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Sponsor/company:	Bristol-Myers Squibb and Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00263003
		Study Code:	PM_L_0094
Generic drug name:	Irbesartan / Hydrochlorothiazide	**Date:**	06/12/2007

Title of the study:	A Randomized, Open-Label Comparative Study of Irbesartan/ hydrochlorothiazide and Irbesartan in the Treatment of Mild to Moderate Hypertension.	
Investigator(s):	Dr. Chiao-Lin Chuang, Dr. Wu-Chang Yang, Dr. Chao-Fu Chang, Dr. Chih-Ching Lin, Dr. Yao-Ping Lin,	
Study center(s):	Taipei Veterans General Hospital	
Study period: June 2005 to January 2006 Date first subject enrolled: 14/06/2005 Date last subject completed: 17/01/2006		**Phase of development:** Phase IV
Objectives:	1) To compare the reduction in office BP following a 8-week regimen of irbesartan/hydrochlorothiazide versus irbesartan. 2) To compare the reduction in office BP after 4-week regimen of irbesartan/hydrochlorothiazide versus irbesartan. 3) To compare the response rate (defined as office SBP/DBP reduce more than 10mmHg from Week 0) of patients after 4-week and 8-week regimen of irbesartan/hydrochlorothiazide versus irbesartan. 4) To compare the proportion of patients requiring titration after 4 week regimen of irbesartan/hydrochlorothiazide versus irbesartan. To ascertain the safety and tolerability of irbesartan/ hydrochlorothiazide versus irbesartan.	
Methodology:	Open-Label, Randomized, Comparative, Single Center	
Number of subjects:	Planned: 40 Randomized: 20 Treated: 40	

Diagnosis and criteria for inclusion:	**Inclusion criteria** - Patients aged between 20-70 years, with mild-moderate hypertension with office diastolic BP (DBP) 90-109 mmHg and/or systolic BP (SBP) 140-179 mmHg. **Exclusion criteria** - Females: who were pregnant or breast-feeding. - Office diastolic BP = 110 mmHg or office systolic BP = 180 mmHg. - History of significant cardiovascular diseases which includes: a. acute myocardial infarction within six months or any ischemic heart disease requiring medication. b. cerebrovascular disease. - History of significant renal diseases including: a. serum creatinine > 3.0 mg/dl. b. creatinine clearance < 30 ml/min. - Severe biliary cirrhosis and cholestasis. - Refractory hypokalemia, hypercalacemia. - History of autoimmune disease, collagen vascular disease, multiple drug allergies, bronchospastic disease or other malignancies requiring current medication. - Hepatic disease as indicated by any of the following: a. SGOT or SGPT > 3× upper limit of normal. b. Serum bilirubin > 2× upper limit of normal. - Any other condition or therapy that, in the investigator's opinion, or as indicated in the product(s) label may pose a risk to the patient or interfere with the study objectives. - Any other investigational drug given within 30 days of initiation of therapy, and participation in other clinical studies while enrolled in this protocol.
Investigational product:	Irbesartan/hydrochlorothizade (COAPROVEL®, Sanofi-Synthelabo) Irbesartan (APROVEL®, Sanofi-Synthelabo)
Dose Regimen:	• **Irbesartan/hydrochlorothizade:** 150mg/12.5mg per day, titrating to 150mg/12.5mg bid per day if office DBP = 90 mmHg and/or office SBP = 140 mmHg at week 4. • **Irbesartan:** 150mg per day, titrating to 150mg bid per day if office DBP = 90 mmHg and/or office SBP = 140 mmHg at week 4.
Duration of treatment:	Eligible patients started the treatment medication at Week 0 (± 4-day window). Patients were followed up at Week 4 and 8. At each visit, a physical examination, office BP, HR and adverse events were checked. At the end of the study (Week 8), a routine laboratory studies were performed.

Criteria for evaluation:	• **Primary criteria** Change in office BP from baseline to Week 8. • **Secondary criteria** Change in office BP from baseline to Week 4, the response rate of patients at Week 4 and Week 8, the proportion of patients requiring titration at We ek 4, and drug safety and tolerability.
Statistical methods:	• **Efficacy Analysis** The primary efficacy outcome, change in office BP from baseline to Week 8, and the secondary efficacy outcome, change in office BP at Week 4 were compared between the two groups using analysis of covariance with the baseline value as covariate. The secondary efficacy outcomes, the response rate at Week 4 and Week 8, and the proportion of patients requiring titration at Week 4 were compared by Fisher's Exact Test. • **Safety Evaluation** Adverse events, including those that were serious or resulted in discontinuation of study therapy were evaluated and described in depth. The number of patients who discontinued the study prematurely was summarized by treatment group and by reason(s) for premature discontinuation. The incidences of adverse events in the treatment group were compared using Fisher's Exact Test, and the marked laboratory abnormalities were summarized.

Results	• **Study Subjects and Conduct** A total of 40 patients were enrolled and randomized to the study, 20 patients were randomized to each group. The first patient was enrolled on 14 June 2005, and the last patient completed the study on 17 January 2006. Of the 40 patients, a total 35 patients who had at least one post-treatment evaluation were included in intent-to-treat population; 16 patients in CoAprovel® group and 19 patients in Aprovel® group, and a total of 30 patients who completed the 8-week treatment were included in per-protocol population; 13 patients in CoAprovel® group and 17 patients in Aprovel® group. • **Efficacy** After 8-week regimen of study drug, the reduction in mean SBP was 23.01 mmHg for CoAprovel® group and 17.94 mmHg for Aprovel® group, respectively. There was statistically improve within each treatment group, and no difference between the two treatment groups was found (p-value = 0.2857). For DBP, the reduction was 12.28 mmHg for CoAprovel® group and 6.74 mmHg for Aprovel® group, respectively. There was also statistically improve within each treatment group, and no statistically significant between the two treatment groups was found (p-value = 0.0559). In addition, there was statistically significant between the two treatment groups in DBP for per-protocol population (p-value = 0.0477). Following a 4-week regimen fo study drug, the reduction in mean SBP was 19.09 mmHg for CoAprovel® group and 13.59 mmHg for Aprovel® group, respectively. There was statistically improve within each treatment group, and no difference between the two treatment groups was found (p-value = 0.2940). For DBP, the reduction was 9.54 mmHg for CoAprovel® group and 7.39 mmHg for Aprovel® group, respectively. There was also statistically improve within each treatment group, and no statistically significant between the two treatment groups was found (p-value = 0.5386). The response rate of patients following a 4-week and 8-week regimen of study drug were 75.0% and 81.3% for CoAprovel® group and 57.9% and 73.7% for Aprovel® group, respectively. There was not statistically significant between the two treatment groups. In addition, 4 of 16 (25.0%) patients in CoAprovel® group and 11 of 19 (57.9%) patients in Aprovel® group required titration after 4-week regimen of study drug. Regardless of there was not statistically significant between the two treatment group (p-value = 0.0866), the proportion of patients requiring titration of CoAprovel® group was less than Aprovel® group obviously. • **Safety** A total of 18 (45.0%) patients experienced at least one adverse event; 9 (45.0%) patients in each treatment group. The more frequently reported body system was the nervous system disorders (5 patients in CoAprovel® group, 4 patients in Aprovel® group) and infections and infestations (2 patients in CoAprovel® group, 4 patients in Aprovel® group). One serious adverse event (kidney multiple simple cysts with cyst rupture induced gross hematuria, moderate degree) which was not related to study drug was reported by one patient in CoAprovel® group.

	Among above adverse events, 7 (17.5%) patients experienced at least one drug-related adverse event; 4 (20.0%) patients in CoAprovel® group, 3 (15.0%) patients in Aprovel® group. These drug-related adverse events included dizziness and headache. In addition, for laboratory value and heart rate, no clinical significant difference between the two treatment groups was found at the end of treatment period.
Date of report:	March 8, 2006