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 Study Report**		
Name of finished product: to be determined				
Name of active ingredient: BIBR 1048 MS, dabigatran etexilate mesilate		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 5 April 2007	**Number:** U07-3126	**Study period (dates):** 10 November 2005 – 4 September 2006		

Title of study:	Open label, randomised exploratory dose response study in pharmacodynamics and safety of BIBR 1048 (110 mg b.i.d. and 150 mg b.i.d.) for 12 weeks in patients with non-valvular atrial fibrillation in comparison to warfarin
Investigator:	[redacted] MD, [redacted]
Study centres:	Multicentre study
Publication (reference):	Data of this study has not been published
Clinical phase:	II
Objectives:	The primary objective was to evaluate the safety of BIBR 1048 (dabigatran etexilate) administered orally at doses of 110 and 150 mg twice daily, for 12 weeks in patients with non-valvular atrial fibrillation (paroxysmal, persistent or permanent) in comparison with warfarin.
Methodology:	Randomised, open-label study
No. of subjects:	
planned:	entered: 150
actual:	enrolled: 211
	Dabigatran etexilate 110 mg b.i.d.: entered: 53 treated: 46 analysed (for primary endpoint): 46
	Dabigatran etexilate 150 mg b.i.d.: entered: 59 treated: 58 analysed (for primary endpoint): 58
	Warfarin: entered: 62 treated: 62 analysed (for primary endpoint): 62

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Diagnosis and main criteria for inclusion:	Non-valvular atrial fibrillation (paroxysmal, persistent or permanent) <u>Inclusion criteria</u> • Non-valvular atrial fibrillation (paroxysmal, persistent or permanent) diagnosed from electrocardiogram (ECG) at least twice within 1 year before the date of informed consent • An additional risk factor for thromboembolism; one or more of the following conditions/events: hypertension, diabetes mellitus, left-side heart failure, a previous ischemic stroke or transient ischemic attack, aged of 75 years or older, or a history of coronary artery diseases • Age of 20 years or older • Written informed consent
Test product:	Dabigatran etexilate 110 mg and 150 mg capsules
dose:	110 mg b.i.d., 150 mg b.i.d.
mode of admin.:	po
batch no.:	110 mg: 504593, 150 mg: 505005
Duration of treatment:	12 weeks
Reference therapy:	Warfarin potassium 1 mg tablet
dose:	Adjusted dose, target international normalised ratio (INR) range of ≥2.0 - ≤3.0 (≥1.6 - ≤2.6 for patients aged 70 or more), usually once daily in the morning or evening
mode of admin.:	po
batch no.:	615051

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Criteria for evaluation:

Efficacy:

- A composite clinical endpoint including the incidence of ischemic or haemorrhagic stroke (fatal or non-fatal), transient ischemic attacks, systemic embolism, myocardial infarction (fatal or non-fatal), other major adverse cardiac events, and death
- The incidence of each thromboembolic event: ischemic or haemorrhagic stroke (fatal or non-fatal), transient ischemic attack, systemic embolism, myocardial infarction (fatal or non-fatal), other major adverse cardiac events, and death
- Anticoagulation effects

  D-dimer, soluble fibrin, activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), INR, 11-dehydrothromboxane B2
- The steady-state pharmacokinetics of total dabigatran (plasma concentration, AUC, C_{max} and other pharmacokinetic parameters by population pharmacokinetic analysis), which will be reported separately

Safety:

The primary endpoints were the following safety endpoints.

- Incidence of bleeding event

  Bleeding events were classified as major bleeding and minor bleeding events
- Incidence and severity of adverse events
- Discontinuation of the study drug due to adverse events
- Changes in laboratory test values

Statistical methods: Descriptive statistics, ANOVA, population pharmacokinetic analysis (will be reported separately)

SUMMARY – CONCLUSIONS:

Efficacy results: No patients of the dabigatran groups experienced thromboembolic events. One patient of the warfarin group experienced an ischemic stroke with haemorrhagic transformation (haemorrhagic cerebral infarction). Ischemic stroke coded as cerebral infarction was reported in 1 patient during the screening period and in 1 patient during the post treatment period in the 150 mg b.i.d. group.

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Efficacy results (cont.):

Trough plasma concentrations of total dabigatran indicated that steady-state conditions were attained on or before the time of the first assessment after 4-10 days of dabigatran etexilate administration. Trough concentration increased proportionally with increasing dose. Females showed slightly higher trough concentrations than males, although there was imbalance in number of patients. A trend towards elevated trough concentration with decreasing creatinine clearance was observed.

The anti-coagulation effect of dabigatran etexilate was assessed by evaluating aPTT, ECT and INR at the same time as the measurements of drug plasma concentration. These markers also indicated that steady-state conditions were attained on or before the time of the first assessment after 4-10 days of dabigatran etexilate administration. Trough ECT values were significantly prolonged after administration of dabigatran etexilate. There was a close correlation between aPTT or ECT and total dabigatran plasma concentration. The prolongation of coagulation markers, aPTT and ECT, by dabigatran etexilate administration was longer in the 150 mg b.i.d. group than that in the 110 mg b.i.d. group.

Plasma D-dimer and soluble fibrin were stable at low levels during treatment with either dabigatran etexilate or warfarin. Urinary 11-dehydrothromboxane B2 concentrations were lower in patients who concomitantly received aspirin compared with patients without concomitant administration of aspirin.

Safety results:

No patients in the 110 mg b.i.d. group experienced major bleeding events. Major bleeding events occurred in 1 patient (1.7%) from the 150 mg b.i.d. group (prostatic haemorrhage) and in 2 patients (3.2%) from the warfarin group (haemorrhagic cerebral infarction and retinal haemorrhage due to macular degeneration). All the three patients received aspirin.

Major or clinically relevant bleeding events occurred dose-dependently in the dabigatran groups, the incidence was however lower in the 110 mg b.i.d. and 150 mg b.i.d. groups than in the warfarin group: 2/46 (4.3%) in the 110 mg b.i.d. group, 5/58 (8.6%) in the 150 mg b.i.d. group, and 7/62 (11.3%) in the warfarin group. Aspirin increased the incidence of major or clinically relevant bleeding events.

Any bleeding events occurred dose-dependently in the dabigatran groups. The incidence in the 110 mg b.i.d. group (21.7%) was similar to that in the warfarin group (24.2%) and the incidence in the 150 mg b.i.d. group (34.5%) was higher than that in the warfarin group (24.2%).

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Safety results (cont.):	No patients in the dabigatran groups had liver function test values exceeded twice the upper limit of normal range. No serious adverse events related to the investigational drug occurred in the dabigatran groups.
Conclusions:	After oral administration in patients with atrial fibrillation, the trough plasma concentration of total dabigatran and the anti-coagulation effect reached steady-state levels on or before the time of the first assessment after 4-10 days of dabigatran etexilate administration. Increasing dose resulted in a proportional increase in trough drug concentration. Trough ECT values were significantly prolonged after administration of dabigatran etexilate. There was a close correlation between coagulation markers (aPTT and ECT) and plasma concentration of total dabigatran. The trough drug concentration and coagulation marker response in this Japanese study were comparable with data from the preceding PETRO study, which was performed in Europe and the US. The safety results showed that 110 mg b.i.d. and 150 mg b.i.d. of dabigatran etexilate was well-tolerated and appeared not to have higher bleeding risk than warfarin in patients with non-valvular atrial fibrillation. The safety, pharmacokinetic, pharmacodynamic and efficacy results of this study conducted in Japanese patients with non-valvular atrial fibrillation at moderate to high risk of stroke were similar to those of a study (PETRO, 1160.20) conducted almost exclusively in Caucasians in Europe and the United States. These data support the inclusion of Japanese patients in ongoing and future multinational clinical evaluations of dabigatran etexilate.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and/or results for primary and secondary endpoints of the trial.

Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
Adverse event overall summary (primary endpoint)	Table 15.3.1.2: 1
Frequency [N (%)] of patients with adverse events leading to treatment discontinuation (primary endpoint)	Table 15.3.1.3: 5
Frequency [N (%)] of patients with adverse events by intensity, treatment, primary system organ class and preferred term (primary endpoint)	Table 15.3.1.2: 6
Frequency of patients N [%] categorized by multiples of the reference range limits for laboratory tests (primary endpoint)	Table 15.3.2: 5
Thromboembolic events − full analysis set (secondary endpoint)	Table 15.2.1: 1
Trough aPTT after 110 mg and 150 mg dabigatran etexilate b.i.d. (secondary endpoint)	Table 11.5.3: 1
Trough ECT after 110 mg and 150 mg dabigatran etexilate b.i.d. (secondary endpoint)	Table 11.5.3: 3
Trough INR after 110 mg and 150 mg dabigatran etexilate b.i.d. (secondary endpoint)	Table 11.5.3: 5
Steady-state pharmacokinetics of total dabigatran trough plasma Concentration (secondary endpoint)	Table 15.5.3: 1

Table 15.1.1: 1 Disposition of patients

	DBGTRN110bid N (%)	DBGTRN150bid N (%)	Warfarin N (%)	Total N (%)
Enrolled				211
Not entered/randomised				37
Entered/randomised	53	59	62	174
Not treated	7	1	0	8
Treated	46 (100.0)	58 (100.0)	62 (100.0)	166 (100.0)
Not prematurely discontinued from trial medication	41 (89.1)	49 (84.5)	57 (91.9)	147 (88.6)
Prematurely discontinued from trial medication	5 (10.9)	9 (15.5)	5 (8.1)	19 (11.4)
Adverse event	4 (8.7)	8 (13.8)	4 (6.5)	16 (9.6)
Worsening of disease under study	0	1 (1.7)	0	1 (0.6)
Worsening of other pre-existing disease	1 (2.2)	0	0	1 (0.6)
Other adverse event	3 (6.5)	7 (12.1)	4 (6.5)	14 (8.4)
Non compliant with protocol	1 (2.2)	1 (1.7)	1 (1.6)	3 (1.8)
Consent withdrawn	0	0	0	0
Other	0	0	0	0
Completed planned observation time	41 (89.1)	49 (84.5)	57 (91.9)	147 (88.6)
Not completed planned observation time	5 (10.9)	9 (15.5)	5 (8.1)	19 (11.4)
Adverse event	4 (8.7)	8 (13.8)	4 (6.5)	16 (9.6)
AE study dis. worse	0	1 (1.7)	0	1 (0.6)
AE oth. dis. worse	1 (2.2)	0	0	1 (0.6)
AE other	3 (6.5)	7 (12.1)	4 (6.5)	14 (8.4)
Lack of efficacy	0	0	0	0
Non compl. protocol	1 (2.2)	1 (1.7)	1 (1.6)	3 (1.8)
Lost to follow-up	0	0	0	0
Consent withdrawn	0	0	0	0
Other	0	0	0	0

Patient [redacted] of entered/randomised patients in the warfarin group was not randomised

Table 15.3.1.2: 1 Adverse event overall summary – safety set

Treatment analysis: Safety analysis

	DBGTRN110bid N (%)	DBGTRN150bid N (%)	Warfarin N (%)
Number of patients	46 (100.0)	58 (100.0)	62 (100.0)
Patients with any AE	29 (63.0)	49 (84.5)	41 (66.1)
Patients with severe AEs	0	2 (3.4)	2 (3.2)
Patients with investigator defined drug-related AEs	9 (19.6)	21 (36.2)	14 (22.6)
Patients with other significant AEs (according to ICH E3)	3 (6.5)	6 (10.3)	2 (3.2)
Patients with AEs leading to discontinuation of trial drug	3 (6.5)	8 (13.8)	4 (6.5)
Patients with significant non-serious AEs (pre-specified events)	0	0	0
Patients with serious AEs	0	6 (10.3)	5 (8.1)
Imm life-threatening	0	1 (1.7)	0
Disability/incap.	0	0	1 (1.6)
Req.hospitalisation	0	5 (8.6)	5 (8.1)
Other	0	2 (3.4)	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 9.1 was used for reporting

Table 15.3.1.3: 5 Frequency [N (%)] of patients with adverse events leading to treatment discontinuation by treatment, primary system organ class and preferred term – safety set

Any bleeding [adjudicated]
Treatment analysis: Safety analysis

System organ class/ Preferred term	DBGTRN110bid N (%)	DBGTRN150bid N (%)	Warfarin N (%)
Number of patients	46 (100.0)	58 (100.0)	62 (100.0)
Total with adverse events leading to treatment discontinuation	1 (2.2)	2 (3.4)	2 (3.2)
Nervous system disorders	0	0	1 (1.6)
Haemorrhagic cerebral infarction	0	0	1 (1.6)
Eye disorders	0	0	1 (1.6)
Macular degeneration	0	0	1 (1.6)
Retinal haemorrhage	0	0	1 (1.6)
Gastrointestinal disorders	0	1 (1.7)	0
Rectal haemorrhage	0	1 (1.7)	0
Renal and urinary disorders	1 (2.2)	0	0
Haematuria	1 (2.2)	0	0
Reproductive system and breast disorders	0	1 (1.7)	0
Prostatic haemorrhage	0	1 (1.7)	0

Percentages are calculated using total number of patients per treatment as the denominator.

MedDRA version 9.1 was used for reporting

Table 15.3.1.2: 6 Frequency [N (%)] of patients with adverse events by intensity, treatment, primary system organ class and preferred term – safety set

Treatment analysis: Safety analysis

System organ class/ Preferred term	Mild			Mod		
	DBGTRN110bid N (%)	DBGTRN150bid N (%)	Warfarin N (%)	DBGTRN110bid N (%)	DBGTRN150bid N (%)	Warfarin N (%)
Number of patients	46 (100.0)	58 (100.0)	62 (100.0)	46 (100.0)	58 (100.0)	62 (100.0)
Total with adverse events	28 (60.9)	46 (79.3)	35 (56.5)	1 (2.2)	1 (1.7)	4 (6.5)
Infections and infestations	10 (21.7)	13 (22.4)	12 (19.4)	0	0	0
Nasopharyngitis	5 (10.9)	10 (17.2)	8 (12.9)	0	0	0
Chronic sinusitis	2 (4.3)	0	0	0	0	0
Bronchitis acute	1 (2.2)	0	0	0	0	0
Gastroenteritis viral	1 (2.2)	0	1 (1.6)	0	0	0
Influenza	1 (2.2)	0	0	0	0	0
Sinusitis	1 (2.2)	0	0	0	0	0
Urinary tract infection	1 (2.2)	0	0	0	0	0
Anisakiasis	0	1 (1.7)	0	0	0	0
Bronchiolitis	0	1 (1.7)	0	0	0	0
Infection	0	1 (1.7)	0	0	0	0
Pneumonia	0	0	0	0	0	0
Rhinitis	0	1 (1.7)	0	0	0	0
Diverticulitis	0	0	1 (1.6)	0	0	0
Keratitis herpetic	0	0	1 (1.6)	0	0	0
Pulmonary tuberculosis	0	0	1 (1.6)	0	0	0
Upper respiratory tract infection	0	0	1 (1.6)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.7)	0	0	0	0
Prostate cancer	0	1 (1.7)	0	0	0	0

Percentages are calculated using total number of patients per treatment as the denominator.

MedDRA version 9.1 was used for reporting

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

SUBSTRATES : Bilirubin, total

Treatment/ Visit	< LL	[LL, UL]	(UL, 2*UL]	(2*UL, 3*UL]	(3*UL, 5*UL]
DBGTRN110bid					
Baseline	0	43 (93.5)	3 (6.5)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 4	0	41 (97.6)	1 (2.4)	0	0
Week 8	0	37 (92.5)	3 (7.5)	0	0
Week 12	0	37 (90.2)	4 (9.8)	0	0
Min Post Baseline	0	46 (100.0)	0	0	0
Max Post Baseline	0	40 (87.0)	6 (13.0)	0	0
Last Value on Treatment	0	42 (91.3)	4 (8.7)	0	0
DBGTRN150bid					
Baseline	0	56 (96.6)	2 (3.4)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 2	0	1 (100.0)	0	0	0
Week 4	0	50 (94.3)	3 (5.7)	0	0
Week 8	0	44 (91.7)	4 (8.3)	0	0
Week 12	0	48 (96.0)	2 (4.0)	0	0
Min Post Baseline	0	57 (98.3)	1 (1.7)	0	0
Max Post Baseline	0	51 (87.9)	7 (12.1)	0	0
Last Value on Treatment	0	55 (94.8)	3 (5.2)	0	0
Warfarin					
Baseline	0	58 (93.5)	4 (6.5)	0	0
Week 1	0	1 (100.0)	0	0	0
Week 4	0	55 (94.8)	3 (5.2)	0	0
Week 8	0	54 (91.5)	5 (8.5)	0	0
Week 12	0	57 (96.6)	2 (3.4)	0	0
Min Post Baseline	0	59 (98.3)	1 (1.7)	0	0
Max Post Baseline	0	52 (86.7)	8 (13.3)	0	0
Last Value on Treatment	0	58 (96.7)	2 (3.3)	0	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

SUBSTRATES : Bilirubin, total

Treatment/ Visit	> 5*UL
DBGTRN110bid	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
DBGTRN150bid	
Baseline	0
Week 1	0
Week 2	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
Warfarin	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

ENZYMES : AST/GOT, SGOT

Treatment/ Visit	< LL	[LL, UL]	(UL, 2*UL]	(2*UL, 3*UL]	(3*UL, 5*UL]
DBGTRN110bid					
Baseline	0	45 (97.8)	1 (2.2)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 4	0	42 (100.0)	0	0	0
Week 8	0	40 (100.0)	0	0	0
Week 12	0	41 (100.0)	0	0	0
Min Post Baseline	0	46 (100.0)	0	0	0
Max Post Baseline	0	46 (100.0)	0	0	0
Last Value on Treatment	0	46 (100.0)	0	0	0
DBGTRN150bid					
Baseline	0	57 (98.3)	1 (1.7)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 2	0	1 (100.0)	0	0	0
Week 4	0	50 (94.3)	3 (5.7)	0	0
Week 8	0	48 (100.0)	0	0	0
Week 12	1 (2.0)	46 (92.0)	3 (6.0)	0	0
Min Post Baseline	1 (1.7)	57 (98.3)	0	0	0
Max Post Baseline	0	54 (93.1)	4 (6.9)	0	0
Last Value on Treatment	1 (1.7)	54 (93.1)	3 (5.2)	0	0
Warfarin					
Baseline	0	61 (98.4)	1 (1.6)	0	0
Week 1	0	1 (100.0)	0	0	0
Week 4	0	58 (100.0)	0	0	0
Week 8	0	56 (94.9)	3 (5.1)	0	0
Week 12	0	56 (94.9)	3 (5.1)	0	0
Min Post Baseline	0	60 (100.0)	0	0	0
Max Post Baseline	0	55 (91.7)	5 (8.3)	0	0
Last Value on Treatment	0	57 (95.0)	3 (5.0)	0	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

ENZYMES : AST/GOT, SGOT

Treatment/ Visit	> 5*UL
DBGTRN110bid	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
DBGTRN150bid	
Baseline	0
Week 1	0
Week 2	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
Warfarin	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

ENZYMES : ALT/GPT, SGPT

Treatment/ Visit	< LL	[LL, UL]	(UL, 2*UL]	(2*UL, 3*UL]	(3*UL, 5*UL]
DBGTRN110bid					
Baseline	0	45 (97.8)	1 (2.2)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 4	0	42 (100.0)	0	0	0
Week 8	0	40 (100.0)	0	0	0
Week 12	0	40 (97.6)	1 (2.4)	0	0
Min Post Baseline	0	46 (100.0)	0	0	0
Max Post Baseline	0	45 (97.8)	1 (2.2)	0	0
Last Value on Treatment	0	45 (97.8)	1 (2.2)	0	0
DBGTRN150bid					
Baseline	0	57 (98.3)	1 (1.7)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 2	0	1 (100.0)	0	0	0
Week 4	0	51 (96.2)	2 (3.8)	0	0
Week 8	0	46 (95.8)	2 (4.2)	0	0
Week 12	0	46 (92.0)	4 (8.0)	0	0
Min Post Baseline	0	56 (96.6)	2 (3.4)	0	0
Max Post Baseline	0	54 (93.1)	4 (6.9)	0	0
Last Value on Treatment	0	54 (93.1)	4 (6.9)	0	0
Warfarin					
Baseline	0	61 (98.4)	1 (1.6)	0	0
Week 1	0	1 (100.0)	0	0	0
Week 4	0	57 (98.3)	1 (1.7)	0	0
Week 8	0	57 (96.6)	2 (3.4)	0	0
Week 12	0	56 (94.9)	3 (5.1)	0	0
Min Post Baseline	0	60 (100.0)	0	0	0
Max Post Baseline	0	56 (93.3)	4 (6.7)	0	0
Last Value on Treatment	0	57 (95.0)	3 (5.0)	0	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

ENZYMES : ALT/GPT, SGPT

Treatment/ Visit	> 5*UL
DBGTRN110bid	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
DBGTRN150bid	
Baseline	0
Week 1	0
Week 2	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
Warfarin	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

ENZYMES : Alkaline phosphatase

Treatment/ Visit	< LL	[LL, UL]	(UL, 2*UL]	(2*UL, 3*UL]	(3*UL, 5*UL]
DBGTRN110bid					
Baseline	1 (2.2)	42 (91.3)	3 (6.5)	0	0
Week 1	1 (25.0)	3 (75.0)	0	0	0
Week 4	1 (2.4)	41 (97.6)	0	0	0
Week 8	0	38 (95.0)	2 (5.0)	0	0
Week 12	1 (2.4)	40 (97.6)	0	0	0
Min Post Baseline	2 (4.3)	44 (95.7)	0	0	0
Max Post Baseline	1 (2.2)	43 (93.5)	2 (4.3)	0	0
Last Value on Treatment	2 (4.3)	44 (95.7)	0	0	0
DBGTRN150bid					
Baseline	3 (5.2)	53 (91.4)	2 (3.4)	0	0
Week 1	0	4 (100.0)	0	0	0
Week 2	0	1 (100.0)	0	0	0
Week 4	2 (3.8)	49 (92.5)	2 (3.8)	0	0
Week 8	2 (4.2)	45 (93.8)	1 (2.1)	0	0
Week 12	3 (6.0)	46 (92.0)	1 (2.0)	0	0
Min Post Baseline	3 (5.2)	55 (94.8)	0	0	0
Max Post Baseline	2 (3.4)	53 (91.4)	3 (5.2)	0	0
Last Value on Treatment	3 (5.2)	54 (93.1)	1 (1.7)	0	0
Warfarin					
Baseline	0	61 (98.4)	1 (1.6)	0	0
Week 1	0	1 (100.0)	0	0	0
Week 4	0	57 (98.3)	1 (1.7)	0	0
Week 8	0	58 (98.3)	1 (1.7)	0	0
Week 12	0	59 (100.0)	0	0	0
Min Post Baseline	0	60 (100.0)	0	0	0
Max Post Baseline	0	59 (98.3)	1 (1.7)	0	0
Last Value on Treatment	0	60 (100.0)	0	0	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2

Table 15.3.2: 5 Frequency of patients N [%] categorized by multiples of the reference range limits

ENZYMES : Alkaline phosphatase

Treatment/ Visit	> 5*UL
DBGTRN110bid	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
DBGTRN150bid	
Baseline	0
Week 1	0
Week 2	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0
Warfarin	
Baseline	0
Week 1	0
Week 4	0
Week 8	0
Week 12	0
Min Post Baseline	0
Max Post Baseline	0
Last Value on Treatment	0

Key: [or] = include limit in category, (or) = exclude limit in category

Source data: Appendix 16.2, Listing 8.2 sa\et_lab.sas 14MAR2007

Table 15.2.1: 1 Thromboembolic events – full analysis set

	DBGTRN110mg	DBGTRN150mg	Warfarin	Total
Number of Patients	46(27.7)	58(34.9)	62(37.3)	166(100.0)
Stroke				
No	46(100.0)	58(100.0)	61(98.4)	165(99.4)
Yes	0(0.0)	0(0.0)	1(1.6)	1(0.6)
Stroke type				
No stroke	46(100.0)	58(100.0)	61(98.4)	165(99.4)
Ischemic stroke	0(0.0)	0(0.0)	1(1.6)	1(0.6)
Systemic thromboembolism				
No	46(100.0)	58(100.0)	62(100.0)	166(100.0)
TIA				
No	46(100.0)	58(100.0)	62(100.0)	166(100.0)
Myocardial infarction				
No	46(100.0)	58(100.0)	62(100.0)	166(100.0)
Other major adverse cardiac events				
No	46(100.0)	58(100.0)	62(100.0)	166(100.0)
Death				
No	46(100.0)	58(100.0)	62(100.0)	166(100.0)

Table 11.5.3: 1 Trough aPTT after oral administration of 110 mg and 150 mg dabigatran etexilate b.i.d.

	Trough aPTT [s]									
	110 mg b.i.d.					150 mg b.i.d.				
	V 2	V 3	V 5	V 7	Mean[1)]	V 2	V 3	V 5	V 7	Mean[1)]
N	46	41	40	40	43	58	55	50	48	55
gMean	32.4	40.2	40.9	41.8	41.0	34.0	45.0	45.0	44.1	45.3
gCV [%]	12.7	16.4	16.2	17.3	14.8	25.0	20.7	17.9	18.2	17.6
Mean	**32.6**	**40.8**	**41.5**	**42.4**	**41.5**	**35.7**	**46.0**	**45.7**	**44.8**	**46.0**
CV [%]	13.2	17.6	19.1	18.2	16.5	53.8	21.6	18.1	20.7	18.2
SD	4.32	7.17	7.94	7.70	6.85	19.2	9.92	8.26	9.30	8.36
Min	24.9	27.3	32.4	29.1	30.3	26.7	31.7	32.2	32.5	33.3
Median	32.3	39.4	40.2	40.5	39.6	33.7	44.5	45.3	42.4	44.3
Max	49.8	68.1	80.6	70.8	73.2	177	82.9	66.1	84.0	74.4

1) Intra-individual mean of Visits 3, 5 and 7
BI Trial No.: 1160.0049
Source data: Table 15.6.1: 3, 15.6.1: 4, 15.6.2: 1 and 15.6.2: 2

Table 11.5.3: 3 Trough ECT after oral administration of 110 mg and 150 mg dabigatran etexilate b.i.d.

	Trough ECT [s]									
	110 mg b.i.d.					**150 mg b.i.d.**				
	V 2	**V 3**	**V 5**	**V 7**	**Mean[1)]**	**V 2**	**V 3**	**V 5**	**V 7**	**Mean[1)]**
N	46	41	40	40	43	58	55	50	48	55
gMean	35.6	53.4	51.4	52.7	52.5	36.3	63.2	58.9	56.9	61.3
gCV [%]	9.39	23.5	23.1	24.1	20.4	10.5	35.3	27.7	28.5	30.3
Mean	**35.7**	**54.9**	**52.7**	**54.2**	**53.6**	**36.5**	**67.4**	**61.2**	**59.4**	**64.3**
CV [%]	9.22	25.5	24.5	25.6	21.3	11.1	42.2	29.8	34.1	34.7
SD	3.29	14.0	12.9	13.9	11.4	4.06	28.5	18.2	20.3	22.3
Min	28.5	37.1	36.5	36.6	37.5	30.4	35.9	36.4	36.8	40.1
Median	35.8	50.7	49.6	50.8	51.5	36.3	60.9	57.1	53.6	58.4
Max	43.0	101	91.0	98.2	86.2	54.7	199	117	148	151

1) Intra-individual mean of Visits 3, 5 and 7
BI Trial No.: 1160.0049
Source data: Table 15.6.1: 8, 15.6.1: 9, 15.6.2: 3 and 15.6.2: 4

Table 11.5.3: 5 Trough INR after oral administration of 110 mg and 150 mg dabigatran etexilate b.i.d.

	Trough INR									
	110 mg b.i.d.					**150 mg b.i.d.**				
	V 2	**V 3**	**V 5**	**V 7**	**Mean[1)]**	**V 2**	**V 3**	**V 5**	**V 7**	**Mean[1)]**
N	46	41	40	39	43	58	55	50	49	55
gMean	1.87	1.35	1.35	1.43	1.38	2.03	1.49	1.46	1.49	1.50
gCV [%]	35.7	14.0	16.6	21.2	13.7	33.4	20.0	18.0	25.2	19.2
Mean	**1.98**	**1.36**	**1.37**	**1.46**	**1.40**	**2.14**	**1.52**	**1.48**	**1.55**	**1.53**
CV [%]	34.4	14.0	19.2	28.6	14.1	32.5	23.2	18.8	39.0	21.7
SD	0.679	0.190	0.263	0.419	0.197	0.696	0.354	0.279	0.606	0.333
Min	0.900	1.00	1.00	1.10	1.07	1.00	1.10	1.10	1.10	1.13
Median	1.90	1.30	1.30	1.40	1.40	2.10	1.40	1.40	1.40	1.43
Max	3.80	1.90	2.60	3.70	2.00	4.30	3.00	2.30	5.30	3.00

1) Intra-individual mean of Visits 3, 5 and 7
BI Trial No.: 1160.0049
Source data: Table 15.6.1: 13, 15.6.1: 14, 15.6.2: 5 and 15.6.2: 6

15.5.3 Overall summary of pharmacokinetic parameters

Table 15.5.3: 1 Comparison of pharmacokinetic parameters by treatment and visit

	Trough plasma concentration of total dabigatran							
$C_{pre,ss}$	110 mg b.i.d.				150 mg b.i.d.			
[ng/mL]	Visit 3	Visit 5	Visit 7	Mean	Visit 3	Visit 5	Visit 7	Mean
N	41	40	39	43	55	50	49	55
gMean	53.1	55.6	63.0	58.3	78.1	78.2	75.1	82.0
gCV [%]	69.0	62.5	62.1	58.5	75.8	68.1	63.3	64.8
Mean	64.2	65.4	73.4	66.9	98.3	92.8	90.2	97.7
CV [%]	67.3	60.8	57.5	52.2	77.4	58.4	72.2	65.0
SD	43.2	39.7	42.2	34.9	76.1	54.2	65.2	63.5
Min	14.0	20.6	18.0	19.7	17.1	15.0	25.1	26.8
Median	51.4	53.3	63.8	64.5	79.1	77.8	70.5	80.1
Max	201	200	227	159	463	242	329	340

BI Trial No.: 1160.0049
Source data: Section 15, Tables 5.2.1: 1, 5.2.1: 2, 5.2.1: 3, 5.2.1: 4, 5.2.1: 6, 5.2.1: 7, 5.2.1: 8, 5.2.1: 9