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®		**EudraCT No.:** 2008-005248-17	
Name of active ingredient: Dabigatran etexilate, BIBR 1048 MS		**Page:** 1 of 10	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 June 2013	**Trial No. / U No.:** 1160.71 / U13-3509-01	**Date of trial:** 16 DEC 2008 – 21 Dec 2012	**Date of revision:** Not applicable

Title of trial:	RELY-ABLE long term multi-center extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial and a cluster randomised trial to assess the effect of a knowledge translation intervention on patient outcomes
Coordinating Investigator:	[redacted]
Trial sites:	Multicenter study; cf. Appendix 16.1.4
Publication (reference):	None
Clinical phase:	IIIb
Objectives:	To evaluate the long-term safety of 2 doses of dabigatran. To evaluate the efficacy of subject customized audit and feedback compared to general information on best practice to reduce cardiovascular outcomes. The analyses for the evaluation of the second objective will be performed by Population Health Research Institute (PHRI). A separate TSAP will be prepared by PHRI for the evaluation of the second objective.
Methodology:	RELY-ABLE was an extension of the RE-LY trial, a cluster randomized trial of a knowledge translation intervention using audit and feedback to improve management of atrial fibrillation (AF) over 28 months or longer. The subjects remained on the randomized doses from RE-LY and continued double-blind treatment for up to 43 months for subjects from some countries.
No. of subjects:	
planned:	entered: 8,000 approximately 1. dabigatran etexilate 110 mg bid. (two times daily): N=~4,000 2. dabigatran etexilate 150 mg bid.: N=~4,000
actual:	enrolled: 5897 entered: 5891 treated: 5883 Treatment: Dabigatran etexilate 110 mg twice daily: treated: 2927 analyzed: 2914 Treatment: Dabigatran etexilate 150 mg twice daily: treated: 2956 analyzed: 2937

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Diagnosis and main criteria for inclusion:	**Diagnosis:** At the time of entry into RE-LY, paroxysmal, persistent or permanent AF with at least one risk factor for stroke (one of: congestive heart failure / left ventricular dysfunction / age ≥ 75 years / previous stroke, systemic embolism or transient ischemic attack / age ≥ 65 years with hypertension or diabetes or coronary artery disease) **Inclusion Criteria:** 1) Randomization to dabigatran etexilate in RE-LY (1160.26) and no premature discontinuation of study medication 2) Investigator determines it is clinically appropriate for patient to continue receiving long-term treatment with oral anticoagulation
Test product:	dabigatran etexilate
dose:	110 mg bid., 150 mg bid.
mode of admin.:	Oral administration with water and / or food
batch no.:	cf. Appendix 16.1.6
Duration of treatment:	up to 43 months
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Please see description below of criteria for efficacy and safety.
Efficacy Endpoints:	**Dabigatran:** **Primary Efficacy Endpoints**: Since the objective of this trial is safety, there are no primary efficacy endpoints **Secondary Efficacy Endpoints**: Stroke (including hemorrhagic), non-CNS systemic embolism, pulmonary embolism, acute MI, DVT, and all deaths (includes deaths from bleeding)

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Safety Endpoints:	**Primary Safety Endpoint**: Major bleeds **Secondary Safety Endpoints**: Life-threatening bleeds, minor bleeds, any bleeds (major plus minor), and intra-cranial hemorrhage. **Knowledge translation:** Composite of vascular death, stroke, MI, major bleeds, systemic embolic event (SEE), and cardiovascular hospitalization. The analyses for the evaluation this composite endpoint will be performed by Population Health Research Institute (PHRI) and reported separately.
Safety	Safety parameters included SAEs and AEs resulting in the discontinuation of dabigatran, elevations in liver transaminases, bilirubin and hepatic dysfunction, GI AEs, dyspepsia, hospitalizations, clinical laboratory, vital signs, and physical examination.
Statistical methods:	Descriptive statistics, Kaplan Meier estimates, Cox regression
RESULTS:	
Efficacy / clinical pharmacology results:	An interim report was prepared for data collected up to 28 month timepoint (U12-3549-02). This final report represents data collected up through Month 43. Comparison of the RE-LY baseline data for RELY-ABLE subjects with the RELY-ABLE baseline showed the following: • RELY-ABLE subjects were 2 years older with a decline in creatinine clearance values (75.8 mL/min to 72.3 mL/min) and a progression of AF to more permanent AF (32.8% at RELY baseline and 49.2% RELY-ABLE baseline). • Numerical increases in most stroke risk factors except for heart failure. • $CHADS_2$ scores shifted for some subjects to 3+ and higher category. Other baseline characteristics were well balanced across the treatment groups. Subjects who did not participate in the RELY-ABLE trial were slightly older, and more were female compared to the RELY-ABLE population. There were some ethnic and regional differences between the cohorts. Stroke risk factors were varied, but heart failure and MI were more frequent in those who did not rollover into RELY-ABLE. $CHADS_2$ scores were also higher in those that did not rollover into RELY-ABLE.

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Efficacy / clinical pharmacology results (Cont.):

Secondary Efficacy Endpoints

Table 2.1 summarizes the frequencies and annualized rates of outcome events during the RELY-ABLE period.

Composites

Stroke/SEE: During the RELY-ABLE period, the annualized event rate of subjects with stroke/SEE was numerically higher for DE 110 (1.60%) compared to DE 150 (1.47%). The HR for stroke/SEE for DE 110 versus DE 150 was 1.09 with a 95% CI of 0.84-1.42.

The annualized event rate for subjects in the combined RE-LY plus RELY-ABLE study period showed that stroke/SEE was numerically lower for DE 150 (0.93%) compared to DE 110 (1.08%); the HR for stroke/SEE for DE 110 versus DE 150 was 1.17 (95% CI 0.92-1.48).

Stroke/SEE/all cause death: During the RELY-ABLE period, the annualized event rate of subjects with stroke/SEE/death was numerically higher for DE 110 (4.40%) compared to DE 150 (4.02%). The HR for stroke/SEE/death for DE 110 versus DE 150 was 1.10 with a 95% CI of 0.94-1.29.

Stroke/SEE/pulmonary embolism/MI/vascular death: During the RELY-ABLE period, the annualized event rate of subjects with stroke/SEE/PE/MI/vascular death was numerically higher for DE 110 (3.51%) compared to DE 150 (3.32%). The HR for stroke/SEE/PE/MI/vascular death for DE 110 versus DE 150 was 1.06 with a 95% CI of 0.89-1.27.

Stroke/SEE/pulmonary embolism/MI/all cause death/major bleed (Net Clinical Benefit [NCB]): During the RELY-ABLE period, the annualized event rates of NCB were 6.65% for DE 110 and 7.14% for DE 150. There were relatively few SEEs and PEs, with all-cause death and major bleeding contributing most to this endpoint. DE 150 had a slightly higher event rate, which was driven by major bleeds (3.59% for DE 150 versus 2.79% for DE 110). The HR was 0.93; 95% CI [0.82, 1.05].

Individual Components

Stroke: Overall, the annualized stroke rate in the RELY-ABLE period was 1.39% and 1.26% for the DE 110 and DE 150 groups, respectively. Hemorrhagic stroke was similar between the 2 groups and occurred at an annualized rate of 0.14% for DE 110 and 0.14% for DE 150. The annualized

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Efficacy / clinical pharmacology results (Cont.):

rate for ischemic stroke was 1.16% for DE 110 compared to 1.01% for DE 150. The annualized rate for stroke of uncertain classifications was 0.10% for DE 110 compared to 0.15% for DE 150.

Systemic embolism: The annualized rates of systemic embolism (SEE) in the RELY-ABLE period were 0.25% and 0.23% in the DE 110 and DE 150 treatment groups.

Transient ischemic attack: The annualized rates for TIA in the RELY-ABLE period were 0.70% in the DE 110 group and 0.70% in the DE 150 group.

Pulmonary embolism: The annualized rates for pulmonary embolism in the RELY-ABLE period were 0.10% and 0.12% in the DE 110 and DE 150 treatment groups.

Myocardial infarction: The annualized rates of MI in the RELY-ABLE period were 0.72% and 0.66% for the DE 110 and DE 150 groups, respectively. During the RE-LY study, MI (including silent MI) rates were slightly higher (0.82% and 0.81% for DE 110 and DE 150), which is likely due to methodologic differences (no adjudication and silent MI was not assessed in the RELY ABLE trial). In the RE-LY plus RELY-ABLE period, the annualized rate of all MIs (including silent MI) was 0.62% for the DE 110 group and 0.51% for the DE 150 group.

Deep vein thrombosis: The annualized rates of deep vein thrombosis in the RELY-ABLE period were 0.06% and 0.11% in the DE 110 and DE 150 treatment groups.

Death: During the RELY-ABLE period, the annualized rate for all cause death was 3.18% and 2.99% for the DE 110 and DE 150 groups, respectively. There were a total of 449 deaths, 231 in the DE 110 and 218 in DE 150 treatment groups. Approximately 53% of the deaths were vascular in origin.

Subgroups

During the RELY-ABLE period, stroke and Stroke/SEE rates were consistent for all subgroups evaluated. There were no clinically relevant treatment by-subgroup interactions. Event rates for the endpoints evaluated were higher with increasing age. Stroke/SEE event rates were also higher in subjects with lower creatinine clearance values and in subjects with a previous stroke/SEE/TIA event. Males had a higher annualized rate of MI.

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Safety results:

Table 2.2 summarizes the frequencies and annualized rates of safety outcome events during the RELY-ABLE period.

Bleeding events: All categories of bleeding generally occurred more frequently in the DE 150 group compared to the DE 110 group during RELY-ABLE. The risk of major bleeds was significantly lower for DE 110 treatment [0.77, 95% CI (0.64, 0.93) p=0.0055]. Annualized rates for major bleeding were 2.79% and 3.59% for the DE 110 and DE 150 groups, respectively. For the RE-LY plus RELY-ABLE period, DE 110 and DE 150 had major bleed rates of 2.08% and 2.49%, respectively.

During the RELY-ABLE period, life threatening bleeds, intracerebral hemorrhage, and major GI bleeds were consistent with the rates in RE LY and were numerically lower for the DE 110 group. Similar patterns in the rates were shown in the RE-LY plus RELY-ABLE period, although overall event rates were lower.

During the RELY-ABLE period, the most common site for major bleeds was GI followed by surgical. By criteria for major bleeding, the highest frequency of criteria for major bleeding was a drop in hemoglobin ≥ 20 g/L. By critical area/organ, GI major bleeding occurred at annualized rates of 1.22% for DE 110 and 1.36% for DE 150.

During the RELY-ABLE period, subjects treated with DE 110 had a lower rate of minor bleeding events and any bleeding events, where any bleeding events was different between DE 110 and DE 150, in favor of DE 110 (p=0.0002). Similar patterns were shown in the RE-LY and RELY-ABLE combined period, although overall event rates were lower.

Subgroup: Age was a strong predictor for major bleeding. The greater the age of the subject, the higher the annualized event rate for major bleeds.

Renal dysfunction was associated with a higher risk of major bleeding for both treatments across the CrCl ranges evaluated; there were too few subjects with CrCl < 30 mL/min to draw conclusions. In all categories (except for CrCl < 30 mL/min), the annualized rate for major bleeding was higher for subjects treated with DE 150 compared to DE 110.

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Safety results (Cont.):

Adverse Events: Non-serious AEs were only collected during RELY-ABLE period if they led to discontinuation of study medication or were associated with an SAE. The incidence of reported AEs/SAEs was 40.7% in the DE 110 group and 43.1% in the DE 150 group. There were 10.5% of subjects in the DE 110 and 11.5% of subjects in the DE 150 treatment groups that discontinued the trial drug due to an AE. By SOC, discontinuation of treatment due to GI disorders occurred most frequently, (1.8% and 2.8% for DE 110 and DE 150, respectively), with GI hemorrhage resulting in discontinuation most often (0.6% in both groups).

Dyspepsia and Abdominal Discomfort: During the RELY-ABLE period, survey results showed that dyspepsia and abdominal discomfort were reported with no apparent dose-dependent pattern for DE 110 and DE 150 (subjects currently reporting the events: 2.4% and 1.9%, respectively, and subjects previously and currently experiencing the events: 6.9% and 6.4% respectively). It should be noted that dyspepsia data were collected retrospectively and as such their interpretation should be made with caution.

Symptoms of dyspepsia were most improved with the use of proton pump inhibitors and taking DE with meals. For the DE 110 and 150 groups, symptoms improved in 91.3% and 89.1% of proton pump inhibitor users, and in 87.7% and 89.2% of subjects who took dabigatran with meals, respectively.

GI Adverse Events: There was no consistent dose response relationship with respect to GI AEs, and only abdominal pain was reported in > 1% of subjects (1.2% and 1.5% for DE 110 and DE 150, respectively).

Serious Adverse Events: During the RELY-ABLE period, reported SAEs were generally similar for both treatment groups. The reported incidence of SAEs was 35.3% and 37.7%, for DE 110 and DE 150, respectively. The most frequently reported SAEs for DE 110 and DE 150 were pneumonia (3.1% and 3.4%), atrial fibrillation (2.9% and 3.2%), cardiac failure (2.4% and 3.0%), cardiac failure congestive (2.3% and 2.4%), and chest pain (1.2% and 1.6%).

Death was an exempted event, only fatal AEs that were considered as drug related were collected. The incidence of AEs with fatal outcomes was higher in the DE 110 group than in the DE 150 group (4.0% versus 3.3%, respectively), but was consistent with an elderly population with non-valvular AF receiving anticoagulant therapy.

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Safety results (Cont.):	*Hospitalizations*: During the RELY-ABLE period, 1267 subjects in the DE 110 group (annualized rate of 17.43%) and 1302 in the DE 150 group (annualized rate of 17.84%) had been hospitalized at least once. The annualized rate for total hospitalizations was 31.83% and 33.22% for DE 110 and DE 150, respectively. The majority of hospitalizations were due to non-cardiovascular reasons. *Other safety measures*: There were no new safety findings in this trial compared to spontaneous reporting and existing clinical trial or other data.
CONCLUSIONS:	During more than 2.5 additional years of follow up after RE-LY, rates of ischemic and hemorrhagic stroke, and of major bleeds, on DE 110 and on DE 150 were consistent with the event rates reported during the RE-LY study; providing evidence for long-term efficacy and safety of dabigatran etexilate in subjects with AF not caused by a heart valve problem at risk for stroke and blood clots. The risk of major bleeds was significantly lower for DE 110 treatment. Annualized rates for major bleeding were 2.79% and 3.59% for the DE 110 and DE 150 groups, respectively. The annualized rates for all cause death was 3.18% in the DE 110 group and 2.99% in the DE 150 group, with approximately half of the deaths being vascular in origin. Adverse events were consistent with an elderly population with non-valvular AF receiving anticoagulant therapy. No new safety concerns were identified.

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Table 2: 1 Frequency and annualized rate of subjects with outcome events RELY-ABLE

	DE 110mg bid N (%)	DE 150mg bid N (%)
Subjects treated	2914	2937
Subject-years	7267	7297
Subjects with stroke/SEE	116 (1.60)	107 (1.47)
Stroke	101 (1.39)	92 (1.26)
Ischemic stroke	84 (1.16)	74 (1.01)
Hemorrhagic stroke	10 (0.14)	10 (0.14)
Stroke of uncertain classifications	7 (0.10)	11 (0.15)
Disabling/fatal stroke[1]	50 (0.69)	46 (0.63)
Fatal stroke	18 (0.25)	16 (0.22)
Systemic embolism (SEE)	18 (0.25)	17 (0.23)
Transient ischemic attack	51 (0.70)	51 (0.70)
All cause death	231 (3.18)	218 (2.99)
Vascular death	118 (1.62)	118 (1.62)
Myocardial infarction	52 (0.72)	48 (0.66)
Pulmonary embolism	7 (0.10)	9 (0.12)
Deep vein thrombosis	4 (0.06)	8 (0.11)

1. By the modified Rankin scale.
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 last visit - date of first dose study medication in the RELY-ABLE period + 1) of all treated subjects / 365.25.
Annualized event rate (%) = 100 * Number of subjects with event / subject-years.

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Table 2: 2 Frequency and annualized rate of subjects with safety outcome events - RELY-ABLE

	DE 110mg bid N (%)	DE 150mg bid N (%)
Subjects treated	2914	2937
Subject-years	7267	7297
Major bleeding	203 (2.79)	262 (3.59)
Life threatening major bleeding	113 (1.55)	124 (1.70)
Fatal bleeding	19 (0.26)	16 (0.22)
ICH	20 (0.28)	24 (0.33)
GI major bleeding	89 (1.22)	99 (1.36)
Other MBEs	114 (1.57)	159 (2.18)
Minor bleeding	544 (7.49)	655 (8.98)
Any bleeds	686 (9.44)	817 (11.20)

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 last visit - date of first dose study medication in the RELY-ABLE period + 1) of all treated subjects / 365.25.
Annualized event rate (%) = 100 * Number of subjects with event / subject-years.

Trial Synopsis - Appendix

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

Results for	presented in
Patient disposition	Table 15.1.1: 1

Table 15.1.1: 1 Summary of subject disposition-RELY-ABLE

	DE 110mg bid N	DE 110mg bid (%)	DE 150mg bid N	DE 150mg bid (%)	Total N	Total (%)
Enrolled					5897	
Entered					5891	
Not treated					8	
Treated	2927		2956		5883	
Excluded from analysis	13		19		32	
Included in analysis	2914	(100.0)	2937	(100.0)	5851	(100.0)
Completed study on medication	2446	(83.9)	2438	(83.0)	4884	(83.5)
Death (on study medication)	151	(5.2)	139	(4.7)	290	(5.0)
Premature discontinuation of study medication (main reason)	468	(16.1)	499	(17.0)	967	(16.5)
Outcome event	63	(2.2)	69	(2.3)	132	(2.3)
Major/minor bleed	30	(1.0)	44	(1.5)	74	(1.3)
Other	33	(1.1)	25	(0.9)	58	(1.0)
Serious AE not related to outcome event	41	(1.4)	45	(1.5)	86	(1.5)
Non-serious AE	70	(2.4)	76	(2.6)	146	(2.5)
Hospitalization (not including surgery, outcome)	18	(0.6)	17	(0.6)	35	(0.6)
Hospitalization due to surgery including procedures (excluding outcome events)	37	(1.3)	40	(1.4)	77	(1.3)
Reduced creatinine clearance	53	(1.8)	55	(1.9)	108	(1.8)
Elevated LFT result	7	(0.2)	3	(0.1)	10	(0.2)
Patients refused to take study medication	65	(2.2)	76	(2.6)	141	(2.4)
Missing	1	(0.0)	0	(0.0)	1	(0.0)
Other	113	(3.9)	118	(4.0)	231	(3.9)
Death	1	(0.0)	1	(0.0)	2	(0.0)
Procedure	6	(0.2)	7	(0.2)	13	(0.2)
Withdrawal of consent/discontinuing study participation	21	(0.7)	25	(0.9)	46	(0.8)
Site Closed	4	(0.1)	3	(0.1)	7	(0.1)
Physician decision	47	(1.6)	38	(1.3)	85	(1.5)
Non-Compliance	3	(0.1)	11	(0.4)	14	(0.2)
Patient elected	7	(0.2)	9	(0.3)	16	(0.3)
Site closed for cause	19	(0.7)	19	(0.6)	38	(0.6)
Other	5	(0.2)	5	(0.2)	10	(0.2)

Patients who died on study medication or within six days of last study medication are considered as completers
 Outcome events: stroke, major bleed, MI, SEE, PE, TIA, minor bleed
Excluded from analysis: patients from sites 1059 and 246 are excluded from main analyses
Patient [redacted] was not eligable but was treated

Table 15.1.1: 1 Summary of subject disposition-RELY-ABLE

	DE 110mg bid N (%)	DE 150mg bid N (%)	Total N (%)
Premature discontinuation of study medication-vital status available	289 (9.9)	322 (11.0)	611 (10.4)
Died	42 (1.4)	49 (1.7)	91 (1.6)
Stroke/SEE(excluding stroke/SEE prior to death)	2 (0.1)	1 (0.0)	3 (0.1)

Patients who died on study medication or within six days of last study medication are considered as completers
Outcome events: stroke, major bleed, MI, SEE, PE, TIA, minor bleed
Excluded from analysis: patients from sites 1059 and 246 are excluded from main analyses
Patient [redacted] was not eligable but was treated