis GJ, de Zeeuw D. Renoprotective therapy: titration against urinary protein excretion. Lancet 1999;354:352-3.

Study period: Date first **patient** enrolled: 15-01-2004 Date last **patient** completed: 12-07-2005			**Phase of development:** Phase II
Objectives:	To evaluate the effects and safety of irbesartan on proteinuria in hypertensive patients with type ? diabetes mellitus.		
Methodology:	Randomized, double-blind, placebo- control, multicenters study		
Number of patients/subjects:	Planned: 360	Randomized: 241	Treated: 218

Evaluated:	**Efficacy:** Primary: Urine albumin excretion rate (UAER). *Secondary:* SeSBP, SeDBP, Total cholesterol, Triglycerides HDL cholesterol, LDL cholesterol, glycated hemoglobin.	**Safety:** Evaluation of the safety was based upon the assessment of AE and clinically important changes in laboratory parameters. Particular attention was given to those events which resulted in discontinuation of study drug or which were serious in nation.
Diagnosis and criteria for inclusion:	1. Given written informed consent; 2. Aged 30-75 ; 3. Male patients; non lactating and non pregnant females using adequate contraception; 4. Fasting plasma glucose of untreated type II diabetes mellitus patients =7.0 mmol/L, or the time between diagnosis of type II diabetes mellitus and treatment > 3 monthes; 5. The patients of normal BP, or hypertensive patients receiving antihypertensive medication, Seated systolic blood pressure (SeSBP) is between 120-180mmHg and the Seated diastolic blood pressure (SeDBP) is between 80-110mmHg; 6. Evidence of albuminuria defined as an AER of 20 and 500 ug/minute on a single timed overnight collection. Before randomization the patient must quality with two AERs of 3 days intervals in the absence of confounding factors such as urinary tract infection, acute febrile illness and cardiac failure. The two AERs measurement should be in the above defined range and the variability between the two AERs measurement must be <35%. Value of basal AER is calculated as the mean of the 2 measurements. The UAER measured using immunity nephelometer method (DCA2000); 7. Serum creatinine < 150umol/L(1.7mg/dl) and serum potassium in the normal lab. range (3.5-5.5 mol/L); 8. 18 Kg/m2=BMI= 35Kg/m2;	
Investigational product: Dose: Administration:	Irbesartan capsules strength 150 mg 300mg Irbesartan group will be initiated at one irbesartan and one placebo for 2 weeks and titrated at two capsules if well tolerated after 2 weeks , this dose will be maintained throughout the study without further dose-adjustment (2 capsules daily in the morning will be taken from randomization to study end)	
Duration of treatment: 24 weeks		**Duration of observation:** 24 weeks

Reference therapy: Dose: Administration:	Placebo, matching capsules no Placebo group: 2 placebo capsules daily as a single morning intake
Criteria for evaluation:	
Efficacy:	**Primary:** Urine albumin excretion rate (UAER) **Secondary:** SeSBP, SeDBP, Total cholesterol, Triglycerides, HDL cholesterol, LDL cholesterol , glycated hemoglobin. Evaluation of the safety was based upon the assessment of AE and clinically important changes in laboratory parameters. Particular attention was given to those events which resulted in discontinuation of study drug or which were serious in nation

Statistical methods:	**Efficacy**: The tests were two-sided and a 5% significance level used throughout. The comparison between patients on irbesartan and patients on placebo will be the primary comparison. To maintain an overall two-sided significance level of 5% in the pairwise comparison between irbesartan groups and placebo, the comparisons will be made at 2.5% level (Bonferroni adjustment). The primary endpoint parameter was the change from baseline in overnight UAER after 6 months treatment, and compared the overnight UAER of different groups by ANCONA. The baseline value was defined as the mean of the two measurements realized during the randomization period, the UAER were be log-transformed before analysis. The secondary endpoint parameter, the changes from baseline in BP, Total cholesterol, Triglycerides, HDL cholesterol, LDL cholesterol , HbA1c were compared between groups by analysis of variance after 6 monthes treatment using ANCONA. In addition, endpoint analyses will be performed: when 6 monthes evaluation outcomes are not obtained, the last available outcome will be used in its place **Safety:** All patients who receive study drug will be evaluated for safety. All adverse events recorded during the study will be coded according to the WHO Adverse Reactions Terminology and assigned to a system-organ class by the sponsor. They will be listed by patient including time of onset, time from the first administration of study drug, duration, intensity, action taken, corrective therapies, outcome, relationship to study drug and seriousness. The treatment emergent adverse events will be summarized under treatment group by tabulating: 1) the frequency of reports of each unique event and the frequency of reports in each system-organ class; 2) the number and the percentage of patients experiencing each adverse event and the number of patients belonging to each system-organ class; 3) the number and percentage of patients experiencing one or more events. The incidence of most frequently occurring events and the cardiovascular events will be compared between treatment using appropriate chisquare test. The concomitant medications will be coded according the WHO drug code. They will be summarized under treatment group by tabulating the number and percentage of patients having received each medication and belonging to each therapeutic class Special attention will be focused on diabetes mellitus, glycemia and hypertension treatments. Individual data for laboratory parameters, vital signs, funduscopic and ECG parameters will be listed and values outside the reference range and pre-specified marked changes baseline will be flagged, Listing of patients with abnormal values will be provided. The baseline laboratory value for each patient is defined as the last available value prior to randomization. Results and changes from baseline of laboratory will be summarized by mean, standard error of the mean, minimum and maximum at each timepoint. Analysis of variance will be used to compare treatments

Summary:	
Efficacy results:	The clinical results showed the mean value changes of UAER from baseline after 24 weeks for ITT population in the irbesartan and placebo groups decreased 0.14 and 0.000 respectively, and irbesartan was significantly better than placebo ($p<0.05$) with regard to decreased risk of developing clinical proteinuria by ANCONA excepting the difference observed between centers, baseline and HbA1c, The analysis results for PP population were similar to those observed for the ITT population. Mean decreases from baseline in DBP at 24 weeks treatment endpoint were observed in both of two treatment groups by ANCONA excepting the difference observed between centers and baseline ($p<0.05$), the reductions in SBP and DBP observed in irbesartan group were greater than in the placebo group and differences between the two groups were statistically significant ($p<0.05$). The remedy is routine antihypertensive such as administration of ACE-?and ARB in placebo group. There were no statistically significant differences in both of the two groups for the analysis of mean change from baseline in Triglycerides and HDL cholesterol at 24 weeks endpoint. The changes of LDL cholesterol from baseline at 24 weeks endpoint increased sightly in placebo group and decreased sightly in irbesartan group, the difference of two groups were statistically significant ($p<0.001$). There were no statistically significant differences between the two groups for the analysis of mean change from baseline in HbA1c during the treatment period.
Safety results:	Overall, AEs occurred with similar frequency between the irbesartan-treated subjects (44.26%) and the placebo-treated subjects (51.69%). The frequency of drug related AE is 14.75% (18 cases), 12.71% (15cases) respectively in irbesartan and placebo group, the events of dizziness, cephalalgia, constipation , serum Cr increasement and hypotension, hyperpotassium occurred frequently in placebo and irbesartan group respectively. There are 4 SAEs in placebo group. The intestinal adhesion, myocardial infarctin (MI), ulcerous colonitis, precordium complaint was all one case, and were judged no relation with study drug. All patients were catabatic by treatment, There are 2 SAEs in irbesartan group, one patient is ictal death, the possible cause is asystolia abruptly, the other patient occurred retina desquamate and eyeground bleeding in the left eye and hospitalized, and were catabatic by treatment, they were judged no relation with study drug. No drug relative SAE occurred. In addition to the more occurring events of serum potassium increasing in irbesartan-treated group compared to placebo-treat group, no significant changes were observed in blood routine, urine routine, serum chemistry, ECG and vital sign between the two treatment groups.
Date of report:	12-10-2005