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<b>Study No.:</b> ACT2545
<b>Title:</b> A multicentre dose finding study of once daily injection of Natural Pentasaccharide for the prevention of deep vein thrombosis after total hip replacement.
<b>Rationale:</b> A previous clinical study in man of fondaparinux sodium (FX), a selective inhibitor of activated factor X (factor Xa), indicated that a 3 mg twice daily (b.i.d.) dose may be effective in the prevention of thrombosis. However, the long-half life of FX indicated that it may also be efficacious when administered once daily (o.d.).
<b>Phase:</b> IIa
<b>Study Period:</b> January 1995 to December 1995.
<b>Study Design:</b> Multicentre, randomised, open-label, dose finding study, with an enoxaparin (EN) calibration group (CG). Randomization was stratified by mode of anesthesia (general or spinal/epidural).
<b>Centres:</b> 19 centres in 3 countries: 10 France, 5 The Netherlands, 4 Belgium.
<b>Indication:</b> Prevention of deep vein thrombosis (DVT) and symptomatic pulmonary embolism (PE) in subjects undergoing total hip replacement (THR) surgery.
<b>Treatment:</b> Subjects were randomly allocated to receive either FX o.d. or EN o.d. by subcutaneous (s.c.) injection in 2 phases: Phase I: FX 4 mg o.d. or EN 40 mg o.d (1 <sup>st</sup> CG) or Phase II FX 2 mg o.d. or EN 40 mg o.d (2 <sup>nd</sup> CG). FX was administered for 7 days from Day 2 (first injection planned 6 hours after surgery) to Day 8. EN was administered for 8 days, from Day 1 to Day 8, (first injection planned 12 hours before surgery and the first post-operative injection planned 6 hours after surgery).
<b>Objectives:</b> To assess antithrombotic effect and safety of o.d. FX injection starting post-operatively in DVT prophylaxis to subjects undergoing total hip replacement.
<b>Primary Outcome/Efficacy Variable:</b> The primary endpoint was the incidence of any DVT; DVT was assessed on Day 8 ±1 by phlebography. A central evaluation was performed blindly by two independent experts.
<b>Secondary Outcome/Efficacy Variable(s)</b> <u>Secondary efficacy variables:</u> Incidences of proximal and distal DVT; incidence of non-fatal and fatal pulmonary embolism (PE). <u>Safety variables:</u> Major and minor bleeding rates evaluated blindly by an independent committee. Major bleeding was defined as a clinically overt hemorrhage (except drain <500 mL/day) in addition to one of the following criteria: hemoglobin reduction to <8 g/dL or hemoglobin decrease >2 g/dL over any 48-hour period between Day 3 and Day 9 inclusive, or reoperation or intracranial bleeding or retroperitoneal or withdrawn. Minor bleeding was defined as bleeding not meeting the criteria for major bleeding. Other safety variables were adverse events (AEs). <u>Pharmacokinetics:</u> Plasma concentrations were assessed at inclusion, on Day 2 pre-operatively and 2 hours post-dosing, and on Days 3, 5 and 7 before dosing and 2 hours post-dosing. The limits of quantification (LOQ) were 0.062 mg/L for FX and 0.05 IUAXa/mL for EN. Because the calibration curves of the two assay methods used different standards, anti-Xa activity of the two drugs was expressed in two different units, mg/L for FX and IUAXa/mL for EN. For this reason, the anti-Xa activity of the two drugs cannot be compared.
<b>Statistical Methods:</b> <u>Sample size:</u> A total of 60 evaluable subjects in the FX groups and 30 evaluable subjects with EN in each step were required by the protocol. Success of a FX dose regimen was defined as the Bayesian probability (P) that the event rate was < x % was greater than 80%. With x = 15 % for DVT and x = 6 % for major bleeding, a FX dose was to be accepted if strictly less than 7 DVTs (P = 0.864) and less than 3 cases of major bleeding (P = 0.803) were observed in 60 subjects. It can be shown that if x = 15 %, then EN outcome was considered acceptable if strictly less than 3 subjects out of 30 experience a DVT. <u>Populations analysed:</u> <i>Intent-to-treat (ITT) population:</i> this population included all subjects who received at least one study drug injection. <i>Per protocol (PP) population:</i> Subjects were included in this population if they did not have major protocol violations. They were excluded if they refused to continue in the study for the maximum study treatment period possible; they did not have a phlebography or had a phlebography inadequate for interpretation; had only an unilateral phlebography (unless a proximal DVT was shown); had phlebography excluding venous thrombosis performed before Day 7 or after Day 9; they had not received surgery. <u>Statistical tests used:</u> The numbers of subjects with any DVTs, proximal DVTs and distal DVTs were summarised using counts and percentages. Exact 95% confidence intervals (CIs) were computed in the two FX groups and in the EN groups

(combined or not) on the PP and ITT populations. Relative risks between FX groups and EN groups (combined or not) were estimated, and 90% CIs, using Taylor's method, were computed on the PP population.

Haemorrhages deemed as major by the independent committee were summarised using counts and percentages, and exact 95% CIs computed. EN groups were combined.

Plasma concentrations before dosing and 2 hours post-dosing were summarised at each time point using the mean and standard deviation (SD).

**Study Population:** Men or post-menopausal women aged >40 years with a body weight 50-100 kg inclusive, who were undergoing first single non revision total hip replacement (subsequently amended to non revision total hip replacement), with no contra-indication to undergo a phlebography on Day 8 ± 1. Subjects were excluded from study participation based on their bleeding risk at the time of randomisation (eg known bleeding tendency, thrombocytes <150x10<sup>9</sup>/l, prothrombin time <65%, APTT/control >1.2 or other medical condition associated with a bleeding risk), or other significant conditions (eg history of PE or DVT, serum creatinine >2.3mg% (200umol/L), severe hepatic disease or uncontrolled severe high blood pressure SBP/DBP >200/120mmHg) or use of anticoagulant or fibrinolytic therapy within 1 week prior to randomisation.

	<b>FX 4 mg</b>	<b>FX 2 mg</b>	<b>EN 40 mg</b>
Number of subjects:			
Planned enrolment, N	100	100	100
Randomised, N	86	78	79
Randomised and treated (ITT population), N	77	77	75
PP population, N	63	61	62
Completed study drug, n (%)	82 (95.3)	75 (96.2)	76 (96.2)
Total number of subjects withdrawn from study drug, n (%)	4 (4.7)	3 (3.8)	3 (3.8)
Withdrawn due to AEs/SAEs, n (%)	1 (1.2)	1 (1.3)	1 (1.3)
Withdrawn due to lack of efficacy, n (%)	1 (1.2)	0	1 (1.3)
Withdrawn for other reasons, n (%)	2 (2.3)	2 (2.6)	1 (1.3)
<b>Demographics:</b>	<b>FX 4 mg</b>	<b>FX 2 mg</b>	<b>EN 40 mg</b>
N (ITT population)	77	77	75
Females: Males	44:33	47:30	37:38
Mean Age, years (SD)	65.6 (10.7)	66.9 (8.9)	64.5 (9.9)
Caucasian, n (%)	75 (97.4)	77 (100.0)	75 (100.0)
<b>Primary Efficacy Results:</b>			
<b>Subjects with DVT (PP population)</b>			
	<b>FX 4mg (N = 63)</b>	<b>EN 40 mg (1<sup>st</sup> CG) (N = 32)</b>	
Total DVTs, n (%) [95% CI]	6 (9.52) [3.58, 19.59]	3 (9.38) [1.98, 25.02]	
Relative risk (All DVTs) [90% CI]	1.02 [0.34, 3.07]		
	<b>FX 2mg (N = 61)</b>	<b>EN 40 mg (2<sup>nd</sup> CG) (N = 30)</b>	
Total DVTs, n (%) [95% CI]	8 (13.11) [5.84, 24.22]	1 (3.33) [0.08, 17.22]	
Relative risk (All DVTs) [90% CI]	3.93 [0.72, 21.66]		
<b>EN groups combined</b>	<b>FX (Not applicable)</b>	<b>EN 40 mg (N = 62)</b>	
Total DVTs, n (%) [95% CI]	-	4 (6.45) [1.79, 15.70]	
<b>Subjects with DVT (ITT population)</b>			
	<b>FX 4mg (N = 77)</b>	<b>EN 40 mg (1<sup>st</sup> CG) (N = 42)</b>	
Total DVTs, n (%) [95% CI]	20 (25.97) [16.64, 37.23]	13 (30.95) [17.62, 47.09]	
	<b>FX 2mg (N = 77)</b>	<b>EN 40 mg (2<sup>nd</sup> CG) (N = 33)</b>	

Total DVTs, n (%) [95% CI]	24 (31.17) [21.09, 42.74]	4 (12.12) [3.40, 28.20]	
<b>EN groups combined</b>	<b>FX (Not applicable)</b>	<b>EN 40 mg (N = 75)</b>	
Total DVTs, n (%) [95% CI]	-	17 (22.67) [13.79, 33.79]	
<b>Secondary Outcome Variable(s):</b>			
<b>Subjects with proximal and distal DVT (PP population)</b>			
	<b>FX 4mg (N = 63)</b>	<b>EN 40 mg (1<sup>st</sup> CG) (N = 32)</b>	
Proximal DVTs, n (%) [95% CI]	5 (7.94) [2.63, 17.56]	1 (3.13) [0.08, 16.22]	
Distal DVTs, n (%) [95% CI]	3 (4.76) [0.99, 13.29]	3 (9.38) [1.98, 25.02]	
	<b>FX 2mg (N = 61)</b>	<b>EN 40 mg (2<sup>nd</sup> CG) (N = 30)</b>	
Proximal DVTs, n (%) [95% CI]	2 (3.28) [0.40, 11.35]	1 (3.33) [0.08, 17.22]	
Distal DVTs, n (%) [95% CI]	6 (9.84) [3.70, 20.19]	0 [0, 11.57]	
	<b>EN groups combined</b>		
	<b>FX (Not applicable)</b>	<b>EN 40 mg (N = 62)</b>	
Proximal DVTs, n (%) [95% CI]	-	2 (3.23) [0.39, 11.17]	
Distal DVTs, n (%) [95% CI]	-	3 (4.84) [1.01, 13.50]	
<b>Subjects with PE: None reported</b>			
<b>Safety results:</b>			
<b>Incidence of bleeding (ITT population)</b>	<b>FX 4 mg (N = 77)</b>	<b>FX 2 mg (N = 77)</b>	<b>EN 40 mg (N = 75)</b>
Major bleeding, n (%) [95% CI]	2 (2.6) [0.32, 9.07]	1 (1.3) [0.03, 7.02]	3 (4.0) [0.83, 11.25]
Minor bleeding, n (%)	18 (23.4%)	18 (23.4%)	10 (13.3%)
<b>Adverse event results: AEs were reported during the study period up to Day 10.</b>			
<b>Adverse Events (ITT population)</b>	<b>FX 4 mg (N = 77)</b>	<b>FX 2 mg (N = 77)</b>	<b>EN 40 mg (N = 75)</b>
Subjects with any AE(s), n (%)	41 (53.3)	47 (61.0)	42 (56.0)
Most frequent AEs in each treatment group, n (%):			
Haemorrhage of operative wound	14 (18.2)	13 (16.9)	11 (14.7)
Anaemia	5 (6.5)	13 (16.9)	10 (13.3)
Nausea	6 (7.8)	10 (13.0)	8 (10.7)
Vomiting	5 (6.5)	10 (13.0)	6 (8.0)
Hypotension	5 (6.5)	7 (9.1)	10 (13.3)
Injection site reaction	5 (6.5)	6 (7.8)	2 (2.7)
Fever	1 (1.3)	2 (2.6)	5 (6.7)
Insomnia	5 (6.5)	0	3 (4.0)
Pain	4 (5.2)	2 (2.6)	2 (2.7)
Dizziness	4 (5.2)	1 (1.3)	0
Abdominal pain	1 (1.3)	2 (2.6)	3 (4.0)
Urinary tract infection	3 (3.9)	0	2 (2.7)
Hematoma	2 (2.6)	3 (3.9)	0
Headache	1 (1.3)	3 (3.9)	1 (1.3)
Urinary retention	3 (3.9)	1 (1.3)	0
Diarrhoea	2 (2.6)	2 (2.6)	1 (1.3)
Healing impaired	1 (1.3)	3 (3.9)	0
Accidental injury	2 (2.6)	2 (2.6)	2 (2.7)
Rash maculo-papular	1 (1.3)	2 (2.6)	2 (2.7)
Constipation	1 (1.3)	2 (2.6)	1 (1.3)
Hepatic enzymes increased	0	2 (2.6)	1 (1.3)
Allergic reaction	0	2 (2.6)	0
<b>Serious Adverse Events</b>			

All SAEs (non-fatal) (ITT population)	FX 4 mg (N = 77)	FX 2 mg (N = 77)	EN 40 mg (N = 75)
	n (%)	n (%)	n (%)
<b>Subjects with any SAE(s) [n considered by Investigator to be related to study medication]</b>	5 (6.5) [1]	3 (3.9) [1]	4 (5.3) [3]
Haemorrhage of operative wound	4 (5.2) [1]	1 (1.3) [0]	3 (4.0) [2]
Anaemia	1 (1.3) [0]	0	1 (1.3) [0]
Accidental injury	1 (1.3) [0]	1 (1.3) [0]	0
Infection	1 (1.3) [0]	0	0
Hepatic enzymes increased	0	1 (1.3) [0]	0
Gastrointestinal haemorrhage	0	0	1 (1.3) [1]
<b>Subjects with fatal SAEs:</b>	0	0	0
<b>Pharmacokinetics:</b>			
	FX 4 mg	FX 2 mg	EN 40 mg
<b>Plasma concentrations before dosing</b>	<b>Mg/L</b>	<b>Mg/L</b>	<b>IUAXa/mL</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
	<b>N</b>	<b>N</b>	<b>N</b>
Day 0	0 69	0 68	0.006(0.021) 68
Day 3	0.193(0.087) 70	0.086(0.075) 67	0.83(0.078) 61
Day 5	0.192(0.125) 46	0.090(0.066) 38	0.030(0.065) 35
Day 7	0.241(0.143) 46	0.132(0.097) 51	0.036(0.058) 47
<b>Plasma concentrations 2 hours after dosing</b>	<b>Mg/L</b>	<b>Mg/L</b>	<b>IUAXa/mL</b>
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
	<b>N</b>	<b>N</b>	<b>N</b>
Day 3	0.601(0.234) 71	0.367(0.156) 65	0.329(0.138) 61
Day 5	0.678(0.213) 45	0.400(0.147) 38	0.344(0.148) 36
Day 7	0.768(0.359) 48	0.431(0.170) 50	0.299(0.119) 43

**Conclusion:**

The study suggests that a 4 mg daily dose of FX started post-operatively has an antithrombotic effect in subjects undergoing total hip replacement. This was supported by the results with a 2 mg daily dose of FX. The incidence of major bleeding was <3% at these two FX doses. Adverse events were reported in 41(53%) of the 4mg FX group, 47 (61%) of the 2 mg FX group, and 42 (56%) of the EN group. The most frequently reported adverse events were hemorrhage of operative wound, anemia, nausea, vomiting, and hypotension. SAEs were reported in 5 (6.5%) and 2 (3.9%) subjects in the FX 4mg and 2mg groups respectively, and in 4 (5.3%) subjects in the EN group. There were no deaths reported in any group.

**Publications:**

Pentasaccharide org31540/sr90107a clinical trials update: lessons for practice. Turpie, A. G. Am Heart J 2001; 142(2 Suppl):S9-15

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