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Study No.: 63113
Title: A randomized, assessor-blind, dose reducing, phase II study to assess the safety and efficacy of 10, 8, 6 and 4 mg Org31540/SR90107A and standard treatment with intravenous fragmin in patients with chronic intermittent haemodialysis
Rationale: Hemodialysis is associated with numerous changes in blood composition. Its impact on the hemostasis system requires anti-coagulation to maintain patency of the extracorporeal circuit. Org31540/SR90107A (also known as fondaparinux [FX]), is a selective inhibitor of activated factor X (factor Xa) and inhibits thrombin formation without direct inactivation of thrombin itself. It is anticipated that single intravenous (IV) injections of FX may potentially be suitable for use as antithrombotic during dialysis in subjects on chronic intermittent hemodialysis.
Phase: II
Study Period: 9 August 1996 to 31 January 1997
Study Design: An assessor-blind, 6-period, 2-block cross-over study using 4 sequential dose-reducing FX dose levels. In the first block, a 10mg FX dose was randomized with an "individually optimized" IV dalteparin (DAL) dose. In the second block, the "individually optimized" IV DAL dose was randomized with 3 fixed-sequence FX doses of 8, 6 and 4mg.
Centres: A single centre in the The Netherlands
Indication: Chronic intermittent haemodialysis
Treatment: FX was provided as 1.0mL syringes (10mg/mL). Dosages of 10, 8, 6 or 4mg were administered intravenously as bolus injection for 30 seconds within a period of 5 minutes prior to connection of the subject's circulation to the extra-corporeal circuit. DAL was provided as 10 000 IU/mL ampoules for intravenous injection. Subjects were to receive 6 injections in total, with a 1-week interval between adjacent administrations. If major bleeding occurred, a study endpoint was reached and all further study treatment was stopped.
Objectives: The primary objectives were: To assess the safety and efficacy of 4 dose levels of FX administered as a single bolus IV injection to subjects who were on chronic intermittent hemodialysis treatment To confirm the mode of action of FX by showing the prevention of fibrin formation To show a dose-effect relationship with regard to above mentioned targets
Primary Outcome/Efficacy Variable: The maintenance of patency of the extra-corporeal circuit was considered as the primary efficacy parameter.
Secondary Outcome/Efficacy Variable(s): <u>Efficacy:</u> Plasma fibrinopeptide A (FPA), plasma thrombin-AT-III complex (TAT), the degree of clotting in the capillary filter, bubble chamber and buffer chamber. <u>Pharmacokinetics:</u> Plasma FX concentrations or anti-Xa activity (for Fragmin): Cmax, dialysis half-life, elimination half-life, decrease of exposure (AUC). <u>Safety:</u> Adverse events (AEs) and bleeding (minor and major as assessed by the Investigator). Major bleeding was defined as: 1) death due to bleeding complication; 2) intra-cranial bleeding or bleeding within a critical organ; 3) bleeding requiring surgery; or 4) any bleeding which the investigator considered to be clearly excessive or unusual. Minor bleeding was defined as any bleeding which was not from the dialysis needle insertion or venepuncture site and which was not categorized as a major bleeding.
Statistical Methods: <u>Populations analysed:</u> Safety and tolerability analyses were based on all subjects treated. The bioanalytical analysis (including efficacy evaluations) was based on the individual data of the study completers (defined as subjects who received all 6 treatment regimens, or who received one of the DAL regimens and all dosage regimens of FX with a higher dosage than the one that was associated with spontaneous cessation of the extra-corporeal circulation). <u>Statistical tests used:</u> Patency of the extra-corporeal circuit was to be compared between the first "individually optimized" DAL treatment and each of the FX doses, using a McNemar Chi-square test. 95% confidence intervals for the difference in percentage response (i.e., those who maintain patency of the extra-corporeal circulation) were to be calculated. <u>Pharmacokinetic Analyses:</u> Based on plasma FX concentrations or anti-factor-Xa activity (for DAL): maximum concentration (Cmax), dialysis half-life, elimination half-life, decrease of exposure AUC were summarized.
Study Population: Male or female subjects who were on chronic intermittent hemodialysis with DAL as an anticoagulant, 2 or 3 times per week, with a body weight not <45kg and not >95kg and having good venous accessibility. Subjects were

excluded if they were dialyzed through a subclavian vein access; had evidence of more than a trace of clotting in the dialyzer during the previous 10 dialysis sessions with the "individually optimized" DAL dose; significant medical conditions (ischemic or hemorrhagic cerebral stroke or myocardial infarction; history of clinically significant bleeding/coagulation disorder; thrombocytes < 120 x 10 ⁹ /L, PT > 1.3 times the normal value (before dialyses); a ratio APTT/control > 1.3 (before dialyses); blood pressure systolic/diastolic blood pressure >180/110mmHg (after dialysis)) or the use of an anticoagulant, fibrinolytic agent or aspirin within 14 days prior to inclusion or requiring anticoagulation other than with DAL.									
Number of Subjects:					Total				
Planned, N					20				
Randomised, N					15				
Completed, n (%)					12 (80)				
Total number subjects withdrawn, n (%)					3 (20)				
Withdrawn due to AE/SAE, n (%)					1 (6.7)				
Withdrawn due to lack of efficacy, n (%)					0				
Withdrawn for other reasons, n (%)					2 (13.3)				
Demographics					Total				
N (All Randomized Subjects)					15				
Females: Males					13:2				
Mean Age, years (Standard Deviation [SD])					64.6 (10.5)				
Caucasian, n (%)					7 (47)				
Primary Efficacy Results:									
Patency of the extra-corporeal circuit, the primary efficacy outcome measure in this study, was maintained during all dialysis sessions involving DAL and FX. Therefore, no statistical analyses were considered necessary.									
Secondary Outcome Variables (Study Completers):									
Median (Min-Max) FPA Concentrations (ng/mL)									
Treatment	Assessment								
	Start of Dialysis			1 Hour			End of Dialysis		
	Median	Min-Max	N	Median	Min-Max	N	Median	Min-Max	N
DAL ^a	8.1	1.5-70.3	12	3.8	1.4-8.0	11	7.8	3.3-25.0	11
DAL ^b	5.3	1.0-77.9	12	3.7	2.2-9.8	11	13.6	3.2-25.3	11
4mg ^c	6.4	3.5-61.9	11	11.4	5.5-48.4	12	9.4	5.5-39.4	11
6mg ^c	7.9	2.1-62.1	12	10.9	4.5-44.9	12	14.6	4.6-104	12
8mg ^c	6.8	2.2-93.3	10	9.5	4.5-25.1	11	10.9	2.6-90.7	12
10mg ^c	7.1	4.1-55.8	11	8.2	2.2-23.8	11	8.5	3.1-23.8	10
a. Block A									
b. Block B									
c. Doses of FX									
Median (Min-Max) AUC for TAT Concentrations									
Treatment	Assessment								
	AUC(0-72 Hrs)			AUC(0-24 Hrs)			AUC(0-4 Hrs [During Dialysis])		
	Median	Min-Max	N	Median	Min-Max	N	Median	Min-Max	N
DAL ^a	416	321-2345	12	147	107-872	12	35	19-105	12
DAL ^b	517	303-2439	12	177	111-434	12	37	17-53	12
4mg ^c	501	412-1252	12	198	153-796	12	76	33-593	12
6mg ^c	543	365-939	10	190	109-692	12	47	19-275	12
8mg ^c	439	355-957	12	169	116-622	12	53	21-274	12
10mg ^c	538	260-2162	11	159	113-562	11	38	25-217	11
a. Block A									
b. Block B									
c. Doses of FX									
Degree of Clotting in the Capillary Filter Chamber at the End of the Dialysis Session									
Treatment	No Clotting		Trace of Clotting		Moderate or Marked		Several Large Clots		
	Number of Subjects								
DAL Block A	9		3		0		0		
DAL Block B	7		1		4		0		
FX 4mg	4		4		2		2		
FX 6mg	5		5		2		0		

FX 8mg	6	4	2	0		
FX 10mg	5	6	1	0		
Degree of Clotting in the Bubble Chamber						
Treatment	Degree of Clotting	1 Hour N=12	2 Hours N=12	3 Hours N=12	4 Hours N=10	
		Number of Subjects				
DAL Block A	No Clotting	11	11	11	7	
	Trace of Clotting	1	1	1	3	
	Moderate/Marked	0	0	0	0	
DAL Block B	No Clotting	12	12	12	7	
	Trace of Clotting	0	0	0	3	
	Moderate/Marked	0	0	0	0	
FX 4mg	No Clotting	11	5	5	1	
	Trace of Clotting	1	3	1	3	
	Moderate/Marked	0	4	6	6 ^a	
FX 6mg	No Clotting	12	9	8	3	
	Trace of Clotting	0	2	1	2	
	Moderate/Marked	0	1	3	5	
FX 8mg	No Clotting	10	9	7	5	
	Trace of Clotting	2	3	3	2	
	Moderate/Marked	0	0	2	3	
FX 10mg	No Clotting	10	10	8	4	
	Trace of Clotting	1	1	3	4	
	Moderate/Marked	1	1	1	2	
a. Includes 1 subject with "several large clots." The distribution of subjects over the categories "no clotting," "trace of clotting," and "moderate/marked clotting" defined the degree of clotting per treatment and per assessment.						
Degree of Clotting in the Buffer Chamber						
Treatment	Degree of Clotting	1 Hour N=12	2 Hours N=12	3 Hours N=12	4 Hours N=10	
		Number of Subjects				
DAL Block A	No Clotting	12	12	12	6	
	Trace of Clotting	0	0	0	4	
	Moderate/Marked	0	0	0	0	
DAL Block B	No Clotting	12	10	9	6	
	Trace of Clotting	0	2	3	4	
	Moderate/Marked	0	0	0	0	
FX 4mg	No Clotting	10	3	2	2	
	Trace of Clotting	2	6	7	5	
	Moderate/Marked	0	3	3	3 ^a	
FX 6mg	No Clotting	12	8	6	3	
	Trace of Clotting	0	3	6	6	
	Moderate/Marked	0	1	0	1	
FX 8mg	No Clotting	10	7	8	6	
	Trace of Clotting	2	4	3	2	
	Moderate/Marked	0	1	1	2	
FX 10mg	No Clotting	10	9	7	5	
	Trace of Clotting	2	2	4	3	
	Moderate/Marked	0	1	1	2	
a. Includes 1 subject with "several large clots." The distribution of subjects over the categories "no clotting," "trace of clotting," and "moderate/marked clotting" defined the degree of clotting per treatment and per assessment.						
PK Results:						
Parameter	FX				DAL	
	4 mg	6 mg	8 mg	10 mg	Block A	Block B

Cmax (ng/mL; IU/mL) ^a	n	12	12	12	12	13	12	
	mean	1024	1279	1690	1677	1.7	1.64	
	SD	311	230	407	336	0.55	0.39	
Dialysis half-life (hours) ^b	n	12	12	11	11	13	12	
	mean	12.97	15.08	10.46	11.33	4.86	5.51	
	SD	3.51	11.49	2.85	6.09	3.3	3.12	
Elimination half-life (post-dialysis) (hours)	n	11	11	12	11	7	10	
	mean	63.59	59.25	63.63	69.87	86.33	87.64	
	SD	16.23	16.04	24.1	20.26	30.3	63.11	
Decrease of exposure (0-4h) due to dialysis(%) ^c	n	7	8	8	8	6	8	
	mean	22.89	16.35	21.91	16.1	30.78	27.8	
	SD	12.48	7.77	10.18	5.59	8.66	8.78	
<p>a. ng/mL for FX, IU/mL for DAL</p> <p>b. Dialysis half-life: the half-life during the 4 hour dialysis period</p> <p>c. Decrease of exposure: the decrease in AUC(0-4) during dialysis when compared to the calculated AUC(0-4) without dialysis</p>								
Safety Results (All Subjects Treated):								
Bleeding Results, n (%)						Total N=13		
Major Bleeding						0		
Minor Bleeding						9 (69)		
AEs – On-Therapy: AEs were collected during the study period, defined as the time from the moment the subject was listed on the master subject log until the end of treatment with study medication or until the last assessment (whichever was the latest).								
				Total N=13				
AEs – On-Therapy				DAL Block A	DAL Block B	FX 4mg	FX 6mg	FX 8mg
Subjects with Any AEs, n(%)				2 (15)	2 (15)	4 (31)	2 (15)	2 (15)
Serious Adverse Events - On-Therapy				DAL Block A	DAL Block B	FX 4mg	FX 6mg	FX 8mg
All SAEs (fatal & non-fatal)				0	0	0	0	0
Conclusion:								
Patency of the extra-corporeal circuit, the primary efficacy outcome measure in this study, was maintained during all dialysis sessions. In each of the DAL treatment blocks 2 subjects experienced AEs, and in the 4mg, 6mg and 8mg FX treatment groups, 4, 2 and 2 subjects respectively experienced AEs. No subject experienced an SAE in this study. A total of 9 episodes of minor bleeding were documented within all treatments groups, none of which was recorded as an AE.								
Publications:								
No Publication								

Date Updated: 13-Sep-2005