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 986BS		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 30 APR 2003	**Number:** U03-1268-01	**Study period (dates):** 7 - 10/2002		**Date of Revision:** 20 SEP 2004

Title of study:	Tolerability and pharmacokinetics/-dynamics of single rising doses of 0.1 mg, 0.3 mg, 1.0 mg, 2.5 mg, 5.0 mg, and 10.0 mg BIBT 986 BS (IV infusion over 30 minutes) in healthy male subjects. Placebo controlled, double blind randomised at each dose level.
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre Boehringer Ingelheim Pharma KG, D-88397 Biberach/Riss
Publication (reference):	-
Clinical phase:	I
Objectives:	To assess the tolerability of BIBT 986 BS after intravenous infusions of 0.1, 0.3, 1.0, 2.5, 5.0, and 10 mg To assess the pharmacokinetics of BIBT 986 BS after intravenous infusion To assess the effect of BIBT 986 BS on blood coagulation parameters
Methodology:	Single rising dose i.v. tolerability, randomised, placebo controlled, blinded at each dose level
No. of subjects:	
planned:	72 (9 active substance + 3 placebo per dose group)
actual:	47 entered in the trial, 46 treated
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 55 years
Test product:	BIBT 986 BS ampoule 10 mg/10 mL
dose:	0.1, 0.3, 1, 2.5, 5 and 10 mg
mode of admin.:	IV
batch no.:	B020509
Duration of treatment:	1 x 1 day (30 minutes)
Reference therapy:	BIBT 986 BS placebo ampoule 10 mL
dose:	--
mode of admin.:	IV
batch no.:	B020508
Criteria for evaluation:	

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Efficacy:	Pharmacokinetics: $AUC_{0-\infty}$, AUC_{0-tz}, C_T, $t_{1/2}$, CL, V_{ss}, urinary excretion of BIBT 986 BS
	Pharmacodynamics: blood coagulation tests: aPTT, PT (INR), ECT, TT
Safety:	Pulse rate, systolic & diastolic blood pressure, ECG, histamine, laboratory parameters, adverse events
Statistical methods:	Descriptive statistics

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Plasma samples were analysed with regard to BIBT 986 BS. Descriptive statistics of pharmacokinetic parameters of BIBT 986 BS after administration of 0.1 mg, 0.3 mg, 1 mg, and 2.5 mg BIBT 986 BS given as single 30 min intravenous infusion of BIBT 986 CL were as follows:

BIBT 986 BS dose		**0.1 mg (N=9)**		**0.3 mg (N=9)**		**1 mg (N=8)**		**2.5 mg (N=9)**	
Parameter	**Unit**	**gMean**	**% gCV**	**gMean**	**% gCV**	**gMean**	**% gCV**	**gMean**	**% gCV**
AUC_{0-tz}	[ng·h/mL]	4.62	47.3	22.2	27.2	107	12.5	268	22.3
$AUC_{0-\infty}$	[ng·h/mL]	6.97	54.1	27.8	26.9	119	14.5	285	19.1
C_T	[ng/mL]	4.84	19.2	13.2	12.4	51.4	10.3	131	16.0
$t_{1/2}$	[h]	1.32	69.0	3.30	25.5	4.18	10.8	4.9	14.5
CL	[L/h]	14.3	54.1	10.8	26.9	8.40	14.5	8.77	19.1
$CL_{R,0-4}$	[L/h]	5.19	27.1	4.52	15.2	4.30	15.7	4.81	21.0
V_{ss}	[L]	23.1	19.7	39.9	13.8	37.2	7.94	41.3	18.9

Source data: Appendix 16.3.2, Tables 41-44

BIBT 986 BS exhibits linear pharmacokinetics, and both AUC and Cmax increased in a dose-proportional manner following administration of 0.1 mg to 2.5 mg BIBT 986 BS, particularly in the 1 mg and 2.5 mg dose groups. For the 2.5 mg dose group, the percent of dose recovered in urine as BIBT 986 BS was on average 57.6 %. Thus, renal excretion is a major elimination pathway in man.

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Pharmacodynamic results:

Doses below 0.3 mg BIBT 986 BS resulted in comparable pharmacodynamic activity to the placebo group. There was a dose-dependent prolongation of blood coagulation time from 0.3 mg to 2.5 mg BIBT 986 BS. For aPTT, INR, and ECT, the average maximal response was 2.2, 1.8, and 2.4 times the baseline activity for the 2.5 mg dose, respectively. For TT, the maximal response was approximately 17 times the baseline activity. Maximum responses were reached 0.42 h to 0.55 h after start of infusion. By 12 h post-dose, the activity for all four endpoints had returned close to baseline.

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:

Eight of the 46 treated subjects reported at least one adverse event during screening (n=1), treatment with BIBT 986 BS (n=5) or placebo (n=2). Subject [redacted] was not treated due to a severe vasovagal attack prior to the start of study drug infusion. All other events were of mild intensity except in one subject with moderate headache.

Four subjects reported headache. Nasopharyngitis (common cold) was reported by two subjects, and diarrhoea by another one. Subject [redacted] had asymptomatic ventricular premature beats up to 8 per minute. None of the AEs was regarded study drug related.

Conclusions:

Single doses up to 2.5 mg of BIBT 986 given as intravenous infusion over 30 minutes were well tolerated. Especially neither increased bleeding tendency, nor signs of histamine release were observed.

BIBT 986 is likely to increase heart rate, especially when given at higher doses (> 0.3 mg). The observed heart rate increase influences the QT interval but does not prolong the ventricular de- and repolarization.