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Study No: BDR3780		
Title : A single dose bioequivalence study comparing a new formulation of Org31540/SR90107A and the reference formulation in healthy male subjects		
Rationale: SR90107A/Org31540, also known as fondaparinux (FX), is a selective inhibitor of activated factor X (factor Xa) appropriate for treatment of venous thromboembolic events (VTE). The concentration of FX used for previous phase IIB and phase III studies was 10 mg/mL; the proposed formulation to be marketed for the prevention of VTE and PE (pulmonary embolism) in major orthopaedic surgery of the lower limbs was 5 mg/mL. The only difference between the two formulations was the concentration. This study was designed to examine bioequivalence between the reference formulation (10 mg/mL) and the new formulation (5 mg/mL).		
Phase: 1		
Study Period: 18 November 1999-10 December 1999		
Study Design: Single center, open-label, randomized, two-period, cross-over study		
Centres: 1 in France		
Indication: None		
Treatment: Subjects received a single 2.5 mg subcutaneous (s.c.) dose of the randomly assigned formulation of FX (10 mg/mL or 5 mg/mL) during the first treatment period and, after a wash-out period of 7 days, they received the alternate formulation during the second treatment period. FX was administered following an overnight fast in each case.		
Objectives: To determine the bioequivalence between a new formulation (concentration 5 mg/mL) and the reference formulation (concentration 10 mg/mL) of a single s.c. 2.5 mg dose of FX under fasted conditions		
Statistical Methods: <u>Population:</u> All subjects who received the study drug were analyzed for safety and tolerability. Only subjects who completed the study were included in the pharmacokinetic analysis. No assessment of pharmacodynamic activity was performed. <u>Pharmacokinetics:</u> Log-transformed values of C_{max} , AUC_{last} and AUC_{inf} , and rank-transformed t_{max} were analyzed by a mixed model. For C_{max} , AUC_{last} and AUC , estimates with 90% confidence intervals (CIs) for formulation ratios were obtained by first computing differences in estimates within the mixed model framework, and then converting to ratios of adjusted geometric means using the anti-log transformation. Bioequivalence was concluded if the 90% CI for the ratio was included within the equivalence reference interval [0.8 , 1.25]. The formulation difference for t_{max} was calculated and the corresponding 90% CIs obtained using the Hodges-Lehmann approach. Within, between, and total-subject standard deviations (SD) and 95% CIs were estimated according to the Graybill and Burdick recommended procedures. <u>Safety:</u> Results and changes from baseline for laboratory parameters and supine vital signs were summarized using the mean, standard error of the mean (SEM), minimum and maximum at each time point. Ivy Nelson bleeding time and activated partial thromboplastin time (aPTT) were analyzed descriptively.		
Study Population: Subjects were male, Caucasian, aged 18-35 yrs, 65-95 kg and body mass index (BMI) 18-30 kg/m ² , with normal comprehensive clinical assessments, 12-lead electrocardiogram [ECG] and laboratory parameters, and no known history of disease or tendency for bleeding. Smoking and caffeine were prohibited for the duration of the study.		
Number of Subjects:	Total for each treatment	
Planned N	16	
Dosed N	16	
Completed, n (%)	16 (100)	
Total number of Subjects Withdrawn, n (%)	0 (0.0)	
Withdrawn due to Adverse Events, n (%)	0 (0.0)	
Withdrawn due to Lack of Efficacy, n (%)	0 (0.0)	
Withdrawn for Other Reasons, n (%)	0 (0.0)	
Demographics	Sequence: 5 mg/mL - 10 mg/mL [New - Reference]	Sequence: 10 mg/mL - 5 mg/mL [Reference - New]
N	8	8
Males, n	8	8
Age in years, mean (SD)	24.3 (3.2)	24.5 (2.8)
Weight in kg, mean (SD)	74.7 (9.0)	73.1 (9.5)

Caucasian, n (%)	8 (100)	8 (100)
Pharmacokinetics (PK) Endpoints, mean (SD):		
	10mg/mL (Reference formulation)	5mg/mL (New formulation)
	N = 16	N = 16
C _{max} (mg/L)	0.318 (0.039)	0.340 (0.037)
AUC _{last} (mg.h/L)	4.90 (0.93)	5.30 (1.07)
AUC (mg.h/L)	6.29 (1.18)	6.65 (1.20)
t _{max} (h)	1.69 (0.52)	1.69 (0.36)
	Relative Ratio (5 mg/mL /10 mg/mL)	
C _{max} , adjusted geometric mean [90% CI]	1.07 [1.03 ; 1.11]	
AUC _{last} , adjusted geometric mean [90% CI]	1.08 [1.04 ; 1.12]	
AUC, adjusted geometric mean [90% CI]	1.06 [1.03 ; 1.09]	
Safety results:		
Adverse Events (AEs):	10mg/mL (Reference formulation)	5mg/mL (New formulation)
N	16	16
Number of subjects with AEs, n (%)	2 (12.5)	3 (18.8)
Most Frequent AEs, n (%)		
Hematoma	2 (12.5)	1 (6.3)
Serious Adverse Events n (%) [n considered by the investigator to be related, possibly related, or probably related to study medication]:		
Number of subjects with SAEs- -includes fatal and non-fatal events	0	0
Conclusion: See publication below.		
Publications: The pharmacokinetics of fondaparinux sodium in healthy volunteers. F Donat. Clin Pharmacokinet 2002; 41 sup.2 : 1-9. Absence of interaction of fondaparinux sodium with digoxin in healthy volunteers. Mant, T., Fournie, P., Ollier, C., Donat, F., and Necciari, J. Clin Pharmacokinet 2002; 41 Suppl 2(39-45) The pharmacokinetics of fondaparinux sodium in healthy volunteers. Donat, F., Duret, J. P., Santoni, A., Cariou, R., Necciari, J., Magnani, H., and de Greef, R. Clin Pharmacokinet 2002; 41 Suppl 2(1-9) Abstract: Fondaparinux (arixtra), a new selective factor xa inhibitor, does not interact with the pharmacokinetics and pharmacodynamics of digoxin in healthy volunteers. T. Mant , P. Fournie, and C. Ollier, F. Donat . Necciari 2 7th Congress of the European Haematology Association 6/6/2002 Florence, Italy		

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