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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00283036
		Study Code:	L_8793
Generic drug name:	APROVE	**Date:**	13 May 2008

Title of the study:	Efficacy and Tolerability of Posology Adaptation of irbesartan in Ambulatory Hypertensive Patients
Investigator(s):	Pr KRIM Messad Internal Medicine Department, EHS DOUIRA ALGER - ALGERIA
Study center(s):	17 centers - Algeria
Publications (reference):	NA
Study period: Date first patient enrolled: 23-Apr-2005 Date last patient completed: 21-May-2006	**Phase of development:** Phase IV
Objectives:	Primary objective: To evaluate in patients responders but not normalized by a 6-week irbesartan 150 mg treatment, the efficacy of 2 treatment strategies (DBP at week 12): 1/ Maintaining the same dosage of Irbesartan 150 mg/day during additional 6 weeks treatment ; 2/ Doubling the dosage of irbesartan (300 mg/day) during additional 6 weeks treatment; Secondary objective: To evaluate irbesartan safety To compare the decrease of SBP and DBP between the 2 treatment strategies.

Methodology:	Multicentric, randomized, open label, comparative study, The study duration is 12 weeks divided in two parts: Part 1: during 6 weeks, patients will receive 150 mg/day of irbesartan. Part 2: After 6 week treatment, the diastolic blood pressure will allocate the patients, according to their treatment response, into two groups : DBP < 90 mmHg : **normalized patients (group 1)** DBP ≥ 90 mmHg : - Decrease of DBP < 10 mmHg :**non responders (group 3)** - Decrease of DBP ≥ 10 mmHg **: responders but not normalized (group 2)** The normalized patients (group 1) will continue irbesartan 150mg/day during 6 additional weeks. The non responders patients (group 3) will receive a double dosage of irbesartan, i.e. 300mg/day, during 6 additional weeks. **The responders but not normalized patients (group 2) will be randomized in** : • **Group A:** patients will continue irbesartan 150mg/day during 6 additional weeks. • **Group B:** patients will receive a double dosage of irbesartan 300mg/day during 6 additional weeks. The comparison will be based on the efficacy within the two groups (A and B).		
Number of patients:	Planned: 200	Included and treated: 183	Randomized: 14
Evaluated:	Efficacy: Week 6: 168 Week 12: 163	Safety: 183	
Diagnosis and criteria for inclusion:	Patient with mild or moderate hypertension defined by seated DBP between 90 mmHg and 110 mmHg and seated SBP between 140 mmHg and 180 mmHg. Patient newly diagnosed and untreated or patients already treated but uncontrolled, and for whom this treatment was stopped at least 2 weeks prior to inclusion.		
Investigational product: Dose: Administration:	irbesartan 150 mg/day or 2x150mg/day Oral route		
Duration of treatment: 12 weeks	**Duration of observation:** 12 weeks		
Reference therapy:	NA		
Criteria for evaluation::			
Efficacy:	- Change from baseline in seated DBP at week 12. - Number of responders and normalized patients at week 6 and week 12.		

Safety:	Adverse events reported by the patient/subject or noted by the investigator
Statistical methods:	The study population will be analyzed in intention to treat: it will include all the patients having at least one evaluation on irbesartan treatment. Efficacy: The efficacy analysis will be based on the blood pressure values on week 12 and on the evaluation between day 0 (at baseline) and week 12. After the distribution variable's study, the groups comparison will be performed by parametric tests (Student test, ANOVA) or with non parametric tests (test of Mann-Whitney, test of Kruskall-Wallis). Safety: Number and frequency of the adverse events (number of patients presenting at least one adverse event during the study).
Summary:	A total of 183 patients were included and treated (mean age 57 ± 11 y). 46 % men, mean age: 54 ± 11 y. 54 % women, mean age: 60 ± 11 y. 57 out of 183 (33%) were previously treated before inclusion. Mean SBP/DBP at inclusion was:161.8 ± 9.6 / 97.4 ± 4.5mm Hg Mean duration of HTN was less than one year in 60% of the patients. 18 patients were lost to follow up (15 at week 6 and 3 at week 12)

Efficacy results:

- **<u>At week 6,</u>** 168 patients were evaluated and mean SBP/DBP was: 140.3 ± 15.4/ 83.4 ± 9.5 mm Hg

The repartition of the patients according to the treatment answer was:

Answer at 6 weeks	Number of patients	Frequency
Normalized (group 1)	129	76.8 %
Patients non responders (group 3)	25	14.9 %
Patients responders but not normalized (group 2)	**14**	**8.3 %**
Total	168	100 %

Only the 14 patients of group 2 (responders but not normalized) were randomised:

Group A : 7 patients (irbesartan 150 mg/day)

Group B: 7 patients (irbesartan 300 mg/day)

- **<u>At week 12,</u>** the evaluation concerned 163 patients. Three patients were lost to follow up after 6 weeks of treatment (2 in group 1 and 1 in group 2) and two patients were withdrawn due to adverse events (1 in group 1 and 1 in group 3)

  - Group 1 : 126 patients normalized at week 6
  - Group 3 : 24 patients non responders at week 6
  - **Group 2 : 13 patients responders but not normalized** at week 6

    Group A: 7 patients,

    Group B: 6 patients.

The mean DBP decrease between day 0 and week 12 was 14.1 ± 4.3 mmHg in group A, and 19.5 ± 6.2 mmHg in group B, (p = 0.24).

The mean SBP decrease was 16.7 ± 6.5 mmHg in group A, and 24.3 ± 7.8 mmHg in group B, (p = 0.07)

Among the 7 patients of group A, 5 patients were normalised at week 12 (DBP m < 90 mmHg) and among the 6 patients of group B, 4 were normalized (p = 0.85).

In the whole population of the study (163 patients), mean SBP/DBP at week 12 was 134.8 ± 14 / 80.8 ± 7.7 mmHg and mean SBP/DBP decrease from baseline was 26.9 ± 15.6 /16.6 ± 7.6mmHg.

Safety results:

Adverse events have been registered in 3 patients :

- Dermatosis in one patient normalized at week 6 (group 1) who was not withdrawn from treatment
- Headache and myalgia in one patient non responder at week 6 (group 3) who was withdrawn from treatment between week 6 and week 12
- Nausea and vomiting in one patient normalized at week 6 (group 1) who withdrawn from treatment between week 6 and 12.

Date of report: 23-Apr-2008