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Study No.: 63118
Title: European Pentasaccharide Hip Elective Surgery Study (EPHESUS): A multicenter, randomized, double-blind comparison of once daily subcutaneous Org31540/SR90107A with enoxaparin for the prevention of deep vein thrombosis or symptomatic pulmonary embolism in patients undergoing elective hip replacement surgery.
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 is appropriate for prevention of venous thromboembolic events (VTE), i.e. deep vein thrombosis (DVT) both symptomatic and asymptomatic, and/or fatal and non-fatal 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 was compared with low molecular weight heparin(LMWH) (enoxaparin [EN] 40 mg once daily (o.d.)) for the prevention of VTE in subjects who have undergone hip replacement surgery.
Phase: III
Study Period: 4 December 1998 - 28 January 2000.
Study Design: Multinational, multicentre, randomised, double-blind, double-dummy, parallel-group study.
Centres: 74 centres in 16 countries (3 Austria, 5 Belgium, 5 Czech Republic, 15 Denmark, 6 Finland, 7 France, 4 Germany, 1 Greece, 3 Hungary, 1 Italy, 5 The Netherlands, 5 Norway, 2 Poland, 3 Spain, 6 Sweden and 3 United Kingdom).
Indication: Prevention of DVT and symptomatic PE in subjects undergoing primary elective total hip replacement (THR) surgery, or revision of at least one component of a THR.
Treatment: The administration of FX (2.5 mg o.d. as subcutaneous (s.c.) injection) started post-operatively at 6 ± 2 hours after surgery closure. Administration of EN (40 mg o.d. as SC injection) started pre-operatively at 12 ± 2 hours before the start of surgery, then post-operatively at least 12 hours after the pre-operative dose but not more than 24 hours after surgery. Respective placebo to each drug was administered to protect the double-blind (double-dummy method). Study treatment was given up to Day 7 ± 2 (Day 1 was the day of surgery) or until the mandatory venogram was obtained, whichever came first. A mandatory venogram had to be performed between Day 5 and Day 11, but not more than two calendar days after the last study treatment administration.
Objectives: To evaluate the efficacy of o.d. SC injections of FX 2.5 mg compared with o.d. SC injections of EN 40 mg, for the prevention of VTEs (i.e. DVT or symptomatic PE), in subjects undergoing primary elective THR surgery, or revision of component(s) of a THR.
Primary Outcome/Efficacy Variable: The primary endpoint was the cluster of the following VTE outcome results recorded up to Day 11: adjudicated venogram positive for DVT or adjudicated symptomatic/asymptomatic DVT; adjudicated PE. All venograms, scheduled or unscheduled, and other available diagnostic tests (ultrasonography, ventilation/perfusion lung scan, pulmonary angiography or spiral computed tomography scan, autopsy report, etc.) were adjudicated blindly by independent experts of the Central Independent Adjudication Committee (CIAC).
Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoints: All DVTs, all proximal DVTs, distal DVTs only, and non-fatal and fatal 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. Safety: The main endpoint was the incidence of major bleeding (any Investigator-reported unusual bleeding adjudicated as a major bleeding event by the CIAC) recorded between the first injection of study drug (active drug or placebo) and Day 11. Major bleeding was defined as: fatal bleeding; clinically overt bleeding including retroperitoneal or intracranial bleeding, or bleeding into a critical organ (eye, spine, pericardium, adrenal gland); re-operation due to bleeding/haematoma at the operative site; clinically overt bleeding leading to a fall in haemoglobin (Hgb) ≥ 2 g/dL (1.6 mmol/L) and/or a transfusion ≥ 2 units of packed red blood cells or whole blood AND for which the combined calculated index was ≥ 2 . Other safety variables were: minor bleeding (defined as clinically overt bleeding not meeting the criteria for major bleeding and considered more than expected in the clinical context), transfusion requirements, adverse events (AEs)/serious AEs (SAEs), deaths, and changes in laboratory parameters recorded between the first injection of study drug and Day 11. In addition, all safety parameters were recorded between the first injection and Day 49 Pharmacokinetics: Plasma concentrations of both study drugs were measured in all subjects at 1 to 3 hours after the morning dose on the last day. Plasma concentrations were assessed using validated assay methods.
Statistical Methods: Sample size: Based on previous studies, an estimate of a VTE event rate of 5% was assumed for the FX group and 9%

for the EN group. Therefore, with 800 evaluable (non-missing efficacy assessment) subjects per group, the power to detect a significant difference (with a 2-sided significance level (alpha) of 0.05) between the FX group and the EN group was greater than 85%. Thus, approximately 2200 subjects were to be randomised, assuming that approximately 30% of subjects were expected to have a missing evaluation for the primary efficacy analysis.

Populations analysed:

'All treated subjects': This population (included in the safety analyses) was defined as all randomised study subjects who received at least one dose of study drug (placebo or active drug).

'Primary efficacy': This population (used for the primary efficacy analysis) was a subset of the 'all treated subjects' population that included those subjects who underwent the appropriate surgery (i.e. elective hip replacement surgery), with a non-missing VTE assessment up to Day 11.

Statistical tests used: All efficacy parameters were analysed according to the intent-to-treat (ITT) principle. The VTE, DVT, proximal DVT, symptomatic VTE rates up to Day 11, as well as the symptomatic VTE rate up to Day 49 and the incidence of major bleeding, 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 Wilcoxon rank sum tests for continuous data. Pharmacokinetic data were analysed using descriptive statistics (mean, standard deviation [SD]) for FX and EN plasma concentrations. Regression analyses and analyses of variance (ANOVA) were applied to test for the effects of the covariates, age, weight, creatinine clearance and gender on the plasma concentrations of both drugs.

Study Population: Subjects were eligible if they were undergoing either an elective, primary, THR surgery, or a revision of at least one component of a THR; ≥18 years of age; men, or women of non-childbearing potential or of childbearing potential and having a negative pregnancy test within 48 hours prior to surgery or first study drug administration, whichever came first; written informed consent.

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 x10⁹/L), medical condition associated with a bleeding risk), or those relating to contrast dyes during venography (eg serum creatinine >2mg/dL (180umol/L) or hypersensitivity to contrast media) or use of anticoagulant or fibrinolytic therapy within 2 days prior to first dose of study medication

Number of subjects	FX 2.5 mg o.d.	EN 40 mg o.d.
Planned, N	1100	1100
Randomised, N	1155	1154
Randomised and treated, N ('All Treated' population)	1140	1133
All treated subjects with appropriate surgery, N	1129	1123
Primary efficacy population, N	908	919
Completed study drug, n (%)	1070 (93.9)	1075 (94.9)
Total number subjects withdrawn from study drug, n (%)	70 (6.1)	58 (5.1)
Withdrawn due to AE/SAE n (%)	18 (1.6)	15 (1.3)
Withdrawn due to lack of efficacy n (%)	7 (0.6)	5 (0.4)
Withdrawn for other reasons n (%)	45 (3.9)	38 (3.4)
Demographics	FX 2.5 mg o.d.	EN 40 mg o.d.
N ('All Treated' population)	1140	1133
Females:Males	647:493	660:473
Mean age, years (SD)	65.1 (11.3)	65.5 (11.1)
Caucasian, n (%)	1128 (99.0)	1125 (99.4)
Primary Efficacy Results:		
Subjects with VTE up to Day 11 (Primary efficacy population)	FX 2.5 mg o.d.	EN 40 mg o.d.
n/N (%)	37/908 (4.1)	85/919 (9.2)
95% CI	[2.9, 5.6]	[7.5, 11.3]
Difference (FX – EN) (%)	-5.2	
Exact 95% CI for difference	[-8.1, -2.7]	
p-value (Fisher's exact test)	<0.001	
Secondary Outcome Variable(s):		
Subjects with any DVT up to Day 11 (Efficacy evaluable population)	FX 2.5 mg o.d.	EN 40 mg o.d.
n/N (%)	36/908 (4.0)	83/918 (9.0)
95% CI	[2.8, 5.4]	[7.3, 11.1]

Difference (FX – EN) (%)	-5.1	
Exact 95% CI for difference	[-8.0, -2.6]	
Subjects with any proximal DVT up to Day 11 (Efficacy evaluable population)	FX 2.5 mg o.d.	EN 40 mg o.d.
n/N (%)	6/922 (0.7)	23/927 (2.5)
95% CI	[0.2, 1.4]	[1.6, 3.7]
Difference (FX – EN) (%)	-1.8	
Exact 95% CI for difference	[-3.7, -0.5,]	
Subjects with distal only DVT up to Day 11 (Efficacy evaluable population)	FX 2.5 mg o.d.	EN 40 mg o.d.
n/N (%)	30/909 (3.3)	67/917 (7.3)
95% CI	[2.2, 4.7]	[5.7, 9.2]
Subjects with non-fatal PE up to Day 11 (All Treated subjects who underwent appropriate surgery)	FX 2.5 mg o.d.	EN 40 mg o.d.
n/N (%)	2/1129 (0.2)	2/1123 (0.2)
Subjects with fatal PE up to Day 11 (All Treated subjects who underwent appropriate surgery)	FX 2.5 mg o.d.	EN 40 mg o.d.
n/N (%)	0/1129 (0)	0/1123 (0)
All subjects with antithrombotic curative treatment initiated after VTE assessment up to Day 11 (All Treated subjects who underwent appropriate surgery with VTE assessment up to Day 11)	FX 2.5 mg o.d. N = 997	EN 40 mg o.d. N = 999
Total, n (%)	40 (4.0)	88 (8.8)
Heparin (UFH, LMWH)/heparinoids, n (%)	39 (3.9)	80 (8.0)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids, n (%)	0	5 (0.5)
Other (not heparin or vitamin K antagonist), n (%)	1 (0.1)	2 (0.2)
None reported, n (%)	0	1 (0.1)
All subjects with antithrombotic curative treatment initiated following the qualifying VTE assessment (Primary efficacy population)	FX 2.5 mg o.d. N = 908	EN 40 mg o.d. N = 919
Total, n (%)	31 (3.4)	80 (8.7)
Heparin (UFH, LMWH)/heparinoids, n (%)	30 (3.3)	72 (7.8)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids, n (%)	0	5 (0.5)
Other (not heparin or vitamin K antagonist), n (%)	1 (0.1)	2 (0.2)
None reported, n (%)	0	1 (0.1)
Adjudicated symptomatic VTE (All treated subjects who underwent appropriate surgery)	FX 2.5 mg o.d. N = 1129	EN 40 mg o.d. N = 1123
Up to Day 11, n (%)	5 (0.4)	3 (0.3)
95% CI	[0.1, 1.0]	[0.1, 0.8]
Difference (FX – EN) (%)	0.2	
Exact 95% CI for difference	[-0.6, 1.4]	
Up to Day 49, n (%)	12 (1.1)	9 (0.8)
95% CI	[0.6, 1.8]	[0.4, 1.5]
Difference (FX – EN) (%)	0.3	
Exact 95% CI for difference	[-0.8, 1.8]	
Safety results:		
Bleeding ('All Treated' population)	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
Adjudicated bleeding results from first injection to Day 11, n (%)		
Major bleeding	47 (4.1)	32 (2.8)
Fatal bleeding	0	0
Minor bleeding	44 (3.9)	38 (3.4)
Any bleeding	91 (8.0)	70 (6.2)
Adjudicated bleeding results from first injection to Day 49, n (%)		

Major bleeding	49 (4.3)	33 (2.9)
Fatal bleeding	0	0
Minor bleeding	45 (3.9)	43 (3.8)
Any bleeding	94 (8.2)	76 (6.7)
Subjects requiring transfusion, n (%)		
Up to Day 11	714 (62.6)	690 (60.9)
Up to Day 49	717 (62.9)	697 (61.5)
Adverse event results: 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.		
	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
Adverse Events – from first injection to Day 11 (All treated subjects)	n (%)	n (%)
Subjects with any AE(s)	666 (58.4)	660 (58.3)
10 most frequent AEs in each treatment group:		
Anaemia	226 (19.8)	190 (16.8)
Nausea	121 (10.6)	115 (10.2)
Insomnia	119 (10.4)	111 (9.8)
Constipation	83 (7.3)	102 (9.0)
Wound drainage increased	77 (6.8)	64 (5.6)
Vomiting	66 (5.8)	55 (4.9)
Fever	65 (5.7)	67 (5.9)
Hypotension	59 (5.2)	56 (4.9)
Haematoma	57 (5.0)	45 (4.0)
Haemorrhage Not Otherwise Specified (NOS)	44 (3.9)	54 (4.8)
	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
Adverse Events – from first injection to Day 49 (All treated subjects)	n (%)	n (%)
Subjects with any AE(s)	701 (61.5)	687 (60.6)
10 most frequent AEs in each treatment group:		
Anaemia	228 (20.0)	192 (16.9)
Nausea	124 (10.9)	119 (10.5)
Insomnia	124 (10.9)	113 (10.0)
Constipation	85 (7.5)	106 (9.4)
Wound drainage increased	80 (7.0)	67 (5.9)
Fever	71 (6.2)	69 (6.1)
Vomiting	69 (6.1)	56 (4.9)
Haematoma	63 (5.5)	48 (4.2)
Hypotension	60 (5.3)	58 (5.1)
Haemorrhage NOS	44 (3.9)	57 (5.0)
Serious Adverse Events		
	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
All SAEs (fatal & non-fatal) - from first injection to Day 11 (All treated subjects)	n (%) [related]	n (%) [related]
Subjects with any SAE(s) [number considered by Investigator to be related to study medication]	46 (4.0) [8]	37 (3.3) [3]
Surgical site reaction	6 (0.5) [0]	6 (0.5) [0]
Haematoma	5 (0.4) [3]	4 (0.4) [0]
Post-operative haemorrhage	4 (0.4) [4]	1 (0.1) [0]
Anaemia	4 (0.4) [1]	0

Myocardial infarction	2 (0.2) [0]	5 (0.4) [0]
Bone disorder	2 (0.2) [0]	1 (0.1) [0]
Cerebrovascular disorder	2 (0.2) [0]	1 (0.1) [0]
Oedema peripheral	1 (0.1) [1]	2 (0.2) [0]
Post-operative wound infection	1 (0.1) [0]	2 (0.2) [1]
Wound drainage increased	1 (0.1) [0]	2 (0.2) [0]
Cardiac arrest	1 (0.1) [0]	1 (0.1) [0]
Fever	1 (0.1) [0]	1 (0.1) [0]
Fibrillation atrial	1 (0.1) [0]	1 (0.1) [0]
Gait abnormal	1 (0.1) [0]	1 (0.1) [0]
Haemorrhage NOS	1 (0.1) [1]	1 (0.1) [0]
Pneumonia	1 (0.1) [0]	1 (0.1) [0]
Anaemia haemolytic	1 (0.1) [0]	0
Brain stem disorder	1 (0.1) [0]	0
Cellulitis	1 (0.1) [0]	0
Cholelithiasis	1 (0.1) [0]	0
Confusion	1 (0.1) [0]	0
Convulsions Grand Mal	1 (0.1) [0]	0
Cyanosis	1 (0.1) [0]	0
Duodenal ulcer	1 (0.1) [0]	0
Dyspnoea	1 (0.1) [0]	0
Fatigue	1 (0.1) [0]	0
Gastric ulcer	1 (0.1) [0]	0
Haematuria	1 (0.1) [0]	0
Hernia congenital	1 (0.1) [0]	0
Hypotension	1 (0.1) [0]	0
Ileus	1 (0.1) [0]	0
Leg pain	1 (0.1) [0]	0
Melanoma malignant	1 (0.1) [0]	0
Oesophagitis	1 (0.1) [0]	0
Pallor	1 (0.1) [0]	0
Pancreatitis	1 (0.1) [0]	0
Paraesthesia	1 (0.1) [1]	0
Paresis	1 (0.1) [0]	0
Post-operative pain	1 (0.1) [0]	0
Renal function abnormal	1 (0.1) [0]	0
Respiratory insufficiency	1 (0.1) [0]	0
Rigors	1 (0.1) [0]	0
Sepsis	1 (0.1) [0]	0
Spinal cord compression	1 (0.1) [0]	0
Sweating increased	1 (0.1) [0]	0
Syncope	1 (0.1) [0]	0
Urinary tract infection	1 (0.1) [0]	0
Angina pectoris	0	2 (0.2) [0]
Arthrosis	0	1 (0.1) [0]
Cardiac failure	0	1 (0.1) [0]
Chest pain	0	1 (0.1) [0]
Colitis	0	1 (0.1) [0]
Death	0	1 (0.1) [0]
GI haemorrhage	0	1 (0.1) [0]
Hypoxia	0	1 (0.1) [0]
Ileus paralytic	0	1 (0.1) [0]
Myocardial ischaemia	0	1 (0.1) [0]

Osteosclerosis	0	1 (0.1) [0]
Peptic ulcer haemorrhagic	0	1 (0.1) [1]
Purpura	0	1 (0.1) [1]
Rash	0	1 (0.1) [0]
Respiratory depression	0	1 (0.1) [0]
Tachycardia	0	1 (0.1) [0]
	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
All SAEs (fatal & non-fatal) - from first injection to Day 49 (All treated subjects)	n (%)	n (%)
Subjects with any SAE(s)	96 (8.4)	85 (7.5)
Surgical site reaction	27 (2.4) [not available (na)]	27 (2.4) [na]
Post-operative wound infection	7 (0.6) [na]	6 (0.5) [na]
Haematoma	6 (0.5) [na]	7 (0.6) [na]
Bone disorder	5 (0.4) [na]	3 (0.3) [na]
Cerebrovascular disorder	5 (0.4) [na]	1 (0.1) [na]
Post-operative haemorrhage	5 (0.4) [na]	1 (0.1) [na]
Anaemia	5 (0.4) [na]	0
Myocardial infarction	3 (0.3) [na]	6 (0.5) [na]
Dizziness	3 (0.3) [na]	0
Dyspnoea	3 (0.3) [na]	0
Fibrillation atrial	2 (0.2) [na]	2 (0.2) [na]
Leg pain	2 (0.2) [na]	2 (0.2) [na]
Renal function abnormal	2 (0.2) [na]	1 (0.1) [na]
Cholecystitis	2 (0.2) [na]	0
Haematuria	2 (0.2) [na]	0
Ileus	2 (0.2) [na]	0
Nausea	2 (0.2) [na]	0
Urinary tract infection	2 (0.2) [na]	0
Oedema peripheral	1 (0.1) [na]	5 (0.4) [na]
Wound drainage increased	1 (0.1) [na]	3 (0.3) [na]
Angina pectoris	1 (0.1) [na]	2 (0.2) [na]
Chest pain	1 (0.1) [na]	2 (0.2) [na]
Haemorrhage NOS	1 (0.1) [na]	2 (0.2) [na]
Pneumonia	1 (0.1) [na]	2 (0.2) [na]
Cardiac arrest	1 (0.1) [na]	1 (0.1) [na]
Cardiac failure	1 (0.1) [na]	1 (0.1) [na]
Duodenal ulcer	1 (0.1) [na]	1 (0.1) [na]
Embolism pulmonary	1 (0.1) [na]	1 (0.1) [na]
Fever	1 (0.1) [na]	1 (0.1) [na]
Gait abnormal	1 (0.1) [na]	1 (0.1) [na]
Sepsis	1 (0.1) [na]	1 (0.1) [na]
Anaemia haemolytic	1 (0.1) [na]	0
Brain stem disorder	1 (0.1) [na]	0
Cellulitis	1 (0.1) [na]	0
Cholelithiasis	1 (0.1) [na]	0
Confusion	1 (0.1) [na]	0
Convulsions Grand Mal	1 (0.1) [na]	0
Cyanosis	1 (0.1) [na]	0
Diarrhoea	1 (0.1) [na]	0
Fatigue	1 (0.1) [na]	0
Gastric ulcer	1 (0.1) [na]	0
Gastroenteritis	1 (0.1) [na]	0
Headache	1 (0.1) [na]	0

Hernia congenital	1 (0.1) [na]	0
Hypotension	1 (0.1) [na]	0
Joint dislocation	1 (0.1) [na]	0
Melanoma malignant	1 (0.1) [na]	0
Oesophagitis	1 (0.1) [na]	0
Pallor	1 (0.1) [na]	0
Pancreatitis	1 (0.1) [na]	0
Paraesthesia	1 (0.1) [na]	0
Paresis	1 (0.1) [na]	0
Peritonitis	1 (0.1) [na]	0
Post-operative pain	1 (0.1) [na]	0
Renal calculus	1 (0.1) [na]	0
Respiratory insufficiency	1 (0.1) [na]	0
Rigors	1 (0.1) [na]	0
Skin ulceration	1 (0.1) [na]	0
Spinal cord compression	1 (0.1) [na]	0
Sweating increased	1 (0.1) [na]	0
Syncope	1 (0.1) [na]	0
Thrombocythaemia	1 (0.1) [na]	0
Vomiting	1 (0.1) [na]	0
Vision abnormal	1 (0.1) [na]	0
Abscess	0	1 (0.1) [na]
Adenocarcinoma NOS	0	1 (0.1) [na]
Arthrosis	0	1 (0.1) [na]
Cardiac failure left	0	1 (0.1) [na]
Colitis	0	1 (0.1) [na]
Death	0	1 (0.1) [na]
Duodenal ulcer haemorrhagic	0	1 (0.1) [na]
GI haemorrhage	0	1 (0.1) [na]
Hypoxia	0	1 (0.1) [na]
Ileus paralytic	0	1 (0.1) [na]
Myocardial ischaemia	0	1 (0.1) [na]
Nystagmus	0	1 (0.1) [na]
Osteosclerosis	0	1 (0.1) [na]
Peptic ulcer haemorrhagic	0	1 (0.1) [na]
Phlebitis superficial	0	1 (0.1) [na]
Purpura	0	1 (0.1) [na]
Rash	0	1 (0.1) [na]
Renal failure acute	0	1 (0.1) [na]
Respiratory depression	0	1 (0.1) [na]
Suicide attempt	0	1 (0.1) [na]
Tachycardia	0	1 (0.1) [na]
Tachycardia supraventricular	0	1 (0.1) [na]
Transient ischaemic attack	0	1 (0.1) [na]
Uncodeable event	0	1 (0.1) [na]
Urine abnormal	0	1 (0.1) [na]
Vertigo	0	1 (0.1) [na]
Subjects with fatal SAEs		
	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
Deaths from time of first injection (all treated subjects)	n (%)	n (%)
Subjects with SAE between first injection & Day 11:		
Leading to death between first injection & Day 11	0	2 (0.2)

Leading to death between Days 12 & 49	1 (0.1)	0
Subjects with SAE between Days 12 & 49:		
Leading to death between Days 12 & 49	1 (0.1)	2 (0.2)
Leading to death after Day 49	0	1 (0.1)
Total deaths between first injection & Day 49:	2 (0.2)	4 (0.4)
Total deaths reported	2 (0.2)	5 (0.4)
	FX 2.5 mg o.d. (N = 1140)	EN 40 mg o.d. (N = 1133)
Deaths between first injection and Day 49 by adjudication criterion (all treated subjects)	n (%)	n (%)
Fatal PE	1 (0.1)	0
Haemorrhagic death	0	0
Death not associated with VTE or bleeding	1 (0.1)	4 (0.4)
Total deaths	2 (0.2)	4 (0.4)
Pharmacokinetics results: Mean values are for 1 to 3 hours after last morning dose.		
	FX 2.5 mg o.d.	EN 40 mg o.d.
Last morning dose (active)		
N	742	295
Mean plasma concentration (SD) [Median], mg/L	0.429 (0.153) [0.433]	4.405 (1.845) [4.198]
Last morning dose (placebo)		
N	-	457
Mean plasma concentration (SD) [Median], mg/L	-	1.428 (0.921) [1.289]

Conclusion:

See publication below.

Publications:

Lassen MR. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. *Lancet* 2002; 359: 1715-20.

Abstract: Pentasaccharide (fondaparinux, arixtra®) versus enoxaparin for the prevention of venous thromboembolism (vte) in major orthopedic surgery: subgroup analyses on efficacy. Michael R. Lassen, Bengt Eriksson, Kenneth A. Bauer, Alexander G. G. Turpie. American Society of Hematology 43rd Annual Meeting 12/7/2001 Orlando, FL, USA

Abstract: Superior efficacy of fondaparinux versus enoxaparin for the prevention of venous thromboembolism in major orthopaedic surgery is maintained whatever patients, anesthesia and procedures characteristics. Eriksson, B I, Bauer, K A, Lassen, M R, Turpie, A G G, Bauersachs, R M, and Fondaparinux Orthopedic Prophylaxis Studies Investigators 7th Congress of the European Association of Hospital Pharmacists 3/20/2002 Vienna, Austria

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Date Updated: 27-May-2005