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<b>Study No:</b> 63103					
<b>Title :</b> A repeated rising-dose, placebo-controlled study of the safety, tolerability, pharmacokinetics and pharmacodynamics of subcutaneous Org31540/SR90107A administered for 7 consecutive days to healthy male and female elderly volunteers					
<b>Rationale:</b> This study was to investigate effects of Org31540/SR90107A/ fondaparinux (FX) administered subcutaneously to healthy elderly volunteers in doses ranging from 3mg twice daily (BD) up to 12mg once daily (OD).					
<b>Phase:</b> I					
<b>Study Period:</b> 3 August 1992 to 4 November 1992					
<b>Study Design:</b> Single centre, open-label, placebo-controlled, sequential, repeated rising-dose (for 7 consecutive days) study					
<b>Centres:</b> 1 in the UK					
<b>Indication:</b> None					
<b>Treatment:</b> Each treatment group included 5 subjects; 4 subjects in each treatment group were dosed and the fifth subject was given placebo (PBO), for seven days. Treatment regimens were: Group 1: 3mg BD Group 2: 6mg OD Group 3: 6mg BD Group 4: 9mg BD, Group 5 12mg OD					
<b>Objectives:</b> To determine and compare the safety, tolerability, pharmacokinetic and pharmacodynamic profiles of repeated, rising, subcutaneous dose-regimens of FX administered in the range of 3mg to 12mg, OD or BD dosing, to groups of five healthy, elderly male and female subjects, including 1 subject on placebo.					
<b>Statistical Methods:</b> <u>Populations analysed:</u> Subjects analysed for efficacy had completed treatment according to the protocol at the time of analysis. All subjects were included in the safety analysis. For any analysis, the results were combined for the 4 PBO-treated subjects (1 from each dosage level), assuming that there was no time-dependent effect. <u>Pharmacokinetics:</u> As the daily dose and dosing interval (OD or BD) differed, $C_{max}$ and $AUC_{0-t}$ were normalised to a daily dose of 6mg before performing statistical analyses. The dose effect was only evaluated on the BD regimen using the Kruskal-Wallis test. The dose-regimen effect, taking into account the dosing interval (OD or BD), was evaluated on Days 1 and 7 for $t_{max}$ , $t_{1/2}$ (Day 7 only), and $C_{max}$ and $AUC_{0-t}$ (Day 7 only) normalised to 6mg/day, by the Kruskal-Wallis test. The influence of body weight and creatinine clearance values on normalised $C_{max}$ (Day 1), normalised $AUC_{0-t}$ (Day 7). Renal clearance ( $CL_R$ ), was assessed using Pearson's correlation analysis. The gender effect was studied on $C_{max}$ and $AUC_{0-t}$ (both Days 1 and 7) by the Kruskal-Wallis test. <u>Pharmacodynamics:</u> Mean bleeding times were presented per dose group at Day 0, 4 or 6 (whichever had the highest value) and at Day 8 (earlier if premature termination occurred), 24 hours after the final injection. <u>Safety:</u> Descriptive methods were used to analyse safety data; abnormal laboratory values were tabulated and vital signs were summarised for each dosing level by means and standard deviations (SDs).					
<b>Study Population:</b> Healthy, male and female volunteers, aged 65 to 85 years inclusive, Caucasian, weight $\pm$ 30% average for height and frame (minimum 45 kg), and smoking <10 cigarettes/day. Excluded were any clinically significant abnormal laboratory test at screening, presence of diabetes other than diet-controlled, presence of cancer or any clinically significant cardiac, respiratory, metabolic, renal, hepatic, gastrointestinal, venereal, hematologic, neurologic or psychiatric diseases. Also excluded were subjects with significant infection or known inflammatory process, personal or family history of bleeding disorder or positive fecal occult blood testing at screening.					
<b>Number of Subjects:</b>			<b>All</b>		
Planned N			35*		
*7 dose regimens were planned; however, only 5 were studied. In Group 5 (12mg OD), no PBO subject was included; in total 24 subjects participated in the study.					
	<b>Group 1 3mg BD</b>	<b>Group 2 6mg OD</b>	<b>Group 3 6mg BD</b>	<b>Group 4 9mg BD</b>	<b>Group 5 12mg OD</b>
Dosed N	5	5	5	5	4
Completed, n (%)	5(100)	5(100)	5(100)	4(80)	3(75)

Total Number Subjects Withdrawn, n (%)	0	0	0	1(20)	1(25)	
Withdrawn due to Adverse Events, n (%)	0	0	0	0	1(25)	
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0	0	
Withdrawn for Other Reasons, n (%)	0	0	0	1(20)	0	
<b>Demographics</b>	<b>Group 1 3mg BD</b>	<b>Group 2 6mg OD</b>	<b>Group 3 6mg BD</b>	<b>Group 4 9mg BD</b>	<b>Group 5 12mg OD</b>	<b>PBO</b>
N	4	4	4	4	4	4
Females: Males	2:2	2:2	2:2	2:2	3:1	2:2
Age in years, mean (SD)	69.8 (4.5)	70.0 (3.7)	72.5 (6.5)	69.5 (1.7)	66.8 (2.4)	68.5 (2.7)
Caucasian, n (%)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)
<b>Pharmacokinetics/pharmacodynamics Endpoints:</b>						
Pharmacokinetics: Mean values (SD)	<b>Group 1 3mg BD. n = 4</b>	<b>Group 2 6mg QD n = 4</b>	<b>Group 3 6mg BD n = 4</b>	<b>Group 4 9mg BD n = 4</b>	<b>Group 5 12mg QD n = 4</b>	
<b>Day 1</b>						
<b>t<sub>max</sub> (h)</b>	1.88 (0.75)	3.00 (2.12)	2.13 (0.63)	5.21 (4.49)	1.75 (0.29)	
Dose effect, p-value	0.3140					
<b>C<sub>max</sub> (mg/L)</b>	0.412 (0.048)	0.714 (0.290)	0.804 (0.201)	1.313 (0.387)	1.839 (0.307)	
Dose regimen effect, p-value	0.6140					
Gender effect, p-value	0.1591					
Creatinine clearance effect, p-value	0.1886					
Body weight effect, p-value	0.0054					
<b>AUC<sub>0-t</sub> (mg.h/L)</b>	3.32 (0.42)	10.63 (3.23)	6.88 (1.53)	11.28 (2.38)	26.13 (4.58)	
Gender effect, p-value	0.2388					
<b>Day 7</b>						
<b>t<sub>max</sub> (h)</b>	1.50 (0.01)	1.65 (0.24)	1.32 (0.24)	2.05 (0.67)	1.50	
Dose regimen effect, p-value	0.1007					
<b>t<sub>1/2</sub> (h)</b>	15.6 (2.8)	16.9 (3.9)	17.5 (0.7)	19.3 (9.1)	20.7	
Dose regimen effect, p-value	0.9419					
<b>C<sub>max</sub> (mg/L)</b>	0.945 (0.179)	1.253 (0.349)	1.799 (0.212)	2.494 (0.478)	2.575	
Dose regimen effect, p-value	0.4297					
Gender effect, p-value	0.4702					
<b>AUC<sub>0-t</sub> (mg.h/L)</b>	8.11 (1.52)	16.71 (4.17)	15.65 (1.79)	23.01 (3.78)	34.70	
Dose regimen effect, p-value	0.9651					
Gender effect, p-value	0.6304					
Body weight effect, p-value	0.0473					
Creatinine clearance effect, p-value	0.0010					
<b>CL<sub>R</sub> (mL/min)</b>	2.77 (0.73)	3.34 (0.87)	4.06 (1.08)	3.85 (1.00)	4.81	
Dose regimen effect, p-value	0.03624					
Creatinine clearance effect, p-value	0.0015					
<b>Pharmacodynamics:</b>						
<b>Mean bleeding time (min:sec)</b>	<b>Group 1 3mg BD</b>	<b>Group 2 6mg OD</b>	<b>Group 3 6mg BD</b>	<b>Group 4 9mg BD</b>	<b>Group 5 12mg OD</b>	<b>PBO</b>
Day 0	5:26	6:11	6:30	5:52	6:00	5:45
Day 4 or 6 <sup>a</sup>	5:15	7:11 <sup>c</sup>	5:56	7:15	6:37	5:45
Day 8 <sup>b</sup>	6:03	5:22	5:41	7:41	6:56	5:26

<sup>a</sup>Whichever had the highest value.

<sup>b</sup>24 hours after the last injection, which for 2 subjects was earlier than Day 8 due to premature termination of study treatment.

<sup>c</sup>This number does not include the high value of Subject 9 (BT = 27:15 at Day 6). Repetition of the assessment 3 hours later scored 8:30. The mean value using the second measurement of Subject 9 was 7:11.

**Safety results:**

<b>Adverse Events:</b>	<b>Group 1 3mg BD</b>	<b>Group 2 6mg OD.</b>	<b>Group 3 6mg BD</b>	<b>Group 4 9mg BD</b>	<b>Group 5 12mg OD</b>	<b>PBO</b>
N	4	4	4	4	4	4
No. subjects with AEs n (%)	3 (75.0)	4 (100.0)	4 (100.0)	4 (100.0)	4 (100.0)	3 (75.0)
Most Frequent AEs						
Purpura, n (%)	0 (0)	0 (0)	1 (25)	2 (50)	3 (75)	0 (0)
Hematoma	0 (0)	4 (100)	3 (75)	4 (100)	4 (100)	0 (0)
Headache	1 (25)	1 (25)	2 (50)	1 (25)	0 (0)	2 (50)
Procedural site reaction	2 (50)	0 (0)	0 (0)	3 (75)	0 (0)	1 (25)
Bullous eruption	0 (0)	0 (0)	3 (75)	0 (0)	0 (0)	0 (0)
<b>Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:</b>						
Subjects with Fatal/non-Fatal SAEs	0	0	0	0	0	0

**Publications:**

Boneu B. Pharmacokinetics and tolerance of the natural pentasaccharide (SR90107A/ORG31540) with high affinity to antithrombin III in man. *Thromb Haemost* 74 (6):1468-1473, 1995

The pharmacokinetics of fondaparinux sodium in healthy volunteers. Donat, F., Duret, J. P., Santoni, A., Cariou, R., Necciari, J., Magnani, H., and de Greef, R. *Clin Pharmacokinet* 2002; 41 Suppl 2(1-9)

Abstract: Pharmacokinetics of fondaparinux sodium in young and elderly healthy subjects: a highly favourable profile. Donat, F, Duret, J P, Santoni, A, Cariou, R, Necciari, J, Magnani, H, de Greef, R, and Alban, S 7th Congress of the European Association of Hospital Pharmacists 3/20/2002 Vienna, Austria

Abstract: Pharmacokinetics of fondaparinux in young and elderly healthy subjects: a highly favourable pharmacokinetic profile. Donat, F, Duret, J P, Sanotoni, A, Cariou, R, Necciari, J, Magnani, H, and de Greef, R 20th World Congress of the International Union of Angiology 4/7/2002 New York, USA

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