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.

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®		**EudraCT No.:** 2005-001999-12	
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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 (5-10 days) with a parenteral anticoagulant approved for this indication. RE-COVER
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre study (231 enrolling centres, including 228 randomising centres) conducted in 29 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 2.0-3.0) for 6 month treatment of acute symptomatic venous thromboembolism (VTE) following initial treatment (5−10 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 2.0-3.0)

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No. of subjects:	
planned:	entered: at least 2550 patients to obtain a minimum of 46 VTEs
actual:	enrolled: 2630 entered: 2564 Dabigatran etexilate: entered: 1280 patients; treated: 1273 patients; analysed (for primary endpoint): 1274 patients Warfarin: entered: 1284 patients; treated: 1266 patients; analysed (for primary endpoint): 1265 patients The analysis of the primary endpoint was based on the full analysis set (FAS), with allocation of patients to treatment groups as randomised. The discrepancy in the numbers of patients treated and analysed for the primary endpoint is due to 1 patient who started the study with a different treatment (warfarin) than he had been randomised to (dabigatran).
Diagnosis and main criteria for inclusion:	Adult 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
dose:	150 mg bid (dose calculated as free base)
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Warfarin
dose:	As needed to maintain an International Normalised Ratio (INR) of 2.0-3.0
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6

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Duration of treatment:	6 months
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary efficacy endpoint: 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). Secondary efficacy endpoints (within 6 months): 1. Composite of recurrent symptomatic VTE and all deaths 2. Symptomatic DVT 3. Symptomatic PE 4. Deaths related to VTE 5. All deaths All recurrent VTEs 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: 1. Incidence of bleeding events - Major Bleeding Events (MBEs) - MBEs and Clinically Relevant Bleeding Events (CRBEs) - any bleeding events (MBEs, CRBEs, and nuisance bleeding events) 2. Adverse Events (AEs; including findings in the physical examination) 3. Discontinuation of study treatment due to AEs 4. Laboratory measures, especially Liver Function Tests (LFTs) 5. Acute Coronary Syndrome (ACS) 6. ECG and vital signs All bleeding events and all suspected ACS 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 trial aimed to demonstrate (1) non-inferiority of dabigatran vs. warfarin and, if non-inferiority was confirmed, (2) superiority of dabigatran over warfarin for the primary endpoint (i.e. the composite of recurrent symptomatic VTE and deaths related to VTE within 6 months) in patients with acute symptomatic VTE. The overall significance level was controlled by a priori ordering of hypotheses.

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 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.

Hazard ratios were calculated based on the times to first occurrence of the components of the composite primary endpoint using a proportional hazards model (Cox regression). Risk differences were calculated using stratified Kaplan-Meier estimates of the cumulative risk at Day 180 after randomisation.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Of 2539 treated patients, 15.2% prematurely discontinued trial medication (dabigatran: 16.0%, warfarin: 14.5%). Discontinuations of trial medication due to AEs were reported for 9.9% of patients in the dabigatran group and 8.1% of patients in the warfarin group.

Demographics and baseline characteristics of the treated patients were balanced across treatment arms. The mean age was 54.7 years; 58.4% of patients were male. Most patients (94.8%) were of white ethnicity (Black ethnicity: 2.6%, Asian: 2.6%). The majority of patients came from Europe (Western Europe: 31.2%, Central Europe: 29.9%) and North America (17.4%).

The index event was symptomatic DVT alone in 68.9% of patients, symptomatic PE alone in 21.3%, and both symptomatic PE and DVT in 9.6%. Thus, 31.0% of patients had symptomatic PE with or without DVT at presentation. 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, 61.8% of patients had symptomatic or

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Efficacy / clinical pharmacology results: (continued)

asymptomatic PE (with or without DVT), and 88.3% of patients had symptomatic or asymptomatic DVT (with or without PE at baseline). In addition, 4 patients (0.2%) had locally confirmed VTE as index event that was eventually not confirmed by the independent central adjudication committee.

The most frequent risk factors were VTE prior to the index event (25.6% overall), a history of venous insufficiency (19.4%), surgery / trauma (19.1%), prolonged immobilisation (15.6%), and recent systemic use of oestrogens (10.8%). Active cancer at any time was present in 6.9% of patients (active cancer at baseline: 4.8%, active cancer diagnosed during the study: 2.2%).

The use of NSAIDs concomitantly with active study drug (warfarin / dabigatran) was reported by 15.3% of patients in the dabigatran arm and 18.8% of patients in the warfarin arm; ASA was used by 7.5% vs. 7.7% of patients. The use of P-gp inhibitors or inducers was uncommon. The use of at least one type of restricted medications (including restricted anticoagulants) during the treatment with active study medication was reported in 8.3% of all patients (dabigatran: 6.7%, warfarin: 10.0%), mostly LMWHs (1.3% vs. 2.4%) and NSAIDs with a half-life of >12 hours (1.2% vs. 2.2%). All but 2 patients were treated for the index event with parenteral therapy.

The percentage of non-compliant patients (assessing either dabigatran or its matching placebo) was low (dabigatran: 2.0%, warfarin: 2.5%). Patients in the warfarin arm had a mean number of 15.9 INR measurements during the trial. The number of INR measurements per patient was highest in the first month after randomisation (mean: 8.2) and decreased thereafter. The mean percentage of time in the INR target range (2−3) overall was 59.9% (median: 63.0%).

Primary endpoint

All efficacy analyses were based on the full analysis set (FAS), comprising 2539 patients (dabigatran: 1274, warfarin: 1265). The primary endpoint occurred in 34 patients in the dabigatran group and in 32 patients in the warfarin group; the hazard ratio was 1.05 (95% CI 0.65, 1.70, p-value for non-inferiority <0.0001). The cumulative risk for the primary endpoint at Day 180 was 2.4% in the dabigatran arm and 2.2% in the warfarin arm. The risk difference was 0.4% (95% CI −0.8%, 1.5%, p-value for non-inferiority <0.0001). Based on the pre-defined non-inferiority margins for hazard ratio (2.75) and risk difference

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(3.6%), dabigatran was demonstrated to be non-inferior to warfarin for the primary endpoint. Superiority of dabigatran over warfarin could not be demonstrated. As expected, the risk for the primary endpoint was associated with the presence of the risk factors 'active cancer at baseline' and 'initial symptomatic PE'.

A number of pre-defined and post-hoc 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 1.15, 95% CI 0.67, 1.97), a per-protocol analysis (HR 1.03, 95% CI 0.63, 1.69), and an analysis considering unexplained death as VTE-related (HR 1.11; 95% CI 0.69, 1.78).

The treatment effect of dabigatran was generally consistent across patient subpopulations. Possible subgroup-by-treatment interactions (indicated by p-values of <0.1) for the primary endpoint were identified for previous VTE ($p = 0.07$), more than 1 parenteral therapy for the index VTE ($p = 0.04$), and concomitant use of NSAIDs ($p = 0.03$). In patients with concomitant intake of NSAIDs, the risk for the primary endpoint was higher in the dabigatran group than in the warfarin group (HR 4.93, 95% CI 1.05, 23.23). For patients without concomitant intake of NSAIDs, the HR for the primary endpoint was 0.82 (95% CI 0.48, 1.38). For all other subgroups, the confidence intervals for the treatment comparisons within subgroup categories included 1. Due to the large number of comparisons, these observations may have occurred by chance.

Secondary endpoints

There were numerically fewer DVTs and fewer fatal PEs, but more symptomatic PEs in the dabigatran group than in the warfarin group. 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 0.76, 95% CI 0.40, 1.42), fatal PE (HR 0.33, 95% CI 0.03, 3.15), recurrent symptomatic VTE and all death (HR 1.00, 95% CI 0.69, 1.46), symptomatic non-fatal PE (HR 2.0, 95% CI 0.86, 4.68), and all death (HR 0.94, 95% CI 0.54, 1.63). The hazard ratio for the composite of symptomatic, non-fatal PE and fatal PE was 1.54 (95% CI 0.72, 3.30). Sensitivity analyses of the composite of recurrent symptomatic VTE and all deaths, VTE-related deaths, and all deaths up to the last contact date

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Efficacy / clinical pharmacology results: (continued)	likewise showed no statistically significant treatment difference. *PK and PD assessments* The gMean trough plasma concentration of total dabigatran for patients in the dabigatran group at Visit 4 (n=850) was 59.7 ng/mL (Visit 9: 59.5 ng/mL, 746 patients). Increased trough plasma concentrations of total dabigatran were found in elderly patients and patients with renal impairment. The concomitant use of P-gp inhibitors was associated with an increased trough dabigatran concentration. There seemed to be an association between the occurrence of bleeding events and increased trough dabigatran concentrations. Patients with MBEs (80.1 ng/mL) and with MBEs or CRBEs (73.0 ng/mL) tended to have higher dabigatran trough concentrations than patients without bleeding events (58.5 ng/mL). The logistic regression curves indicated that the rate of MBEs and any bleeds increased with the concentration of total dabigatran, while the rate of VTE events seemed to decrease with the concentration of total dabigatran. The dabigatran concentration (based on unscheduled, event-triggered blood samples) was lower in patients with symptomatic DVT and symptomatic PE and higher in patients with MBE. The results for aPTT and ECT showed the expected dabigatran effect on these coagulation markers. Differences in the coagulation parameters (aPTT, ECT) among patient subgroups generally reflected the differences that were seen in the trough concentration of total dabigatran among patient subgroups.
Safety results:	*Observation time, exposure, and interruptions* Patients were observed for a median of 193 days (dabigatran) and 191 days (warfarin). The median exposure to any study drug, i.e. dabigatran or warfarin including their matching placebos, was identical in both treatment groups (181 days); the median exposure to active study drug (i.e. dabigatran or warfarin) was 174 days (dabigatran) and 180 days (warfarin). Interruptions of any study drug were documented in 11.2% (dabigatran) and 13.7% (warfarin) of patients. Patients were exposed for a median of 9 days to initial parenteral therapy. *Bleeding events* The incidence of MBEs (based on any study drug and censored washout) was

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Safety results: (continued)

1.6% (dabigatran) and 1.9% (warfarin), with a HR of 0.82 (95% CI 0.45, 1.48). MBEs were adjudicated as fatal in 1 patient per treatment group (1 additional warfarin patient died of an MBE not adjudicated as fatal). In the dabigatran group, 1 symptomatic bleeding into a critical area or organ occurred, while there were 9 such events in the warfarin group. The number of intracranial haemorrhages was 0 vs. 3. Gastrointestinal bleeds were the most frequent MBEs (9 vs. 5 events).

The incidences of any bleeding events were 16.3% (dabigatran) and 22.1% (warfarin). The HR was 0.71 (95% CI 0.59, 0.85), indicating a statistically significant treatment difference. The most frequently reported bleeding locations were urogenital (53 vs. 95 events), nasal (40 vs. 107 events), and gastrointestinal bleeds (53 vs. 35 events). In general, results of the subgroup analyses for any bleeding events were consistent across various patient subgroups. There were 3 subgroups with a treatment-by-subgroup interaction p-value below 0.1. These were the subgroups according to presence or absence of prolonged immobilisation (p=0.03), presence or absence of surgery and/or trauma (p=0.03), and intake vs. no intake of P-gp inhibitors (p=0.07). In brief, patients with the additional risk factor (prolonged immobilisation or surgery/trauma) had a similar bleeding risk in both treatment groups; there tended to be a lower bleeding risk in the dabigatran group (compared with the warfarin group) for patients without the additional risk factor.

For the analysis of bleeding events based on active study drug intake and a censored washout (if an open-label anticoagulant was started), incidences of MBEs were 1.4% (dabigatran) and 1.9% (warfarin); the HR was 0.70 (95% CI 0.38, 1.31). Incidences of any bleeding events were 14.7% (dabigatran) and 22.0% (warfarin); the HR was 0.62 (95% CI 0.51, 0.75).

Adverse events

Based on the intake of any study drug and a censored washout, the incidence of treatment-emergent AEs was 66.3% (dabigatran) and 67.6% (warfarin). There were 3 PTs with an incidence of at least 5% in either treatment group: headache (6.2% vs. 7.0%), pain in extremity (5.0% vs. 5.6%), and epistaxis (2.8% vs. 6.3%). AEs assessed as drug-related by the investigator were reported for 15.3% and 18.1% of patients. The proportions of patients who discontinued study drug due to AEs were 9.0% and 6.8%. PE (1.2% vs. 0.6%) and DVT (1.3% vs. 1.1%)

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Safety results: (continued)

most frequently led to discontinuation of study drug.

During the treatment period, SAEs (including fatal events) were reported for 13.0% of patients in the dabigatran group and 11.8% in the warfarin group. Immediately life-threatening SAEs were reported for 0.9% (dabigatran) and 0.5% (warfarin) of patients. SAEs that caused disability and/or incapacity occurred in 0.6% (dabigatran) and 0.2% (warfarin) of patients. The most frequently reported SAEs on PT level were PE (1.1% vs. 0.6%), DVT (0.8% vs. 0.7%), dyspnoea (0.4% vs. 0.8%), pneumonia (0.4% vs. 0.6%), and haematuria (0.3% vs. 0.7%).

During the conduct of this trial, 56 patients were known to have died at any time post randomisation. Of these, 27 had been randomised to dabigatran (2.1% of treated patients in this group) and 29 to warfarin (2.3%). Of the 27 patients randomised to dabigatran, 25 had fatal outcomes associated with AEs during or following the intake of active study drug: 14 during active treatment (including the day after last intake of active study drug) and 11 in the period after active treatment was stopped. Of the 29 patients randomised to warfarin, 19 patients had fatal outcomes associated with AEs that started during active treatment (including the day after last intake) and 10 patients in the period after active treatment was stopped. Three deaths were due to AEs considered to be drug-related (1 vs. 2); these 3 patients died of bleeding events.

The analysis of the time to AEs leading to discontinuation of any study drug (based on any study drug and uncensored washout) had a HR of 1.24 (95% CI 0.95, 1.61); incidences were 9.7% vs. 7.9%.

The analysis of AEs based on active study drug and censored washout yielded consistent results with those from the any study drug analysis. AE incidences were 62.8% (dabigatran) and 67.5% (warfarin). The 3 most frequently reported AEs were the same as for the any study drug analysis, and also incidences were identical.

Acute coronary syndrome events

A total of 14 ACS events (12 MIs, 2 ischaemia / unstable angina events) that were adjudicated as definite ACS occurred after first administration of active study drug, i.e. during or after the period of active study drug intake (dabigatran: 9 patients, warfarin: 5 patients). Five (dabigatran) and 3 patients (warfarin)

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Safety results: (continued)	reported the event during treatment with active study drug (including the day after last intake of active study drug); 4 (dabigatran) and 2 patients (warfarin) had a definite ACS event after stopping active study drug. For the 4 dabigatran patients, the time from last intake of dabigatran to onset of the ACS was 4 days, 14 days, 24 days and 31 days, respectively. The 2 warfarin patients had the ACS 15 and 16 days after last intake of warfarin, respectively. Of the 14 patients with definite ACS, 1 patient (warfarin) died from the definite ACS event (adjudicated as both MI and cardiac death); onset of the event was 15 days after the last warfarin dose. *Clinical laboratory and vital signs* The analyses 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. Decreases with possible clinical significance were most frequently reported for haematocrit (3.5% vs. 3.8% of patients) and haemoglobin (3.5% vs. 4.1%). For all 4 LFTs, numerically higher frequencies of PCSAs were noted in the warfarin group than in the dabigatran group. During treatment with active study drug (including the 6-day washout period), 6 patients (2 vs. 4) developed ALT values of >3 x ULN followed by elevations of total bilirubin of >2 x ULN within 30 days (potential Hy's law cases). In all 6 cases, the LFT elevations could be explained by biliary obstruction or other AEs. 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 following initial treatment with an approved parenteral anticoagulant therapy. No statistically significant treatment differences were seen for the primary nor the pre-specified secondary endpoints including MBE. The rate of any bleeding events was significantly lower for the dabigatran treatment regimen than for the warfarin regimen, and there were no intracranial haemorrhages on dabigatran compared to 3 on warfarin. Although numerically more discontinuations of study drug due to AEs were noted for the dabigatran regimen, dabigatran etexilate was well tolerated.

Trial Synopsis - Appendix

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

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Number of VTE and deaths until 224 days after randomization	Table 15.2.2.6: 1

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

	Dabigatran N (%)	Warfarin N (%)	Total N (%)
Enrolled			2630
Not entered/randomised			66
Entered/randomised	1280	1284	2564
Not treated	7	18	25
Treated	1273 (100.0)	1266 (100.0)	2539 (100.0)
Not prematurely discontinued from trial medication	1069 (84.0)	1083 (85.5)	2152 (84.8)
Prematurely discontinued from trial medication	204 (16.0)	183 (14.5)	387 (15.2)
AE:worsening of disease under study*	35 (2.7)	25 (2.0)	60 (2.4)
AE:worsening of other pre-existing diseases	15 (1.2)	12 (0.9)	27 (1.1)
AE:other (including bleeding)	76 (6.0)	65 (5.1)	141 (5.6)
Bleeding events^	14 (1.1)	22 (1.7)	36 (1.4)
Other than bleeding events$	62 (4.9)	43 (3.4)	105 (4.1)
Non compliant with protocol	21 (1.6)	35 (2.8)	56 (2.2)
Lost to follow-up	9 (0.7)	6 (0.5)	15 (0.6)
Patient refused to continue medication µ	39 (3.1)	36 (2.8)	75 (3.0)
Other	9 (0.7)	4 (0.3)	13 (0.5)

* : 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 discontinued 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 group as treated.

Table 15.2.2.6: 1 Overview of centrally adjudicated recurrent VTE and all deaths until 224 days after randomization - FAS

Number of VTE until the end of post treatment period and deaths up to 224 days

	Dabigatran	Warfarin
Treated	1274	1265
VTE and all deaths	58	56
All deaths	25	25
- Fatal PE	1	3
- Bleeding	1	2
- Acute Myocardial Infarction	1	0
- Cancer	9	10
- Unexplained	5	1
- Other	8	9
Symptomatic PE	16	8
Symptomatic DVT	17	23

Fatal PE are not counted as symptomatic PE if occured on the same day
This analysis includes events which occurred from randomization up to end of post treatment period for VTE
and deaths until 224 days (included) after randomization
Patients are assigned to treatment groups as randomized

Source data: Appendix 16.2, Listing 6.1 eot\vtedea_224_over.sas 03SEP2009