Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Pradaxa®		**EudraCT No.:** 2014-003890-40	
BI Investigational Product: Dabigatran etexilate (BIBR 1048)		**Page:** 1 of 10	
Report Date: 11 April 2017	**Trial No. / Doc. No.:** 1160.204 / c14388942-01	**Dates of Trial:** 13 May 2015 to 14 Nov 2016	**Date of Revision:** Not applicable

Title of Trial:	**R**andomised **E**valuation of dabigatran etexilate **C**ompared to warfar**I**n in pulmona**R**y vein ablation: assessment of an uninterrupted peripro**C**ed**U**ral ant**I**coagulation s**T**rategy (The RE-CIRCUIT Trial)
Coordinating Investigator:	[redacted], MD
Trial Sites:	104 sites in 11 countries
Publications:	The results of the trial have been published: Calkins H, Willems S, et al. N Engl J Med 2017; 10.1056/NEJMoa1701005
Clinical Phase:	IV
Objectives:	The primary objective of this trial was to assess the safety of an uninterrupted dabigatran etexilate periprocedural anticoagulant regimen compared with an uninterrupted periprocedural warfarin regimen in non-valvular atrial fibrillation (NVAF) patients undergoing ablation of AF in a PROBE (prospective, randomised, open label, blinded endpoint) active-controlled trial. Secondary objectives were to assess additional safety and efficacy endpoints in this clinical setting.
Methodology:	PROBE active-controlled trial
No. of Patients:	
Planned:	Entered (randomised): 724
Actual:	Enrolled (screened): 704 Entered: 678

Patients entered, treated, and analysed for the primary endpoint:

	Entered	Treated	Analysed
Dabigatran etexilate	339	338	317
Warfarin	339	338	318

Note that the planned number of 724 entered patients was based on early assumptions during trial preparation. Recruitment goals for the trial were later adapted.

Diagnosis:	Patients with NVAF undergoing catheter ablation for atrial fibrillation.

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Main Criteria for Inclusion:	Male or female patients who were at least 18 years old, and: • eligible for treatment with dabigatran etexilate 150 mg twice daily according to the local label • treatment-naive or on oral anticoagulant treatment with a vitamin K antagonist, dabigatran etexilate, rivaroxaban, apixaban, or edoxaban • with paroxysmal or persistent NVAF with a planned catheter ablation for AF unless performed as an investigational ablation technique. • AF must have been documented at least once within the 24 months prior to screening
BI Investigational Product:	Dabigatran etexilate
Dose:	150 mg twice daily
Mode of Admin.:	Oral
Batch Nos.:	B141003275, B151001178
Comparator Product:	Warfarin
Doses:	1, 3, and 5 mg (dose adjusted to INR target range)
Mode of Admin.:	Oral
Batch Nos.:	1 mg: B141003276, B141003277, B151001226, E131307-0008L001 3 mg: B141003278, B141003279, B151001228, E131307-0008L002 5 mg: B141003280, B141003281, B151001229, E131307-0008L003
Duration of Treatment:	4 to 8 weeks prior to ablation and 2 months after ablation; overall 3 to 4 months
Criteria for Evaluation:	
Efficacy	The primary endpoint was a safety endpoint (see Safety Criteria below). <u>Secondary endpoint of efficacy</u> The secondary endpoint of efficacy was the incidence of the composite of 'stroke, systemic embolism, or transient ischemic attack (TIA)'during the ablation procedure and up to 2 months post-ablation. <u>Further endpoints of efficacy</u> Incidence of the following endpoints:

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	• Events during the ablation procedure and up to 1 month post-ablation:
	  o Stroke, systemic embolism, or TIA (composite endpoint)
	• Events during the whole treatment period:
	  o Myocardial infarction (MI)
	  o Stroke (total, ischaemic, haemorrhagic, undetermined)
	  o TIA
	  o Systemic embolism
	  o Stroke, systemic embolism, or TIA (composite endpoint)
	Secondary and further endpoints of safety are described below.

Safety	<u>Primary endpoint</u>
	The primary endpoint of the trial was the incidence of major bleeding events (MBEs), as defined by the International Society on Thrombosis and Haemostasis (ISTH), during the ablation procedure and up to 2 months post-ablation.
	<u>Secondary endpoints of safety</u>
	Incidence during the ablation procedure and up to 2 months post-ablation of:
	• Minor bleeding events
	• 'ISTH MBE, stroke, systemic embolism, or TIA' (composite endpoint combining safety and efficacy)
	<u>Further endpoints of safety</u>
	1. Incidences of the following endpoints:
	• Events during the ablation procedure and up to 1 month post-ablation:
	  o ISTH MBEs
	  o Pericardial tamponade
	  o Vascular access complication
	• Deaths during the ablation procedure and up to 2 months post-ablation
	• Events during the whole treatment period:
	  o Cardiovascular, non-cardiovascular, and undetermined cause of death
	  o Bleeding events
	  - ISTH MBEs (overall and by location)
	  - Minor bleedings
	  - ISTH MBE, stroke, systemic embolism, or TIA (composite endpoint combining safety and efficacy)
	2. Adverse events (AEs)

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Statistical Methods: The trial was exploratory and there was no confirmatory hypothesis. The primary analysis was based on the 'ablation set' of patients, which included all randomised patients who were treated with at least 1 tablet/capsule and who started the ablation procedure. For the primary endpoint, point estimates for the incidence of adjudicated ISTH MBEs and their 2-sided 95% confidence intervals (CIs) were presented based on the normal approximation of independent binomial distribution without stratification. In addition, the risk difference of dabigatran etexilate vs. warfarin, its 2-sided 95% CI, and corresponding p-value were presented. As a sensitivity analysis, these data were also analysed using exact methods. Another sensitivity analysis was the calculation of the hazard ratio based on the unstratified Cox proportional hazards model. For secondary and further endpoints, frequency counts and percentages were calculated. No interim analysis was planned or performed. General safety analyses were mainly performed on the treated set, which included all patients who were randomised and subsequently treated with at least 1 tablet/capsule. For AEs, descriptive analyses were performed. No AEs of special interest were specified for the trial.

SUMMARY - CONCLUSIONS:

Trial Patients and Compliance with Trial Protocol:

A total of 704 patients were enrolled in the trial. Of these, 678 patients were randomised and 676 were treated, and 26 were screening failures. Of the treated patients, 635 patients started the ablation procedure. The following text summarises the disposition, compliance, and patient characteristics based on the ablation set.

Most of the patients completed the trial (622 patients, 98.0%). Premature trial discontinuation was most commonly due to AEs and due to withdrawal of informed consent. Most patients completed the treatment period (620 patients, 97.6%), with similar results in both treatment groups. Discontinuation of trial medication was most commonly due to AEs and refusal to continue trial medication. Important protocol violations were reported for 25.6% of patients in the dabigatran etexilate (DE) group and 35.5% of patients in the warfarin group.

The mean patient age was 59.2 years (median 60.0 years, range 25 to 84 years). There were 475 male patients (74.8%) and 160 female patients (25.2%). The majority of the patients were White (75.9%). More than half of the patients were from Western Europe (51.8%). The CHA_2DS_2-VASc score at baseline was similar between the treatment groups (DE: 2.0, warfarin: 2.2), as was the mean activated clotting time during the ablation procedure (DE: 330 s, warfarin: 342 s).

Exposure results were consistent with the study design and similar across the treatment groups. In line with the overall treatment duration of 3 to 4 months,

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most patients (>97%) in the ablation set were treated for at least 12 weeks. The mean treatment duration was 103.3 days overall.

In the DE group 98.4% of patients achieved treatment compliance of 80 to 120%. In the warfarin group, the mean % of time that patients in the warfarin group were in the target INR range was 67.0%.

Efficacy Results:

Secondary endpoint of efficacy

Only 1 event was observed for the composite endpoint of stroke/systemic embolism/TIA during the ablation procedure and up to 2 months post-ablation. It was a TIA event in the warfarin group. No myocardial infarction or stroke was reported in the trial.

Further endpoints of efficacy

Further endpoints assessed during the ablation procedure and up to 1 month post-ablation were analysed based on the ablation set. Further endpoints assessed over the whole treatment period were analysed based on the treated set.

The composite endpoint of stroke/systemic embolism/TIA was reported for only 1 patient overall (warfarin group) up to 1 month post-ablation and for 3 patients over the whole treatment period (DE: 1 patient, warfarin: 2 patients); see Table 1.

Table 1 Further endpoints of efficacy, N (%)

	DE 150 mg	Warfarin
Endpoints assessed during the ablation procedure and up to 1 month post-ablation		
Patients in the ablation set, N (100%)	317	318
Stroke/systemic embolism/TIA (composite)	0	1 (0.3)
Endpoints assessed over the whole treatment period		
Patients in the treated set, N (100%)	338	338
Stroke/systemic embolism/TIA (composite)	1 (0.3)	2 (0.6)
TIA	1 (0.3)	1 (0.3)
Systemic embolism	0	1 (0.3)

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Primary endpoint

Treatment with DE resulted in a statistically significant reduction of the occurrence of ISTH MBEs compared with warfarin treatment in the patients in the ablation set (exploratory analysis). The frequency of MBEs was 1.6% in the DE group and 6.9% in the warfarin group (Table 2). The risk difference was -5.3% (95% CI -8.4, -2.2%). The hazard ratio of DE vs. warfarin based on the unstratified Cox proportional hazards model was 0.224 (95% CI 0.08, 0.59).

Analyses of the primary endpoint in a variety of subgroups by demographics, baseline characteristics, anticoagulation status, and type of ablation showed results that were generally consistent with the results for the overall population.

Table 2 Adjudicated ISTH MBEs during the ablation procedure and up to 2 months post-ablation

	DE 150 mg	Warfarin
Patients in the ablation set, N (100%)	317	318
Patients with event, N (%)	5 (1.6)	22 (6.9)
95% CI [%][1]	(0.2, 2.9)	(4.1, 9.7)
Risk difference vs. warfarin [%]	-5.3	
95% CI [%][1]	(-8.4, -2.2)	
p-value[2]	0.0009	
Hazard ratio vs. warfarin[3]	0.224	
95% CI[4]	(0.08, 0.59)	

[1] Based on the normal approximation of independent binomial distributions
[2] Based on the chi-square test
[3] Cox proportional hazards model
[4] Wald confidence limits

Secondary endpoints of safety

The composite endpoint of ISTH MBE/stroke/systemic embolism/TIA occurred more frequently in the warfarin group during the ablation procedure and up to 2 months post-ablation (Table 3). This result was driven by the treatment imbalance seen for MBEs. There were similar frequencies of minor bleedings in both treatment groups. Subgroup analyses of the secondary endpoints showed results that were consistent with those for the overall population.

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Table 3 Secondary endpoints of safety, N (%)

	DE 150 mg	Warfarin
Patients in the ablation set, N (100%)	317	318
ISTH MBE/stroke/systemic embolism/TIA (composite)	5 (1.6)	23 (7.2)
Minor bleeding	59 (18.6)	54 (17.0)

Further endpoints of safety

ISTH MBEs were less frequent in the DE group than the warfarin group, both up to 1 month post-ablation (1.3 vs. 6.6%) and over the whole treatment period (1.8 vs. 6.8%); see Table 4. The location of MBEs over the whole treatment period was most commonly reported as 'other MBE' (DE: 2 events, warfarin: 12 events) or pericardial (2 vs. 6 events). Note that events were categorised based on pre-defined locations or otherwise categorised as 'other MBE'. For minor bleeds there were similar frequencies in both treatment groups over the whole treatment period.

The composite endpoint of ISTH MBE/stroke/systemic embolism/TIA occurred more frequently in the warfarin group over the whole treatment period; once again this result was driven by the treatment imbalance seen for MBEs.

Pericardial tamponade up to 1 month post-ablation was less frequent in the DE group (0.3 vs. 1.9%). There were similar frequencies of vascular access complications across treatments (11.4% and 14.5%). No patient died.

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Safety Results:

Table 4 Further endpoints of safety, N (%)

	DE 150 mg	Warfarin
Endpoints assessed during the ablation procedure and up to 1 month post-ablation		
Patients in the ablation set, N (100%)	317	318
ISTH MBEs	4 (1.3)	21 (6.6)
Pericardial tamponade	1 (0.3)	6 (1.9)
Vascular access complication	36 (11.4)	46 (14.5)
Endpoints assessed over the whole treatment period		
Patients in the treated set, N (100%)	338	338
MBEs (ISTH)	6 (1.8)	23 (6.8)
Location of MBEs [events], total	6	24
Other major bleeding event	2	12
Pericardial	2	6
Gastrointestinal	2	2
Intracranial	0	2
Intramuscular with compartment syndrome	0	1
Retroperitoneal	0	1
ISTH MBE/stroke/systemic embolism/TIA (composite)	7 (2.1)	24 (7.1)
Minor bleedings	69 (20.4)	66 (19.5)

General safety

AE frequencies were generally comparable between the treatment groups, with 69.1% of all patients reporting at least 1 AE during treatment (Table 5). The majority of AEs were mild or moderate in intensity. Severe AEs were less frequent in the DE group than the warfarin group (3.3 vs. 6.2%). AEs by system organ class with an overall frequency >10% were cardiac disorders (DE: 27.8%, warfarin: 31.7%), gastrointestinal disorders (DE: 18.6%, warfarin: 15.7%), 'general disorders and administration site conditions' (DE: 13.3%, warfarin: 15.4%), 'respiratory, thoracic and mediastinal disorders' (DE: 9.8%, warfarin: 10.7%), and vascular disorders (DE: 8.9%, warfarin: 14.5%). AEs at the preferred-term level with an overall frequency >5% were atrial fibrillation (DE: 13.3%, warfarin: 14.5%), atrial flutter (DE: 5.9%, warfarin: 5.6%), and palpitations (DE: 5.0%, warfarin 5.6%).

AEs leading to treatment discontinuation were numerically more frequent in the DE group than the warfarin group (5.6 vs. 2.4%) in the treated set. The imbalance was largely driven by gastrointestinal disorders (DE: 8 patients/2.4%,

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warfarin: 1 patient/0.3%); all of these 8 gastrointestinal events in the DE group were mild or moderate in intensity. AEs leading to treatment discontinuation that were reported for at least 2 patients in a treatment group were gastritis (DE: 4 patients/1.2%, warfarin: 0 patients) and atrial thrombosis (DE: 2 patients/0.6%, warfarin: 1 patient/0.3%). There were notably fewer AEs leading to treatment discontinuation in the ablation set (10 patients/1.6%) than in the treated set (27 patients/4.0%). In the ablation set, there were no marked differences between the treatment groups for such AEs (DE: 1.9%, warfarin: 1.3%).

Drug-related AEs as assessed by the investigator were reported for 20.7% of patients in the DE group and 17.5% of patients in the warfarin group. The only drug-related AE with an overall frequency >2% was haematoma (DE: 1.8%, warfarin: 3.3%).

Serious AEs (SAEs) were reported for 18.6% of patients in the DE group and 22.2% of patients in the warfarin group. The only SAEs with a frequency >2% in any treatment group were atrial flutter (DE: 5.9%, warfarin: 5.6%) and atrial fibrillation (DE: 1.8%, warfarin: 3.8%).

Table 5 Adverse event overall summary, N (%)

	DE 150 mg	Warfarin	Total
Patients in the treated set, N (100%)	338	338	676
Patients with any AE	225 (66.6)	242 (71.6)	467 (69.1)
Severe AEs	11 (3.3)	21 (6.2)	32 (4.7)
Investigator-defined drug-related AEs	70 (20.7)	59 (17.5)	129 (19.1)
Other significant AEs (according to ICH E3)	11 (3.3)	8 (2.4)	19 (2.8)
AEs leading to discontinuation of trial medication	19 (5.6)	8 (2.4)	27 (4.0)
SAEs	63 (18.6)	75 (22.2)	138 (20.4)
Fatal	0	0	0
Immediately life-threatening	1 (0.3)	2 (0.6)	3 (0.4)
Disability/incapacity	0	1 (0.3)	1 (0.1)
Requiring hospitalisation	26 (7.7)	34 (10.1)	60 (8.9)
Prolonged hospitalisation	13 (3.8)	22 (6.5)	35 (5.2)
Congenital anomaly	0	0	0
Other	29 (8.6)	27 (8.0)	56 (8.3)

Patients could be counted in more than 1 seriousness criterion.

The analysis of standard laboratory parameters (haematology and blood chemistry) showed similar results in the 2 treatment groups. Generally, mean

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	changes from baseline to the last value on treatment were small and did not show any relevant differences between the treatment groups. The majority of patients had clinical laboratory values within the investigator´s reference range limits throughout the trial. Possibly clinically significant abnormalities (PCSAs) in the clinical laboratory evaluations were overall rare and there were no marked treatment differences. The most frequent PCSA overall was increased serum glucose (DE: 3.4%, warfarin: 5.3%). The results for blood pressure and pulse rate were similar in both treatment groups. Mean values for systolic blood pressure, diastolic blood pressure, and pulse rate showed no marked changes from baseline to the end of treatment.
Conclusions:	In this exploratory study, treatment with dabigatran etexilate resulted in a statistically significant reduction in adjudicated ISTH MBEs when compared with INR-adjusted warfarin. This clinically relevant difference was noted from the time of the ablation and was sustained until 8 weeks after the ablation. No thromboembolic events occurred in the dabigatran etexilate group during or after the ablation and the incidence of minor bleeds was similar in both treatment groups. Periprocedural anticoagulation with uninterrupted dabigatran etexilate 150 mg twice daily was a safe, effective, and well-tolerated treatment option in patients undergoing AF ablation compared with uninterrupted vitamin K antagonist.