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			
Name of active ingredient: BIBR 1048, dabigatran etexilate		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 Jul 2009	**Trial No. / U No.:** 1160.42 / U09-3247-01	**Date of trial:** 06 JAN 2004 – 21 JAN 2009	**Date of revision:** Not applicable

Title of trial:	Long-term, open-label follow-up treatment of patients with atrial fibrillation who have been previously treated with BIBR 1048 in the PETRO trial (Trial 1160.20). (PETRO Extension trial: **PETRO-Ex**)	
Coordinating Investigator:	[redacted]	
Trial sites:	Multicenter trial cf. Appendix 16.1.4	
Publication (reference):	P07-11021	Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study). Am J Cardiol. 2007. 100: 1419-1426.
	P09-06700	Wallentin LC, Ezekowitz M, Simmers TA, Pedersen KE, Stangier J, Nehmiz G, Hettiarachchi R, Reilly P, PETRO Investigators. Safety and efficacy of a new oral direct thrombin inhibitor dabigatran in atrial fibrillation: a dose-finding trial with comparison to warfarin. 27th Cong of the European Society of Cardiology (ESC), Stockholm. 2005. 3-7 Sep 2005 (Poster).
Clinical phase:	IIa	
Objectives:	The primary objective of this trial was to study the long-term safety and efficacy of dabigatran etexilate, with or without concomitant chronic treatment with acetylsalicylic acid (ASA), in patients with atrial fibrillation, and other additional risk factors for thromboembolic events.	
Methodology:	Open-label, non-randomized, 4-dose group study of dabigatran etexilate (150 mg qd, 150 mg bid, 300 mg qd, 300 mg bid) with additional ASA at the discretion of the investigator. There was no control group.	

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No. of subjects:	
planned:	entered: 361
actual:	enrolled: 361 Treatment 150 mg QD: entered: 98 treated: 102 analysed (for primary endpoint): 102 Treatment 150 mg BID: entered: 89 treated: 356 analysed (for primary endpoint): 356 Treatment 300 mg QD: entered: 50 treated: 90 analysed (for primary endpoint): 90 Treatment 300 mg BID: entered: 124 treated: 161 analysed (for primary endpoint): 161
Diagnosis and main criteria for inclusion:	Paroxysmal, persistent or permanent (chronic) non-rheumatic atrial fibrillation , coronary artery disease and at least one additional risk factor for thromboembolic events.
Test product:	BIBR 1048
dose:	150 mg qd, 150 mg bid, 300 mg qd, 300 mg bid
mode of admin.:	Oral capsules, with food and water
batch nos.:	9030144, 9050060, 605412, 702896
Reference therapy:	None
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	Initially 2 years, extended an additional 5 years.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa			
Name of active ingredient: BIBR 1048, dabaigatran etexilate		**Page:** 3 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 Jul 2009	**Trial No. / U No.:** 1160.42 / U09-3247-01	**Date of trial:** 06 JAN 2004 – 21 JAN 2009	**Date of revision:** Not applicable

Criteria for evaluation:

Efficacy / clinical pharmacology:

A composite clinical endpoint including the incidence of stroke (fatal + non-fatal), TIAs, systemic thromboembolism, myocardial infarction (fatal + non-fatal), other major adverse cardiac events, and all-cause mortality

Secondary efficacy endpoints:

- Net clinical cost (NCC) as measured by the composite clinical endpoint of stroke/TIA/systemic thromboembolism/MI/death plus major bleeds
- The occurrence rates of
  - stroke (fatal and non-fatal)
  - transient ischemic attacks (TIAs)
  - systemic thromboembolism
  - myocardial infarction (fatal &non-fatal)
  - other major cardiac events
  - all cause mortality

Safety:

The primary safety endpoint was the incidence of bleeding.

- Bleeding events were independently and blindly adjudicated. They were classified as major and minor and were further subdivided into clinically significant and nuisance bleeds.

Other safety criteria:

- The incidence of all adverse events, notably bleeding.
- Standard laboratory assessments, including liver function tests.
- Changes in physical examination.
- Discontinuation of therapy due to an adverse event.

Statistical methods:

Descriptive statistics, frequencies of events

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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Name of active ingredient: BIBR 1048, dabaigatran etexilate		**Page:** 4 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 Jul 2009	**Trial No. / U No.:** 1160.42 / U09-3247-01	**Date of trial:** 06 JAN 2004 – 21 JAN 2009	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The normalized incidence of the primary efficacy endpoint (composite of stroke/TIA, STE, MI/MACE and all-cause death) was lowest on 300 mg BID (2.4% per year) and highest on 50 mg BID (17.0% per year), and intermediate on 150-300 mg daily dose (5.0%per year on 150 mg QD, 5.7% per year on 150 mg BID, 4.5% per year on 300 mg QD).

Stroke rate (any stroke) was lowest in the BID treated patients (0% per year with 300 mg BID, 1.1% per year with 150 mg BID). On 300 mg QD, it was 1.7% per year, and ≥4.3% per year for 150 mg QD and 50 mg BID.

The endpoint of non-CNS thromboembolic event and stroke was lowest in the dabigatran 300mg BID (1.2% per year) and 150 mg BID (1.3% per year). At 300 mg QD, it was 2.1% per year, while at dose levels below 150 mg BID, the annualized stroke and thromboembolic event rate was ≥5%.

Intra-individual variability of trough plasma concentration was 38.9% (gCV based on ANOVA) in patients with longer term follow up not taking interfering medications.

Pharmacokinetic and pharmacodynamic values and their relationship did not change while patients received dabigatran etexilate for more than four years.

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Name of active ingredient: BIBR 1048, dabaigatran etexilate		**Page:** 5 of 7	**Synopsis No.:**
Module:		**Volume:**	
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Safety results:

Total exposure to dabigatran etexilate was 1250 patient years in this trial, with dosing regimens of 150 mg BID and 300 mg QD representing 67% and 19% of the total exposure, respectively. After the transition into the extension trial, there was a continuing decline in patient participation over time. More than half of the patients who entered the extension study remained on treatment for more than 4 years.

Adjudicated bleeding events were considered the primary safety endpoint. Most categories of bleeding events were dose-related with higher doses of dabigatran etexilate associated with a higher time-normalized bleeding incidence. For those patients with “any bleed” or “any major or minor/relevant bleeding” as defined by the protocol, gastrointestinal bleeds were most common, including rectal hemorrhage, gingival bleeding, hemorrhoidal hemorrhage, hematochezia and melena. Within the other SOCs, the preferred terms most commonly reported were, epistaxis, hematoma, contusion and hematuria. The risk of bleeding events was relatively consistent over the period of the study. The frequency of any bleeding and major bleeding was almost double in patients treated with ASA plus dabigatran compared to dabigatran alone.

Those bleeding events considered major, as outlined by the protocol, were gastrointestinal or CNS in nature (cerebral haemorrhage, haemorrhagic stroke, haematomyelia and intracranial haemorrhage). Of the 6 fatal bleeding events, 3 were due to cerebral hemorrhage, and 1 each was due to gastrointestinal hemorrhage, ruptured aortic aneurysm and aortic dissection. These events all occurred in patients treated with a daily dose of 300 mg; 5 during treatment with 150 mg BID and one receiving 300 mg QD.

Adverse events categorized as related to the gastrointestinal system were most frequently reported, including nausea, dyspepsia, diarrhoea, constipation, upper abdominal pain. Nervous system disorders were dizziness and headache. The frequencies of these non-bleeding events generally appear higher as the dose is increased, although when considering patient years of exposure there was no apparent dose relationship. Selected GI events (pain/dyspepsia/gastritis) were evaluated over time throughout 0-3, 3-6 and >6 months of dabigatran exposure. There were no discernable time-effect trends.

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Name of active ingredient: BIBR 1048, dabaigatran etexilate		**Page:** 6 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 Jul 2009	**Trial No. / U No.:** 1160.42 / U09-3247-01	**Date of trial:** 06 JAN 2004 – 21 JAN 2009	**Date of revision:** Not applicable

Safety results (continued):

Discontinuation of study medication due to AEs occurred in approximately one-third of patients who entered this trial. The frequencies of discontinuation were highest for outcome events (11.1%), followed by bleeding events (7.9%), cardiac events (7.9%) and gastrointestinal events (7.2%). Preferred terms with a frequency of ≥0.9% were ischemic stroke, hematuria, cardiac arrest and cardiac failure.

Serious adverse events occurred in approximately half the patients participating in this trial. Cardiac disorders was the SOC contributing the highest frequency of SAEs, including cardiac failure, atrial fibrillation, bradycardia, congestive heart failure, myocardial infarction, unstable angina and angina pectoris. SAEs in the Infections and infestations SOC were mostly pneumonia, no other preferred terms in this SOC were reported at a frequency above 0.7%. Nervous system SAEs were mostly syncope, dizziness, and ischemic stroke. Within the Gastrointestinal disorder SOC, SAEs included inguinal hernia and gastrointestinal haemorrhage.

There were 28 deaths that occurred during the trial, plus 5 post-treatment and one post-study death. Five of these deaths were considered drug related; three patients with cerebral hemorrhage, one with GI hemorrhage and one case of cardiogenic shock/cardiac arrest.

The incidence of liver enzyme elevations was generally low. ALT or AST increases greater than three times the upper limit of normal were 1.5% per year across all treatments. There were 5 cases of AST and ALT elevations greater than 3 times the upper limit of normal with concomitant bilirubin elevations >1.2 times the upper limit of normal, and only 3 cases total if the bililrubin criteria is increased to greater than 2 times the upper limit of normal. In all cases, except the patient with pancreatic cancer/liver metastases, the liver enzymes returned to normal. Five patients discontinued trial medication due to increases in liver function tests.

There were no significant findings relevant to vital signs or ECGs in this trial.

This long term safety trial demonstrated dabigatran etexilate was generally well tolerated since over 50% of the entered patients were treated for more than 4 years. The most commonly observed adverse events were bleeding, as would be expected with any anticoagulant. In this study, bleeding adverse events appear to be generally dose-related. The 150 mg dose BID appears to have an acceptable safety profile with long term use of up to five years.

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Name of active ingredient: BIBR 1048, dabaigatran etexilate		**Page:** 7 of 7	**Synopsis No.:**
Module:		**Volume:**	
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Conclusions:

Dabigatran etexilate at a total daily dose of 300 mg/day was generally well tolerated in this long term safety trial, which included exposure up to 5 years. Over half of the entered patients continued to receive dabigatran etexilate through the end of the trial. Doses of dabigatran etexilate below 150 mg per day had high rates of thromboembolic events and low bleeding rates, whereas dabigatran etexilate doses of 600 mg per day produced unacceptable bleeding rates with low stroke incidences. Concomitant use of ASA with dabigatran etexilate increased the rate of both major and minor bleeding approximately two-fold. A daily dose of 300 mg/day, either 300 mg QD or 150 mg BID, was well tolerated with a relatively low stroke rate. A dabigatran etexilate dose of 150 mg BID appears to provide the best risk-benefit ratio.

The assessment of intra-individual variability in trough plasma concentrations and coagulation prolongation at trough indicated a relatively stable and reproducible exposure to dabigatran etexilate for over 4 years.

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 secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1: 2
Rate of any stroke with incidence per 100 treatment years	Table 15.2: 1
Bleeding events with incidence per 100 treatment years	Table 15.3.2.1: 1

Table 15.1.1: 2 Disposition of patients in PETRO-Ex trial - all patients by treatment at entry

	150 mg QD	150 mg BID	300 mg QD	300 mg BID	Total
Enrolled					361
Not Entered					0
Entered	98	89	50	124	361
Not Treated	0	0	0	0	0
Treated	98 (100.0)	89 (100.0)	50 (100.0)	124 (100.0)	361 (100.0)
NOT Prematurely Discontinued	50 (51.0)	52 (58.4)	29 (58.0)	77 (62.1)	208 (57.6)
Prematurely Discontinued	48 (49.0)	37 (41.6)	21 (42.0)	47 (37.9)	153 (42.4)
Adverse Events	36 (36.7)	25 (28.1)	13 (26.0)	33 (26.6)	107 (29.6)
Worsening of Disease Under Study	2 (2.0)	2 (2.2)	1 (2.0)	3 (2.4)	8 (2.2)
Worsening of Other Pre-existing Disease	4 (4.1)	2 (2.2)	4 (8.0)	0 (0.0)	10 (2.8)
Other Adverse Event	30 (30.6)	21 (23.6)	8 (16.0)	30 (24.2)	89 (24.7)
Administrative	5 (5.1)	5 (5.6)	5 (10.0)	5 (4.0)	20 (5.5)
Non Compliant with Protocol	4 (4.1)	0 (0.0)	2 (4.0)	2 (1.6)	8 (2.2)
Lost to Follow-Up	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.3)
Consent Withdrawn	1 (1.0)	4 (4.5)	3 (6.0)	3 (2.4)	11 (3.0)
Other	7 (7.1)	7 (7.9)	3 (6.0)	9 (7.3)	26 (7.2)

Table 15.2: 1 Clinical events - outcome endpoints

	50 mg QD	50 mg BID	150 mg QD	150 mg BID	300 mg QD	300 mg BID	Total Dab.
# patients ever	1	105	102	356	90	161	432
Cumulative exposure (patient years)	0.05	23.51	60.43	842.06	242.04	82.01	1250.10
Any stroke	0 (0.0)	1 (4.3)	3 (5.0)	9 (1.1)	4 (1.7)	0 (0.0)	17 (1.4)
Ischaemic (as judged by inv.)	0 (0.0)	1 (4.3)	3 (5.0)	4 (0.5)	4 (1.7)	0 (0.0)	12 (1.0)
Haemorrhagic (as judged by inv.)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.6)	0 (0.0)	0 (0.0)	5 (0.4)
Unclassified/ undistiguishable (by inv.)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any TIA	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.4)	0 (0.0)	3 (0.2)
Non-CNS systemic thromboembolism	0 (0.0)	2 (8.5)	0 (0.0)	2 (0.2)	1 (0.4)	1 (1.2)	6 (0.5)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.1)	1 (0.4)	0 (0.0)	10 (0.8)
Other MACE	0 (0.0)	2 (8.5)	0 (0.0)	9 (1.1)	2 (0.8)	1 (1.2)	14 (1.1)
All cause death	0 (0.0)	0 (0.0)	0 (0.0)	23 (2.7)	5 (2.1)	0 (0.0)	28 (2.2)
Primary endpoint (composite)	0 (0.0)	4 (17.0)	3 (5.0)	48 (5.7)	11 (4.5)	2 (2.4)	68 (5.4)
Ischemic stroke, TIA, non-CNS-TE, MI, MACE, Death	0 (0.0)	4 (17.0)	3 (5.0)	46 (5.5)	11 (4.5)	2 (2.4)	66 (5.3)
Stroke, non-CNS-TE	0 (0.0)	2 (8.5)	3 (5.0)	11 (1.3)	5 (2.1)	1 (1.2)	22 (1.8)

Number of cases, with incidence per 100 patient years in parentheses (total exposure, approximating exposure to event)

Table 15.3.2.1: 1 Clinical events - bleeding events - by treatment regimen at onset (no ASA subdivision)

	50 mg QD	50 mg BID	150 mg QD	150 mg BID	300 mg QD	300 mg BID	Total Dab.	Warfarin	Total
# patients ever	1	105	102	356	90	161	432	70	502
Cumulative exposure (patient years)	0.05	23.51	60.43	842.06	242.04	82.01	1250.10	15.75	1265.85
Major	0 (0.0)	0 (0.0)	4 (6.6)	26 (3.1)	2 (0.8)	6 (7.3)	36 (2.9)	0 (0.0)	36 (2.8)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.6)	1 (0.4)	0 (0.0)	6 (0.5)	0 (0.0)	6 (0.5)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Critical organ	0 (0.0)	0 (0.0)	2 (3.3)	11 (1.3)	1 (0.4)	2 (2.4)	15 (1.2)	0 (0.0)	15 (1.2)
Operation	0 (0.0)	0 (0.0)	1 (1.7)	5 (0.6)	0 (0.0)	1 (1.2)	6 (0.5)	0 (0.0)	6 (0.5)
Transfusion>=2 units	0 (0.0)	0 (0.0)	1 (1.7)	11 (1.3)	1 (0.4)	2 (2.4)	15 (1.2)	0 (0.0)	15 (1.2)
Hgb drop>=20 g/L	0 (0.0)	0 (0.0)	1 (1.7)	14 (1.7)	1 (0.4)	5 (6.1)	21 (1.7)	0 (0.0)	21 (1.7)
Multiple (*)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)
Clinically relevant only (**)	0 (0.0)	2 (8.5)	3 (5.0)	38 (4.5)	14 (5.8)	16 (19.5)	69 (5.5)	4 (25.4)	73 (5.8)
Any major or clinically relevant bleed	0 (0.0)	2 (8.5)	7 (11.6)	64 (7.6)	16 (6.6)	22 (26.8)	103 (8.2)	4 (25.4)	107 (8.5)
Nuisance bleed only (**)	0 (0.0)	4 (17.0)	6 (9.9)	60 (7.1)	20 (8.3)	26 (31.7)	109 (8.7)	8 (50.8)	117 (9.2)
Any bleed	0 (0.0)	6 (25.5)	13 (21.5)	124 (14.7)	36 (14.9)	48 (58.5)	198 (15.8)	12 (76.2)	210 (16.6)

Number of cases, with incidence per 100 patient years in parentheses (total exposure, approximating exposure to event)
(*) Independence of episodes after individual assessment, based on time distance and other characteristics
(**) If a patient has, for the same treatment, several events of different types, only the worst one is counted