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Sponsor/company:	Bristol-Myers Squibb and Sanofi-Aventis	**ClinicalTrials.gov Identifier:**	NCT00350038
		Study Code:	L_8759
Generic drug name:	Irbesartan	**Date:**	18/01/ 2008

Title of the study:	The effects of Aprovel, Lipanor and their combination onto the endothelial functions of dyslipidemic patients measured by laser Doppler flow-metry.		
Investigator(s):	Gyula Pados MD Leading Physician, head of Dept.		
Study center(s):	4th Department of Medicine – Independent Lipid Unit and Working Group of Clinical Pharmacology, Municipal Szent Imre Hospital H-1115 Budapest, Tétényi út 12–16. Hungary		
Publications (reference):	NA		
Study period: Date first **patient** enrolled: 14 Jun 2005 Date last **patient** completed: 10 Feb 2007		**Phase of development:** Phase IV	
Objectives:	**Primary objectives:** Assessing if ciprofibrate, added to the angiotensin II receptor blocker irbesartan, improves the microvascular reactivity in patients having metabolic syndrome and high cardiovascular risk. **Secondary objectives:** Reduction of blood pressure; measurement and comparison of atherogenic small dense LDL, oxidised LDL concentrations, paraoxonase activity and CRP and registration of the adverse events in the two groups.		
Methodology:	**Open label, randomized, comparative, parallel assignment.**		
Number of patients:	Planned: 70	Randomized: 60	Treated: 60
Evaluated:	Efficacy: 39	Safety: 59	
	Of a total of 60 enrolled and randomized patients, those with an Ach-induced maximal vasodilatation (1 to 3) exceeding 1000% of the initial value at Visit 1 should have been omitted from the evaluation, prior to the assessment of efficacy. The final assessment of efficacy included 39 patients.		

Diagnosis and criteria for inclusion:	Medium/severe hypertension (systolic value: 150 to 180 mmHg and/or diastolic value: 85 to 110 mmHg). Adiposity (BMI >27 kg/m²) Metabolic syndrome Dyslipidaemia (triglyceride 1.7 to 2.3 mmol/l) and/or cholesterol 5.2 to 6.2 mmol/l Left ventricular hypertrophy (demonstrated by ECHO-I within 1 year), cardiac muscle mass index >120 g/m² in male patients and >98 g/m² in female patients. Damaged endothelial function determined by Laser Doppler flowmetry.
Investigational product: Dose: Administration: **Duration of treatment:** 6 months	Irbesartan 150 mg once daily oral **Duration of observation:** 6 months
Reference therapy: Dose: Administration:	Add on Ciprofibrate 100 mg once daily oral
Criteria for evaluation:	
Efficacy:	*Primary:* Microvascular reactivity (measurement, by laser-Doppler flowmetry, of the endothel-dependent vasodilatation induced by acetylcholine and sodium nitroprusside administered into the skin of the forearm by iontoforesis). *Secondary:* Reaching the target blood pressure values (<140/90 mmHg, in a diabetic population <130/80 mmHg), as well as comparing the effects of both medicines on the parameters indicating atherogenic risk (atherogenic small dense LDL, oxidised LDL concentrations, paraoxonase activity and CRP) Co-secondary endpoint: finally collecting the possible adverse events and safety parameters.

Safety:	Adverse events reported by the patient/subject or noted by the investigator. The usual standard hematology and blood chemistry were collected.
Statistical methods:	*Primary endpoint:* Analysis of the change in the endothelial function is performed by repeated measures variance analysis. The effect of the treatment is characterised by the mean difference between the treatment groups and its 95% confidence interval. *Secondary:* Analysis of the secondary parameters of efficacy (atherogenic small dense LDL, oxidised LDL concentrations, paraoxonase activity, CRP, and blood pressure) has been performed by repeatedly measured variance analysis. Statistical tests used in the course of the study: Paired Samples Test and Pearson's Correlation have been used for statistical evaluation and descriptive statistics were done for the demographical parameters, the description of treatments and the evaluation of laboratory data.

Summary of the results:	The study has been completed by 59 high-risk patients with metabolic syndrome (hypertension, dyslipidaemia, overweight) and left ventricular hypertrophy (10 males, 49 females; mean age 53,7 years). 39 patients (21 in Group 'A' [irbesartan monotherapy], and 18 in Group 'B' [irbesartan + ciprofibrate],) were eligible for the evaluation of the efficacy. *Primary:* Endothel-dependent and endothel-independent vasodilatation improved significantly in all (39) evaluated patients. As for the endothel-dependent vasodilatation, there was no difference between the two treatment groups, but the endothel-independent vasodilatation improved significantly better in the Aprovel-Lipanor group. This may be related to the significant change of triglyceride and HDL *Secondary:* Having evaluated the examination parameters of the 39 patients, we may highlight that among the lipid parameters a significant improvement occurred in triglyceride, HDL-Ch, and ApoB (ciprofibrate effect). The systolic blood pressure decreased significantly both in Group 'A' and in Group 'B', the difference was not significant – thus ciprofibrate, added to irbesartan, has not increased the reduction of blood pressure. Although examinations of paraoxonase showed an increase of beneficial rate (19%) in the ciprofibrate group, however the increase was not significant. The oxLDL decreased by 9% in the ciprofibrate group, but also this was not significant. Fibrinogen levels decreased significantly in both groups, but to a greater extent upon the effect of ciprofibrate treatment. The safety parameters did not change in both groups of this study and the investigators did not report any adverse events.
Efficacy results:	*Primary endpoint:* The microvascular endothelial function (vasodilation to iontophoretically administered ACh) was impaired in 39 patients at baseline, and increased significantly after the 6 months irbesartan and irbesartan/ciprofibrate therapy (616,31±230 % to 809,31±372 %; p<0,01). There was a significant increase in the endothel independent vasodilation, as well (631,10±317 % to 777,61±414 %; p<0,05). The change in the endothel-dependent vasodilation was similar in the two treatment groups, whereas the change in the endothel-independent vasodilation was significantly more pronounced in the Group „B" (p<0,05). *Secondary endpoints:* Systolic blood pressure decreased significantly by 19 mmHg in Group "A" and 17,4 mmHg in Group „B" respectively The plasma level of triglycerides and Apo B were decreased only in the Group „B" from 2.17 to 1.19 mmol/l; (p=0,000), and from 1.13 to 0.94 mmol/l (p=0,047), respectively. Plasma level of fibrinogen significantly decreased in both groups with a greater decrease in Group „B" (Group "A": from 4.09 to 3.98 g/l; Group „B" : 4.07 to 3.5 g/l; p=0,049). Plasma HDL-Ch level showed a tendency to increase 11,5 % (NS), while plasma hsCRP a tendency to decrease by 16 % (NS) in the Group „B".
Safety results:	The safety parameters did not change in both groups of this study and the investigators did not report any adverse events.
Date of report:	19 Dec 2007