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Study No: 63128
Title: A phase I interaction trial to investigate the pharmacodynamics and pharmacokinetics of 10 mg subcutaneous Org31540/SR90107A and intravenous recombinant Factor VIIa, in healthy male volunteers.
Rationale: In-vitro studies have indicated that rVIIa might be able to reverse anticoagulant activity of Org31540/SR90107A (fondaparinux [FX]). Administration of rVIIa to rabbits pre-treated with FX resulted in thrombin generation in the presence of ex vivo administered Tissue Factor (TF). The relevance of this effect in vivo, however, has not been confirmed thus far, although rVIIa has been shown to be an important agent in controlling bleeding episodes in various clinical scenarios. If thrombin generation can be achieved, this provides a rationale for the use of rVIIa in the case of a hemorrhagic complication in a patient being treated with a pentasaccharide. The objective of the present study therefore was to investigate the effects of rVIIa on inhibition of thrombin generation induced by FX, in young healthy male volunteers.
Phase: I
Study Period: 10 September 2001 to 07 November 2001.
Study Design: Single center, partly double-blind, placebo-controlled, randomized, parallel design.
Centres: 1 study centre in The Netherlands
Indication: None
Treatment: The subjects received a single subcutaneous (sc) dose of 10 mg FX or placebo (PBO). Two hours thereafter, rVIIa at a dose of 90 µg/kg (or an equivalent amount of PBO) was administered as an intravenous (iv) bolus injection. The treatment groups were as follows: Group A: FX 10 mg and rVIIa 90 µg/kg Group B: PBO and rVIIa 90 µg/kg Group C: FX 10 mg and rVIIa PBO
Objectives: Primary: To study the effects of rVIIa on inhibition of thrombin generation by FX in healthy volunteers. Secondary: To determine the pharmacokinetic interaction of FX and rVIIa
Statistical Methods: Pharmacokinetics: Descriptive statistics were computed for the FX and (baseline-corrected, [bc]) rVIIa concentrations in plasma for the following PK parameters: FX: peak concentration (C_{max}) and its time of occurrence (t_{max}), the terminal elimination half-life ($t_{1/2}$), the area under the concentration-versus-time curve ($AUC_{0-t_{last}}$, $AUC_{0-\infty}$), the mean residence time (MRT), the (weight-normalized) apparent clearance (CL_{app} and $wn-CL_{app}$) and (weight-normalized) the apparent volume of distribution ($V_{z,app}$ and $wn-V_{z,app}$). rVIIa: the (baseline-corrected) C_{max} and $C_{max, bc}$ and t_{max} , $t_{1/2}$, $AUC_{0-t_{last}}$, AUC_{0-6} , AUC_{0-22} , and MRT. Drug-interaction testing using an Analysis of Variance with the 95% confidence interval (CI) on the log-transformed PK parameters was carried out.
Pharmacodynamics: The following parameters were summarized by descriptive statistics and by graphically presenting the arithmetic means and standard error for the parameters by treatment group and visit: thrombin-antithrombin complex (TAT), prothrombin activation fragment (F1+2) Ex vivo thrombin generation assay (C_{max} and $T_{1/2 max}$ with and without tissue factor (TF)) Endogenous thrombin potential (ETP) Activated partial thromboplastin Time (aPTT), prothrombin time (PT). Inferential statistics were performed comparing AUC and peak values of group A (FX and rVIIa) to group C (FX and placebo rVIIa) and group A to group B (placebo FX and rVIIa). Groups B and C were not compared using inferential statistics. AUC and peak values were analyzed by an analysis of covariance, using the log-transformed baseline value as covariate and the log-transformed AUC or peak value as dependent variable. An estimate of the differences and the 95% CIs was derived and was back-transformed into ratios. Parametric assumptions of the analysis of covariance were not tested. No adjustment for multiple comparisons were made. All tests were 2-sided. P-values of paired t-tests were computed comparing post-baseline values to baseline values for each post-baseline visit within treatment groups. The p-values were interpreted as a descriptive statistic for the comparison of the visits. Safety: Safety results were presented descriptively. Populations analyzed: The analysis of the pharmacokinetic (PK) and pharmacodynamic (PD) parameters was performed on all subjects for

whom at least one PD and one PK parameter could be calculated according to the protocol, and who did not have any protocol violations interfering with PK and PD assessments (The All-Subjects-Evaluable Population). The safety data was summarized for all subjects who were treated with study medication (All subjects-Treated Population (AST)).				
Study Population: Healthy, young, drug-free, male volunteers aged 18-45 years with a normal coagulation status. Other key inclusion criteria included normal screening laboratory values. Key exclusion criteria included a history of concurrent disease of any organ system, a history of bleeding diathesis or thrombosis, or a history of major trauma or surgery within the past year.				
Number of Subjects:	FX + rVIIa	PBO + rVIIa	FX + rVIIa PBO	Total
Planned N	8	4	4	16
Randomized (ASR population) N	8	4	4	16
Dosed (AST population) N	8	4	4	16
All-Subjects-Evaluable population, N	8	4	4	16
Completed n (%)	8	4	4	16
Total Number Subjects Withdrawn, n (%)	0	0	0	0
Withdrawn due to Adverse Events, n (%)	0	0	0	0
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0
Withdrawn for Other Reasons, n (%)	0	0	0	0
Demographics				
N (ITT)	8	4	4	16
Females: Males	0:8	0:4	0:4	0:16
Mean Age in Years (SD)	26.4 (8.6)	25.3 (5.0)	24.5 (1.0)	25.6 (6.3)
Mean Weight in Kg (SD)	70.82 (14.05)	84.75 (14.83)	73.28 (12.75)	74.92 (14.28)
Caucasian, n (%)	7 (87.5)	3 (75.0)	3 (75.0)	13 (81.3)
Pharmacokinetics (PK), pharmacodynamics (PD), PK/PD Endpoints:				
Summary of PK parameters (All-Subjects-Evaluable)	FX		rVIIa	
	FX + rVIIa	FX + rVIIa PBO	FX + rVIIa	rVIIa + PBO
	N=8	N=4	N=8	N=4
$C_{max(bc)}$ * mg/L, %, mean (SD) The unit first stated refers to FX, the second to rVIIa	1.24 (0.231)	1.12 (0.102)	124 (20.4)	186 (26.7)
t_{max} , h, median (minimum-maximum)	2.19 (1.47-3.00)	2.20 (1.47-4.00)	0.50 (0.47-1.00)	0.47 (0.42-1.00)
$AUC_{0-tlast}$, mg•h/L, % •h, mean (SD)	20.5 (3.07)	18.9 (1.78)	658 (268)	542 (186)
$AUC_{0-\infty}$, mg•h/L, mean (SD)	23.3 (3.43)	21.2 (2.35)	not applicable (n.a.)	n.a.
AUC_{0-22} , % •h, mean (SD)	n.a.	n.a.	658 (268)	652 (115)
AUC_{0-6} , % •h, mean (SD)	n.a.	n.a.	373 (70.5)	451 (30.1)
$t_{1/2}$, h, mean (SD)	15.9 (2.35)	16.1 (2.03)	2.68 (0.68)	2.84 (1.94)
MRT, h, mean (SD)	22.4 (2.81)	21.8 (2.57)	5.15 (2.01)	3.42 (0.880)
CL_{app} , L/h, mean (SD)	0.383 (0.0607)	0.414 (0.0432)	n.a.	n.a.
$wn-CL_{app}$, L/h, mean (SD)	0.00550 (0.000627)	0.00575 (0.00126)	n.a.	n.a.
$V_{z,app}$, L, mean (SD)	8.80 (1.87)	9.58 (1.27)	n.a.	n.a.
$wn-V_{z,app}$, L, mean (SD)	0.125 (0.00846)	0.132 (0.0256)	n.a.	n.a.
*bc: baseline corrected for rVIIa				
PK drug interaction test results (All-Subjects-Evaluable)				

Interaction effect of rVIIa on FX pharmacokinetics	Point Estimate of true Ratio test/reference†	95% CI	Drug Interaction (Present/absent) ††
C _{max}	1.10	0.90-1.34	absent
AUC _{0-tlast}	1.08	0.89-1.30	absent
AUC _{0-∞}	1.09	0.90-1.32	absent
t _{1/2}	0.99	0.82-1.19	absent
Interaction effect of FX on rVIIa pharmacokinetics			
C _{max(bc)}	0.67	0.53-0.83	present
AUC _{0-tlast}	1.19	0.75-1.88	absent
AUC ₀₋₆	0.81	0.65-1.02	absent
AUC ₀₋₂₂	0.96	0.63-1.46	absent
t _{1/2}	1.07	0.61-1.87	absent
†FX only and rVIIa only treatments were taken as reference and the combination treatment as test.			
††Drug interaction absent (present): point estimate inside (outside) acceptance range 0.80-1.25			
Total-subject coefficients of variation (CV) (%)	FX Total CV (%)		
C _{max}	14.9		
AUC _{0-tlast}	13.9		
AUC _{0-∞}	14.1		
PD (All-Subjects-Evaluable population)			
Summary of statistical results - Primary comparison	Estimated effect of rVIIa compared to PBO in the presence of FX		
Parameters of in vivo thrombin generation	Estimated Ratio [95% CI]	p-value	
F1+2			
AUC(2-8h) ⁺	1.34 [1.05, 1.71]	0.022	
Peak value (2-8h)	1.28 [0.97, 1.69]	0.077	
TAT			
AUC(2-8h) ⁺	1.60 [0.79, 3.24]	0.176	
Peak value (2-8h)	1.34 [0.67, 2.69]	0.382	
Parameters of ex vivo thrombin generation			
ETP AUC(2-8h) ⁺	1.09 [1.00, 1.20]	0.056	
Thrombin generation assay + TF C _{max}			
AUC(2-8h) ⁺	1.16 [1.02, 1.31]	0.022	
Thrombin generation assay + TF T1/2 _{max}			
AUC(2-8h) ⁺	0.62 [0.50, 0.77]	<0.001	
Thrombin generation assay – TF C _{max}	0.88 [0.66, 1.17]	0.347	
AUC(2-8) ⁺			
Thrombin generation assay – TF T1/2 _{max}			
AUC(2-8h) ⁺	0.90 [0.71, 1.13]	0.331	
Clotting Times			
PT AUC(2-8h) ⁺	0.74 [0.69, 0.79]	<0.001	
aPTT AUC(2-8h) ⁺	0.95 [0.91, 0.99]	0.015	
+ AUC(2-8h) = AUC(2-8h) divided by actual time span			
Summary of statistical results - Secondary comparison	FX + rVIIa	PBO + rVIIa	FX + rVIIa PBO
Parameters of in vivo thrombin generation	N=8	N=4	N=4
F1+2, nmol/L			
Baseline, mean	0.66	0.87	0.80
24-h value, mean	0.59	0.83	0.54
Change from baseline, mean	-0.07	-0.05	-0.26
Paired t-test, p-value	0.105	0.713	0.045
TAT, µg/L			
Baseline, mean	4.6	5.5	4.3
24-h value, mean	3.9	3.0	2.5

Change from baseline, mean	-0.7	-2.5	-1.8
Paired t-test, p-value	0.423	0.244	0.076
Parameters of ex vivo thrombin generation			
ETP, %			
Baseline, mean	90	77	88
24-h value, mean	81	80	82
Change from baseline, mean	-9	3	-7
Paired t-test, p-value	0.011	0.273	0.025
+TF C _{max}			
Baseline, mean	0.505	0.535	0.374
24-h value, mean	0.444	0.596	0.378
Change from baseline, mean	-0.062	0.061	0.004
Paired t-test, p-value	0.081	0.051	0.853
+TF T _{1/2} _{max}			
Baseline, mean	168	150	153
24-h value, mean	208	144	189
Change from baseline, mean	40	-6	36
Paired t-test, p-value	0.010	0.150	0.153
-TF C _{max}			
Baseline, mean	0.313	0.347	0.197
24-h value, mean	0.209	0.373	0.235
Change from baseline, mean	-0.105	0.027	0.038
Paired t-test, p-value	0.032	0.194	0.209
-TF T _{1/2} _{max}			
Baseline, mean	836	713	860
24-h value, mean	1037	689	1023
Change from baseline, mean	201	-24	163
Paired t-test, p-value	0.146	0.885	0.555
Clotting Times			
PT, sec			
Baseline, mean	13.2	12.6	13.2
24-h value, mean	12.2	11.3	12.6
Change from baseline, mean	-1.0	-1.3	-0.7
Paired t-test, p-value	0.001	0.013	0.049
aPTT, sec			
Baseline, mean	34	34	34
24-h value, mean	37	33	36
Change from baseline, mean	3.5	-0.2	2.2
Paired t-test, p-value	0.006	0.695	0.011
Safety results: All safety data from the in-treatment period, defined as the time from first administration of the trial medication on Day 1 until follow-up (within 7 days after administration of trial medication) were used for the safety analysis.			
Adverse Events:	FX + rVIIa	PBO + rVIIa	FX + RVIIa PBO
N (AST population)	8	4	4
No. subjects with AEs n (%)	4 (50)	1 (25)	1 (25)
Any AE occurring in more than one subject in any group, n (%)			
Headache	2 (25)	0	0
Hematoma	2 (25)	0	0
Serious Adverse Events n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:			
No. subjects with Fatal/non Fatal SAEs	0	0	0

Publications:

Bijsterveld NR, Moons AH, Boekholdt SM et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* 106:2550-4, 2002

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