Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product:				
Name of active ingredient: BIBR 1048 MS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:** I	**Page:** to		**Addendum No.:**
Report date: 23 October 2001	**Number:** 1160.5	**Study period (years):** 1 - 3 / 2001		

Title of study:	Tolerability of single rising doses of 0.1 mg, 1 mg, and 5 mg BIBR 953 ZW IV (placebo-controlled in each dose group; substudy 1) and absolute and relative bioavailability of 100mg BIBR 1048 tablet and of solution and of 1 mg or 5 mg BIBR 953 ZW IV (randomised, three-way crossover; substudy 2).	
Investigator:	[redacted]	
Study centre(s):	Human Pharmacological Centre BI Pharma KG	
Publication (reference):	No	
Clinical phase:	I	
Objectives:	To assess (1) the tolerability of BIBR 953 ZW intravenous infusions at 0.1, and 5 mg BIBR 953 ZW and (2) the absolute bioavailability of 100 mg BIBR1048 administered as 'acid free' tablet formulation (TF1) and (3) the bioavailability of the 100 mg tablet of BIBR 1048 relative to the tartaric acid solution of 100 mg dose strength and (4) the absolute bioavailability of the 100 mg tartaric acid solution of BIBR 1048 MS	1
Methodology:	Single dose treatment with 100 mg BIBR 1048 MS tablet vs solution vs 1 or 5 mg BIBR 953 in a 3-way crossover design, and single rising dose IV tolerability	
No. of subjects entered:		
total:	30	
each treatment:	12 (100 mg BIBR 1048 MS tablet vs solution vs BIBR 953 IV), 18 (BIBR 953 IV)	
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 50 years	
Test product:	BIBR 1048 MS film-coated tablet	BIBR 953 ZW ampoule
dose:	100 mg	0.1, 1 and 5 mg
mode of admin.:	p.o.	IV
batch no.:	B000506	B001004
Duration of treatment:	1 x 1 day (substudy 1), 3 x 1 day (substudy 2)	

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Reference therapy:	BIBR 1048 MS tartaric acid solution	BIBR 953 ZW placebo ampoule
dose:	100 mg	-
mode of admin.:	p.o.	IV
batch no.:	B001110 (solvent), B001112 (powder)	-
Criteria for evaluation:		
Efficacy:	Primary variables: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tf}$, C_{max} (oral administration), urinary excretion of BIBR 953 ZW and conjugates after IV administration Secondary variables: blood coagulation test, PT (INR), aPTT	
Safety:	Pulse rate, systolic & diastolic blood pressure, ECG, lab., adverse events	
Statistical methods:	Descriptive statistics, ANOVA 90 % CI for the treatment ratios, AUCtablet/AUCsolution, Cmax,tablet/Cmax,solution	

SUMMARY - CONCLUSIONS:

Efficacy results:

The tolerability and the pharmacokinetic profile of BIBR 953 ZW administered as intravenous infusions at 0.1, 1 and 5 mg BIBR 953 ZW and the absolute bioavailability of 100 mg BIBR1048 administered as 'acid free' tablet formulation (TF1) and solution as well as the bioavailability of the 100 mg tablet of BIBR 1048 relative to the tartaric acid solution of 100 mg dose strength were assessed. Plasma concentrations of total BIBR 953 ZW (after alkaline cleavage of glucuronide conjugates) was measured in all plasma and urine samples. In plasma and urine samples collected after IV BIBR 953 ZW, additionally free BIBR 953 ZW (without alkaline cleavage) was determined. A validated HPLC-MS/MS assay was used to determine BIBR 953 ZW concentrations. In parallel to BIBR 953 ZW plasma concentration measurements, aPTT and INR was measured. After intravenous infusion BIBR 953 ZW displayed dose-proportional kinetics with absorption and elimination following parallel time courses and very similar terminal half-lives with geometric mean values of approximately 6.5 hr following 1 and 5 mg BIBR 953 ZW. Primary pharmacokinetic endpoints AUC0-∞ and C29 were dose proportional as evidenced by comparison of the dose-normalised AUC0-∞. For the 5 mg dose, both AUC0-∞ and C29 showed low intersubject variability (less than 20% gCV%) and values were comparable across substudies with AUC0-∞ ranging from 758-770 ng.hr/mL and C29 from 233 to 265 ng/mL. Geometric mean values of half-life ranged from 6.46 to 7.82 hr across both dose groups in both substudies. Geometric mean volume of distribution ranged from 61.5 to 73.3 L.

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BIBR 953 ZW is eliminated primarily by the kidneys with urinary excretion accounting for up to approximately 80% of the dose. Geometric mean total and renal clearance ranged from 108-110 mL/min and 93-97 mL/min, respectively. Renal excretion also followed dose-proportional kinetics. After both oral formulations of BIBR 1048 MS absorption was similarly rapid in onset with quantifiable concentrations of metabolite BIBR 953 ZW observed at the first sampling timepoint of 0.5 hr. The time to maximum concentration of BIBR 953 ZW was similar in both treatment groups with median values of 2 and 1.5 hr following tablet and solution, respectively. The tablet formulation displayed higher bioavailability relative to the solution. Both AUC0-∞ and Cmax were increased with geometric mean AUC0-∞ values of 587 and 520 ng.hr/mL and Cmax values of 83.4 and 75.2 ng/mL following 100 mg tablet and solution, respectively. When expressed as a geometric mean % relative bioavailability AUC0-∞ and Cmax values following the tablet were 113% and 111%, respectively of those following solution. With regards to absolute bioavailability both formulations displayed low bioavailability with geometric means of 3.8% (range 2.10 - 5.59) and 3.4% (range 2.35 - 4.27) for the tablet and solution, respectively. . The prolongation of aPTT and the increase in INR paralleled the plasma concentrations of BIBR 953 ZW indicating a close correlation between aPTT and INR with plasma concentrations of the direct thrombin inhibitor BIBR 953 ZW. The aPTT showed dose dependent prolongation with a geom. mean maximum aPTT ratio of 1.08, 1.32 and 1.97 attained with 0.1 mg, 1 mg, and 5 mg BIBR 953 ZW administered by intravenous infusion. The maximum INR was 1.25, 1.31 and 1.84 after IV administration of 0.1, 1 and 5 mg BIBR 953 ZW. Intravenous infusion of 5 mg BIBR 953 ZW to 12 healthy male subjects increased aPTT by a factor of 1.83. With oral administration of the 100 mg BIBR 1048 solution, the maximum geom. mean prolongation of aPTT was 1.49. With the 100 mg BIBR 48 tablet TF1, a geom. mean maximum aPTT ratio of 1.44 was attained. The corresponding geom. mean maximum INRs were 1.72 (5 mg infusion), 1.33 (100 mg tablet), and 1.31 (100 mg solution).

Safety results:

Conclusions: