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<b>Study No.:</b> 63129
<b>Title:</b> A multinational, randomized, double-blind comparison of once daily subcutaneous fondaparinux sodium with placebo for the prevention of venous thromboembolic events in acutely ill medical patients (ARTEMIS).
<b>Rationale:</b> Two Phase II dose-finding and 4 Phase III double-blind studies demonstrated the efficacy of fondaparinux sodium (FX) (2.5mg once-daily [o.d.]) in the reduction of venous thromboembolic events [VTE]) compared to enoxaprin (EN) in subjects undergoing major orthopedic surgery of the lower limbs. The incidence of major and minor bleeding with FX was similar to that of EN. In this study (FX) was compared with placebo (PBO) in preventing VTE in acutely ill medical subjects.
<b>Phase:</b> III
<b>Study Period:</b> 18 March 2002 to 4 March 2003
<b>Study Design:</b> Multicenter, multinational, randomized, double-blind, PBO-controlled study
<b>Centres:</b> 35 centers in 8 countries (Czech Republic (10), Poland (6), United Kingdom (2), Denmark (6), Australia (4), Sweden (4), Mexico (2), and The Netherlands(1))
<b>Indication:</b> Prevention of VTE, i.e. deep vein thrombosis (DVT) or symptomatic pulmonary embolism (PE), in acutely ill medical subjects
<b>Treatment:</b> The administration of FX (2.5mg o.d. as a subcutaneous [s.c.] injection) or PBO started 2 hours after randomization. Study treatment was to be given at least up to and including Day 6 but not after Day 14. A venogram had to be performed within 1 day after stopping treatment on Day 6 to 15, or earlier in case of symptomatic VTE.
<b>Objectives:</b> To assess the efficacy and safety of FX 2.5mg o.d. in the prevention of VTE, i.e. DVT or symptomatic PE, in acutely ill medical subjects.
<b>Primary Outcome/Efficacy Variable:</b> The primary efficacy outcome was the composite of the following VTE events recorded up to Day 15 or up to the first venogram, whichever came first: venogram positive for DVT, symptomatic DVT, non-fatal PE, or fatal PE. All venograms and other available diagnostic tests (ultrasonography, ventilation/perfusion lung scan, pulmonary angiography or spiral computed tomography scan, autopsy report, etc) were blindly adjudicated by experts of the Central Independent Adjudication Committee (CIAC).
<b>Secondary Outcome/Efficacy Variable(s):</b> The secondary efficacy outcomes were the components of the primary efficacy outcome considered separately during the same time period: DVT, proximal DVT, distal only DVT, PE and symptomatic VTE (DVT and/or PE).
<b>Statistical Methods:</b> <u>Analysis Populations:</u> The "primary efficacy" population consisted of all randomized subjects with a non-missing primary efficacy outcome. The "efficacy evaluable" population consisted of all randomized subjects with a non-missing outcome for the efficacy assessment under consideration. The "as treated" population consisted of all randomized patients who received at least 1 dose of study drug, this population was used for analysis of safety. Subjects were analyzed as randomized in all efficacy and safety analyses. <u>Analysis Methods:</u> The primary efficacy analysis was the comparison of FX and PBO using a 2-sided Fisher's exact test at an error level of 5%. Point estimates and 2-sided 95% confidence interval (CI) (binomial method) per treatment group were calculated as well as 2-sided 95% CIs (normal approximation) on odds ratio, relative risk and the difference between the 2 treatment groups (FX - PBO). For the main safety analysis, major bleeding from the first study drug injection up to 2 calendar days after the last study drug injection, were compared between the 2 treatment groups using Fisher's exact test. 95% CIs on the differences between the 2 treatment groups were computed..
<b>Study Population:</b> Subjects were acutely ill medical subjects, aged $\geq 60$ years and expected to require bed rest for at least 4 days at the moment of inclusion, hospitalized for: congestive heart failure New York Heart Association (NYHA) class III/IV, and/or acute respiratory illness in the presence of chronic lung disease, and/or acute infectious or inflammatory disease. Subjects were excluded from study participation based on their bleeding risk at the time of randomisation (eg active clinically significant bleeding or 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) or use of anticoagulant or fibrinolytic therapy within 48 hours prior to randomisation.

	PBO	FX
Number of Subjects:		
Planned (Evaluable), N	400 (280)	400 (280)
Randomized, N	420	429
Primary Efficacy Population, N	323	321
Randomized and Treated (As treated Population), N	414	425
Completed Study Drug, n (%)	370 (89.4)	377 (88.7)
Total Number Subjects Withdrawn From Study Drug, n (%)	44 (10.6)	48 (11.3)
Withdrawn Due to AE/SAE, n (%)	13 (3.1)	18 (4.2)
Withdrawn Due to Lack of Efficacy n (%)	2 (0.5)	3 (0.7)
Withdrawn for Other Reasons n (%)	29 (7.0)	27 (6.4)
<b>Demographics</b>	<b>PBO</b>	<b>FX</b>
N (As Treated Population)	414	425
Females: Males	230:184	253:172
Mean Age, years (SD)	74.5 (8.2)	75.0 (8.2)
Caucasian, n (%)	403 (97.3)	405 (95.3)
<b>Primary Efficacy Results (Primary Efficacy Population):</b>		
<b>Subjects With VTE up to Day 15 or First Venogram</b>	<b>PBO N=323</b>	<b>FX N=321</b>
n (%)	34 (10.5)	18 (5.6)
95% CI	[7.4, 14.4]	[3.4, 8.7]
Difference (%)	-4.9	
95% CI	[-9.1, -0.7]	
p-value (Fisher's Exact Test)	0.029	
<b>Secondary Outcome Variables (Efficacy Evaluable Population):</b>		
<b>Subjects With Any DVT Up to Day 15 or First Venogram</b>	<b>PBO</b>	<b>FX</b>
Either Side n/N (%)	29/318 (9.1)	18/321 (5.6)
95% CI	[6.2, 12.8]	[3.4, 8.7]
Both Sides n/N (%)	4/342 (1.2)	1/345 (0.3)
95% CI	[0.3, 3.0]	[0.0, 1.6]
Difference (%)	-3.5	
95% CI	[-7.6, 0.5]	
<b>Subjects With Any Proximal DVT Up to Day 15 or First Venogram</b>	<b>PBO</b>	<b>FX</b>
Either Side n/N (%)	7/324 (2.2)	5/324 (1.5)
95% CI	[0.9, 4.4]	[0.5, 3.6]
Both Sides n/N (%)	0/348 (0.0)	0/346 (0.0)
95% CI	[0.0, 1.1]	[0.0, 1.1]
Difference (%)	-0.6	
95% CI	[-2.7, 1.5]	
<b>Subjects With Distal Only DVT Up to Day 15 or First Venogram</b>	<b>PBO</b>	<b>FX</b>
Either Side n/N (%)	23/320 (7.2)	14/320 (4.4)
95% CI	[4.6, 10.6]	[2.4, 7.2]
Both Sides n/N (%)	3/342 (0.9)	0/348 (0.0)
95% CI	[0.2, 2.5]	[0.0, 1.1]
<b>Subjects With Symptomatic VTE as Components of the Primary Efficacy Outcome (All Randomized Subjects)</b>	<b>PBO N=420</b>	<b>FX N=429</b>
Primary Efficacy Period VTE n (%)	5 (1.2)	0
DVT n (%)	0	0
Non-fatal PE n (%)	0	0
Fatal PE n (%)	5 (1.2)	0
Difference (%)	-1.2	
95%CI	[-2.2, -0.2]	
<b>Safety Results:</b>		
<b>Adverse event results:</b> An on therapy AE was defined as an AE with onset from first injection to 2 calendar days after the last injection of study drug.		

	<b>PBO N = 414</b>	<b>FX N = 425</b>
<b>Most Frequent Adverse Events – On-Therapy (As Treated Population)</b>	<b>n (%)</b>	<b>n (%)</b>
Subjects With Any AE(s)	197 (47.6)	219 (51.5)
10 Most Frequent AEs in Each Group		
Constipation	21 (5.1)	34 (8.0)
Insomnia	11 (2.7)	19 (4.5)
Nausea	13 (3.1)	15 (3.5)
Diarrhoea	13 (3.1)	13 (3.1)
Urinary Tract Infection	7 (1.7)	11 (2.6)
Hypokalaemia	11 (2.7)	11 (2.6)
Dyspepsia	4 (1.0)	10 (2.4)
Anxiety	8 (1.9)	10 (2.4)
Cholelithiasis	7 (1.7)	9 (2.1)
Confusion	3 (0.7)	8 (1.9)
Hypertension	4 (1.0)	8 (1.9)
Moniliasis	7 (1.7)	8 (1.9)
Cardiac Failure	7 (1.7)	7 (1.6)
Fever	8 (1.9)	6 (1.4)
Headache	7 (1.7)	6 (1.4)
Abdominal Pain	7 (1.7)	5 (1.2)
<b>Serious Adverse Events</b>		
<b>All SAEs (Fatal and Non-fatal) From First Injection to 2 Calendar Days After the Last Injection (As Treated Population)</b>	<b>PBO N = 414</b>	<b>FX N = 425</b>
	<b>n (%) [related]</b>	<b>n (%) [related]</b>
Subjects With Any SAEs [Number Considered by the Investigator to Be Related to Study Medication]	21 ( 5.1) [0]	20 ( 4.7) [2]
Subjects with		
Cardiac Failure	6 ( 1.4) [0]	4 ( 0.9) [0]
Respiratory Insufficiency	0	3 ( 0.7) [0]
Pneumothorax	2 ( 0.5) [0]	1 ( 0.2) [0]
Respiratory Disorder	1 ( 0.2) [0]	1 ( 0.2) [0]
Bronchitis	0	1 ( 0.2) [0]
Pneumonia	0	1 ( 0.2) [0]
Cardiac Arrest	1 ( 0.2) [0]	1 ( 0.2) [0]
Arrhythmia Ventricular	0	1 ( 0.2) [0]
Fibrillation Atrial	0	1 ( 0.2) [0]
Fibrillation Ventricular	0	1 ( 0.2) [0]
Angina Pectoris	0	1 ( 0.2) [0]
Endocarditis	0	1 ( 0.2) [0]
Myocardial Ischaemia	0	1 ( 0.2) [0]
Haemoptysis	1 ( 0.2) [0]	1 ( 0.2) [1]
Confusion	0	1 ( 0.2) [0]
Adenoma Adrenal	0	1 ( 0.2) [0]
Hallucination	0	1 ( 0.2) [0]
Anaemia	0	1 ( 0.2) [1]
Infection Bacterial	0	1 ( 0.2) [0]
Inflicted Injury	0	1 ( 0.2) [0]
Respiratory Depression	2 ( 0.5) [0]	0
Pneumonia Lobar	1 ( 0.2) [0]	0
Pulmonary Carcinoma	1 ( 0.2) [0]	0
Myocardial Infarction	2 ( 0.5) [0]	0
Myocardial Rupture (Post Infarct)	1 ( 0.2) [0]	0
Embolism Pulmonary	2 ( 0.5) [0]	0

Haematuria	1 ( 0.2) [0]	0
Intestinal Obstruction	1 ( 0.2) [0]	0
Bile Duct Carcinoma	1 ( 0.2) [0]	0
Cholelithiasis	1 ( 0.2) [0]	0
Osteoporosis	1 ( 0.2) [0]	0
Neoplasm Not Otherwise Specified	1 ( 0.2) [0]	0
Renal Carcinoma	1 ( 0.2) [0]	0
<b>Fatal Serious adverse events during the treatment period (Day of first dose to 2 days after last dose)</b>	<b>PBO N = 414</b>	<b>FX N = 425</b>
Subjects With Any fatal SAEs [Number Considered by the Investigator to Be Related to Study Medication]	14 (3.4) [0]	8 (1.9) [0]
Cardiac failure	1 (0.2) [0]	0
Pneumonia lobar	1 (0.2) [0]	0
Embolism pulmonary	2 (0.5) [0]	0
Myocardial rupture (post infarct)	1 (0.2) [0]	0
Myocardial infarction	1 (0.2) [0]	0
Renal carcinoma	1 (0.2) [0]	0
Cardiac failure	5 (1.2) [0]	1 (0.2) [0]
Heart failure	2 (0.5) [0]	1 (0.2) [0]
Respiratory insufficiency	0	2 (0.5) [0]
Haemoptysis	0	1 (0.2) [1]
Endocarditis	0	1 (0.2) [0]
Cardiac arrest	0	1 (0.2) [0]
Arrhythmia ventricular	0	1 (0.2) [0]
<b>Conclusion:</b> See publication below.		
<b>Publications:</b> Fondaparinux in medical patients: the ARTEMIS study. <i>Blood</i> 2003;102:abstract 42 AT Cohen  Thromboprophylaxis with fondaparinux in acutely ill medical patients with moderate renal impairment. <i>International Union of Angiology</i> May 22-26, 2004 Rome, Italy Poster ARTEMIS Cohen  Thromboprophylaxis with fondaparinux in acutely ill medical patients aged 75 years or more. <i>International Union of Angiology</i> May 22-26, 2004 Rome, Italy Poster ARTEMIS Cohen  Thromboprophylaxis with fondaparinux in acutely ill medical patients with moderate renal impairment. <i>European Hematology Association</i> June 10-13, 2004 Geneva, Switzerland Poster ARTEMIS Cohen  Thromboprophylaxis with fondaparinux in acutely ill medical patients with moderate renal impairment, Cohen, <i>European Hematology Association, Geneva, Switzerland, June 10-13, 2004.</i> ( poster)  Abstract: Fondaparinux for the prevention of vte in acutely ill medical patients. session type: oral session. Alexander T. Cohen, B. L. Davidson A. S. Gallus M. R. Lassen W. Tomkowski A. G. G. Turpie R. G. Cariou JEM. Egberts 45th Annual Meeting and Exposition of the American Society of Hematology 12/5/2003 San Diego, CA; USA  Abstract: Fondaparinux vs. placebo for the prevention of venous thromboembolism in acutely ill medical patients (artemis). Cohen A. T., Gallus A. S. Lassen M. R. Tomkowski W. Turpie T A. G. Davidson B. L. Cariou R. G. Lensing A. W. A. Egberts J. F. M. 19th Congress of the International Society on Thrombosis and Haemostasis and 49th Annual Scientific and Standardisation Committee Meeting 7/12/2003 Birmingham; UK  Abstract: Benefit of fondaparinux in medical patients: a subgroup analysis. Cohen, AT , Gallus, AG, Davidson, BL , Lassen, MR , Prins, MH , Tomkowski, W , Turpie, AGG, Egberts, JFM , and Lensing, AWA 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: Results of the ARTEMIS study. Cohen, A. T. , Davidson, B. L. , Gallus, A. S., Lassen, M. R. , Prins, M. H. ,		

Tomkowski, W. , Turpie, A. G. G. , Egberts, J. F. M. , and Lensing, A. W. A. 21st World Congress of the International Union of Angiology 5/22/2004 Rome; Italy

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