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Study No: BDR4979	
Title: A single dose bioequivalence study comparing a new formulation of fondaparinux sodium at 12.5 mg/mL and the reference formulation at 10 mg/mL, in healthy male subjects. Open, randomized, crossover and single center study	
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). A clinical program studied the benefit of FX in the VTE indication with a formulation at 10 mg/mL; the actual dose administered was 5, 7.5 or 10 mg depending on body weight (<50 kg, 50-100 kg, >100 kg, respectively). The to-be-marketed formulation in the VTE indication was 12.5 mg/mL FX. This study was designed to assess the bioequivalence between the two formulations (10 mg/mL and 12.5 mg/mL) after a single 10 mg dose of FX administered subcutaneously (s.c.) in healthy subjects.	
Phase: 1	
Study Period: 11 January 2002 - 02 October 2002	
Study Design: Single center, open-label, randomized, two-period, cross-over study	
Centres: 1 in France	
Indication: None	
Treatment: Following a 10-hour overnight fast, subjects received a single 10 mg FX dose s.c. of the randomly assigned formulation of FX (10 mg/mL or 12.5 mg/mL) during the first treatment period and, after a wash-out period of 7 days, received the alternate formulation during the second treatment period.	
Objectives: To determine the bioequivalence between a formulation of FX at 12.5 mg/mL and the reference formulation at 10 mg/mL.	
Statistical Methods: <u>Population:</u> All subjects who took study drug were analyzed for safety and tolerability. Subjects with evaluable data were included in the pharmacokinetic (PK) analysis. <u>Pharmacokinetics:</u> Log-transformed values of AUC _{last} , AUC and C _{max} , and rank-transformed values of t _{max} were analyzed by a mixed model. For AUC _{last} , AUC _{inf} and C _{max} , 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 ratio of adjusted geometric means by the anti-log transformation. Bioequivalence was concluded if the 90% CI for the ratio was included within the bioequivalence reference interval [0.80, 1.25]. In order to provide additional information, but not to support the bioequivalence assessment, the formulation difference for t _{max} and the corresponding 90% CI (based on the Hodges-Lehmann approach) were calculated. <u>Safety:</u> Treatment-emergent adverse events (AEs) were listed and summarized by formulation. Flag-and-count analysis of potentially clinically significant abnormalities (PCSAs) was performed on laboratory parameters, ECG and vital signs (raw and derived values) obtained at the end-of-study visit and on-treatment whenever applicable according to a pre-defined PCSA list.	
Study Population: Subjects were male, Caucasian, aged 18-40 yrs, 60-90 kg and body mass index (BMI) 18-28 kg/m ² , with normal comprehensive clinical assessments, 12-lead electrocardiogram [ECG] and laboratory parameters, and no known history of disease, tendency for bleeding or drug allergy. Subjects were excluded if they suffered from frequent headaches, migraine, nausea or vomiting, were undergoing dental care, or were doing anything that required intensive muscular effort before and during the study.	
Number of Subjects:	All
Planned N	16
Dosed N	32
Completed, n (%)	32
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	All
N	32
Males	32
Age in years, mean (SD)	30.2 (5.6)
Weight in kg, mean (SD)	71.60 (6.63)
Caucasian, n (%)	32
Pharmacokinetics (PK), pharmacodynamics (PD), PK/PD Endpoints:	

Due to an improper use of the catheter for pharmacokinetic blood sampling (mandril soaked in heparin solution that interfered with quantification of FX in plasma), unexpectedly and unreasonably high FX concentrations were obtained for the first 16 included subjects. For this reason, the bioequivalence of the 2 formulations could not be documented from these first 16 subjects leading to the inclusion of 16 additional subjects evaluable from a PK perspective. In the present PK analysis, only results on the 16 evaluable subjects were presented. No PD analysis was carried out.		
	Reference Formulation (10 mg/mL)	New Formulation (12.5 mg/mL)
	N = 16	N = 16
C _{max} (mg/L), mean (coefficient of variation (CV)%)	0.852 (25)	0.893 (13)
t _{max} (h), median (minimum – maximum)	2.5 (1.5 – 10.0)	2.5 (1.0 – 4.0)
AUC _{last} (mg.h/L), mean (CV%)	13.2 (24)	14.4 (29)
AUC (mg.h/L), mean (CV%)	14.8 (22)	15.9 (26)
t _{1/2} (hour), mean (CV%)	15.7 (25)	17.0 (26)
	Relative Ratio (12.5 mg/mL / 10 mg/mL)	
C _{max} , geometric mean [90% CI]	1.07 [0.96, 1.18]	
t _{max} (h), median [minimum - maximum]	-0.375 [-1.00, 0.00]	
AUC _{last} , geometric mean [90% CI]	1.08 [0.92, 1.27]	
AUC , geometric mean [90% CI]	1.07 [0.93, 1.23]	
Safety results:		
Adverse Events: 32 subjects (16 in the initial study and 16 in the amended study) were analyzed in the safety section.	Reference Formulation (10 mg/mL)	New Formulation (12.5 mg/mL)
N	32	32
Number of subjects with AEs, n (%)	6 (18.8)	4 (12.5)
Most Frequent AEs, n (%)		
Headache	4 (12.5)	2 (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
Publications: No Publication		

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