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Study No.: 63123		
Title: A multicentre, randomized, open-label study comparing the efficacy and safety of once daily (o.d.) Org31540/SR90107A versus adjusted dose intravenous (i.v.) unfractionated heparin (UFH) in the initial treatment of acute symptomatic pulmonary embolism (PE) (MATISSE-PE)		
Rationale: UFH was the recommended treatment at the time of this study, for symptomatic PE but requires lengthy i.v. infusion with hospitalisation. Studies have shown that fondaparinux (FX), a synthetic and selective inhibitor of activated factor X (factor Xa), may be an appropriate treatment for prevention of PE and requires only a single daily dose as a subcutaneous (s.c.) injection, making it a more convenient treatment regimen. This study was to evaluate whether a once daily (o.d.) dose of FX was at least as effective as adjusted-dose i.v. UFH.		
Phase: III		
Study Period: 17 May 2000 – 12 June 2002		
Study Design: Multicenter, multinational, randomized, parallel group, non-inferiority, open-label study		
Centres: 214 centers in 20 countries: USA (67), Canada (15), Argentina (3), Australia (12), Austria (3), Belgium (4), Brazil (8), Czech Republic (4), Denmark (6), Finland (2), France (19), in Germany (10), Israel (5), Italy (13), The Netherlands (13), Poland (8), 5 Spain (5), Sweden (6), Switzerland (6), and UK (5)..		
Indication: Initial treatment of acute symptomatic PE		
Treatment: Subjects were randomized to FX or UFH. FX group: o.d. s.c. injections, 5.0 mg in subjects with body weight <50 kg, 7.5 mg in subjects with body weight between 50 and 100 kg inclusive, and 10.0 mg in subjects with body weight >100 kg. UFH group: initial i.v. bolus injection (≥5000 USP heparin units [HU]) then a continuous infusion starting at a rate of ≥1250 USP HU per hour adjusted to maintain activated Partial Thromboplastin Time (aPTT) at 1.5 to 2.5 x control. The duration of treatment was at least 5 daily injections of FX or not less than 108 hours of UFH 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 an o.d. s.c. injection of FX is at least as effective as adjusted-dose (aPTT, 1.5-2.5 x control) i.v. UFH, in the initial treatment of subjects with a confirmed diagnosis of acute symptomatic PE.		
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was recurrent VTE up to Day 97, adjudicated by a Central Independent Adjudication Committee (CIAC) and defined as the composite of symptomatic non-fatal venous thromboembolic events (VTE) (deep vein thrombosis(DVT) and/or PE), or fatal VTE (death related to VTE or unexplained 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: Analysis Populations: The “all randomized” population consisted of all randomized subjects regardless of whether they received study drug (FX or UFH). This population was used for analysis of efficacy. The “As treated” population consisted of all randomized subjects who took at least one dose of study drug (FX or UFH) and who were analysed in the treatment group according to the treatment actually received. This population was used for analysis of safety. Efficacy analyses: the primary analysis was the calculation of the difference in the crude VTE rates between the two treatment groups (FX minus UFH) with its 2-sided 95% confidence interval (CI) (normal approximation); the pre-specified non-inferiority margin was 3.5%. All pre-specified statistical testing was performed using 2-sided 95% CIs. Fisher’s exact tests were used to compare the two treatment groups on the main efficacy and safety parameters. Safety analyses: main safety outcomes between the two treatment groups were compared using two-sided Fisher’s exact tests; statistical comparison of AEs (with incidence >2% in either treatment group) used Chi-square tests; laboratory parameters were compared using Wilcoxon rank sum test.		
Study Population: Subjects with confirmed acute symptomatic PE aged ≥18 yrs were eligible for participation in the study. Exclusion criteria included: a PE requiring thrombolysis or surgical thrombectomy, 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 (100x10 ⁹ /L), or known bleeding disorder), or those relating to venography (such as serum creatinine >2mg/dL (180umol/L) or hypersensitivity to contrast media) or use of anticoagulant or thrombolytic therapy for more than 24 hours prior to randomization.		
	FX	UFH

Number of Subjects:		
Planned, N	1100	1100
All Randomized (Primary Efficacy Population), N	1103	1110
All Randomized and Treated Population	1090	1094
As treated, N	1092	1092
Total Number who discontinued study drug prematurely, N (% of All Randomized and Treated Population)	129 (11.8)	259 (23.7)
Withdrawn due to lack of efficacy (DVT or PE), n (%)	8 (0.7)	7 (0.6)
Withdrawn due to non-fatal AEs/SAEs, n (%)	25 (2.3)	42 (3.8)
Withdrawn for other reasons, n (%)	95 (8.8)	210 (19.2)
Demographics: (All Randomized population)	FX	UFH
Females : Males, n:n	601:501	633:477
Mean Age, years (Standard Deviation [SD])	62.6 (16.2)	62.3 (16.7)
Caucasian n (%)	1035 (93.9)	1039 (93.6)
Primary Efficacy Results (All Randomized population):		
Subjects with recurrent VTE up to Day 97	FX	UFH
n/N (%)	42/1103 (3.8)	56/1110 (5.0)
95% confidence interval (CI)	[2.8; 5.1]	[3.8; 6.5]
Difference (FX - UFH) (%)	-1.2	
95% CI for difference: lower bound; upper bound	[-3.0; 0.5]	
Secondary Outcome Variable(s) (All Randomized population):		
Subjects with any symptomatic DVT only up to Day 97	FX	UFH
n/N (%)	12/1103 (1.1)	17/1110 (1.5)
95% CI	[0.6; 1.9]	[0.9; 2.4]
Difference (FX - UFH) (%)	-0.4	
95% CI for difference: lower bound; upper bound	[-1.4; 0.5]	
Subjects with non-fatal PE up to Day 97	FX	UFH
n/N (%)	14/1103 (1.3)	24/1110 (2.2)
95% CI	[0.7; 2.1]	[1.4; 3.2]
Difference (FX - UFH) (%)	-0.9	
95% CI for difference: lower bound; upper bound	[-2.0; 0.2]	
Subjects with fatal VTE up to Day 97	FX	UFH
n/N (%)	16/1103 (1.5)	15/1110 (1.4)
95% CI	[0.8; 2.3]	[0.8; 2.2]
Difference (FX - UFH) (%)	0.1	
95% CI for difference: lower bound; upper bound	[-0.9; 1.1]	
Safety results: (As Treated Population): All AEs and SAEs reported during the initial treatment period starting with first study drug administration and ending 3 days after study drug was stopped if CLcr \geq 50mL/min, 4 days if 30 \leq CLcr<50mL/min and 9 days if CLcr<30mL/min or was missing. Deaths reported during the entire study period from first injection up to day 97.		
Most frequent Adverse Events During the Initial Treatment Period	FX N = 1092	UFH N = 1092
Subjects with any AE(s), n(%)	598 (54.8)	651 (59.6)
10 most frequent, n (%):		
Constipation	80 (7.3)	93 (8.5)
Insomnia	60 (5.5)	75 (6.9)
Headache	68 (6.2)	65 (6.0)
Nausea	48 (4.4)	53 (4.9)
Fever	52 (4.8)	47 (4.3)
Epistaxis	19 (1.7)	41 (3.8)
Prothrombin decreased	23 (2.1)	34 (3.1)
Back Pain	21 (1.9)	34 (3.1)
Coughing	33 (3.0)	26 (2.4)
Hepatic enzymes increased	3 (0.3)	30 (2.7)
Urinary tract infection	29 (2.7)	24 (2.2)

Abdominal pain	26 (2.4)	28 (2.6)
Diarrhea	25 (2.3)	27 (2.5)
Chest pain	24 (2.2)	26 (2.4)
Serious Adverse Events		
All SAEs (fatal & non-fatal) During the Initial Treatment Period	FX N = 1092	UFH N = 1092
Subjects with any fatal or non-fatal SAE(s) n (%) [considered by the investigator to be related to the study medication]	59 (5.4) [20]	68 (6.2) [17]
Haematoma	6 (0.5) [5]	2 (0.2) [1]
Anaemia	3 (0.3) [1]	2 (0.2) [1]
Cardiac arrest	3 (0.3) [0]	1 (0.1) [0]
Cardiac failure	3 (0.3) [0]	3 (0.3) [0]
Dyspnoea	3 (0.3) [0]	2 (0.2) [0]
Gastrointestinal haemorrhage	3 (0.3) [3]	4 (0.4) [2]
Haemorrhage nos	3 (0.3) [2]	0
Myocardial infarction	3 (0.3) [0]	0
Ovarian carcinoma	3 (0.3) [0]	2 (0.2) [1]
Haematuria	2 (0.2) [0]	0
Pancreas neoplasm malignant	2 (0.2) [0]	0
Pneumonia	2 (0.2) [0]	7 (0.6) [0]
Vaginal haemorrhage	2 (0.2) [1]	1 (0.1) [1]
Aortic stenosis	1 (0.1) [0]	0
Bronchitis	1 (0.1) [0]	0
Cardiac tamponade	1 (0.1) [0]	0
Cerebral haemorrhage	1 (0.1) [0]	2 (0.2) [2]
Cerebrovascular disorder	1 (0.1) [0]	0
Cholecystitis	1 (0.1) [0]	0
Circulatory failure	1 (0.1) [1]	1 (0.1) [1]
Colitis haemorrhagic	1 (0.1) [1]	0
Coughing	1 (0.1) [0]	0]
Cyst nos	1 (0.1) [0]	0
Death	1 (0.1) [0]	0
Dehydration	1 (0.1) [0]	0
Diabetes mellitus	1 (0.1) [0]	0
Embolism pulmonary	1 (0.1) [0]	5 (0.5) [1]
Haemarthrosis	1 (0.1) [1]	0
Haemorrhage intracranial	1 (0.1) [0]	0
Hypercalcaemia	1 (0.1) [0]	0
Infection	1 (0.1) [0]	2 (0.2) [0]
Intestinal obstruction	1 (0.1) [0]	1 (0.1) [0]
Metastases nos	1 (0.1) [0]	0
Muscle weakness	1 (0.1) [0]	0
Pericarditis	1 (0.1) [0]	0
Pleural effusion	1 (0.1) [0]	0
Pleural effusion	1 (0.1) [0]	1 (0.1) [0]
Prostatic specific antigen incr.	1 (0.1) [0]	0
Prothrombin decreased	1 (0.1) [0]	1 (0.1) [1]
Pulmonary carcinoma	1 (0.1) [0]	1 (0.1) [0]
Pulmonary infarction	1 (0.1) [0]	4 (0.4) [0]
Respiratory disorder	1 (0.1) [0]	1 (0.1) [0]
Tachycardia supraventricular	1 (0.1) [0]	0
Tachycardia ventricular	1 (0.1) [0]	0
Torsade de pointes	1 (0.1) [0]	0
Abdominal pain	0	1 (0.1) [0]
Adenocarcinoma nos	0	1 (0.1) [0]

Aggressive reaction	0	1 (0.1) [0]
Aneurysm	0	1 (0.1) [0]
Brain stem disorder	0	1 (0.1) [0]
Cardiomyopathy	0	1 (0.1) [0]
Cellulitis	0	1 (0.1) [0]
Chest pain	0	1 (0.1) [0]
Confusion	0	2 (0.2) [0]
Convulsions	0	1 (0.1) [1]
Diarrhoea	0	1 (0.1) [0]
Diverticulitis	0	1 (0.1) [0]
Endometrial neoplasm malignant	0	1 (0.1) [1]
Fracture pathological	0	1 (0.1) [0]
Gastric ulcer haemorrhagic	0	1 (0.1) [0]
Haematemesis	0	1 (0.1) [1]
Haemoptysis	0	1 (0.1) [1]
Hepatic cirrhosis	0	1 (0.1) [0]
Hepatic enzymes increased	0	4 (0.4) [3]
Hypokalaemia	0	1 (0.1) [0]
Hypotension	0	1 (0.1) [0]
Intestinal ischaemia	0	1 (0.1) [0]
Joint dislocation	0	1 (0.1) [0]
Lymphadenopathy	0	1 (0.1) [0]
Malaise	0	1 (0.1) [0]
Monoplegia	0	1 (0.1) [0]
Neoplasm nos	0	1 (0.1) [0]
Non-Hodgkin's lymphoma	0	1 (0.1) [0]
Oedema	0	1 (0.1) [1]
Parkinsonism aggravated	0	1 (0.1) [0]
Pneumothorax	0	1 (0.1) [0]
Pulmonary infiltration	0	1 (0.1) [0]
Renal carcinoma	0	1 (0.1) [0]
Renal function abnormal	0	1 (0.1) [0]
Respiratory insufficiency	0	1 (0.1) [0]
Sepsis	0	4 (0.4) [0]
Thrombocytopenia	0	1 (0.1) [1]
Thrombophlebitis	0	1 (0.1) [0]
Thrombosis	0	1 (0.1) [0]
Thrombosis coronary	0	1 (0.1) [0]
Vomiting	0	1 (0.1) [0]
Fatal Serious Adverse Events during initial treatment period	FX N=1092	UFH N=1092
Subjects with any fatal SAE(s) n (%) [considered by the investigator to be related to the study medication]	12 (1.1) [1]	23 (21) [3]
Cerebrovascular disorder	1 (0.1) [0]	0
Cardiac arrest	3 (0.3) [0]	1 (0.1) [0]
Embolic pulmonary	1 (0.1) [0]	5 (0.5) [1]
Haemorrhage intracranial	1 (0.1) [0]	0
Pulmonary carcinoma	1 (0.1) [0]	1 (0.1) [0]
Metastases nos	1 (0.1) [0]	0
Dyspnoea	1 (0.1) [0]	1 (0.1) [0]
Cardiac failure	1 (0.1) [0]	1 (0.1) [0]
Circulatory failure	1 (0.1) [0]	0
Death	1 (0.1) [0]	0
Hepatic cirrhosis	0	1 (0.1) [0]
Renal carcinoma	0	1 (0.1) [0]

Abdominal pain	0	1 (0.1) [0]
Pneumonia	0	2 (0.2) [0]
Renal function abnormal	0	1 (0.0) [0]
Gastrointestinal haemorrhage	0	1 (0.1) [1]
Non-hodgkin's lymphoma	0	1 (0.1) [0]
Neoplasm nos	0	1 (0.1) [0]
Ovarian carcinoma	0	1 (0.1) [0]
Adenocarcinoma nos	0	1 (0.1) [0]
Cerebral haemorrhage	0	1 (0.1) [1]
Chest pain	0	1 (0.1) [0]
Malaise	0	1 (0.1) [0]

Conclusion:

See publication below.

Publications:

Büller, H. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-702.

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 *European Association of Hospital Pharmacists* March 17-19, 2004 Sevilla, Spain

Initial outpatient treatment of pulmonary embolism with fondaparinux (Arixtra®): The MATISSE-PE trial *European Hematology Association* June 10-13, 2004 Geneva, Switzerland

Fondaparinux in the treatment of deep-vein thrombosis and pulmonary embolism. *European Hematology Association* June 10-13, 2004 Geneva, Switzerland

Fondaparinux in the treatment of deep-vein thrombosis and pulmonary embolism, Buller, *International Union of Angiology, Rome, Italy, May 22-26, 2004.* (oral)

Initial outpatient treatment of pulmonary embolism with fondaparinux (Arixtra®), Buller, *International Union of Angiology, Rome, Italy, May 22-26, 2004.* (oral)

Fondaparinux in the initial treatment of pulmonary embolism in overweight patients, Piovella, *International Union of Angiology, Rome, Italy, May 22-26, 2004.* (oral)

Initial outpatient treatment of pulmonary embolism with fondaparinux (Arixtra®): The MATISSE-PE trial, Piovella, *European Hematology Association, Geneva, Switzerland, June 10-13, 2004.* (poster)

Fondaparinux in the treatment of deep-vein thrombosis and pulmonary embolism, Buller, *European Hematology Association, Geneva Switzerland, June 10-13, 2004.* (poster)

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-PE trial, a multicenter, randomized, open study comparing once-daily fondaparinux (arixtra) with adjusted-dose intravenous unfractionated heparin (ufh) in the initial treatment of acute symptomatic pulmonary embolism (pe). 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 Seattle, WA;

USA

Abstract: Initial outpatient treatment of venous thromboembolism with fondaparinux (arixtra®): the matisse trials. Buller, H 2 1 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: Initial outpatient treatment of pulmonary embolism with fondaparinux (arixtra®): the matisse-pe trial. F. Piovella, Matisse investigators 9th Congress of the European Haematology Association 6/10/2004 Geneva; Switzerland

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 Geneva; Switzerland

Abstract: Initial outpatient treatment of pulmonary embolism (pe) with fondaparinux (arixtra®). Buller, H. 21st World Congress of the International Union of Angiology 5/22/2004 Rome; Italy

Abstract: Fondaparinux in the initial treatment of pulmonary embolism in overweight patients. Piovella, F. 21st World Congress of the International Union of Angiology 5/22/2004 Rome; Italy

Abstract: Fondaparinux in the initial treatment of pulmonary embolism in overweight patients. Piovella, F. 21st World Congress of the International Union of Angiology 5/22/2004 Rome; Italy

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