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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00443612
		Study Code:	IRBEH_L_00702
Generic drug name:	Irbesartan+Hydrochlorothiazide	**Date:**	22 September 2009

Title of the study:	A Randomized, Open-Label, Crossover Comparative Study of Irbesartan/Hydrochlorothiazide 150/12.5mg and Irbesartan 150mg in the Treatment of Mild to Moderate Hypertension (IRBEH_L_00702)
Investigator(s):	Dr. Fu-Tien Chiang No.7 Chung San South Road, Taipei
Study center(s):	*National Taiwan University Hospital*
Publications (reference):	*J of Human Hypertension* 2008, 22, 266-274 *Therapeutics* 1998, 20(3):398-409. *Am J Hypertens* 2005, 18:1482-1488 *J. Of Clin Hypertens (Greenwich)* 2005, 7(10):578-586 *Curr Hypertens Rep* 2001, 3:61-67 *Am J Hypertens* 1999; 12:797–805 *Proc Natl Acad Sci* USA 1996; 93:9114–9119

Study period:			Phase of development:
Date first patient/subject enrolled:	07-sep-2006	Date of first signed informed consent	IV
Date last patient/subject completed:	25-oct-2008	Date of last patient last visit	

Objectives:	<u>Primary Objective:</u> To compare the reduction in office BP following a 12-week regimen of irbesartan/hydrochlorothiazide 150/12.5mg versus irbesartan150mg. <u>Secondary Objectives:</u> 1) To compare the change in forearm vascular resistance following a 12-week regimen of irbesartan/hydrochlorothiazide 150/12.5mg versus irbesartan150mg. 2) To assess changes of serum proinflammatory cytokine, markers of cardiovascular risks, oxidative stress and circulating adhesion molecule including thiobarbiturate acid reactive substances (TBARS), C-reactive protein (CRP), interleukin 6 (IL-6), and vascular cell adhesion molecule 1 (VCAM-1). 3) To compare the response rate (defined as office SBP/DBP reduce more than 10mmHg from baseline or SBP/DBP <140/90 mmHg). 4) To ascertain the safety and tolerability of irbesartan/hydrochlorothiazide 150/12.5mg versus irbesartan150mg when administered once daily. 5) To assess the relationship between angiotensin II type I (AT1) receptor gene polymorphism and BP reduction.		
Methodology:	This study was a phase IV, randomized, open-label, cross-over comparison of irbesartan/hydrochlorothiazide 150/12.5mg versus irbesartan150mg in the treatment of untreated or uncontrolled mild to moderate hypertension, i.e., office diastolic blood pressure (office DBP) of 90 to 109 mmHg and/or office systolic blood pressure (office SBP) of 140 to 179 mmHg. This was a crossover design with two 12-week treatment periods. After 1 week of wash out, patients were randomized to either CoAprovel (Irbesartan/hydrochlorothiazide: 150mg/12.5mg per day) or Aprovel (Irbesartan 150mg) and enter into a treatment period of 12 weeks (treatment period 1). After 1 week of washout, patients were then crossed over to the alternate regimen for another 12 weeks (treatment period 2). Entire treatment period per patient was approximately 26 weeks. A total of 60 subjects were planned to be recruited for this study which was conducted at National Taiwan University Hospital.		
Number of patients/subjects:	Planned: 60	Randomized: 56	Treated: 56
Evaluated:	Efficacy: 44 (ITT population)	Safety: 56 (Safety population)	
	Sixty patients diagnosed to have hypertension were screened. Excluding 4 screening failures, 56 patients entered the treatment period 1 and 45 patients in treatment period 2. There were 12 patients in total early withdrawn from the study. In Treatment Period 1, there were 11 patients early withdrawn, 6 on irbesartan and 5 on irbesartan/HCTZ. In Treatment Period 2, only 1 patient on irbesartan was early withdrawn. 44 patients included in the efficacy intent-to-treat population (ie, those patients who took at least one dose of randomized study medication and had at least one post-treatment efficacy evaluation in the last 12 weeks of both treatment periods) were equally distributed in both groups. Patients included in the safety population were 56 in either the Irbesartan/Hydrochlorothiazide 150/12.5mg group or in the Irbesartan 150mg group. AEs were analyzed according to the treatment received at the time of the event		
Diagnosis and criteria for inclusion:	Patients aged between 20-80 years, with untreated or uncontrolled mild-moderate hypertension [office diastolic BP (DBP) 90-109 mmHg and/or systolic BP (SBP) 140-179 mmHg]		

Investigational product: Dose: Administration:	Irbesartan/hydrochlorothizade (COAPROVEL®, sanofi-aventis) 150mg/12.5mg per day Oral	
Duration of treatment: 24 weeks		Duration of observation: 26 weeks
Reference therapy: Dose: Administration:	Irbesartan (APROVEL®, sanofi-aventis) 150mg per day Oral	
Criteria for evaluation:		
Efficacy:	<u>Primary criteria</u> Change of blood pressure from baseline to the end of 12-week treatment periods <u>Secondary criteria</u> Change in forearm vascular resistance, TBARS, CRP, IL-6, and VCAM-1 from baseline to the end of 12-week treatment, response rate of patients at the end of 12-week treatment, drug safety and tolerability, gene polymorphism related to BP reduction.	
Safety:	Incidence of AE, marked laboratory abnormalities and SAEs	
Statistical methods:	<u>Efficacy Analysis</u> The primary efficacy outcome, change in office BP from baseline to the end of 12-week treatment periods, will be compared between the two groups using Student's paired t-test. The secondary efficacy outcomes, change in forearm vascular resistance, TBARS, CRP, IL-6, and VCAM-1 from baseline to the end of 12-week treatment, response rate at the end 12-week treatment will be compared by analysis of variance, and Student's paired t-test. <u>Safety Evaluation</u> Adverse events, including those that were serious or resulted in discontinuation of study therapy will be evaluated and described in depth. The number of patients who discontinued the study prematurely will be summarized by treatment received at time of event and by reason(s) for premature discontinuation. The incidence of adverse events and marked laboratory abnormalities in the treatment groups will be compared using Chi-square or Fisher's Exact Test.	

Summary:	
Efficacy results:	The mean changes in the office DBP and office SBP from baseline to the end of 12-week treatment periods were compared. The last observation carried forward (LOCF) procedure was used to estimate the missing data of last visit observation for efficacy variables. There was no imputation for intermediate missed data. Irbesartan 150mg significantly ($p<0.0001$) reduced the value of office SBP and DBP from baseline by 12.6±13.66mmHg and 6.9±9.31mmHg, while Irbesartan/HCTZ 150/12.5mg significantly ($p<0.0001$) reduced office SBP and DBP by 16.1±13.76 mmHg and 9.1±9.63 mmHg respectively. No statistically significant difference between the two treatment groups was observed for SBP or DBP ($p = 0.234$ and $p = 0.278$). Irbesartan 150mg group had significantly reduced the value of vascular resistance by 229 ± 274.15 at week 12. Although Irbesartan/HCTZ group resulted in a greater reduction, 237 ± 280.59, than Irbesartan group, no statistically significant difference between two treatment groups was observed after 12-week ($p=0.908$). Regarding serum oxidative stress and inflammatory markers, the changes from baseline to the end of 12-week treatment were not significantly different between the two treatment groups. As for treatment response rate, it was defined as reduction in office SBP/DBP of more than 10 mmHg from baseline (Week 0/Week 13). The response rate at week 12 for SBP was 95.45% on Irbesartan 150mg group, compared with 93.18% on Irbesartan / HCTZ 150/12.5mg group. For DBP, the response rate was 84.09% for Irbesartan 150mg group, compared with 93.18% for Irbesartan / HCTZ 150/12.5mg group. No statistical significant difference was found between the two treatment groups in these response rates (p-value=1.000 and 0.1570, respectively).
Safety results:	Fifty-six patients who received any amount of study drug (safety population) were included in the safety analysis. Most of lab data in the 2 study groups were within the normal range after 12-week treatment period. Some minor lab abnormalities were observed but no clinical significant difference between the two treatment groups was found at the end of treatment period. A total of 36 (64.29%) patients experienced at least one adverse event and totally 72 adverse events were found among the 36 patents. 19 patients on irbesartan occurred 35 adverse events and the other 17 patients with 37 adverse events were on irbesartan/HCTZ. Only 22 drug-related AEs were reported in 10 subjects (3 patients receiving irbesartan and 7 patients receiving irbesartan/HCTZ) and these were all mild in severity. No serious adverse event was reported. The most frequently reported body system with adverse events was respiratory system disorders (upper respiratory infection in 8 patients), followed by nervous system (dizziness in 7 patients) and cardiovascular system. Among 12 early withdrawn patients, only two were due to adverse events. One experienced insomnia, dizziness, chest discomfort and constipation. The other one was due to chest discomfort, numbness, dizziness and headache. These 2 adverse events were both from irbesartan/HCTZ group and were both mild in severity.
Date of report:	13-Aug-2009