

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.

<b>Study No.:</b> DRI4090
<b>Title:</b> A multicenter, randomized, double-blind, placebo controlled, parallel group, dose response study of subcutaneous Org31540/SR90107A in the prevention of venous thromboembolism after elective total hip replacement surgery.
<b>Rationale:</b> The use of fondaparinux (FX), a selective inhibitor of activated factor X (factor Xa), for prevention of deep vein thrombosis (DVT) and/or pulmonary embolism (PE) after major orthopedic surgery of the lower limbs is supported by the results of clinical studies conducted in Europe and the US. The present Phase II/III Japanese study was conducted to evaluate the dose-response efficacy and safety in venous thromboembolism (VTE) prophylaxis of FX administered subcutaneously (s.c.) at 0.75, 1.5, 2.5 and 3.0 mg doses to subjects undergoing total hip replacement (THR) surgery, and to compare the efficacy with placebo (PBO).
<b>Phase:</b> II/III
<b>Study Period:</b> 09 October 2001 – 10 June 2003.
<b>Study Design:</b> Multicentre, randomised, double-blind, PBO controlled, parallel group, dose response study.
<b>Centres:</b> 57 active centres in Japan.
<b>Indication:</b> Prevention of DVT and symptomatic PE in subjects undergoing primary elective THR surgery or a revision surgery of the THR.
<b>Treatment:</b> Once daily s.c. dosing of FX 0.75, 1.5, 2.5 or 3.0 mg, or PBO for at least 10 calendar days, (a maximum of 14 days) from Day 2 to Day 11 or 15. The first dose of study drug was administered 24± 2 hours after surgical closure (Day 1 was the day of surgery). A mandatory venogram had to be performed between Day 11 and Day 17 but not later than two calendar days after the last study drug administration.
<b>Objectives:</b> <b>Primary</b> - To demonstrate the dose response effect of FX on the prophylaxis of VTE [i.e., DVT and PE] after THR. <b>Secondary</b> -To compare efficacy (incidence of VTE) and safety (incidence of major bleeding) of FX for prophylaxis of VTE after THR between each dose of FX and PBO.
<b>Primary Outcome/Efficacy Variable:</b> The primary endpoint was the cluster of the following VTE outcomes recorded up to Day 17 or to first venogram, whichever occurred first: adjudicated mandatory venogram positive for DVT between Day 11 and Day 17; adjudicated symptomatic DVT; adjudicated positive fatal or non-fatal PE. All venograms, scheduled or unscheduled, and other available diagnostic tests (ultrasonography, ventilation/perfusion lung scan, pulmonary angiography or spiral computed tomography scan, autopsy report, etc.) were adjudicated blindly by independent experts of the Central Independent Adjudication Committee of Efficacy (CIACE).
<b>Secondary Outcome/Efficacy Variable(s):</b> <b>Secondary Efficacy Endpoints:</b> These included all DVTs, all proximal DVTs, distal DVTs only, symptomatic VTE (DVT and/or PE), symptomatic DVT, non-fatal and fatal PE up to Day 17. <b>Safety:</b> The main safety endpoint was the incidence of major bleeding [any Investigator-reported bleeding adjudicated as a major bleeding event by the Central Independent Adjudication Committee of Safety (CIACS)] recorded during the treatment period, (i.e., from first injection of study drug to 2 days after the last dose). Major bleeding was defined as: fatal bleeding, clinically overt bleeding including retroperitoneal, intracranial, or bleeding into a critical organ (eye, adrenal gland, pericardium, spine); re-operation due to bleeding/haematoma at the operative site; clinically overt bleeding leading to a haemoglobin (Hb)-fall $\geq 2$ g/dL (1.6 mmol/L) within 48 hours of the bleed; clinically overt bleeding that required a transfusion of red blood cell or whole blood derived from $\geq 900$ mL of whole blood within 48 hours of the bleed (excluding the autologous transfusion except for the treatment of bleeding adverse event [AE]); clinically overt bleeding leading to the bleeding index $\geq 2$ (within 48 hours of the bleed, calculated as “number of units* transfused” + pre-bleed Hb (g/dL) – post-bleed Hb (g/dL). Other safety variables were: minor bleeding (defined as clinically overt bleeding not meeting the criteria for major bleeding and considered more than expected in the clinical context), transfusion requirements, AEs/serious adverse events (SAEs) and deaths. *450 mL of whole blood or red blood cell derived from 450 mL of whole blood is considered as 1 unit.
<b>Statistical Methods:</b> <b>Populations analysed:</b> <b>All-treated-subjects (ATS):</b> This population was defined as all randomised subjects who had received at least one dose of the study drug (PBO or active compound), and was used for the safety analyses. <b>ITT:</b> Used for the analysis of the primary efficacy endpoint, this population consisted of subjects who received at least 1 dose of study drug, had undergone the appropriate surgery and had non-missing date of operation, and had an available VTE evaluation for the primary endpoint (according to the adjudication forms by CIACE). <b>Efficacy evaluable population:</b> For analysis of DVT, by side or site was based on the ITT population but subjects included had

to have available data for the parameter being considered.					
<i>Per-protocol (PP)</i> : This population consisted of all subjects from the ITT population who had no major protocol violations that interfered with the primary efficacy endpoint and was used to support the results of the ITT analyses.					
Statistical tests used:					
The incidence of subjects with VTE was analysed across treatment groups with a 2-sided trend test on proportions at the 0.05 significance level. If a significant dose response was demonstrated, pairwise comparisons using Fisher's exact test between each of the FX groups and PBO were performed at the 0.05 significance level using hierarchical testing starting with the highest dose. Point estimates and exact 95% confidence interval (CI) for the number (%) of subjects with VTE per treatment group were calculated as well as odds ratios, relative risk, and risk differences with their exact CI for each pairwise comparison. Safety data were summarised by treatment group using descriptive statistics for the ATS population.					
<b>Study Population</b> : Subjects undergoing primary elective THR surgery or a revision of a THR; $\geq 20$ years of age. Exclusion criteria were based on the Japanese labelling for anti-coagulants in force at the time of study conduct (eg active, clinically significant bleeding; documented congenital or acquired bleeding tendency/disorders or other medical condition associated with a bleeding risk), or those relating to use of 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 1 week prior to first dose of study medication.					
	<b>PBO</b>	<b>FX mg</b>			
		<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
Number of subjects:					
Planned enrolment (evaluable), N	80 (56)	80 (56)	80 (56)	80 (56)	80 (56)
Randomised, N	82	82	82	82	83
ATS population, N	82	80	80	81	83
ITT population, N	74	62	65	68	70
PP population, N	71	59	63	67	68
Completed study drug, n (%)	77 (93.9)	71 (88.8)	74 (92.5)	78 (96.3)	76 (91.6)
Reached DVT endpoint**	2 (2.4)	0	0	0	0
Reached PE endpoint**	0	1 (1.2)	0	0	2 (2.4)
Total withdrawn from study drug, n (%)	3 (3.7)	8 (10.0)	6 (7.5)	3 (3.7)	5 (6.0)
Withdrawn due to AE/SAE n (%)	2 (2.4)	6 (7.5)	5 (6.3)	3 (3.7)	5 (6.0)
Withdrawn due to lack of efficacy n (%)	-	-	-	-	-
Withdrawn for other reasons n (%)	1 (1.2)	2 (2.6)	1 (1.3)	0	0
<b>Demographics</b>					
	<b>PBO</b>	<b>FX mg</b>			
		<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
<b>N (ATS population)</b>	<b>82</b>	<b>80</b>	<b>80</b>	<b>81</b>	<b>83</b>
Females: Males	64:18	69:11	60:20	74:7	66:17
Mean Age, years (SD)	62.3 (12.4)	60.8 (9.8)	60.9 (10.1)	61.5 (10.8)	62.7 (11.4)
Race, n (%)	Not available	na	na	na	na
<b>Primary Efficacy Results:</b>					
	<b>PBO</b>	<b>FX mg</b>			
		<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
<b>Subjects with VTE up to day 17 (ITT population)</b>	<b>N = 74</b>	<b>N = 62</b>	<b>N = 65</b>	<b>N = 68</b>	<b>N = 70</b>
n (%)	25 (33.8)	15 (24.2)	3 (4.6)	5 (7.4)	10 (14.3)
95% confidence interval (CI)	[23.2, 45.7]	[14.2, 36.7]	[1.0, 12.9]	[2.4, 16.3]	[7.1, 24.7]
Cochran-Armitage trend test (P)*	<0.001				
Comparisons with PBO	-				
Fisher's exact test (P)**	-	0.26	<0.001	<0.001	0.006
Odds ratio	-	0.626	0.095	0.156	0.327
Exact 95% CI	-	[0.272, 1.414]	[0.018, 0.343]	[0.044, 0.459]	[0.128, 0.792]
Relative risk	-	0.716	0.137	0.218	0.423
Exact 95% CI	-	[0.307, 1.411]	[0.008, 0.480]	[0.034, 0.610]	[0.139, 0.937]
Risk difference (%)	-	-9.6	-29.2	-26.4	-19.5

Exact 95% CI	-	[-27.5, 7.3]	[-45.5, -14.5]	[-43.0, -11.5]	[-36.5, -4.0]	
*Comparisons across all 5 treatment populations using the values of the doses as score (0, 0.75, 1.5, 2.5 and 3.0 mg). **Pair-wise comparison between each of FX populations with PBO population.						
<b>Secondary Outcome Variable(s):</b>						
<b>Subjects with any DVT up to Day 17 (Efficacy Evaluable Population)</b>	<b>PBO</b>	<b>FX mg</b>				
		<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>	
n/N (%)	25/74 (33.8)	15/62 (24.2)	3/65 (4.6)	5/68 (7.4)	10/70 (14.3)	
95% confidence interval (CI)	[23.2, 45.7]	[14.2, 36.7]	[1.0, 12.9]	[2.4, 16.3]	[7.1, 24.7]	
Odds ratio	-	0.626	0.095	0.156	0.327	
Exact 95% CI	-	[0.272, 1.414]	[0.018, 0.343]	[0.044, 0.459]	[0.128, 0.792]	
Relative risk	-	0.716	0.137	0.218	0.423	
Exact 95% CI	-	[0.307, 1.411]	[0.008, 0.480]	[0.034, 0.610]	[0.139, 0.937]	
Risk difference (%)	-	-9.6	-29.2	-26.4	-19.5	
Exact 95% CI	-	[-27.5, 7.3]	[-45.5, -14.5]	[-43.0, -11.5]	[-36.5, -4.0]	
<b>Subjects with any proximal DVT up to Day 17 (Efficacy Evaluable Population)</b>						
n/N (%)	9/76 (11.8)	2/66 (3.0)	0/70 (0)	0/72 (0)	1/72 (1.4)	
95% confidence interval (CI)	[5.6, 21.3]	[0.4, 10.5]	[0, 5.1]	[0, 5.0]	[0, 7.5]	
Odds ratio	-	0.233	0	0	0.105	
Exact 95% CI	-	[0.024, 1.196]	[0, 0.511]	[0, 0.497]	[0.002, 0.801]	
Relative risk	-	0.256	0	0	0.117	
Exact 95% CI	-	[0.003, 1.860]	[0, 1.708]	[0, 1.662]	[0, 1.662]	
Risk difference(%)	-	-8.8	-11.8	-11.8	-10.5	
Exact 95% CI	-	[-24.6, 3.2]	[-26.1, -1.7]	[-26.0, -2.0]	[-25.1, 0.1]	
<b>Subjects with distal only DVT up to Day 17 (Efficacy Evaluable Population)</b>						
n/N (%)	17/73 (23.3)	13/63 (20.6)	3/65 (4.6)	5/68 (7.4)	9/70 (12.9)	
95% confidence interval (CI)	[14.2, 34.6]	[11.5, 32.7]	[1.0, 12.9]	[2.4, 16.3]	[6.1, 23.0]	
<b>Subjects with symptomatic VTE up to Day 17 (ATS population)</b>						
n/N (%) [n with symptomatic DVT]	1/82 (1.2) [1]	0/80 (0)	0/80 (0)	0/81 (0)	0/83 (0)	
<b>Safety results:</b>						
<b>Bleeding results (ATS Population)</b>		<b>PBO</b>	<b>FX mg</b>			
<b>Adjudicated bleeding from first injection up to 2 calendar days after last injection</b>			<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
		<b>N = 82</b>	<b>N = 80</b>	<b>N = 80</b>	<b>N = 81</b>	<b>N = 83</b>
Major bleeding	n (%)	0	1 (1.3)	0	2 (2.5)	0
	95% CI	[0, 4.4]	[0, 6.8]	[0, 4.5]	[0.3, 8.6]	[0, 4.3]
Minor bleeding only	n (%)	0	3 (3.8)	2 (2.5)	4 (4.9)	0
	95% CI	[0, 4.4]	[0.8, 10.6]	[0.3, 8.7]	[1.4, 2.2]	[0, 4.3]
Any bleeding	n (%)	0	4 (5.0)	2 (2.5)	6 (7.4)	0
	95% CI	[0, 4.4]	[1.4, 12.3]	[0.3, 8.7]	[2.8, 15.4]	[0, 4.3]
<b>Blood transfusion from first injection up to 2 calendar days after last injection (ATS Population)</b>		<b>PBO</b>	<b>FX mg</b>			
			<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
		<b>N = 82</b>	<b>N = 80</b>	<b>N = 80</b>	<b>N = 81</b>	<b>N = 83</b>
n (%) subjects with transfusion		12 (14.6)	7 ( 8.8)	10 (12.5)	10 (12.3)	13 (15.7)
<b>Adverse event results:</b> On-therapy AEs were reported from first injection of study drug to up to 2 calendar days after last injection.						
<b>Adverse events (ATS Population)</b>		<b>PBO</b>	<b>FX mg</b>			
			<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
		<b>N = 82</b>	<b>N = 80</b>	<b>N = 80</b>	<b>N = 81</b>	<b>N = 83</b>

Subjects with any AE(s), n (%)	61 (74.4)	60 (75.0)	68 (85.0)	61 (75.3)	68 (81.9)
5 Most frequent AEs in each treatment group, n (%):					
Constipation	12 (14.6)	9 (11.3)	16 (20.0)	17 (21.0)	13 (15.7)
Insomnia	9 (11.0)	5 (6.3)	16 (20.0)	9 (11.1)	12 (14.5)
Hepatic function abnormal	11 (13.4)	10 (12.5)	11 (13.8)	2 (2.5)	7 (8.4)
Myalgia	11 (13.4)	6 (7.5)	10 (12.5)	5 (6.2)	11 (13.3)
Thrombocytopenia	8 (9.8)	6 (7.5)	9 (11.3)	8 (9.9)	6 (7.2)
GGT increased	4 (4.9)	6 (7.5)	3 (3.8)	8 (9.9)	9 (10.8)
SGPT increased	3 (3.7)	5 (6.3)	1 (1.3)	5 (6.2)	9 (10.8)
Phosphatase alkaline increased	4 (4.9)	7 (8.8)	3 (3.8)	4 (4.9)	7 (8.4)
Back pain	2 (2.4%)	4 (5.0%)	6 (7.5%)	6 (7.4%)	5 (6%)
Skin reaction localised	2 (2.4%)	6 (7.5%)	3 (3.8%)	3 (3.7%)	2 (2.4%)
<b>Serious Adverse Events:</b>					
<b>SAEs ( fatal &amp; non-fatal) ATS population</b>	<b>PBO</b>	<b>FX mg</b>			
		<b>0.75</b>	<b>1.5</b>	<b>2.5</b>	<b>3.0</b>
	<b>N = 82</b>	<b>N = 80</b>	<b>N = 80</b>	<b>N = 81</b>	<b>N = 83</b>
Subjects with any SAE(s) n (%) [related]	0	2 (2.5) [2]	0	0	0
Tachycardia supraventricular	0	1 (1.3) [1]	0	0	0
Hepatic function abnormal	0	1 (1.3) [0]	0	0	0
Cerebrovascular disorder	0	1 (1.3) [1]	0	0	0
<b>Subjects with fatal SAEs (All treated subjects)</b>	0	0	0	0	0

**Conclusion:**

A statistically significant dose effect relationship for prevention of VTE (including DVT and PE) in subjects with THR was demonstrated with FX at doses of 0.75, 1.5, 2.5, and 3.0 mg. The VTE rate in the 1.5mg, 2.5mg and 3.0mg FX groups was statistically significantly lower than PBO. The incidence of major bleeding in any group was 2.5% or less. AEs were reported in 60(75%), 68(85%), 61(75%), 68(82%) and 61(74%) subjects in the FX 0.75mg, 1.5mg, 2.5mg and 3.0mg and PBO groups respectively. The most frequently reported AEs were constipation, insomnia, hepatic function abnormal, and myalgia. SAEs were reported in 2(2.5%) subjects in FX 0.75mg group, with no SAEs reported in any other group. There were no deaths reported in any group.

**Publications:**

No Publication

Date Updated: 13-Sep-2005