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Sponsor / Company: Sanofi **Drug substance(s):** otamixaban (XRP0673)	**Study Identifiers:** NCT01120314, U1111-1116-5821 **Study code:** POP6537
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, moderate, and severe renal impairment, and in matched subjects with normal renal function (POP6537)	
Study center(s): 3 centers in US	
Study period: Date first subject enrolled: 09/Apr/2010 Date last subject completed: 06/Jul/2011	
Phase of development: 1	
Objectives: **-** To study effect of mild, moderate, and severe renal impairment (RI) on the pharmacokinetics (PK) of otamixaban - To assess the pharmacodynamic (PD) effects of otamixaban on subjects with mild, moderate, and severe RI and in matched subjects with normal renal function	
Methodology: Phase 1, multi-center, open-label study	
Number of subjects**:** Planned: 48 Randomized: 48 Treated: 48 **Evaluated:** Pharmacodynamics: 48 Safety: 48 Pharmacokinetics: 48	
Diagnosis and criteria for inclusion: Male and female subjects between 18 and 79 years of age inclusive, with mild, moderate, and severe RI (defined as creatinine clearance [CL_{CR}] from 50 to 80, 30 to 50, and <30 mL/min, respectively) and matched subjects (by age, gender, and body weight) with normal renal function (defined as CL_{CR} >80 mL/min)	

Study treatments

Investigational medicinal product(s): Otamixaban

Route(s) of administration: Intravenous (IV)

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 period 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, and 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 plasma PK parameters using a noncompartmental method. Otamixaban urine concentrations and volume were used to calculate urine PK parameters using Excel (Excel 2003, Microsoft).

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 minute after end of bolus(C_{1min}), Clearance (CL), volume of distribution at steady state (V_{ss}), and terminal half-life ($t_{½z}$), AUC from time zero to 72 hours (AUC_{0-72}), cumulated amount excreted in urine from time 0-72 hours after start of drug administration (A_{e0-72}), fraction of the dose excreted in urine from time 0-72 hours (F_{e0-72}), and renal clearance from time 0-72 hours (CL_{R0-72}).

Pharmacokinetic/Pharmacodynamics 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, 24.17, 24.33, 24.67, 25, 26, 28, 30, 32, 36, 48 and 72 hours after the start of the bolus. Urine sampling at predose, 0 to 12 hours, 12 to 24 hours, 24 to 30 hours, 30 to 36 hours, 36 to 48 hours, and 48 to 72 hours after the start of the bolus injection. The plasma and urine concentrations of otamixaban were determined using validated liquid chromatography – tandem mass spectrometry (LC-MS/MS) methods with a lower limit of quantification (LLOQ) of 1.00 ng/mL for plasma and 10.0 ng/mL for urine.

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 (clinically 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 and urine were listed by subject and population group, and also summarized for each population group using descriptive statistics. As primary analysis, the relationship between log-transformed PK parameters (C_{eoi}, AUC, AUC_{last} and CL_{R0-72}) and log-transformed CL_{CR} levels was analyzed by a linear regression model. Estimates and 90% confidence intervals (CIs) for mean intercept and log of creatinine slope was provided. A plot of individual PK parameters versus CL_{CR} slope values, along with mean regression line were also provided. As secondary analysis, for log-transformed parameters C_{eoi}, AUC, AUC_{last} and CL_{R0-72}, the effect of population group on otamixaban PK parameters were analyzed using a linear fixed effects model. Estimates and 90% CIs for the geometric means ratio of each renal population group versus healthy population group were provided. For $t_{1/2z}$, an estimate and 90% CI for geometric mean of each population group were also provided.

Summary:

Population characteristics: Demographic characteristics were similar across the populations in the study. The characteristics for the RI were consistent in the groups with the definition using the Cockroft-Gault formula for renal clearance.

Pharmacodynamic results: No differences in the PD parameters (aPTT, PT, and INR) were observed between the 4 groups. The PD parameters increased immediately following the bolus IV dose and were elevated throughout the 24-hour infusion. The parameters returned to baseline following termination of the IV infusion of otamixaban.

Safety results: The frequency of TEAEs observed in the 4 groups was: 9/16 healthy subjects, 3/8 subjects with mild RI, 8/8 subjects with moderate RI, and 12/16 subjects with severe RI. No serious adverse event (SAE) was reported. The majority of AEs were bleeding events.

The frequency of bleeding TEAEs observed in the 4 groups was: 6/16 healthy subjects, 3/8 subjects with mild RI, 6/8 subjects with moderate RI, and 11/16 subjects with severe RI. The most frequently reported bleeding TEAE was vessel puncture site hemorrhage (2 in healthy subjects, 3 in subjects with mild RI, 3 in subjects with moderate RI, and 2 in subjects with severe RI). In severe RI, bleeding events included epistaxis (n=3), gingival bleeding (n=3), occult blood positive (n=3), and vessel puncture site hemorrhage (n=2). Other bleeding events included vessel puncture site hematoma ([n=3] comprising of 1 healthy subject, 1 subject with moderate RI, and 1 subject with severe RI), occult blood positive ([n=3] in healthy subjects), infusion site hemorrhage ([n=2] in healthy subjects), epistaxis ([n=2] in subjects with moderate RI), and ecchymosis ([n=2] comprising of 1 subject with mild RI and 1 subject with severe RI).

Non-bleeding TEAEs reported in more than 1 subject were diarrhea (n=3), headache (n=2), and anemia (n=2). These latter events were observed in subjects who experienced bleedings and presented borderline hemoglobin values at baseline.

There were no PCSAs that were clinically relevant for the laboratory values or for vital signs and ECGs. One subject with severe RI had a prolonged increase in QTc interval from baseline; QTc was prolonged from T6H throughout the end of study with no QTc interval >500ms.

Pharmacokinetic results:

Otamixaban pharmacokinetic parameters

	Healthy	Mild RI	Moderate RI	Severe RI
N	16[a]	8	8	16[a]
C_{1min}	585 ± 494	523 ± 488	555 ± 317	526 ± 367
(ng/mL)	(360) [84.4]	(288) [93.3]	(482) [57.0]	(391) [69.7]
C_{eoi}	386 ± 95.1	528 ± 245	555 ± 201	720 ± 221
(ng/mL)	(375) [24.6]	(466) [46.4]	(520) [36.2]	(686) [30.6]
AUC_{last}	9760 ± 2050	12300 ± 4760	12800 ± 4280	16700 ± 4390
(ng•h/mL)	(9560) [21.0]	(11400) [38.6]	(12200) [33.4]	(16100) [26.3]
AUC	9920 ± 2050	12500 ± 4780	12900 ± 4280	16800 ± 4390
(ng•h/mL)	(9730) [20.7]	(11600) [38.3]	(12300) [33.0]	(16200) [26.1]
$t_{1/2z}$	21.1 ± 6.40	20.2 ± 5.47	18.4 ± 3.48	14.1 ± 3.43
(h)	(20.2) [30.3]	(19.4) [27.1]	(18.1) [18.9]	(13.7) [24.2]
CL	20600 ± 6090	19200 ± 7960	15500 ± 4010	11900 ± 4270
(mL/h)	(19900) [29.6]	(17900) [41.4]	(15000) [25.9]	(11300) [36.0]
V_{ss}	86500 ± 37200	78700 ± 37100	63700 ± 17600	51500 ± 15300
(mL)	(80100) [43.0]	(73000) [47.2]	(61300) [27.6]	(49600) [29.7]
A_{e0-72}	38300 ± 8860	36200 ± 10200	16300 ± 7470	15500 ± 6290
(µg)	(37400) [23.1]	(34700) [28.2]	(15000) [45.8]	(14200) [40.6]
F_{e0-72}	19.4 ± 3.29	17.3 ± 4.45	8.85 ± 3.96	8.64 ± 3.86
(%)	(19.2) [17.0]	(16.8) [25.7]	(8.11) [44.7]	(7.78) [44.7]
CL_{r0-72}	4140 ± 1590	3090 ± 526	1360 ± 596	951 ± 326
(mL/h)	(3900) [38.4]	(3050) [17.0]	(1230) [43.8]	(885) [34.3]

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

[a]N = 15 for urine parameters.

The primary linear regression analysis showed a significant increase in otamixaban exposure (C_{eoi}, AUC_{last} and AUC) as well as CL_{r0-72} with decrease in CL_{CR} over the range of 15.2 to 116 mL/min ($p<0.001$).

Results of statistical analyses of pharmacokinetic data: Regression model for C_{eoi}, AUC_{last}, and AUC, Point estimates with 90% confidence intervals

		Slope	
Parameter	**Effect**	**Estimate**	**90% CI**
Log(C_{eoi})	Mean intercept	6.10	(5.01 to 7.19)
	Log(Creat. clearance) slope	-0.41	(-0.55 to -0.27)
	Age slope	0.01	(0 to 0.02)
	Weight slope	0.02	(0.01 to 0.02)
Log (AUC_{last})	Mean intercept	9.48	(8.53 to 10.42)
	Log (Creat. Clearance) slope	-0.35	(-0.46 to -0.23)
	Age slope	0.01	(0 to 0.01)
	Weight slope	0.01	(0.01 to 0.02)
Log (AUC)	Mean intercept	9.50	(8.56 to 10.43)
	Log (Creat. Clearance) slope	-0.34	(-0.46 to -0.22)
	Age slope	0.01	(0 to 0.01)
	Weight slope	0.01	(0.01 to 0.02)

Results of statistical analyses of pharmacokinetic data: Regression model for CL_{r0-72}, Point estimates with 90% confidence intervals

		Slope	
Parameter	**Effect**	**Estimate**	**90% CI**
Log(CL_{R0-72})	Mean intercept	2.98	(2.01 to 3.96)
	Log (Creat. clearance) slope	1.15	(1.02 to 1.28)
	Age slope	0.01	(0.00 to 0.02)
	Weight slope	-0.01	(-0.01 to 0.00)

Results of the secondary analysis in the table below indicated that otamixaban exposure (Ceoi, AUClast, and AUC) in subjects with mild and moderate RI was comparable to that in healthy matched subjects, but was higher in subjects with severe RI.

Point estimates with 90% confidence intervals

Parameter	Comparison	Estimate	90% CI
C_{eoi}	Mild RI vs Healthy	1.08	(0.83 to 1.40)
	Moderate RI vs Healthy	1.20	(0.93 to 1.56)
	Severe RI vs Healthy	1.86	(1.51 to 2.30)
AUC_{last}	Mild RI vs Healthy	1.07	(0.86 to 1.33)
	Moderate RI vs Healthy	1.15	(0.92 to 1.43)
	Severe RI vs Healthy	1.72	(1.43 to 2.05)
AUC	Mild RI vs Healthy	1.07	(0.86 to 1.33)
	Moderate RI vs Healthy	1.14	(0.92 to 1.42)
	Severe RI vs Healthy	1.70	(1.42 to 2.03)

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