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Study No: 63108	
Title: An interaction study with subcutaneously administered Org31540/SR90107A and oral warfarin in healthy male volunteers (Protocol 63108)	
Rationale: The planned development of Org31540/SR90107A, also known as fondaparinux (FX), involved investigation of its safety and efficacy in the prophylaxis and treatment of diagnosed deep venous thrombosis. Therefore, a combination of subcutaneously administered FX and oral warfarin was envisaged. For this reason, the potential interaction of oral warfarin with FX was studied.	
Phase: I	
Study Period: Jul 1996 to Oct 1996	
Study Design: A randomised, 3-way cross-over, placebo-controlled double blind design.	
Centres: A single centre in The Netherlands.	
Indication: None	
Treatment: Subjects received the following treatments: (A) five 4 mg injections FX at 24-h intervals administered subcutaneously (0, 24, 48, 72, and 96 h) and placebo warfarin tablets at 72, and 96 h; (B) five placebo FX injections at 24-h intervals administered subcutaneously (0, 24, 48, 72, and 96 h), and warfarin at 72 h (15 mg), and 96 h (10 mg); and (C) five 4 mg injections FX at 24-h intervals administered subcutaneously (0, 24, 48, 72, and 96 h), and warfarin at 72 (15 mg), and 96 h (10 mg). The washout period between treatments was two weeks.	
Objectives: To investigate possible pharmacokinetic (PK) and pharmacodynamic (PD) interactions between subcutaneously administered FX and oral warfarin in healthy male volunteers.	
Statistical Methods: Pharmacokinetics: The following parameters were computed using the FX concentrations data over time to estimate potential effects of co-administration with warfarin: area under the plasma concentration-versus-time curve as a function of time from time zero to the time of the last quantifiable concentration (AUC_{0-last}), area under the curve for plasma concentrations as a function of time extrapolated to infinity ($AUC_{0-\infty}$), terminal half-life, clearance/F (CL/F), $AUC_{72h-last}$, time to reach peak concentration (t_{max}), and measured peak concentration (C_{max}) after the final dose. Parameters were compared between FX and FX + warfarin treatments using paired t-tests. Results were reported using 95% confidence intervals (CI) of the difference. Pharmacodynamics : Activated partial thromboplastin time (APTT) and prothrombin time (PT) parameters were analyzed using area under the effect curve (AUEC) above average pre-value divided by the corresponding time span. Maximal effect (E_{max}) and t_{max} were calculated for APTT and PT. Additionally, APTT and PT AUECs divided by the corresponding time span but not corrected for pre-value were compared between the 3 treatments using paired t-tests. For factor VII, an average pre-value was calculated as the mean of the value before treatment and at t=71.5 hours; parameters were analyzed using the difference between pre-value and time-corrected AUEC from t=71.5 hours to 121.5 hours relative to the first dose. Contrasts were calculated (using paired t-tests). Data for fragment 1+2 were analyzed with and without deletion of several suspected outliers. Fragment 1+2, factor VIIa, and the ratio of factor VIIa/VII were analyzed using AUECs divided by the corresponding time span but not corrected for pre-value. They were compared between the 3 treatments using paired t-tests. Safety: Safety parameters were listed.	
Study Population: Subjects were male, aged 18 to 40 years, healthy and with a normal coagulation screen. They had a body weight within 70-130% of the ideal body weight for age and height and a normal supine blood pressure. Key exclusion criteria included a history of clinically relevant cardiovascular, gastrointestinal, hepatic, renal, endocrine, pulmonary, neurologic, psychiatric or skin disease. Also excluded was a personal or family history of any disorder of hemostasis, any surgery within 3 months prior to the study, or any history of major trauma in the past year or recent history of minor head trauma, as well as a positive result on fecal occult blood testing on screening.	
Number of Subjects:	All Subjects
Planned N	Not available
Dosed, N	12
Completed, n (%)	12 (100)
Total Number Subjects Withdrawn, n (%)	0
Withdrawn due to Adverse Events (AEs), n (%)	0
Withdrawn due to Lack of Efficacy, n (%)	0
Withdrawn for Other Reasons, n (%)	0
Demographics	

N (All Subjects)		12	
Males		12	
Mean Age in Years (Range)		22 (19-27)	
Mean Weight in kg (Range)		72 (61-87)	
Race, n (%):		Not available	
Pharmacokinetics Endpoints: Estimates for Assessment of Potential Interaction with Warfarin			
Parameter	Endpoint Estimate	FX	FX + Warfarin
AUC _{0-∞} (mg.h/L)	Mean (SD)	37.5 (3.5)	38.4 (2.8)
	CV%	9.3	7.4
CL/F (mL/min)	Mean (SD)	7.8 (0.7)	7.6 (0.6)
	CV%	8.9	7.5
AUC _{72-last} (mg.h/L)	Mean (SD)	17.2 (1.8)	17.6 (1.5)
	CV%	10.6	8.4
C _{max} (ng/mL)	Mean (SD)	562 (42)	591 (47)
	CV%	7.5	8.0
t _{max} (h)	Mean (SD)	2.0 (0.4)	1.8 (0.7)
	CV%	21	39
t _{1/2} (h)	Mean (SD)	13.8 (1.5)	14.1 (1.8)
	CV%	10.9	12.6
Percentage Increase in FX Exposure Due to Warfarin (95% CI)			
Parameter	Percentage Increase (95%)		
AUC _{0-last} (mg.h/L)	2.4 (-1.1, 6.1)		
AUC _{72-last} (mg.h/L)	2.8 (-2.8, 8.7)		
C _{max} (ng/mL)	5.1 (-1.1, 11.7)		
Pharmacodynamics Endpoints			
	FX	Warfarin	FX + Warfarin
Prothrombin time			
AUEC _{time corrected} (sec)	14.47 (1.06)	17.09 (1.45)	17.35 (1.99)
Difference versus FX only	-	2.62	2.88
95% CI for difference	-	(1.9, 3.33)	(1.84, 3.92)
E _{max} (sec)*	17.1 (6.3)	25.3 (5.1)	26.2 (6.7)
Difference versus FX only	-	8.2	9.1
95% CI for difference	-	(3.6, 12.7)	(4.0, 14.2)
t _{max} **	***	122.4 (5.5)	117.3 (7.1)
Change from Baseline (SD)	0.15 (0.72)	2.92 (1.42)	2.82 (1.73)
APTT			
AUEC _{time corrected} (sec)	38.4 (3.4)	38.7 (3.1)	41.6 (3.9)
Difference versus FX	-	-	3.23
95% CI for difference	-	-	(1.74, 4.73)
Difference versus warfarin	-	-	2.93
95% CI for difference	-	-	(2.08, 3.77)
E _{max} (sec)	42.5 (5.0)	47.8 (8.3)	51.7 (10.6)
Difference versus FX	-	-	9.13
95% CI for difference	-	-	(1.44, 16.8)
Difference versus warfarin	-	-	3.93
95% CI for difference	-	-	(1.14, 6.71)
t _{max} (sec)	77.3 (14.2)	125.8 (14.1)	113.9 (13.2)
Difference versus warfarin	-	-	11.9
95% CI for difference	-	-	(-1.9, 25.7)
Change from baseline, mean (SD)	3.10 (3.84)	3.24 (4.59)	4.96 (1.53)
Factor VII			
Change from pre-value, mean (SD)	-0.018 (9.5)	-43.80 (17.2)	-49.40 (15.5)
Factor VIIa			
AUEC _{time corrected} (mU/mL)	52.3 (13.5)	37.6 (7.9)	34.6 (7.2)

Ratio Factor VIIa/VII			
AUEC _{time corrected} (mU/mL)/%	0.69 (0.19)	0.70 (0.19)	0.68 (0.20)
Bleeding time (sec)			
Pre-treatment, mean (SD)	125 (54)	129 (50)	122 (46)
Post-treatment, mean (SD)	136 (52)	123 (28)	111 (29)
Difference, mean (SD)	11 (65)	-6 (54)	-12 (58)
*E _{max} = maximal PT value. **t _{max} = average time to reach maximal PT value, from start of FX administration. ***Since PT did not exceed baseline levels following FX-only treatment, calculation of t _{max} was not performed.			
Safety Results:			
Adverse Events: Any AE That Occurred in >1 Subject in Any Group	FX	Warfarin	FX + Warfarin
N (All Subjects)	12	12	12
No. Subjects With AEs, n (%)	7 (58.3)	5 (41.7)	6 (50.0)
Hematoma	2 (16.7)	0	2 (16.7)
Headache	2 (16.7)	2 (16.7)	1 (8.3)
Asthenia	0	2 (16.7)	0
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:			
No. Subjects With Non-fatal SAEs	0	0	0
No. Subjects With Fatal SAEs	0	0	0
Publications:			
Faaij, RA. Absence of interaction between the synthetic pentasaccharide fondaparinux sodium and oral warfarin. <i>Clin Pharmacokinet</i> 2002;41 sup.2 : 27-29			
Donat, F. The pharmacokinetics of fondaparinux sodium in healthy volunteers <i>Clin Pharmacokinet</i> 2002;41 sup.2 : 1-9			
Faaij, RA.			
Interaction study between Org31540 /SR90107A (sc) and oral warfarin in healthy volunteers. <i>Thromb Haemost</i> 1997; suppl. (June): 491 (abstract).			

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