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Sponsor / Company: Sanofi **Drug substance(s):** otamixaban (XRP0673)	**Study Identifiers:** NCT01126086, U1111-1116-8891 **Study code:** POP6207
Title of the study: An open-label pharmacokinetic, pharmacodynamic and tolerability study of otamixaban given as a single 80 µg/kg bolus plus 100 µg/kg/h continuous infusion for 24 hours in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function.	
Study center(s): 3 Centers in US	
Study period: Date first subject enrolled: 07/May/2010 Date last subject completed: 18/Apr/2011	
Phase of development: 1	
Objectives: - The primary objective was to study effect of mild and moderate hepatic impairment (HI) on the pharmacokinetics (PK) of otamixaban, - The secondary objective was to assess the pharmacodynamics (PD) effects of otamixaban on subjects with mild and moderate HI and in matched subjects with normal hepatic function.	
Methodology: Phase 1, multi-center, open-label, parallel group study. At least 3 patients with mild HI were dosed first, and based on the results of the safety (PD) assessment; a decision was made to include subjects with moderate HI to complete the trial.	
Number of subjects: Planned: 24 Randomized: 25 Treated: 25 **Evaluated** Pharmacodynamic: 24 Safety: 25 Pharmacokinetics 24	
Diagnosis and criteria for inclusion: Subjects at least 18 years of age with mild (defined as a Child-Pugh rating score of 5 to 6) or moderate (defined as a Child-Pugh rating score of 7 to 9) HI, healthy matched (by age, gender, and weight) subjects.	
Investigational medicinal product(s): Otamixaban Route(s) of administration: Intravenous (IV) bolus injection followed by continuous 24-hour infusion Dose regimen: Bolus injection of 0.080 mg/kg (80 µg/kg) over 1 minute followed by continuous infusion of 0.100 mg/kg/h (100 µg/kg/h) for 24 hours [all dose units were converted from micrograms (µg/kg, µg/kg/h) to milligrams (mg/kg or mg/kg/h) in the report]	

Duration of treatment: 24 hours

Duration of observation: 44 days (including a 2-28 day screening period, a treatment period of 5 days, and a follow up of 8-11 days)

Criteria for evaluation:

Pharmacodynamics: activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR).

Safety:

Clinical laboratory tests: hematology, chemistry, urinalysis, fecal occult blood test.

Clinical evaluations: vital signs, physical exam, electrocardiograms (ECGs), and adverse events (AEs).

Pharmacokinetics: Otamixaban plasma concentrations were used to determine the following PK parameters using a non-compartmental method.

Primary: Concentration at the end of infusion (C_{eoi}), area under the plasma concentration versus time curve from time 0 to the real time, t_{last} (AUC_{last}), area under the plasma concentration-time curve extrapolated to infinity (AUC);

Secondary: Concentration at 1 min after end of bolus (C_{1min}), clearance (CL), volume of distribution at steady state (V_{ss}), and terminal half-life ($t_{½z}$).

Pharmacokinetic sampling times and bioanalytical methods: Blood samples for the PK evaluation were collected prior to the start of the bolus injection (predose) and at 2 and 15 minutes, 3, 6, 12, 16, 24 hours, 24 hours 10 minutes, 24 hours 20 minutes, 24 hours 40 minutes, 25, 26, 28, 30, 32, 36, 48 and 72 hours after the start of the bolus. The plasma concentrations of otamixaban were determined using a validated liquid chromatography – tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.00 ng/mL.

Statistical methods:

Pharmacodynamics:

Coagulation parameters (aPTT, PT, and INR) were summarized by population group.

Safety:

The safety analysis was based on the review of individual values (clinical significant abnormalities) and descriptive statistics (summary tables, graphics) by population group. All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0, and the number and percentage of subjects with treatment emergent AEs (TEAEs) were summarized by population group. Potentially clinically significant abnormalities (PCSAs; definitions according to version 2.0 dated 14 September 2009) for clinical laboratory, vital sign, and ECG (automatic reading) data and out of normal range values for clinical laboratory data were flagged and summarized in frequency tables by population group.

Pharmacokinetics:

All concentrations and PK parameters of otamixaban in plasma were listed by subject and population group, and also summarized for each population group using descriptive statistics. For log-transformed parameters C_{eoi}, $AUC_{last,}$ and AUC, the effect of population group on otamixaban PK parameters were analyzed using a linear fixed effects model. Estimates and 90% confidence interval (CI) for the geometric means ratio of each hepatic population group versus healthy population group were provided for C_{eoi}, AUC_{last}, and AUC. For $t_{1/2z}$, an estimate and 90% CI for geometric mean of each population group were provided.

Summary:

Population characteristics: Demographic characteristics were similar in the 3 population groups.

Pharmacodynamic results: No difference in PD parameters (aPTT, PT and INR) was observed in the 3 groups. The PD parameters increased immediately following the IV bolus injection, maintained at steady state during 24-hour infusion, and returned to baseline following termination of IV infusion of otamixaban.

Safety results: A total of 26 TEAEs (12 bleeding, 14 non-bleeding TEAEs) were reported in 15 subjects (6 healthy subjects, 2 subjects with mild HI, 7 subjects with moderate HI).

The 12 bleeding TEAEs were reported in 10 subjects (2 healthy subjects, 2 subjects with mild HI, and 6 subjects with moderate HI). All were assessed as mild. Four bleeding events that occurred during infusion included vessel puncture site haematoma/haemorrhage, gingival bleeding, and haematuria. Three bleeding events that occurred within the first 3 hours of completion of infusion were 2 vessel puncture site haematoma or 1 epistaxis. Positive fecal occult blood was noted in 5 subjects with moderate HI: on Day 3 in 4 subjects and on Day 8 in the remaining subject.

The most frequently reported non-bleeding TEAEs were in nervous system disorders (headache) and gastrointestinal disorders.

No clinically relevant PCSA values for laboratory, vital sign, and ECG parameters were observed.

Pharmacokinetic results:

Otamixaban pharmacokinetic parameters

PK Parameter	Healthy	Mild HI	Moderate HI
N	8	8	8
C_{eoi} (ng/mL)	378 ± 130 (360) [34.4]	368 ± 82.3 (360) [22.4]	584 ± 132 (570) [22.5]
AUC_{last} (ng•h/mL)	9270 ± 2870 (8910) [31.0]	8680 ± 1190 (8610) [13.7]	14800 ± 3480 (14500) [23.4]
AUC (ng•h/mL)	9430 ± 2870 (9080) [30.5]	8850 ± 1170 (8780) [13.2]	15100 ± 3370 (14800) [22.4]
$t_{1/2z}$ (h)	24.2 ± 6.47 (23.5) [26.8]	23.4 ± 7.20 (22.3) [30.8]	20.5 ± 13.1 (18.0) [63.9]
CL (L/h)	23.9 ± 6.32 (23.1) [26.5]	24.8 ± 7.69 (23.9) [31.0]	13.6 ± 3.88 (13.1) [28.5]
V_{ss} (L)	106 ± 58.3 (95.6) [55.0]	117 ± 64.4 (107) [55.1]	73.4 ± 35.9 (67.8) [48.9]

Tabulated values are Mean ± SD (Geometric Mean) [CV%]

Point estimates with 90% confidence intervals

Parameter	Comparison	Estimate	90% CI
C_{eoi}	Mild HI vs Healthy	1.02	(0.79 to 1.31)
	Moderate HI vs Healthy	1.54	(1.19 to 1.98)
AUC_{last}	Mild HI vs Healthy	0.98	(0.79 to 1.22)
	Moderate HI vs Healthy	1.60	(1.29 to 1.99)
AUC	Mild HI vs Healthy	0.98	(0.80 to 1.21)
	Moderate HI vs Healthy	1.60	(1.29 to 1.97)

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