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**.

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| **Name of company:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Pradaxa® | | **EudraCT No.:** 2007-002631-86 | |
| **Name of active ingredient:** Dabigatran etexilate mesilate | | **Page:** 1 of 8 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 22 SEP 2011 | **Trial No. / U No.:** 1160.46 / U11-2298-01 | **Dates of trial:** 17 JUN 2008 – 5 MAY 2011 | **Date of revision:** Not applicable |



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| **Title of trial:** | A phase III, randomised, double blind, parallel-group study of the efficacy and safety of oral dabigatran etexilate (150 mg bid) compared to warfarin (INR 2.0-3.0) for 6 month treatment of acute symptomatic venous thromboembolism, following initial treatment for at least 5 days with a parenteral anticoagulant approved for this indication. RE-COVER II |
| **Coordinating Investigator:** | [redacted] |
| **Trial sites:** | Multi-centre study (208 centres, conducted in 31 countries worldwide) |
| **Publication (reference):** | Data of this study have not been published. |
| **Clinical phase:** | III |
| **Objectives:** | To compare the safety and efficacy of oral dabigatran etexilate (150 mg bid) and warfarin (target INR of 2.0 to 3.0) for 6 month treatment of acute symptomatic venous thromboembolism (VTE) following initial treatment (at least 5 days) with a parenteral anticoagulant approved for this indication in patients with acute symptomatic unilateral or bilateral deep vein thrombosis (DVT) of the leg involving proximal veins and / or pulmonary embolism (PE) |
| **Methodology:** | Randomised, double-blind, double-dummy, parallel-group, active controlled trial with a planned duration of 6 months of treatment, comparing fixed-dose dabigatran etexilate (150 mg bid) with warfarin (target INR 2.0 to 3.0) |
| **No. of patients:** | |
| **planned:** | At least 2550 patients (1275 per treatment group) to be entered to obtain a minimum of 46 patients with confirmed recurrent VTE events |
| **actual:** | Enrolled: 2701<br>Dabigatran etexilate:<br>Randomised: 1294; treated: 1280; analysed (for primary endpoint): 1279<br>Warfarin:<br>Randomised: 1295; treated: 1288; analysed (for primary endpoint): 1289 |

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| **Diagnosis and main criteria for inclusion:** | Adult male or female patients (≥18 years) with acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins, and/or acute symptomatic PE confirmed by definitive objective clinical testing for whom at least 6 months of anticoagulant therapy was considered appropriate by the investigator and who provided written informed consent |
| **Test product:** | Dabigatran etexilate capsule and matching placebo |
| **dose:** | 150 mg bid (dose calculated as free base) |
| **mode of admin.:** | Oral (capsule) |
| **batch no.:** | Refer to Appendix 16.1.6 |
| **Reference therapy:** | Warfarin tablet and matching placebo |
| **dose:** | As needed to maintain an International Normalised Ratio (INR) of 2.0 to 3.0 |
| **mode of admin.:** | Oral (tablet) |
| **batch no.:** | Refer to Appendix 16.1.6 |
| **Duration of treatment:** | The treatment period was 6 months and included a single-dummy period (oral and parenteral therapy period) and a double-dummy period (oral only therapy period). During the single-dummy period, patients received parenteral anticoagulant therapy and additionally either warfarin or warfarin placebo. As soon as a patient had received at least 5 days of parenteral therapy and had an INR value of ≥2.0 at 2 consecutive measurements, the double-dummy period was to be initiated, and the initial parenteral therapy was to be discontinued. The double-dummy period started with the initiation of treatment with dabigatran etexilate / matching placebo. Treatment with warfarin / matching placebo was to be continued, and the dose was to be adjusted according to the INR of the patient (true INR for patients randomised to dabigatran etexilate placebo / warfarin, sham INR for patients randomised to dabigatran etexilate / warfarin placebo). |
| **Criteria for evaluation:** | |
| **Efficacy:** | *Primary efficacy endpoint*<br>Composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined as the composite incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography, or spiral [helical] CT). |

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| **Efficacy (continued):** | *Secondary efficacy endpoints:*<br>1. Composite of recurrent symptomatic VTE and all deaths<br>2. Symptomatic DVT<br>3. Symptomatic PE<br>4. Deaths related to VTE<br>5. All deaths<br>All VTE required objective verification by definitive diagnostic evaluation. All recurrent VTEs and all deaths were centrally adjudicated by an independent committee that was blinded to treatment allocation. Adjudicated results were used in the analyses. |
| **Safety:** | Safety was assessed based on:<br>1. Incidence of bleeding events<br>- Major Bleeding Events (MBEs)<br>- MBEs and Clinically Relevant Bleeding Events (CRBEs)<br>- any bleeding events (MBEs, CRBEs, and nuisance bleeding events)<br>2. Adverse Events (AEs; including findings in the physical examination)<br>3. Discontinuation of study treatment due to AEs<br>4. Laboratory measures, especially Liver Function Tests (LFTs)<br>5. Acute Coronary Syndrome (ACS)<br>6. Vital signs<br>All safety endpoints were assessed during treatment and the 6 days following the last intake of study medication. All bleeding events were centrally adjudicated by an independent committee that was blinded with regard to the treatment allocation of patients. Adjudicated results were used in the analyses of bleeding events. |
| **Statistical methods:** | This trial aimed to demonstrate (1) non-inferiority of dabigatran etexilate versus warfarin and, if non-inferiority was confirmed, (2) superiority of dabigatran etexilate over warfarin for the primary endpoint (i.e. the composite of recurrent symptomatic VTE and deaths related to VTE until the end of the post-treatment period) in patients with acute symptomatic VTE. The overall significance level was controlled by a priori ordering of hypothesis testing.<br>The primary analysis was a test for non-inferiority with the non-inferiority margin simultaneously defined as 2.75 in hazard ratio and 3.6% in risk difference at Month 6 (i.e. Day 180). The choice of the non-inferiority margins guaranteed that at least 57% of the warfarin effect versus placebo was preserved |

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| **Statistical methods (continued):** | regarding the hazard ratio and at least 75% of the warfarin effect versus placebo was preserved regarding the risk difference, both based on the lower bounds of the 95% CIs.<br><br>Hazard ratios were calculated based on the time to occurrence of the primary endpoint using a proportional hazards model (Cox regression including factors for treatment, active cancer at baseline, symptomatic PE at baseline, and the interaction between active cancer and symptomatic PE). The overall risk difference estimates were obtained based on the Kaplan-Meier estimates at 6 months (180 days) after adjusting for the stratification factors active cancer at baseline and symptomatic PE at baseline. |
| **SUMMARY – CONCLUSIONS:** | |
| **Efficacy results:** | Of the 2568 treated patients, 14.4% prematurely discontinued study medication, with a similar proportion in both treatment groups (dabigatran etexilate: 14.7%, warfarin: 14.1%). Discontinuations of study medication due to AEs were similar and reported in 8.0% of patients in the dabigatran etexilate group and 7.8% of patients in the warfarin group.<br><br>Demographics and baseline characteristics of the treated patients were balanced across the treatment arms. The mean age was 54.9 years. More than half of all patients (60.6%) were male. Most patients were white (77.6%) or Asian (20.9%). The majority of patients were randomised in Europe (Central Europe: 32.8%, Western Europe: 17.4%), followed by Asia (20.0%).<br><br>The index event was symptomatic DVT alone for 68.1% of patients, symptomatic PE alone in 23.2% of patients, and both symptomatic PE and DVT in 8.6%. In addition to the symptomatic DVT / PE that qualified the patients for inclusion in this trial, baseline testing established the presence of co-existing asymptomatic VTE in a substantial proportion of patients. Overall, 63.9% of patients had symptomatic or asymptomatic PE (with or without DVT), and 84.7% of patients had symptomatic or asymptomatic DVT (with or without PE). All patients were treated for the index event with parenteral anticoagulant therapy.<br><br>The most frequent risk factors were previous VTE (17.5% overall), followed by surgery / trauma (17.2%), a history of venous insufficiency (15.8%), and prolonged immobilisation (13.7%). Active cancer at any time was present in 6.0% of patients (active cancer at baseline: 3.9%, active cancer diagnosed during |

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**Efficacy results (continued):**

the study: 2.1%). The most frequent medical history was hypertension, documented for 35.1% of patients.

Regarding the use of selected medication of interest, the use of NSAIDs concomitantly with study drug was reported by 22.4% of patients; ASA was used by 9.4% of patients. The concomitant use of P-gp inhibitors or inducers was uncommon. Restricted medication was used concomitantly with study drug by 10.9% of patients. Most frequently reported was the use of NSAIDs with a half-life of >12 hours (4.0% of patients) and the chronic systemic use of corticosteroids (3.3%).

The percentage of patients who were non-compliant with dabigatran etexilate / placebo was low (dabigatran etexilate: 2.3%, warfarin: 1.7%). Patients in the warfarin arm had a mean number of 16.3 INR measurements during the trial. The number of INR measurements per patient in the warfarin group was highest in the first month after randomisation (mean: 8.5) and decreased thereafter. The mean percentage of time in the INR target range of 2.0 to 3.0 was 56.9% (median 57.8%).

*Primary endpoint*

Primary endpoint events (VTE and VTE-related death) occurred in 34 patients in the dabigatran etexilate treatment group and in 30 patients in the warfarin group up to the end of the post-treatment period; the hazard ratio was 1.13 (95% CI 0.69, 1.85, p = 0.0002 for non-inferiority). The cumulative risk for the primary endpoint at 6 months was 2.4% in the dabigatran etexilate group and 2.2% in the warfarin group. The risk difference was 0.2 (95% CI -1.0, 1.3, p<0.0001 for non-inferiority). Based on the prespecified non-inferiority margins of 2.75 for the hazard ratio and of 3.6% for the risk difference, dabigatran etexilate was shown to be non-inferior to warfarin. Superiority of dabigatran etexilate over warfarin could not be demonstrated. The risk for VTE recurrence increased when active cancer was present at baseline, but without between-group differences. No relevant difference in VTE recurrence risk was seen in patients with or without symptomatic PE at baseline.

A number of predefined sensitivity analyses of the primary endpoint were performed, all of which supported the results of the primary analysis, and demonstrated the overall robustness of the results. Sensitivity analyses included an on-treatment analysis (HR 0.96, 95% CI 0.56, 1.65), a per-protocol analysis (HR 1.10, 95% CI 0.67, 1.81), and an analysis considering unexplained death as

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**Efficacy results (continued):**

VTE-related (HR 1.12, 95% CI 0.71, 1.76). Subgroup analyses of the primary endpoint also showed results consistent with the primary analysis.

*Secondary endpoints*

In the dabigatran etexilate group, there were numerically more patients with symptomatic DVT (dabigatran etexilate: 28 patients, warfarin: 17 patients) and with fatal PE (3 vs. 0 patients) but fewer patients with symptomatic (non-fatal) PE (9 vs. 15 patients) than in the warfarin arm. However, no statistically significant difference by treatment group was found in the rates of any of the secondary endpoints, i.e. for symptomatic DVT (HR 1.65, 95% CI 0.90, 3.01), symptomatic non-fatal PE (HR 0.59, 95% CI 0.26, 1.35), recurrent symptomatic VTE and all death (HR 1.09, 95% CI 0.75, 1.60), and all death (HR 1.04, 95% CI 0.61, 1.77).

**Safety results:**

*Observation time, exposure, and interruptions*

Patients were observed in this trial for a median of 210 days in both treatment groups. The median exposure to any study drug, i.e. dabigatran etexilate or warfarin including their matching placebos was 181 days in the dabigatran etexilate group and 180 days in the warfarin group. Interruptions of any study drug were documented in 11.0% (dabigatran etexilate) and 19.6% (warfarin) of patients. The most frequent reason for interruptions were a too high or too low INR, with a higher frequency in the warfarin treatment group (13.8%) than in the dabigatran etexilate group (1.2%). Patients in both treatment groups were exposed for a median of 9 days to initial parenteral therapy administered for the treatment of the index VTE.

*Bleeding events*

Major bleeding events were reported for 15 patients (1.2%) randomised to dabigatran etexilate and 22 patients (1.7%) randomised to warfarin. The HR of dabigatran etexilate vs. warfarin for MBEs was 0.69 (95% CI 0.36, 1.32). Of the 15 dabigatran etexilate patients, 8 had the bleeding event in the single-dummy period, so that only 7 patients had a major bleeding event while actually taking dabigatran etexilate. Of the 22 warfarin patients, 4 of the bleeding events were in the single-dummy period, so 18 patients had the bleeding event while on warfarin alone. MBEs were adjudicated as fatal in 1 patient (warfarin treatment group). In the dabigatran etexilate group, there were 6 symptomatic bleeding events into a critical area or organ, while there were 4 such events in the

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**Safety results (continued):**

warfarin group. In terms of bleeding location (investigator-assessed), gastrointestinal bleeds were most frequent (6 vs. 10 events). Two patients in each treatment group were reported with intracranial MBEs.

The incidence of any bleeding events was lower for the dabigatran etexilate group (15.6%) than for the warfarin group (22.1%). The HR for any bleeding event was 0.67 (95% CI 0.56, 0.81), indicating a significant treatment difference. The most frequently reported bleeding location (investigator assessment) was urogenital (51 vs. 75 events), followed by nasal bleeds (43 vs. 76 events) and gastrointestinal bleeds (48 vs. 33 events). In general, results of the subgroup analyses for any bleeding events were consistent across various patient subgroups. The number of blood transfusions required for bleeding events was similar in both treatment groups (19 patients, 1.5% in each treatment group), but patients in the warfarin group needed more units of blood on average (dabigatran etexilate: 5.4 units, warfarin: 2.6 units).

*Adverse events*

The overall incidence of treatment-emergent reported AEs was similar in the 2 treatment groups (dabigatran etexilate: 66.6%, warfarin: 71.1%). The most frequently reported AEs by preferred term were headache (4.5% vs. 5.4% of patients) and pain in extremity (6.0 % vs 5.4%). No relevant differences between treatment arms were observed in the incidence of AEs of severe intensity (9.3% vs. 8.9%) and serious AEs (12.2% and 11.9%). The most common reported SAEs were infections and infestations, mostly pneumonia which was more frequent in the dabigatran etexilate group. Adverse events assessed in this double-blind study by the investigators as related to study drug were reported less frequently in the dabigatran etexilate group (15.2%) than in the warfarin group (21.9%). Adverse events that led to treatment discontinuation were reported at the same rates in both treatment groups (7.8%) and were mainly related to therapy failure (DVT: 1.4% vs. 1.3%, PE: 0.7% vs. 0.5%), investigations (0.9% vs. 1.0%), and gastrointestinal disorders (0.7% vs. 1.0%); the time to discontinuation of study drug was not significantly different (HR 1.00; 95% CI 0.76, 1.32).

During the conduct of this trial, 59 patients were known to have died at any time post randomisation. Of these, 31 had been randomised to dabigatran etexilate (2.4% of randomised patients in this group) and 28 to warfarin (2.2%). One patient randomised (to dabigatran etexilate) never received study drug but is

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**Safety results (continued):**

included in the above number of deaths. Cancer was the most common cause of death in both groups. The frequency of confirmed definite or likely ACS events was low, occurring in 0.4% of dabigatran etexilate and in 0.2% of warfarin treated patients. More confirmed myocardial infarctions occurred in patients in the dabigatran etexilate group than in the warfarin group. One likely cardiac death occurred in a patient in the warfarin group.

*Clinical laboratory and vital signs*

The analyses of mean changes from baseline to the last value on treatment did not reveal any meaningful differences between the treatment groups. Possibly clinically significant abnormalities were most frequently reported for haematocrit (decreases in 4.4% vs. 4.9% of patients ) and haemoglobin (decreases: 3.6% vs. 4.4%). The more frequent occurrence of these decreases in the warfarin group may be explained by the more frequent bleeding events in this group. During treatment with active study drug, 3 patients (dabigatran etexilate: 1, warfarin: 2) developed ALT or AST values of >3 x ULN followed or accompanied by elevations of total bilirubin of>2 x ULN within 30 days (potential Hy's law cases). In the dabigatran etexilate treated patient the LFT elevations could be explained by liver-related baseline conditions or AEs (fatty liver disease, cholecystolithiasis). In the two warfarin cases, values returned to normal with the next visit. A further patient, randomised but never treated with dabigatran etexilate, had liver parenchymal disease at baseline and was discontinued from the study 3 days later when hepatospleenomegaly was diagnosed. For vital signs, no differences between treatment groups were noted.

**Conclusions:**

This trial demonstrated that dabigatran etexilate was non-inferior to warfarin for the treatment of acute symptomatic VTE (i.e. preventing recurrent VTEs). No statistically significant treatment differences were seen for the primary nor the prespecified secondary efficacy and safety endpoints including MBE. The rate of any bleeding events was significantly lower for the dabigatran etexilate treatment regimen than for the warfarin regimen. Dabigatran etexilate and warfarin appeared to be safe and well tolerated in this population.

## Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide complete disposition results and results of secondary endpoints, as summarised below.

| Results for | presented in |
|---|---|
| Patient disposition | Table 15.1.1: 1 |
| Symptomatic PE (Fatal and Non-fatal) | Table 15.2.2.5: 2 |

Table 15.1.1: 1 Patient disposition at the end of treatment - All patients

| | Dabigatran N (%) | Warfarin N (%) | Total N (%) |
|---|---|---|---|
| Enrolled | | | 2701 |
| Not entered/randomized | | | 112 |
| Entered/Randomized | 1294 | 1295 | 2589 |
| Not treated | 14 | 7 | 21 |
| Treated | 1280 (100.0) | 1288 (100.0) | 2568 (100.0) |
| Not Prematurely discontinued from trial medication | 1092 ( 85.3) | 1106 ( 85.9) | 2198 ( 85.6) |
| Prematurely discontinued from trial medication | 188 ( 14.7) | 182 ( 14.1) | 370 ( 14.4) |
| Adverse event | 102 ( 8.0) | 101 ( 7.8) | 203 ( 7.9) |
| AE: Worsening of disease under study * | 28 ( 2.2) | 23 ( 1.8) | 51 ( 2.0) |
| AE: Worsening of other pre-existing disease | 22 ( 1.7) | 15 ( 1.2) | 37 ( 1.4) |
| AE: Other (including bleeding) | 52 ( 4.1) | 63 ( 4.9) | 115 ( 4.5) |
| Bleeding events ^ | 10 ( 0.8) | 19 ( 1.5) | 29 ( 1.1) |
| Other than bleeding events ¤ | 42 ( 3.3) | 44 ( 3.4) | 86 ( 3.3) |
| Non-compliant with protocol | 39 ( 3.0) | 37 ( 2.9) | 76 ( 3.0) |
| Lost to follow-up | 6 ( 0.5) | 3 ( 0.2) | 9 ( 0.4) |
| Patient refused to continue medication µ | 33 ( 2.6) | 38 ( 3.0) | 71 ( 2.8) |
| Other | 8 ( 0.6) | 3 ( 0.2) | 11 ( 0.4) |

* : i.e. symptomatic DVT or PE based on investigator´s assessment.
^ : Bleeding includes patients who discontinued due to any bleeding event which did or did not clinically require cessation of study drug.
¤ : This line only counts patients who discontinued due to an other AE but who did not discontinue due to a bleeding.
µ : Patient could decide whether to continue trial without taking study drug or to withdraw from study permanently.
All information in table is based on investigator assessments in eCRF pages. Patients are assigned to treatment groups as treated.

Source data: Appendix 16.2.1, Listing 1 zctr\disp_ds.sas 30JUN2011

Table 15.2.2.5: 2 Hazard ratio for centrally adjudicated recurrent symptomatic fatal and non-fatal PE - FAS - Until the end of post treatment period

| | Dabigatran | Warfarin |
|---|---|---|
| Treated | 1279 | 1289 |
| Number of patients with recurrent symptomatic fatal and non-fatal PE | 10 | 15 |
| Hazard Ratio Estimate (95% CI)# | | 0.66 (0.29,1.46) |
| p-value for superiority | | 0.3021 |

Until the end of post treatment period: From randomization to day after last intake of warf/pbo for roll-over pats, to day of trial completion for other pats who completed treatment as planned and to last contact date for pats who prematurely discontinued treatment
#: obtained from the Cox model with factors treatment, active cancer at baseline,
symptomatic PE at baseline, and the interaction between active cancer at baseline and symptomatic PE at baseline
Patients are assigned to treatment groups as randomized
Source data: Appendix 16.2.6, Listing 1, 2 zctr\peall_hr.sas 30JUN2011