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Study No.: DRI3196
Title: A multicentre, randomised, dose-ranging study comparing Org31540/SR90107A with heparin as adjunctive therapy to recombinant tissue plasminogen activator and Aspirin in acute myocardial infarction (AMI) (PENTALYSE)
Rationale: Org31540/SR90107A, also known as fondaparinux (FX), offers potential as an antithrombotic therapy with a better benefit to risk ratio than existing heparin-based therapies in combination with thrombolytic agents. The doses tested in this dose-ranging study were selected according to previous data in animal models, healthy subjects and subjects.
Phase: II
Study Period: 25 May 1998 to 15 Jul 1999
Study Design: This was a multicentre, open-label, angiography assessor blind, randomised, dose-ranging, active-controlled, parallel group design.
Centres: This study was conducted in 7 study centres in Belgium, 6 in France, 6 in Germany, 1 in the Netherlands, 1 in Switzerland, and 3 in the United Kingdom.
Indication: AMI
Treatment: Subjects were assigned to 1 of 4 treatment groups: 4mg FX plus recombinant tissue-plasminogen activator (rt-PA) and Aspirin; 8mg FX plus rt-PA and Aspirin; 12mg FX plus rt-PA and Aspirin; unfractionated heparin (UFH) plus rt-PA and Aspirin. The daily dose of FX was reduced by 2mg if body weight was <60kg, and increased by 2mg if body weight was >90kg, except for 12mg: no dose increase, and for 4mg: no dose decrease. Duration of treatment: FX 4 mg, 8 mg and 12 mg groups: Five (\pm 1) days. Subjects received a single intravenous (i.v.) bolus of FX on Day 1, followed by a daily subcutaneous (s.c.) administration for 4 (\pm 1) days. UFH group: Subjects received an i.v. bolus on Day 1 followed by an i.v. infusion for 48 to 72 hours. rt-PA and aspirin: Subjects received front loaded rt-PA (Actilyse) on Day 1. A 15 mg i.v. bolus was followed by i.v infusion of 0.75 mg/kg (up to 50 mg) over 30 minutes then 0.5 mg/kg (up to 35 mg) over 60 minutes. The maximum total dose was 100 mg. A daily dose of 150 to 325 mg aspirin was administered daily throughout the study. The first dose was as non-enteric coated tablet or was given intravenously.
Objectives: The primary objective was to assess the safety and tolerability of 3 dose regimens of FX combined with rt-PA and Aspirin in AMI.
Primary Outcome/Efficacy Variable: Recovery of patency of MI-related coronary artery "Thrombolysis In Myocardial Infarction" (TIMI) Grade 3 flow, 90 minutes after the start of thrombolytic therapy and on Day 6 \pm 1.
Secondary Outcome/Efficacy Variable(s): Efficacy: Incidence of death, reinfarction, emergency revascularization procedure, and combined events during the 30 \pm 7-day study period. Safety: The primary safety endpoint of the study was the incidence of primary intracranial bleeding or blood transfusion (whole blood or packed red cells) during the 30 \pm 7-day study period. Secondary safety endpoints were any bleeding events reported as unusual by the investigators. Other safety variables included adverse events (AEs) and serious AEs (SAEs) which were monitored from first injection and up to 72 hours after the last dose. Pharmacokinetics: Plasma concentrations of FX, measured at screening, 90 minutes after first dose, before and 1 hour after the second dose, and before, 3 hours and 8 hours after dosing on Day 4. No pharmacokinetic parameters were calculated.
Statistical Methods: Efficacy: Coronary endpoint: Calculation of the incidence of a TIMI Grade 3 flow and its associated exact 95% confidence interval (CI) by treatment group. A comparison of TIMI flow grades as a binary variable (Grade 3 or not) using a trend test for the FX groups at each time point was performed. Clinical endpoints: 95% CI on percentages and Kaplan-Meier Curves for MI + death and for the cluster of clinical endpoints. Incidence of all revascularizations summarised using counts and percentages according to the following

classes: ≥ 90 minutes, [90 minutes to Day 5], [Day 5 to Day 7], >Day 7; calculation of associated 95% CI by treatment group.				
Safety: Primary safety endpoint (intracranial bleeding and/or transfusion of whole blood or packed red cells): Calculation of the crude incidence of the primary safety endpoint up to Day 37 and associated 95% CI. A trend test restricted to the FX groups was performed.				
Pharmacokinetics: Standard descriptive statistics by dose, including body weight adjustment of observed FX plasma concentrations for each scheduled time point.				
According to the incidence of bleeding complications in a previous study, the lower limit of the 90% CI of the observed incidence was not to be higher than 0.8% for primary intracranial bleeding and 8% for transfused patients. In a treatment group not prematurely curtailed, the number of subjects who experienced primary intracranial bleeding or blood transfusion was not to exceed 12 subjects (15%). With 80 subjects per group, the power to detect differences between 2 dose groups (setting to 15% the worst group) was 0.31, 0.58, and 0.85 for 8%, 5%, and 2% lowest incidence of "transfused" subjects, respectively.				
The analysis of safety and clinical efficacy endpoints was carried out on the all-treated data set defined as the population of all randomised subjects who received ≥ 1 dose of study drug. For coronary angiography results, the main analysis was performed on 90-minute and Day 6 \pm 1 per-protocol (PP) populations. The 90-minute PP population was defined as the all-treated population from which subjects without 90-minute evaluation were removed as well as subjects with poor compliance with the study drug treatment or prohibited treatment between the beginning of study drug and the 90-minute evaluation. The Day 6 \pm 1 PP population was defined as the all-treated population from which subjects without Day 6 \pm 1 evaluation or without earlier treatment failure were removed as well as subjects with bad compliance according to study drug or prohibited treatment between the beginning of study drug and the Day 6 \pm 1 evaluation.				
Study Population: Subjects of either sex aged between 21 and 75 years old presenting with ischaemic pain lasting at least 30 minutes, ST-segment elevation ≥ 0.1 mV in ≥ 2 limb leads or ≥ 0.2 mV in 2 or more contiguous precordial leads, for whom planned treatment was initiated within 6 hours after onset of pain were eligible to be included in the study. The main exclusion criteria were recent coronary intervention (e.g. stent implantation, coronary bypass grafting), current therapeutic anticoagulation, known renal insufficiency with creatinine ≥ 1.8 mg/dL, history of stroke, transient ischemic attack, any structural brain disease, or neurosurgery, and hypertension.				
Number of Subjects:	FX 4mg	FX 8mg	FX 12mg	UFH
Planned, N	80	80	80	80
Randomised, N	84	80	83	86
All Treated, N	81	77	83	85
Per Protocol 90-minutes, N	79	74	79	84
Per Protocol Day 6 \pm 1, N	48	50	45	56
Completed, n (% of all treated)	66 (81.5)	58 (75.3)	60 (72.3)	70 (82.4)
Total Number Subjects Withdrawn n (% of all treated)	15 (18.5)	19 (24.7)	23 (27.7)	15 (17.6)
Withdrawn due to AEs, n (% of all treated)	2 (2.5)	10 (13.0)	11 (13.3)	5 (5.9)
Withdrawn due to Lack of Efficacy n (% of all treated)	9 (11.1)	5 (6.5)	10 (12.0)	3 (3.5)
Withdrawn for other reasons, n (% of all treated)	4 (4.9)	4 (5.2)	1 (1.2)	7 (8.2)
Demographics				
N (All Treated)	81	77	83	85
Females: Males	12:69	13:64	14:69	17:68
Mean Age, years (SD)	59.7 (9.2)	56.4 (11.4)	57.8 (10.1)	56.2 (10.7)
Caucasian n(%)	79 (97.5)	77 (100.0)	83 (100.0)	85 (100.0)
Primary Efficacy Results:				
Recovery of patency: 90-Minute TIMI Grade 3 Flow (Per-Protocol 90-minute Population)	FX 4mg N=79	FX 8mg N=74	FX 12mg N=79	UFH N=84
Grade 3 at 90 minutes, n (%)	51 (64.6)	51 (68.9)	47 (59.5)	57 (67.9)
Exact 95% CI	53.0, 75.0	57.1, 79.2	47.9, 70.4	56.8, 77.6
Recovery of patency: Day 6\pm1 TIMI Grade 3 Flow (Per-Protocol Day 6\pm1 Population)	FX 4mg N=48	FX 8mg N=50	FX 12mg N=45	UFH N=56
Grade 3 on Day 6 \pm 1	39 (81.3)	44 (88.0)	40 (88.9)	42 (75.0)
Exact 95% CI	67.4, 91.1	75.7, 95.5	75.9, 96.3	61.6, 85.6
Secondary Outcome Variables:				
Clinical Endpoints Which Occurred Up to Day 7 (All Treated)	FX 4mg N=81	FX 8mg N=77	FX 12mg N=83	UFH N=85
All Deaths, n (%)	0	0	2 (2.4)	0 ^a

Non-fatal MI, n (%)		3 (3.7)	0	2 (2.4)	2 (2.4) ^a
Death or MI, n (%)		3 (3.7)	0	4 (4.8)	2 (2.4) ^a
Revascularisation ^b , n (%)		21 (25.9)	25 (32.5)	26 (31.3)	34 (40.5) ^a
Any Event, n (%)		22 (27.2)	25 (32.5)	29 (34.9)	34 (40.5) ^a
Exact 95% CI for 'any event'		17.9, 38.2	22.2, 44.1	24.8, 46.2	29.9, 51.7
^a Number of subjects with no evaluation. Percentages were computed using the total of subjects with an evaluation.					
^b Excluding 90-minute revascularization					
Clinical Endpoints Which Occurred Up to Day 37 (All Treated)		FX 4mg N=81	FX 8mg N=77	FX 12mg N=83	UFH N=85
All Deaths		2 (2.5)	2 (2.6)	2 (2.4)	1 (1.2) ^a
Non-fatal MI		5 (6.2)	0	4 (4.9)	3 (3.6) ^a
Death or MI		7 (8.6)	2 (2.6)	6 (7.3)	4 (4.8) ^a
Revascularisation ^b		30 (37.0)	30 (39.0)	33 (39.8)	43 (51.2) ^a
At Least 1 Event		33 (40.7)	31 (40.3)	37 (44.6)	45 (53.6) ^a
Exact 95% CI for 'any event'		29.9, 52.2	29.2, 52.1	33.7, 55.9	42.4, 64.5
^a Number of subjects with no evaluation. Percentages were computed using the total of subjects with an evaluation.					
^b Excluding 90-minute revascularization					
Subjects who Reached Primary Safety Endpoint During the 30±7 Day Study Period (All Treated)		FX 4mg N=81	FX 8mg N=77	FX 12mg N=83	UFH N=85
Subjects With Intracranial Bleeding, n (%)		1 (1.2)	0	0	0
Transfused Subjects, n (%)		3 (3.7)	7 (9.1)	6 (7.2)	6 (7.1)
Exact 95% CI		0.8, 10.4	3.7, 17.8	2.7, 15.1	2.7, 14.9
Subjects Who Reached the Primary Safety Endpoint, n (%)		4 (4.9)	7 (9.1)	6 (7.2)	6 (7.1)
Exact 95% CI		1.4, 12.2	3.7, 17.8	2.7, 15.1	2.7, 14.9
Unusual Bleeding Events During the Study Period (All Treated)		FX 4mg N=81	FX 8mg N=77	FX 12mg N=83	UFH N=85
Unusual Bleeding, n (%)		20 (24.7)	37 (48.1)	42 (51.2)	22 (26.2)
Exact 95% CI		15.8, 35.5	36.5, 59.7	39.9, 62.4	17.2, 36.9
Pharmacokinetic parameters					
Mean plasma concentrations (mg/L)		FX 4mg N=81	FX 8mg N=77	FX 12mg N=83	
1.5 h post dose Day 1	n	66	66	65	
	mean	0.476	0.786	0.935	
	SD	0.330	0.489	0.399	
Predose Day 2	n	52	45	49	
	mean	0.145	0.221	0.305	
	SD	0.110	0.080	0.177	
1 h Postdose day 2	n	58	56	59	
	mean	0.460	0.773	1.088	
	SD	0.179	0.328	0.442	
Predose Day 4	n	56	47	53	
	mean	0.193	0.340	0.443	
	SD	0.091	0.111	0.166	
3 h post dose Day 4	n	62	49	56	
	mean	0.690	1.059	1.377	
	SD	0.284	0.262	0.284	
8h Postdose Day 4	n	61	46	51	
	mean	0.539	0.785	1.101	
	SD	0.220	0.210	0.266	
Safety Results: An on therapy AE was defined as an AE with onset on or after the first study drug medication to 72 hours after the last study drug administration (or three calendar days when the time of the last injection was not available). An on therapy SAE was defined as for AEs.					
Most Frequent Adverse Events – On-Therapy (All Treated)					
		FX 4mg	FX 8mg	FX 12mg	UFH

	N=81 n(%)	N=77 n(%)	N=83 n(%)	N=85 n(%)
Subjects with any AEs	53 (65.4)	64 (83.1)	65 (78.3)	55 (64.7)
5 most frequent AEs in each treatment group:				
Haematoma	14 (17.3)	21 (27.3)	29 (34.9)	10 (11.8)
Haemorrhage Not Otherwise Specified (NOS)	6 (7.4)	14 (18.2)	14 (16.9)	5 (5.9)
Vomiting	6 (7.4)	4 (5.2)	4 (4.8)	4 (4.7)
Abdominal Pain	6 (7.4)	2 (2.6)	4 (4.8)	4 (4.7)
Nausea	1 (1.2)	1 (1.3)	4 (4.8)	4 (4.7)
Arrhythmia Ventricular	2 (2.5)	2 (2.6)	4 (4.8)	2 (2.4)
Hypotension	4 (4.9)	6 (7.8)	3 (3.6)	6 (7.1)
Fever	3 (3.7)	2 (2.6)	2 (2.4)	6 (7.1)
Chest Pain	3 (3.7)	5 (6.5)	2 (2.4)	2 (2.4)
Back Pain	6 (7.4)	7 (9.1)	8 (9.6)	6 (7.1)
Headache	2 (2.5)	3 (3.9)	3 (3.6)	6 (7.1)
Hepatic Enzymes Increased	3 (3.7)	5 (6.5)	5 (6.0)	2 (2.4)
Serious Adverse Events - On-Therapy (All Treated)				
n (%) [n considered by the investigator to be related to study medication]				
	FX 4mg N=81 n(%) [related]	FX 8mg N=77 n(%) [related]	FX 12mg N=83 n(%) [related]	UFH N=85 n(%) [related]
Subjects With Any SAE	3 (3.7) [1]	7 (9.1) [5]	8 (9.6) [5]	5 (5.9) [3]
Haemorrhage NOS	0	3 (3.9) [3]	1 (1.2) [1]	1 (1.2) [1]
Haematoma	0	0	1 (1.2) [1]	1 (1.2) [1]
Cerebral Haemorrhage	1 (1.2) [1]	0	0	0
Epistaxis	0	1 (1.3) [1]	0	0
Haematemesis	0	0	1 (1.2) [1]	0
Haemorrhage Retroperitoneal	0	0	1 (1.2) [1]	0
Ocular Haemorrhage	0	0	0	1 (1.2) [1]
Thrombophlebitis Arm Superficial	0	0	1 (1.2) [0]	0
Cardiac Failure	1 (1.2) [0]	0	1 (1.2) [0]	1 (1.2) [0]
Cardiac Failure Left	0	1 (1.3) [1]	0	0
Circulatory Failure	1 (1.2) [0]	0	0	0
Hypotension	0	0	1 (1.2) [0]	0
Ventricular Septal Defect	0	1 (1.3) [0]	0	0
Pulmonary Oedema	1 (1.2) [0]	0	1 (1.2) [0]	0
Chest Pain	0	1 (1.3) [1]	0	0
Pericardial Effusion	0	0	1 (1.2) [1]	0
Hydronephrosis	0	0	0	1 (1.2) [0]
Cerebrovascular Disorder	0	1 (1.3) [0]	0	0
	n(%) [related]	n(%) [related]	n(%) [related]	n(%) [related]
Subjects With Fatal SAEs	2 (2.5) [0]	2 (2.6) [0]	2 (2.4) [1]	1 (1.2) [1]
Acute Pulmonary Oedema	1 (1.2) [0]	0	0	0
Haemodynamic Troubles Following Cardiac Surgery	1 (1.2) [0]	0	0	0
Cardiocirculatory Arrest	0	1 (1.3) [0]	0	0
Ventricular Fibrillation	0	1 (1.3) [0]	0	0
Cardiogenic Shock	0	0	1 (1.2) [0]	0
Severe Retroperitoneal Bleeding	0	0	1 (1.2) [1]	0
Bleed at Site of Groin Puncture	0	0	0	1 (1.2) [1]
Conclusion:				
See publication below				

Publications:

Coussement, PK. A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction. The Pentalyse study. *Eur Heart J*. 2001; 22:1716–1724.

New data in treatment of acute coronary syndromes. Van de Werf, F. *Am Heart J* 2001; 142(2 Suppl):S16-21

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