Clinical Study Synopsis for Public Disclosure

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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: 23 April 2004	**Number:** U04-1270	**Study period (dates):** 06 DEC 02 – 19 MAY 03		

Title of study:	Investigation of the effect of 0.9, 2.25 or 4.5 mg of BIBT 986 over 1 hour, followed by 0.2, 0.5 or 1.0 mg/hour of BIBT 986 for 7 hours given as IV infusion on tissue factor triggered coagulation in a randomised, placebo controlled, dose escalation design in healthy male volunteers
Investigator:	[redacted]
Study centre:	[redacted] Austria
Publication (reference):	There are no published data from this trial.
Clinical phase:	I
Objectives:	To compare with placebo the anticoagulant activity of three dosages of BIBT 986 on parameters of coagulation, platelet activation and inflammation in a model of tissue factor triggered activation of the coagulation system; to examine the safety of BIBT 986 in this setting
Methodology:	Randomised, dose escalation, placebo controlled, double-blind within each dose group, group control, single centre
No. of subjects:	
planned:	64
actual:	64 (16 pilot + 48 main study subjects) Dose steps 1 and 2: 15+5, dose step 3: 18+6 (active + placebo)
Diagnosis and main criteria for inclusion:	Healthy male subjects, age 18 to 40 years
Test product:	BIBT 986 CL vial
dose:	Dose step 1: 0.9 mg for 1 hour, followed by 0.2 mg/h for 7 hours Dose step 2: 2.25 mg for 1 hour, followed by 0.5 mg/h over 7 hours Dose step 3: 4.5 mg for 1 hour, followed by 1.0 mg/h for 7 hours
mode of admin.:	IV
batch no.:	B020801
Duration of treatment:	1 x 1 day, 8 hour infusion

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Reference therapy:	BIBT 986 CL placebo vial
dose:	(matching placebo)
mode of admin.:	IV
batch no.:	B020505
Criteria for evaluation:	
Efficacy:	Coagulation: F_{1+2} (prothrombin fragment), D-dimer, aPTT, PT, ECT, TT, TAT complexes, Protein C activity, thrombomodulin, tissue factor mRNA, platelet count Fibrinolysis: plasmin antiplasmin complexes Platelet activation: soluble P-selectin, Endothelial activation: soluble E-selectin, Inflammation: tumor necrosis factor alpha, interleukin-6, Primary haemostasis: closure times measured with the collagen/ epinephrine (CEPI-CT) and collagen/ADP cartridges (CADP-CT)
Safety:	Adverse events, vital signs, routine lab, histamine, ECG
Statistical methods:	Descriptive statistics

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics:
Plasma levels of BIBT 986 were generally detectable in all dose groups for at least 24 hours after start of infusion. Plasma concentration time profiles and pharmacokinetic parameters of the pilot study were comparable to those of the main study. The administration of LPS had no influence on the pharmacokinetics of BIBT 986. BIBT 986 exhibits at least bi-exponential disposition pharmacokinetics. The geometric mean terminal half life was 5.24 h, 5.03 h, and 6.26 h in the 0.2 mg/hour, 0.5 mg/hour, and 1 mg/hour dose groups, respectively. AUC, C_{max}, and C_{ss} increased in a dose-proportional manner. The total clearance was comparable with 127 mL/min, 119 mL/min, and 133 mL/min in the 0.2 mg/hour, 0.5 mg/hour, and 1 mg/hour dose groups, respectively. The volume of distribution at steady state was moderate with 29.3 L to 33.7 L across dose groups. BIBT 986 showed low interindividual variability for all pharmacokinetic parameters (%gCV <26%).

Pharmacodynamics:
Blood coagulation times as assessed by aPTT, PT (INR), TT, and ECT increased in a dose-dependent manner. In the pilot study, aPTT prolongations were approximately 1.3-fold, 1.9-fold, and 2.3-fold relative to baseline during maintenance dose infusion of dose groups 0.2 mg/hour, 0.5 mg/hour, and 1 mg/hour, respectively. The correlations of BIBT 986 plasma concentrations and prolongations of these coagulation markers relative to baseline were comparable to those observed in previous studies [BI 1192.1 and BI 1192.2].
The effects of BIBT 986 on LPS endotoxin-induced coagulation were assessed by prothrombin fragment (F_{1+2}), D-dimer, and thrombin-antithrombin complexes (TAT). BIBT 986 significantly suppressed LPS-induced thrombin generation: LPS infusion enhanced F_{1+2} levels 5.33-fold in the placebo group, compared to 1.35-fold in the highest BIBT 986 dose group. The $AUEC_{0-tz}$ and the E_{max} for F_{1+2}, D-Dimer, and TAT were significantly lower in all dose groups compared to placebo ($p \leq 0.0002$ for all dose groups vs. placebo). The inter-individual variability was considerably higher in the placebo group compared to the active dose groups.
BIBT 986 had no influence on markers of inflammation as assessed by TNF alpha and IL-6 ($p > 0.05$ for all dose groups vs. placebo). Consistently, all TNF alpha-dependent processes such as fibrinolysis (assessed by PAP) or endothelial activation (assessed by E-selectin) remained unaltered. Similarly, BIBT 986 had no influence on LPS-induced changes in the platelet activation marker P-selectin.

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Safety results:	No deaths and no serious adverse events occurred in this study. In total, 37 subjects (57.8%) experienced adverse events over the entire study. In the pilot phase 4 subjects (2 in the placebo group [diarrhea and fatigue (n=1), and pharyngolaryngeal pain (n=1)] , 1 in the 0.5 mg/hour dose group (Exanthema), and 1 in the 1 mg/hour dose group (diarrhea, nausea, and vomiting) reported adverse events. In the main study, 33 subjects reported adverse events (8 in the placebo group, 10 in 0.2 mg/hour dose group, 8 in the 0.5 mg/hour dose group, and 7 in the 1 mg/hour dose group). Overall, the adverse events with the highest incidences occurred in the following system organ classes: nervous system disorders (26 subjects, 40.6%), general disorders and administration site conditions (13 subjects, 20.3%), gastrointestinal disorders (5 subjects, 7.8%), and musculoskeletal and connective tissue disorders (5 subjects, 7.8%). In the system organ class nervous system disorders 'headache' (total 25 subjects, 39.1%) had the highest incidence. In the system organ class general disorders and administration site conditions 'feeling cold' (9 subjects, 14.1%) was reported most frequently. Within the system organ class gastrointestinal disorders vomiting (3 subjects, 4.7%) had the highest incidence and in the system organ class musculoskeletal and connective tissue disorders 'pain in limb' (4 subjects, 6.3%) was most frequent. In the main phase, 51.6% of all subjects reported an adverse event. Most adverse events were of 'mild' intensity; for 7 subjects adverse events with 'moderate' intensity were reported. These adverse event were 'feeling cold' (n=1) in the placebo group, 'ear pain' (n=1), 'facial paresis' (n=1), and 'headache NOS' (n=1) in the 0.5 mg/hour dose group; and 'vomiting NOS' (n=1), and 'headache NOS' (n=3) in the 1 mg/hour dose group. During the main study phase, 2 subjects had an adverse event with the intensity 'severe', both subjects were in the 0.2 mg/hour dose group and both subjects reported 'headache NOS' as adverse event. All subjects recovered from their adverse events and none of the adverse events was assessed as being related to the study drug. Flu-like and cold-like symptoms were attributed to LPS infusion. No relevant changes in haematology, clinical laboratory parameters, and vital signs were observed. No effect of BIBT 986 on histamine release was observed.
Conclusions:	The pharmacokinetics of BIBT 986 BS were dose-linear over the dose range tested and were not affected by LPS administration. The aPTT response to BIBT 986 changed as a result of LPS injection and was lower than in healthy volunteers with no activated coagulation. BIBT 986 fully suppressed LPS-induced coagulation as determined by F_{1+2}, TAT, and D-dimer concentrations over the dose range tested. BIBT 986 had no effect on parameters of inflammation like IL-6 or TNF alpha. There were no safety concerns with respect to the administration of BIBT 986.