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.:** 2007-007536-25	**Synopsis No.:**
Name of active ingredient: dabigatran etexilate		**Page:** 1 of 4	
Module:		**Volume:** {hyperlink }	
Disclosure synopsis date: 17 DEC 2013	**Trial No. / U No.:** 1160.73 / U11-1334-02	**Date of trial:** 02 JAN 2009 – 07 AUG 2010	**Date of revision :** 04 APR 2011

Title of trial:	Randomized, open-label study of dabigatran etexilate, a novel, oral, direct thrombin-inhibitor in clinical development, in elective percutaneous coronary intervention. (D-Fine)
Principal Investigator:	[redacted]
Trial sites:	Thoraxcentre, Erasmus Medical Centre, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands Maasstadhospital, location Zuider Groene Hilledijk 315, 3075 EA Rotterdam, The Netherlands St. Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands Medical Centre Alkmaar, Wilhelminalaan 12, 1815 JD Alkmaar, The Netherlands
Publication (reference):	Data of this study have not been published
Clinical phase:	II
Objectives:	Assess whether two doses of dabigatran etexilate (110 mg or 150 mg) as compared to unfractionated heparin (UFH), both in addition to a standard dual antiplatelet regimen, provide sufficient anticoagulation in the setting of elective PCI.
Methodology:	Prospective, randomized, open-label, controlled, parallel group trial

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No. of subjects actual:	entered: 50 enrolled: 53 Treatment Dabigatran Etexilate 110 mg: entered: 20 treated: 20 analysed (for primary endpoint): FAS 19, PPS 17 Treatment Dabigatran Etexilate 150 mg: entered: 21 treated: 21 analysed (for primary endpoint): FAS 21, PPS 18 Treatment Unfractionated Heparin: entered: 10 treated: 10 analysed (for primary endpoint): 10
Diagnosis and main criteria for inclusion:	Patients with coronary artery disease undergoing elective percutaneous coronary intervention (PCI).
Test product:	dabigatran etexilate
dose:	110 mg or 150 mg 3 capsules before PCI procedure
mode of admin.:	oral
batch no.:	Batch number 091002903/700139721 110 mg Batch number 091002903/700139721 150 mg
Reference therapy:	unfractionated heparin
dose:	50-70 U/kg to maintain an ACT of 300-350 sec
mode of admin.:	intravenous
batch no.:	Differed per site as this was not issued as IMP
Duration of treatment:	Dabigatran was started 24 hours prior to the procedure, with a total of 3 capsules. For heparin, a single bolus was given in the catheterization lab. Both treatment groups received additional treatment according to the protocol.

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Criteria for evaluation: **Efficacy / clinical pharmacology:**	Anticoagulant effect was determined based on the number of patients who needed rescue anticoagulant therapy and/or had clinical signs of catheter related thrombosis during the PCI procedure. Secondary endpoints were the number of patients who experienced catheter-related thrombi requiring rescue anticoagulation therapy; abrupt vessel closure, new thrombus with reduced reflow or no reflow; catheter-related thrombi not resulting in clinical complications including guide-catheter (wire) thrombosis. Geometric mean (gMean) total dabigatran peak concentrations (2 h post-dose, just before PCI) were 98.4 ng/mL (84.9% gCV) for the 110 mg dose group and 161 ng/mL (65.2% gCV) for the 150 mg dose group. In patients with mild renal impairment (CrCl >50 but <80 mL/min) gMean 2 h post-dose ("peak") and 10 h post-dose ("trough") concentrations were approximately 60% and 42% higher, respectively, than in patients with normal renal function (CrCl ≥80 mL/min).
Safety:	Secondary safety events were the number of patients with bleeding events: major bleeding by project bleeding classification which occurred up to 3 days or discharge; any major bleeding by Thrombosis in Myocardial Infarction (TIMI) criteria, dabigatran Phase III trials bleeding classification criteria which occurred up to 3 days or discharge; any minor bleeding by TIMI criteria, dabigatran Phase III trials bleeding classification criteria which occurred up to 3 days or discharge. Further endpoints were the composite of major bleeding by project and TIMI bleeding classifications occurring up to 3 days or discharge (whatever came first) and clinical ischemic events assessed by the composite endpoint of mortality, non-fatal myocardial infarction, stroke (distinguished by type) ad clinically driven coronary revascularization. Other Adverse Events (serious and non-serious)
Statistical methods:	Descriptive statistics, means, medians, measures of variability, frequencies.

SUMMARY – CONCLUSIONS:

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Efficacy / clinical pharmacology results:	Exposure to total dabigatran increased proportional to dose; renal function was a relevant factor for dabigatran's PK in this patient population. The primary endpoint (rescue medication and/or clinical signs of catheter related thrombus during the PCI) occurred in 5 (5/41= 12%) patients in the dabigatran treatment group and in 1 (1/10= 10%) patient in the UFH group. In the per protocol analysis 1 patient in the dabigatran was left out of the analysis compared to the FAS. No significant differences between treatments were found but the small numbers yielded wide 95% confidence intervals. There was 1 patient with thrombosis in the heparin and 5 patients with MI in the pooled dabigatran groups.
Safety results:	The main analyses of bleeding events were based on the intake of any study drug. Only one minor bleeding was documented in a patient treated with UFH. This was a puncture site haematoma and was procedure-related.

Conclusions:	In general, dabigatran and UFH were safe and well tolerated in this population of patients with elective PCI for angina pectoris. The incidence of AEs (including bleeding events and outcome events) was similar for both treatment regimens. It can be concluded from this small trial that patients receiving 3 doses of DE prior to elective PCI did not achieve plasma levels that are obtained in non-valvular atrial fibrillation patients effectively treated for stroke prevention. Furthermore, it cannot be recommended to use only three doses of DE prior to elective PCI in the absence of iv heparin during the PCI. It cannot be determined from this study what plasma levels (and/or DE dosing regimen) might be required to allow the conduct of elective PCI without the use of supplemental UFH. Also it can be concluded that the safety of 3 doses of DE prior to elective PCI was confirmed.

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 and adverse event results as well as the results of secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Percent of patients who required anticoagulation and/or had clinical signs of catheter related thrombosis: from 22 to 165 minutes (primary endpoint)	Table 15.2.1.1: 1
Percent of patients who experienced catheter related thrombi requiring rescue anticoagulation therapy: from 22 to 165 minutes (secondary endpoint)	Table 15.2.2.1: 1
Percent of patients who experienced abrupt vessel closure, new thrombus with reduced reflow or no reflow: from 22 to 165 minutes (secondary endpoint)	Table 15.2.2.1: 2
Percent of patients who experienced catheter related thrombi not resulting in clinical complications including guide-catheter (wire) thrombosis: from 22 to 165 minutes (secondary endpoint)	Table 15.2.2.1: 3
Number of patients with bleeding events (secondary endpoint)	Table 15.3.5: 2
AE Summary	Table 15.3.2: 1

Table 15.1.1: 1 Summary of patient disposition

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE Combined N (%)	Heparin N (%)	Total N (%)
Enrolled					53
Not randomised					0
Randomised	22	21	43	10	53
Not treated	2	0	2	0	2
Treated	20 (100.0)	21 (100.0)	41 (100.0)	10 (100.0)	51 (100.0)
Not prematurely discontinued from trial medication	19 (95.0)	21 (100.0)	40 (97.6)	9 (90.0)	49 (96.1)
Prematurely discontinued from trial medication	1 (5.0)	0 (0.0)	1 (2.4)	1 (10.0)	2 (3.9)
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of disease under study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non compliant with protocol	1 (5.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (2.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Refused cont. medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (2.0)

Table 15.2.1.1: 1 Proportion of patients who require rescue anticoagulant and/or have clinical signs of catheter related thrombosis
FAS

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE Combined N (%)	Heparin N (%)
Total number of patients in analysis set	19 (100.00)	21 (100.00)	40 (100.00)	10 (100.00)
Number of patients requiring Rescue anticoagulant and/or catheter related thrombosis	2 (10.53)	3 (14.29)	5 (12.50)	1 (10.00)
Comparison to Heparin				
Odds ratio	1.000	1.500	1.250	
95% CI	(0.078,12.757)	(0.134,16.819)	(0.128,12.252)	

Source data: Appendix 16.2, Listing 6.1.1

Table 15.2.2.1: 1 Proportion of patients who experienced catheter related thrombi requiring rescue anticoagulation therapy
FAS

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE Combined N (%)	Heparin N (%)
Total number of patients in analysis set	19 (100.00)	21 (100.00)	40 (100.00)	10 (100.00)
Number of patients requiring Catheter related thrombi requiring rescue anticoagulation therapy	0	0	0	0

Source data: Appendix 16.2, Listing 6.1.1 rescue.sas 10MAR2011

Table 15.2.2.1: 2 Proportion of patients who experienced abrupt vessel closure, new thrombus with reduced flow or no reflow
FAS

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE Combined N (%)	Heparin N (%)
Total number of patients in analysis set	19 (100.00)	21 (100.00)	40 (100.00)	10 (100.00)
Number of patients requiring Abrupt vessel closure, new thrombus with reduced flow, or no-reflow	2 (10.53)	1 (4.76)	3 (7.50)	0

Source data: Appendix 16.2, Listing 6.1.1 rescue.sas 10MAR2011

Table 15.2.2.1: 3 Proportion of patients who experienced catheter related thrombi not resulting in clinical complications including guide-catheter (wire) thrombosis - FAS

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE Combined N (%)	Heparin N (%)
Total number of patients in analysis set	19 (100.00)	21 (100.00)	40 (100.00)	10 (100.00)
Number of patients requiring Catheter related thrombi not resulting in clinical complications	0	0	0	0

Source data: Appendix 16.2, Listing 6.1.1 rescue.sas 10MAR2011

Table 15.3.5: 2 Location of bleed outcome events
treated set

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE Combined N (%)	Heparin N (%)
Total number of patients in analysis set	20 (100.0)	21 (100.0)	41 (100.0)	10 (100.0)
Total number of patients with a bleed outcome event	0	0	0	1 (10.0)
Location of bleed				
Other	0	0	0	1 (10.0)

Table 15.3.2: 1 Adverse event overall summary - treated set

	DE 110mg bid N (%)	DE 150mg bid N (%)	DE combined N (%)	Heparin N (%)
Number of patients	20 (100.0)	21 (100.0)	41 (100.0)	10 (100.0)
Patients with any AE	5 (25.0)	9 (42.9)	14 (34.1)	3 (30.0)
Patients with severe AEs	0 (0.0)	2 (9.5)	2 (4.9)	0 (0.0)
Patients with investigator defined drug-related AEs	2 (10.0)	0 (0.0)	2 (4.9)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with other significant AEs (according to ICH E3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	1 (5.0)	0 (0.0)	1 (2.4)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prol.hospitalisation	1 (5.0)	0 (0.0)	1 (2.4)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 13.1