

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No: 63105
Title: A study to evaluate safety, tolerability and pharmacokinetics of 2, 4, 6, 12, 16, 18, and 20 mg of the pentasaccharide Org31540/SR90107A, administered as a single intravenous bolus injection to healthy elderly subjects
Rationale: Clinical use of intravenously (IV) administered Org31540/SR90107A, also known as fondaparinux (FX), will include significant numbers of elderly subjects. Therefore, it was considered mandatory from a safety and regulatory point of view to obtain information on the safety/tolerability and pharmacokinetics (PK) of FX after single IV administration to healthy elderly subjects.
Phase: I
Study Period: 12 April 1995 to 23 October 1995
Study Design: An assessor-blind, placebo-controlled, partially randomized, 2-period, sequential overlapping study.
Centres: A single centre in The Netherlands
Indication: None
Treatment: FX 2mg, 4mg, 6mg, 12mg, 16mg, 18mg, and 20 mg or matching placebo (PBO). Each treatment was administered as a single IV bolus injection over 30 seconds per treatment period. The dosing occasions for each subject were separated by a wash-out interval of 2 weeks. The study was performed using 4 sequential overlapping groups (I-IV) of 10 healthy elderly subjects each: Group I received either FX 2mg (treatment A) or PBO; then subsequently received FX 6mg (treatment C) or PBO Group II received FX 4mg (treatment B) or PBO; then subsequently received FX 12mg (treatment D) or PBO Group III received FX 16mg (treatment E) or PBO; then subsequently received FX 20mg (treatment G) or PBO Group IV received FX 18mg (treatment F) or PBO only
Objectives: To assess at the dose levels of 2mg, 4mg, 6mg, 12mg, 16mg, 18mg, and 20mg, the safety/tolerability and PK of FX administered as a single intravenous bolus injection to healthy elderly subjects.
Statistical Methods: Safety: All safety parameters were listed and descriptive statistics were applied. Analyses were performed on the population of all subjects treated. Pharmacokinetics (PK): Non-compartmental PK parameters were derived from the FX plasma and urine concentrations. The following key PK parameters were derived for each of the 7 dose levels from the plasma concentrations: peak concentration (C_{max}), area under the concentration-time curve extrapolated to infinity (AUC_{inf}) half life associated with λ_z ($t_{1/2,z}$), where λ_z is the elimination rate constant associated with the terminal elimination phase total plasma clearance (CL) renal clearance (CL_R) cumulative urinary excretion over 72hours (Fe_{0-72}) volume of distribution associated with the terminal elimination phase (V_z) volume of distribution at steady state (V_{ss}) Concentration related parameters are presented here in acid equivalents. Descriptive statistics (mean, standard deviation [SD], and coefficients of variation [CV]) of the assessed PK parameters were calculated by dose. Dose proportionality testing: For log-transformed and dose-normalized AUC_{inf} and C_{max} , different analyses of variance (ANOVA) were performed by period and by group to test for differences between doses. Pharmacodynamics (PD): All PD data were listed individually and summary statistics were applied. No formal statistical analysis of the data was performed. PD parameters included bleeding time, activated partial thromboplastin time (APTT), prothrombin time (PT) and antithrombin III (AT-III)
Study Population: Healthy male and female elderly subjects aged between 65 and 85 years within 70% and 130% of their ideal weight but not <45kg were included. Subjects with history of clinically significant bleeding or coagulation disorder, use of aspirin or NSAID within 5 days prior to study, positive fecal occult blood, presence of diabetes requiring drug therapy, cancer or clinically relevant cardiac, respiratory, metabolic, renal, hepatic, gastrointestinal, venereal, hematologic, neurologic, psychiatric disease or

active infection or inflammatory process were excluded.								
Number of Subjects:		PBO	Group I	Group II	Group III	Group IV		
Planned, N		8	8	8	8	8		
Dosed, N		8	8	8	9	8		
Completed, n (%)		8 (100)	8 (100)	8 (100)	8 (89)	8 (100)		
Total Number Subjects Withdrawn, n (%)		0	0	0	1 (11)	0		
Withdrawn due to Adverse Events, n (%)		0	0	0	1 (11)	0		
Withdrawn due to Lack of Efficacy, n (%)		0	0	0	0	0		
Withdrawn for Other Reasons, n (%)		0	0	0	0	0		
Demographics								
N (Completed)		8	8	8	8	8		
Females: Males		4:4	3:5	4:4	2:6	4:4		
Mean Age in Years (sd)		F	70.0 (1.83)	67.7 (1.53)	73.5 (2.65)	68.0 (4.24)	68.5 (3.00)	
		M	71.3 (4.35)	69.8 (6.98)	70.3 (3.95)	69.2 (3.19)	71.8 (5.19)	
Mean Weight in Kg (sd)		F	59.7 (12.31)	70.6 (12.72)	68.7 (10.47)	76.1 (1.27)	69.1 (7.44)	
		M	71.4(9.17)	79.8 (5.92)	84.0 (8.63)	82.4 (11.80)	81.4 (6.65)	
Race, n (%)		NA	NA	NA	NA	NA		
NA, not available								
PK/PD Endpoints:								
Key PK Parameters Obtained After Non-compartmental Analysis								
Parameter	Unit	Dose Level (Mean, SD, CV%)						
		2mg n=8	4mg n=8	5.5mg n=8	12mg n=8	16mg n=8	18mg n=8	20mg n=8
$C_{max,acid}$	(ng.mL ⁻¹)	604.5	1114.7	1159.9	2488.1	3172.7	3491.7	3836.5
		131.2	301.7	115.8	516.5	315.4	275.3	392.2
		21.7	27.1	10.0	20.8	9.9	7.9	10.2
$AUC_{inf,acid}$	(ng.h/mL ⁻¹)	6001.8	12175.3	12601.2	28103.3	30882.1	37927.6	38839.8
		1773.9	2930.5	2647.2	6257.9	7252.3	6905.8	8305.4
		29.6	24.1	21.0	22.3	23.5	18.2	21.4
$t_{1/2,z}$	(h)	16.9	18.4	18.3	16.6	16.4	17.0	16.5
		4.1	2.4	3.2	2.2	2.5	2.2	2.6
		24.4	13.1	17.4	13.2	15.3	12.9	15.6
CL	(mL.min ⁻¹)	5.3	5.1	6.6	6.5	7.9	7.1	7.8
		1.8	1.4	1.2	1.4	1.8	1.2	1.6
		33.4	27.5	18.7	21.8	22.7	17.1	20.8
CL_R (renal clearance)	(mL.min ⁻¹)	–	4.8	4.5	4.6	6.5	6.8	7.9
		–	1.0	1.2	0.9	1.8	1.6	2.2
		–	20.4	25.4	18.9	27.9	22.9	28.3
Fe_{0-72}	(%)	–	7.9	10.2	9.1	10.9	10.3	10.9
		–	1.8	1.2	1.4	1.2	1.5	0.9
		–	22.2	11.5	15.0	10.7	14.7	8.6
V_z	(L)	7.4	7.9	10.2	9.1	10.9	10.3	10.9
		1.9	1.8	1.2	1.4	1.2	1.5	0.9
		25.0	22.2	11.5	15.0	10.7	14.7	8.6
V_{ss} (volume at steady state)	(L)	6.5	7.1	9.0	8.4	9.7	9.2	9.6
		1.5	1.4	0.9	1.4	0.9	1.2	0.8
		22.2	20.3	10.5	16.7	9.2	12.7	8.1
PK: Dose proportionality testing: Statistical tests were applied to AUC_{inf} and C_{max} data for the first treatment period (doses 2, 4, 16 and 18 mg), and separately to AUC_{inf} and C_{max} data for the second period (doses 5.5, 12 and 20 mg). There were no statistically significant differences ($P>0.05$) between the dose-normalized AUC_{inf} and C_{max} for the 2 and 4 mg doses, but the parameter values for these two doses were statistically significantly ($P<0.05$) higher than for the 16 and 18 mg doses. No statistically significant differences between the dose-normalized AUC_{inf} and C_{max} data respectively after 5.5, 12 and 20 mg were observed. A further test was done by group to compare the results after two dose levels within subjects (comparisons between 2 and 5.5 mg, between 4 and 12 mg, and between 16 and 20 mg). This revealed statistically significant differences between the dose normalized AUC_{inf} and C_{max} values for the 2 and 5.5 mg doses ($P<0.05$) and between the dose normalized AUC_{inf} and C_{max} values for the 4 and 12 mg doses ($P<0.05$). There was no statistically significant difference between the values after the 16 and 20								

mg doses (P>0.05).

PD: Bleeding time, APTT, PT and AT-III showed no clear dose-related changes from baseline.

Safety results:

An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Adverse Events:	PBO n=8	2mg n=8	4mg n=8	5.5mg n=8	12mg n=8	16mg n=9	18mg n=8	20mg n=8
N (Total)	4 (50)	8 (100)	7 (87.5)	3 (37.5)	4 (50.0)	5 (55.6)	6 (75.0)	4 (50.0)
No. Subjects with AEs, n (%)								
Most Frequent AEs								
Dizziness	0	0	4 (50.0)	0	2 (25.0)	4 (44.4)	0	0
Headache	2 (25.0)	1 (12.5)	4 (50.0)	1 (12.5)	1 (12.5)	1 (11.1)	3 (37.5)	0
Diarrhea	0	0	0	0	0	0	0	2 (25.0)
Myalgia	0	5 (62.5)	1 (12.5)	0	0	0	0	0
Hemorrhage Not Otherwise Specified	0	3 (37.5)	1 (12.5)	0	1 (12.5)	0	0	0
Serious Adverse Events, n (%)								
[n considered by the investigator to be related, possibly related, or probably related to study medication]:								
	PBO n=8	2mg n=8	4mg n=8	5.5mg n=8	12mg n=8	16mg n=8	18mg n=8	20mg n=8
Subjects with Non-Fatal SAEs	0	0	0	0	0	0	0	1 (12.5) [0]
Angina Pectoris	0	0	0	0	0	0	0	1 (12.5) [0]
Subjects with Fatal SAEs	0	0	0	0	0	0	0	0

Publications:

Donat F. The pharmacokinetics of fondaparinux sodium in healthy volunteers. Clin Pharmacokinet 2002; 41 sup 2: 1-19.

Recombinant factor viia reverses the in vitro and ex vivo anticoagulant and profibrinolytic effects of fondaparinux. Lisman, T., Bijsterveld, N. R., Adelmeijer, J., Meijers, J. C., Levi, M., Nieuwenhuis, H. K., and De Groot, P. G. J Thromb Haemost 2003; 1(11):2368-73

Date Updated: 28-Oct-2005