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 Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa			
Name of active ingredient: Dabigatran, Dabigatran etexilate		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 23 JUN 2010	**Trial No. / U No.:** 1160.81 / U10-3381-01	**Date of trial:** 09 OCT 2009 – 09 NOV 2009	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability and pharmacokinetics study after single and multiple oral doses of dabigatran etexilate capsule (110mg,150 mg b.i.d., 7 days) in healthy Chinese subjects (Open label study)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	1 clinical trial centre in China
Publication (reference):	No
Clinical phase:	I
Objectives:	The objective of the current study is to investigate safety, tolerability and , pharmacokinetics of dabigatran etexilate following oral administration of single and multiple oral doses (110mg, 150 mg b.i.d., 7 days) in healthy Chinese subjects.
Methodology:	Open label study, uncontrolled, single and multiple doses.
No. of subjects:	
planned:	28 subjects (14 in each treatment group).:
actual:	Enrolled: 28 subjects (14 in each treatment group). Entered/randomized: 28 subjects (14 in each treatment group). Completed: 27 subjects (14 in dabigatran etexilate 110 mg bid group and 13 in dabigatran etexilate 150 mg bid group).
Diagnosis and main criteria for inclusion:	Healthy subjects who met the following criteria: - Healthy Chinese subjects as determined by the results of screening - Age ≥18 and ≤45 years - BMI ≥18 and <25 (Weight (kg) / Height (m)2) - Signed written informed consent in accordance with GCP and local legislation
Test product:	dabigatran etexilate
dose:	110mg,150 mg

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mode of admin.:	capsules, p.o. twice daily
batch no.:	807296 (110mg dose), 807667 (150 mg dose)
Reference therapy:	Not applicable
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	Single dose and 7 days multiple dose
Criteria for evaluation:	
Efficacy / clinical pharmacology:	After the 1st dose: Cmax, tmax, AUCτ,1, AUC 0-tz, AUC0-∞,%AUCtz-∞, λz, t1/2, MRTpo, CL/F, Vz/F After the last dose: Cmax,ss, tmax,ss, Cmin,ss, AUCτ,ss, λz,ss, t1/2,ss, MRTpo,ss, CL/F,ss, Vz/F,ss Accumulation ratio: RA,AUC, RA,Cmax, and linearity index (LI)
Safety:	Adverse events, vital signs, ECG, laboratory tests, physical examination
Statistical methods:	Descriptive statistics, regression analysis, analysis of variance
SUMMARY – CONCLUSIONS:	
Demographic and Baseline characteristics	There were 28 healthy subjects (14 males and 14 females) randomized into this study, with ages ranged from 18.8 to 42.9 years old. The mean value was 166cm (range: 153~ 179 cm) in height, 60.5kg (range: 49.5 ~ 74.5 kg) in weight. All of these 28 subjects were Asian (Chinese). 1 out of 28 was ex-smoker and 5 out of 28 subjects were current smokers; 20 out of 28 subjects were non-drinkers.

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Pharmacokinetic results:	After oral administration of dabigatran etexilate in fed condition, the peak concentrations of free and total dabigatran were found at 3-4 hours (median) post dose and the concentration decreased thereafter with the terminal half lives of 8.96-10.9 hours at steady state. The plasma concentration dabigatran reached steady state within 96 hours in dabigatran etexilate 110 mg bid group and within 24 hours in dabigatran etexilate 150 mg bid group. Plasma levels were dose proportional between the two dosing regimens. The accumulation ratios were approximately 1.5 in Cmax and 1.7 in AUC. The portion of glucuronide conjugates to AUCτ,ss of total dabigatran was 10.4-11.4%. The AUCτ,ss and Cmax,ss were 9.1-19.8% higher in female subjects compared with male subjects after 110 mg or 150 mg bid administration.

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Safety results:

There were no serious adverse events, deaths or adverse events of moderate or severe intensity reported during the conduct of the study. One subject had study drug prematurely discontinued due to adverse events and the subject was also prematurely removed from the trial. All adverse events for this patient resolved within 4 days of discontinuing study drug.

There were no reported AEs either in the screening phase or in the post-treatment phase of the study. Seventeen of 28 subjects had treatment emergent adverse events reported by the investigator. However, there were only 14 adverse events for 9 subjects during this trial that were associated with either clinical signs or symptoms. Of the adverse events observable by the subjects, there were 5 subjects in the 150 mg bid group and 4 subjects in the 110 mg bid group. All reported AEs were mild in intensity and resolved without any concomitant treatment or interventions. When considering what was reported as adverse events by the investigator there were 85.7% (12 /14 subjects) in the dabigatran etexilate 150 mg bid group and 35.7% (5 /14 subjects) in the dabigatran etexilate 110 mg bid group. Overall, the most frequently reported drug-related adverse events were elevated alanine aminotransferase, positive occult blood, microscopic haematuria, elevated blood bilirubin, headache and haemorrhoidal haemorrhage. All adverse events in the SOC groupings Investigations and Renal and Urinary Disorders were due solely to abnormal laboratory test results (liver function tests and/or urinalyses).

Six subjects (42.9%) in 150 mg bid group and 2 subjects (14.3%) in 110 mg bid group had elevated ALT values. All of these elevations except in two cases were less than > 2 x upper limit of normal range (ULN). Two subjects in 150 mg bid group had an ALT > 2 x ULN, one of which was also > 3 x ULN. All abnormal ALT values returned to normal range during the follow-up examination. Experience in 359 Chinese patients in RE-LY with an average exposure of 20 months had no relevant differences in their frequencies of liver function test abnormalities compared to warfarin treated patients, suggesting that the observed abnormalities of liver function tests in this study were most likely due to chance.

No clinical significant changes in vital signs or ECG parameters were found.

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Conclusions: The steady state pharmacokinetics of dabigatran were evaluated and compared between Chinese male and female subjects after 110 mg and 150 mg bid administration of dabigatran etexilate. A modest between gender difference in exposure was observed, although less than observed in Caucasians and Japanese. Females had a slightly higher exposure. In general, no difference between the pharmacokinetics of dabigatran in this healthy Chinese volunteer population and results previously obtained in Japanese or Caucasians was observed. The observed safety profile in this study is consistent with results from all other dabigatran studies besides an increased incidence of asymptomatic elevated liver function tests that is most likely a chance finding.