

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 095001
Title: A multicenter, concurrent control, randomized, open-label, assessor-blind, dose-ranging study of Org 31540/SR90107A in the prophylaxis of deep vein thrombosis in subjects undergoing total knee replacement surgery (PENTATAK).
Rationale: Two pilot studies suggest that fondaparinux (FX), a selective inhibitor of activated factor X (factor Xa), is effective for the prevention of venous thromboembolic events (VTE), i.e., deep vein thrombosis (DVT), and/or symptomatic pulmonary embolism (PE), in high-risk situations such as following major orthopaedic surgery of the lower limbs. The primary purpose of this study was to determine the optimal dose of FX for the prophylaxis of DVT following total knee replacement (TKR) surgery.
Phase: IIb
Study Period: November 1996 – March 1998.
Study Design: Multicenter, concurrent control, randomized, open-label, assessor-blind, dose-ranging study.
Centres: 19 study centres in the USA.
Indication: Prevention of DVT and symptomatic PE in subjects undergoing elective TKR surgery.
Treatment: Single daily subcutaneous (s.c.) dosing with FX 0.75, 1.5, 3.0, 6.0 or 8.0 mg, which was started on the day of surgery (Day 1) and continued for a minimum of 5 days up to a maximum of 10 days. The first injection was administered within 6 ± 2 hours after closure of the surgical incision. On Days 2 to 10, the study drug was administered at 08.00h ± 2 hours. If the first dose of study drug had not been administered by 11.59h on Day 1, then the subject was not treated in the study. If the first dose of study drug was administered after 20.00h but before 11.59h on Day 1, the Day 2 dose was not administered less than 12 hours later. All doses given thereafter (for Days 3-10) were administered every 24 hours starting from the time of the Day 2 dose. Ongoing efficacy and safety monitoring was performed and a dose group was discontinued if either the lower limit of the 2-sided 95% confidence interval (CI) for the incidence of DVT exceeded 15% for that dose group (based on the per-protocol (PP) population or the lower limit of the 2-sided 95% CI for the incidence of major bleeding exceeded 3% for that dose group based on the all- treated subjects (ATS) population.
Objectives: The primary objective of this study was to establish the optimal dose of a once daily s.c. injection of FX starting post-operatively and continuing for a minimum of 5 days for venous thrombosis prophylaxis following TKR surgery.
Primary Outcome/Efficacy Variable: The primary endpoint was the incidence of adjudicated, confirmed (i.e., adjudicated as positive) DVT occurring during the treatment period (defined as the period between the administration of the first dose of study drug up to 48 hours following the administration of the last dose of study drug). A central independent adjudication committee (CIAC) adjudicated the efficacy outcomes.
Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoints: The incidence of adjudicated, confirmed PE (non-fatal and fatal); the incidence of adjudicated, confirmed venous thromboembolic events (VTEs), which included PE and DVT. Safety: <i>Bleeding assessments and related criteria:</i> Incidences of major bleeds and minor bleeds only, assessed during both the treatment period and the follow-up period (up to 4-6 weeks post last dose). Bleeding was adjudicated by two independent CIAC. The first CIAC defined major bleeding events as: death due to bleeding; intra-cranial bleeding or bleeding within a critical organ (e.g. eye or adrenal gland); re-operation due to bleeding (haematoma) in the surgical area; clinically overt bleeding and/or quantitative blood loss which the CIAC deemed to be a major bleed. Minor bleeding was defined as overt unusual bleeding not meeting the criteria for major bleeding. Other bleeding criteria assessed were: total blood loss, transfusions, and haemoglobin level. Because this bleeding adjudication was based on criteria that were distinctly different from the internationally accepted criteria for major and minor bleeding, no proper comparison could be made with the bleeding adjudication results for the Phase III studies in the FX development program for VTE prophylaxis in subjects undergoing major orthopedic surgery. Therefore, bleeding was also adjudicated by a second CIAC according to the Hamilton criteria as was done for the Phase III studies in the FX development program for prophylaxis of VTE in major orthopedic surgery. All adjudication committees acted independently and were blinded to treatment allocation. <i>Other safety:</i> Adverse events (AEs), laboratory parameters, and vital signs Pharmacokinetics:

Determination of plasma FX concentrations was planned but was not performed due to technical difficulties.					
Statistical Methods:					
<p><u>Sample size:</u> It was planned that approximately 90 subjects were to be randomised to each dose group with the expectation that 71 subjects per dose group would be included in the per-protocol (PP) population. It was expected that using this sample size it would be possible to characterise the dose response curve based on simulations carried out under various assumptions. Additionally, with this sample size, if the incidence of DVT for the lowest dose group was assumed to be at least 30% versus an incidence of not more than 10% in a higher dose group, with a 2-tailed test at 5% level of significance, the power would be at least 80%.</p> <p><u>Populations analysed:</u></p> <p><i>ATS population:</i> all randomised subjects who were treated with at least one dose of study drug, and was used for the safety analyses.</p> <p><i>Intent-to-Treat (ITT) population:</i> a subpopulation of the ATS population who had TKR surgery and, during the treatment period, an adjudicated evaluable bilateral (or positive unilateral) venogram, or a symptomatic adjudicated, confirmed PE or DVT and was used for the efficacy analyses.</p> <p><i>PP population:</i> This was a subpopulation of the ITT population excluding subjects with major protocol violations and was also used for the efficacy analyses.</p> <p>Subjects were included in the ATS, ITT, and PP population based on the dose they actually received (i.e., as treated).</p> <p><u>Statistical tests used:</u></p> <p><i>Efficacy analyses:</i> The incidences (and 95% CIs) for DVT only (overall, proximal, and distal), PE only, and VTE (DVT and/or PE) were computed for each FX dose group. The relationship of dose and incidence of DVT was examined using a probit model.</p> <p><i>Safety analyses:</i> The incidences (and 95% CIs) of major bleeds and minor bleeds only were computed for each FX dose group. The relationship of dose and incidence of major bleeding events was examined using a probit model. Descriptive statistics were calculated for the volume of blood loss and transfusions. All AEs, including those considered related to study drug (i.e., AEs with a relation to the study drug reported as definitely, probably, or possibly by the investigator) were summarised by system-organ class and preferred term for the treatment period and the follow-up period. For laboratory parameters, descriptive statistics and the number (%) of subjects with post-baseline values outside of defined limits were presented.</p>					
<p>Study Population: Subjects were eligible if they were undergoing TKR surgery; ≥ 18 years of age; males or non-childbearing females (post-menopausal for more than 1 year or with a hysterectomy or bilateral tubal ligation for at least 6 months prior to enrolment). Subjects were excluded if they had had any major orthopaedic surgery within the previous 12 months (changed to 3 months in Amendment 3, effective September 15, 1997); previously had DVT/PE (clinical signs and/or symptoms within last 12 months) or stroke/myocardial infarction (within last 3 months); known congenital or acquired bleeding tendency, or bleeding tendency revealed by a pre-operative test; hypertension; severe renal insufficiency; had received one of a number of forbidden drugs (e.g., heparin or fibrinolytics) within 1 week prior to study start.</p>					
	FX mg				
	0.75	1.5	3.0	6.0	8.0
Number of subjects:					
Planned enrolment (evaluable), N	90 (71)	90 (71)	90 (71)	90 (71)	90 (71)
Randomised, N	54*	91	88	51*	34*
ATS population, N	54	91	88	49	34
ITT population, N	35	74	67	30	22
PP population, N	22	44	44	18	13
Completed study drug, n (% of ATS population)	46 (85.2)	81 (89.0)	78 (88.6)	41 (83.7)	28 (82.4)
Total withdrawn from study drug, n (% of ATS population)	8 (14.8)	10 (11.0)	10 (11.4)	8 (16.3)	6 (17.6)
Withdrawn due to AEs/SAEs, n (%)	2 (3.7)	1 (1.1)	4 (4.5)	4 (8.2)	4 (11.8)
Withdrawn due to lack of efficacy, n (%)	0	0	0	1 (2.0)	0
Withdrawn for other reasons, n (%)	6(11.1)	9(9.9)	6 (6.8)	3 (6.1)	2 (5.8)
* During the course of the study the 0.75 mg dose group was discontinued because the incidence of DVT met the pre-specified stopping rule, and the 6.0 and 8.0 mg dose groups were discontinued because the incidence of major bleeds met the pre-specified stopping rule.					
Demographics:					
	FX mg				

ATS population	0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)	
Females: Males	34:20	54:37	54:34	35:14	26:8	
Mean Age, years (SD)	68.5 (9.4)	69.5 (8.9)	67.9 (9.8)	68.8 (9.6)	69.0 (8.4)	
Caucasian, n (%)	46 (85.2)	83 (91.2)	81 (92.0)	42 (85.7)	26 (76.5)	
Primary Efficacy Results:						
ITT population	FX mg					
Subjects with DVT	0.75 (N = 35)	1.5 (N = 74)	3.0 (N = 67)	6.0 (N = 29)*	8.0 (N = 22)	
Subjects with DVT total						
n (%)	14 (40.0)	21 (28.4)	12 (17.9)	4 (13.8)	4 (18.2)	
[95% CI]	[23.9, 57.9]	[18.5, 40.1]	[9.6, 29.2]	[3.9, 31.7]	[5.2, 40.3]	
Using a probit model, a statistically significant dose response was observed for the incidence of adjudicated DVT for the ITT population (p = 0.006).						
* Subject 01023 had a confirmed PE and is included in the ITT population but was excluded from this table because this subject had no venogram.						
PP population	FX mg					
Subjects with DVT	0.75 (N = 22)	1.5 (N = 44)	3.0 (N = 44)	6.0 (N = 18)	8.0 (N = 13)	
Subjects with DVT total						
n (%)	13 (59.1)	15 (34.1)	6 (13.6)	2 (11.1)	2 (15.4)	
[95% CI]	[36.4, 79.3]	[20.5, 49.9]	[5.2, 27.4]	[1.4, 34.7]	[1.9, 45.4]	
Using a probit model, a statistically significant dose response was observed for the incidence of adjudicated DVT for the PP population (p < 0.001).						
Secondary Outcome Variable(s):						
ITT population	FX mg					
	0.75 (N = 35)	1.5 (N = 74)	3.0 (N = 67)	6.0 (N = 30)	8.0 (N = 22)	
Subjects with confirmed (PE)						
n (%)	0	0	0	1 (3.33)	0	
Subjects with VTEs						
n (%)	14 (40.0)	21 (28.4)	12 (17.9)	5* (16.7)	4 (18.2)	
[95% CI]	[23.9, 57.9]	[18.5, 40.1]	[9.6, 29.2]	[5.6, 34.7]	[5.2, 40.3]	
* Includes the one subject with confirmed PE						
PP population	FX mg					
	0.75 (N = 22)	1.5 (N = 44)	3.0 (N = 44)	6.0 (N = 18)	8.0 (N = 13)	
Subjects with confirmed (PE)						
n (%)	0	0	0	0	0	
Subjects with VTEs*						
n (%)	13 (59.1)	15 (34.1)	6 (13.6)	2 (11.1)	2 (15.4)	
[95% CI]	[36.4, 79.3]	[20.5, 49.9]	[5.2, 27.4]	[1.4, 34.7]	[1.9, 45.4]	
* Because the single subject with a confirmed PE was included in the ITT population but not in the PP population, the PP population VTE results are the same as the PP population DVT results.						
Safety results:						
Bleeding						
	FX mg					
Adjudicated bleeding results - adjudication performed by First CIAC (ATS population)	0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)	
Major bleeding	n (%)	2 (3.7)	3 (3.3)	4 (4.5)	6 (12.2)	4 (11.8)
	[95% CI]	[0.5, 12.7]	[0.7, 9.3]	[1.3, 11.2]	[4.6, 24.8]	[3.3, 27.5]
Minor bleeding only	n (%)	2 (3.7)	9 (9.9)	5 (5.7)	9 (18.4)	4 (11.8)
	[95% CI]	[0.5, 12.7]	[4.6, 17.9]	[1.9, 12.8]	[8.8, 32.0]	[3.3, 27.5]

Total bleeding	n (%)	4 (7.4)	12 (13.2)	9 (10.2)	15 (30.6)	8 (23.5)
	[95% CI]	[2.1, 17.9]	[7.0, 21.9]	[4.8, 18.5]	[18.3, 45.4]	[10.7, 41.2]
FX mg						
Adjudicated bleeding results - adjudication performed Second CIAC (ATS population)		0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
Major bleeding	n (%)	1 (1.9)	1 (1.1)	3 (3.4)	7 (14.3)	3 (8.8)
	[95% CI]	[0, 9.9]	[0, 6.0]	[0.7, 9.6]	[5.9, 27.2]	[1.9, 23.7]
Minor bleeding	n (%)	3 (5.6)	2 (2.2)	6 (6.8)	5 (10.2)	1 (2.9)
	[95% CI]	[1.2, 15.4]	[0.3, 7.7]	[2.5, 14.3]	[3.4, 22.2]	[0.1, 15.3]
Total bleeding	n (%)	4 (7.4)	3 (3.3)	9 (10.2)	12 (24.5)	4 (11.8)
	[95% CI]	[2.1, 17.9]	[0.7, 9.3]	[4.8, 18.5]	[13.3, 38.9]	[3.3, 27.5]
FX mg						
Blood transfusion (ATS population)		0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
Intra-operative*, n (%)		2 (3.7)	8 (8.8)	10 (11.4)	3 (6.1)	1 (2.9)
Peri-operative*, n (%)		8 (14.8)	4 (4.4)	8 (9.1)	5 (10.2)	3 (8.8)
Post-operative*, n (%)		21 (38.9)	24 (26.4)	31 (35.2)	20 (40.8)	20 (58.8)
*intra-operative (the time from induction of anesthesia until closure of the surgical wound), peri-operative (the time from closure of the surgical wound until midnight of Day 1), and post-operative (Days 2-10 or Day 2-last dose)						
Adverse event results: Adverse events were summarised as those collected from the first dose of study drug to 48 hours after the administration of the last dose of study drug (i.e. during the treatment period).						
FX mg						
Adverse events (ATS population)		0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
Subjects with any AE(s) during the treatment period, n (%)		48 (88.9)	86 (94.5)	80 (90.9)	49 (100.0)	34 (100.0)
5 most frequent AEs in each treatment group, n (%):						
Arthralgia		33 (61.1)	63 (69.2)	49 (55.7)	31 (63.3)	23 (67.6)
Constipation		23 (42.6)	43 (47.3)	30 (34.1)	23 (46.9)	21 (61.8)
Nausea		25 (46.3)	39 (42.9)	41 (46.6)	23 (46.9)	15 (44.1)
Fever		22 (40.7)	45 (49.5)	37 (42.0)	31 (63.3)	14 (41.2)
Oedema		15 (27.8)	22 (24.2)	23 (26.1)	10 (20.4)	13 (38.2)
Serious Adverse Events: Serious adverse events (SAEs) were summarised as those collected from the first dose of study drug to 48 hours after the administration of the last dose of study drug (i.e. during the treatment period),.						
FX mg						
SAEs (ATS population)		0.75 (N = 54)	1.5 (N = 91)	3.0 (N = 88)	6.0 (N = 49)	8.0 (N = 34)
Subjects with any SAE(s) during the treatment period, n (%) [related*]		1 (1.9)	1 (1.1)	1 (1.1)	5 (10.2) [4]	4 (11.8) [3]
Myelomatosis multiple		0	0	0	0	1 (2.9) [0]
Anaemia		0	0	0	1 (2.0) [1]	1 (2.9) [1]
Post-operative haemorrhage		0	0	0	2 (4.1) [2]	1 (2.9) [1]
Fever		0	0	0	1 (2.0) [0]	0
Haematoma		0	0	0	1 (2.0) [1]	1 (2.9) [1]
Cerebrovascular disorder		0	0	1 (1.1) [0]	0	0
Pneumonia		0	1 (1.1) [0]	0	0	0
Haemorrhage retroperitoneal		1 (1.9) [0]	0	0	0	0
* Relationship to study drug judged as possible, probable, or definite by the Investigator. All other SAEs were judged as either unrelated or unlikely to be related to study drug.						
Subjects with fatal SAEs (All treated subjects)		0	0	0	0	0

Conclusion:

A statistically significant dose response was observed for the incidence of DVT and the incidence of bleeding in subjects administered FX at doses 0.75, 1.5, 3.0, 6.0 or 8.0 mg per day starting post-operatively and continuing for 5-10 days following TKR surgery. Among the 5 tested doses of FX, 3.0 mg appeared to be the dose with the best benefit/risk ratio. On therapy adverse events were reported in 48 (88.9%) of the 0.75mg FX group, 86 (94.5%) of the 1.5mg FX group, 80 (90.9%) of the 3.0mg FX group, 49 (100%) of the 6.0 mg FX group and 34 (100%) of the 8.0mg FX group. The most frequently reported adverse events were arthralgia, constipation, nausea, fever and oedema. SAEs were reported in 1 (1.9%) of the 0.75mg FX group, 1 (1.1%) of the 1.5mg FX group, 1 (1.1%) of the 3.0mg FX group, 5 (10.2%) of the 6.0 mg FX group and 4 (11.8%%) of the 8.0mg FX group. No deaths were reported.

Publications:

Fondaparinux: a new synthetic and selective inhibitor of factor xa. Bauer, K. A. Best Pract Res Clin Haematol 2004; 17. 17(1. 1):89-104, 89-104.

Date Updated: 26-Jul-2005