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<b>Study No.:</b> EFC2442
<b>Title:</b> 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 hip replacement or a revision. PENTATHLON 2000
<b>Rationale:</b> 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), and/or symptomatic pulmonary embolism (PE), which are major post-operative complications following orthopaedic surgery of the lower limbs. In this 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 the prevention of VTE in subjects who had undergone hip replacement surgery.
<b>Phase:</b> III
<b>Study Period:</b> 21 December 1998 - 05 January 2000.
<b>Study Design:</b> Multinational, multicentre, randomised, double-blind, double-dummy, parallel-group study.
<b>Centres:</b> 139 study centres in 3 countries (15 Australia, 30 Canada, 94 United States of America).
<b>Indication:</b> 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.
<b>Treatment:</b> The administration of FX (2.5 mg o.d. as subcutaneous [s.c.] injection) started post-operatively at 6 ± 2 hours after surgical closure. Administration of EN (30 mg b.i.d. as s.c. injection) started post-operatively at least 12 hours but no more than 24 hours post surgical closure. 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 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.
<b>Objectives:</b> The objective of this study was to evaluate the efficacy of a o.d., post-operative, s.c. injection of FX 2.5 mg compared to b.i.d. post-operative, s.c. injections of EN 30 mg for prevention of VTEs (DVT or symptomatic PE) in subjects having primary elective THR or a revision of component(s) of a THR.
<b>Primary Outcome/Efficacy Variable:</b> 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; and adjudicated PE. All venograms, scheduled or unscheduled, and other diagnostic tests (ultrasonography, ventilation/perfusion, lung scan, pulmonary angiography, spiral computed tomography scan, autopsy report, etc.) were adjudicated blindly by independent experts of the Central Independent Adjudication Committee (CIAC).
<b>Secondary Outcome/Efficacy Variable(s):</b> Secondary efficacy endpoints: All DVTs, all proximal DVTs, distal DVTs only, non-fatal PEs and fatal PEs, up to Day 11; and adjudicated symptomatic VTEs up to Day 49. Institution of curative treatment by the Investigator after local VTE assessment was also reported. <b>Safety:</b> The main safety endpoint was the incidence of major bleeding (any Investigator-reported unusual bleeding adjudicated as major or minor bleeding 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, intracranial, or bleeding into a critical organ (eye, adrenal gland, pericardium, spine); re-operation due to bleeding/haematoma at the operative site; and clinically overt bleeding leading to a fall in haemoglobin >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 parameters 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 and between the first injection of study drug and Day 49. Major bleeding was also recorded between the first injection of study drug and Day 49. <b>Pharmacokinetics:</b> Plasma concentrations of FX were measured in a subset of subjects on Day 4 at pre-defined time periods: before dosing, and 1–3, 4–6 and 8–12 hours post dosing. Plasma concentrations were determined using a validated assay method for which the limit of quantification (LOQ) was 0.042 mg/L.
<b>Statistical Methods:</b> <b>Sample size:</b> The sample size was calculated based on a 2-sided alpha of 0.05, a power greater than 85% and a rate of non

evaluable subjects (missing efficacy assessment) for primary efficacy end-point of approximately 30%. In a previous large dose-ranging study (DRI2643) in the same subject population, a VTE rate of 2.0% was observed with FX 3 mg and 5.9% with 1.5 mg, with approximately 100 per-protocol subjects in either group. Thus, to be conservative, a VTE rate of 5% was assumed for the FX group. In study DRI2643, the observed VTE rate in the EN group was 9.3%. Therefore, with the above assumptions, a total of 1600 evaluable subjects (2200 randomised subjects) would permit detection of a difference between 9% and 5%.

**Populations analysed:**

*All treated subjects (ATS):* 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 population:* Included in the primary efficacy analysis, this population was a subset of the all treated subjects population including those subjects who underwent the appropriate surgery (i.e., elective THR or a revision of components of a THR), with a non-missing VTE assessment up to Day 11, or an adjudicated DVT, non-fatal or fatal PE, recorded 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 and minor only bleeding 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) were calculated on the differences. Statistical comparisons of safety data (other than major bleeding) were made using a Chi-square test for categorical data, and a 2-sample Wilcoxon Rank Sum test for continuous data. For the pharmacokinetic (PK) analysis, descriptive statistics (mean, SD) for FX concentrations were provided at each time period on Day 4. A population PK analysis was also performed on a sub-population of 65 subjects.

**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;  $\geq 18$  years of age; men, or women of non-childbearing potential or women of childbearing potential using effective birth control with a negative pregnancy test within 48 hours prior to randomisation; haemostasis established on the calendar day of surgery, no later than 8 hours after the incision closure; 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 ( $<100 \times 10^9/L$ ), 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).

	<b>FX 2.5 mg o.d.</b>	<b>EN 30 mg b.i.d.</b>
Number of subjects:		
Planned enrolment (evaluable), N	1100 (800)	1100 (800)
Randomised, N	1138	1137
Randomised and treated, N (All Treated subjects population)	1128	1129
All treated subjects with appropriate surgery, N	1126	1128
Primary efficacy population, N	787	797
Completed study drug, n (%)	1067 (94.6)	1063 (94.2)
Total number subjects withdrawn from study drug, n (%)	61 (5.4)	66 (5.8)
Withdrawn due to AEs n (%)	33 (2.9)	35 (3.1)
Withdrawn due to lack of efficacy n (%)	4 (0.4)	2 (0.2)
Withdrawn consent n (%)	19 (1.7)	15 (1.3)
Withdrawn for other reasons n (%)	5 (0.4)	14 (1.2)
<b>Demographics</b>	<b>FX 2.5 mg o.d.</b>	<b>EN 30 mg b.i.d.</b>
N (All Treated subjects population)	1128	1129
Females: Males	572:556	607:522
Mean age, years (SD)	64.6 (12.7)	64.6 (12.6)
Caucasian, n (%)	1059 (93.9)	1057 (93.6)
<b>Primary Efficacy Results:</b>		
<b>Subjects with VTE up to Day 11 (Primary efficacy population)</b>	<b>FX 2.5 mg o.d.</b>	<b>EN 30 mg b.i.d.</b>
n/N (%)	48/787 (6.1)	66/797 (8.3)
95% CI	[4.5, 8.0]	[6.5, 10.4]
Difference (FX - EN) (%)	-2.2	
Exact 95% CI for difference	[-5.5, 0.6]	
P-value (Fisher's exact test)	0.099	
<b>Secondary Outcome Variable(s):</b>		

<b>Subjects with any DVT up to Day 11 (Primary efficacy population)</b>	<b>FX 2.5 mg o.d.</b>	<b>EN 30 mg b.i.d.</b>
n/N (%)	44/784 (5.6)	65/796 (8.2)
95% CI	[4.1, 7.5]	[6.4, 10.3]
Difference (FX - EN) (%)	-2.6	
Exact 95% CI for difference	[-5.9, 0.2]	
<b>Subjects with any proximal DVT up to Day 11 (Primary efficacy population)</b>	<b>FX 2.5 mg o.d.</b>	<b>EN 30 mg b.i.d.</b>
n/N (%)	14/816 (1.7)	10/830 (1.2)
95% CI	[0.9, 2.9]	[0.6, 2.2]
Difference (FX - EN) (%)	0.5	
Exact 95% CI for difference	[-1.0, 2.6]	
<b>Subjects with distal only DVT up to Day 11 (Primary efficacy population)</b>	<b>FX 2.5 mg o.d.</b>	<b>EN 30 mg b.i.d.</b>
n/N (%)	34/796 (4.3)	54/800 (6.8)
95% CI	[3.0, 5.9]	[5.1, 8.7]
<b>Subjects with non-fatal PE up to Day 11 (All treated subjects who underwent appropriate surgery)</b>	<b>FX</b>	<b>EN</b>
n/N (%)	5/1126 (0.4)	0/1128 (0)
<b>Subjects with fatal PE up to Day 11 (All treated subjects who underwent appropriate surgery)</b>	<b>FX</b>	<b>EN</b>
n/N (%)	0/1126 (0)	1/1128 (0.1)
<b>All subjects with curative treatment initiated after VTE assessment up to Day 11 (All treated subjects who underwent appropriate surgery with VTE assessment up to Day 11)</b>	<b>FX 2.5 mg o.d. N = 952</b>	<b>EN 30 mg b.i.d. N = 963</b>
Total, n (%)	49 (5.1)	68 (7.1)
Heparin (UFH, LMWH)/heparinoids, n (%)	40 (4.2)	54 (5.6)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids), n (%)	5 (0.5)	6 (0.6)
Other (not heparin or vitamin K antagonist), n (%)	3 (0.3)	5 (0.5)
None reported, n (%)	1 (0.1)	3 (0.3)
<b>All subjects with curative treatment initiated following the qualifying VTE assessment (Primary efficacy population)</b>	<b>FX 2.5 mg o.d. N = 787</b>	<b>EN 30 mg b.i.d. N = 797</b>
Total, n (%)	45 (5.7)	63 (7.9)
Heparin (UFH, LMWH)/heparinoids, n (%)	37 (4.7)	49 (6.1)
Vitamin K antagonist without heparin (UFH, LMWH)/heparinoids), n (%)	4 (0.5)	6 (0.8)
Other (not heparin or vitamin K antagonist), n (%)	3 (0.4)	5 (0.6)
None reported, n (%)	1 (0.1)	3 (0.4)
<b>Adjudicated symptomatic VTE (All treated subjects who underwent appropriate surgery)</b>	<b>FX 2.5 mg o.d. N = 1126</b>	<b>EN 30 mg b.i.d. N = 1128</b>
Up to Day 11, n/N (%)	10 (0.9)	1 (0.1)
95% CI	[0.4, 1.6]	[0.0, 0.5]
Difference (FX - EN) (%)	0.8	
Exact 95% CI for difference	[-0.0, 1.9]	
Up to day 49, n/N (%)	29 (2.6)	13 (1.2)
95% CI	[1.7, 3.7]	[0.6, 2.0]
Difference (FX - EN) (%)	1.4	
Exact 95% CI for difference	[0.0, 3.1]	
<b>Safety results:</b>		
<b>Bleeding results ('All Treated Subjects' population)</b>	<b>FX (N = 1128)</b>	<b>EN (N = 1129)</b>
Adjudicated bleeding from first injection up to Day 11, n (%)		
Major bleeding	20/1128 (1.8)	11/1129 (1.0)
Fatal bleeding	0	0
Minor bleeding only	17/1128 (1.5)	24/1129 (2.1)

Any bleeding	37/1128 (3.3)	35/1129 (3.1)
Adjudicated bleeding from first injection up to Day 49, n (%)		
Major bleeding	22/1128 (2.0)	13/1129 (1.2)
Fatal bleeding	0	0
Minor bleeding only	22/1128 (2.0)	27/1129 (2.4)
Any bleeding	44/1128 (3.9)	40/1129 (3.5)
Transfusion post-operatively		
Up to Day 11	593/1128 (52.6)	555/1129 (49.2)
Up to Day 49	597/1128 (52.9)	559/1129 (49.5)
<b>Most frequent adverse events - on-therapy:</b> 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.		
<b>Most frequent adverse events – from first injection to Day 11 (All treated subjects)</b>	<b>FX 2.5 mg o.d. (N = 1128)</b>	<b>EN 30 mg b.i.d. (N = 1129)</b>
Subjects with any AE(s), n (%)	854 (75.7)	860 (76.2)
10 most frequent AEs in each treatment group, n (%):		
Anaemia	272 (24.1)	225 (19.9)
Fever	228 (20.2)	238 (21.1)
Nausea	142 (12.6)	168 (14.9)
Constipation	113 (10.0)	103 (9.1)
Oedema	96 (8.5)	64 (5.7)
Purpura	70 (6.2)	56 (5.0)
Vomiting	69 (6.1)	88 (7.8)
Wound drainage increased	64 (5.7)	56 (5.0)
Dizziness	58 (5.1)	67 (5.9)
Bullous eruption	62 (5.5)	57 (5.0)
Hypokalaemia	56 (5.0)	62 (5.5)
<b>Most Frequent Adverse Events – from first injection to Day 49 (All Treated subjects)</b>	<b>FX (N = 1128)</b>	<b>EN (N = 1129)</b>
Subjects with any AE(s), n (%)	871 (77.2)	878 (77.8)
10 most frequent AEs in each treatment group, n (%):		
Anaemia	276 (24.5)	228 (20.2)
Fever	230 (20.4)	239 (21.2)
Nausea	146 (12.9)	172 (15.2)
Constipation	119 (10.5)	107 (9.5)
Oedema	101 (9.0)	72 (6.4)
Vomiting	71 (6.3)	88 (7.8)
Purpura	70 (6.2)	56 (5.0)
Wound drainage increased	67 (5.9)	58 (5.1)
Dizziness	63 (5.6)	69 (6.1)
Oedema peripheral	67 (5.9)	56 (5.0)
Bullous eruption	65 (5.8)	58 (5.1)
<b>Serious Adverse Events:</b> - SAEs 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.		
<b>All SAEs ( fatal &amp; non-fatal) - from first injection to Day 11 (All treated subjects)</b>	<b>FX 2.5 mg o.d. (N = 1128)</b>	<b>EN 30 mg b.i.d. (N = 1129)</b>
n (%) [n considered by the investigator to be related to study medication]		
Subjects with any SAE(s)	54 (4.8) [6]	47 (4.2) [6]
Haematoma	5 (0.4) [3]	1 (0.1) [1]
Ileus	5 (0.4) [0]	1 (0.1) [0]
Inflicted injury	4 (0.4) [0]	1 (0.1) [0]

Surgical site reaction	3 (0.3) [0]	11 (1.0) [0]
Pneumonia	3 (0.3) [0]	2 (0.2) [0]
Tachycardia	2 (0.2) [0]	2 (0.2) [0]
Haematuria	2 (0.2) [0]	1 (0.1) [1]
Myocardial infarction	2 (0.2) [0]	1 (0.1) [0]
Cardiac arrest	2 (0.2) [0]	0
Fever	2 (0.2) [0]	0
Intestinal obstruction	2 (0.2) [0]	0
Post-operative wound infection	2 (0.2) [1]	0
Vomiting	2 (0.2) [0]	0
Angina pectoris	1 (0.1) [0]	2 (0.2) [1]
Post-operative haemorrhage	1 (0.1) [1]	2 (0.2) [1]
Cellulitis	1 (0.1) [0]	1 (0.1) [0]
Chest pain	1 (0.1) [0]	1 (0.1) [0]
Confusion	1 (0.1) [0]	1 (0.1) [0]
Melaena	1 (0.1) [1]	1 (0.1) [1]
Renal failure acute	1 (0.1) [0]	1 (0.1) [0]
Anaemia	1 (0.1) [0]	0
Arthritis	1 (0.1) [0]	0
Death	1 (0.1) [0]	0
Dehydration	1 (0.1) [0]	0
Diarrhoea	1 (0.1) [0]	0
Dyspnoea	1 (0.1) [0]	0
Encephalopathy	1 (0.1) [0]	0
Gastritis	1 (0.1) [0]	0
GI haemorrhage	1 (0.1) [1]	0
Haemorrhage NOS	1 (0.1) [0]	0
Haemorrhage rectum	1 (0.1) [0]	0
Haemorrhoids	1 (0.1) [1]	0
Hypertension	1 (0.1) [0]	0
Megacolon congenital	1 (0.1) [0]	0
Micturition disorder	1 (0.1) [0]	0
Renal tubular necrosis	1 (0.1) [0]	0
Sick sinus syndrome	1 (0.1) [0]	0
Skin ulceration	1 (0.1) [0]	0
Fibrillation atrial	0	2 (0.2) [0]
Asthenia	0	1 (0.1) [0]
Atelectasis	0	1 (0.1) [0]
Coma	0	1 (0.1) [0]
Delirium	0	1 (0.1) [0]
Diarrhoea, clostridium difficile	0	1 (0.1) [0]
Enterocolitis	0	1 (0.1) [0]
Hyperglycaemia	0	1 (0.1) [0]
Hypoaesthesia	0	1 (0.1) [0]
Hypovolaemia	0	1 (0.1) [0]
Ileus paralytic	0	1 (0.1) [0]
Intestinal perforation	0	1 (0.1) [0]
Oedema peripheral	0	1 (0.1) [0]
Pain	0	1 (0.1) [1]
Post-operative pain	0	1 (0.1) [0]

Pneumonitis	0	1 (0.1) [0]
Tachycardia supraventricular	0	1 (0.1) [0]
Transient ischaemic attack	0	1 (0.1) [0]
Urinary tract infection	0	1 (0.1) [0]
<b>All SAEs ( fatal &amp; non-fatal) - from first injection to day 49 (All treated subjects)</b>	<b>FX 2.5 mg o.d. (N = 1128)</b>	<b>EN 30 mg b.i.d. (N = 1129)</b>
Subjects with any SAE(s) n (%)	97 (8.6)	84 (7.4)
Surgical site reaction	19 (1.7) [not available (na)]	23 (2.0) [na]
Post-operative wound infection	10 (0.9) [na]	5 (0.4) [na]
Haematoma	6 (0.5) [na]	4 (0.4) [na]
Ileus	5 (0.4) [na]	1 (0.1) [na]
Inflicted injury	4 (0.4) [na]	6 (0.5) [na]
Myocardial infarction	4 (0.4) [na]	2 (0.2) [na]
Pneumonia	4 (0.4) [na]	2 (0.2) [na]
Cerebrovascular disorder	3 (0.3) [na]	0
Fever	3 (0.3) [na]	0
Chest pain	2 (0.2) [na]	4 (0.4) [na]
Fibrillation atrial	2 (0.2) [na]	2 (0.2) [na]
Tachycardia	2 (0.2) [na]	2 (0.2) [na]
Cellulitis	2 (0.2) [na]	1 (0.1) [na]
Haematuria	2 (0.2) [na]	1 (0.1) [na]
Cardiac arrest	2 (0.2) [na]	0
Cardiac failure	2 (0.2) [na]	0
Haemorrhage rectum	2 (0.2) [na]	0
Intestinal obstruction	2 (0.2) [na]	0
Vomiting	2 (0.2) [na]	0
Confusion	1 (0.1) [na]	4 (0.4) [na]
Angina pectoris	1 (0.1) [na]	2 (0.2) [na]
Post-operative haemorrhage	1 (0.1) [na]	2 (0.2) [na]
Post-operative pain	1 (0.1) [na]	2 (0.2) [na]
Diarrhoea	1 (0.1) [na]	1 (0.1) [na]
Ileus paralytic	1 (0.1) [na]	1 (0.1) [na]
Infection	1 (0.1) [na]	1 (0.1) [na]
Melaena	1 (0.1) [na]	1 (0.1) [na]
Renal failure acute	1 (0.1) [na]	1 (0.1) [na]
Arthritis	1 (0.1) [na]	0
Anaemia	1 (0.1) [na]	0
Death	1 (0.1) [na]	0
Dyspnoea	1 (0.1) [na]	0
Dehydration	1 (0.1) [na]	0
Embolism pulmonary	1 (0.1) [na]	0
Encephalopathy	1 (0.1) [na]	0
Gastritis	1 (0.1) [na]	0
GI haemorrhage	1 (0.1) [na]	0
Haematemesis	1 (0.1) [na]	0
Haemorrhage NOS	1 (0.1) [na]	0
Haemorrhoids	1 (0.1) [na]	0

Hypertension	1 (0.1) [na]	0
Megacolon congenital	1 (0.1) [na]	0
Micturition disorder	1 (0.1) [na]	0
Oedema	1 (0.1) [na]	0
Paranoid reaction	1 (0.1) [na]	0
Paresis	1 (0.1) [na]	0
Sick sinus syndrome	1 (0.1) [na]	0
Skin ulceration	1 (0.1) [na]	0
Renal calculus	1 (0.1) [na]	0
Renal tubular necrosis	1 (0.1) [na]	0
Respiratory disorder	1 (0.1) [na]	0
Strangury	1 (0.1) [na]	0
Syncope	1 (0.1) [na]	0
Pain	0	2 (0.2) [na]
Transient ischaemic attack	0	2 (0.2) [na]
Urinary tract infection	0	2 (0.2) [na]
Abdominal pain	0	1 (0.1) [na]
Asthenia	0	1 (0.1) [na]
Atelectasis	0	1 (0.1) [na]
Bladder carcinoma	0	1 (0.1) [na]
Coma	0	1 (0.1) [na]
Delirium	0	1 (0.1) [na]
Diarrhoea, clostridium difficile	0	1 (0.1) [na]
Enterocolitis	0	1 (0.1) [na]
Fracture pathological	0	1 (0.1) [na]
Hernia inguinal	0	1 (0.1) [na]
Hyperglycaemia	0	1 (0.1) [na]
Hypoaesthesia	0	1 (0.1) [na]
Hypovolaemia	0	1 (0.1) [na]
Intestinal perforation	0	1 (0.1) [na]
Neoplasm malignant aggravated	0	1 (0.1) [na]
Oedema peripheral	0	1 (0.1) [na]
Palpitation	0	1 (0.1) [na]
Peripheral gangrene	0	1 (0.1) [na]
Pneumonitis	0	1 (0.1) [na]
Prostatic disorder	0	1 (0.1) [na]
Sepsis	0	1 (0.1) [na]
Tachycardia supraventricular	0	1 (0.1) [na]
Urinary retention	0	1 (0.1) [na]
Vertigo	0	1 (0.1) [na]
Weight decrease	0	1 (0.1) [na]
<b>Deaths after first injection (All treated subjects)</b>	<b>FX 2.5 mg o.d. (N = 1128)</b>	<b>EN 30 mg b.i.d. (N = 1129)</b>
	<b>n (%)</b>	<b>n (%)</b>
Subjects with SAE between first injection & Day 11:		
Leading to death between first injection & Day 11	3 (0.3)	1 (0.1)
Leading to death between Days 12 & 49	0	1 (0.1)
Subjects with SAE from Day 12:		

Leading to death between Days 12 & 49	3 (0.3)	1 (0.1)
Leading to death after the end of the study	0	1 (0.1)
Total deaths between first injection & Day 49	6 (0.5)	3 (0.3)
Total deaths reported	6 (0.5)	4 (0.4)
<b>Deaths between first injection and Day 49 by adjudication criterion (All treated subjects)</b>	<b>FX 2.5 mg o.d. (N = 1128)</b>	<b>EN 30 mg b.i.d. (N = 1129)</b>
	<b>n (%)</b>	<b>n (%)</b>
Fatal PE	1 (0.1)	2 (0.2)
Death not associated with VTE or bleeding	5 (0.4)	1 (0.1)
Total	6 (0.5)	3 (0.3)
<b>Pharmacokinetic results:</b>		
PK parameters	<b>FX 2.5 mg o.d. N = 64</b>	
$C_{maxss}$ (mg/L), mean (SD)	0.390 (0.119)*	
$C_{minss}$ (mg/L)	0.140 (0.078)*	
AUC (mg/L)	5.71 (2.46)	
*N=53, since steady-state condition was not reached for 11 subjects during treatment. SS = steady state. AUC is also the estimate of AUC in the 0-24 dosing interval at steady state.		

**Conclusion:**

See publication below.

**Publications:**

Turpie AGG. Post-operative fondaparinux versus post-operative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet 2002; 359: 1721-26.

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