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Study No: 63132
Title: A phase I trial to evaluate and compare the safety, pharmacokinetics and pharmacodynamics of a single dose of 7.5mg subcutaneous Org31540/SR90107A in subjects with moderate hepatic impairment and subjects with normal liver function
Rationale: Subjects with hepatic impairment are known to be at an increased risk of bleeding because of haemostatic impairment (including a decrease of antithrombin III [ATIII]) and/or presence of lesions, especially of the gastrointestinal tract. Therefore, this trial was performed with the objective to evaluate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of Org31540/SR90107A, also known as fondaparinux (FX), in subjects with varying degrees of impaired haemostasis secondary to hepatic insufficiency. The dose of 7.5mg FX was, at the time of the study, the maximum dose to be used in any current or future indication in subjects with body weight below 100kg. Taking previous studies into account a single subcutaneous dose of 7.5mg was regarded as justified, from a safety perspective, in subjects with impaired liver function.
Phase: I
Study Period: 28 Oct 2003 to 9 Dec 2003
Study Design: An open label, parallel group, 1 period, single dose design. FX was administered in one group of either male or female subjects with moderate hepatic impairment and a control group consisting of matched (age, gender and weight) subjects with normal liver function.
Centres: 1 centre in the Czech Republic.
Indication: Moderate hepatic impairment
Treatment: A single subcutaneous dose 7.5mg of FX.
Objectives: To determine the PK and PD of a single subcutaneous dose of 7.5mg FX, in moderately hepatically impaired subjects in comparison with matched subjects with normal liver function.
Statistical Methods: <u>Pharmacokinetics:</u> A one-way analysis of variance (ANOVA) was performed on the log _e -transformed values of the parameters measured peak plasma concentration (C _{max}), area under the curve for plasma concentrations as a function of time extrapolated to infinity (AUC _{0-∞}), area under the plasma concentration-versus-time curve as a function of time from time 0 to the last measurable plasma concentration (AUC _{0-last}), and 90% and 95% parametric confidence intervals (CI) for the ratio "hepatic impairment / normal liver function" were derived. No group effect was considered to be present if the 90% CI for C _{max} , AUC _{0-∞} and AUC _{0-last} were fully contained within the 0.80-1.25 acceptance range. An analysis of covariance (ANCOVA) was performed on the log _e -transformed values, alternately including covariates (age, weight, gender, creatinine clearance and baseline ATIII concentration). <u>Pharmacodynamics:</u> Activated partial thromboplastin time (aPTT), prothrombin time (PT) international normalised ratio, (INR) and ATIII were summarised by descriptive statistics (including n, mean, geometric mean, standard deviation (SD), standard error, median, minimum and maximum) both for the original values and for changes from baseline by group and assessment. Parameters were log _e -transformed before inferential statistics were performed for the changes to baseline by time point comparing the impaired to healthy group using a 2-sample t-test. The difference between groups was calculated (expressed as a ratio "impaired/healthy" on the original scale) and was presented including the 95% CI. <u>Safety:</u> Safety results were presented descriptively. No sample size calculations were performed. The number of 8 subjects per treatment group was chosen according to the regulatory guidelines for a Reduced Design.
Study Population: The study was performed in either male or female moderately hepatically impaired subjects aged 18 to 65 years, selected according to the Child-Pugh categorization, with a normal renal function (creatinine clearance ≥ 80 mL/min). Key exclusion criteria for the hepatically impaired group included mild or severe hepatic impairment according to the Child-Pugh categorization, arterial hypertension, hepatic carcinoma, hepatic encephalopathy grade 3, active infection, acute liver failure, drug induced hepatitis, current use of any drug with potential hepatotoxicity, haemoglobin < 8g/dL, platelets < 45 x 10 ⁹ per L. The control group consisted of either male or female volunteers with a normal liver and renal function (creatinine clearance ≥ 80 ml/min), matched in gender, weight and age with the hepatically impaired subjects. Key exclusion criteria for the control group included concurrent illness or history of bleeding diathesis.

Number of Subjects:	Healthy	Hepatically Impaired
Planned, N	8	8
Dosed, N	8	8
Completed, n (%)	8 (100)	8 (100)
Total Number Subjects Withdrawn, N (%)	0	0
Withdrawn due to Adverse Events n (%)	0	0
Withdrawn due to Lack of Efficacy n (%)	0	0
Withdrawn for other reasons n (%)	0	0

Demographics

N (ITT)	8	8
Females: Males	4:4	4:4
Mean Age, Years (SD)	53.1 (6.3)	52.4 (5.4)
Caucasian, n (%)	8 (100)	8 (100)

Pharmacokinetics Endpoints:

Parameter (Unit)	Hepatic Impairment Mean (SD)	Normal Liver Function Mean (SD)	Point Estimate ^a	95% CI	90% CI
C _{max} (ng/mL)	731 (156)	923 (140)	0.78	0.64, 0.95	0.67, 0.92
AUC _{0-last} (mg. h/L)	11.8 (4.02)	17.7 (3.04)	0.64	0.47, 0.86	0.50, 0.81
AUC _{0-∞} (mg. h/L)	12.7 (4.22)	20.3 (4.29)	0.61	0.45, 0.82	0.47, 0.78

a. Point estimate: geometric mean hepatic impairment/geometric mean normal liver function

Pharmacodynamics Endpoints: Estimated Mean (95% CI)

Timepoint	Treatment	aPTT	PT (INR)	ATIII
Day 1 (2 hours)	Healthy	1.17 (1.12, 1.23)	1.05 (1.02, 1.07)	Not Done
	Impaired	1.14 (1.09, 1.20)	1.00 (0.98, 1.02)	
	Impaired: Healthy	0.98 (0.91, 1.04)	0.96 (0.93, 0.99)	
Day 2 (24 hours)	Healthy	1.09 (1.04, 1.14)	1.01 (0.99, 1.04)	1.02 (0.98, 1.05)
	Impaired	1.09 (1.04, 1.15)	0.98 (0.95, 1.00)	1.05 (1.01, 1.09)
	Impaired: Healthy	1.00 (0.94, 1.08)	0.97 (0.93, 1.00)	1.03 (0.98, 1.09)
Day 3 (48 hours)	Healthy	1.08 (1.02, 1.14)	0.96 (0.93, 0.99)	Not Done
	Impaired	1.03 (0.97, 1.09)	0.98 (0.95, 1.01)	
	Impaired: Healthy	0.95 (0.88, 1.03)	1.02 (0.98, 1.06)	
Follow-up	Healthy	1.01 (0.89, 1.14)	0.89 (0.82, 0.96)	1.00 (0.88, 1.13)
	Impaired	1.02 (0.90, 1.15)	0.86 (0.80, 0.93)	1.12 (0.99, 1.28)
	Impaired: Healthy	1.01 (0.85, 1.20)	0.97 (0.87, 1.09)	1.13 (0.94, 1.35)

Safety Results (All Subjects): An on therapy adverse event (AE) or serious AE (SAE) was defined as an AE with onset on or after the start date of study medication until follow-up.

Adverse Events: Any AE That Occurred in >1 Subject in Any Group

	Healthy	Hepatically Impaired
N (ITT)	8	8
No. Subjects With AEs n (%)	2 (25.0)	7 (87.5)
Vessel Puncture Site Haemorrhage ^a	2 (25.0)	2 (25.0)
Injection Site Haemorrhage	0	3 (37.5)
Catheter Site Haemorrhage	0	2 (25.0)

a. Terms 'vessel puncture site haemorrhage' and 'venipuncture site haemorrhage' were combined.

Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:

No. Subjects with Fatal or Non-fatal SAEs n (%)	0	0
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Publications:

No publication

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