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Study No: 63109_B	
Title: Interaction study with Org31540/SR90107A and piroxicam in healthy male volunteers	
Rationale: NSAIDs (non-steroidal anti-inflammatory drugs) are commonly used as over-the-counter analgesics, and may be used concomitantly with anti-thrombotics such as Org31540/SR90107A/fondaparinux (FX) in daily clinical practice. The present study was designed to look at the potential interaction of FX with a model NSAID. Piroxicam (PX) is among the most commonly prescribed anti-inflammatory analgesics in rheumatoid arthritis and related disorders, and is also frequently used as a pain killer for gout, musculoskeletal disorders and primary dysmenorrhea.	
Phase: I	
Study Period: September 1997 to September 1998	
Study Design: A single centre, 3-way crossover, randomised, double-blind, interaction study with a 3-week washout period between treatment periods	
Centres: A single centre in the Netherlands	
Indication: None.	
Treatment: Treatments were FX + PX (A), FX + placebo (PBO) (B), and PX + PBO (C). Subjects were randomised to treatment sequence ABC, CAB, or BCA. PX or PBO was administered for 10 days with 24 hour (h) intervals. Co-administration of FX or PBO with 24h intervals started on the 7th day of PX/PBO administration and continued for 4 days. FX was supplied as pre-filled syringes, containing 10mg FX per mL. FX or matching PBO was injected subcutaneously in the abdominal region. PX or matching PBO was supplied as capsules. One capsule (20mg PX or PBO) was administered per dosing.	
Objectives: To investigate the possible pharmacokinetic (PK) and pharmacodynamic (PD) interaction between subcutaneously administered FX and orally administered PX as a model NSAID.	
Statistical Methods: Pharmacokinetic: Non-compartmental pharmacokinetic analysis was performed on FX concentrations. The following parameters were computed: Area under the curve (AUC_{0-last} and $AUC_{0-\infty}$), terminal half life ($t_{1/2}$), clearance/F, V_z/F , $AUC_{72-last}$, $AUC_{72-\infty}$, d maximal serum concentration (C_{max}) and time to maximal serum concentration (t_{max}) after the first and the last dose. Parameters were compared between FX and + PX treatments using paired t tests. Results were reported using 95% confidence intervals (CI) of the difference. Additionally, the following parameters were calculated for the FX only treatment to obtain an estimate of accumulation and approach to steady state of FX plasma concentrations C_{max} and $AUC_{0-\tau}$ after both single and repeated dose. Based on these parameters accumulation ratios have been calculated for C_{max} and $AUC_{0-\tau}$. The time to steady state has been assessed using an analysis of variance on the pre-dose concentrations (C_{min}). Pharmacodynamic: Pharmacodynamic parameters (APTT and CIPA) were analysed using area under the effect curve (AUEC) above average pre-value divided by the corresponding time span. Additionally, AUECs divided by the corresponding time span but not corrected for pre-value were compared between the 3 treatments. For fecal blood loss, contrasts were calculated for the cumulative excretion rate over the 5-day period. Bleeding time values were analysed by comparing absolute post-dose values between treatment groups. No AUECs were calculated for this parameter because of the low number of measurements. Contrasts were calculated using paired t-tests. Safety: No formal analyses were performed for the safety parameters. All safety data were listed. Data from all subjects randomised who received ≥ 1 dose of study medication were used to assess safety, and all available PK assessments were used for the PK evaluation.	
Study Population: Healthy male volunteers aged 18 to 30 years with a body weight between 55 and 100 kg, with a normal coagulation status and blood pressure and willing to give written informed consent.	
Number of Subjects:	Total
Planned N	Not reported
Dosed N	13
Completed n (%)	12 (92)
Total Number Subjects Withdrawn N (%)	0
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for Other Reasons n (%)	0
Demographics	
N (Total)	13

Females: Males				0:13		
Mean Age in Years (SD)				23 (3.1)		
Mean Weight in Kg (SD)				76.4 (10.9)		
Race n (%)				Not provided in CSR		
PK/PD Endpoints:						
PK Parameter Estimates for FX With or Without PX						
	FX +PX N=13			FX +PBO N=12		
Parameter	Mean	SD	CV%	Mean	SD	CV%
AUC _{0-last} (mg.h/L)	74.1	10.5	14	75.7	10.7	14
T _½ (h)	13.9	1.9	14	13.6	1.5	11
AUC _{0-∞} (mg.h/L)	76.8	11.5	15	78.3	11.5	15
CL/F (mL/h)	464	72	16	455	68	15
Vz/F (L)	9.2	0.9	10	8.8	1.0	11
C _{max} 1st dose (ng/mL)	1068	134	13	1139	144	13
T _{max} 1st dose (h)	2.27	0.60	26	2.54	0.49	19
AUC _{72-last}	24.3	4.3	18	24.3	4.2	17
AUC _{72-∞} (mg.h/L)	27.0	5.4	20	26.8	5.1	19
C _{max} last dose (ng/mL)	1453	214	15	1459	292	20
T _{max} last dose (h)	2.01	0.41	20	2.25	1.43	64
Comparison of PK Parameters of FX With or Without PX (paired students' t-test)						
Parameter	Paired differences treatment A-B ^a			p-value (2-tailed)		
	Mean (SD)	95% of the difference				
		Lower	Upper			
AUC _{0-last} (mg.h/L)	-0.82 (3.98)	-3.35	1.72	0.493		
t _½ (h)	0.31 (1.19)	-0.44	1.07	0.385		
AUC _{0-∞} (mg.h/L)	-0.66 (4.30)	-3.39	2.08	0.607		
CL/F (mL/h)	4.5 (27.4)	-12.9	22.0	0.578		
Vz/F (L)	0.22 (0.66)	-0.20	0.64	0.267		
C _{max} 1st dose (ng/mL)	-70 (70)	-114	-26	0.005		
t _{max} 1st dose (h)	-0.26 (0.62)	-0.65	0.13	0.177		
AUC _{72-last} (mg.h/L)	0.43 (2.09)	-0.892	1.758	0.487		
AUC _{72-∞} (mg.h/L)	0.59 (2.30)	-0.871	2.055	0.392		
C _{max} last dose (ng/mL)	11 (163)	-92	115	0.817		
t _{max} last dose (h)	-0.24 (1.23)	-1.02	0.54	0.511		
^a .Treatment A=FX + PX; Treatment B=FX + PBO Paired samples test (df=11)						
PK Parameters Describing Accumulation of FX During Once Daily Dosing of 10 mg						
FX only, n=12		Single dose	Steady state	Accumulation ratio		
C _{max} (ng/mL)	Mean	1139	1459	1.27		
	SD	144	292	0.13		
	CV%	12.6	20.0	10.4		
AUC _{0-t}	Mean	14.5	18.8	1.30		
	SD	1.8	2.98	0.10		
	CV%	12.6	15.8	8.0		
Activated Partial Thromboplastin Time (APTT) – Time-Corrected Area Under Effect Curves						
Time Span		FX + PX N=13	FX + PBO N=12	PX + PBO N=13		
0-96h, without baseline	Mean (SD) in seconds	43.5 (5.6)	43.5 (5.7)	37.9 (5.0)		
	Range in seconds	36.0 / 53.7	36.4 / 51.7	29.9 / 48.0		
0-96h, corrected for baseline	Mean (SD) in seconds	4.0 (4.5)	3.5 (2.9)	-0.9 (6.3)		

	Range in seconds	-2.1 / 16.8	-1.6 / 8.9	-5.9 / 18.7
72-96h, without baseline correction	Mean (SD) in seconds	42.6 (5.0)	42.8 (5.7)	38.0 (4.0)
	Range in seconds	35.9 / 51.7	35.9 / 52.2	31.8 / 45.4
72-96h, corrected for baseline	Mean (SD) in seconds	3.2 (5.0)	2.7 (4.2)	-0.9 (6.2)
	Range in seconds	-3.0 / 17.4	-7.0 / 9.4	-7.1 / 18.0
Collagen-Induced Platelet Aggregation (CIPA) – Time-Corrected Area Under Effect Curves				
Time Span		FX + PX N=13	FX + PBO N=11	PX + PBO N=13
0-96h; without baseline	Mean (SD) in seconds	17.8 (7.4)	21.7 (3.2)	17.5 (8.2)
	Range in seconds	4.5 / 26.8	15.7 / 25.4	3.0 / 30.3
0-96h corrected for baseline	Mean (SD) in seconds	-2.9 (4.2)	-0.4 (2.5)	-5.9 (7.1)
	Range in seconds	-11.1 / 2.5	-4.5 / 4.1	16.0 / 4.6
72-96h: without baseline correction	Mean (SD) in seconds	17.9 (6.4)	22.2 (3.7)	14.4 (9.5)
	Range in seconds	5.1 / 25.1	15.5 / 27.6	1.5 / 30.6
72-96h: corrected for baseline	Mean (SD) in seconds	-3.3 (4.5)*	-9.0 (9.4)	-3.3 (4.5)
	Range in seconds	-13.9 / 3.6	-29.6 / 4.0	-13.9 / 3.6
* N for this analysis was 12				
Mean Fecal Porphyrin Excretion Rate; Ratio 1 and Ratio 2				
Ratio		FX + PX N=13	FX + PBO N=12	PX + PBO N=13
1	Mean (SD)	6.80 (5.63)	6.78 (5.78)	6.10 (5.32)
	Median	6.03	4.22	4.26
	Range	1.48 / 17.89	0.72 / 18.32	1.23 / 20.30
2	Mean (SD)	18.96 (15.07)	33.06 (43.70)	31.85 (33.82)
	Median	16.84	22.53	21.69
	Range	1.01 / 44.51	0.70 / 148.73	1.46 / 112.47
Safety results: Adverse events on treatment were defined as events occurring from the day of first study drug administration of that period up to the day before the first study drug administration of the next period. The last study treatment period included all adverse events reported from the beginning of this period up to the last assessment. An adverse event starting on Day 1 of a study period, but before the first study drug administration of this period was considered a pre-treatment sign and symptom.				
Adverse Events (All Treated Subjects):		FX + PX N=13	FX + PBO N=12	PX + PBO N=13
No. subjects with AEs n (%)		12 (92.3)	8 (66.7)	10 (76.9)
Most Frequent AEs				
Headache		1 (7.7)	3 (25.0)	0
Abdominal Pain		1 (7.7)	3 (25.0)	0
Dyspepsia		1 (7.7)	2 (16.7)	2 (15.4)
Increased Hepatic Enzymes		1 (7.7)	1 (8.3)	2 (15.4)
Epistaxis		1 (7.7)	0	2 (15.4)
Haematoma		9 (69.2)	3 (25.0)	3 (23.1)
Phlebitis		1 (7.7)	2 (16.7)	0
Pharyngitis		1 (7.7)	2 (16.7)	2 (15.4)

Rhinitis	1 (7.7)	2 (16.7)	0
Upper Respiratory Tract Infection	0	0	2 (15.4)
Serious Adverse Events, n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:			
No. subjects with Fatal/non-Fatal SAEs n (%) [related]	0	0	0

<p>Conclusion: See publication below</p> <p>Publications: Ollier, C. Interaction of fondaparinux sodium with acetylsalicylic acid and piroxicam in healthy male volunteers. Clin Pharmacokinet 2002;41 sup.2 : 31-37.</p> <p>Donat, F. The pharmacokinetics of fondaparinux sodium in healthy volunteers Clin Pharmacokinet 2002;41 sup.2 : 1-9.</p> <p>Absence of interaction of fondaparinux sodium with aspirin and piroxicam in healthy male volunteers. Ollier, C., Faaij, R. A., Santoni, A., Duvauchelle, T., van Haard, P. M., Schoemaker, R. C., Cohen, A. F., de Greef, R., and Burggraaf, J. Clin Pharmacokinet 2002; 41 Suppl 2(31-7)</p> <p>Abstract: Pentasaccharide (fondaparinux, arixtra) and the non-steroidal anti-inflammatory drug piroxicam do not interact in healthy subjects. Koos Burggraaf R. A. Faaij, R. C. Shoemaker R. G. M. van Amsterdam A. F. Cohen Intr. by Kenneth A. Bauer American Society of Hematology 43rd Annual Meeting 12/7/2001 Orlando, FL ; USA</p>
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