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<b>Study No.:</b> DRI2440 – Rembrandt
<b>Title:</b> A Multicentre, Randomized, Double-Blind, Dose Ranging Study of Org31540/SR90107A in the Initial Treatment of Symptomatic Proximal Deep Vein Thrombosis (DVT)
<b>Rationale:</b> Dalteparin (DN) is a low molecular weight heparin (LMWH) established as an effective initial treatment for venous thromboembolic events (VTE), i.e. DVT and pulmonary embolism (PE). However, its use requires lengthy intravenous (i.v.) infusion and hospitalisation. Studies have shown that Org31540/SR90107A, also known as fondaparinux (FX) – a selective inhibitor of activated factor X (factor Xa) – may be appropriate for prevention of PE, but only requires a single daily injection. This study compared the efficacy of 3 different dose levels of FX against DN.
<b>Phase:</b> II
<b>Study Period:</b> 25 March 1997 to 07 August 1998
<b>Study Design:</b> Multinational, multicentre, randomized, double-blind, double-dummy, dose ranging study over 3 months (97 days)
<b>Centres:</b> 32 centers in 8 countries: Canada (8), The Netherlands (7), France (5), Italy (4), Australia (3), Belgium (2), Switzerland (2), and New Zealand (2).
<b>Indication:</b> Prevention of recurrent VTE in subjects with a confirmed diagnosis of DVT without symptomatic PE
<b>Treatment:</b> Subjects were randomized to 1 of the 3 FX test doses or DN. FX groups: subjects received 5mg, 7.5mg or 10mg FX once daily (o.d.) (in the morning) and placebo for DN at 100 IU/kg twice daily (b.i.d.) morning and evening, 12 hours apart), both by subcutaneous (s.c.) injection. Subjects received FX doses for a minimum of 5 days. DN group: subjects received 100 IU/kg DN b.i.d. (morning and evening, 12 hours apart) and 0.5mL, 0.75mL or 1.0mL placebo for FX o.d. (morning), both by s.c. injection. Oral anti-coagulant (OAC): all subjects received an OAC which was initiated on Day 1 or Day 2 and was continued for the next 3 months; OAC treatment was adjusted for international normalized ratio to be between 2 and 3.
<b>Objectives:</b> The main objective was to determine the optimum dose of a o.d. injection of FX administered s.c. in the initial treatment of symptomatic proximal DVT without symptomatic PE.
<b>Primary Outcome/Efficacy Variable:</b> The primary efficacy criterion was the number of positive outcomes in each treatment group. Outcome was determined by the change (improvement, no change, worsening) between baseline and Day 7±1 in thrombus mass, assessed by ultrasonography (US), and in total perfusion score, assessed by perfusion lung scan (PLS). Changes were expressed in a single binary result, a positive outcome was defined as an improvement on US and/or PLS results without deterioration of either test. Deaths occurring less than 24 hours following the last study drug administration and adjudicated as related to PE, by the independent adjudication committee, were considered as a negative outcome.
<b>Secondary Outcome/Efficacy Variable(s)</b> Secondary efficacy endpoint: number of subjects in each group with symptomatic recurrence or extension of VTE within 90 days following randomization and for each of the Day 7±1 US and PLS evaluations. On therapy AEs were defined as events occurring between Day 1 and the end of study drug +2 days.
<b>Statistical Methods:</b> <u>Populations Analyzed:</u> <i>'All Treated Population'</i> : all randomized and treated subjects. <i>'Intention To Treat' (ITT) population</i> (Efficacy Population): subpopulation of all treated subjects excluding subjects with no compression US confirmed symptomatic DVT at inclusion or no possible conclusion (positive or negative outcome) on efficacy assessment. <i>Primary Efficacy Population: 'Per-protocol Population'</i> , subpopulation of ITT excluding those with <5 days FX or DN treatment, wrong FX dose administered >1 time, US and/or PLS performed <Day 6 or >Day 8, and forbidden medications. <u>Efficacy analyses:</u> Presence of a trend among the FX doses for the incidence of subjects with positive primary outcome was assessed using a Cochran-Armitage trend test; pairwise comparisons between FX doses used Fisher's exact test and 95% exact confidence intervals (CI) on the differences between doses were calculated. For comparisons between FX and DN doses relative risks and 95% exact CIs were calculated and Fishers exact tests computed. If no trend was observed between the FX doses the FX groups were combined for the comparison to DN. Fishers exact tests were performed to compare the incidences of subjects with symptomatic recurrent VTE and mean changes in noncompressible diameters and perfusion scores tested between FX groups using ANOVA. <u>Safety analyses:</u>

Trend tests and pairwise comparisons were performed to compare the incidences of subjects with a major, minor or any bleeding event between the dose groups. All AEs summarized by system organ class and preferred term according to the study drug treatment period and the entire study.				
<b>Study Population:</b> Subjects with US confirmed symptomatic proximal deep leg-vein thrombosis (DVT) and aged >18 yrs were eligible for participation in this study. Subjects were excluded if they had symptomatic PE, previously documented DVT in the same leg, surgery within last 5 days, known congenital or acquired bleeding tendency, recent (<4 weeks) or present history of gastrointestinal bleeding or peptic ulcer, previous stroke or myocardial infarction (< 3 months) hypertension; known renal insufficiency, contraindication to heparin or oral anti-coagulant, or recent anticoagulant therapy.				
	<b>FX 5mg</b>	<b>FX 7.5mg</b>	<b>FX 10mg</b>	<b>DN</b>
Number of Subjects:				
Planned evaluable, N	100	100	100	100
Randomized, N	104	111	121	120
ITT Population, N	100	108	115	115
Per-protocol Population, N	84	99	106	107
All Treated Population, N:	103	111	120	119
Total Number Subjects Withdrawn, n (% of All Treated Population)	3 (2.9)	2 (1.8)	6 (5.0)	5 (4.2)
Withdrawn due to AE/SAE, n (% of All Treated Population)	0 (0.0)	1 (0.9)	1 (0.8)	1 (0.8)
Withdrawn due to Lack of Efficacy, n (% of All Treated Population)	1 (1.0)	0 (0.0)	2 (1.7)	2 (1.7)
Withdrawn For Other Reasons, n (% of All Treated Population)	2 (2.0)	1(0.9)	3 (2.5)	2(1.7)
<b>Demographics</b>				
N (All Treated Population)	103	111	120	119
Females: Males n	54:49	54:57	52:68	60:59
Mean Age, years (Standard Deviation [SD])	61.7 (17.6)	57.8 (18.9)	59.6 (16.4)	64.4 (16.0)
Caucasian, n (%)	103 (100)	108 (97.3)	120 (100)	119 (100)
<b>Primary Efficacy Results:</b>				
<b>Positive Outcome (Per-protocol Population)</b>	<b>FX 5mg N=84</b>	<b>FX 7.5mg N=99</b>	<b>FX 10mg N=106</b>	<b>DN N=107</b>
n (%)	39 (46.4)	49 (49.5)	46 (43.4)	50 (46.7)
95% CI	[35.47, 57.65]	[39.29, 59.73]	[33.80, 53.37]	[37.02, 56.62]
<b>Secondary Outcome Variable(s):</b>				
<b>Subjects With Symptomatic Adjudicated Recurrent VTE From 1<sup>st</sup> Injection to Day 97 (All Treated Population)</b>	<b>FX 5mg N=103</b>	<b>FX 7.5mg N=111</b>	<b>FX 10mg N=120</b>	<b>DN N=119</b>
DVT alone, n (%)	2 (1.9)	2 (1.8)	1 (0.8)	3 (2.5)
PE, n (%)	0	0	3 (2.5)	3 (2.5)
Total VTE, n (%)	2 (1.9)	2 (1.8)	4 (3.3)	6 (5.0)
95% CI	[0.24, 6.84]	[0.22, 6.36]	[0.92, 8.31]	[1.87, 10.65]
<b>Safety Results (All Treated Population):</b> All bleeding events, AEs and SAEs reported during the treatment period defined as Day 1, when the first injection of study drug was given, to end of study drug +2 days. Fatal SAEs reported during the entire study period defined as day 1 to day 97.				
<b>Most Frequent AEs-During the Treatment Period</b>	<b>FX 5mg N=103</b>	<b>FX 7.5mg N=111</b>	<b>FX 10mg N=120</b>	<b>DN N=119</b>
Subjects With Any AEs, n(%)	43 (41.7)	42 (37.8)	37 (30.8)	54 (45.4)
5 Most Frequent AEs in Each Treatment Group, n (%):				
Headache	3 (2.9)	1 (0.9)	4 (3.3)	6 (5.0)
Hepatic Enzymes Increased	0 (0.0)	0 (0.0)	0 (0.0)	6 (5.0)
Purpura	2 (1.9)	3 (2.7)	4 (3.3)	5 (4.2)
Constipation	5 (4.9)	5 (4.9)	5 (4.2)	4 (3.4)
Leg Pain	5 (4.9)	1 (0.9)	1 (0.8)	1 (0.8)

Anaemia	4 (3.9)	1 (0.9)	1 (0.8)	1 (0.8)
Nausea	4 (3.9)	1 (0.9)	1 (0.8)	1 (0.8)
Diarrhoea	0 (0.0)	3 (2.7)	2 (1.7)	2 (1.7)
Haematoma	3 (2.9)	4 (3.6)	3 (2.5)	3 (2.5)
Fever	3 (2.9)	4 (3.6)	0	3 (2.5)
Urinary Tract Infection	2 (1.9)	1 (0.9)	3 (2.5)	4 (3.4)
Epistaxis	0 (0.0)	2 (1.8)	0 (0.0)	4 (3.4)
Skin Ulceration	3 (2.9)	0	1 (0.8)	0
Arthralgia	1 (1.0)	3 (2.7)	0	1 (0.8)

**Serious Adverse Events – During the Treatment Period\***

**n (%) [number considered by the investigator to be related to study medication]**

	<b>FX 5mg N=103</b>	<b>FX 7.5mg N=111</b>	<b>FX 10mg N=120</b>	<b>DN N=119</b>
Subjects With SAEs (fatal and non-fatal), n (%)	4 (3.9) [2]	6 (5.4) [0]	3 (2.5) [2]	1 (0.8) [0]
Haematoma	1 (1.0) [1]	1 (0.9) [0]	1 (0.8) [1]	0
Influenza-like Symptoms	1 (1.0) [0]	1 (0.9) [0]	0]	0
Cardiac Failure	0]	1 (0.9) [0]	0	0
Colon Carcinoma	0	1 (0.9) [0]	0	0
Gastric Carcinoma	0	0	1 (0.8) [0]	0
GI Neoplasm Malignant	0	1 (0.9) [0]	0]	0
Haematuria	1 (1.0) [1]	0]	0	0
Ovarian Carcinoma	1 (1.0) [0]	0	0	0
Pancreas Neoplasm Malignant	0	1 (0.9) [0]	0	0
Purpura	0	0	1 (0.8) [1]	0
Rectal Carcinoma	1 (1.0) [0]	0	0	0
Bullous Eruption	0]	0	0	1 (0.8) [0]
<b>Subjects With Fatal SAEs during the treatment period*, n (%) [number consider by the investigator to be related to study medication]</b>	<b>FX 5mg N=103</b>	<b>FX 7.5mg N=111</b>	<b>FX 10mg N=120</b>	<b>DN N=119</b>
Total fatal SAEs during the treatment period	3 (2.9) [0]	2 (1.8) [0]	0	0
Dyspnoea	1 (1.0) [0]	0	0	0
GI Neoplasm Malignant	0	1 (0.9) [0]	0	0
Ovarian Carcinoma	1 (1.0) [0]	0	0	0
Cardiac Failure	0	1 (0.9) [0]	0	0
Rectal Carcinoma	1 (1.0) [0]	0	0	0

\*Treatment period: includes the period up to 2 days after the last FX dose

**Conclusion:**

See publication below.

**Publications:**

The Rembrandt Investigators. Treatment of proximal deep vein thrombosis with a novel synthetic compound (SR90107A/ Org31540) with pure anti-factor Xa activity: A phase II evaluation; *Circulation* 2000;102:2726-31

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