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Study No: 63102
Title: A single, rising dose study of the safety, tolerability, pharmacokinetics and pharmacodynamics of subcutaneous Org31540/SR90107A in healthy male and female elderly volunteers
Rationale: This study investigated the safety, tolerability, pharmacokinetics and pharmacodynamics of rising doses of Org31540/SR90107A (fondaparinux sodium) administered subcutaneously to healthy elderly volunteers.
Phase: I
Study Period: 1992 to 1993
Study Design: A phase I, open-label, placebo-controlled comparison of 6 single, rising, subcutaneous (SC) doses of Org31540/SR90107A.
Centres: A single centre in the United Kingdom
Indication: None
Treatment: The following doses of fondaparinux were administered subcutaneously to healthy elderly volunteers: 0.7mg, 1.5mg, 3mg, 6mg, 12mg, and 18mg. These doses were investigated sequentially, beginning with the lowest dose. Before proceeding to a higher dose, the effects of the previous dose were assessed. During each study session, four subjects (2 male, 2 female) received fondaparinux and one subject was given a placebo. The duration of each subject's participation was a minimum of 4 nights. Subjects were admitted to the study site on the day before dosing, and received fondaparinux or placebo on Day 1. Clinical assessments, observation, and sampling schedules for blood and urine continued through Day 4. Subjects returned for a follow-up observation 7 to 9 days post-dosing.
Objectives: To determine and compare the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of single rising subcutaneous doses of fondaparinux administered sequentially in the range of 0.7mg to 18mg to healthy elderly volunteers.
<p>Statistical Methods:</p> <p>PK: The following PK parameters were determined for each subject from plasma and urinary concentrations of fondaparinux(FX).</p> <p>C_{max} (maximum FX concentration observed in plasma)</p> <p>t_{max} (time to reach C_{max})</p> <p>$t_{1/2}$ (half-life of plasma terminal phase)</p> <p>AUC_{0-obs} (area under the curve computed by trapezoidal method from time 0 to time corresponding to the last concentration above the limit of quantification)</p> <p>AUC_{0-inf} (area under the curve computed from time 0 to infinity)</p> <p>CL/F (apparent plasma clearance)</p> <p>V_d/F (apparent volume of distribution)</p> <p>Ae₀₋₂₄ (amount of FX excreted in urine during the interval 0-24 hours (h) after administration)</p> <p>Fe(%) (percentage of the dose administered excreted in urine in the interval 0-24 h after administration)</p> <p>CL_{R 0-24} (renal clearance in the interval 0-24 h)</p> <p>Summary statistics by dose level were calculated for each PK parameter. No formal statistical analyses were performed owing to the small number of subjects per administered dose (4 subjects per dose).</p> <p>PD: The following PD parameters were determined for each subject</p> <p>APTT (activated partial thromboplasmin time)</p> <p>PT (prothrombin time)</p> <p>bleeding time</p> <p>AT-III (anti thrombin III activity)</p> <p>anti-IIa (anti thrombin IIa activity)</p> <p>Summary statistics were calculated per assessment per dose level. In addition, area under the curve (AUC), minimum and maximum values were calculated for activated partial thromboplasmin time (APTT) and prothrombin time (PT), with descriptive statistics per dose level and gender. An analysis of covariance was performed on the AUC for APTT and PT to test for possible dose or gender effects. In addition, the ratios of APTT as well as PT measurements from subjects administered fondaparinux to that of a control laboratory healthy pool sample assessed were determined.</p> <p>Safety: The statistical analysis was mainly descriptive. Adverse events, changes from the baseline and values out of range</p>

were listed.

Analyses were performed on the population of all subjects treated.

Study Population: Healthy male and female Caucasian subjects aged between 65 and 85 years within 30% of the average weight for height and frame (minimum weight of 45kg), who smoked ≤ 10 cigarettes/day.

Number of Subjects:	PBO	FX 0.7mg	FX 1.5mg	FX 3mg	FX 6mg	FX 12mg	FX 18mg
Planned, N	6	4	4	4	4	4	4
Dosed, N	7	4	4	4	4	4	4
Completed, n (%)	7	4	4	4	4	4	4
Total Number Subjects Withdrawn, n (%)	0	0	0	0	0	0	0
Withdrawn due to Adverse Events, n (%)	0	0	0	0	0	0	0
Withdrawn due to Lack of Efficacy, n (%)	0	0	0	0	0	0	0
Withdrawn for Other Reasons, n (%)	0	0	0	0	0	0	0
Demographics							
N (Total)	7	4	4	4	4	4	4
Females: Males	5:2	2:2	2:2	2:2	2:2	2:2	2:2
Mean Age in Years (SE)	73 (2.26)	69.5 (1.94)	68.75 (1.44)	72.5 (2.99)	71 (1.83)	75.25 (3.09)	74 (2.97)
Mean Weight in Kg (SE)	70.57 (4.27)	69.45 (3.39)	75.45 (8.43)	64.80 (6.62)	74.70 (8.14)	70.83 (5.27)	70.80 (3.58)
Caucasian, n (%)	7 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)

Pharmacokinetic (PK)/Pharmacodynamic (PD) Endpoints:

Mean (SD) Values of Main PK Parameters Obtained After Administration of FX

Dose (mg)	C _{max} (µg/mL)	T _{max} ^a (h)	T _{1/2} (h)	AUC _{0-obs} (µg.h/mL)	CL/F (mL/min)	V _d /F (L)	Ae ₀₋₂₄ (mg)	Fe ₀₋₂₄ (%)	CL _R (mL/min)
0.7	0.061 (0.043)	1.00	–	–	–	–	0.05 (0.06)	7 (9)	–
1.5	0.103 (0.038)	1.71	–	–	–	–	0.26 (0.10)	21 (8)	–
3	0.234 (0.066)	1.50	–	2.79 (1.16)	–	–	0.68 (0.16)	27 (7)	3.5 ^b (0.6)
6	0.636 (0.209)	2.25	16.8 (1.4)	12.71 (6.38)	5.7 ^b (1.9)	8.5 ^b (3.0)	1.26 ^c –	25 ^c –	2.9 ^c –
12	1.456 (0.350)	2.50	16.0 (3.7)	30.47 (2.82)	5.1 (0.4)	8.8 (2.5)	4.11 (0.76)	41 (8)	3.4 (0.3)
18	1.952 (0.219)	2.50	14.8 (2.0)	41.30 (3.67)	5.8 (0.5)	7.1 (1.9)	3.77 ^b (0.90)	25 (6)	2.3 ^b (0.7)

a. Median value

b. n=3

c. n=2

PD: Only a minor statistically insignificant increase of APTT and PT was observed with increasing doses of Org31540/SR90107A. There were no statistically significant difference in PT between males and females; but the assessment of the effect of gender on APTT was inconclusive. No statistically significant effects of drug administration were observed on bleeding time and AT-III. No measurable anti-IIa activity was observed in any of the samples.

APTT and PT ratios subject/control (mean ± SEM) predose and 4 h after drug administration (n=4)

Dose (mg)	APTT predose	APTT 4 h	PT predose	PT 4h
Placebo*	0.88 ± 0.04	0.79 ± 0.05	0.94 ± 0.02	0.96 ± 0.04
0.7	0.90 ± 0.05	0.87 ± 0.08	0.98 ± 0.03	0.96 ± 0.03
1.5	0.88 ± 0.08	0.82 ± 0.04	0.96 ± 0.04	0.94 ± 0.03
3	0.96 ± 0.03	1.00 ± 0.04	0.98 ± 0.03	1.01 ± 0.03
6	1.06 ± 0.07	1.12 ± 0.06	0.96 ± 0.02	1.05 ± 0.02
12	0.90 ± 0.03	1.06 ± 0.02	0.95 ± 0.02	1.11 ± 0.03
18	0.84 ± 0.09	0.99 ± 0.07	0.92 ± 0.02	1.01 ± 0.02

*n = 7 for placebo

Safety results:							
Adverse Events:	PBO	FX 0.7mg	FX 1.5mg	FX 3mg	FX 6mg	FX 12mg	FX 18mg
N (Total)	7	4	4	4	4	4	4
No. Subjects with AEs, n (%)	3(42.9)	2(50.0)	2(50.0)	1(25.0)	3(75.0)	1 (25.0)	2 (50.0)
Most Frequent AEs							
Purpura	0	2(50.0)	0	0	1(25.0)	0	1 (25.0)
Constipation	0	0	0	0	0	1(25.0)	2 (50.0)
Serious Adverse Events, n (%)							
[n considered by the investigator to be related, possibly related, or probably related to study medication]:							
	PBO	FX 0.7mg	FX 1.5mg	FX 3mg	FX 6mg	FX 12mg	FX 18mg
No. Subjects with SAEs (fatal and non-fatal)	0	0	0	0	0	0	0

Publications:
No Publication

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