Boehringer Ingelheim

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.

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa®		**EudraCT No.:** 2005-002536-94	
Name of active ingredient: Dabigatran etexilate mesilate, BIBR 1048 MS		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:**	
Report date: 12 JUL 2011	**Trial No. / U No.:** 1160.47 / U10-2533-01	**Dates of trial:** 26 JUL 2006 – 08 OCT 2010	**Date of revision:** Not applicable

Title of trial:	A phase III, randomised, multicenter, double-blind, parallel-group, active controlled study to evaluate the efficacy and safety of oral dabigatran etexilate (150 mg bid) compared to warfarin (INR 2.0 to 3.0) for the secondary prevention of venous thromboembolism. RE-MEDY
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre study (264 centres, conducted in 33 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 (to obtain a target INR of 2.0 to 3.0) for the long-term treatment and secondary prevention of symptomatic venous thromboembolism (VTE) in patients treated with dabigatran etexilate or standard doses of anticoagulant for 3 to 12 months for confirmed acute symptomatic VTE
Methodology:	Randomised, double-blind, double-dummy, parallel-group, active-controlled trial with a planned duration of 6 to 36 months, comparing fixed-dose dabigatran etexilate (150 mg bid) with warfarin (target INR 2.0 to 3.0).
No. of patients:	
planned:	At least 2400 patients were to be entered to obtain a statistical power of 80% to show non-inferiority in terms of the hazard ratio and the risk difference (according to Protocol Amendment 6, dated 12 December 2008). As per original protocol, the planned total number of patients to be entered was at least 2000 to obtain a minimum of 36 events.
actual:	Enrolled: 2918, entered: 2866 Dabigatran etexilate : entered: 1435 patients; treated: 1430 patients; analysed (for primary endpoint): 1430 patients Warfarin: entered: 1431 patients; treated: 1426 patients; analysed (for primary endpoint): 1426 patients

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Diagnosis and main criteria for inclusion:	Adults (≥18 years) with acute symptomatic proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) as documented via objective testing (qualifying VTE event) who had received anticoagulant therapy for 3 to 12 months prior to screening, and who had provided written informed consent.
Test product:	Dabigatran etexilate
dose:	150 mg bid (dose calculated as free base)
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Warfarin sodium
dose:	1 mg, 3 mg, and 5 mg tablets to target an INR of 2.0 to 3.0
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Duration of treatment:	Six to 36 months, according to Protocol Amendment 6, dated 12 December 2008. Original protocol: 18 months. Protocol Amendment 6 extended the treatment duration of ongoing patients who consented to extend study participation to up to 36 months. As a result of this amendment, 3 cohorts of patients were included in the study: 1. Patients who had completed the trial prior to implementation of this amendment or those not willing to consent to participate as per this amendment; such patients had a planned treatment duration of 18 months. 2. Patients who had been randomised prior to implementation of this amendment and re-consented to trial participation as per this amendment; such patients had a planned treatment duration of between 18 and 36 months. The actual treatment period of such patients may have been shorter than 18 to 36 months in case of a primary outcome event or trial discontinuation due to adverse events or other reasons. 3. Patients randomised after implementation of this amendment but enrolled within 18 months of the planned study close-out. These patients had a planned treatment duration of 6 to <18 months.

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Primary efficacy endpoint:

Composite of recurrent symptomatic venous thromboembolism (VTE) and deaths related to VTE during the planned treatment period.

Secondary efficacy endpoints:

1. Composite of recurrent symptomatic VTE (fatal and non-fatal) and all deaths
2. Symptomatic DVT
3. Symptomatic PE (fatal or non-fatal)
4. Deaths related to VTE (i.e. fatal PE)
5. All deaths

All VTEs required objective verification through 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 all primary analyses.

Safety:

1. Incidence of bleeding events
   a. Major bleeding events (MBEs)
   b. MBEs and clinically relevant bleeding Events (CRBE)
   c. Any bleeding event (MBEs, CRBEs, and nuisance bleeds)
2. Adverse events (AEs)
3. Discontinuation of study treatment due to AEs
4. Laboratory measures, especially liver function tests (LFT)
5. Acute coronary syndrome (ACS)
6. ECG and vital signs

The focus of the safety analyses was on events that occurred during the treatment period including the 6 days following the last intake of study drug. All bleeding events and all suspected ACS events were centrally adjudicated, and all potentially liver-related safety issues were centrally reviewed by independent committees that were blinded with regard to the treatment allocation of patients.

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Statistical methods:

This study aimed to show via hierarchical testing: (1) non-inferiority and, if non-inferiority were demonstrated, (2) superiority of dabigatran etexilate vs. warfarin in the primary efficacy endpoint (i.e. recurrent symptomatic VTE and death related to VTE). The overall significance level was controlled by hierarchical ordering of the hypotheses.

Non-inferiority testing was performed with the non-inferiority margin simultaneously defined as 2.85 in hazard ratio (from a Cox model) and 2.8% in risk difference (from Kaplan-Meier estimates), comparing the treatments. The non-inferiority margins were chosen to preserve at least 70% of the warfarin effect versus placebo in the hazard ratio (based on the point estimate) and 2/3 in the risk difference (based on the lower bound of 95% confidence interval).

The planned sample size and treatment exposure for patients (at least 1200 patients per treatment group) was intended to have at least 80% power to claim non-inferiority with one-sided alpha=0.025 (as per Protocol Amendment 6, dated 12 December 2008). The calculation assumed that the observed pooled hazard rates in the strata at the time of the protocol-specified blinded sample size re-assessment were the true rates and stable throughout the trial for the primary endpoint, and that 20% of patients would discontinue from the trial within each 18-month period. According to the original protocol, the planned sample size was 1000 patients per group for a total of 36 expected events from combined groups, to have at least 85% of power to claim non-inferiority with one-sided alpha=0.025. This calculation assumed an equal hazard rate of 2.0% for both groups for the primary endpoint and a discontinuation rate of 20% over 18 months.

For the primary analysis, the overall hazard ratio (from a Cox model) and the risk difference (from KM estimates) were used with events censored at the planned treatment stop date for the hazard ratio and at the minimum of 18 months (540 days) and the planned treatment stop date for the KM estimates.

SUMMARY – CONCLUSIONS:

Efficacy results:

Of 2856 treated patients, 19.5% prematurely discontinued study medication (dabigatran etexilate group: 19.3%, warfarin group: 19.7%). Discontinuations of study medication due to AEs were reported for 10.3% of patients in the dabigatran etexilate group and 9.0% of patients in the warfarin group. More than half of the patients were classified into cohort 1 (55.0%), 25.6% were classified into Cohort 3, and 19.4% into Cohort 2.

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Efficacy results (continued):

Demographics and baseline characteristics of the treated patients were balanced across treatment arms for most parameters. The mean age was 54.6 years. More than half of all patients (61.0%) were male. Most patients (90.1%) were of white ethnicity. The majority of patients came from Europe (Eastern Europe: 34.1%, Western Europe: 27.5%), followed by patients from North America (11.9%).

The qualifying VTE event was symptomatic DVT alone for 65.1% of patients, symptomatic PE alone in 23.1% of patients, and both symptomatic PE and DVT in 11.7%. For 2 patients (0.1%), the qualifying event was not confirmed by objective clinical testing. Risk factors for recurrent VTE included one or more types of thrombophilia for 18.4% of patients; 7.0% of patients reported a recent immobilisation at baseline. Active cancer at baseline was present in 4.2% of patients. The most frequent baseline medical history was hypertension, documented for 38.6% of patients.

Regarding the use of selected medication of interest, the use of NSAIDs concomitantly with study drug was reported by 18.0% of patients; ASA was used by 6.7% of patients. The concomitant use of P-gp inhibitors or of P-gp inducers was uncommon. Restricted medications (including restricted anticoagulants) were used concomitantly with study drug by 15.2% of patients. Most frequently reported was the use of glycoprotein IIb/IIIa inhibitors (6.2% of patients), followed by LMWH (4.0%).

The percentage of patients who were non-compliant with dabigatran etexilate or its matching placebo was low (overall 1.9% of patients) Patients in the warfarin group had a mean number of 22.9 INR measurements during the trial. The mean time in therapeutic range (INR of 2.0 to 3.0) was 61.5% (median: 65.3%).

Primary endpoint

A primary endpoint event (VTE or VTE-related death) occurred in 26 patients in the dabigatran etexilate treatment group and in 18 patients in the warfarin group during the planned treatment period. The hazard ratio (HR) of dabigatran etexilate vs. warfarin was 1.44 (95% CI 0.78, 2.64, $p = 0.0137$ for non-inferiority). The cumulative risk for the primary endpoint at 18 months was 1.74% in the dabigatran etexilate group and 1.38% in the warfarin group. The risk difference (RD) was 0.38% (95% CI -0.50, 1.25, $p<0.0001$ for non-inferiority). Based on the pre-specified non-inferiority margins of 2.85 for the hazard ratio and of 2.8% for the risk difference, dabigatran etexilate was shown

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Efficacy results (continued):	to be non-inferior to warfarin. Superiority of dabigatran etexilate over warfarin could not be demonstrated. As expected, the risk for VTE recurrence was increased in the presence of the risk factors active cancer at baseline or initial symptomatic PE. Patients with neither of these risk factors had the lowest risk for VTE recurrence. A number of sensitivity analyses based on pooled cohorts were performed for the primary endpoint, including an on-treatment analysis (HR 1.35, 95% CI 0.69, 2.64), an analysis for the entire observation period (HR 1.24, 95% CI 0.71, 2.18), and a per-protocol analysis (HR 1.42, 95% CI 0.77, 2.60). The consistency of all of these analyses, with the upper bound of the confidence interval always below the prespecified non-inferiority margin (2.85), confirmed the robustness of the results for the primary endpoint. Subgroup analyses of the primary endpoint also showed results consistent with the primary analysis. *Secondary endpoints* The secondary efficacy endpoints comprised an additional composite endpoint (recurrent symptomatic VTE and all deaths; HR 1.18, 95% CI 0.75, 1.84) and separate analyses of the components of the composite endpoints: symptomatic DVT (HR 1.32, 95% CI 0.64, 2.71), symptomatic (fatal and non-fatal) PE (HR 2.04, 95% CI 0.70, 5.98), deaths related to VTE (i.e. fatal PE; HR 1.01, 95% CI 0.06, 16.22), and all deaths (HR 0.90, 95% CI 0.47, 1.72). There was no statistically significant difference between treatment groups for any of the secondary endpoints, as the CI of the HR always included 1.0.
Safety results:	*Observation time, exposure, and interruptions* Overall, the median of the observation time was just over 18 months in both treatment groups (dabigatran etexilate: 567 days, warfarin: 566 days). For Cohort 1, the median observation time was similar to that of the overall population, while it was longer in Cohort 2 at about 26 months, and shorter in Cohort 3 at about 11 months. The overall median planned treatment duration was about18 months and it was 18 months in Cohort 1 (540 days in both treatment groups). In Cohort 2, the median planned treatment period was 810 days (about 27 months) in both treatment groups. In Cohort 3, the median times were 314 days (dabigatran etexilate) and 352 days (warfarin).

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Safety results (continued):

The median of the exposure to study drug (with periods of temporary interruption of active study drug included) was 534 days in both treatment groups for the overall population. Values were 538 days in both treatment groups for Cohort 1, 731 days (dabigatran etexilate) vs. 735 days (warfarin) for Cohort 2, and 278 days (dabigatran etexilate) vs. 281 days (warfarin) in Cohort 3.

Interruptions of active study drug were less frequent in the dabigatran etexilate group (21.1% of patients) than in the warfarin group (26.5%). Among patients with at least 1 interruption, the median (cumulative) duration of interruptions was 7 days (dabigatran etexilate) vs. 6 days (warfarin).

Bleeding events

The primary analysis of bleeding events was done using adjudicated events. During the treatment period, MBEs were reported for 13 patients (0.9%), dabigatran etexilate, and 25 warfarin patients (1.8%, warfarin), with a HR of dabigatran etexilate /warfarin of 0.52 (95% CI 0.27, 1.02). The cumulative risk for MBEs at 18 months was statistically significantly lower in the dabigatran etexilate group (0.65%) than in the warfarin group (1.94%), with a risk difference of −1.29% (95% CI −2.20%, −0.38%). One fatal MBE occurred in a patient in the warfarin group. In the dabigatran etexilate group, there were 8 symptomatic bleeding events in a critical area or organ vs. 13 such events in the warfarin group. Gastrointestinal bleeding was the most frequent location of major bleeds in both treatment arms (dabigatran etexilate: 5 events, warfarin: 8 events). Two intracranial haemorrhages were reported in the dabigatran etexilate group and 4 in the warfarin group. No clear-cut rise in the frequency of MBEs in the dabigatran etexilate group with increasing age was observed. Furthermore, there was no relevant treatment-by-subgroup interaction for creatinine clearance, which is a measure of renal function.

The incidence of any bleeding event was significantly lower in the dabigatran etexilate group (19.4%) than in the warfarin group (26.2%), with a HR of dabigatran etexilate vs. warfarin of 0.71 (95% CI 0.61, 0.83). The 2 most frequently reported bleedings by location were urogenital (dabigatran etexilate: 83 events, warfarin: 114 events) and nasal bleeds (64 vs. 146 events). Bleeding rates, locations, and treatment group differences were generally consistent across the evaluated subgroups.

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Safety results (continued):

Adverse events

The incidence of treatment-emergent AEs was similar in both treatment groups (dabigatran etexilate: 72.0%, warfarin: 70.8%). On the preferred term (PT) level, the 3 most frequently reported AEs were nasopharyngitis (7.8% vs. 8.9%), pain in an extremity (7.8% in both treatment groups), and headache (6.0% vs. 7.1%).

AEs considered drug-related by the investigators were less frequent in the dabigatran etexilate group (16.0%) than in the warfarin group (19.6%).The frequencies of patients who discontinued study drug due to AEs with onset during the treatment period were 10.1% in the dabigatran etexilate group and 8.8% in the warfarin group. Adverse events (preferred term) leading to discontinuation with a frequency of at least 0.5% in either treatment group were DVT (dabigatran etexilate: 0.8%, warfarin: 1.1%) and haematuria (0.5% in each group). The frequency of patients who discontinued study drug due to AEs (including AEs during screening) was not significantly different between the dabigatran etexilate group (147 patients, 10.3%) and the warfarin group (129 patients, 9.0%), with a HR of dabigatran etexilate/warfarin of 1.16 (95% CI 0.91, 1.47).

Forty-four patients were known to have died during the conduct of this trial. Of these, 12 patients (0.8%, dabigatran etexilate) and 18 patients (1.3%, warfarin) had AEs with an onset during the treatment period that had fatal outcomes, while 5 patients (0.4%, dabigatran etexilate) and 4 patients (0.3%, warfarin) had AEs with an onset during the post-treatment period that had fatal outcomes. One patient in the dabigatran etexilate group and 4 patients in the warfarin group had AEs starting during the post-study period that had fatal outcomes. One patient died due to an AE that the investigator assessed as drug-related (warfarin group). The patient died of a cerebral haemorrhage assigned to the treatment period.

During the treatment period, the incidences of serious adverse events (SAEs, including fatal events) were 15.9% (dabigatran etexilate) and 15.7% (warfarin). Immediately life-threatening SAEs were reported for 9 dabigatran etexilate (0.6%) and 6 warfarin (0.4%) patients. SAEs causing disability and/or incapacity occurred in 6 dabigatran etexilate (0.4%) and 5 warfarin patients (0.4%). Serious adverse events (PT level) with an incidence of at least 0.5% in either treatment group were DVT (0.7% vs. 0.4%), PE (0.6% vs. 0.2%), chest pain (0.3% vs. 0.6%), abdominal pain (0.3% vs. 0.6%), and prostate cancer (0.3% vs. 0.5%).

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Safety results (continued):	Centrally adjudicated, confirmed ACS events during the treatment period including the 6-day washout occurred in 0.9 vs. 0.2% of the dabigatran etexilate and warfarin treatment patients, respectively. *Clinical laboratory and vital signs* The analysis of mean changes from baseline to the last value on treatment and of transitions relative to the reference ranges did not reveal any meaningful differences between the treatment groups. There was no evidence of a Hy's law case in this study. For vital signs, no relevant differences between treatment groups were noted.
Conclusions:	This trial demonstrated that dabigatran etexilate was non-inferior to well controlled warfarin for the long-term treatment and secondary prevention of symptomatic VTE following initial anticoagulant treatment for 3 to 12 months after an index VTE event. No statistically significant between-treatment differences were found for the primary or any of the secondary endpoints. Dabigatran etexilate and warfarin appeared to be safe and well tolerated in this trial. While there were fewer MBEs and any bleeding events in the dabigatran etexilate group than the warfarin group, more ACS events were reported for dabigatran etexilate than for warfarin.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended table provides complete disposition results.

Results for	presented in
Patient disposition	Table 15.1.1: 1

Table 15.1.1: 1 Disposition of patients at the end of treatment
(all patients, as randomized)

	Dabigatran N(%)	Warfarin N(%)	Total N(%)
Enrolled (screened)			2918
Not entered/randomized			52
Entered/randomized	1435	1431	2866
Not treated	5	5	10
Treated	1430(100.0)	1426(100.0)	2856(100.0)
Not prematurely discontinued from trial medication	1154(80.7)	1145(80.3)	2299(80.5)
Prematurely discontinued from trial medication	276(19.3)	281(19.7)	557(19.5)
Adverse event	147(10.3)	129(9.0)	276(9.7)
AE:Worsening of disease under study*	19(1.3)	19(1.3)	38(1.3)
AE:Worsening of other pre-existing disease	18(1.3)	21(1.5)	39(1.4)
AE other (including bleeding)	110(7.7)	89(6.2)	199(7.0)
Bleeding**	20(1.4)	34(2.4)	54(1.9)
Other than bleeding events***	90(6.3)	55(3.9)	145(5.1)
Non compliant with protocol	23(1.6)	34(2.4)	57(2.0)
Lost to follow up	2(0.1)	6(0.4)	8(0.3)
Patient refused to continue study medication#	64(4.5)	58(4.1)	122(4.3)
Other	40(2.8)	54(3.8)	94(3.3)

Patients are allocated to treatment as randomized, and all information in table is based on investigator assessments in eCRF pages.
*: i.e. symptomatic DVT or PE based on investigator´s assessment
**: Bleeding includes patients who discontinued due to any bleeding event that did or didn't clinically require cessation of study drug
***:This line only counts patients who discontinued due to other AE but who did not discontinue due to a bleeding.
#: Patient could decide whether to continue trial without taking study drug or to withdraw from study permanently.
One patient ([redacted]) did not have the informed consent, and was not counted in this table.
Source data: Appendix 16.2, Listing 1.1 eot20_disp.sas 17JUN2011