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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: -				
Name of active ingredient: BIBT 986 BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 16 September 2004	**Number:** U04-1026	**Study period (dates):** 26 FEB 03 – 02 MAY 03		

Title of study:	Tolerability and pharmacokinetics/-dynamics of 0.5 mg and 1.0 mg (*actual 0.8 mg)* of BIBT 986 BS per hour given as IV infusion over 32 hours in healthy male subjects. Placebo controlled, double blind randomised at each dose level.
Investigator:	[redacted]
Study center(s):	[redacted] D-[redacted]
Publication (reference):	-
Clinical phase:	I
Objectives:	To assess the tolerability of an intravenous infusion of 0.5 and 1.0 mg (*actual 0.8 mg)* BIBT 986 BS per hour over 32 hours as well as pharmacokinetics and the effect on blood coagulation parameters
Methodology:	Continuous intravenous infusion tolerability, randomised, placebo controlled, blinded at each dose level
No. of subjects:	
planned:	entered: 16
actual:	enrolled: 6 + 2 (active substance / placebo) per dose group
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 55 years
Test product:	BIBT 986 BS ampoule 10mg/10mL
dose:	0.5 and 0.8 mg/hour over 32 hours
mode of admin.:	IV
batch no.:	B020801
Duration of treatment:	1 x for 32 hours
Reference therapy:	BIBT 986 BS placebo ampoule 10 mL
dose:	--
mode of admin.:	IV
batch no.:	B020505

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Criteria for evaluation:

Efficacy:

Pharmacokinetics: C_{max}, C_T, C_{ss}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{inf}, CL, V_{ss},V_z, and urinary excretion of BIBT 986 BS

Pharmacodynamics: blood coagulation tests aPTT, ECT, PT (INR), TT

Safety: Systolic & diastolic blood pressure, pulse rate, ECG, laboratory parameters, adverse events

Statistical methods: Descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetic results:

Plasma and urine samples were analysed with regard to BIBT 986 BS. Descriptive statistics of pharmacokinetic parameters of BIBT 986 BS after intravenous infusion of 0.5 mg/h and 0.8 mg/h of BIBT 986 BS over 32 h were as follows:

		0.5 mg/h BIBT 986 for 32 h (N=6)		0.8 mg/h BIBT 986 for 32 h (N=6)	
Parameter	Unit	gMean	gCV (%)	gMean	gCV (%)
AUC_{0-tz}	[ng·h/mL]	2010	19.9	3320	13.8
$AUC_{0-\infty}$	[ng·h/mL]	2020	20.0	3330	13.8
C_{max}	[ng/mL]	64.5	20.8	105	13.2
C_{ss}	[ng/mL]	63.0	20.0	104	13.8
$t_{1/2}$	[h]	12.1	9.82	11.6	9.83
CL	[mL/min]	132	20.0	128	13.8
MRT	[h]	6.55	11.2	6.64	15.6
V_{ss}	[L]	51.9	17.0	51.0	20.0
V_z	[L]	138	23.3	128	17.3
$CL_{R,0-80}$	[mL/min]	77.7	14.2	73.1	13.0
fe_{0-80}	[%]	58.4	19.4	56.8	16.5

Source data: Tables 15.5.2.1: 1 and 15.5.2.1: 2

BIBT 986 BS exhibits linear pharmacokinetics, and both AUC and C_{max} increased in a dose-proportional manner. As 58.4 % and 56.8 % of the total dose are excreted unchanged in urine in the low and high dose group, renal excretion is a major elimination pathway in man. Interindividual variability of pharmacokinetic parameters was below 24 %.

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Pharmacodynamic results:	The pharmacodynamic response, assessed by aPTT, INR, PT and ECT, showed a dose-dependent prolongation of blood coagulation time from 0.5 mg/h to 0.8 mg/h of BIBT 986 BS infused over 32 h. In the 0.5 mg/h dose group, the geometric mean maximal response for aPTT, INR, ECT and TT was 1.5, 1.3, 1.6, and 5.7 times the baseline activity, respectively. In the 0.8 mg/h dose group, the geometric mean maximal response for aPTT, INR, ECT and TT was 1.9, 1.4, 2.2, and 8.9 times the baseline activity, respectively. By 12 - 24 h post-dose, the activity for all four endpoints had returned close to baseline. There was no pharmacodynamic response to placebo. For all four PD measurements, the relationship between BIBT 986 BS concentration and relative increase in baseline activity appeared to be reasonably linear.
Safety results:	Gastrointestinal disorders like pharyngolaryngeal pain or faecal abnormality were reported by two subjects (one subject at screening, one under treatment). Pain in limb were noticed in two cases and erythema was found in one case. A causal relationship between the event and the trial drug was assumed by the investigator in the two pain in limb cases during treatment.
Conclusions:	Intravenous infusion of 0.5 mg/h and 0.8 mg/h BIBT 986 over 32 h was safe and well tolerated. Steady state plasma concentrations were generally reached 24 h after start of infusion, with the dominant half-life considered to be about 6 hours. The increase in $AUC_{0-\infty}$ and C_{max} was dose-proportional over the dose range tested. Interindividual variability of pharmacokinetic parameters was below 24 %. In healthy volunteers, the prolongation of blood coagulation time as assessed by aPTT, PT (INR), TT, and ECT was linearly correlated to BIBT 986 plasma concentrations, and the correlations were comparable to previous observations. BIBT 986 BS was safe and well tolerated in doses up to 0.8 mg over 32 hours. BIBT 986 BS is unlikely to produce QT prolongation or to induce electrophysiological changes to the heart conduction system when given at doses of 0.5 mg and 0.8 mg.