Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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**	Boehringer Ingelheim
Name of finished product: Pradaxa®		**EudraCT No.:**	**Synopsis No.:**
Name of active ingredient: Dabigatran etexilate (BIBR 1048)		**Page:** 3 of 11	
Module:		**Volume:** {hyperlink }	
Disclosure synopsis date: 14 July 2014	**Trial No./ U No.:** 1160.0020 / U06-1615-02	**Study period (dates):** 06 OCT 03 - 03 NOV 04	**Revision date:** 12 December 2008

Title of study:	Prevention of Embolic and Thrombotic Events in Patients with Persistent Atrial Fibrillation. A Dose Exploration Study of BIBR 1048, an Oral Direct Thrombin Inhibitor, with and without Concomitant Acetylsalicylic Acid, in Comparison to Warfarin (PETRO)
Investigator:	[redacted] M.D., Ph.D.
Study center(s):	Multicenter Study in Denmark, Sweden, The Netherlands and The United States of America, cf. Appendix 16.1.4.
Publication (reference):	Main results were presented as poster, at the Congress of the European Society of Cardiology, Stockholm, Sept. 2005.
Clinical phase:	II
Objectives:	To determine the safety and efficacy of BIBR 1048 in patients with non-rheumatic atrial fibrillation (AF), (paroxysmal, persistent, or permanent {chronic}) with or without concomitant treatment with acetylsalicylic acid (ASA).
Methodology:	Randomized, parallel group, double-blind (for BIBR 1048), open-label (for ASA and for warfarin) trial. The design of the trial is a three-by-three factorial, testing 3 doses of BIBR 1048, either alone (no ASA) or in combination with one of two different doses of ASA. In addition, a tenth treatment group of warfarin alone has been chosen as reference treatment.

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No. of subjects:

planned: entered: 476

actual: enrolled: 593 entered: 502

1. **Treatment A: BIBR 1048 50 mg bid**
   entered: 58 treated: 58 analysed (for primary safety endpoint): 58
2. **Treatment B: BIBR 1048 50 mg bid + ASA 81 mg, qd**
   entered: 20 treated: 20 analysed (for primary safety endpoint): 20
3. **Treatment C: BIBR 1048 50 mg bid + ASA 325 mg, qd**
   entered: 27 treated: 27 analysed (for primary safety endpoint): 27
4. **Treatment D: BIBR 1048 150 mg bid**
   entered: 99 treated: 99 analysed (for primary safety endpoint): 91
5. **Treatment E: BIBR 1048 150 mg bid + ASA 81 mg, qd**
   entered: 34 treated: 34 analysed (for primary safety endpoint): 34
6. **Treatment F: BIBR 1048 150 mg bid + ASA 325 mg, qd**
   entered: 33 treated: 33 analysed (for primary safety endpoint): 33
7. **Treatment G: BIBR 1048 300 mg bid**
   entered: 98 treated: 98 analysed (for primary safety endpoint): 98
8. **Treatment H: BIBR 1048 300 mg bid + ASA 81 mg, qd**
   entered: 33 treated: 33 analysed (for primary safety endpoint): 33
9. **Treatment I: BIBR 1048 300 mg bid + ASA 325 mg, qd**
   entered: 30 treated: 30 analysed (for primary safety endpoint): 30
10. **Treatment J: Warfarin, dosed to target INR 2.0 to 3.0**
    entered: 70 treated: 70 analysed (for primary safety endpoint): 70

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Diagnosis and main criteria for inclusion:	Persistent, intermittent or paroxysmal non-rheumatic atrial fibrillation. Inclusion Criteria: -Non-rheumatic atrial fibrillation (paroxysmal, persistent, or permanent {chronic}), documented by ECG within the past 6 months - An additional risk factor for stroke: one or more of the following conditions/events: coronary artery disease, hypertension, DM, symptomatic heart failure or LVD, previous ischemic stroke or TIA or age of greater than 75 years - Treatment with warfarin or other vitamin K dependent anticoagulants for at least 8 weeks prior to inclusion -Age ≥ 18 years -Written, informed consent Exclusion Criteria: - History of valvular heart disease conferring significantly increased risk of thromboembolic events (e.g. clinically significant mitral stenosis or prosthetic valves) - Contraindications to ASA - Contraindication to anticoagulant therapy (previous intracranial hemorrhage, GI hemorrhage within previous 3 months, previous severe hemorrhage with warfarin at therapeutic INR, regular use of non-steroidal anti-inflammatory drugs) - Severe renal impairment (estimated GFR ≤ 30 ml/min.)
Test product:	BIBR 1048 (dabigatran etexilate):
dose:	50 mg bid, 150 mg bid, 300 mg bid
mode of admin.:	oral capsules, with food
batch no.:	9030032 (50 mg BIBR 1048); 9030033 (150 mg BIBR 048); 9030039 (150 mg BIBR 048); 9030042 (150 mg BIBR 048) B030202 (placebo BIRM 1048)

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Test product:	Aspirin (acetylsalicylic acid, ASA)
dose:	81 mg, 325 mg
mode of admin.:	oral tablets, once a day, in the morning taken at the same time as BIBR 1048
batch no.:	C022P (81 mg); 02M569 (325 mg)
Duration of treatment:	12 weeks
Reference therapy:	Warfarin sodium
dose:	Adjusted dose, target INR (international normalized ratio) range 2.0-3.0
mode of admin.:	Oral, once a day in the morning or evening
batch no.:	3D39
Criteria for evaluation:	
Efficacy:	**Primary efficacy endpoint**: There was no primary efficacy endpoint. Dose exploration only. **Secondary efficacy endpoints**: ▪ The change from baseline in plasma concentrations of D-dimer, a breakdown product of fibrin, as a biochemical indicator of activation of the coagulation system ▪ A composite clinical endpoint of any thromboembolic or cardiac event, including the incidence of ischemic stroke (fatal + non-fatal), TIAs, systemic embolism, myocardial infarction (fatal + non-fatal), other major adverse cardiac events and all-cause mortality ▪ Net clinical cost (NCC) as measured by the composite clinical endpoint of stroke/TIA/systemic embolism/MI/death plus major bleeds ▪ The occurrence rates of: o stroke (fatal and non-fatal) o transient ischemic attacks (TIAs) o systemic embolism o myocardial infarction (fatal and non-fatal)

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Criteria for evaluation: **Efficacy (continued):**	o other major cardiac events o all cause mortality Pharmacodynamic/-kinetic parameters: D-dimer, soluble fibrin, 11-dehydrothromboxane, aPTT, ECT, BIBR 953 ZW plasma concentrations
Safety:	The primary safety endpoint was the incidence of bleeding events. **Other safety criteria**: o The incidence of all adverse events, notably bleeding. Bleeding events have been classified as major and minor bleeds. Bleeds have been independently and blindly adjudicated to further subdivide them into clinically relevant and nuisance bleeds. o Standard laboratory assessment of organ functions (e.g. liver function) o Changes in physical examination o Discontinuation of therapy due to an adverse event A DSMB monitored the safety of the patients in the trial on an ongoing basis
Statistical methods:	Descriptive statistics, frequencies of events. Exploratory investigation of relationships between BIBR 1048 and ASA dose and safety, efficacy, D-dimer, pharmacokinetic and pharmacodynamic data.
SUMMARY – CONCLUSIONS:	
Efficacy results:	This study was not powered to evaluate differences between treatment groups for the occurrence of strokes and/or thromboembolic events. It is of interest that the only two thromboembolic events which occurred during the 12 week treatment period were in the low dose dabigatran (50 mg bid) treatment groups. A major objective of the study was to evaluate the pharmacokinetic and pharmacodynamic properties of dabigatran and their interrelationship. Analysis of dabigatran trough plasma concentrations indicated that steady state conditions were attained on or before the time of the first assessment after 4 - 7 days of dabigatran administration. Dabigatran mean trough plasma concentrations were stable, having little variability over the 12 weeks treatment period. Average trough dabigatran plasma concentrations increased proportionately with increasing dose. In female patients, a trend towards modest increases in plasma dabigatran concentrations was observed. On average, trough plasma

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concentrations in female subjects were 12 - 20 % higher than in males. There was no apparent effect of body mass index on dabigatran plasma concentrations. Dabigatran is primarily eliminated via the kidneys. As expected, patients with reduced creatinine clearances had higher plasma dabigatran concentrations. In this trial, the median GFR was 71 mL/min.

The pharmacodynamic effects of dabigatran were assessed by evaluating aPTT and ECT values at the same time as for the dabigatran pharmacokinetic sampling. These samples were centrally analysed to reduce the variability and increase the reliability of these results. There was a close correlation between aPTT and ECT values and dabigatran plasma concentrations. A curvilinear relationship was observed between dabigatran plasma concentrations and aPTT whereas the relationship for ECT with dabigatran plasma concentrations was linear. ECT provided a more sensitive and precise measure of anticoagulation than aPTT. Trough aPTT values had a low interindividual variability, with coefficients of variation between 13 and 21 %. Maximum aPTT values, expressed as the ratio of maximum on therapy value/baseline value were 1.2, 1.5 and 1.8 at doses of 50, 150 and 300 mg dabigatran etexilate bid, respectively. The linear relationship between ECT values and dabigatran plasma concentrations and the higher sensitivity of the ECT response resulted in greater ratios of maximum on therapy/baseline ECT values (1.3, 2.0 and 3.2 for the 50, 150 and 300 mg bid doses). Warfarin produced only minor prolongations on aPTT values.

Plasma D-dimer concentrations rose significantly from Visit 1 to Visit 2 during washout of warfarin. Mean D-dimer trough plasma concentrations after 12 weeks of drug administration were 104 ng/mL (warfarin) and 104 - 124 ng/mL (dabigatran). Change from Visit 1 baseline was related to dose of dabigatran etexilate, with a 17% (p=0.0029), 9% (p=0.011) and 1% (p=0.82) rise in D-dimer for the 50, 150 and 300 mg bid dose groups, respectively. Warfarin treated patients, as expected, had little change from baseline (-7% change, p=0.22). The interindividual variability of mean D-dimer trough concentrations was very high. The coefficients of variation were 64% for the warfarin treatment group and between 81 and 120 % for dabigatran treatment groups.

D-dimer concentrations were not affected by the concomitant administration of ASA. There were also no differences in D-dimer levels observed between CAD and non-CAD patients.

Urinary 11-dehydrothromboxane concentrations were evaluated as well. There

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was an approximate 20% increase in urinary 11-dehydrothromboxane concentrations in the dabigatran without ASA treatment groups compared to the warfarin treatment group. Within the dabigatran alone treatment groups there was no evidence of a dose-response relationship. The addition of aspirin to any dose of dabigatran lowered TXB2 in the urine from 39-64%. The interindividual variability of 11-dehydrothromboxane B2 urine concentrations was moderate, the coefficients of variations were between 38 and 55 % without ASA and 34 and 86% with concomitant ASA.

Soluble plasma fibrin concentrations were evaluated, but were frequently below the lower limit of quantitation of the assay (3 ng/mL). No apparent changes could be seen after 12 weeks of treatment with dabigatran or warfarin. The high variability of soluble fibrin concentrations (coefficient of variation ranging from 61 - 170 %) precluded interpretation of the data.

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Safety results:

The dose-response for any bleeding events was not uniform for dabigatran etexilate, but dependent on whether ASA was concomitantly given or not. Dabigatran etexilate doses up to 150 mg bid administered with or without aspirin (ASA) appeared safe and comparable to full dose warfarin (INR 2.0-3.0) with regard to the observed incidence of all categories of bleeding. Dabigatran alone at 300 mg bid resulted in bleeding rates similar to those seen with 150 mg bid alone. Dabigatran dosed at 300 mg bid concomitantly with ASA resulted in unacceptable rates of bleeding, and was associated with such a substantial risk of major bleeding that the DSMB recommended termination of these two treatment groups..

The incidence of elevated transaminases >3xULN was 0.9% in dabigatran treated patients (4 of 432) and 0% (0 of 70) in warfarin treated patients. There were no reported elevations of bilirubin > 2xULN during the study. Long-term data will be provided when the open label rollover study data is reported.

No patients had elevated transaminases >3xULN followed by bilirubin levels > 1.5 or 2x ULN. One patient had an elevated bilirubin value of 1.45 mg % after her transaminases were elevated to >3x ULN. This patient later died of congestive heart failure. The autopsy showed only passive liver congestion consistent with the known diagnosis of congestive heart failure. One other patient had elevated transaminases subsequent to elevated alkaline phosphatase due to obstructive pancreatitis. This patient later was hospitalized with ischemic bowel and died. Neither case was considered drug-related by the investigator or sponsor.

A dose-response was observed for gastrointestinal discomfort/pain (abdominal discomfort, abdominal pain, dyspepsia, gastritis, oesophageal pain) with dabigatran. In this category, dyspepsia was most frequently observed for higher dosages of dabigatran, whereas no dyspepsia was reported for warfarin. Long-term data will be provided when the open rollover study is reported.

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Conclusions:

The maximal tolerated dose of dabigatran etexilate in patients with non-valvular atrial fibrillation is most likely below 300 mg bid.

The concomitant administration of dabigatran etexilate and ASA appeared to increase all categories of bleeding. The incidence of major bleeding when dabigatran etexilate was given at a dose of 300 mg bid concomitantly with ASA was clinically unacceptable.

Dabigatran etexilate administered at any dose studied in this trial without ASA did not appear to result in increased bleeding rates compared to warfarin, dosed to an INR of 2.0 to 3.0.

Dabigatran plasma concentrations predicted well its pharmacodynamic effects (aPTT and ECT), and demonstrated a dose-response relationship with increasing anticoagulant activity at increasing doses in patients with non-valvular atrial fibrillation.

We conclude that the safety, pharmacokinetic and pharmacodynamic data generated in this study support the continued development of dabigatran for the potential prevention of strokes and systemic thromboembolic events in patients with non-valvular atrial fibrillation.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide disposition results and results of complete primary and additional secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1.1: 1
Plasma concentration BIBR 953 ZW by treatment and visit (Secondary endpoint)	Table 15.5.3.1: 1
Ecarin clotting time change from baseline to 12 weeks (Secondary endpoint)	Table 15.2.2.4: 1
aPTT clotting time change from baseline to 12 weeks (Secondary endpoint)	Table 15.2.2.5: 1
D−dimer change from baseline to 12 weeks (Secondary endpoint)	Table 15.2.2.1: 1
Thromboembolic events (stroke, TIAs, systemic embolism) (Secondary endpoint)	Table 15.2.1: 1
Thromboembolic events (MI, other major cardiac events, death) (Secondary endpoint)	Table 15.2.1: 3
Urinary 11-dehydrothromboxane change from baseline to 12 weeks (Secondary endpoint)	Table 15.2.2.3: 1
Soluble fiber change from baseline to 12 weeks (Secondary endpoint)	Table 15.2.2.2: 1
Major bleeding events (Primary endpoint)	Table 15.3.1.2: 5
Minor/relevant bleeding events (Primary endpoint)	Table 15.3.1.2: 17
Serious adverse events	Table 15.3.1.4: 4

Table 15.1.1.1: 1 Disposition of patients − all patients − 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid
Enrolled				
Not Entered/randomized				
Entered/randomized	58	20	27	99
Not treated	0	0	0	0
Treated	58 (100.0)	20 (100.0)	27 (100.0)	99 (100.0)
NOT prematurely discontinued from trial medication	56 (96.6)	18 (90.0)	26 (96.3)	91 (91.9)
Prematurely discontinued from trial medication	2 (3.4)	2 (10.0)	1 (3.7)	8 (8.1)
Adverse event	2 (3.4)	2 (10.0)	1 (3.7)	6 (6.1)
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Worsening of other pre−existing disease/condition	0 (0.0)	1 (5.0)	0 (0.0)	2 (2.0)
Other adverse event	2 (3.4)	1 (5.0)	1 (3.7)	3 (3.0)
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Lost to follow−up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn (not due to AE)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Planned observation time completed	57 (98.3)	16 (80.0)	26 (96.3)	91 (91.9)
Observation prematurely discontinued	1 (1.7)	4 (20.0)	1 (3.7)	8 (8.1)
Adverse event	1 (1.7)	2 (10.0)	1 (3.7)	6 (6.1)
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Worsening of other pre−existing disease/condition	0 (0.0)	1 (5.0)	0 (0.0)	2 (2.0)
Other adverse event	1 (1.7)	1 (5.0)	1 (3.7)	3 (3.0)
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Lost to follow−up	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)
Consent withdrawn (not due to AE)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)

Table 15.1.1.1: 1 Disposition of patients − all patients − 10 trt.

	BIBR 1048 150 mg bid + ASA 81 mg qd	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd
Enrolled				
Not Entered/randomized				
Entered/randomized	34	33	98	33
Not treated	0	0	0	0
Treated	34 (100.0)	33 (100.0)	98 (100.0)	33 (100.0)
NOT prematurely discontinued from trial medication	32 (94.1)	32 (97.0)	90 (91.8)	27 (81.8)
Prematurely discontinued from trial medication	2 (5.9)	1 (3.0)	8 (8.2)	6 (18.2)
Adverse event	1 (2.9)	1 (3.0)	6 (6.1)	6 (18.2)
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre−existing disease/condition	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.0)
Other adverse event	0 (0.0)	1 (3.0)	6 (6.1)	5 (15.2)
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow−up	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn (not due to AE)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Planned observation time completed	33 (97.1)	32 (97.0)	90 (91.8)	27 (81.8)
Observation prematurely discontinued	1 (2.9)	1 (3.0)	8 (8.2)	6 (18.2)
Adverse event	1 (2.9)	1 (3.0)	6 (6.1)	6 (18.2)
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Worsening of other pre−existing disease/condition	1 (2.9)	0 (0.0)	0 (0.0)	1 (3.0)
Other adverse event	0 (0.0)	1 (3.0)	5 (5.1)	5 (15.2)
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow−up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn (not due to AE)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 15.1.1.1: 1 Disposition of patients − all patients − 10 trt.

	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin	Total
Enrolled			593
Not Entered/randomized			91
Entered/randomized	30	70	502
Not treated	0	0	0
Treated	30 (100.0)	70 (100.0)	502 (100.0)
NOT prematurely discontinued from trial medication	24 (80.0)	68 (97.1)	464 (92.4)
Prematurely discontinued from trial medication	6 (20.0)	2 (2.9)	38 (7.6)
Adverse event	4 (13.3)	0 (0.0)	29 (5.8)
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	1 (0.2)
Worsening of other pre−existing disease/condition	0 (0.0)	0 (0.0)	5 (1.0)
Other adverse event	4 (13.3)	0 (0.0)	23 (4.6)
Non compliant with protocol	0 (0.0)	0 (0.0)	1 (0.2)
Lost to follow−up	0 (0.0)	0 (0.0)	1 (0.2)
Consent withdrawn (not due to AE)	0 (0.0)	1 (1.4)	3 (0.6)
Other	2 (6.7)	1 (1.4)	4 (0.8)
Planned observation time completed	25 (83.3)	67 (95.7)	464 (92.4)
Observation prematurely discontinued	5 (16.7)	3 (4.3)	38 (7.6)
Adverse event	4 (13.3)	0 (0.0)	28 (5.6)
Worsening of disease/condition under study	0 (0.0)	0 (0.0)	2 (0.4)
Worsening of other pre−existing disease/condition	0 (0.0)	0 (0.0)	5 (1.0)
Other adverse event	4 (13.3)	0 (0.0)	21 (4.2)
Non compliant with protocol	0 (0.0)	0 (0.0)	1 (0.2)
Lost to follow−up	0 (0.0)	1 (1.4)	3 (0.6)
Consent withdrawn (not due to AE)	0 (0.0)	1 (1.4)	3 (0.6)
Other	1 (3.3)	1 (1.4)	3 (0.6)

15.5.3 Overall summary of pharmacokinetic parameters

15.5.3.1 Comparison of pharmacokinetic parameters by treatment

Table 15.5.3.1: 1 Comparison of pharmacokinetic parameters by treatment and visit
(Page 1 of 2)

Dabigatran	**50 mg bid**			**150 mg bid**			**300 mg bid**		
	Cpre,ss			**Cpre,ss**			**Cpre,ss**		
	[ng/mL]			**[ng/mL]**			**[ng/mL]**		
	Visit 3	**Visit 5**	**Visit 7**	**Visit 3**	**Visit 5**	**Visit 7**	**Visit 3**	**Visit 5**	**Visit 7**
N	95	91	83	143	140	122	136	135	121
Mean	29.6	30.0	30.2	87.2	95.1	92.7	185	194	207
SD	17.7	20.0	19.0	59.3	67.5	66.3	108	118	129
Min	4.72	2.99	5.19	9.40	9.83	12.7	26.7	29.9	42.9
Median	25.3	23.7	24.0	70.1	70.2	72.9	173	166	179
Max	95.8	106	97.3	379	306	334	682	644	742
CV [%]	59.6	66.6	62.9	68.0	70.9	71.5	58.5	60.6	62.4
gMean	25.1	24.4	24.8	70.8	74.4	74.0	155	163	173
gCV [%]	65.7	75.1	72.5	74.5	83.6	76.4	69.1	67.5	67.8

BI Trial No.: 1160.0020
Source data: Tables 15.5.2.1: 1 to 3

Table 15.5.3.1: 1 Comparison of pharmacokinetic parameters by treatment and visit
(Page 2 of 2)

Dabigatran	50 mg bid Cpre,ss,norm [ng/mL/mg]			150 mg bid Cpre,ss,norm [ng/mL/mg]			300 mg bid Cpre,ss,norm [ng/mL/mg]		
	Visit 3	Visit 5	Visit 7	Visit 3	Visit 5	Visit 7	Visit 3	Visit 5	Visit 7
N	95	91	83	143	140	122	136	135	121
Mean	0.593	0.601	0.604	0.582	0.634	0.618	0.617	0.647	0.689
SD	0.353	0.400	0.380	0.395	0.450	0.442	0.361	0.392	0.430
Min	0.0944	0.0598	0.104	0.0627	0.0655	0.0847	0.0890	0.0997	0.143
Median	0.506	0.474	0.480	0.467	0.468	0.486	0.575	0.553	0.597
Max	1.92	2.12	1.95	2.53	2.04	2.23	2.27	2.15	2.47
CV [%]	59.6	66.6	62.9	68.0	70.9	71.5	58.5	60.6	62.4
gMean	0.501	0.488	0.496	0.472	0.496	0.494	0.517	0.543	0.575
gCV [%]	65.7	75.1	72.5	74.5	83.6	76.4	69.1	67.5	67.8

BI Trial No.: 1160.0020
Source data: Tables 15.5.2.1: 1 to 3

Table 15.2.2.4: 1 ECT: Descriptive statistics for difference from baseline – all treated patients – 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid	BIBR 1048 150 mg bid + ASA 81 mg qd
MEDIAN	8.4	9.4	9.9	24.8	30.9
INTERQUARTILE RANGE	9.3	10.3	15.0	26.0	41.3
MAX	38	26	42	146	117
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.27	1.31	1.35	1.91	2.04
GEOSD of ratio	1.19	1.18	1.24	1.44	1.47
CI_FROM of ratio	1.21	1.20	1.24	1.77	1.78
CI_TO of ratio	1.33	1.42	1.47	2.05	2.34
MAX of ratio	2.21	1.80	2.28	5.29	4.77
MIN of ratio	0.91	1.06	0.98	0.98	1.00
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
Visit 6					
N	55	18	27	91	32
MEAN	17.4	17.8	25.1	57.1	64.9
SD	10.4	13.7	23.9	40.4	47.6
MIN	2	−2	2	12	4
MEDIAN	14.1	16.6	16.4	49.8	55.7
INTERQUARTILE RANGE	16.0	16.5	24.1	41.0	61.5
MAX	46	55	121	235	246
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.51	1.51	1.68	2.57	2.74
GEOSD of ratio	1.22	1.29	1.40	1.46	1.55
CI_FROM of ratio	1.43	1.33	1.47	2.37	2.34
CI_TO of ratio	1.60	1.71	1.92	2.78	3.21
MAX of ratio	2.45	2.74	4.89	8.26	8.00
MIN of ratio	1.06	0.93	1.05	1.31	1.11
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
Visit 7					
N	56	19	26	94	34
MEAN	9.7	12.0	12.0	31.9	42.5
SD	8.2	10.7	9.6	26.2	29.2
MIN	−6	−4	−1	2	−1
MEDIAN	8.0	9.8	10.6	24.2	33.3
INTERQUARTILE RANGE	10.0	17.4	14.0	22.4	43.1
MAX	31	38	45	126	99
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.28	1.34	1.35	1.87	2.16
GEOSD of ratio	1.21	1.26	1.21	1.41	1.47
CI_FROM of ratio	1.22	1.20	1.25	1.74	1.89

Table 15.2.2.4: 1 ECT: Descriptive statistics for difference from baseline – all treated patients – 10 trt.

	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin
MEDIAN	24.2	54.5	68.8	70.3	2.3
INTERQUARTILE RANGE	30.4	46.6	65.6	54.1	3.1
MAX	83	170	289	166	9
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.86	2.71	3.30	3.00	1.08
GEOSD of ratio	1.35	1.51	1.48	1.42	1.07
CI_FROM of ratio	1.68	2.48	2.84	2.62	1.05
CI_TO of ratio	2.07	2.96	3.84	3.45	1.11
MAX of ratio	3.48	6.38	9.40	6.62	1.28
MIN of ratio	1.16	0.79	1.75	1.40	0.92
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
Visit 6					
N	30	84	26	25	14
MEAN	61.6	109.2	134.4	127.4	2.4
SD	39.9	67.3	67.1	62.2	2.8
MIN	11	4	46	34	-0
MEDIAN	46.9	98.1	119.8	112.2	1.6
INTERQUARTILE RANGE	50.8	72.4	47.1	88.0	2.9
MAX	180	336	394	285	10
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	0.0005
GEOMEAN of ratio	2.69	3.96	4.90	4.58	1.07
GEOSD of ratio	1.47	1.64	1.37	1.47	1.08
CI_FROM of ratio	2.33	3.56	4.32	3.91	1.02
CI_TO of ratio	3.10	4.41	5.56	5.37	1.12
MAX of ratio	6.31	11.83	12.45	8.43	1.32
MIN of ratio	1.33	1.04	2.56	2.10	0.99
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	0.0070
Visit 7					
N	33	86	29	27	27
MEAN	32.7	63.6	70.8	74.0	3.1
SD	23.1	44.8	60.3	70.5	2.5
MIN	-7	-34	-1	-6	-2
MEDIAN	27.0	62.4	61.0	62.4	2.6
INTERQUARTILE RANGE	19.5	54.0	73.3	64.0	3.5
MAX	93	233	277	345	8
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.90	2.74	2.73	2.76	1.09
GEOSD of ratio	1.39	1.60	1.78	1.86	1.07
CI_FROM of ratio	1.69	2.48	2.19	2.16	1.06

Table 15.2.2.5: 1 aPTT: Descriptive statistics for difference from baseline – all treated patients – 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid	BIBR 1048 150 mg bid + ASA 81 mg qd
MEDIAN	5.2	6.8	7.2	13.7	15.5
INTERQUARTILE RANGE	5.4	6.2	6.1	9.3	13.6
MAX	21	17	43	50	74
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.19	1.25	1.25	1.43	1.54
GEOSD of ratio	1.16	1.16	1.19	1.30	1.27
CI_FROM of ratio	1.14	1.16	1.16	1.35	1.42
CI_TO of ratio	1.23	1.34	1.34	1.51	1.68
MAX of ratio	1.69	1.74	2.15	2.65	3.00
MIN of ratio	0.74	0.92	0.79	0.21	1.02
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
Visit 6					
N	56	18	27	88	31
MEAN	10.9	9.5	17.9	23.2	33.3
SD	6.9	7.0	20.7	24.5	31.8
MIN	-8	-2	-7	-138	2
MEDIAN	10.9	9.3	14.4	23.0	23.3
INTERQUARTILE RANGE	10.2	10.5	12.7	15.5	16.2
MAX	24	24	97	140	143
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.33	1.30	1.48	1.68	1.89
GEOSD of ratio	1.19	1.20	1.37	1.36	1.45
CI_FROM of ratio	1.27	1.18	1.30	1.57	1.65
CI_TO of ratio	1.39	1.42	1.67	1.79	2.17
MAX of ratio	1.86	1.78	4.03	4.52	6.96
MIN of ratio	0.82	0.93	0.86	0.23	1.04
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
Visit 7					
N	56	19	26	92	33
MEAN	6.4	8.3	8.8	13.5	24.9
SD	5.6	6.1	9.4	18.3	26.1
MIN	-7	-6	-9	-140	-2
MEDIAN	6.0	6.9	6.8	13.4	16.6
INTERQUARTILE RANGE	5.5	5.9	8.6	10.0	19.5
MAX	24	19	47	40	143
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.19	1.27	1.25	1.42	1.67
GEOSD of ratio	1.15	1.18	1.20	1.31	1.39
CI_FROM of ratio	1.15	1.17	1.16	1.34	1.48

Table 15.2.2.5: 1 aPTT: Descriptive statistics for difference from baseline – all treated patients – 10 trt.

	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin
MEDIAN	13.7	23.2	28.5	26.0	7.4
INTERQUARTILE RANGE	10.5	13.6	12.4	16.2	6.2
MAX	53	54	74	116	21
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.43	1.73	1.90	1.83	1.22
GEOSD of ratio	1.26	1.23	1.19	1.24	1.16
CI_FROM of ratio	1.32	1.66	1.78	1.68	1.15
CI_TO of ratio	1.55	1.81	2.03	1.99	1.28
MAX of ratio	2.18	2.65	3.24	2.97	1.55
MIN of ratio	0.65	0.93	1.45	1.13	0.86
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
Visit 6					
N	30	85	26	25	15
MEAN	26.6	37.2	42.1	39.8	12.0
SD	21.2	16.9	12.4	17.8	13.2
MIN	-23	3	24	19	1
MEDIAN	22.5	37.5	40.8	32.7	7.4
INTERQUARTILE RANGE	11.2	20.2	9.6	23.2	9.7
MAX	101	86	80	78	55
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.72	2.11	2.27	2.17	1.33
GEOSD of ratio	1.34	1.30	1.16	1.24	1.25
CI_FROM of ratio	1.55	1.99	2.14	1.99	1.18
CI_TO of ratio	1.92	2.23	2.41	2.38	1.50
MAX of ratio	3.20	3.97	3.45	3.33	2.44
MIN of ratio	0.64	1.06	1.78	1.60	1.02
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	0.0002
Visit 7					
N	33	87	29	27	27
MEAN	14.5	25.0	23.4	27.2	8.8
SD	11.5	12.4	12.7	24.2	6.7
MIN	-14	-3	-1	-8	-4
MEDIAN	12.8	24.5	20.9	24.1	8.6
INTERQUARTILE RANGE	8.0	18.9	12.7	19.8	7.1
MAX	53	58	51	115	26
p-value (2-s) for no change	<.0001	<.0001	<.0001	<.0001	<.0001
GEOMEAN of ratio	1.41	1.75	1.69	1.75	1.26
GEOSD of ratio	1.24	1.25	1.28	1.44	1.17
CI_FROM of ratio	1.31	1.67	1.54	1.51	1.19

Table 15.2.2.1: 1 D-dimer: Descriptive statistics for difference from baseline - per protocol data - 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid	BIBR 1048 150 mg bid + ASA 81 mg qd
MAX of ratio	3.22	2.83	16.17	4.07	2.71
MIN of ratio	0.54	0.58	0.18	0.53	0.71
p-value (2-s) for no change	0.0319	0.0656	0.2055	0.2397	0.0298
LOCF					
N	55	19	26	87	29
MEAN	22.3	12.3	50.2	8.1	29.1
SD	65.4	25.3	182.8	41.6	90.4
MIN	-49	-37	-206	-62	-73
MEDIAN	4.0	12.0	16.0	0.0	17.0
INTERQUARTILE RANGE	43.0	27.0	59.0	26.0	44.0
MAX	309	57	895	243	465
p-value (2-s) for no change	0.0525	0.0694	0.0163	0.3917	0.0213
GEOMEAN of ratio	1.14	1.20	1.20	1.06	1.18
GEOSD of ratio	1.53	1.46	2.06	1.42	1.42
CI_FROM of ratio	1.02	1.00	0.90	0.98	1.03
CI_TO of ratio	1.28	1.44	1.61	1.14	1.35
MAX of ratio	3.22	2.83	16.17	4.07	2.71
MIN of ratio	0.54	0.58	0.18	0.53	0.71
p-value (2-s) for no change	0.0268	0.0455	0.2055	0.1485	0.0156

Table 15.2.2.1: 1 D-dimer: Descriptive statistics for difference from baseline - per protocol data - 10 trt.

	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin
MAX of ratio	8.33	7.50	3.01	2.53	2.90
MIN of ratio	0.22	0.31	0.48	0.52	0.17
p-value (2-s) for no change	0.2407	0.8787	0.4972	0.9450	0.1711
LOCF					
N	32	88	29	29	63
MEAN	8.6	4.2	11.3	-7.9	-5.8
SD	49.2	95.8	82.2	40.9	50.6
MIN	-104	-302	-91	-171	-208
MEDIAN	2.0	0.0	-6.0	0.0	0.0
INTERQUARTILE RANGE	36.5	29.5	37.0	25.0	31.0
MAX	220	748	384	54	167
p-value (2-s) for no change	0.3854	0.5478	0.7170	0.6190	0.3570
GEOMEAN of ratio	1.10	1.00	1.04	0.99	0.93
GEOSD of ratio	1.76	1.51	1.58	1.41	1.56
CI_FROM of ratio	0.90	0.92	0.88	0.87	0.84
CI_TO of ratio	1.35	1.09	1.24	1.14	1.04
MAX of ratio	8.33	7.50	3.01	2.53	2.90
MIN of ratio	0.22	0.31	0.48	0.52	0.17
p-value (2-s) for no change	0.3338	0.9987	0.6175	0.9287	0.2241

Table 15.2.1: 1 Thromboembolic events − all randomised patients − 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 + ASA	50 mg bid 81 mg qd	BIBR 1048 + ASA	50 mg bid 325 mg qd	BIBR 1048 150 mg bid
Total Randomised	58(100.0)		20(100.0)		27(100.0)	99(100.0)
Composite endpoint						
No	57(98.3)		18(90.0)		26(96.3)	99(100.0)
Yes	1(1.7)		2(10.0)		1(3.7)	0(0.0)
Comp.endpoint, not incl. cardiac events						
No	57(98.3)		19(95.0)		27(100.0)	99(100.0)
Yes	1(1.7)		1(5.0)		0(0.0)	0(0.0)
Ischemic stroke						
None	58(100.0)		19(95.0)		27(100.0)	99(100.0)
Fatal	0(0.0)		0(0.0)		0(0.0)	0(0.0)
Non−fatal	0(0.0)		1(5.0)		0(0.0)	0(0.0)
Both	0(0.0)		0(0.0)		0(0.0)	0(0.0)
Transient ischemic attack						
No	58(100.0)		20(100.0)		27(100.0)	99(100.0)
Yes	0(0.0)		0(0.0)		0(0.0)	0(0.0)
Systemic thromboembolism						
No	57(98.3)		19(95.0)		27(100.0)	99(100.0)
Yes	1(1.7)		1(5.0)		0(0.0)	0(0.0)

Table 15.2.1: 1 Thromboembolic events − all randomised patients − 10 trt.

	BIBR 1048 150 mg bid + ASA 81 mg qd	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd
Total Randomised	34(100.0)	33(100.0)	98(100.0)	33(100.0)
Composite endpoint				
No	34(100.0)	33(100.0)	98(100.0)	33(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Comp.endpoint, not incl. cardiac events				
No	34(100.0)	33(100.0)	98(100.0)	33(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ischemic stroke				
None	34(100.0)	33(100.0)	98(100.0)	33(100.0)
Fatal	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Non−fatal	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Both	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Transient ischemic attack				
No	34(100.0)	33(100.0)	98(100.0)	33(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Systemic thromboembolism				
No	34(100.0)	33(100.0)	98(100.0)	33(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Table 15.2.1: 3 Thromboembolic events – all randomised patients (cont.) – 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid	BIBR 1048 150 mg bid + ASA 81 mg qd
Total Randomised	58(100.0)	20(100.0)	27(100.0)	99(100.0)	34(100.0)
Myocardial infarction					
None	58(100.0)	20(100.0)	27(100.0)	99(100.0)	34(100.0)
Fatal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Non-fatal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Both	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other major cardiac event					
No	58(100.0)	19(95.0)	26(96.3)	99(100.0)	34(100.0)
Yes	0(0.0)	1(5.0)	1(3.7)	0(0.0)	0(0.0)
Death					
No	58(100.0)	20(100.0)	27(100.0)	99(100.0)	34(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Table 15.2.1: 3 Thromboembolic events – all randomised patients (cont.) – 10 trt.

	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin
Total Randomised	33(100.0)	98(100.0)	33(100.0)	30(100.0)	70(100.0)
Myocardial infarction					
None	33(100.0)	98(100.0)	33(100.0)	30(100.0)	70(100.0)
Fatal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Non-fatal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Both	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other major cardiac event					
No	33(100.0)	98(100.0)	33(100.0)	30(100.0)	70(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Death					
No	33(100.0)	98(100.0)	33(100.0)	30(100.0)	70(100.0)
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Table 15.2.2.3: 1 TXB2: Descriptive statistics for difference from baseline – all treated patients – 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid	BIBR 1048 150 mg bid + ASA 81 mg qd
Total treated	58	20	27	99	34
TXB2 change to V2 baseline					
Visit 7					
N	44	17	19	73	25
MEAN	596.5	−1816.8	−2779.8	922.0	−1988.6
SD	2896.3	2186.1	2953.3	3874.0	2187.5
MIN	−9506	−8009	−10467	−9316	−6964
MEDIAN	1040.0	−1089.0	−1489.0	607.0	−1808.0
INTERQUARTILE RANGE	2681.0	2527.0	3704.0	2737.0	2490.0
MAX	6917	962	149	18384	2289
p−value (2−s) for no change	0.0139	0.0013	<.0001	0.0706	<.0001
GEOMEAN of ratio	1.26	0.59	0.47	1.19	0.60
GEOSD of ratio	1.89	1.72	1.69	1.94	1.70
CI_FROM of ratio	1.04	0.45	0.36	1.02	0.48
CI_TO of ratio	1.53	0.78	0.60	1.39	0.74
MAX of ratio	9.08	1.48	1.07	9.34	1.80
MIN of ratio	0.24	0.21	0.18	0.21	0.17
p−value (2−s) for no change	0.0185	0.0010	<.0001	0.0282	<.0001

Table 15.2.2.3: 1 TXB2: Descriptive statistics for difference from baseline – all treated patients – 10 trt.

	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin
Total treated	33	98	33	30	70
TXB2 change to V2 baseline					
Visit 7					
N	27	73	25	25	51
MEAN	−1125.9	1059.7	−1822.6	−1337.8	203.5
SD	3566.6	2216.8	2381.7	2279.2	2109.0
MIN	−8619	−4811	−10803	−7943	−4938
MEDIAN	−1104.0	722.0	−1832.0	−1206.0	137.0
INTERQUARTILE RANGE	2716.0	2470.0	2180.0	2530.0	1966.0
MAX	10743	6987	778	2039	6406
p−value (2−s) for no change	0.0155	<.0001	<.0001	0.0051	0.6439
GEOMEAN of ratio	0.70	1.31	0.60	0.58	1.08
GEOSD of ratio	2.33	1.84	1.78	2.83	1.71
CI_FROM of ratio	0.50	1.13	0.47	0.38	0.93
CI_TO of ratio	0.98	1.51	0.76	0.90	1.25
MAX of ratio	5.61	10.76	1.49	3.98	3.42
MIN of ratio	0.16	0.36	0.16	0.02	0.35
p−value (2−s) for no change	0.0361	0.0004	0.0002	0.0158	0.3215

Table 15.2.2.2: 1 Soluble fibrin: Descriptive statistics for difference from baseline − per protocol data − 10 trt.

	BIBR 1048 50 mg bid	BIBR 1048 50 mg bid + ASA 81 mg qd	BIBR 1048 50 mg bid + ASA 325 mg qd	BIBR 1048 150 mg bid	BIBR 1048 150 mg bid + ASA 81 mg qd
Total per protocol	58	19	26	97	32
Visit 7					
N	52	15	25	88	25
MEAN	3.2	0.9	1.2	0.3	−2.0
SD	22.0	2.3	8.4	5.1	9.9
MIN	−7	−0	−21	−19	−38
MEDIAN	0.0	0.0	0.0	0.0	0.0
INTERQUARTILE RANGE	0.3	0.9	0.9	0.5	0.8
MAX	157	9	27	32	19
p−value (2−s) for no change	1.0000	0.0469	0.8672	0.9116	0.4353
GEOMEAN of ratio	1.08	1.19	1.04	1.02	0.88
GEOSD of ratio	1.91	1.44	2.32	1.73	1.95
CI_FROM of ratio	0.90	0.97	0.74	0.91	0.66
CI_TO of ratio	1.29	1.45	1.48	1.15	1.15
MAX of ratio	53.40	3.93	9.31	6.16	3.37
MIN of ratio	0.41	0.94	0.12	0.14	0.12
p−value (2−s) for no change	0.4231	0.0922	0.7990	0.7324	0.3267

Table 15.2.2.2: 1 Soluble fibrin: Descriptive statistics for difference from baseline − per protocol data − 10 trt.

	BIBR 1048 150 mg bid + ASA 325 mg qd	BIBR 1048 300 mg bid	BIBR 1048 300 mg bid + ASA 81 mg qd	BIBR 1048 300 mg bid + ASA 325 mg qd	Warfarin
Total per protocol	33	97	32	29	70
Visit 7					
N	24	83	27	20	54
MEAN	−1.3	2.3	−0.7	−1.9	0.1
SD	8.8	26.8	4.6	12.0	4.0
MIN	−42	−53	−21	−52	−7
MEDIAN	0.0	0.0	0.0	0.0	0.0
INTERQUARTILE RANGE	0.9	1.0	0.0	1.0	1.0
MAX	3	235	4	7	22
p−value (2−s) for no change	0.2604	0.1453	0.6035	0.5898	0.1983
GEOMEAN of ratio	1.03	0.97	1.00	0.96	0.93
GEOSD of ratio	1.51	2.12	1.64	2.17	1.67
CI_FROM of ratio	0.86	0.83	0.82	0.67	0.81
CI_TO of ratio	1.22	1.15	1.22	1.38	1.07
MAX of ratio	1.93	79.20	2.40	3.27	5.13
MIN of ratio	0.21	0.05	0.13	0.05	0.31
p−value (2−s) for no change	0.7409	0.7498	0.9933	0.8321	0.3344

Table 15.3.1.2: 5 Major bleeding events central – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset															
	Screening		BIBR 50 mg bid		BIBR 50 mg qd		BIBR 50 mg bid + ASA 81 mg qd		BIBR 50 mg qd + ASA 81 mg qd		BIBR 50 mg bid + ASA 325 mg qd		BIBR 50 mg qd + ASA 325 mg qd		BIBR 150 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data																
Total Treated	502	100.0	59	100.0	1	100.0	21	100.0	0		27	100.0	0		100	100.0
Total with any Adverse Event	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Gastrointestinal disorders	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Gastric ulcer	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Gastrointestinal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Lower gastrointestinal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Rectal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.2: 5 Major bleeding events central – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset															
	BIBR 150 mg qd		BIBR 150 mg bid + ASA 81 mg qd		BIBR 150 mg qd + ASA 81 mg qd		BIBR 150 mg bid + ASA 325 mg qd		BIBR 150 mg qd + ASA 325 mg qd		BIBR 300 mg bid		BIBR 300 mg qd		BIBR 300 mg bid + ASA 81 mg qd	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data																
Total Treated	3	100.0	36	100.0	1	100.0	33	100.0	1	100.0	105	100.0	3	100.0	34	100.0
Total with any Adverse Event	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9
Gastrointestinal disorders	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9
Gastric ulcer	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9
Gastrointestinal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lower gastrointestinal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Rectal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.2: 5 Major bleeding events central – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset													
	BIBR 300 mg qd + ASA 81 mg qd		BIBR 300 mg bid + ASA 325 mg qd		BIBR 300 mg qd + ASA 325 mg qd		Warfarin		Post-Treat		Post-Study		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data														
Total Treated	2	100.0	30	100.0	1	100.0	70	100.0	502	100.0	502	100.0	502	100.0
Total with any Adverse Event	0	0.0	3	10.0	0	0.0	0	0.0	0	0.0	0	0.0	4	0.8
Gastrointestinal disorders	0	0.0	3	10.0	0	0.0	0	0.0	0	0.0	0	0.0	4	0.8
Gastric ulcer	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Gastrointestinal haemorrhage	0	0.0	1	3.3	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Lower gastrointestinal haemorrhage	0	0.0	1	3.3	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Rectal haemorrhage	0	0.0	1	3.3	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2

MedDRA version 7.1 was used for reporting

Table 15.3.1.2: 17 Minor/relevant bleeding events central – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset															
	Screening		BIBR 50 mg bid		BIBR 50 mg qd		BIBR 50 mg bid + ASA 81 mg qd		BIBR 50 mg qd + ASA 81 mg qd		BIBR 50 mg bid + ASA 325 mg qd		BIBR 50 mg qd + ASA 325 mg qd		BIBR 150 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data																
Total Treated	502	100.0	59	100.0	1	100.0	21	100.0	0		27	100.0	0		100	100.0
Total with any Adverse Event	0	0.0	0	0.0	0	0.0	1	4.8	0		1	3.7	0		9	9.0
Eye disorders	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Eye haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Gastrointestinal disorders	0	0.0	0	0.0	0	0.0	1	4.8	0		1	3.7	0		2	2.0
Gingival bleeding	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Haematochezia	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Haemorrhoidal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Melaena	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Mouth haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Rectal haemorrhage	0	0.0	0	0.0	0	0.0	1	4.8	0		1	3.7	0		0	0.0
Injury, poisoning and procedural complications	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Contusion	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Investigations	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.2: 17 Minor/relevant bleeding events central – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset															
	BIBR 150 mg qd		BIBR 150 mg bid + ASA 81 mg qd		BIBR 150 mg qd + ASA 81 mg qd		BIBR 150 mg bid + ASA 325 mg qd		BIBR 150 mg qd + ASA 325 mg qd		BIBR 300 mg bid		BIBR 300 mg qd		BIBR 300 mg bid + ASA 81 mg qd	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data																
Total Treated	3	100.0	36	100.0	1	100.0	33	100.0	1	100.0	105	100.0	3	100.0	34	100.0
Total with any Adverse Event	0	0.0	2	5.6	0	0.0	2	6.1	0	0.0	6	5.7	0	0.0	4	11.8
Eye disorders	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0	0	0.0
Eye haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0	0	0.0
Gastrointestinal disorders	0	0.0	0	0.0	0	0.0	1	3.0	0	0.0	1	1.0	0	0.0	3	8.8
Gingival bleeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Haematochezia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Haemorrhoidal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9
Melaena	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Mouth haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9
Rectal haemorrhage	0	0.0	0	0.0	0	0.0	1	3.0	0	0.0	1	1.0	0	0.0	1	2.9
Injury, poisoning and procedural complications	0	0.0	0	0.0	0	0.0	1	3.0	0	0.0	0	0.0	0	0.0	0	0.0
Contusion	0	0.0	0	0.0	0	0.0	1	3.0	0	0.0	0	0.0	0	0.0	0	0.0
Investigations	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.2: 17 Minor/relevant bleeding events central – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset													
	BIBR 300 mg qd + ASA 81 mg qd		BIBR 300 mg bid + ASA 325 mg qd		BIBR 300 mg qd + ASA 325 mg qd		Warfarin		Post-Treat		Post-Study		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data														
Total Treated	2	100.0	30	100.0	1	100.0	70	100.0	502	100.0	502	100.0	502	100.0
Total with any Adverse Event	0	0.0	3	10.0	0	0.0	4	5.7	1	0.2	0	0.0	33	6.6
Eye disorders	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Eye haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Gastrointestinal disorders	0	0.0	2	6.7	0	0.0	0	0.0	1	0.2	0	0.0	12	2.4
Gingival bleeding	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Haematochezia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Haemorrhoidal haemorrhage	0	0.0	1	3.3	0	0.0	0	0.0	0	0.0	0	0.0	3	0.6
Melaena	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	1	0.2
Mouth haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Rectal haemorrhage	0	0.0	1	3.3	0	0.0	0	0.0	0	0.0	0	0.0	6	1.2
Injury, poisoning and procedural complications	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Contusion	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Investigations	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.4: 4 Number of patients with serious adverse events by treatment at onset, MedDRA system organ class and preferred term – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset															
	Screening		BIBR 50 mg bid		BIBR 50 mg qd		BIBR 50 mg bid + ASA 81 mg qd		BIBR 50 mg qd + ASA 81 mg qd		BIBR 50 mg bid + ASA 325 mg qd		BIBR 50 mg qd + ASA 325 mg qd		BIBR 150 mg bid	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data																
Total Treated	502	100.0	59	100.0	1	100.0	21	100.0	0		27	100.0	0		100	100.0
Total with any Serious Adverse Event	0	0.0	5	8.5	0	0.0	2	9.5	0		1	3.7	0		10	10.0
Cardiac disorders	0	0.0	0	0.0	0	0.0	2	9.5	0		0	0.0	0		3	3.0
Acute coronary syndrome	0	0.0	0	0.0	0	0.0	1	4.8	0		0	0.0	0		0	0.0
Angina pectoris	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Atrial fibrillation	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Atrial thrombosis	0	0.0	0	0.0	0	0.0	1	4.8	0		0	0.0	0		0	0.0
Bradycardia	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Cardiac failure	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Cardiac failure congestive	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0
Ventricular fibrillation	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Ventricular tachycardia	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		1	1.0
Gastrointestinal disorders	0	0.0	0	0.0	0	0.0	0	0.0	0		1	3.7	0		1	1.0
Abdominal pain	0	0.0	0	0.0	0	0.0	0	0.0	0		0	0.0	0		0	0.0

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.4: 4 Number of patients with serious adverse events by treatment at onset, MedDRA system organ class and preferred term – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset															
	BIBR 150 mg qd		BIBR 150 mg bid + ASA 81 mg qd		BIBR 150 mg qd + ASA 81 mg qd		BIBR 150 mg bid + ASA 325 mg qd		BIBR 150 mg qd + ASA 325 mg qd		BIBR 300 mg bid		BIBR 300 mg qd		BIBR 300 mg bid + ASA 81 mg qd	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data																
Total Treated	3	100.0	36	100.0	1	100.0	33	100.0	1	100.0	105	100.0	3	100.0	34	100.0
Total with any Serious Adverse Event	0	0.0	4	11.1	0	0.0	2	6.1	0	0.0	3	2.9	0	0.0	4	11.8
Cardiac disorders	0	0.0	3	8.3	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0	2	5.9
Acute coronary syndrome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	2.9
Angina pectoris	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Atrial fibrillation	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	1	1.0	0	0.0	1	2.9
Atrial thrombosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Bradycardia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cardiac failure	0	0.0	2	5.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cardiac failure congestive	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ventricular fibrillation	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ventricular tachycardia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Gastrointestinal disorders	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	5.9
Abdominal pain	0	0.0	1	2.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

(Continued)

MedDRA version 7.1 was used for reporting

Table 15.3.1.4: 4 Number of patients with serious adverse events by treatment at onset, MedDRA system organ class and preferred term – all treated patients

MedDRA system organ class MedDRA preferred term	Treatment at Onset													
	BIBR 300 mg qd + ASA 81 mg qd		BIBR 300 mg bid + ASA 325 mg qd		BIBR 300 mg qd + ASA 325 mg qd		Warfarin		Post-Treat		Post-Study		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Summary Data														
Total Treated	2	100.0	30	100.0	1	100.0	70	100.0	502	100.0	502	100.0	502	100.0
Total with any Serious Adverse Event	0	0.0	4	13.3	0	0.0	2	2.9	3	0.6	2	0.4	41	8.2
Cardiac disorders	0	0.0	0	0.0	0	0.0	1	1.4	1	0.2	1	0.2	14	2.8
Acute coronary syndrome	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
Angina pectoris	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	2	0.4
Atrial fibrillation	0	0.0	0	0.0	0	0.0	1	1.4	1	0.2	0	0.0	5	1.0
Atrial thrombosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Bradycardia	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	1	0.2
Cardiac failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	0.6
Cardiac failure congestive	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Ventricular fibrillation	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Ventricular tachycardia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Gastrointestinal disorders	0	0.0	3	10.0	0	0.0	0	0.0	1	0.2	0	0.0	9	1.8
Abdominal pain	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2

(Continued)

MedDRA version 7.1 was used for reporting