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Sponsor / Company: sanofi-aventis **Drug substance(s):** ataciguat (HMR1766)	**Study Identifier:** NCT00443287 **Study code:** DFI6174
Title of the study: A randomized, double-blind, placebo-controlled, parallel group trial of HMR1766 assessing the efficacy and safety of 3 doses of HMR1766 (25, 100, 200 mg OD) versus placebo with cilostazol, 100 mg BID as a calibrator, administered for 26 weeks in patients with Peripheral Arterial Disease (PAD) Fontaine stage II	
Study center(s): 68 active centers in 7 countries Austria, Canada, France, Poland, Russia, South Africa, and the United States of America	
Study period: Date first patient enrolled: 27/Feb/2007 Date last patient completed: 08/Oct/2008	
Phase of development: 2b	
Objectives: Primary: To demonstrate the efficacy of 6 months treatment with HMR1766 (ataciguat sodium) for improvement in walking distance in patients with intermittent claudication (Fontaine stage II PAD). Secondary: • To assess the safety and tolerability of 3 different regimens of ataciguat; • To assess steady state pharmacokinetics (PK) in a subset of about 90 patients, in selected sites; • To build a population PK model in all study patients.	
Methodology: This was a randomized, placebo-controlled, double-blind, 5-parallel-group study of 3 dose regimens of HMR1766 versus placebo with cilostazol as a calibrator on top of clopidogrel (75 mg once daily [OD]). After a screening visit, Visit 1, eligible patients entered a placebo run-in phase of 4 to 6 weeks to assess the stability of each patient's initial claudication distance (ICD). Patients who successfully completed the run-in phase were centrally randomized via an interactive voice response system in a 1:1:1:1:1 ratio to 1 of the 5 treatment groups at the baseline visit. Randomization was stratified for presence or absence of diabetes mellitus conducted in a patient population with intermittent claudication (Fontaine stage II PAD). The treatment period was 26 weeks (182 days). A follow-up visit was scheduled 5 to 7 days after the end-of-treatment for all patients. A patient was considered to have completed the study once he/she attended all scheduled visits and completed all study-specific procedures. In case of discontinuation, the patient was to return for the end-of-treatment visit assessment normally held at Week 26.	

Number of patients: Planned: 550 (to be equally allocated to 5 study groups of HMR1766 25, 100, 200 mg, placebo, and cilostazol 100 mg)
Randomized: 553 (placebo: 111, HMR1766 25 mg: 111, HMR1766 100 mg: 113, HMR1766 200 mg: 106, cilostazol: 112)
Treated: 553 (placebo: 111, HMR1766 25 mg: 111, HMR1766 100 mg: 113, HMR1766 200 mg: 106, cilostazol: 112)

Evaluated:
Efficacy: placebo: 111, HMR1766 25 mg: 111, HMR1766 100 mg: 113, HMR1766 200 mg: 106, cilostazol: 112
Safety: placebo: 111, HMR1766 25 mg: 111, HMR1766 100 mg: 113, HMR1766 200 mg: 106, cilostazol: 112
Pharmacokinetics: Placebo: 21, HMR1766 25 mg: 21, HMR1766 100 mg: 22, HMR1766 200 mg: 17, cilostazol: 15

Diagnosis and criteria for inclusion:

Major inclusion criteria at screening: Stable symptoms of intermittent claudication of lower extremities, secondary to chronic occlusive arterial disease from atherosclerosis etiology; ICD of 30 to 250 meters at constant workload treadmill test; and ankle/brachial index of 0.9 to 0.5.

Major inclusion criteria at randomization: Mean ICD of 30 to 250 meters calculated by averaging the constant workload treadmill test performed at the end of the run-in phase and the previous one performed at screening; the maximum change (measured in log) in the claudication distance between those 2 ICD measurements was not to exceed 0.25.

Investigational product: HMR1766 liquid-filled soft gelatin capsules of 25 and 50 mg

Dose: 25, 100, 200 mg

Administration: By mouth (PO), once daily (OD)

Duration of treatment: 26 weeks

Duration of observation: 31 to 33 weeks (including 4 to 6 weeks for run-in phase and 5 to 7 days for post-treatment follow-up).

Reference therapy:

Placebo matching the appearance of HMR1766 25 mg and 50 mg soft gelatin capsules, and cilostazol 100 mg tablets

Dose: Not applicable

Administration: PO, OD (HMR1766 or placebo) and BID (cilostazol or placebo)

Cilostazol ("calibrator") 100 mg tablets

Dose: 100 mg

Administration: PO, BID

Criteria for evaluation:

Efficacy: The primary efficacy variable was ICD (in meters), which was measured during a constant load treadmill test (3.2 kilometers per hour [2 miles per hour] at a 12% grade). The secondary efficacy variable was absolute claudication distance (ACD) (in meters), which was measured during a constant load treadmill test (3.2 kilometers per hour [2 miles per hour] at a 12% grade.

Safety: Safety variables consisted of adverse events reported by the patient or noted by the Investigator, including those resulting in death, treatment discontinuation and serious adverse events, laboratory parameters (standard hematology and blood chemistry and coagulation), vital signs (standing and supine systolic and diastolic blood pressure and heart rate), and electrocardiogram (ECG). The evaluation was based on predefined potentially clinically significant abnormalities (PCSAs) for laboratory, vital signs, and ECG parameters.

Pharmacokinetics: Pharmacokinetic parameters for HMR1766 included maximum observed concentration in plasma (Cmax), time to maximum concentration (tmax), trough (predose) concentration in plasma (Ctrough), average concentration in plasma (Cavg) for the dosing interval of 24 hours, and the area under the concentration curve for the dosing interval of 24 hours (AUC0-24).

Pharmacokinetic sampling times and bioanalytical methods: Pharmacokinetic parameters were assessed in a subset of approximately 100 patients; 7 samples were drawn prior to and at 0, 1, 2, 3, 4, 6, and 8 hours after study drug intake at either the 6-week (Day 42) or 12-week (Day 84) visits. Plasma concentrations of HMR1766 were assessed in the remainder of the patients at the 6- or 12-week visit and in all patients at the 26-week visit; samples were collected at these visits prior to study drug intake and at 1 to 4 hours after drug intake for population kinetic evaluation. Samples were analyzed by means of a validated liquid chromatographytandem mass spectrometry assay with a lower limit of quantification of 0.01µg/mL.

Statistical methods:

Analyses of primary efficacy variable:

The primary efficacy variable,ICD, was analyzed as the relative change from baseline to 26 weeks and expressed in percentages. Since the distribution of ICD measurements is often variable, a natural logarithmic transformation was used to reduce the effect of the variability and the effect of extreme values.

The change from baseline in log-transformed ICD at 26 weeks was analyzed using analysis of covariance (ANCOVA) in the intent-totreat (ITT) population. The model included 2 fixed effects, treatment and randomization stratum (presence or absence of diabetes mellitus), and the log-transformed baseline ICD assessment as a covariate.

A 2-sided linear trend test at the 5% significance level was performed to access the dose response of HMR1766 within the framework of the ANCOVA model. The estimate of linearity was defined as:

$$\text{Contrast} = 3*\log(\text{ICD200}) + 1*\log(\text{ICD100}) - 1*\log(\text{ICD25}) - 3*\log(\text{ICDPlacebo}),$$

where log(ICD200) was the least-square (LS) mean for the HMR1766 200 mg dose group. The remaining terms, log(ICD100), log(ICD25), and log(ICDPlacebo), in the contrast were the LS means for their respective treatment groups. The LS mean difference and the associated standard errors of mean and 95% confidence intervals were then back-transformed.

Analyses of secondary efficacy variable:

The ANCOVA model and the linear trend test described for ICD were applied to the secondary efficacy variable, change from baseline in log-transformed ACD at 26 weeks in the ITT population.

Analyses of PK variables:

Descriptive statistics (number of patients, means, standard deviations (SDs), medians, and ranges) were provided for plasma concentrations of HMR1766 at nominal times, predose and postdose at the Week 6 (or Week 12), and Week 26 visits for the HMR1766 dose group in both PK populations.

Descriptive statistics (number of patients, means, SDs, coefficients of variation, and ranges) were provided for PK parameters Cmax, Ctrough, Cavg and AUC0-24 at nominal times at the Week 6 and Week 12 visits combined for the ataciguat dose group in the PK substudy population.

For Cmax and AUC0-24, dose proportionality was evaluated for both weeks combined using the log-transformed power model with dose as the fixed effect.

Summary:

Efficacy results:

In the ITT population, HMR1766 improved ICD at 26 weeks by 37.4%, 31.5%, and 40.4% from baseline in the 25 mg, 100 mg, and 200 mg treatment groups, respectively, compared to 40.3% in the placebo group and 32.4% in the cilostazol group. The test of linear trend in ICD across placebo and the 3 HMR1766 groups was not statistically significant.

No statistically significant differences in ICD were observed between placebo and each of the HMR1766 treatment groups. Cilostazol was not different from placebo. In addition, no statistically significant differences in ICD were observed between cilostazol and any of the HMR1766 treatment groups.

In the ITT population, HMR1766 improved ACD at 26 weeks by 26.6%, 27.0%, and 30.9% from baseline in the 25 mg, 100 mg, and 200 mg treatment groups, respectively, compared to 28.0% in the placebo group and 26.5% in the cilostazol group. The test of linear trend in ACD across placebo and the 3 HMR1766 groups was not statistically significant.

Safety results:

In this group of patients with intermittent claudication, the incidence of treatment-emergent adverse events (TEAEs) was similar in the placebo and HMR1766 groups. The system organ classes with the most frequently reported events were infections and infestations, investigations, gastrointestinal disorders, and nervous system disorders. Among these SOCs, the incidence of TEAEs in the HMR1766 groups did not increase with increasing dose.

Five patients died during the study; 3 as a result of serious TEAEs (1 patient each from the placebo, HMR1766 25 mg, and cilostazol groups). And 2 patients died during the follow-up period.

Serious TEAEs were reported in 4.5% of patients in the HMR1766 25 mg group, 8.8% in the 100 mg group, and 3.8% in the 200 mg group compared with 7.2% in the placebo group and 8.9% in the cilostazol group. The SOC with the most frequently reported events were cardiac disorders with the same incidence between HMR1766 25 mg group, HMR1766 100 mg group, and placebo group. No cardiac disorder was reported in HMR1766 200 mg group. None of the individual preferred terms were reported in more than 1 patient in the HMR1766 groups.

Treatment-emergent adverse events leading to withdrawal of study drug were reported in 2.7% of patients in the HMR1766 25 mg group, 8.0% in the HMR1766 100 mg group, and 6.6% in the HMR1766 200 mg group compared with 8.1% in the placebo group and 7.1% in the cilostazol group.

Treatment-emergent adverse events occurred infrequently and no dose-response relationship was observed with HMR1766.

Few patients in the HMR1766 groups had TEAEs related to laboratory values, vital signs and ECG changes. No medically relevant ECG changes were identified for HMR1766

Pharmacokinetic results:

Mean trough values obtained immediately predose (Ctrough) were lowest for the low dose group (0.79 µg/mL) and similar for both higher dose groups of HMR1766 (3.9 µg/mL; 3.6 µg/mL). Cavg increased dose-dependently (1.35 µg/mL, 7.23 µg/mL, 10.38 µg/mL). Cmax also increased dose-dependently and slightly more than proportional to dose (1.89 µg/mL, 12.66 µg/mL, 22.07 µg/mL). The AUC for the dosing interval of 24 h increased dose-dependently and almost proportional to dose (31.08 µg*h/mL, 173.54 µg*h/mL, 245.68 µg*h/mL).

The populationkinetic evaluation will be presented in a stand-alone report.

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