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Study No.: AR3103414
Title: A multicenter, randomized, double-blind, parallel group trial to demonstrate the efficacy of fondaparinux sodium in association with Intermittent Pneumatic Compression versus Intermittent Pneumatic Compression used alone for the prevention of venous thromboembolic events in subjects at increased risk undergoing major abdominal surgery (APOLLO)
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), and/or symptomatic pulmonary embolism (PE), which are major post-operative complications following orthopedic surgery of the lower limbs. It was expected that the improved benefit /risk ratio of FX would also be observed in other high-risk VTE situations such as abdominal surgery. In this confirmatory study, FX 2.5 mg in combination with Intermittent Pneumatic Compression (IPC) was compared with placebo in combination with IPC for the prevention of VTE in subjects who have undergone abdominal surgery and are at increased risk for VTE.
Phase: III
Study Period: 26 November 2001 – 27 October 2004
Study Design: Multicenter, randomized, double-blind, placebo-controlled, parallel-group study
Centers: 50 centers in the US
Indication: Prevention of venous thromboembolic events in subjects at increased risk undergoing major abdominal surgery in association with IPC.
Treatment: 2.5 mg FX sodium (or FX placebo) given subcutaneously (s.c.) starting 6-8 hours post-operatively and then once daily for 7 ±2 days (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 10, but not more than one calendar day after the last study treatment administration. All subjects were also to have IPC therapy concomitantly.
Objectives: The primary objective was to demonstrate efficacy of FX 2.5 mg o.d. s.c. injections, started post-operatively versus placebo for the prevention of VTE, i.e. DVT and symptomatic PE, up to day 10, in subjects at increased risk of VTE undergoing abdominal surgery and receiving background mechanical prophylaxis with IPC.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the cluster of one or more of the following VTE outcomes, evaluated (by an independent adjudicating committee) up to the first venogram or up to Day 10, whichever came first (hereafter stated as “up to day 10”): venogram positive for DVT between Day 5 and Day 10, symptomatic DVT and/or non-fatal PE, fatal PE.
Secondary Outcome/Efficacy Variables: Secondary efficacy endpoints: Any DVT, any proximal DVT, and distal only DVT recorded up to Day 10; adjudicated symptomatic VTE (DVT, non fatal PE, and fatal PE) recorded up to Day 10 and up to Day 32 (whole study period); adjudicated VTE and all deaths recorded up to Day 10; adjudicated symptomatic VTE and all deaths recorded up to Day 32. Initiation of curative treatment after VTE assessment used for the primary endpoint evaluation. Safety: The main safety endpoint was the incidence of major bleeding (any investigator-reported unusual bleeding, recorded during the treatment period [between the first injection of study drug and 2 calendar days after the last injection]) and adjudicated as a major bleeding event by the Central Adjudication Committee (CAC). Major bleeding was defined as: fatal bleeding, surgical bleeding leading to intervention; non-surgical site bleeding: retroperitoneal or intracranial bleeding, or bleeding into a critical organ (eye, adrenal gland, pericardium, spine) or leading to intervention, and/or a bleeding index ≥2. Other safety variables were: major bleeding between first injection and Day 32 (whole study period), minor bleeding (any overt bleeding not meeting definition of major bleeding), transfusion requirements, adverse events (AEs/serious adverse events [SAEs]), and deaths.
Statistical Methods: Sample Size: Based on the assumption of a VTE rate of 12% in the placebo group and an expected odds ratio reduction of 50% in the FX group, with 375 evaluable subjects per group, the study would have 79% power to detect a significant difference (two-sided $\alpha = 0.05$) between the two treatment groups. Therefore, approximately 1070 subjects were to be randomized in order to have 750 subjects with available adequate VTE assessment (375 per group). A blinded in-stream data review by the Steering Committee (SC) showed a lower global event rate than expected (4% on the first 800 subjects randomized), so the SC recommended increasing the planned number of subjects to 1310 in order to have 918 subjects with available adequate VTE assessment (459 per group). Based on a revised assumption of a VTE rate of 5.33% in the placebo group and an odds ratio reduction of 50% in the FX group, with 459 evaluable subjects, the study was expected to have 47% power to detect a significant difference (two-sided $\alpha = 0.05$) between

the two treatment groups.

Analysis populations:

'Randomized': This population was defined as all subjects who signed informed consent and were planned to receive study drug.

'All Treated': This population was defined as all randomized subjects who received at least one dose of study drug, where subjects were analyzed according to originally assigned treatment group..

'As Treated': This population (included in the safety analyses) was defined as all randomized subjects who received at least one dose of study drug, where subjects were analyzed according to actual treatment received. Subjects who received both treatments were analyzed in the FX group.

'Primary Efficacy': This population (used for the primary efficacy analysis) was defined as all randomized subjects who received at least one dose of study drug, underwent abdominal surgery lasting longer than 45 minutes, and with a non-missing primary efficacy assessment up to and including Day 10. Subjects were analyzed "as randomized" in all efficacy analyses on an intent-to-treat (ITT) principle.

Efficacy analysis: The main efficacy analysis was performed on data from the first injection up to the first venogram or Day 10 (whichever occurred first). For adjudicated VTE, any DVT, proximal DVT, adjudicated symptomatic VTE, and adjudicated symptomatic VTE plus all deaths, the incidence, percentage and associated 95% confidence interval (CI) was presented, the percentage difference (FX - placebo), percentage odds ratio reduction (ORR), percentage relative risk reduction (RRR) and 95% CI were calculated and the two groups compared using a two-sided Fishers Exact Test. A significance level of 4.8% was used for the primary efficacy comparison to account for the interim analysis.

Safety analysis: The main safety analysis was performed for the period running from the first study drug injection up to 2 calendar days after the last study drug injection (treatment period). Additional safety analyses were performed for the period running from first study drug injection up to Day 32. For the number of active injections, the two treatment groups were compared using a Wilcoxon rank sum test. For major, minor, and any bleeds, the percentage difference (FX - placebo) and corresponding 95% CIs were calculated. The two treatment groups were compared using a two-sided Fisher's exact test.

Study Population: Subjects were eligible if they were undergoing abdominal surgery (defined as surgery between the diaphragm and the pelvic floor), lasting longer than 45 min (from anesthesia induction to incision closure); over 40 years old.

Exclusion criteria were based on the labeling of low molecular weight heparin in force at the time of study conduct (e.g. 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 (e.g. serum creatinine $>2 \text{ mg/dL}$ [$180 \mu\text{mol/L}$] or hypersensitivity to contrast media), or those relating to trial methodology (e.g. current or recent DVT, contraindication to heparin or oral anti-coagulant, use of anticoagulant or fibrinolytic therapy during the screening period).

	FX 2.5 mg o.d.	Placebo
Number of Subjects:		
Planned enrolment (evaluable), N	655 (459)	655 (459)
Randomized, N	650	659
Randomized and treated, N ('all treated' Population)	636	649
As Treated population, N	635	650
Primary efficacy population, N	424	418
Completed study drug, n (% of all treated population)	579 (91.0)	591 (91.1)
Total number subjects withdrawn from study drug, N (% of all treated population)	57 (9.0)	58 (8.9)
Withdrawn due to Adverse Events n (% of all treated population)	23 (3.6)	17 (2.6)
Withdrawn due to Lack of Efficacy n (% of all treated population)	1 (0.2)	2 (0.3)
Withdrawn for other reasons n (% of all treated population)	33 (5.2)	39 (6.0)
Demographics	FX 2.5 mg o.d.	Placebo
N (all treated population)	636	649
Males:Females	314:322	321:328
Mean Age, years (SD)	60.0 (12.16)	60.2 (12.24)
Caucasian, n (%)	542 (85.2)	559 (86.1)
Primary Efficacy Results:		
Subjects with VTE up to Day 10 (Primary Efficacy Population)	FX 2.5 mg o.d.	Placebo
n/N (%)	7/424 (1.7%)	22/418 (5.3)
% ORR by FX	-69.8%	

Nominal 95% CI for ORR	(-87.3, -27.9)	
p-value (Fisher's exact test)	0.004	
Secondary Outcome Variable(s):		
Subjects with any DVT up to Day 10 (Primary Efficacy Population)		
n/N (%)	7/423 (1.7)	22/418 (5.3)
% ORR by FX	-69.7	
95% CI for ORR	(-87.2, -28.3)	
Subjects with any proximal DVT up to Day 10 (Primary Efficacy Population)		
n/N (%)	1/423 (0.2)	7/417 (1.7)
% ORR by FX	-86.1	
95% CI for ORR	(-98.3, 13.3)	
Subjects with any distal only DVT up to Day 10 (Primary Efficacy Population)		
n/N (%)	6/422 (1.4)	17/417 (4.1)
95% CI	(0.5; 3.1)	(2.4; 6.4)
Adjudicated symptomatic VTE up to Day 10 (Randomized Population)		
n/N (%)	1/650 (0.2)	1/659 (0.2)
Adjudicated Symptomatic VTE up to Day 32 (Randomized Population)		
n/N (%)	2/650 (0.3)	4/659 (0.6)
Adjudicated VTE and all deaths up to Day 10 (Randomized Population)		
n/N (%)	9/650 (1.4)	24/659 (3.6)
Adjudicated Symptomatic VTE and all deaths up to Day 32 (Randomized Population)		
n/N (%)	9/650 (1.4)	8/659 (1.2)
All subjects with antithrombotic curative treatment initiated after VTE assessment up to Day 10 (Primary Efficacy Population)		
Total, n/N (%)	8/ 424 (1.9)	16/418 (3.8)
LMW heparin(oid)s, n/N (%)	8/424 (1.9)	13/418 (3.1)
Other than heparin or Vitamin K, n/N (%)	0	1/418 (0.1)
Medication not reported, n/N (%)	0	2/418 (0.5)
Safety Results:		
Bleeding Assessments and Related Criteria ('As Treated' Population)	FX 2.5 mg o.d.	Placebo
Adjudicated bleeding results during treatment period, n (%)		
Major bleeding	10/635 (1.6)	1/650 (0.2)
Fatal bleeding	0	0
Minor bleeding	5/635 (0.8)	3/650 (0.5)
Any bleeding	15/635 (2.4)	4/650 (0.6)
Adjudicated bleeding results during whole study period, n (%)		
Major bleeding	16/635 (2.5)	2/650 (0.3)
Fatal bleeding	3/635 (0.5)	0
Minor bleeding	4/635 (0.6)	4/650 (0.6)
Any bleeding	20/635 (3.1)	6/650 (0.9)
Subjects requiring transfusion, n(%)		
Treatment period	63/635 (9.9)	43/650 (6.6)
Whole study period	76/635 (12.0)	61/650 (9.4)
Adverse event results: AEs and SAEs were recorded during the treatment period, which is from first injection of study medication continuing to 2 calendar days after the last injection.		
	FX 2.5 mg o.d. (N = 635)	Placebo (N = 650)

Adverse Events – treatment period (as treated subjects)	n (%)	n (%)
Subjects with any AEs	406 (63.9)	361 (55.5)
10 most frequent AEs in each treatment group		
Hypokalemia	43 (6.8)	43 (6.6)
Pyrexia	40 (6.3)	47 (7.2)
Anemia post-operative	27 (4.3)	19 (2.9)
Anemia	27 (4.3)	18 (2.8)
Post-operative ileus	24 (3.8)	15 (2.3)
Pruritus	22 (3.5)	21 (3.2)
Headache	22 (3.5)	12 (1.8)
Insomnia	19 (3.0)	15 (2.3)
Confusional state	19 (3.0)	16 (2.5)
Post-operative infection	14 (2.2)	14 (2.2)
Ileus	13 (2.0)	13 (2.0)
Serious Adverse Events		
	FX 2.5 mg o.d. (N = 635)	Placebo (N = 650)
All SAEs (fatal and non-fatal) – treatment period (All Treated subjects)	n (%) [related]	n (%) [related]
Subjects with any SAE(s), by MedDRA Organ Class [number considered by investigator to be related to study medication]	70 (11.0) [8]	66 (10.2) [4]
<i>Injury, Poisoning, and Procedural Complications</i>		
Post-operative ileus	14 (2.2) [0]	6 (0.9) [0]
Post-procedural hemorrhage	5 (0.8) [3]	1 (0.2) [1]
Wound dehiscence	4 (0.6) [0]	1 (0.2) [0]
Anastomotic leak	2 (0.3) [0]	0
Post-procedural hematoma	2 (0.3) [2]	0
Incision site hemorrhage	1 (0.2) [1]	1 (0.2) [1]
Colonic perforation	1 (0.2) [0]	0
Post-operative femur fracture	1 (0.2) [0]	0
Hematuria traumatic	1 (0.2) [1]	0
Intestinal stoma complication	1 (0.2) [0]	0
Post-procedural pain	1 (0.2) [0]	0
Urinary anastomotic leak	1 (0.2) [0]	0
Anemia postoperative	0	1 (0.2) [0]
Incision site complication	0	1 (0.2) [0]
Post-procedural diarrhea	0	1 (0.2) [0]
Post-operative fever	0	1 (0.2) [0]
<i>Gastrointestinal Disorders</i>		
Ileus	5 (0.8) [0]	5 (0.8) [0]
Nausea	2 (0.3) [0]	1 (0.2) [0]
Abdominal pain	2 (0.3) [0]	0
Peritonitis	2 (0.3) [0]	0
Abdominal compartment syndrome	1 (0.2) [0]	0
Abdominal symptom	1 (0.2) [0]	0
Gastric outlet obstruction	1 (0.2) [0]	0
Gastrointestinal hemorrhage	1 (0.2) [0]	0
Pancreatitis acute	1 (0.2) [0]	0
Small intestinal obstruction	0	3 (0.5) [0]
Diarrhea	0	1 (0.2) [0]
Dysphagia	0	1 (0.2) [0]
Enterocutaneous fistula	0	1 (0.2) [0]
Gastrointestinal motility disorder	0	1 (0.2) [0]
Small intestinal perforation	0	1 (0.2) [0]
<i>Infections and Infestations</i>		

Sepsis	7 (1.1) [0]	0
Pneumonia	3 (0.5) [0]	3 (0.5) [0]
Post-operative infection	2 (0.3) [1]	3 (0.5) [0]
Lobar pneumonia	1 (0.2) [0]	0
Wound infection	1 (0.2) [0]	0
Post-operative abscess	0	3 (0.5) [0]
Abdominal abscess	0	2 (0.3) [0]
Urinary tract infection	0	2 (0.3) [0]
Gastroenteritis	0	1 (0.2) [0]
Hematoma infection	0	1 (0.2) [1]
Infection	0	1 (0.2) [0]
Influenza	0	1 (0.2) [0]
Subcutaneous abscess	0	1 (0.2) [0]
<i>Cardiac Disorders</i>		
Cardiac failure congestive	3 (0.5) [0]	0
Arrhythmia	2 (0.3) [0]	0
Arrhythmia supraventricular	1 (0.2) [0]	0
Cardiac failure	1 (0.2) [0]	0
Sick sinus syndrome	1 (0.2) [0]	0
Atrial fibrillation	0	2 (0.3) [0]
Angina pectoris	0	1 (0.2) [0]
<i>Respiratory, Thoracic and Mediastinal Disorders</i>		
Respiratory failure	2 (0.3) [0]	1 (0.2) [0]
Pneumonia aspiration	1 (0.2) [0]	2 (0.3) [0]
Respiratory distress	1 (0.2) [0]	1 (0.2) [0]
Atelectasis	1 (0.2) [0]	0
Hypoxia	1 (0.2) [0]	0
Lung infiltration	1 (0.2) [0]	0
Pulmonary edema	0	2 (0.3) [0]
Asthma	0	1 (0.2) [0]
Chronic obstructive airways disease exacerbated	0	1 (0.2) [0]
Pleural effusion	0	1 (0.2) [0]
<i>Vascular Disorders</i>		
Hypotension	3 (0.5) [0]	0
Flushing	1 (0.2) [0]	0
Pallor	1 (0.2) [0]	0
Phlebothrombosis	1 (0.2) [0]	0
Jugular vein thrombosis	0	1 (0.2) [0]
<i>Renal and Urinary Disorders</i>		
Renal failure acute	3 (0.5) [0]	0
Renal insufficiency	1 (0.2) [0]	1 (0.2) [0]
Hematuria	1 (0.2) [0]	0
Urinary retention	0	2 (0.3) [0]
Calculus urinary	0	1 (0.2) [0]
<i>Psychiatric Disorders</i>		
Anxiety	1 (0.2) [0]	0
Confusional state	1 (0.2) [0]	0
Mental status changes	1 (0.2) [0]	0
Delirium	0	1 (0.2) [0]
<i>Skin and Subcutaneous Tissue Disorders</i>		
Dermatitis allergic	2 (0.3) [0]	0
<i>General Disorders and Administration Site Conditions</i>		
Asthenia	1 (0.2) [0]	0
Pyrexia	0	2 (0.3) [0]
Impaired healing	0	1 (0.2) [0]

<i>Nervous System Disorders</i>		
Vocal cord paresis	1 (0.2) [0]	0
Encephalopathy	0	1 (0.2) [0]
Ischemic stroke	0	1 (0.2) [0]
<i>Investigations</i>		
Liver function test abnormal	1 (0.2) [0]	0
<i>Metabolism and Nutrition Disorders</i>		
Dehydration	0	2 (0.3) [0]
Diabetes mellitus	0	1 (0.2) [0]
Hypokalemia	0	1 (0.2) [0]
<i>Surgical and Medical Procedures</i>		
Vena cava filter insertion	0	2 (0.3) [0]
<i>Blood and Lymphatic System Disorders</i>		
Thrombocytopenia	0	1 (0.2) [1]
Subjects with fatal SAEs		
	FX 2.5 mg o.d. (N = 635)	Placebo (N = 650)
Deaths – treatment period (as treated subjects)	n (%) [related]	n (%) [related]
Subjects with any fatal SAEs, [number considered by investigator to be related to study medication]	1 (0.2) [0]	2 (0.3) [0]
Cardiac failure	1 (0.2) [0]	0
Abdominal abscess	0	1 (0.2) [0]
Respiratory failure	0	1 (0.2) [0]
Conclusion:		
<p>FX significantly reduced the incidence of adjudicated VTE from 5.3% (placebo group) to 1.7% in subjects at increased risk of VTE undergoing abdominal surgery and receiving background mechanical prophylaxis with IPC. In the FX group, there was a reduced incidence of any DVT, proximal DVT, distal DVT, and adjudicated VTEs and all deaths, each up to Day 10, plus symptomatic VTEs up to Day 32. In the FX group, there was also a reduced number of subjects with antithrombotic curative treatment initiated after VTE assessment up to Day 10. The incidences of non-fatal PEs, and adjudicated symptomatic VTE, each up to Day 10, were the same between the treatment groups. There were no fatal PEs up to Day 10. In the placebo group, there was a reduced incidence of symptomatic VTEs and all deaths up to Day 32. The rates of major bleeding and all bleeding were significantly higher in the FX group compared with placebo during the treatment period and during the whole study period. In the FX group, 406 subjects reported non-serious AEs during the treatment period, with the most frequently reported being hypokalemia and pyrexia. In the placebo group, 361 subjects reported non-serious AEs during the treatment period, with the most frequently reported being hypokalemia and pyrexia. In the FX group, 70 subjects reported SAEs during the treatment period, with the most frequently reported being post-operative ileus and sepsis. In the placebo group, 66 subjects reported SAEs during the treatment period, with the most frequently reported being post-operative ileus and ileus. There was 1 fatality in the FX group and 2 fatalities in the placebo group during the treatment period.</p>		
Publications:		
No Publication		

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