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<b>Study No:</b> 63106		
<b>Title:</b> A four-period cross-over study to assess the absolute bioavailability, safety and tolerability of the pentasaccharide Org31540/SR90107A, after single dose subcutaneous administration of 2, 4 and 8 mg compared with 4 mg intravenous administration to healthy elderly subjects		
<b>Rationale:</b> It is anticipated that subcutaneous (SC) administration of Org31540/SR90107A (fondaparinux sodium [FX]) in clinical practice will include significant numbers of elderly subjects. Therefore, it was essential to obtain information on the absolute bioavailability, safety and tolerability of FX after single dose SC administration in the same population. In this present study the safety/tolerability and pharmacokinetic (PK) data, including SC bioavailability, collected after single dose administration of FX at various SC dose levels and one intravenous (IV) injection to healthy elderly subjects was examined.		
<b>Phase:</b> I		
<b>Study Period:</b> November 1995 to February 1996		
<b>Study Design:</b> Single center, randomized, open-label, four-period, cross-over study		
<b>Centers:</b> 1 study center in The Netherlands		
<b>Indication:</b> None		
<b>Treatment:</b> Each subject received 4 single doses of FX in randomized order, with administration separated by at least 7 days: 2 mg in 0.2 mL SC, 4 mg in 0.4 mL SC, 8 mg in 0.8 mL SC and IV bolus injection of 4 mg diluted in 0.9% saline to a volume of 5 mL administered over 30 seconds.		
<b>Objectives:</b> To assess the absolute bioavailability, safety and tolerability of FX after single dose SC administration of 2, 4 and 8 mg to healthy elderly subjects.		
<b>Statistical Methods:</b> Populations analyzed: All treated subjects were included in the safety analysis. Subjects were presented in the treatment group "as treated" if different from "as randomized". Subjects who discontinued prematurely in one period before entering another period were analyzed in the periods they ran through. Statistical tests used: Pharmacokinetics: The following PK parameters were determined: FX plasma concentrations: maximum plasma concentration ( $C_{max}$ ), time to reach maximum plasma concentration ( $t_{max}$ ), area under the plasma concentration-time curve (both $AUC_{(0-t)}$ & $AUC_{(0-inf)}$ ), total plasma clearance (CL for IV dose, CL/F for SC dose), absolute bioavailability (F), MRT, volume of distribution associated with the terminal elimination phase ( $V_z$ )/F, elimination rate constant associated with terminal elimination phase ( $\lambda_z$ ), and half-life associated with the terminal elimination phase ( $t_{1/2}$ ). In addition, urinary parameters (amount and fraction of dose excreted [Ae, Fe] and renal clearance [CL <sub>ren</sub> ]) based on FX concentrations in urine were also determined. The absolute bioavailability, defined as $F = (AUC_{sc} \cdot Dose_{iv}) / (AUC_{iv} \cdot Dose_{sc})$ , was calculated for each of the dose levels along with the 90% confidence intervals (CI). The parametric analysis was performed using the analysis of variance (ANOVA) approach on the logarithmically transformed parameter values. Nonparametric 90% CIs were calculated for $t_{max}$ . For each of the planned dose levels descriptive statistics (mean, median, range and SD) of the assessed pharmacokinetic parameters were calculated. Dose linearity with respect to the 3 SC treatments was investigated by application of the same (bio-)equivalence methods to the logarithmically transformed $AUC_{inf}$ and $C_{max}$ data after dose-correction. In addition a power model approach was applied to quantify potential dose-disproportionality in the parameters. Potential gender effects on $C_{max}$ and $AUC_{inf}$ were investigated in an ANOVA. Pharmacodynamics: Activated partial thromboplastin time (APTT) and prothrombin time (PT) were presented descriptively and individually in tabular format. No formal statistical analyses were performed. Safety: All safety parameters were listed and descriptive statistics were calculated.		
<b>Study Population:</b> Healthy elderly male and female subjects aged between 60 and 85 years at the pre-study screening and not less than 45 kg weight. Good physical and mental condition as evidenced by medical history, clinical laboratory and full physical examination. Negative screens for alcohol, salicylic acid and drugs of abuse. Not more than moderately smoking.		
<b>Number of Subjects:</b>	<b>FX</b>	
	Female	Male
Planned N	12	12

Dosed N	11	14		
Completed n (%)	11	13		
Total Number Subjects Withdrawn N (%)	0	1		
Withdrawn due to Adverse Events n (%)	0	0		
Withdrawn due to Lack of Efficacy n (%)	0	0		
Withdrawn for Other Reasons n (%)	0	1*		
*Subject withdrawn due to elevated Ca+ at screening				
<b>Demographics</b>				
N (All Subjects treated)	12	14		
Mean Age in Years (SD)	65.1 (4.0)	65.9 (4.6)		
Mean Weight in Kg (SD)	67.9 (8.4)	81.5 (14.1)		
Caucasian, n (%)	11 (100)	13(93)		
<b>Pharmacokinetics (PK),pharmacodynamics (PD), PK/PD Endpoints:</b>				
<b>Descriptive statistics of PK parameters</b>	<b>FX 2 mg SC</b>	<b>FX 4 mg SC</b>	<b>FX 8 mg SC</b>	<b>FX 4 mg IV</b>
	<b>N=23*</b>	<b>N=24</b>	<b>N=24</b>	<b>N=25</b>
C <sub>max</sub> acid, ng.mL <sup>-1</sup> , mean (SD)	278.7 (83.09)	478.3 (103.1)	911.0 (181.3)	858.7 (157.4)
Coefficient of variation (CV), %	29.8	21.6	19.9	18.3
t <sub>max</sub> , h, mean (SD)	2.2 (0.83)	2.6 (1.2)	2.3 (0.81)	Not applicable (n.a.)
CV%	37.7	46.2	35.2	n.a.
AUC <sub>inf</sub> acid, ng.h.mL <sup>-1</sup> , mean (SD)	5632 (1289.3)	10003 (2391.3)	19237 (3701.1)	9673 (1832.3)
CV%	22.3	23.9	19.2	18.9
AUC <sub>0-t</sub> acid, ng.h.mL <sup>-1</sup> , mean (SD)	4633.0 (1044.2)	8918 (2234.8)	17910 (3237.7)	8639 (1728.5)
CV%	22.5	25.1	18.1	20.0
t <sub>1/2</sub> , h, mean (SD)	20.7 (7.30)	19.2 (4.15)	18.8 (2.08)	20.3 (4.16)
CV%	35.3	21.6	11.1	20.5
λ <sub>z</sub> (h <sup>-1</sup> ), mean (SD)	0.0367 0.0103	0.0384 0.0117	0.0373 0.0038	0.0357 0.0079
CV%	28.1	30.5	10.2	22.1
MRT, h, mean (SD)	16.2 (3.50)	17.5 (3.13)	19.4 (1.37)	17.3 (3.03)
CV%	21.6	17.9	7.1	17.5
CL(/F) , mL.min <sup>-1</sup> , mean (SD)	5.97 (1.38)	6.17 (1.6)	6.28 (1.27)	6.24 (1.32)
CV%	23.1	25.9	20.2	21.2
V <sub>z</sub> (/F) L, mean (SD)	10.2 (2.36)	10.0 (2.72)	10.1 (1.72)	10.8 (2.41)
CV%	23.1	27.3	17.0	22.3
Fe <sub>(0-72h)</sub> ** %, mean (SD)	64 (6)	66 (6)	65 (6)	64 (7)
CV%	10	9	10	11
CLren *** mL/min <sup>-1</sup> , mean (SD)	4.00 (0.89)	4.43 (1.23)	4.37 (1.07)	4.25 (0.77)
CV%	22.3	27.7	24.6	18.2
* n=23 for 2 mg SC treatment, as data from one subject was not used				
** For Fe, n=23, 22, 22, 23 for 2 mg SC, 4 mg SC, 8 mg SC and 4 mg IV, respectively.				
*** For CLren n=23, 22, 23 and 24, for 2 mg SC, 4 mg SC, 8 mg SC and 4 mg IV, respectively.				
<b>Mean cumulative urinary excretion of FX</b>	<b>FX 2 mg SC</b>	<b>FX 4 mg SC</b>	<b>FX 8 mg SC</b>	<b>FX 4 mg IV</b>
	<b>N= 23</b>	<b>N=22</b>	<b>N=22</b>	<b>N=23</b>
0 to 5 h, % of the dose (SD)	11 (20)	11 (3)	11 (3)	14 (4)
0 to 8.5 h, % of the dose (SD)	22 (30)	23 (4)	23 (4)	25 (5)
0 to 24.5 h, % of the dose (SD)	47 (6)	48 (5)	48 (6)	47 (5)
0 to 48.5h, % of the dose (SD)	61 (6)	62 (6)	61 (6)	60 (6)

0 to 72.5 h, % of the dose (SD)	64 (6)	66 (6)	65 (6)	64 (7)
<b>Bioavailability and dose proportionality, results of statistical analysis</b>	<b>test/reference</b>	<b>Point estimate of ratio [90 % CI]</b>		
AUC <sub>inf</sub> (dose- normalized)	2 mg SC/4 mg IV	1.12 [1.07-1.18]		
	4 mg SC/4 mg IV	1.07 [1.02-1.12]		
	8 mg SC/4 mg IV	1.07 [1.02-1.13]		
	4 mg SC/2 mg SC	0.95 [0.91-1.00]		
	8 mg SC/2 mg SC	0.96 [0.91-1.00]		
	8 mg SC/4 mg SC	1.00 [0.96-1.05]		
C <sub>max</sub> (dose-normalized)	4 mg SC/2 mg SC	0.95 [0.90-0.99]		
	8 mg SC/2 mg SC	0.93 [0.88-0.97]		
	8 mg SC/4 mg SC	0.98 [0.93-1.03]		
	<b>Test - reference</b>	<b>Median Difference h, [90 % CI]</b>		
t <sub>max</sub>	4 mg SC - 2 mg SC	-0.50 [-0.75-0.00]		
	8 mg SC - 2 mg SC	0.00 [-0.50-0.00]		
	8 mg SC - 4 mg SC	0.25 [0.00-0.75]		
<b>PD Assessments</b>	<b>FX 2 mg SC</b>	<b>FX 4 mg SC</b>	<b>FX 8 mg SC</b>	<b>FX 4 mg IV</b>
APTT and PT values per dose level	<b>N=24</b>	<b>N=24</b>	<b>N=24</b>	<b>N=25</b>
APTT values, mean (SD)				
2 min pre-dose	33.54 (6.23)	33.02 (5.91)	34.23 (4.54)	34.05 (4.89)
after 2 hours	36.68 (6.60)	36.69 (5.42)	38.52 (5.02)	37.52 (4.71)
after 24 hours	35.33 (5.32)	35.26 (5.09)	36.15 (4.32) <sup>a</sup>	35.13 (4.14)
PT values, mean (SD)				
2 min pre-dose	12.88 (0.61)	12.92 (0.65)	12.79 (0.59)	13.00 (0.58)
after 2 hours	13.21 (0.83)	13.38 (0.77)	13.54 (0.59)	13.24 (0.66)
after 24 hours	12.63 (0.77)	12.67 (0.82)	13.04 (1.40) <sup>a</sup>	12.64 (0.64)
<sup>a</sup> N=23				
<b>Safety results:</b>				
Adverse events (AEs) and serious AEs (SAEs) starting within each treatment period (the day of first study dose administration of the considered study period, up to the day before the first study drug administration of the next period) were taken into account. The last treatment period included all the AEs from the start of this period to the last assessment, 72 h after each drug administration.				
<b>Adverse Events:</b>	<b>FX 2 mg SC</b>	<b>FX 4 mg SC</b>	<b>FX 8 mg SC</b>	<b>FX 4 mg IV</b>
N (All treated subjects)	<b>N=24</b>	<b>N=24</b>	<b>N=24</b>	<b>N=25</b>
No. subjects with AEs n (%)	14 (58.3)	14 (58.3)	14 (58.3)	13 (52.0)
Any AE occurring in more than one subject in any group, n (%)				
Dizziness	1 (4.2)	0	4 (16.7)	2 (8.0)
Headache	10 (41.7)	11 (45.8)	7 (29.2)	7 (28.0)
Diarrhoea	1 (4.2)	0	2 (8.3)	3 (12.0)
Nausea	2 (8.3)	4 (16.7)	1 (4.2)	2 (8.0)
Vomiting	2 (8.3)	3 (12.5)	0	2 (8.0)
Upper respiratory tract infection	0	1 (4.2)	1 (4.2)	2 (8.0)
<b>Serious Adverse Events n (%)</b> [n considered by the investigator to be related, possibly related, or probably related to study medication]:				

No. subjects with SAEs -includes fatal and non-fatal events	0	0	0	0
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**Conclusion:**

See publication below.

**Publications:**

F Donat. The pharmacokinetics of fondaparinux sodium in healthy volunteers. Clin Pharmacokinet 2002;41 sup.2 : 1-9

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