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Study No.: 095-002
Title: A multicenter, multinational, randomized, double-blind comparison of subcutaneous Org31540/SR90107A with enoxaparin in the prevention of deep vein thrombosis and symptomatic pulmonary embolism after elective major knee surgery or a revision (PENTAMAKS).
Rationale: Studies have shown that fondaparinux (FX), a selective inhibitor of activated factor X (factor Xa), at a 2.5 mg once daily (o.d.) dose may be appropriate for prevention of venous thromboembolic events (VTE), i.e. deep vein thrombosis (DVT), and/or symptomatic pulmonary embolism (PE), which are major post-operative complications following orthopaedic surgery of the lower limbs. In this pivotal confirmatory study, FX 2.5 mg once daily (o.d.) was compared with low molecular weight heparin, (LMWH enoxaparin [EN] 30 mg twice daily [b.i.d.]) for prophylaxis of VTE in subjects who had undergone elective major knee surgery or a revision of component(s).
Phase: III
Study Period: 24 December 1998 – 17 January 2000.
Study Design: Multinational, multicentre, randomised, double-blind, parallel-group study.
Centres: 54 study centres in the USA and 10 centres in Canada.
Indication: Prevention of DVT and symptomatic PE in subjects undergoing elective major knee surgery or a revision of at least 1 component. Elective major knee surgery was defined as surgery requiring resection of the distal end of the femur or proximal end of the tibia.
Treatment: The administration of FX (2.5 mg o.d. as subcutaneous [s.c.] injection) started 6 ± 2 hours after surgical closure on Day 1 (day of surgery) and that of EN (30 mg b.i.d. as s.c. injection) at least 12 hours but less than 24 hours after surgical closure. To protect the blind (double-dummy method) all subjects received placebo (PBO) to the active treatment they were not receiving. Study treatment was given up to 7 ± 2 days after surgical closure or until the final venogram (positive unscheduled or mandatory) was obtained, whichever came first. A mandatory venogram had to be performed between Day 5 and Day 11, but not more than 2 calendar days after the last study treatment administration.
Objectives: To demonstrate superior efficacy of o.d., post-operative, s.c. injection of FX 2.5 mg compared to b.i.d., post-operative, s.c. injection of EN 30 mg in the prevention of VTEs (DVT and PE) in subjects undergoing elective major knee surgery or a revision of component(s).
Primary Outcome/Efficacy Variable: The primary endpoint was the cluster of the following VTE outcomes recorded up to Day 11: adjudicated venogram positive for DVT or adjudicated symptomatic or asymptomatic DVT; adjudicated non-fatal PE or fatal PE. All venograms, scheduled or unscheduled, were adjudicated by a blinded Central Independent Adjudication Committee (CIAC).
Secondary Outcome/Efficacy Variable(s): <u>Secondary efficacy variables:</u> All DVTs, all proximal DVTs, distal DVTs only, and non-fatal or fatal symptomatic PEs, up to Day 11; adjudicated symptomatic VTEs up to Day 49. Institution of curative treatment by the Investigator after local VTE assessment was also reported.
Statistical Methods: <u>Sample size:</u> Based on a Phase II study of VTE prophylaxis during knee replacement, the DVT and/or PE rate was 17.7% with a 95% CI of [10%,29%] for the FX 3.0 mg group and 28.8% with a 95% CI of [19%,42%] for the FX 1.5 mg group. In the current study, a dose of FX 2.5mg was used. Based on publications and the Phase II knee replacement study, it was assumed that the DVT rate for EN was between 25% and 34%. Sample size was calculated for various scenarios of estimated event rates. A sample size of 319 evaluable subjects per group would allow the detection of a difference of 23% and 34% between FX and EN (based on 2-sided chi-square test with continuity correction, and using a type-I error of 5% and 85% power). Thus, approximately 912 subjects were to be randomised, assuming an approximate 30% non-evaluable rate. <u>Populations analysed:</u> <i>All treated subjects (ATS) population:</i> This population, included in the safety analyses, was defined as all randomised subjects who received at least one dose of study drug (active drug or PBO). <i>Primary efficacy population:</i> This population, included in the primary efficacy analysis, was a subset of the all treated subjects population that included subjects who underwent the appropriate surgery (i.e., elective major knee surgery) and had a VTE assessment up to Day 11. All efficacy parameters were analysed according to the intent-to-treat (ITT) principle. <u>Statistical tests used:</u> The VTE, DVT, proximal DVT, and symptomatic VTE rates up to Day 11, the symptomatic VTE rate up to Day 49, and

the incidences of major bleeding and minor bleeding only up to Day 11 and up to Day 49 were compared between the two treatment groups using a 2-sided Fisher's exact test; 95% 2-sided exact confidence intervals (CIs) on the differences were calculated. Statistical comparisons of safety data (other than major bleeding) were made using a Chi-square test for categorical data, and 2-sample t-tests for continuous data.

Study Population: .The study population had to conform to the following criteria: men or women (of non-childbearing potential, i.e., post-menopausal or with hysterectomy or bilateral tubal ligation), or women of childbearing potential using highly effective birth control and having a negative pregnancy test within 48 hours prior to randomisation; aged ≥ 18 years; undergoing either an elective major knee surgery or a revision of at least one component (enrollment of subjects with surgery limited to an osteotomy was not permitted); and haemostasis established on the calendar day of surgery, no later than 8 hours after closure of the incision. Exclusion criteria were based on the labelling of LMWH in force at the time of study conduct (eg active clinically significant bleeding, presence or history of low platelet count ($<100 \times 10^9/L$), medical condition associated with a bleeding risk), or those relating to contrast dyes during venography (eg serum creatinine $>2\text{mg/dL}$ ($180\mu\text{mol/L}$) or hypersensitivity to contrast media).

	FX 2.5 mg o.d.	EN 30 mg b.i.d
Number of subjects:		
Planned enrolment (evaluable), N	456 (319)	456 (319)
Randomised, N	526	523
Randomised and treated, N (ATS population)	517	517
All treated subjects with appropriate surgery, N	517	517
Primary efficacy population, N	361	363
Completed study drug, n (% of ATS population)	481 (93.0)	481 (93.0)
Total Number Subjects Withdrawn from study drug, n (% of ATS population)	36 (7.0)	36 (7.0)
Withdrawn due to AEs/SAEs, n (% of ATS population)	20 (3.9)	13 (2.5)
Withdrawn due to lack of efficacy, n (% of ATS population)	2 (0.4)	6 (1.2)
Withdrawn consent, n (% of ATS population)	7 (1.4)	11 (2.1)
Withdrawn for other reasons, n (% of ATS population)	7 (1.4)	6 (1.2)
Demographics: (ATS population)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
Females:Males	313:204	294:223
Mean Age, years (SD)	67.5 (10.7)	67.5 (10.2)
Caucasian, n (%)	465 (89.9)	449 (86.8)
Primary Efficacy Results:		
Subjects with adjudicated VTE with a qualifying examination up to Day 11 (Primary efficacy population)	FX 2.5 mg o.d. (N = 361)	EN 30 mg b.i.d (N = 363)
n (%)	45 (12.5)	101 (27.8)
95% CI	[9.2, 16.3]	[23.3, 32.7]
Difference (FX - EN), %	-15.4	
Exact 95% CI for difference	-22.3, -9.3	
p-value (Fisher's exact test)	<0.001	
Secondary Outcome Variable(s):		
Subjects with adjudicated examination for assessment of DVT up to Day 11 by location of DVT (Efficacy evaluable subjects)	FX 2.5 mg o.d.	EN 30 mg b.i.d
Any DVT (either side)		
n/N (%)	45/361 (12.5)	98/361 (27.1)
95% CI	[9.2, 16.3]	[22.6, 32.0]
Difference (FX - EN)	-14.7	
Exact 95% CI for difference	[-21.4, -8.4]	
Any proximal DVT (either side)		
n/N (%)	9/368 (2.4)	20/372 (5.4)
95% CI	[1.1, 4.6]	[3.3, 8.2]
Difference (FX - EN)	-2.9	
Exact 95% CI for difference	[-7.6, 0.4]	
Distal DVT only (either side)		
n/N (%)	35/372 (9.4)	78/366 (21.3)

95% CI	[6.6, 12.8]	[17.2, 25.9]
Subjects with non-fatal PE up to Day 11 (All treated subjects who underwent appropriate surgery)	FX	EN
n/N (%)	1/517 (0.2)	4/517 (0.8)
Subjects with fatal PE up to Day 11 (All treated subjects who underwent appropriate surgery)	FX	EN
n/N (%)	0/517 (0)	0/517 (0)
All subjects who initiated curative antithrombotic treatment based on any investigator assessment of VTE (all treated subjects population)	FX 2.5 mg o.d. (N = 443)^a	EN 30 mg b.i.d (N = 442)^a
Total, n (%)	67 (15.1)	111 (25.1)
Heparin (UFH, LMWH)/heparinoids ^b , n (%)	50 (11.3)	76 (17.2)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids, n (%)	7 (1.6)	25 (5.7)
Other than heparin or vitamin K antagonist, n (%)	5 (1.1)	4 (0.9)
No medication reported, n (%)	5 (1.1)	6 (1.4)
All subjects with curative antithrombotic treatment based on the qualifying VTE assessment (Primary efficacy population)	FX 2.5 mg o.d. (N = 361)	EN 30 mg b.i.d (N = 363)
Total, n (%)	54 (15.0)	100 (27.5)
Heparin (UFH, LMWH)/heparinoids, n (%)	40 (11.1)	67 (18.5)
Vitamin K antagonist without heparin ^b (UFH, LMWH)/heparinoids, n (%)	7 (1.9)	23 (6.3)
Other than heparin or vitamin K antagonist, n (%)	4 (1.1)	4 (1.1)
No medication reported, n (%)	3 (0.8)	6 (1.7)
^a Number of subjects with any VTE assessment up to Day 11		
^b Did not take into account heparin flushes up to 200 IU/day		
Adjudicated symptomatic VTE (all treated subjects who underwent appropriate surgery)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
Up to Day 11, n (%)	3 (0.6)	7 (1.4)
95% confidence interval (CI)	[0.1, 1.7]	[0.5, 2.8]
Difference (FX - EN)	-0.8	
Exact 95% CI for difference	[-3.3, 1.1]	
Up to Day 49, n/N (%)	5 (1.0)	10 (1.9)
95% confidence interval (CI)	[0.3, 2.2]	[0.9, 3.5]
Difference (FX - EN)	-1.0	
Exact 95% CI for difference	[-3.8, 1.1]	
Safety results:		
Bleeding results (all treated subjects population)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
Adjudicated bleeding up to Day 11, n (%)		
Major bleeding	11 (2.1)	1 (0.2)
Fatal bleeding	0	0
Minor bleeding only	14 (2.7)	19 (3.7)
Any bleeding	25 (4.8)	20 (3.9)
Adjudicated bleeding up to Day 49, n (%)		
Major bleeding	11 (2.1)	2 (0.4)
Fatal bleeding	0	0
Minor bleeding only	16 (3.1)	19 (3.7)
Any bleeding	27 (5.2)	21 (4.1)
Post-operative transfusion, n (%)		
Up to Day 11	222 (42.9)	197 (38.1)
Up to Day 49	224 (43.3)	197 (38.1)
Adverse event results: On-therapy AEs were defined with onset during 2 periods of time, the period between the first injection (active or not) and Day 11, and the period between the first injection and Day 49. When an event began in the first period and became serious or led to death after Day 11, the event was not counted as serious or death during the first period.		

Adverse Events – On-Therapy from time of first injection to Day 11 (all treated subjects population)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
Subjects with any AE(s), n (%)	424 (82.0)	419 (81.0)
10 Most frequent AEs in each treatment group, n (%):		
Anaemia	135 (26.1)	109 (21.1)
Fever	134 (25.9)	157 (30.4)
Nausea	101 (19.5)	98 (19.0)
Oedema	70 (13.5)	63 (12.2)
Constipation	67 (13.0)	59 (11.4)
Purpura	46 (8.9)	49 (9.5)
Rash erythematous	41 (7.9)	36 (7.0)
Vomiting	41 (7.9)	40 (7.7)
Urinary retention	36 (7.0)	29 (5.6)
Pruritis	35 (6.8)	29 (5.6)
Hypokalaemia	33 (6.4)	50 (9.7)
Confusion	33 (6.4)	29 (5.6)
Adverse Events – On-Therapy from time of first injection to Day 49 (all treated subjects population)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
Subjects with any AE(s), n (%)	430 (83.2)	427 (82.6)
10 Most frequent AEs in each treatment group, n (%):		
Anaemia	138 (26.7)	111 (21.5)
Fever	137 (26.5)	160 (30.9)
Nausea	103 (19.9)	99 (19.1)
Oedema	72 (13.9)	69 (13.3)
Constipation	71 (13.7)	61 (11.8)
Purpura	48 (9.3)	50 (9.7)
Rash erythematous	44 (8.5)	37 (7.2)
Vomiting	41 (7.9)	40 (7.7)
Pruritis	37 (7.2)	31 (6.0)
Urinary retention	36 (7.0)	29 (5.6)
Hypokalaemia	33 (6.4)	50 (9.7)
Serious Adverse Events		
All SAEs (fatal & non-fatal) - On-therapy from first injection to Day 11 (all treated subjects population)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
	n (%)	n (%)
Subjects with any SAE(s) [Relationship to study drug judged as likely]	38 (7.4) [6]	28 (5.4) [3]
Anaemia	5 (1.0) [1]	2 (0.4) [1]
Fever	3 (0.6) [1]	1 (0.2) [0]
Post-operative wound infection	3 (0.6) [1]	0
Cellulitis	2 (0.4) [0]	2 (0.4) [0]
Tachycardia supraventricular	2 (0.4) [0]	1 (0.2) [0]
Pneumonia	2 (0.4) [0]	0
Ileus	1 (0.2) [1]	3 (0.6) [0]
Haematoma	1 (0.2) [1]	2 (0.4) [2]
Arrhythmia	1 (0.2) [0]	1 (0.2) [0]
Fibrillation atrial	1 (0.2) [0]	1 (0.2) [0]
Myocardial infarction	1 (0.2) [0]	1 (0.2) [0]
Nausea	1 (0.2) [0]	1 (0.2) [0]
Pain	1 (0.2) [0]	1 (0.2) [0]
Bone disorder	1 (0.2) [0]	0
Bronchitis	1 (0.2) [0]	0
Chest pain	1 (0.2) [0]	0
Coagulation disorder	1 (0.2) [1]	0
Convulsions	1 (0.2) [0]	0

Dizziness	1 (0.2) [0]	0
Haemarthrosis	1 (0.2) [0]	0
Hypotension postural	1 (0.2) [0]	0
Leg pain	1 (0.2) [0]	0
Moniliasis	1 (0.2) [0]	0
Pulmonary oedema	1 (0.2) [0]	0
Renal tubular necrosis	1 (0.2) [1]	0
Respiratory depression	1 (0.2) [0]	0
Spinal cord compression	1 (0.2) [0]	0
Thrombophlebitis deep	1 (0.2) [0]	0
Withdrawal syndrome	1 (0.2) [0]	0
Hypoxia	0	3 (0.6) [0]
Neuropathy	0	2 (0.4) [0]
Vascular disorder	0	2 (0.4) [0]
Abdomen enlarged	0	1 (0.2) [0]
Arthropathy	0	1 (0.2) [0]
Cardiac failure	0	1 (0.2) [0]
Gait abnormal	0	1 (0.2) [0]
Haematemesis	0	1 (0.2) [0]
Hypoaesthesia	0	1 (0.2) [0]
Infection	0	1 (0.2) [0]
Oesophagitis	0	1 (0.2) [0]
Surgical site reaction	0	1 (0.2) [0]
Tachycardia ventricular	0	1 (0.2) [0]
Fatal SAEs - On-therapy from first injection to Day 11 (all treated subjects population)	FX 2.5 mg o.d. (N = 517)	EN 30 mg b.i.d (N = 517)
Subjects with any on-therapy fatal SAE	1 (0.2) [0]	2 (0.4) [0]
Respiratory arrest / respiratory depression	1 (0.2) [0]	0
Arrhythmia	0	1 (0.2) [0]
Tachycardia ventricular	0	1 (0.2) [0]

Conclusion:

See publication below.

Publications:

Bauer KA. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med 2001; 345: 1305-10.

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