Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa®		**EudraCT No.:** 2011-002285-27	
Name of active ingredient group: Dabigatran etexilate (BIBR 1048)		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 MAR 2014	**Trial No.** 1160.113 **Doc. No.:** c01952747-02	**Date of trial:** 02 NOV 2011 – 03 JUN 2013	**Date of revision:** Not applicable

Title of trial:	A **R**andomised, phase II study to **E**valuate the s**A**fety and pharmacokinetics of ora**L** dab**IG**atran etexilate in patients after heart valve replaceme**N**t (**RE-ALIGN**) This trial was prematurely discontinued.
Coordinating Investigators:	[redacted]
Trial sites:	Multicentre trial in 39 sites in 10 countries
Publication (reference):	Van de Werf F, Brueckmann M, Connolly S et al. Am Heart J 2012;163 (6):931-937.e1 [P12-07232] and Eikelboom J, Connolly S, Brueckmann M, et al. NEJM 2013; 369 (13), 1206 - 1214 [P13-10607]. Any discrepancies noted between the results from the CTR 1160.113 and the publication are due to the pooled analysis and the different analysis sets.
Clinical phase:	II
Objectives:	The primary objective of this study was to validate the dosing algorithm for dabigatran etexilate (DE) in patients receiving a mechanical heart valve.
Methodology:	This was a prospective, randomised, open label, blinded endpoint (PROBE), active comparator (warfarin) trial. This study included 2 patient populations (A and B; for details on patients included under Populations A and B refer to section on diagnosis and main criteria for inclusion) who were randomised to receive either DE or warfarin in a ratio of 2:1 (DE:warfarin). This study was terminated prematurely due to safety concerns arising during conduct of the trial. Following an unblinded interim safety review it was decided as of 11 Oct 2012 that only patients in Population B should continue study treatment whereas patients in Population A were discontinued and immediately transitioned to an alternative anticoagulant. As of 28 Nov 2012, the study was completely terminated due to safety concerns which arose from additional safety measures undertaken in Population B patients. All remaining ongoing patients were immediately transitioned to a non-study anticoagulant.

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No. of subjects:

planned: entered: a minimum of 405 and up to 650 (at least 270 patients on DE and at least 135 patients on warfarin)

actual: enrolled: 328 patients
entered: 252 patients

Treatment	Entered	Treated	Analysed (for primary endpoint)
DE 150 mg b.i.d.	24	24	22
DE 220 mg b.i.d.	90	87	74
DE 300 mg b.i.d.	54	51	48
All DE	168	162	144
Warfarin	84	81	

DE: dabigatran etexilate; b.i.d.: twice daily

Diagnosis and main criteria for inclusion: Population A included patients who had undergone elective implantation of bileaflet mechanical heart valves (MHV) in the aortic and/or mitral position during the current hospital stay and not started oral anticoagulation.

Population B included patients who had undergone elective implantation of a bileaflet MHV in the mitral position more than 3 months prior to randomisation and were currently taking an oral anti-coagulant.

Patients receiving a coronary artery bypass graft (CABG) concomitantly with the valve replacement could be included in both Populations A and B. Patients had to be ≥18 years and ≤75 years of age to be included in both patient populations with the disease criteria specified above.

Test product: Dabigatran etexilate (DE)

doses: 1 capsule of 150 mg (150 mg), 2 capsules of 110 mg (220 mg), or 2 capsules of 150 mg (300 mg) twice daily

mode of admin.: Oral

batch nos.: 005478 and 201437 (110 mg); 005480 and 201666 (150 mg)

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Reference therapy:	Warfarin
doses:	1 mg, 3 mg, or 5 mg tablets; warfarin was dosed according to target International Normalisation Ratio, as recommended in guidelines, and deemed appropriate by investigator
mode of admin.:	Oral
batch nos.:	OB52UP (1 mg); OB38UW (3 mg); OC21UG (5 mg)
Duration of treatment:	12 weeks
Criteria for evaluation:	No primary or secondary efficacy endpoints were defined in this trial.
Efficacy / clinical pharmacology:	The primary pharmacokinetic (PK) endpoint of this study was the logarithm of the $C_{trough,ss}$ responses and were assessed separately at Visits 3, 4, 5, and end of treatment (EOT) i.e. 1, 2, 4, and 12 weeks after randomisation. As the trial was stopped prematurely, EOT may not be 12 weeks after randomisation for most of the patients. Analysis was also planned to be performed at Visit 6 (after implementation of Protocol amendment 4); however no plasma blood samples were available at this visit and hence this analysis was not performed. The key secondary endpoints were the cumulative probability distributions for the predicted $C_{trough,ss}$ based on the PK model from the RE-LY study and observed $C_{trough,ss}$ in all DE treated patients, together and by dose group. Exploratory clinical efficacy outcome events (OEs) evaluated in this trial included: any event of death, venous thromboembolism (VTE), myocardial infarction (MI), transient ischaemic attack (TIA), stroke, systemic embolism (SSE), and valve thrombosis.
Safety:	No primary or secondary safety endpoints were defined in this trial. Other safety outcome events evaluated in this trial included adverse events (AEs), any bleeding events, and major bleeding events.
Statistical methods:	Primary PK endpoint: ANOVA (analysis of variance) model on the logarithmic scale Secondary endpoints: Graphical methods

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Disposition

A total of 252 patients were randomised in this trial. Of these 252 randomised patients, 243 patients (Population A: 191, Population B: 52) received treatment with study medication and were included in the treated set. Of the 243 treated patients, 172 (70.8%) patients completed the planned treatment duration with trial medication. In total, 228 patients completed the trial (Population A: 180, Population B: 48) and 15 patients discontinued trial prematurely (Population A: 11, Population B: 4) with the most common reason being withdrawal of consent in 6 patients (Population A: 2, Population B: 4); this duration included the 6 month follow up period implemented post Urgent Safety Memo (USM) dated 11 Oct 2012 for Population A and the 6 month follow up period implemented post USM dated 28 Nov 2012 for Population B.

Overall, 71 (29.2%) treated patients discontinued trial medication prematurely. In total 8 (3.3%) DE treated patients switched to warfarin therapy during the trial. Overall, 158 (65.0%) treated patients continued into the 1160.138 extension study.

Demographic characteristics, exposure, and compliance

Treated patients had a mean age (SD) of 56.2 years (9.5), with a mean body mass index of 28.1 kg/m^2. Most of the patients were White (89.7%), and 64.6% were males. The median exposure to the study drug (excluding interruptions) was similar for the DE treated patients and warfarin treated patients (all DE: 82 days, warfarin: 80 days). Overall, mean compliance for all patients receiving treatment with DE ranged from 50% to 108%. For patients on warfarin, 54.6 mean% of time (SD=27.94), the INR was within the target range defined by the investigator.

Pharmacokinetics

Primary endpoint:

The primary endpoint compared observed and predicted plasma concentrations of total dabigatran at trough by visit. The primary endpoint was not met for Visits 3 and 4 as the 90% confidence intervals (CIs) were outside the predefined range of 80% to 125% (see table below). The 90% CIs were within the acceptance range for Visit 5 and EOT.

Efficacy / clinical pharmacology results (continued):

Comparison of observed and predicted plasma concentrations of total dabigatran at trough by visit – Pharmacokinetic set

	Observed		Predicted					
Visit	N	gMean plasma concentration of total dabigatran [ng/mL]	N	gMean plasma concentration of total dabigatran [ng/mL]	gMean ratio Observed : Predicted [%]	90% confidence interval [%]		Intra-indiv. gCV [%]
Visit 3	130	73.9	130	99.5	74.2	68.1	80.9	43.9
Visit 4	26	84.1	26	99.6	84.5	70.3	101.4	40.2
Visit 5	112	104.4	112	109.4	95.5	88.7	102.8	34.3
EOT	54	108.2	54	104.8	103.3	86.4	123.4	59.8

EOT end of treatment

Secondary endpoints:

The secondary endpoints were assessed by means of P-P plots. The assessment of P-P plots show that the plotted points fall within the acceptance region at Visits 3, 4, and 5 and outside the acceptance region at EOT.

At earlier visits, Population A observed trough concentrations were lower than the predicted trough concentrations based on the PK model from RE-LY. Consistently throughout all dose groups, Population A also showed lower trough concentrations of total dabigatran at the earlier visits compared to the concentrations observed in Population B. At Visit 3, the geometric mean (gMean) concentration was 66.0 ng/mL (geometric coefficient of variation, gCV: 74.1%) in Population A compared to a gMean of 122 ng/mL (gCV: 54.9%) in Population B. At Visit 5, the gMeans (gCV) were 97.9 ng/mL (62.3%) and 128 (44%) for Populations A and B, respectively. There was no trend to lower or higher concentrations in patients who experienced an outcome or bleeding event, respectively. This is most likely related to the very small numbers of patients with events. The reasons for lower than predicted exposure in Population A remain unknown.

Efficacy / clinical pharmacology results (continued):

Clinical efficacy OEs:

The exploratory efficacy OEs were adjudicated by the Independent Adjudication Committee (IAC) and the adjudicated results are presented in the table below. In general, the incidences of OEs were higher in the patients treated with DE compared with warfarin treated patients. In total, 2 patients (0.8%) died in this trial. One patient who had been randomised to DE (DE 300 group) died (cardiac death) during the post-treatment period and the second patient randomised to the warfarin group died (due to unknown cause) during the on-treatment period. There were no SSEs and VTEs reported in this trial. Stroke was reported exclusively in the DE treated patients.

Summary of patients with adjudicated efficacy outcome events (on- and intermittent-off−treatment events) based on patient population - Treated set

	DE 150		DE 220		DE 300		All DE		Warfarin		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
All patients	24		93		84		162		89		243	
Death	0	(0.0)	0	(0.0)	1	(1.2)	1	(0.6)	1	(1.1)	2	(0.8)
MI	1	(4.2)	1	(1.1)	0	(0.0)	2	(1.2)	0	(0.0)	2	(0.8)
TIA	0	(0.0)	0	(0.0)	1	(1.2)	1	(0.6)	1	(1.1)	2	(0.8)
Stroke	0	(0.0)	3	(3.2)	2	(2.4)	5	(3.1)	0	(0.0)	5	(2.1)
Valve thrombosis[1]	0	(0.0)	2	(2.2)	0	(0.0)	2	(1.2)	0	(0.0)	2	(0.8)

Due to dose up−titrations on DE and switches from DE to warfarin, patients could appear in more than 1 column, but were counted in the 'All DE' and 'Total' columns only once.
Events occurring from first study drug intake until last study drug intake + 6 days were considered.

[1] Without clinical symptoms

Safety results: Other safety outcome events: The summary of other safety outcome events is presented in the table below. Overall, 78.6% of the treated patients reported with at least one AE. The proportion with any AE was numerically higher in the DE treated patients compared with the warfarin treated patients (all DE: 78.4%, warfarin: 75.3%). A total of 30 (12.3%; all DE: 19, warfarin: 11) patients reported serious AEs (SAEs). No SAEs were fatal as deaths were reported as OEs in this trial (2 patients died). Overall, the most frequently reported AEs (by preferred term level) were atrial fibrillation (10.7%) followed by diarrhoea (8.6%) and pericardial effusion (8.2%).

Summary of other safety outcome events (on- and intermittent-off−treatment events) - Treated set

	All DE		Warfarin		Total	
	n	(%)	n	(%)	n	(%)
Number of patients	162	(100)	89	(100)	243	(100)
Patients with any AE	127	(78.4)	67	(75.3)	191	(78.6)
Patients with AEs leading to discont. of study drug	9	(5.6)	2	(2.2)	11	(4.5)
Patients with SAEs	19	(11.7)	11	(12.4)	30	(12.3)
Fatal	0	(0.0)	0	(0.0)	0	(0.0)
Immediately life-threatening	1	(0.6)	0	(0.0)	1	(0.4)
Disability/incapacity	0	(0.0)	0	(0.0)	0	(0.0)
Requiring hospitalisation	13	(8.0)	8	(9.0)	21	(8.6)
Prolonged hospitalisation	6	(3.7)	3	(3.4)	9	(3.7)
Congenital anomaly	0	(0.0)	0	(0.0)	0	(0.0)
Other	1	(0.6)	0	(0.0)	1	(0.4)
Any bleeding events[1]	33	(20.4)	10	(11.2)	43	(17.7)
Major bleeding events[1]	7	(4.3)	1	(1.1)	8	(3.3)

Due to switches from DE to warfarin, patients could appear in more than 1 column, but were counted in the 'Total' column only once.
Events occurring from first study drug intake until last study drug intake + 6 days were considered.
[1] Adjudicated by IAC

Safety results (continued):	*Bleeding events (safety outcome events)* The proportion of bleeding events was higher in the DE treated patients compared with the warfarin treated patients (all DE: 20.4%, warfarin: 11.2%). Major bleeding occurred in 7 patients (4.3%) treated with DE and 1 (1.1%) patient treated with warfarin; all these major bleedings were pericardial bleedings.
Conclusions:	The primary endpoint was not met for Visits 3 and 4 as the geometric mean ratios of observed/predicted trough plasma concentrations of total dabigatran were 74.2% (90%, CI: 68.1% – 80.9%) and 84.5% (90% CI: 70.3% – 101.4%), respectively. The 90% CIs for Visits 5 and EOT were within the acceptance range as geometric mean ratios were 95.5% (90% CI 88.7% – 102.8%) and 103.3% (90% CI 86.4% – 123.4%), respectively. The key secondary endpoint by means of P-P plot shows the plotted points to fall within the acceptance region for Visits 3, 4, and 5 and outside the acceptance region for EOT. Differences in the dabigatran exposure could be observed at the early trial visits between the 2 study populations with lower than expected exposure in Population A. Overall, incidences of thromboembolic events and bleeding events were higher in the DE treated patients as compared with the warfarin treated patients leading to premature termination of the trial. In conclusion, DE should not be used in patients with MHV for the prevention of thromboembolic events.