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Study No.: DRI2643
Title: A multicenter, randomized, parallel, double-blind, dose ranging study of subcutaneous Org31540/SR90107A with an assessor blind, comparative control group of subcutaneous LMWH in the prevention of deep vein thrombosis after elective total hip replacement. Pentathlon
Rationale: Pilot studies suggested that fondaparinux (FX), a selective inhibitor of activated factor X (factor Xa), is effective in prevention of deep vein thrombosis (DVT) in high risk situations. Therefore the aim of this study was to determine the optimal dose of FX, testing in parallel 5 dose regimens against a comparative control group of low molecular weight heparin (LMWH, enoxaparin [EN]), for prophylaxis of venous thromboembolic events (VTEs), which included DVT (both symptomatic and asymptomatic) and symptomatic pulmonary embolism (PE, fatal or non-fatal) occurring during the treatment period.
Phase: II
Study Period: 01 November 1996 - 03 March 1998.
Study Design: Multicentre, randomised, parallel, dose ranging study of FX with an assessor-blind, comparative control group of EN.
Centres: 70 study centres in 3 countries: 50 USA, 10 Canada and 10 Australia.
Indication: Prevention of DVT and symptomatic PE in subjects undergoing elective total hip replacement (THR) or revision of a primary procedure.
Treatment: Subjects received either a once daily (o.d.) subcutaneous (s.c.) injection of FX 0.75, 1.5, 3.0, 6.0 or 8.0 mg starting 6 ± 2 hours post-operatively on Day 1 (day of surgery), or twice daily (b.i.d.) s.c. injection of EN 30 mg that started within 12 to 24 hours post-operatively (Day 1 or Day 2). Subjects were treated for a minimum of 5 days from Day 1 and until the final venogram was obtained, up to a maximum of 10 days.
Objectives: To determine the optimum dose of o.d., s.c. injection of FX starting post-operatively and continuing for a minimum of 5 days for VTE prophylaxis compared with b.i.d., s.c. injection of a LMWH in subjects undergoing elective total hip replacement. To determine the concentration of FX or EN anti-Xa activity in plasma in this subject population.
Primary Outcome/Efficacy Variable: The primary endpoint was the incidence of subjects with adjudicated mandatory venogram positive for DVT and/or symptomatic adjudicated PE. Independent experts of the Central Independent Adjudication Committee (CIAC) evaluated blindly all venograms and lung scans performed during the study.
Secondary Outcome/Efficacy Variable(s): <u>Secondary efficacy variables:</u> Incidence of each VTE (proximal and/or distal DVT and non-fatal and fatal PE) taken separately.
Statistical methods: <u>Sample size:</u> A total of 140 evaluable subjects per FX group and 210 evaluable subjects in the EN group were required by the protocol. The sample size of the FX groups was calculated in order to obtain a certain width of the 95% CI of the doses for different VTE rates using a logit model including the five FX tested doses. A total of 140 subjects per FX group allowed to obtain a 95 % CI of ± 1.5 mg for a dose that would be associated with a VTE incidence of 7.5 %. In addition, it was verified that 140 subjects per group allowed to detect a difference between the lowest FX tested dose and the recommended dose(s) with sufficient power. The sample size of the EN group was calculated to allow demonstration that the FX selected dose was at least as effective as EN (unilateral equivalence, VTE incidence of 7.5% with FX and of 12 % with EN, non-inferiority margin = 3 %). <u>Populations:</u> <i>All treated subjects (ATS) (safety population):</i> All subjects randomised and treated with at least one dose of study medication. <i>Intent-to-treat (ITT) population (efficacy population):</i> Subpopulation of ATS population, including subjects who underwent hip replacement surgery with an adjudicated evaluable bilateral (or positive unilateral) scheduled venogram performed between Day 5 and Day 10 (or before Day 5 with DVT) or a symptomatic adjudicated PE but no more than 24 hours after last dose. <i>Per protocol (PP) population (efficacy population):</i> Subpopulation of ITT population, which excluded subjects with major protocol deviations of less than 5 days of study treatment and first injection not on time, and forbidden concomitant medications or procedures.

Efficacy analyses:						
The primary analysis was a logistic regression among FX doses based on the per protocol population. Pairwise comparisons between the lowest FX dose (0.75 mg) and the other completed doses (1.5 mg, 3.0 mg) using Fisher's exact tests as well as 95 % exact confidence interval (CI) on differences and relative risks were performed as secondary analyses. Pairwise comparisons between the EN group and the three completed FX groups using Fisher's exact tests as well as 95 % exact CIs on differences and relative risks were also performed as secondary analyses. Similar analyses were performed for the ITT population.						
Safety analyses:						
<i>Adverse events:</i> All AEs were summarised by organ class and preferred term according to the period in which they occurred, i.e. the treatment period or the follow-up period. Related AEs, i.e. AEs reported by the investigators as likely or unknown to be related to study drug, were also summarised by organ class and preferred term for these two periods.						
Study Population: Males or females of non-childbearing potential ≥ 18 years of age undergoing elective primary hip replacement or revision of a primary procedure. Exclusion criteria were 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 ($<100 \times 10^9/L$), or known bleeding disorder), or those relating to venogram (such as creatinine clearance >1.6 mg/dL; or hypersensitivity to contrast media) or use of anticoagulant or thrombolytic therapy one week prior to the start of the study.						
	FX mg					EN mg
	0.75	1.5	3.0	6.0	8.0	60
Number of subjects:						
Planned enrolment, N	180	180	180	180	180	270
Randomised, N	185	190	181	73	52	269
AST population, N	184	188	177	72	52	260
ITT population, N	119	120	115	45	23	171
PP population, N	102	101	101	44	22	150
Completed study drug, n(%) (ATS population)	170(92.4)	173(92.0)	164(92.7)	60(83.3)	39(75.0)	233(89.6)
Total withdrawn from study drug, n(%) (ATS population)	14(7.6)	15(8.0)	13(7.3)	12(16.7)	13(25.0)	27(10.4)
Withdrawn due to AEs/SAEs, n(%)	8(4.3)	8(4.3)	7(4.0)	10(13.9)	9(17.3)	18(6.9)
Withdrawn due to lack of efficacy, n(%)	0	0	0	0	0	1(0.4)
Withdrawn consent (included in other reasons)	NS	NS	NS	NS	NS	NS
Withdrawn for other reasons, n(%)	6(3.2)	7(3.7)	6(3.4)	2(2.8)	4(7.7)	8(3.1)
Demographics (AST population):	FX mg					EN mg
	0.75	1.5	3.0	6.0	8.0	60
	N = 184	N = 188	N = 177	N = 72	N = 52	N = 260
Females: Males	82:102	88:100	80:97	35:37	25:27	123:137
Mean Age, years (SD)	64.4(12.1)	65.1(12.1)	63.8(11.2)	65.4(10.2)	66.2(14.1)	64.5(12.0)
Caucasian, n (%)	164 (89.1)	172 (91.5)	164 (92.7)	68 (94.4)	48 (92.3)	236 (90.8)
Primary Efficacy Results:						
Subjects with adjudicated VTE (PP population)	FX mg					EN mg
	0.75	1.5	3.0	6.0	8.0	60
	N = 102	N = 101	N = 101	N = 44	N = 22	N = 150
n (%)	13(12.7)	6(5.9)	2(2.0)	2(4.5)	0	14(9.3)
95% CI	[7.0, 20.8]	[2.2, 12.5]	[0.2, 7.0]	[0.6, 15.5]	[0, 15.4]	[5.2, 15.2]
p-value for dose response (logit model)	p=0.003					
	FX mg					
	1.5				3.0	

Absolute difference with 0.75 mg		-6.8					-10.8
Exact 95% CI for difference		[-18.4, 3.0]					[-21.7, 2.1]
Fisher exact test results (p)		0.147					0.005
		FX mg					
		0.75	1.5	3.0	6.0	8.0	60
Absolute difference with EN		3.4	-3.4			-7.4	
Exact 95% CI for difference		[-5.9, 14.5]	[-12.2, 5.7]			[-15.4, 0.6]	
Fisher exact test results (p)		0.412	0.477			0.019	
Secondary Outcome Variable(s):							
Subjects with adjudicated DVT (PP population)		FX mg					EN mg
		0.75	1.5	3.0	6.0	8.0	60
		N = 102	N = 101	N = 101	N = 44	N = 22	N = 150
Total DVT	n (%)	11(10.8)	6(5.9)	2(2.0)	2(4.5)	0	14(9.3)
	95% CI	[5.5, 18.5]	[2.2, 12.5]	[0.2, 7.0]	[0.6, 15.5]	[0, 15.4]	[5.2, 15.2]
Total proximal DVT	n (%)	3(2.9)	5(5.0)	1(1.0)	1(2.3)	0	5(3.3)
	95% CI	[0.6, 8.4]	[1.6, 11.2]	[0, 5.4]	[0.1, 12.0]	[0, 15.4]	[1.1, 7.6]
Total distal DVT	n (%)	8(7.8)	1(1.0)	1(1.0)	1(2.3)	0	11(7.3)
	95% CI	[3.5, 14.9]	[0, 5.4]	[0, 5.4]	[0.1, 12.0]	[0, 15.4]	[3.7, 12.7]
	95% CI	[3.5, 13.9]	[0.5, 7.1]	[0, 4.8]	[0.1, 11.8]	[0, 14.8]	[4.1, 12.7]
Subjects with adjudicated symptomatic confirmed VTE (ATS population)		FX mg					EN mg
		0.75	1.5	3.0	6.0	8.0	60
		N = 184	N = 188	N = 177	N = 72	N = 52	N = 260
VTE	n (%)	3(1.6)	0	5(2.8)	2(2.8)	1(1.9)	7(2.7)
	95% CI	[0.3, 4.7]	[0, 1.9]	[0.9, 6.5]	[0.3, 9.7]	[0.1, 10.3]	[1.1, 5.5]
DVT, n		1	0	3	2	0	4
Non-fatal PE, n		2	0	3	0	1	2
Fatal PE, n		0	0	0	0	0	1
Safety results:							
Adverse event results: AEs were defined during the treatment period defined as a minimum of 5 days from Day 1 (Day of surgery) and until the final venogram was obtained, up to a maximum of 10 days							
Adverse events (ATS population)		FX mg					EN mg
		0.75	1.5	3.0	6.0	8.0	60
		N = 184	N = 188	N = 177	N = 72	N = 52	N = 260
Subjects with any AE(s) during the treatment period, n (%)		182(98.9)	181(96.3)	174(98.3)	71(98.6)	51(98.1)	247(95.0)
5 most frequent AEs in each treatment group, n (%):							
Fever		93(50.5)	92(48.9)	88(49.7)	39(54.2)	25(48.1)	89(34.2)
Constipation		73(39.7)	73(38.8)	78(44.1)	39(54.2)	25(48.1)	85(32.7)
Anaemia		53(28.8)	60(31.9)	69(39.0)	26(36.1)	21(40.4)	63(24.2)
Nausea		61(33.2)	64(34.0)	59(33.3)	28(38.9)	27(51.9)	49(18.8)
Oedema peripheral		53(28.8)	54(28.7)	47(26.6)	21(29.2)	18(34.6)	77(29.6)
Post-operative pain		39(21.2)	52(27.7)	42(23.7)	19(26.4)	12(23.1)	9(3.5)
Serious Adverse Events:							
Subjects with SAEs (fatal and non-fatal) (ATS population)		FX mg					EN mg
		0.75	1.5	3.0	6.0	8.0	60
		N = 184	N = 188	N = 177	N = 72	N = 52	N = 260

Subjects with any SAE(s) during the treatment period, n (%) [number considered by Investigator to be related to study medication]	12(6.5) [0]	6(3.2) [0]	12(6.8) [3]	12(16.7) [2]	7(13.5) [3]	11(4.2) [1]
Post-operative haemorrhage	0	0	3(1.7)[1]	4(5.6)[0]	5(9.6)[3]	3(1.2)[0]
Surgical site reaction	2(1.1)[0]	1(0.5)[0]	4(2.3)[0]	1(1.4)[0]	1(1.9)[0]	3(1.2)[0]
Fever	0	0	0	0	1(1.9)[0]	0
Haematoma	0	0	1(0.6)[1]	2(2.8)[1]	0	0
Anaemia	0	1(0.5)[0]	1(0.6)[0]	1(1.4)[0]	0	0
Myocardial infarction	3(1.6)[0]	0	0	0	0	0
Wound drainage increased	0	0	1(0.6)[1]	1(1.4)[0]	0	0
Cardiac failure	0	1(0.5)[0]	1(0.6)[0]	0	0	0
Transient ischaemic attack	1(0.5)[0]	0	0	0	0	1(0.4)[0]
Angina pectoris	0	0	0	1(1.4)[0]	0	0
GI Haemorrhage	0	0	0	1(1.4)[0]	0	0
Haemorrhage NOS	0	0	0	1(1.4)[1]	0	0
Ileus	0	0	1(0.6)[0]	0	0	0
Pneumonia	0	0	1(0.6)[0]	0	0	0
NPN increased	0	0	1(0.6)[0]	0	0	0
Micturition disorder	0	0	1(0.6)[0]	0	0	0
Arrhythmia	0	0	1(0.6)[0]	0	0	0
Cardiac failure left	0	1(0.5)[0]	0	0	0	0
Dysphagia	0	1(0.5)[0]	0	0	0	0
Hypotension	0	1(0.5)[0]	0	0	0	0
Hypoxia	0	1(0.5)[0]	0	0	0	0
Paresis	0	1(0.5)[0]	0	0	0	0
Renal failure acute	0	1(0.5)[0]	0	0	0	0
Cheyne-Stokes respiration	1(0.5)[0]	0	0	0	0	0
Coagulation disorder	1(0.5)[0]	0	0	0	0	0
Delirium	1(0.5)[0]	0	0	0	0	0
Gout	1(0.5)[0]	0	0	0	0	0
Intestinal obstruction	1(0.5)[0]	0	0	0	0	0
Intestinal necrosis	1(0.5)[0]	0	0	0	0	0
Angioedema	0	0	0	0	0	1(0.4)[1]
Arthralgia	0	0	0	0	0	1(0.4)[0]
Confusion	0	0	0	0	0	1(0.4)[0]
Myocardial ischaemia	0	0	0	0	0	1(0.4)[0]
Post-operative wound infection	0	0	0	0	0	1(0.4)[0]
Thrombocytopenia	0	0	0	0	0	1(0.4)[0]
Subjects with fatal SAEs (ATS population)						
	FX mg					EN mg
	0.75	1.5	3.0	6.0	8.0	60
	N = 184	N = 188	N = 177	N = 72	N = 52	N = 260
Fatal SAEs during the study, n (%)	4 (2.2) [0]	0	0	0	0	2(0.8) [0]
Myocardial infarction (MI)	2(1.0) [0]	0	0	0	0	0
Dyspnoea	1(0.5) [0]	0	0	0	0	0
Intestinal necrosis	1(0.5) [0]	0	0	0	0	0
Carcinoma	0	0	0	0	0	1(0.4) [0]
Embolism pulmonary	0	0	0	0	0	1(0.4) [0]
	FX mg					EN mg
	0.75	1.5	3.0	6.0	8.0	60
	N = 184	N = 188	N = 177	N = 72	N = 52	N = 260

Deaths during the study by adjudication criterion, n (%)	3 (1.6)	0	0	0	0	1(0.4) [0]
Fatal PE	0	0	0	0	0	1(0.4) [0]
Death not associated with VTE or bleeding	3 (1.6) [0]	0	0	0	0	0

Conclusion:

See publication below.

Publications:

Turpie AG. Dose-dependent activity of Arixtra in the prophylaxis of deep vein thrombosis following total hip replacement: Rationale of dose selection with a Phase II study (Pentathlon). *N Engl J Med* 2001; 344: 619-25.

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