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Study No.: ACT2445
Title: Pilot efficacy study of a single I.V. injection of Pentasaccharide (SR90107A/ORG 31540) in patients undergoing coronary angioplasty
Rationale: Percutaneous transluminal coronary angioplasty (PTCA) a means of achieving myocardial revascularization is becoming dramatically more common. Heparin is usually prescribed for 12 to 48 hours during and after the procedure in order to ensure continuous patency and to prevent early reocclusion. This anticoagulation method limits the incidence rate of abrupt occlusion to between 4.4% and 8.3%. However, the pharmacological activity of heparin is partially neutralised by components of the platelet release reaction such as platelet factor 4. On the other hand, its antithrombotic activity is related to its unique pentasaccharide sequence which alone exhibits a high-affinity binding to AT III. Thus SR90107A/ORG31540, (also known as fondaparinux [FX]), which is chemically identical to this pentasaccharide sequence and is therefore endowed with pure anti-activated factor X activity, may be effective in preventing thrombotic reocclusion during or after PTCA procedure.
Phase: II
Study Period: Sep 1995 to Apr 1996
Study Design: An open-label non-controlled trial. The study was to be stopped as soon as 3 cases of abrupt vessel closure (AVC) had occurred.
Centres: A single centre in France.
Indication: Effective anticoagulation during PTCA
Treatment: A single 12 mg intravenous (i.v.) dose of FX over 5 minutes.
Objectives: To assess the efficacy of an i.v. bolus injection of 12 mg of FX administered before PTCA based on the rate of abrupt vessel closure as assessed by angiography at 24 hours after PTCA.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the occurrence of AVC at 24 hours (on coronary angiography) defined as "cessation of flow determined by angiography during the procedure or within 24 hours after the PTCA procedure, lasting more than 10 minutes, not relieved by i.v., intracoronary, or sublingual nitroglycerin, and associated with ischaemic pain and electrocardiogram (ECG) changes".
Secondary Outcome/Efficacy Variables: Secondary endpoints included: Visual estimation of coronary lesions (dissection, embolism, non-occlusive flap, occlusion secondary to dissection, non-occlusive spasm, recoil, stretch, occlusion of other vessels) Subsequent interventions (perfusion catheter, stenting, atherectomy, thrombolytic therapy, coronary artery bypass graft (CABG), cardiopulmonary support) Clinical complications (chest pain, ventricular fibrillation, ventricular tachycardia, hypotension, Q-wave or non Q-wave myocardial infarction, other ECG changes) Pharmacokinetics analyses included: Maximum plasma concentration observed (C _{max}) Plasma elimination half-life (T _{1/2}) Area under the curve for plasma concentrations as a function of time from time zero to the time of the last quantifiable concentration (AUC _{last}) Area under the curve for plasma concentrations as a function of time extrapolated to infinity (AUC _{inf}), Plasma clearance extrapolated to infinity (Cl) Volume of distribution extrapolated to infinity (V _d) of FX as determined from plasma concentrations of the drug at T-1h, T+10min, T2h, T8h, T12h, T23h, T48h Safety assessments included: Peripheral vascular complications Other adverse events (AEs) Vital signs ECG Haematology Biochemistry Blood coagulation Laboratory test measurements Adverse events (AEs) were monitored from the day of injection to one day later. Serious adverse events (SAEs) were

monitored on the day of medication and up to 30 days later.	
<p>Statistical Methods: The number of evaluable subjects was set at 60. Success of the FX dose was defined as the Bayesian probability point of 95% that the AVC rate was <10%. The rate of abrupt vessel closure at 24 hours and its 95% binomial confidence interval were computed. Visual estimation of coronary angiography was performed, including the calculation of the rate of primary success of PTCA, coronary complications and coronary dissections. Artery or stenosis stretch, balloon and artery recoil and acute gain were computed. Standard descriptive statistics were calculated for Cmax, AUClast, AUCinf, T½, CI and Vd. T½, Vd, and CI were tested for evidence of a significant correlation with body weight, age, creatinine clearance using a Spearman correlation-test with a 1% type 1 error. Analyses of variance were performed on log-transformed Cmax, AUClast, AUCinf, T½, CI and Vd normalised to body weight using a model including gender effect with a 5% type 1 error. A t-test was used to test the gender effect on body weight and age.</p> <p>Efficacy analyses were performed on the evaluable population. Subjects were not considered evaluable: 1) if there was a need for intra-aortic balloon pump or cardiopulmonary support during the percutaneous technique; 2) in case of failure of recross wire or inflation; 3) in case of coronary dissection of types C, D, E, or F observed at the end of PTCA. Safety analyses were performed on the treated population.</p>	
<p>Study Population: Males or post-menopausal females aged 18 to 75 years undergoing PTCA with stenosis ≥70% in at least 1 artery selected for balloon angioplasty, a history of stable or unstable angina, or history of myocardial infarction whose body weight was ≥50kg and ≤100kg inclusive were eligible. Exclusion criteria included myocardial infarction or clinical symptoms of unstable angina within the previous week, left ventricular ejection fraction < 30%, increased known congenital or acquired bleeding tendency or bleeding tendency revealed by one or more pre-operative tests, serum creatinine > 200 µmol/L, hypertension, recent treatment with forbidden medication (e.g. thrombolytics, anticoagulants) which cannot be stopped in time for entry into the study, recent stroke (6 months), pulmonary embolism or DVT (2 weeks), trauma/surgical operation (2 weeks), or gastrointestinal bleeding/peptic ulcer (4 weeks).</p>	
Number of Subjects:	FX 12mg
Planned (Evaluable), N	60
Entered, N	71
Completed, n (% of subjects entered)	61 (86)
Total Number Subjects Withdrawn, n (% of subjects entered)	10 (14)
Withdrawn due to Adverse Events n (% of subjects entered)	0
Withdrawn due to Lack of Efficacy n (% of subjects entered)	0
Withdrawn for other reasons n (% of subjects entered)	10 (14)
Demographics	FX 12mg
N (Evaluable)	61
Females: Males	12:49
Mean Age, years (SD)	56.5 (11.9)
Race n (%): Caucasian,	61 (100)
Primary Efficacy Results (Evaluable Subjects):	FX 12mg
Abrupt Vessel Closure	N=61
Number (%) of AVC	2 (3.28)
95% CI	0.40, 11.35
Secondary Outcome Variables Closure (Evaluable Subjects):	FX 12mg
Visual Estimation of Coronary Lesions	
Successful PTCA, Number Sites/Subjects	63/61
Absolute Diminuation of Stenosis >20% Observed	63/61
Residual Stenosis <50% Observed	63/61
Coronary Dissection Observed, Number Sites/Subjects	
Day 1 and/or Day 2	27/26
Day 3	1/1
Coronary Complications Day 1 and/or Day 2	19/17
Occlusions of Other Vessels on Day 1, Number Sites/Subjects	16/15
Subsequent Interventions	
Total Revascularization Procedures, Number Subjects	8
Day 1 Thrombolytic Therapy	2
Day 1 Stent	1
Day 2 Stent	6

Day 2 Perfusion Catheter	1
Day 2 Thrombolytic Therapy	1
Day 3 Stent	1
Pharmacokinetic Results	FX 12mg
Cmax (mg/L)	
n	69
Mean (SD)	1.92 (0.35)
Coefficient of Variation (CV%)	18
AUClast (mg.h/L)	
n	69
Mean (SD)	22.71 (4.99)
CV%	22
T1/2 (h)	
n	63
Mean (SD)	15.53 (2.96)
CV%	19
AUCinf (mg.h/L)	
n	59
Mean (SD)	25.18 (5.91)
CV%	23
Cl (mL/min)	
n	59
Mean (SD)	7.32 (1.66)
CV%	23
Vd (L)	
n	59
Mean (SD)	9.45 (1.45)
CV%	15
Safety Results: An on therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.	
Most Frequent Adverse Events – On-Therapy (Treated Population)	FX 12mg N=71 n (%)
Subjects with Any AEs	19 (26.8)
Haematoma	13 (18.3)
Injection Site Reaction	3 (4.2)
Cerebral Haemorrhage	1 (1.4)
Injection Site Inflammation	1 (1.4)
Back Pain	1 (1.4)
Syncope	1 (1.4)
Anaemia	1 (1.4)
Allergic Reaction	1 (1.4)
Serious Adverse Events - On-Therapy (Treated Population) n (%) [n considered by the investigator as likely to be related to study medication]	FX N=71 n (%) [related]
Subjects with non-fatal SAEs	2 (2.8) [1]
Haematoma	1 (1.4) [1]
Cerebral Haemorrhage	1 (1.4) [0]
Subjects with fatal SAEs	0

Conclusion:

See publications below.

Publications:

Schiele FJ, Vuilleminot AR, Meneveau NF, et al. Initial experience of a sulphated pentasaccharide, a pure factor Xa inhibitor, in coronary angioplasty. Supplement to Circulation, vol. 94, no. 8, I-742, October 15, 1996. Abstract no. 4340.

Vuilleminot A, Schiele F, Meneveau N, et al. Efficacy of a synthetic pentasaccharide, a pure factor Xa inhibitor, as an antithrombotic agent - A pilot study in the setting of coronary angioplasty. Thromb Haemost 1999; 81: 214-220

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