Boehringer Ingelheim

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® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran etexilate (BIBR 1048)		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Title of trial:	An open label, non-comparative, pharmacokinetic and pharmacodynamic study to evaluate the effect of Dabigatran Etexilate on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) undergoing primary unilateral elective total knee or hip replacement surgery
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre trial in 10 sites in 6 countries (Austria, Canada, Czech Republic, Finland, Sweden, Netherlands).
Publication (reference):	Data from this trial have not been published
Clinical phase:	IV
Objectives:	To assess the comparability of the back-calculated dabigatran concentration in plasma via calibrated Hemoclot® and the measured dabigatran concentrations assessed in a central laboratory. To perform regression analysis of total dabigatran plasma concentration vs. corresponding coagulation times (Hemoclot® clotting time, activated partial thromboplastin time [aPTT], ecarin clotting time [ECT]).
Methodology:	Multicentre, open-label, non-comparative, uncontrolled study
No. of patients:	
planned:	100
actual:	screened: 142 treated: 112 completed treatment: 100

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran Etexilate		**Page:** 2 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Diagnosis and main criteria for inclusion:	Male or female Caucasian patients, at least 18 years old, with moderate renal impairment (creatinine clearance 30-50 mL/min) undergoing primary unilateral elective total knee or hip replacement could be included. Patients with chronic treatment with anticoagulants or an excessive risk of bleeding were excluded.
Test product:	Dabigatran etexilate
dose:	75 mg single dose (1 capsule) initiated 1-4 h post-surgery, then 150 mg (2 capsules) once daily.
mode of admin.:	Oral
batch no.:	905062, 810249, 106230, 104194, 001127, 108543, 201220B, 205535 (shipped to the sites but not administered to any patients)
Reference therapy:	Not applicable
Duration of treatment:	10 days with follow-up on Day 14 (±2) for total knee replacement (TKR) patients and Day 38 (±2) for total hip replacement (THR) patients.
Criteria for evaluation:	
Clinical pharmacology:	Primary endpoints: • Back-calculated dabigatran concentration in plasma using Hemoclot® calibrated with dabigatran standards determined in the local study site's laboratory • Back-calculated dabigatran concentration in plasma using Hemoclot® calibrated with dabigatran standards determined in the central laboratory • Measured total dabigatran plasma concentrations determined in a central laboratory using HPLC-MS/MS Other endpoints: Pharmacokinetic (PK) parameters (based on concentrations measured by HPLC-MS/MS): • $C_{pre,N}$ (pre-dose concentration of the analyte in plasma immediately before administration of the Nth dose after N-1 doses were administered and taken directly from the observed analyte plasma concentration-time data)

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran Etexilate		**Page:** 3 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Clinical pharmacology (continued):

- $C_{24,ss}$ (steady state concentration of the analyte in plasma at 24 h after the last drug administration is taken directly from the observed analyte plasma concentration-time data)
- $C_{pre,ss}$ (pre-dose steady state concentration of the analyte immediately before administration of the next drug administration is taken directly from the observed analyte plasma concentration-time data)
- $C_{max,ss}$ (maximum concentration in the dosing interval tau is taken directly from the observed analyte plasma concentration-time data)
- $AUC_{\tau,ss}$ (area under the concentration-time curve within the dosing interval τ at steady state)
- $t_{max,ss}$ (time that is required to reach Cmax,ss is taken directly from the analyte plasma concentration-time data observed), and
- $\lambda_{z,ss}$ (apparent terminal rate constant λ at steady state)

Pharmacodynamic (PD) parameters:

- Hemoclot® clotting time (diluted thrombin time, dTT) determined in the central and local laboratories
- aPTT, determined in the central laboratory
- ECT, determined in the central laboratory

Safety:

Monitoring for adverse events (AEs) of special interest (major bleeding events [MBEs], symptomatic venous thromboembolism [VTE], deep vein thrombosis [DVT], transfusions, alanine aminotransaminase/aspartate aminotransaminase elevations); recording other bleeding events; monitoring for AEs; physical examination; laboratory evaluations.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran Etexilate		**Page:** 4 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Statistical methods: Back-calculated plasma concentration of dabigatran based on Hemoclot® clotting times at the study sites and back-calculated plasma concentration of dabigatran based on the centrally determined Hemoclot® clotting times were compared with dabigatran plasma concentrations determined by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). The calibration of the Hemoclot® test was performed using a set of dabigatran calibrator samples in order to get a regression equation for the estimation of the dabigatran concentration in the same sample. Descriptive analyses were performed for all PK parameters and all AEs. No interim analysis was performed during this trial.

SUMMARY – CONCLUSIONS:

Trial subjects and compliance with trial protocol:

In total, 89.3% of the 112 treated patients completed the study without having discontinued study treatment prematurely. Of the 12 (10.7%) patients who prematurely discontinued dabigatran etexilate treatment, 11 patients discontinued due to AEs. Of these, 10 patients discontinued treatment due to the following AEs: fatal acute myocardial infarction (1 patient), rash vesicular urticaria (1), atrial fibrillation (1), haematoma and contusion (1), gastritis haemorrhagic and haematemesis (1), haematemesis (1), pyelonephritis (1), diverticulitis and gastric ulcer (1), blood creatinine increased and gastric ulcer (1), and blood creatinine increased (1). One patient discontinued treatment due to an AE considered a worsening of her disease (haemorrhoidal haemorrhage) and 1 patient discontinued for other reasons unrelated to safety (assessments of PK, PD, and biomarkers were not accepted by the patient).

Of the 112 treated patients, 13 were excluded from the patient set for back-calculation of dabigatran (correct calculation set [CCS]) due to wrong dosage of treatment (9), non-compliance (5) and/or missing data (2), leaving 99 patients in the CCS. Further 29 patients were excluded from the per-protocol set (PPS) due to forbidden concomitant medication only, leaving 70 patients in the PPS.

Of the 142 screened patients, 112 were treated with dabigatran etexilate, of which a higher proportion was female (69.6%).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran Etexilate		**Page:** 5 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Trial subjects and compliance with trial protocol (continued):	The mean age was 79.1 ± 6.5 years; all patients were Caucasian. Hypertension was reported in 70.54% of treated patients. Other medical conditions reported in >10% of patients included history of cancer (22.32%), diabetes mellitus (16.96%), history of renal disease (14.29%), and history myocardial infarction (12.50%). The most common baseline conditions (>30% patients) were hypertension, osteoarthritis, and hypercholesterolaemia. Overall, 92% of patients took dabigatran etexilate reliably. Concomitant medication with an impact on bleeding, VTE, or anticoagulation/platelets was reported by 111 (99.11%) treated patients. The most commonly reported concomitant medications were acetylsalicylic acid for 53 (47.32%) patients, followed by paracetamol for 49 (43.75%) patients, and tranexamic acid for 40 (35.71%) patients.
Clinical pharmacology results:	In general, back-calculation of dabigatran concentrations by local Hemoclot® was not possible for most patients; only for 27/99 patients (27.3%) the calibration curve and the patient-specific quality control points were within the pre-specified limits, facilitating valid back-calculation of dabigatran concentration. In contrast, central back-calculation was valid for all 97 investigated patients. Out of the valid local Hemoclot® back-calculations, with the result 'below the limit of quantification' (BLQ, i.e. <50 ng/mL), 8.7% were measured by HPLC-MS/MS to be ≥50 ng/mL; the maximum concentration measured by HPLC-MS/MS was 115 ng/mL. Out of the valid central Hemoclot® back-calculations with a BLQ result, 18.2% were measured by HPLC-MS/MS to be ≥50 ng/mL; the mean concentration measured was 70.1 ng/mL and the maximum was 250 ng/mL. The quantifiable valid back-calculated concentrations were 2.2% (90% CI: -2.4 - 6.9%) higher locally than the concentrations measured by the reference method (HPLC-MS/MS); the central Hemoclot® underestimated the actual dabigatran concentrations by 7.6% (90% CI: 5.3 – 9.9%), which is within the acceptance limits of ±15% deviation from the target concentrations. These results indicate that effective use of Hemoclot® in local laboratories requires proper set-up and validation of the assay according to the instructions of the manufacturer and the specific guidance for the individual coagulation analysers.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran Etexilate		**Page:** 6 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Clinical pharmacology results (continued):	Geometric mean plasma concentrations (54.3 ng/mL) of total dabigatran determined by HPLC-MS/MS at trough appeared stable after Day 3. The 10th to 90th percentile (P10-P90) range was 12.1-91.6 ng/mL on Day 2 and increased to 16.4-124 ng/mL after the PK profile ($C_{24,ss}$). Inter-individual variability for the PK parameters ($C_{pre,2}$, $C_{pre,3}$, $C_{pre,4}$, $C_{pre,5}$, $C_{pre,6}$, $C_{pre,ss}$, $C_{24,ss}$, $AUC_{\tau,ss}$, $C_{max,ss}$) seem moderate to high with a geometric coefficient of variation ranging from 74.0% to 90.5%. The median $t_{max,ss}$ was 2.17 h. Following the PK profile, prolongation of aPTT, ECT, and dTT was seen for all clotting time assays when compared with baseline values. The PK/PD relationship did not deviate relevantly from linearity for dTT and ECT or from the E_{max} model for aPTT.
Safety results:	Of the 112 treated patients, 95 (84.8%) were treated for 10 days (overall range: 2 to 14 days). During treatment, 100 (89.3%) patients experienced AEs, 10 (8.9%) patients experienced serious adverse events (SAEs), and 11 (9.8%) patients experienced AEs leading to discontinuation of dabigatran etexilate. Overall, the investigator reported bleeding events for 20 (17.9%) patients (11 patients undergoing THR, 9 undergoing TKR). Most of the reported bleedings occurred at the surgical site; 5 (4.5%) patients experienced gastrointestinal bleeding. Bleeding events were classified as clinically relevant for 13 (11.6%) patients; MBEs were reported for only 4 (3.6%) patients. No bleedings occurred in critical organs. One third of the patients received blood transfusions as surgical routine and only 12 patients due to other bleeding events or reasons. None of the treated patients had a thromboembolic event. Four patients (3.6%) were reported with signs of DVT, but none of these were confirmed as DVT. The most frequent AEs (>20% patients) by system organ class (SOC) were gastrointestinal disorders (58.9%); general disorders and administration site conditions (26.8%); investigations (25.0%); musculoskeletal and connective tissue disorders (24.1%); and injury, poisoning and procedural complications (23.2%). The most common AEs at the preferred term level were nausea in 45 (40.2%) patients, vomiting in 37 (33.0%) patients, and arthralgia in 23 (20.5%) patients.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa® (EU), Pradax® (Canada)		**EudraCT No.:** 2010-018723-26	
Name of active ingredient: Dabigatran Etexilate		**Page:** 7 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 APR 2014	**Trial No.:** 1160.86 **Doc. No.:** c01954741-02	**Date of trial:** 20 Sep 2010 – 05 Apr 2013	**Date of revision:** Not applicable

Safety results (continued):	AEs leading to discontinuation were most frequently reported in the SOC gastrointestinal disorders. The most frequently reported drug-related AEs (>5% of patients) were haematoma and wound haematoma. Most AEs were mild or moderate in intensity; only 7 (6.3%) patients had AEs that were assessed as severe in intensity. Four patients reported SAEs that were considered to be related to study drug by the investigator and led to treatment discontinuation (diverticulitis, gastritis haemorrhagic, and 2 cases each of gastric ulcer and haematemesis); 1 SAE was fatal (acute myocardial infarction). Laboratory parameters were recorded only at screening; during the observation period, laboratory measures were recorded as necessary and clinically relevant findings were recorded as AEs or SAEs.
Conclusions:	This method comparison study confirmed that Hemoclot® is an adequate assay to estimate dabigatran concentrations and is comparable with the HPLC-MS/MS reference method in the calibrated range of approximately 50 to 500 ng/mL if adequately calibrated. It was found that effective use of Hemoclot® in local laboratories requires proper set-up and validation of the assay according to the instructions of the manufacturer and the specific guidance for the individual coagulation analysers. Dabigatran plasma concentrations measured by HPLC-MS/MS and concentrations back-calculated by Hemoclot® in the central laboratory were consistent and within the acceptance limits. This was also true for dabigatran concentrations measured by HPLC-MS/MS in the central laboratory and concentrations back-calculated by Hemoclot® in local laboratories when the assay was established appropriately. Therefore, it is crucial to perform the Hemoclot® assay with adequate calibration. As expected, the PK/PD relationship was linear for dTT and ECT and non-linear for aPTT. The types of AEs, SAEs, and AEs leading to discontinuation of dabigatran etexilate reported were consistent with the known safety profile according to the Pradaxa® Summary of Product Characteristics; no new safety issues for the use of dabigatran etexilate in patients undergoing THR or TKR were raised.