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Study No.: ACT1840
Title: A multicentre pilot study of natural pentasaccharide (SR90107A /Org31540) for the prevention of deep venous thrombosis after total hip replacement.
Rationale: Evidence from pre-clinical animal studies and human pharmacokinetic (PK) studies indicates that fondaparinux sodium (FX), a selective inhibitor of activated factor X (factor Xa), is effective in the prevention of venous thromboembolic events (VTE), i.e. deep vein thrombosis (DVT), and/or symptomatic pulmonary embolism (PE). The clinically effective dose had yet to be established. It was planned that three dose levels be tested successively, i.e. 3 mg, 4.5 mg, and 6 mg of FX twice daily in the first part of a two-stage randomised study. The dose tested in the second stage was not to be defined until one of the groups in the first stage was found to be safe and sufficiently effective.
Phase: II
Study Period: 30 September 1993 – 13 August 1994.
Study Design: Multicentre, randomised, open-label, pilot, two-stage, low molecular weight heparin (LMWH)-calibrated study.
Centres: 9 centres in Europe: 6 France; 2 Belgium; 1 The Netherlands.
Indication: Prevention of DVT and symptomatic PE in subjects undergoing total hip replacement (THR) surgery.
Treatment: Subjects were randomly allocated in a ratio of 3:2 to receive either FX b.i.d. or nadroparin calcium (NC) once daily (o.d.) by subcutaneous (s.c.) injection for 8 days. Fondaparinux sodium was initiated as a single 2 mg dose, 10-12 hours prior to start of surgery (Day 0), which was then increased to 3 mg b.i.d. post-operatively up to Day 6. NC was administered as a 100 anti-Xa ICU dose once daily (o.d.) from Day 0 to Day 3 starting 10-12 hours prior to start of surgery (Day 0), followed by 150 anti-Xa ICU/kg o.d. from Day 4 to Day 6. An interim analysis conducted at the end of this first stage of the study concluded that no further subjects needed to be recruited for evaluation of the proximal DVT rate.
Objectives: To assess the antithrombotic effect of FX in the prevention of DVT in subjects after total hip replacement surgery.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the incidence of subjects with an independently-assessed proximal DVT.
Secondary Outcome/Efficacy Variable(s): <u>Secondary efficacy variables:</u> Incidences of distal DVT, any DVT, non-fatal and fatal PE, and possible signs and symptoms of DVT. <u>Safety variables:</u> Independently reviewed incidence of major (defined as clinically overt hemorrhage [except drain <500ml] in addition to one of the following criteria: hemoglobin level decrease or reoperation or intracranial or retroperitoneal bleeding or withdrawal of the subject) and minor (defined as non-major) bleeds and thrombopenia; laboratory variables; vital signs and ECG results. <u>Pharmacokinetics:</u> Plasma concentrations were assessed using a validated assay method with limits of quantification (LOQ) of FX 0.062 mg/L and IUAXa 0.05 /ml.
Statistical Methods: <u>Sample size:</u> In the FX groups, p_1 was defined as the incidence rate below which the drug was considered of real interest; p_0 ($>p_1$) was the incidence rate above which the drug was considered non-effective. The tested null hypothesis was $H_0: p > p_0$, and the alternative was $H_1: p < p_1$, with c defined as the DVT threshold value. It can be shown that if $p_0 = 0.20$, $p_1 = 0.10$, $n = 60$, and $c = 9$, then $\alpha = 0.213$ and $\beta = 0.073$. Therefore a FX dose was to be accepted if strictly <10 DVTs were observed in 60 evaluable subjects, with more than 90% probability of accepting H_1 if it was true, and around 20% probability of rejecting H_0 even if it was true. For the calibration group, p'_1 was defined as the incidence rate above which the performance of NC would be considered unexpectedly poor; p'_0 ($<p'_1$) was the incidence rate at the lower end of where the expectations lay. It can be shown that if $p'_0 = 0.05$, $p'_1 = 0.15$, $n' = 40$ and $c' = 4$, then $\alpha < 0.048$ and $\beta = 0.263$. Therefore the outcome was to be considered acceptable, with appropriate alpha significance level and power, if strictly less than 5 out of 40 evaluable subjects experienced a proximal DVT. If strictly more than 4 major haemorrhages were observed in a FX group, the ongoing step was to be discontinued, and a lower dose started. If strictly more than 3 major haemorrhages were observed in the calibration group, then a pre-specified decision algorithm was used. These computations were based on a tail probability lower than 5%. The sample size for the second stage was computed data-conditionally, so as to demonstrate a 90% confidence that

the true value for the proximal DVT rate is lower than 20%.

Populations analysed:

Efficacy evaluable population: subjects were included in this population if, (i) they took at least one dose of study medication and had an elective hip operation, and (ii) had a proximal DVT confirmed by phlebography or had a bilateral phlebography performed within one day of Study Day 7, which was adequate for interpretation.

Compliant completers' population: Subjects were included in this population, if in addition to being considered evaluable, they took all study medication and had no protocol violations.

Intent-to treat (ITT)/safety population: subjects were included in this population if they took at least one dose of study medication and had an elective hip operation.

Statistical tests used: For the primary efficacy variable of proximal DVT, the probability that the FX incidence rate was from a population with a proximal DVT rate of 10%, 15% and 20% was to be computed in each group. In addition, the relative risks of proximal DVT in the FX group compared with the NC group were to be estimated and confidence intervals computed by the Taylor method.

Study Population: Men or post-menopausal women ≥ 40 years of age, undergoing surgery for total hip replacement (single non revision total hip replacement), were eligible for participation in the study. Subjects were excluded if they had had a trauma or surgical operation within the previous 3 months; previously had DVT/PE or stroke/myocardial infarction (within last 6 months); known congenital or acquired bleeding tendency, or bleeding tendency revealed by a pre-operative test; recent (≤ 4 weeks) or present history of gastrointestinal bleeding or peptic ulcer; hypertension; severe renal insufficiency; had received one of a number of forbidden drugs which could not be stopped in time for entry into the study (e.g., fibrinolytics within 1 week prior to study start).

	FX 3 mg b.i.d.			NC (100-150 anti-Xa ICU)		
Number of subjects:						
Planned enrolment, N	60			40		
Randomised, N	69			46		
Randomised and treated (ITT population), N	64			45		
Subjects with venograms, N	61			42		
Efficacy evaluable population, N	58			42		
Completer compliant population, N	54			36		
Completed study drug, n (% of all randomized subjects)	64 (92.8)			42 (91.3)		
Total number of subjects withdrawn from study drug, n (% of all randomized subjects)	5 (7.2)			4 (8.7)		
Withdrawn due to AEs/SAEs, n (%)	2 (2.9)			0		
Withdrawn due to lack of efficacy, n (%)	1(1.4)			1 (3.6)		
Withdrawn for other reasons, n (%)	2 (2.8)			3(1.2)		
Demographics:	FX 3 mg b.i.d.			NC (100-150 anti-Xa ICU)		
N (ITT population)	64			45		
Females: Males	39:25			28:17		
Mean Age, years (SD)	65.9 (9.6)			66.8 (8.8)		
Caucasian, n (%)	Not stated (NS)			NS		
Primary Efficacy Results:						
Subjects with proximal DVT	FX 3 mg b.i.d.			NC (100-150 anti-Xa ICU)		
	N	n (%)	Incidence rate [95% CI]	N	n (%)	Incidence rate [95% CI]
ITT population	64	7 (10.9)	0.11 [0.045, 0.212]	45	6 (13.3)	0.13 [0.051, 0.268]
Evaluable population	58	2 (3.4)	0.03 [0.004, 0.119]	42	3 (7.1)	0.07 [0.015, 0.195]
Compliant completer population	54	2 (3.7)	0.04 [0.005, 0.127]	36	3 (8.3)	0.08 [0.018, 0.225]
Statistical analysis	Within FX group			FX versus NC		
	Incidence	p-value		Relative risk [95% CI]		

	rate	10%	15%	20%	
ITT population	0.11	0.616	0.474	0.084	0.82 [0.295,2.279]
Evaluable population	0.03	0.124	0.010	0.001	0.48 [0.084,2.763]
Compliant completer population	0.04	0.167	0.017	0.001	0.44 [0.078,2.529]
Secondary Outcome Variable(s):					
Subjects with distal DVT	FX 3 mg b.i.d.			NC (100-150 anti-Xa ICU)	
	N	n (%)	Incidence rate [95% CI]	N	n (%) Incidence rate [95% CI]
ITT population	64	5 (7.8)	0.08 [0.026, 0.173]	45	13 (28.9) 0.29 [0.164, 0.443]
Evaluable population	58	1 (1.7)	0.02 [0.000, 0.092]	42	10 (23.8) 0.24 [0.121, 0.395]
Compliant completer population	54	1 (1.9)	0.02 [0.000, 0.099]	36	10 (27.8) 0.28 [0.142, 0.452]
Statistical analysis FX vs NC					
Relative risk [95% CI]					
ITT					
0.27 [0.104, 0.705]					
Evaluable population					
0.07 [0.010, 0.544]					
Compliant completer population					
0.07 [0.009, 0.499]					
Subjects with any DVT	FX 3 mg b.i.d.			NC (100-150 anti-Xa ICU)	
	N	n (%)	Incidence rate [95% CI]	N	n (%) Incidence rate [95% CI]
ITT population	64	8 (12.5)	0.13 [0.056, 0.232]	45	14 (31.1) 0.31 [0.182, 0.466]
Evaluable population	58	3 (5.2)	0.05 [0.011, 0.144]	42	11 (26.2) 0.26 [0.139, 0.420]
Compliant completer population	54	3 (5.6)	0.06 [0.012, 0.154]	36	11 (30.6) 0.31 [0.163, 0.481]
Statistical analysis FX-NC					
Relative risk [95% CI]					
ITT					
0.40 [0.184, 0.877]					
Evaluable population					
0.20 [0.059, 0.664]					
Compliant completer population					
0.18 [0.054, 0.607]					
Subjects with PE (ITT population)	FX 3 mg b.i.d. (N = 64)			NC (100-150 anti-Xa ICU) (N = 45)	
N (%)	0			0	
Safety results:					
Incidence of independently reviewed bleeding (ITT population)	FX 3 mg b.i.d. (N = 64)			NC (100-150 anti-Xa ICU) (N = 45)	
Major bleeding, n (%)	3 (4.7)			0	
Minor bleeding, n (%)	12 (18.8)			4 (8.9)	
Any bleeding, n (%)	15 (23.4)			4 (8.9)	
Thrombopenia, n (%)	7 (10.9)			2 (4.4)	
Adverse event results: AEs were defined as those observed and/or reported during the study.					
Adverse Events (ITT population)	FX 3 mg b.i.d. (N = 64)			NC (100-150 anti-Xa ICU) (N = 45)	
Subjects with any AE(s), n (%)	37 (57.8)			26 (57.8)	
10 most frequent AEs in each treatment group, n (%):					
Anaemia	11 (17.2)			1 (2.2)	
Liver function tests abnormal	7 (10.9)			3 (6.7)	
Diarrhoea	4 (6.3)			2 (4.4)	
Pain	5 (7.8)			1 (2.2)	

Vesiculobullous rash	5 (7.8)	1 (2.2)				
Gamma glutamyl transpeptidase increased	4 (6.3)	1 (2.2)				
Fever	3 (4.7)	2 (4.4)				
Nausea	2 (3.1)	2 (4.4)				
Haemorrhage	2 (3.1)	1 (2.2)				
Erythrocytes abnormal	2 (3.1)	1 (2.2)				
Electrocardiogram abnormal	2 (3.1)	0				
Hypokalemia	0	2 (4.4)				
Abdominal pain	0	2 (4.4)				
Vomiting	0	2 (4.4)				
Serious Adverse Events: SAEs were defined as those observed and/or reported during the study						
All SAEs (non-fatal) (ITT population)	FX 3 mg b.i.d. (N = 64)	NC (100-150 anti-Xa ICU) (N = 45)				
	n (%) [n related]	n (%) [n related]				
Subjects with any SAE(s) [number considered by Investigator to be related to study medication; for all others the relationship was unknown]	4 (6.3) [2]	0 [0]				
Haemorrhage	2 (3.2) [1]	0 [0]				
Anaemia	1 (1.6) [1]	0 [0]				
Pain	1 (1.6) [0]	0 [0]				
Subjects with fatal SAEs	None					
Pharmacokinetics:						
	FX 3 mg b.i.d.			NC (100-150 anti-Xa ICU)		
Plasma concentration	FX mg/L			AntiXa IU/ml		
N	54	55	55	37	37	40
Day	0	1	5	0	1	5
Mean (SD)	0.17 (0.10)	0.54 (0.22)	0.80 (0.31)	0.09 (0.05)	0.21 (0.08)	0.28 (0.13)
Median (minimum-maximum)	0.15 (0.00-0.56)	0.49 (0.16-1.25)	0.74 (0.24-2.00)	0.07 (0.00-0.20)	0.20 (-0.02-0.42)	0.26 (0.00-0.70)

Conclusion:

The proximal DVT rate in the FX group was statistically significantly lower than the pre-specified cut-off rate of 15% for the evaluable and compliant completer populations, but not the ITT population. However the relative risk versus NC had a wide CI and therefore no distinction between the treatment groups could be made. The incidence of distal DVTs and any DVT was lower in the FX group than in the NC group. No subjects experienced a PE. In the FX group 37 subjects reported non-serious AEs with the most frequently reported being anemia and abnormal liver function tests. In the NC group 26 subjects reported non-serious AEs with the most frequently reported being abnormal liver function tests, diarrhea, fever and nausea. Four SAEs were reported in the FX group – 2 hemorrhages, 1 case of anemia and 1 case of pain. No SAEs were reported in the NC group. No fatalities were reported in the study.

Publications:

No Publication

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