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Study No.: DRI4757
Title: 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 knee replacement surgery.
Rationale: 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 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 knee replacement (TKR) surgery, and to compare the efficacy with placebo (PBO).
Phase: II/III
Study Period: 16 October 2001 – 28 August 2003.
Study Design: Multicentre, randomised, double-blind, PBO-controlled, parallel-group, dose response study.
Centres: 56 active centres in Japan.
Indication: Prevention of DVT and symptomatic PE in subjects undergoing elective primary TKR surgery or a revision surgery of the TKR.
Treatment: 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.
Objectives: Primary - To demonstrate the dose response effect of FX on the prophylaxis of VTE [DVT and PE] after TKR. Secondary -To compare efficacy (incidence of VTE) and safety (incidence of major bleeding) of FX for prophylaxis of VTE after TKR between each dose of FX and PBO.
Primary Outcome/Efficacy Variable: 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 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).
Secondary Outcome/Efficacy Variable(s): Secondary efficacy endpoints:- These included all DVTs, all proximal DVTs, distal DVTs only, symptomatic VTE (DVT and/or PE), symptomatic DVT, non-fatal and fatal PEs, up to Day 17. Safety: 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)]. This was 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 ≥ 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 ≥ 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 ≥ 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.
Statistical Methods: Populations analysed: All-treated-subjects (ATS): This population was defined as all randomised subjects who received at least one dose of the study drug (PBO or active compound), and was used for the safety analyses. ITT: Used for the analysis of the primary endpoint, this population consisted of subjects who had received at least 1 dose of study drug, had undergone the appropriate surgery, and had an available VTE evaluation for the primary endpoint (according to the adjudication forms by CIACE). Efficacy evaluable population: 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 efficacy of 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 a 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 all-treated-subjects (ATS) population.					
Study Population: Subjects who were undergoing elective primary TKR surgery or a revision surgery of a TKR; ≥ 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.					
	PBO	FX mg			
		0.75	1.5	2.5	3.0
Number of subjects:					
Planned enrolment (evaluable), N	85 (60)	85 (60)	85 (60)	85 (60)	85 (60)
Randomised, N	87	86	87	86	86
ATS population, N	87	86	85	84	84
ITT population, N	75	79	75	74	74
Per-protocol population, N	74	74	74	74	74
Completed study drug, n (%)	80 (92.0)	81 (94.2)	78 (91.8)	78 (92.9)	79 (94.0)
Reached DVT endpoint	0	1 (1.2)	0	0	0
Total withdrawn from study drug, n (%)	7 (8.0)	4 (4.7)	7 (8.2)	6 (7.1)	5 (6.0)
Withdrawn due to AE/SAE, n (%)	4 (5.0)	4 (4.7)	3 (3.5)	2 (2.4)	4 (4.8)
Withdrawn due to lack of efficacy, n(%)	-	-	-	-	-
Withdrawn consent, n (%)	1 (1.1)	0	4 (4.7)	4 (4.8)	0
Withdrawn for other reasons, n (%)	2 (2.3)	0	0	0	1 (1.2)
Demographics					
	PBO	FX mg			
		0.75	1.5	2.5	3.0
N (ATS population)	87	86	85	84	84
Females: Males	72:15	71:15	67:18	67:17	74:10
Mean Age, years (SD)	70.4 (7.9)	71.4 (8.7)	70.5 (8.0)	71.2 (7.8)	71.5 (7.6)
Race, n (%)	Not available (na)	na	na	na	na
Primary Efficacy Results:					
	PBO	FX mg			
		0.75	1.5	2.5	3.0
Subjects with confirmed VTE up to Day 17 (ITT population)	N =75	N =79	N = 75	N = 74	N = 74
n (%)	49 (65.3)	27 (34.2)	16 (21.3)	12 (16.2)	7 (9.5)
95% confidence interval (CI)	[53.5, 76.0]	[23.9, 45.7]	[12.7, 32.3]	[8.7, 26.6]	[3.9, 18.5]
Cochran-Armitage trend test (P)*	p<0.001				
Comparisons with PBO	-				
Fisher's exact test (P)**	-	p<0.001	p<0.001	p<0.001	p<0.001
Odds ratio	-	0.276	0.144	0.103	0.055
Exact 95% CI	-	[0.134, 0.564]	[0.065, 0.316]	[0.043, 0.238]	[0.019, 0.146]
Relative risk	-	0.523	0.327	0.248	0.145
Exact 95% CI	-	[0.316, 0.788]	[0.159, 0.554]	[0.100, 0.446]	[0.037, 0.311]
Risk difference(%)	-	-31.2	-44.0	-49.1	-55.9

Exact 95% CI		-	[-47.0, -15.3]	[-58.1, -28.0]	[-63.8, -34.3]	[-69.7, -42.1]
*Comparisons across all 5 treatment populations using the values of the doses as score (PBO, 0.75, 1.5, 2.5 and 3.0 mg). **Pair-wise comparison between each of FX populations with PBO population.						
Secondary Outcome Variable(s):						
		PBO	FX mg			
			0.75	1.5	2.5	3.0
Subjects with any DVT up to Day 17 (Efficacy Evaluable Population)						
n/N (%)		49/75 (65.3)	27/79 (34.2)	16/75 (21.3)	12/74 (16.2)	7/74 (9.5)
95% confidence interval (CI)		[53.5, 76.0]	[23.9, 45.7]	[12.7, 32.3]	[8.7, 26.6]	[3.9, 18.5]
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Risk difference(%)		-	-31.2	-44.0	-49.1	-55.9
Exact 95% CI		-	[-47.0, -15.3]	[-58.1, -28.0]	[-63.8, -34.3]	[-69.7, -42.1]
Subjects with any proximal DVT up to Day 17 (Efficacy Evaluable Population)						
n/N (%)		11/77 (14.3)	2/81 (2.5)	1/75 (1.3)	0/75 (0)	0/75 (0)
95% confidence interval (CI)		[7.4, 24.1]	[0.3, 8.6]	[0, 7.2]	[0, 4.8]	[0, 4.8]
Odds ratio		-	0.152	0.081	0	0
Exact 95% CI		-	[0.016, 0.740]	[0.002, 0.592]	[0, 0.370]	[0, 0.370]
Relative risk		-	0.173	0.093	0	0
Exact 95% CI		-	[0.002, 1.084]	[0, 1.114]	[0, 1.114]	[0, 1.114]
Risk difference (%)		-	-11.8	-13.0	-14.3	-14.3
Exact 95% CI		-	[-26.8, -0.5]	[-27.9, -2.4]	[-28.8, -4.4]	[-28.8, -4.4]
Subjects with distal only DVT up to Day 17 (Efficacy Evaluable Population)						
n/N (%)		42/75 (56.0)	26/79 (32.9)	15/76 (19.7)	12/75 (16.0)	7/74 (9.5)
95% confidence interval (CI)		[44.1, 67.5]	[22.7, 44.4]	[11.5, 30.5]	[8.6, 26.3]	[3.9, 18.5]
Subjects with symptomatic VTE up to Day 17 (ATS population)						
n/N (%) [n with symptomatic DVT]		0/87 (0)	1/86 (1.2) [1]	0/85 (0)	0/84 (0)	0/84 (0)
Safety results:						
Bleeding results (ATS population)		PBO	FX mg			
Adjudicated bleeding from 1st injection to 2 calendar days after last injection			0.75	1.5	2.5	3.0
		N=87	N=86	N = 85	N = 84	N = 84
Major bleeding	n (%)	1 (1.1)	0	0	1 (1.2)	1 (1.2)
	95% CI	[0, 6.2]	[0, 4.2]	[0, 4.2]	[0, 6.5]	[0, 6.5]
Minor bleeding only	n (%)	3 (3.4)	0	5 (5.9)	2 (2.4)	3 (3.6)
	95% CI	[0.7, 9.7]	[0, 4.2]	[1.9, 13.2]	[0.3, 8.3]	[0.7, 10.1]
Any bleeding	n (%)	4 (4.6)	0	5 (5.9)	3 (3.6)	4 (4.8)
	95% CI	[1.3, 11.4]	[0, 4.2]	[1.9, 13.2]	[0.7, 10.1]	[1.3, 11.7]
Blood transfusion from first injection to up to 2 calendar days after last injection (ATS population)		PBO	FX mg			
			0.75	1.5	2.5	3.0
		N = 87	N = 86	N = 85	N = 84	N = 84
N (%) subjects with transfusion		20 (23.0 %)	15 (17.4 %)	19 (22.4 %)	21 (25.0 %)	19 (22.6 %)

Adverse event results: On-therapy AEs were reported from first injection of study drug to up to 2 calendar days after last injection.					
Adverse events (ATS population)	PBO	FX mg			
		0.75	1.5	2.5	3.0
	N = 87	N = 86	N = 85	N = 84	N = 84
Subjects with any AE(s), n (%)	65 (74.7)	61 (70.9)	67 (78.8)	68 (81.0)	61 (72.6)
5 most frequent AEs in each treatment group, n (%):					
Constipation	11 (12.6)	16 (18.6)	12 (14.1)	8 (9.5)	12 (14.3)
Hepatic function abnormal	6 (6.9)	10 (11.6)	7 (8.2)	10 (11.9)	13 (15.5)
Insomnia	9 (10.3)	13 (15.1)	8 (9.4)	10 (11.9)	5 (6.0)
Anaemia	6 (6.9)	10 (11.6)	8 (9.4)	11 (13.1)	9 (10.7)
Diarrhoea	10 (11.5)	3 (3.5)	5 (5.9)	3 (3.6)	5 (6.0)
Haemorrhage NOS	9 (10.3)	2 (2.3)	9 (10.6)	7 (8.3)	6 (7.1)
Thrombocytopenia	7 (8.0)	8 (9.3)	9 (10.6)	7 (8.3)	6 (7.1)
Post-operative haemorrhage	7 (8.0)	6 (7.0)	5 (5.9)	8 (9.5)	7 (8.3)
Rash erythematous	7 (8.0)	4 (4.7)	2 (2.4)	4 (4.8)	5 (6.0)
NOS = not otherwise specified					
Serious Adverse Events					
SAEs (fatal & non-fatal) ATS population	PBO	FX mg			
		0.75	1.5	2.5	3.0
	N = 87	N = 86	N = 85	N = 84	N = 84
Subjects with any SAE(s), n (%) [related]	1 (1.1) [1]	0	0	0	1 (1.2) [0]
Skin necrosis	0	0	0	0	1 (1.2) [0]
Gastric ulcer	1 (1.1) [0]	0	0	0	0
Gastrointestinal haemorrhage	1 (1.1) [1]	0	0	0	0
Subjects with fatal SAEs (All treated subjects)	0	0	0	0	0

Conclusion.

A dose effect relationship for prevention of VTE (including DVT and PE) in subjects with TKR was observed with s.c. administration of FX 0.75, 1.5, 2.5, and 3.0 mg. The VTE rate in all FX groups was statistically significantly lower than PBO. The incidence of major bleeding in any group was 1.2% or less. AEs were reported in 61(71%), 67(79%), 68(81%), 61(73%) and 65(75%) subjects in the FX 0.75mg, 1.5mg, 2.5mg, and 3.0mg and PBO groups respectively. The most frequently reported AEs were constipation, hepatic function abnormal, insomnia, and anaemia. SAEs were reported in 1(1.2%) and 1(1.1%) subjects in FX 3.0mg, and PBO groups respectively, with no SAEs reported in other groups. There were no deaths reported in any group.

Publications:

No Publication

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