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: BIBR 1048 MS, dabigatran etexilate mesilate		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 05 December 2006	**Number:** U06-3420	**Study period (dates):** 01 May 2006 - 16 July 2006		

Title of study:	Pharmacokinetics, safety and pharmacodynamics after multiple oral doses of dabigatran etexilate capsule (110 mg and 150 mg b.i.d., 7 days) in healthy Japanese and Caucasian male subjects (open label study)
Investigator:	[redacted]
Study center:	Medical Corporation Kouryokai CPC Clinic 4-18-38 Toso, Kagoshima, Japan
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	To investigate and compare pharmacokinetics, safety and pharmacodynamics of dabigatran etexilate following oral administration of multiple doses (110 mg and 150 mg b.i.d., 7 days) in healthy male subjects between Japanese and Caucasians
Methodology:	Multiple-dose, open-label study
No. of subjects:	
planned:	48 (24 Japanese and 24 Caucasian subjects)
actual:	Japanese subjects Dabigatran etexilate 110 mg b.i.d. for 7 days: enrolled: 12, entered: 12, treated: 12, analysed (for primary endpoint): 11 Dabigatran etexilate 150 mg b.i.d. for 7 days: enrolled: 12, entered: 12, treated: 12, analysed (for primary endpoint): 12 Caucasian subjects Dabigatran etexilate 110 mg b.i.d. for 7 days: enrolled: 12, entered: 12, treated: 12, analysed (for primary endpoint): 12 Dabigatran etexilate 150 mg b.i.d. for 7 days: enrolled: 12, entered: 12, treated: 12, analysed (for primary endpoint): 12

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Diagnosis and main criteria for inclusion:	Japanese or Caucasian healthy male subjects without finding of clinical relevance or evidence of a clinically relevant concomitant disease based upon a complete medical history, including the physical examination, vital signs (blood pressure, pulse rate and body temperature), 12-lead electrocardiogram (ECG), clinical laboratory tests Caucasian subjects were from a well-defined Caucasian population: both parents of Caucasians. The subjects understood the subject information form written in English and lived in Japan for 8 years or less Age: ≥20 and ≤45 years Body mass index (BMI): ≥18.5 and ≤29.9 kg/m^2
Test product: **dose:** **mode of admin.:** **batch no.:**	Dabigatran etexilate capsules 110 mg b.i.d. and 150 mg b.i.d. po 110 mg capsule: 06031, 150 mg capsule: 06032
Duration of treatment:	7 days
Reference therapy: **dose:** **mode of admin.:** **batch no.:**	Not applicable - - -
Criteria for evaluation:	
Efficacy:	Pharmacokinetic parameters C_{max}, t_{max}, $AUC_{\tau,1}$ (after the first dose) $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$, $C_{pre,N}$, $R_{A,Cmax}$, $R_{A,AUC}$ (after the last dose) Pharmacodynamic parameters Activated partial thromboplastin time (aPTT), ecarin clotting time (ECT)
Safety:	Adverse events, vital signs, ECG, laboratory tests
Statistical methods:	Descriptive statistics, regression analysis, analysis of variance, confidence interval

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacokinetics and pharmacodynamics:

The peak concentrations of free and total dabigatran were found at 3-4 hours after administration and the concentration decreased thereafter with the terminal $t_{1/2}$ of 9.28-13.7 hours at steady state. The plasma concentration reached a steady state within 48 hours. Parent drug (BIBR 1048 BS) and intermediate metabolites were not detected in the trough plasma sample and were detected at low levels in the samples obtained within 3 hours after drug administration on Day 7. The contribution of glucuronide conjugates to $AUC_{\tau,ss}$ of total dabigatran was 10-15%.

The values of $AUC_{\tau,ss}$ and $C_{max,ss}$ were approximately 30% higher in Japanese compared with Caucasians after 110 mg b.i.d. administration, which were not statistically significant. At 150 mg b.i.d., the difference between ethnic groups was smaller. Coagulation markers showed longer prolongation in Japanese after the first dose in the 110 mg group but the difference was smaller on Day 7. In 150 mg b.i.d. group, the extent of prolongation was comparable in Japanese and Caucasians. The relationships between drug concentration and coagulation marker response were comparable in Japanese and Caucasians.

In this study, the exposure to target therapeutic doses was compared between two ethnic groups. The higher dose showed comparable exposure in Japanese and Caucasians. The lower dose resulted in a slightly higher exposure in Japanese, but this was not considered clinically relevant based on the relationship of the coagulation response to the plasma concentration.

Safety results:

Adverse events were reported in 4 Japanese subjects only. Nausea and periodonititis occurred in the 110 mg b.i.d. group, and abdominal pain and gingival bleeding occurred in the 150 mg b.i.d group during treatment period or within 3 days after the last dose. All the adverse events were mild to moderate in intensity. Gingival bleeding was reported as a bleeding event in one Japanese subject who received 150 mg b.i.d. The event was mild in intensity and disappeared within about 10 minutes without treatment. One Japanese subject in the 110 mg group discontinued from the study due to adverse event (periodontitis). No severe or serious adverse events were reported.

Dipstick urinalysis for blood and fecal occult blood test showed negative in all subjects.

Dabigatran etexilate was safe at multiple doses of 110 mg and 150 mg b.i.d. for 7 days in Japanese and Caucasian subjects.

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Conclusions:

The pharmacokinetics and pharmacodynamics were evaluated and compared in Japanese and Caucasians after 110 mg and 150 mg b.i.d. administration of dabigatran etexilate. The peak concentrations were found at 3-4 hours after administration and the concentration thereafter decreased with the terminal $t_{1/2}$ of 9.28-13.7 hours. The plasma concentration reached a steady state within 48 hours. The parent drug (BIBR 1048 BS) and intermediate metabolites were not detected in the trough plasma sample and were detected at low levels in the samples obtained within 3 hours after drug administration on Day 7. The contribution of glucuronide conjugates to the $AUC_{\tau,ss}$ of total dabigatran was 10-15%. At 110 mg b.i.d., there was an approximately 30% difference in exposure, which was neither statistically nor clinically relevant. At 150 mg b.i.d., the differences between Japanese and Caucasians were even smaller. The data in this study did not support any consistent racial difference in pharmacokinetic and pharmacodynamic parameters.

Dabigatran etexilate was safe at multiple doses of 110 mg and 150 mg b.i.d. for 7 days in Japanese and Caucasian subjects.