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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2005-003894-26	
Name of active ingredient: Dabigatran etexilate, BIBR 1048		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 16 Oct 2009	**Trial No. / U No.:** 1160.26 / U09-3249-02	**Date of trial:** 20 DEC 2005 – 15 MAR 2009	**Date of revision:** 05 Jan 2011

Title of trial:	Randomized Evaluation of Long term anticoagulant therapY (RE-LY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® study)
Coordinating Investigators:	[redacted]
Trial sites:	Multicentre study; cf. Appendix 16.1.4
Publication (reference):	P09-05487 Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157(5):805-810. P09-11055 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. Epub 2009 Aug 30. P10-10125 Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010;18;376(9745):975-83. P10-10136 Lane DA, Lip GY. Quality of anticoagulation control in atrial fibrillation. Lancet. 2010;376(9745):935-7.
Clinical phase:	III
Objectives:	The primary objective of this trial was to demonstrate the efficacy and safety of dabigatran etexilate in subjects with non-valvular atrial fibrillation and at least one additional risk factor for stroke for the prevention of stroke and systemic embolism.
Methodology:	Prospective, randomized, open label, blinded endpoint evaluation (PROBE), controlled, parallel group, non-inferiority trial.

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No. of subjects:	
planned:	enrolled (screened): 20,377; entered (randomized): 18,113
actual:	Treatment: Dabigatran etexilate 110 mg twice daily entered: 6015, treated: 5983 Treatment: Dabigatran etexilate 150 mg twice daily entered: 6076, treated: 6059 Treatment: Warfarin sodium, adjusted dose entered: 6022, treated: 5998
Diagnosis and main criteria for inclusion:	Subjects ≥18 years of age with non-valvular atrial fibrillation (AF) with at least one additional risk factor for stroke (i.e., previous ischemic stroke, transient ischemic attack [TIA], or systemic embolism; left ventricular dysfunction; age ≥75 years (or age ≥65 if subject has one of diabetes mellitus, history of coronary artery disease [CAD], or hypertension).
Test product:	Dabigatran etexilate, BIBR 1048
dose:	1. One capsule each 110 mg twice daily (total daily dose 220 mg) 2. One capsule each 150 mg twice daily (total daily dose 300 mg)
mode of admin.:	Oral
batch no.:	cf. Appendix 16.1.6
Reference therapy:	Warfarin sodium tablet BP
dose:	Adjusted dose (1, 3, and 5 mg tablets); target International Normalized Ratio (INR) range 2.0 to 3.0. Warfarin potassium (1 mg strength) was required for use in Japan.
mode of admin.:	Oral

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batch no.:	cf. Appendix 16.1.6 Warfarin sodium salt supplied by IVAX used in 43 countries. Warfarin potassium salt used in Japan; manufactured by Nissin Seiyaku Co., Ltd.
Duration of treatment:	Maximum 36 months
Criteria for evaluation: **Efficacy / clinical pharmacology:**	Primary efficacy endpoint: • incidence of stroke (including hemorrhagic) and systemic embolism Secondary efficacy endpoints are composites of: • incidence of stroke (including hemorrhagic), systemic embolism, all death • incidence of stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction (MI), or vascular deaths (includes deaths from bleeding) Other efficacy endpoints: • individual occurrence or composites of any ischemic stroke (fatal and non-fatal), systemic embolism, pulmonary embolism, acute MI, TIAs, vascular death (includes deaths from bleeding), all deaths, and hospitalizations • Net Clinical Benefit (NCB) as measured by the composite of the clinical endpoint of stroke, systemic embolism, pulmonary embolism, acute MI, all cause deaths, and major bleeds
Safety:	Safety endpoints: • bleeding events (major and minor), intracerebral hemorrhage, other intracranial hemorrhage (ICH), hepatobiliary events including clinically relevant changes in liver function tests (LFTs) and hepatic dysfunction, and other adverse events (AEs)
Statistical methods:	Proportional hazards model, descriptive statistics

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SUMMARY – CONCLUSIONS: The initial FDA review of the RE-LY trial detected some inconsistencies in the INR and transfusion data. To ensure data integrity, measures to evaluate data quality and to detect possible unreported outcome events were implemented. Based on data analyses incorporating all newly reported events and the impact of the data plausibility checks, the primary and secondary efficacy and safety conclusions of RE-LY remain unchanged from those of the original analysis. The re-analysis confirmed the robustness and reliability of the conclusions from RE-LY. The results and conclusions from the re-analyses are summarized below.

Efficacy / clinical pharmacology results: Overall, this study demonstrated that both doses of dabigatran were non-inferior to warfarin ($p<0.0001$) and DE 150 was superior to warfarin ($p=0.0001$) for the primary efficacy endpoint (stroke/SEE). The yearly stroke/SEE rates (i.e., yearly event rate for number of subjects with event) were 1.54%, 1.11% and 1.71% for the DE 110, DE 150 and warfarin groups, respectively. The relative risk reductions for stroke/SEE by DE 110 and DE 150 were 9% and 34%, respectively.

Results for the secondary endpoints were consistent with the pattern observed for the primary endpoint; DE 110 was similar to warfarin, while DE 150 was superior. The yearly event rate for the composite endpoint stroke/SEE/death was 4.85%, 4.32% and 5.20% in the DE 110, DE 150 and warfarin groups, respectively. The risk reduction by DE 110 for stroke/SEE/death was 7% in comparison to warfarin, which was not statistically significant, while the relative risk reduction by DE 150 was 17%, which was significantly less than warfarin ($p=0.0015$).

For the composite of ischemic stroke, SEE, PE, MI (including silent MIs), TIA hospitalization and all cause death, the risk reductions were 8% and 3%, for DE 110 and DE 150, respectively, with corresponding p-values of 0.002 and 0.3. When risk and benefit were considered (NCB endpoint) DE 110 was similar to warfarin and DE 150 was superior. Yearly event rates were 7.34%, 7.11% and 7.91% for the DE 110, DE 150 and warfarin groups. Risk reduction by DE 110 and DE 150 were 8% and 10%, respectively, with corresponding p values of 0.1 and 0.03.

DE 110 and DE 150 reduced the risk of all cause death by 9% and 12%, respectively, compared to warfarin (p values of 0.1308 and 0.0517, respectively). More than 60% of all deaths were attributed to vascular death. Vascular death was also reduced by 10% ($p=0.2081$) and 15% ($p=0.0430$) for DE 110 and DE 150, respectively, compared to warfarin.

DE 150 had a lower ischemic stroke rate than warfarin (0.86% vs. 1.14%, respectively).

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DE 150 was superior to warfarin for ischemic stroke (p=0.0296), while DE 110 was slightly less effective but not statistically different from warfarin (p=0.3139).

Both doses of dabigatran significantly reduced the occurrence of hemorrhagic stroke compared to warfarin (p≤0.0001). Event rates were 0.12% and 0.10% for the DE 110 and DE 150 groups compared to 0.38% for warfarin.

There was a higher frequency of MIs reported in the dabigatran groups compared to warfarin. The yearly event rate for clinical symptomatic MI was 0.73%, 0.74% and 0.56% for DE 110, DE 150 and warfarin, respectively. The yearly event rate for silent MI was 0.09%, 0.07% and 0.08% for DE 110, DE 150 and warfarin, respectively. Risk ratios vs. warfarin for MI (combined symptomatic+silent MIs) were 1.29 for DE 110 and 1.27 for DE 150 with corresponding p-values of 0.09 and 0.1240. Most of the differences between treatments were due to events that occurred off study drug.

The efficacy of dabigatran was consistent for all subgroups evaluated.

Clinical Pharmacology

Trough and post dose plasma concentrations of total dabigatran after oral administration of dabigatran etexilate at steady state were dose proportional between the 110 mg and 150 mg doses with high inter-individual variability (74-82%).

Based on univariate analysis, plasma concentration increased with increasing age, decreasing body weight, and decreasing creatinine clearance. Plasma concentrations were also higher in females with no effect of ethnic origin.

Increased dabigatran concentrations were associated with increases in major bleeds, any bleeding and bleeding leading to discontinuation. Associations of dabigatran plasma concentrations and ischemic stroke were small and not meaningful. There was an association of hemorrhagic stroke and dabigatran plasma concentrations. However, the number of events was small.

Subjects with major bleeding events had longer aPTT times compared to those without bleeding events. No clear association between aPTT times and bleeding was observed.

Safety results: Bleeding events included major bleeds, hemorrhagic strokes, intracranial hemorrhages, and minor bleeding. Both doses of dabigatran resulted in a significantly lower incidence of total (any) bleeding, life-threatening bleeding, hemorrhagic stroke, and subdural and/or ICH compared to warfarin.

Dabigatran treatment resulted in lower rates of major bleeding events compared with

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warfarin treatment (yearly rate: 2.87%, 3.32%, and 3.57% for DE 110, DE 150 and warfarin, respectively), reducing the risk of major bleeds compared with warfarin (20% for DE 110, p=0.0026; 7% for DE 150, p=0.3146).

Compared with warfarin treatment, DE 110 and DE 150 treatment resulted in a significantly lower risk of intracranial hemorrhage (ICH) (hazard ratios 0.30 and 0.41, p<0.0001 for both comparisons).

Compared with warfarin treatment, DE 110 and DE 150 treatment resulted in a significantly lower risk of life-threatening bleeds (hazard ratios 0.67 and 0.80 for DE 110 and DE 150 versus warfarin, p=0.0001 and p=0.0305, respectively)

The lower dose of dabigatran resulted in significantly lower rates of major bleeds compared to the high dose (2.87% for DE 110; 3.32% for DE 150, hazard ratio 0.86, p=0.0429). There was no significant difference between dabigatran doses in the risk of hemorrhagic stroke, life-threatening bleeds, or ICH.

DE 150 subjects ≥75 years of age had a slightly higher rate of major bleeds compared with warfarin. For subjects <75 years of age, DE 110 and DE 150 had a lower rate of major bleeds compared with warfarin.

Dabigatran treatment resulted in a higher incidence of major gastrointestinal bleeds (1.14% DE 110, 1.57% DE 150; 1.07% warfarin) and any gastrointestinal bleeds (5.41% DE 110, 6.13% DE150 and 4.02% warfarin) compared with warfarin, especially in subjects ≥75 years of age (1.85% and 6.42% DE 110, 2.43% and 7.32 DE 150; and 1.38% and 4.26% warfarin, respectively).

Subjects treated with dabigatran had a slightly higher incidence of AEs compared with warfarin (78.6%, 78.3%, and 75.9% for DE 110, DE 150 and warfarin, respectively). GI adverse events were reported more frequently on dabigatran with no consistent dose-response relationship.

SAEs were generally similar for dabigatran and warfarin subjects and were consistent with an elderly population with AF receiving anticoagulant therapy (21.2%, 21.3%, and 22.6% for DE 110, DE 150, and warfarin, respectively).

Dyspepsia, diarrhea, and nausea were the most frequently reported GI AEs in dabigatran subjects; dyspepsia was reported more frequently for dabigatran compared with warfarin (6.2%, 5.7%, and 1.4% for DE 110, DE 150, and warfarin, respectively). The risk for

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	dyspepsia with dabigatran treatment occurred in the first few weeks of treatment and remained approximately twice that of warfarin. However, SAEs or discontinuations due to dyspepsia were infrequent. The risk for LFT elevations was greater for warfarin compared with dabigatran for minor elevations (ALT/AST 1 to 3xULN) up to the most severe (ALT/AST elevations up to 10xULN or ALT/AST >3xULN associated with total bilirubin >2xULN)
Conclusions:	Based on data analyses incorporating all newly reported events and the impact of the data plausibility checks, the primary and secondary efficacy and safety conclusions of RE-LY remain unchanged. The re-analysis confirmed the robustness and reliability of the conclusions from RE-LY. The RE-LY study results demonstrate that dabigatran etexilate, 110 mg twice daily, is non-inferior to warfarin in the prevention of stroke and systemic embolism in subjects with non-valvular AF and at least one risk factor for stroke. The dose of 150 mg twice daily is superior to warfarin in the prevention of stroke and systemic embolism. In addition, for both doses there is a reduced risk of intracranial hemorrhage, and any bleeding in the dabigatran treated subjects compared to warfarin. The risk of myocardial infarction was low but more frequent in the dabigatran groups. There were increases in the risk of GI bleeding in subjects treated with either dose of dabigatran compared to warfarin. These effects must be balanced against the overall benefits seen in the dabigatran subjects. For DE 150 there was a reduced risk of ischemic and hemorrhagic stroke, systemic embolism, intracranial hemorrhage, total (any) bleeding, and vascular death and all-cause mortality. For DE 110, there was a reduced risk of hemorrhagic stroke, intracranial hemorrhage, major bleeding, and total bleeding. It is concluded that in AF subjects with moderate to high risk of stroke, dabigatran has similar or superior efficacy compared to standard treatment, with clinically meaningful reductions in the major bleeding risks associated with a standard anticoagulant regimen.

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 additional secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Event rates and hazard ratios for the composite endpoint of stroke, SEE, PE, MI, vascular death	Table 15.2.6.2: 1
Hazard ratios for the composite endpoints of stroke, SEE, PE, MI including silent MI, vascular death	Table 15.2.6.2: 2

Table 15.1.1: 1 Summary of subject disposition

	DE 110mg bid N	%	DE 150mg bid N	%	Warfarin N	%	Total N	%
Enrolled(screened)							20377	
Not entered							2264	
Entered(randomized)	6015		6076		6022		18113	
Not Treated	32	(100.0)	17	(100.0)	24	(100.0)	73	(100.0)
Completed follow up	14	(43.8)	7	(41.2)	5	(20.8)	26	(35.6)
Withdrew consent or lost to follow up or other	18	(56.3)	10	(58.8)	19	(79.2)	47	(64.4)
Treated	5983	(100.0)	6059	(100.0)	5998	(100.0)	18040	(100.0)
Completed study	5780	(96.6)	5824	(96.1)	5756	(96.0)	17360	(96.2)
Completed on study medication	4610	(77.1)	4627	(76.4)	4849	(80.8)	14086	(78.1)
Completed follow up but stopped study medication prematurely*	1170	(19.6)	1197	(19.8)	907	(15.1)	3274	(18.1)
Outcome events	421	(7.0)	431	(7.1)	333	(5.6)	1185	(6.6)
Serious AEs not related to outcome events	194	(3.2)	196	(3.2)	148	(2.5)	538	(3.0)
Patient preference	393	(6.6)	408	(6.7)	331	(5.5)	1132	(6.3)
Elevated LFT result	25	(0.4)	16	(0.3)	11	(0.2)	52	(0.3)
Hospitalisation	139	(2.3)	148	(2.4)	154	(2.6)	441	(2.4)
Adverse Event	296	(4.9)	325	(5.4)	192	(3.2)	813	(4.5)
Other	444	(7.4)	492	(8.1)	371	(6.2)	1307	(7.2)
Premature discontinuation	203	(3.4)	235	(3.9)	242	(4.0)	680	(3.8)
Withdrew consent	128	(2.1)	145	(2.4)	139	(2.3)	412	(2.3)
Vital status available at study termination	81	(1.4)	99	(1.6)	105	(1.8)	285	(1.6)
Lost to follow up	17	(0.3)	31	(0.5)	41	(0.7)	89	(0.5)
Vital status available at study termination	6	(0.1)	16	(0.3)	23	(0.4)	45	(0.2)
Other	58	(1.0)	59	(1.0)	62	(1.0)	179	(1.0)

*: Subjects may be counted in more than one of the sub-classes below

Source data: Appendix 16.2.1, Listing 1, 2, Appendix 16.2.2, Listing 2 scs26\disp.sas 03APR2010

Table 15.2.6.2: 1 Frequency and yearly event rate (%) for the composite endpoint of stroke, SEE, PE, MI including silent MI, vascular death - randomized set

	DE 110mg bid N (%)	DE 150mg bid N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-year	11899	12033	11794
Subjects with composite endpoint	507 (4.26)	443 (3.68)	513 (4.35)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
SEE	15 (0.13)	13 (0.11)	21 (0.18)
PE	14 (0.12)	18 (0.15)	12 (0.10)
MI	87 (0.73)	89 (0.74)	66 (0.56)
Silent MI	11 (0.09)	8 (0.07)	9 (0.08)
Vascular death	289 (2.43)	274 (2.28)	317 (2.69)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.
In case of recurrent event, the first event was considered
Subject-years = sum(date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: Appendix 16.2.6, Listing 1, 2, 3, 8, 9, 11, Appendix 16.2.7, Listing 1.1 sce26\sspph.sas 07APR2010

Table 15.2.6.2: 2 Hazard ratios and 95% CIs for the composite endpoints of stroke, SEE, PE, MI including silent MI, vascular death randomized set

	DE 110mg bid vs Warfarin	DE 150mg bid vs Warfarin
Hazard ratio (SE)	0.98 (0.06)	0.84 (0.05)
95% CI	0.87, 1.11	0.74, 0.96
P-value	0.7508	0.0093

In case of recurrent event, the first event was considered.

Source data: Appendix 16.1.9.2, Statdoc 6.7.1 sce26\t_coxph.sas 07APR2010