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Study No.: EFC2441
Title: A multicentre, randomized, double-blind study comparing the efficacy and safety of once daily (o.d.) Org31540/SR90107A versus twice daily (b.i.d.) enoxaparin in the initial treatment of acute symptomatic deep vein thrombosis (DVT) (MATISSE-DVT)
Rationale: At the time of this study, the currently approved treatment for venous thromboembolic events (VTE) was either unfractionated heparin (UFH), or low molecular weight heparin (LMWH, e.g., enoxaparin sodium [ENX]), given for 5 to 10 days together with International Normalized Ratio (INR) adjusted vitamin K antagonist therapy that was continued for 3 months or longer. However, heparins are animal-sourced products and expose subjects to severe immunoallergic reactions such as heparin-induced thrombocytopenia, and to other non-hemorrhagic adverse drug reactions. Therefore, there is room to improve the therapeutic management of subjects with DVT. Studies have shown that fondaparinux (FX), a synthetic and selective inhibitor of activated factor X (factor Xa), may be appropriate for prevention of DVT. This study was to evaluate whether a o.d. dose of FX was at least as effective as b.i.d. ENX.
Phase: III
Study Period: 05 April 2000 to 18 October 2001
Study Design: A multicenter, randomized, double-blind, double-dummy, parallel group, non-inferiority study
Centres: 154 centers in 23 countries: USA (25) Denmark (3), Norway (2) Sweden (6), Australia (16), France (9), Belgium (9), Netherlands (7), Czech Republic (7), Spain (5), Portugal (4), Greece (3), Italy (9), Poland (4), Germany (6), Hungary (3), Switzerland (6), Great Britain (5), Austria (3), Argentina (8), Canada (9), South Africa (3), and New Zealand (2).
Indication: Initial treatment of acute symptomatic DVT
Treatment: Subjects were randomized to receive 1 of the following 2 treatments: Fondaparinux sodium (FX) subcutaneous (s.c.) according to body weight: 5mg (body weight <50 kg), 7.5mg (body weight 50-100 kg inclusive), or 10mg (body weight >100 kg) o.d.; or ENX 0.4mL s.c. b.i.d. (1mg/kg) The duration of treatment was at least 5 days and was to be initiated within 6 hours post-randomization. Vitamin K antagonist therapy was initiated within 72 hours after first study drug administration to reach International Normalized Ratio (INR) of 2.5, and continued up to Day 90±7.
Objectives: To demonstrate that a o.d. s.c. injection of FX was at least as effective as a b.i.d. s.c. injection of ENX in the initial treatment of subjects with a confirmed diagnosis of acute symptomatic DVT.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was recurrent VTE up to Day 97, adjudicated by a blinded Central Independent Adjudication Committee (CIAC) and defined as the composite of: Symptomatic non-fatal VTE (DVT and/or pulmonary embolism [PE]) Fatal VTE (death related to VTE or unexplained death [i.e., death for which VTE could not be ruled out]).
Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoint: The individual components of the primary efficacy endpoint.
Statistical Methods: <u>Populations Analyzed:</u> The primary efficacy analysis was performed on the 'all randomized subjects' population. Safety analyses were performed on the 'as treated subjects' (subjects analyzed according to the treatment actually received) and 'all randomized' populations. The following 2 periods were used in efficacy and safety analyses: Whole study period up to Day 97. This period was the main period for the primary efficacy analysis (from day of randomization) and also used for safety analyses (from the first study drug administration) Initial treatment period, starting with first study drug administration and ending 3 days after study drug was stopped if CLCr≥50mL/min, 4 days if 30≤CLCr<50mL/min and 9 days if CLCr<30mL/min or was missing. This period was the main period for safety analyses and also used for the secondary analyses of the primary efficacy endpoint. <u>Efficacy Analyses:</u> The primary efficacy analysis was the calculation of the difference in the crude VTE rates between the 2 treatment groups, FX minus ENX, with its 2-sided 95% confidence interval (CI) (normal approximation). The pre-specified non-inferiority margin was 3.5%. <u>Safety Analyses:</u> Two-sided Fisher's exact tests were used to compare main safety outcomes between the 2 treatment groups. Statistical comparison of AEs (with an incidence >2% in either treatment group) was made using Chi-square test, and laboratory parameters were compared using Wilcoxon rank sum test.
Study Population: Subjects with confirmed diagnosis of acute symptomatic DVT in the trifurcation of the calf veins

and/or more proximal veins, aged ≥ 18 yrs were eligible for participation in the study. Exclusion criteria included symptomatic PE and those based on the labelling of LMWH in force at the time of study conduct (such as active clinically significant bleeding, presence or history of low platelet count ($100 \times 10^9/L$), or known bleeding disorder), or those relating to venography (such as serum creatinine $>2\text{mg/dL}$ ($180\mu\text{mol/L}$) or hypersensitivity to contrast media) or use of anticoagulant or thrombolytic therapy for more than 24 hours prior to randomization.		
Number of Subjects:	FX	ENX
Planned, N	1100	1100
All Randomized, N	1098	1107
All Randomized and Treated	1093	1099
As Treated Population	1091	1101
Completed, n (%)	1031 (94.3)	1022 (93.0)
Total Number Subjects Who Prematurely Discontinued Study Drug, n (% of All Randomized and Treated Population)	62 (5.7)	77 (7.0)
Due to AEs n (%)	18 (1.6)	25 (2.3)
Withdrawn due to lack of efficacy, n (%) Reached endpoint – DVT/PE	14 (1.3)	8 (0.7)
Other reasons, n (%)	30 (2.8)	44 (4.0)
Demographics (All Randomized population)	FX	ENX
Females: Males, n:n	517:581	529:578
Mean Age, years (Standard Deviation [SD])	61.1 (16.7)	61.5 (16.5)
Caucasian, n (%)	1063 (96.8)	1078 (97.4)
Primary Efficacy Results (All Randomized population):		
	FX N=1098	ENX N=1107
Subjects With recurrent symptomatic VTE up to Day 97, n (%)	43 (3.9)	45 (4.1)
95% CI	[2.8, 5.2]	[3.0, 5.4]
Difference FX - ENX	-0.1	
95% CI for Difference	[-1.8, 1.5]	
Secondary Outcome Variables (All Randomized population):		
	FX N=1098	ENX N=1107
Subjects With Symptomatic DVT Only up to Day 97, n (%)	18 (1.6)	28 (2.5)
95% CI	[1.0, 2.6]	[1.7, 3.6]
Difference FX - ENX	-0.9	
95% CI for Difference	[-2.1, 0.3]	
Subjects with Non-fatal PE up to Day 97, n (%)	20 (1.8)	12 (1.1)
95% CI	[1.1, 2.8]	[0.6, 1.9]
Difference FX - ENX	0.7	
95% CI for Difference	[-0.3, 1.7]	
	FX N=1098	ENX N=1107
Subjects with Fatal VTE up to Day 97, n (%)	5 (0.5)	5 (0.5)
95% CI	[0.1, 1.1]	[0.1, 1.1]
Difference FX - ENX	0.0	
95% CI for Difference	[-0.6, 0.6]	
Safety Results (As Treated Population): All bleeding events, AEs and SAEs reported during the initial treatment period. Deaths reported during the entire study period from first injection up to day 97		
Most Frequent AEs During the Initial Treatment Period	FX N=1091	ENX N=1101
Subjects with any AEs, n (%)	391 (35.8)	467 (42.4)
10 most frequent AEs in each treatment group, n (%)		
Nausea	27 (2.5)	29 (2.6)
Constipation	21 (1.9)	32 (2.9)
Diarrhea	15 (1.4)	22 (2.0)
Vomiting	13 (1.2)	14 (1.3)

Bruise	9 (0.8)	24 (2.2)
Hematoma	13 (1.2)	17 (1.5)
Fever	25 (2.3)	32 (2.9)
Hepatic Enzymes Increased	4 (0.4)	52 (4.7)
SGPT Increased	2 (0.2)	47 (4.3)
SGOT Increased	1 (0.1)	31 (2.8)
Headache	35 (3.2)	37 (3.4)
Coughing	14 (1.3)	7 (0.6)
Pneumonia	13 (1.2)	5 (0.5)
Insomnia	25 (2.3)	19 (1.7)
Urinary Tract Infection	23 (2.1)	20 (1.8)
Serious Adverse Events		
SAEs During the Initial Treatment Period	FX N=1091	ENX N=1101
Subjects with any fatal or non-fatal SAE(s), n (%) [considered by the investigator to be related to study medication]	44 (4.0) [11]	41 (3.7) [14]
Hematoma	5 (0.5) [4]	4 (0.4) [4]
Gastrointestinal Hemorrhage	3 (0.3) [1]	3 (0.3) [2]
Hematuria	2 (0.2) [0]	3 (0.3) [3]
Duodenal Ulcer Hemorrhagic	2 (0.2) [1]	0
Hemarthrosis	1 (0.1) [1]	1 (0.1) [1]
Hemorrhage Not Otherwise Specified (NOS)	0	2 (0.2) [2]
Hemorrhage Rectum	0	2 (0.2) [2]
Vaginal Hemorrhage	1 (0.1) [1]	1 (0.1) [0]
Bleeding Time Increased	0	1 (0.1) [0]
Cerebral Hemorrhage	1 (0.1) [0]	0
Circulatory Failure	1 (0.1) [0]	0
Epistaxis	1 (0.1) [1]	0
Hemorrhage Retroperitoneal	1 (0.1) [1]	0
Hepatic Hemorrhage	1 (0.1) [1]	0
Melaena	1 (0.1) [1]	0
Prothrombin Decreased	1 (0.1) [0]	0
Thrombosis Arterial Leg	1 (0.1) [0]	0
Thrombosis Venous Arm	1 (0.1) [0]	0
Fever	1 (0.1) [0]	1 (0.1) [0]
Pain	1 (0.1) [0]	1 (0.1) [0]
Chest Pain	1 (0.1) [0]	0
Condition Aggravated	1 (0.1) [0]	0
Leg Pain	0	1 (0.1) [0]
Edema Peripheral	1 (0.1) [0]	0
Bladder Carcinoma	1 (0.1) [0]	0
Cervix Carcinoma	0	1 (0.1) [0]
Colon Carcinoma	1 (0.1) [0]	0
Endometrial Neoplasm Malignant	0	1 (0.1) [0]
Neoplasm Malignant	0	1 (0.1) [0]
Neoplasm Malignant Aggravated	1 (0.1) [0]	0
Pulmonary Carcinoma	1 (0.1) [0]	0
Uterine Fibroid	0	1 (0.1) [0]
Abscess	0	1 (0.1) [1]
Infection	1 (0.1) [0]	0
Otitis Media	1 (0.1) [0]	0
Post-operative Wound Infection	1 (0.1) [0]	0
Sepsis	0	1 (0.1) [0]
Stupor	1 (0.1) [0]	1 (0.1) [0]
Coma	1 (0.1) [0]	0

Convulsions	0	1 (0.1) [0]
Headache	0	1 (0.1) [0]
Hypertension Intracranial	1 (0.1) [0]	0
Diabetes Mellitus	2 (0.2) [0]	0
Gout	0	1 (0.1) [0]
Hyperglycemia	0	1 (0.1) [0]
Pneumonia	3 (0.3) [0]	0
Pleurisy	1 (0.1) [0]	0
Pneumonia Lobar	1 (0.1) [0]	0
	FX N=1091	ENX N=1101
Respiratory Insufficiency	1 (0.1) [0]	0
Inflicted Injury	1 (0.1) [0]	2 (0.2) [0]
Metastases NOS	0	1 (0.1) [0]
Intestinal Obstruction	0	3 (0.3) [0]
Cardiac Arrest	1 (0.1) [0]	0
Fibrillation Ventricular	0	1 (0.1) [0]
Tachycardia Supraventricular	0	1 (0.1) [0]
Cholelithiasis	0	1 (0.1) [0]
Hepatic Function Abnormal	0	1 (0.1) [0]
Athropathy	0	1 (0.1) [0]
Arthrosis	1 (0.1) [0]	0
Cystitis	0	1 (0.1) [0]
Hydronephrosis	0	1 (0.1) [0]
Cellulitis	1 (0.1) [0]	0
Cardiac Failure	0	1 (0.1) [0]
LE Syndrome	1 (0.1) [0]	0
Angina Pectoris	0	1 (0.1) [0]
Anemia	0	1 (0.1) [0]
Prostatic Disorder	0	1 (0.1) [0]
Rash	0	1 (0.1) [1]
	FX N=1091	ENX N=1101
Subjects with fatal SAEs during the treatment period	9 (0.8) [0]	2 (0.2) [0]
Pneumonia lobar	1 (0.1) [0]	0
Neoplasm malignant aggravated	1 (0.1) [0]	0
Coma	1 (0.1) [0]	0
Hemorrhage retroperitoneal	1 (0.1) [0]	0
Cardiac arrest	1 (0.1) [0]	0
Colon carcinoma	1 (0.1) [0]	0
Hepatic hemorrhage	1 (0.1) [0]	0
Pneumonia	1 (0.1) [0]	0
Hypertension intracranial	1 (0.1) [0]	0
Endometrial neoplasm malignant	0	1 (0.1) [0]
Hepatic function abnormal	0	1 (0.1) [0]
Conclusion: See publication below.		
Publications: Buller HR. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004 Jun 1;140 (11):867-73. Fondaparinux in the treatment of deep-vein thrombosis and pulmonary embolism, Buller, European Hematology Association, Geneva, Switzerland, June 10-13, 2004.		

Fondaparinux (Arixtra®) is at least as effective and as safe as unfractionated heparin or low-molecular-weight heparin in the initial treatment of symptomatic venous thromboembolism): The MATISSE trials, Piovella, European Association of Hospital Pharmacists, Sevilla, Spain, March 17-19, 2004.

Initial outpatient treatment of venous thromboembolism with fondaparinux (Arixtra): The MATISSE trials, Buller, *American Society of Haematology, San Diego, USA, December 4-7, 2004.* (oral)

Efficacy and safety of fondaparinux (Arixtra) in the initial treatment of venous thromboembolism in obese patients, Buller, *American Society of Haematology, San Diego, USA, December 4-7, 2004.* (oral)

Abstract: The matisse-dvt trial, a randomized, double-blind study comparing once-daily fondaparinux (arixtra®) with the low-molecular-weight heparin (LMWH) enoxaparin, twice daily, in the initial treatment of symptomatic deep-vein thrombosis (dvt). The Matisse Investigators 19th Congress of the International Society on Thrombosis and Haemostasis and 49th Annual Scientific and Standardisation Committee Meeting 7/12/2003 Birmingham; UK

Abstract: Fondaparinux, a pentasaccharide vs unfractionated heparin (UH) or low molecular weight heparin (lmwh) for pulmonary embolism (pe) or deep vein thrombosis (dvt): the matisse trials. B.L. Davidson, the Matisse Steering Committee and Investigators. 99th International Conference of the American Thoracic Society 5/16/2003

Abstract: Initial outpatient treatment of venous thromboembolism with fondaparinux (arixtra®): the matisse trials. Buller, H 20th Congress of the International Society on Thrombosis and Haemostasis held jointly with the 51st Annual Meeting of the Scientific and Standardization Committee 8/6/2005 Sydney; Australia

Abstract: Fondaparinux in the treatment of deep-vein thrombosis and pulmonary embolism. H.R. Buller, 9th Congress of the European Haematology Association 6/10/2004

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