Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Pradaxa®		**EudraCT No.:** 2007-004301-99	
Name of active ingredient: Dabigatran etexilate		**Page:** 1 of 10	**Synopsis No.:**
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Report date: 25 Feb 2010	**Trial No. / U No.:** 1160.67 / U10-1294-03	**Dates of trial:** 14 MAR 2008 – 2 OCT 2009	**Date of revision** 12 NOV 2010

Title of trial:	**R**andomis**E**d **D**abigatran **E**texilate dose-finding study in patients with acute coronary syndromes post index **E**vent with additional risk factors for cardiovascular complications also receiving aspirin and clopidogrel: **M**ulti-centre, prospective, placebo-controlled, group dose escalation trial (RE-DEEM STUDY)
Coordinating Investigators:	[redacted]
Trial sites:	International multi-centre trial with 161 trial sites in 24 countries (Europe, North America and Asia)
Publication (reference):	Results of this trial have been presented at the American Heart Association Scientific Sessions, 14-18. Nov 2009, Orlando, USA: Oldgren J, Budaj A, Granger CB et al. Circulation 2009;120(21):2160-2161 (P09-14652)
Clinical phase:	II
Objectives:	Dose-finding of dabigatran etexilate in patients with acute coronary syndromes post index event, who also received aspirin and clopidogrel, through means of a safety evaluation with particular reference to major, clinically relevant minor, other minor and any bleeding events and a pharmacodynamic assessment using a coagulation biomarker (D-dimer, F1.2) after 1 and 4 weeks and over the time course of the study.
Methodology:	Prospective, randomised, double-blind, placebo-controlled, group dose-escalation study with a DSMB as decision-making body for group dose-escalation and on-going safety.

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No. of patients:

planned: Entered: approximately 1800 patients; using adaptive randomisation.

actual: Enrolled: 2024 patients
Entered: 1878 patients

Treatment	Entered	Treated	Analysed (for primary endpoint)
Placebo	373	371	371
DE 50 mg b.i.d.	372	369	369
DE 75 mg b.i.d.	371	368	368
DE 110 mg b.i.d.	411	406	406
DE 150 mg b.i.d.	351	347	347

DE: dabigatran etexilate; b.i.d.: twice daily
Note that patients with moderate renal impairment (creatinine clearance >30 and ≤50 mL/min) were to be allocated to treatment from the next lower dabigatran etexilate dose level (with the exception of placebo and 50 mg DE) in order to achieve similar drug exposures. Nevertheless they are presented in the dose groups they were originally randomised to.

Diagnosis and main criteria for inclusion: Patients with acute coronary syndromes with increased troponin levels within 14 days post index myocardial infarction (ST or non-ST elevation) who also received aspirin and clopidogrel could be included. Patients had to have at least 1 additional risk factor for cardiovascular complications: age ≥65 years, diabetes on treatment, previous myocardical infarction, peripheral arterial disease, left bundle branch block, congestive heart failure, moderate renal insufficiency (creatinine clearance between 30 and 60 mL/min), or no revascularisation for index event.

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Test product:	Dabigatran etexilate
dose:	1 capsule of 50 mg, 75 mg, 110 mg, or 150 mg twice daily
mode of admin.:	p.o.

batch no.:	50 mg	75 mg	110 mg	150 mg
	B071003703	B071003704	804013	710472
	B071002573	B071002574	706325	706324
		B081001496		

Reference therapy:	Matching placebo
dose:	1 capsule twice daily
mode of admin.:	p.o.
batch no.:	706239
Duration of treatment:	6 months treatment in all patients
Criteria for evaluation	The primary endpoint in this trial was a safety endpoint and is described in the safety section below.
Efficacy / clinical pharmacology:	Secondary endpoints of efficacy included: - Change in coagulation biomarkers (D-dimer, F1.2) after 1 and 4 weeks of treatment (dabigatran etexilate/matching placebo) – criterion for efficacy of an active dose was at least 30% reduction in D-dimer in relation to placebo - Description of the time courses of D-dimer and F1.2 over the course of the study - Composite of cardiovascular death, non-fatal myocardial infarction and non-haemorrhagic stroke during 6 months of treatment - Composite of all-cause death, non-fatal myocardial infarction, severe recurrent ischaemia, and non-haemorrhagic stroke during 6 months of treatment - Individual occurrence of the efficacy outcome events (OEs) death (cardiovascular and all-cause), non-fatal myocardial infarction, severe recurrent ischaemia and non-haemorrhagic stroke during 6 months of treatment - Exploratory evaluation of the bleeding risk versus total dabigatran trough plasma concentration and the relationship of biomarkers to dabigatran trough plasma levels

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Criteria for evaluation (continued) **Safety:**	The primary endpoint was the composite of major bleeding events (MBEs, ISTH definition) and clinically relevant minor bleeding events (CRBEs) during 6 months of treatment. Additionally the individual occurrences of the following bleeding events during 6 months of treatment were evaluated: MBEs, CRBEs, not clinically relevant minor and any (major and minor) bleeding events. All bleeding events (as well as all potential efficacy OEs) were adjudicated by an independent Clinical Event Committee. The laboratory evaluation included haematology, clinical blood chemistry, and liver function tests (LFTs); blood samples were collected before administration of the trial drug at several visits in the treatment period. Adverse events (AEs) were described at the level of MedDRA terminology - MedDRA Preferred Term and MedDRA System Organ Class.
Statistical methods:	Primary endpoint: Logistic model for linear trend (dose response) and Cochran-Armitage linear trend test; survival analysis: Kaplan-Meier plots and log-rank test. Secondary endpoints: Biomarkers: Analysis of covariance (ANCOVA), logistic model for linear trend (dose response) and Cochran-Armitage linear trend test Composite endpoints of efficacy OEs: Descriptive PK/PD: Descriptive Safety: Descriptive The main (safety and efficacy) analyses of patients with moderate renal impairment (creatinine clearance ≥30 and <50 mL/min) were performed at the dose-level to which they were randomised.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	A total of 1878 patients were randomised into this study. Of the 1861 treated patients, 17.4% of patients discontinued treatment prematurely. Most patients discontinued trial medication due to an AE or refused to continue with study medication. Overall, a higher proportion of patients in the 2 highest dose level groups (11.8% in DE 110 and 9.8% in DE 150) discontinued treatment due to an AE than in the other treatment groups (8.4% to 8.7%; placebo: 8.4%). Most of the AEs leading to treatment discontinuation were other AEs (i.e. neither related to a worsening of the study disease nor of any other pre-existing disease).

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Efficacy / clinical pharmacology results (continued):

Demographics and baseline characteristics of the randomised patients were reasonably balanced across treatment groups. The mean age was 61.8 years. The majority of patients (76.0%) were male. Most patients (77.1%) were white. Most patients were from Central Europe (49.6%), followed by Western Europe (22.7%) and Asia (22.3%).

The index event was STEMI for 60.0% of randomised patients and NSTEMI for 40.0% of patients; 54.6% of all randomised patients received PCI for the index event. Two thirds of patients had a medical history of hypertension (66.3%), other baseline conditions included hyperlipidaemia (37.3%), angina pectoris (37.3%), and coronary artery disease (35.3%).

Almost all patients (99.2%) received dual antiplatelet therapy with aspirin and either clopidogrel or ticlopidine at baseline. The use of dual antiplatelet therapy decreased slightly over the course of the study: 83.8% of randomised patients were still on dual antiplatelet therapy immediately after last intake of trial medication. The majority of patients used concomitant medication during the trial: 99.1% of patients used concomitant cardiovascular therapy. Adherence to cardiovascular therapy recommended by guidelines was good: 71.1% of patients received ACE inhibitors, 13.5% received ARBs, 85.7% received beta-blocking agents and 83.2% received lipid-lowering therapy. A total of 19.1% used antithrombotic therapy (other than the background antiplatelet therapy) at least once during the study. The concomitant use of P-gp inhibitors was uncommon in this trial (fewer than 60 patients overall)

Secondary endpoints

D-dimer concentrations were reduced in all active treatment groups and the placebo group after 1 and 4 weeks of treatment. The reductions at Week 1 and Week 4 were similar in all active treatment groups (reductions by approximately 50% after 1 week and by approximately 70% after 4 weeks of treatment). Compared with placebo (reduction by approximately 10% after 1 week and by approximately 50% after 4 weeks of treatment), the reductions at Week 1 and Week 4 were statistically significantly greater in all 4 active treatment groups

Similarly, F1.2 concentrations were reduced in all active treatment groups and the placebo group after 1 and 4 weeks of treatment. Compared with placebo, the reductions at Week 1 and Week 4 were statistically significantly greater in the DE 75, DE 110, and DE 150 treatment groups.

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Efficacy / clinical pharmacology results (continued):

For both D-dimer and F1.2, the proportions of patients with any reduction from baseline concentrations increased with the DE dose; the Cochran-Armitage linear trend test across all treatment groups was statistically significant. Similar results were obtained for sensitivity analyses of the proportions of patients with at least a 30% reduction of each biomarker concentration.

Additional secondary endpoints were the individual and composite occurrences of centrally adjudicated efficacy OEs (cardiovascular and all-cause death, non-fatal MI, severe recurrent ischaemia, and non-haemorrhagic stroke) during 6 months of treatment. The overall incidence of the individual components and the 2 composite endpoints was low. Moreover, this study was not statistically powered to evaluate differences between treatment groups for the occurrence of efficacy OEs. Numerically, for the 2 composite endpoints (composite of cardiovascular death, non-fatal MI and non-haemorrhagic stroke and composite of all-cause death, non-fatal MI, severe recurrent ischaemia, and non-haemorrhagic stroke) the lowest incidences of events during the study were reported in the DE 110 group. Numerically, for most composite and individual efficacy OEs, the risk of an event was higher for the lower dose groups and lower for the higher dose groups, when compared with placebo. Notably there were fewer cardiac deaths and fewer fatal MIs in the 2 highest DE treatment groups, compared to placebo. For the first 2 weeks after the index event, the probability of experiencing an efficacy OE seemed to be highest in the placebo group (Kaplan-Meier survival analysis). Sensitivity analyses for events occurring during the follow-up period did not reveal a pattern consistent with a rebound effect.

The usefulness of the D-dimer measurement as an indicator of clinical efficacy was assessed by examining the degree of association between the reduction in D-dimer concentration (regardless of treatment group) and the probability of experiencing an efficacy OE. A linear logistic regression test indicated a significant association between the incidence of an efficacy OE and whether the patient had had a reduced D-dimer concentration at Week 1 for both composite endpoints and for cardiovascular death and all-cause death.

Clinical pharmacology

Trough plasma concentrations of total dabigatran after oral administration of dabigatran etexilate at steady state were dose proportional in the dose range of 50 to 150 mg b.i.d. (gMean of $C_{pre,ss}$: 19.6 to 65.2 ng/mL). The inter-individual variability was high in all 4 dose groups (gCV of $C_{pre,ss}$: 75 to 83%).

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Efficacy / clinical pharmacology results (continued):	Plasma dabigatran concentrations increased with increasing age, decreasing body weight, and decreasing creatinine clearance. Plasma concentrations were higher in females than in males, with no apparent effect of ethnic origin. In patients concomitantly using proton pump inhibitors, the trough plasma concentration of total dabigatran was slightly lower than in patients without proton pump inhibitor intake. Patients who experienced an MBE or CRBE during the on-treatment period had higher mean trough plasma dabigatran concentrations than patients without any bleeding events. Patients experiencing events in either of the 2 composite efficacy endpoints had similar trough plasma concentrations as patients without such events.
Safety results:	*Exposure and treatment interruptions* The median exposure to the study drug was identical in all treatment groups (182 days). Interruptions of any study drug (DE or DE matching placebo) were documented for 21.3% (placebo) and 22.9% (DE combined) of patients. The mean duration of interruptions was 2.3 days (placebo) and 2.5 days (DE combined). *Bleeding events* For the primary endpoint, the incidences of the composite of MBEs/CRBEs were 2.2% (placebo) and 5.9% (DE combined), with a modest dose-dependent increase of bleeding events among the DE groups (Cochran-Armitage test for linear trend). The highest incidences of MBEs/CRBEs were reported for patients in the 2 highest dose groups (DE 110: 7.9%, DE 150: 7.8%). The HRs of the DE 110 and DE 150 groups versus placebo were 3.92 (95% CI 1.72, 8.95) and 4.27 (95% CI 1.86, 9.81), respectively. MBEs (ISTH definition) were documented for 0.5% (placebo) and 1.1% (DE combined) of patients. CRBEs were reported for 1.6% of patients receiving placebo and for 4.9% of patients in the DE combined group. The incidences of any bleeding events were 6.7% (placebo) and 12.7% (DE combined). Overall, very few patients experienced multiple bleeding events. Major bleeding events (TIMI definition) occurred in 0.3% (placebo) and 0.5% (DE combined) of patients. For the subgroups age (<65 years, ≥65 and <75 years, ≥75 years) and sex, the p-value for homogeneity of the treatment effect across all categories within a subgroup (logistic regression interaction test) was below 0.05. Thus, the

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Safety results (continued):

incidence of MBEs/CRBEs did not increase in the same dose-dependent manner within all categories of these 2 subgroups. With increasing DE doses, the incidence of MBEs/CRBEs appeared to be higher for female patients and for patients aged ≥65 years.

The most frequently reported sites of bleeding were gastrointestinal (placebo: 1.4%, DE combined: 3.4%), nasal (placebo: 0.8%, DE combined: 3.4%), and oral bleeding events (placebo: 0.5%, DE combined: 1.3%).

Adverse events

Overall, the incidences of reported AEs were similar in all treatment groups (placebo: 54.7%, DE combined: 57.2%) and did not appear to be dose-dependent. On preferred term (PT) level, only angina pectoris was reported with an incidence of at least 5% in any treatment group (placebo and DE 75: 5.7%). The most frequent AEs on system organ class (SOC) level were gastrointestinal disorders (placebo: 13.5%, DE combined: 16.2%), cardiac disorders (placebo: 14.3%, DE combined: 14.0%), and respiratory, thoracic and mediastinal disorders (placebo: 9.2%, DE combined: 11.7%).

AEs assessed as drug-related by the investigator were reported for 4.9% (placebo) and 10.6% (DE combined) of patients. The SOC with the highest incidence of drug-related AEs was gastrointestinal disorders (placebo: 1.9%, DE combined: 4.6%), with gastrointestinal haemorrhage (placebo: 0%, DE combined: 0.5%) and rectal haemorrhage as most frequently reported drug-related AEs. Rectal haemorrhage was experienced by 0.5% of patients in the placebo and DE combined groups (maximum DE 110: 1.0%). For the second most frequently reported SOC (respiratory, thoracic and mediastinal disorders), the treatment difference between the placebo and DE groups is explained by epistaxis (placebo: 0.3%, DE combined: 1.9%) which is the only AE appearing to be dose-dependent.

The proportions of patients who discontinued the study drug due to AEs were 8.4% (placebo) and 9.8% (DE combined). On SOC level, gastrointestinal disorders most frequently led to treatment discontinuation (placebo: 1.6%, DE combined: 2.8%), with a modest dose-dependent increase in AEs among the DE groups. The frequencies of AEs of severe intensity were similar in all individual treatment groups. On SOC level, cardiac disorders were the most frequently reported severe AEs (placebo: 3.0%, DE combined: 2.3%), followed by general

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Safety results (continued):

disorders and administration site conditions (placebo: 1.6%, DE combined: 1.2%). Within the SOC cardiac disorders, most patients in all groups experienced myocardial infarction (placebo: 2.2%, DE combined: 0.9%). Within the SOC general disorders and administration site conditions, the most frequently reported AEs on PT level were death (placebo: 0.8%, DE combined: 0.3%), and sudden death (placebo: 0.5%, DE combined: 0.6%).

During the conduct of the trial, 51 patients were known to have died at any time post randomisation. One patient died before first intake of study drug. Of the 1861 treated patients, 41 patients died during the on-treatment period: 13 patients (3.5%) had been randomised to placebo and 28 patients (1.9%) had been randomised to DE (DE 50: 7 patients, DE 75: 10, DE 110: 4, DE 150: 7). Three patients (0.2%) died during the post-treatment period; 2 of these patients had received DE 110 and 1 patient had been treated with DE 50. Six patients (0.3%) died during the post-study period. Of the 50 treated patients who died, sudden death (placebo: 0.5%, DE combined: 0.6% of treated patients), death (placebo: 0.8%, DE combined: 0.3% of treated patients), and myocardial infarction (placebo: 1.1%, DE combined: 0.1% of treated patients) were the 3 most common PTs.

All efficacy OEs and bleeding events were also reported as AEs but not necessarily as serious AEs (SAEs). Generally, efficacy OEs and bleeding events which occurred before Visit 10 and which met the criteria of an SAE were not to be reported as an SAE but only as an efficacy OE or bleeding event. However, if any efficacy OE occurred before Visit 10 and was deemed related to study medication, it was also to be reported as an SAE. SAEs were reported for 8.6% (placebo) and 8.1% (DE combined) of patients during the on-treatment period. Importantly, there was no dose-dependent increase in the frequency of SAEs for increasing doses of DE. On SOC level, the most frequently reported SAEs were cardiac disorders (placebo: 3.8%, DE combined: 3.7%), followed by general disorders and administration site conditions (placebo: 0.5%, DE combined: 1.1%). The next most frequent SOC was infections and infestations (placebo: 0.5%, DE combined: 0.7%). During the off-treatment, post-treatment, and post-study periods 2.7%, 0.7%, and 1.2% of patients had SAEs.

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Safety results (continued):	*Clinical laboratory and vital signs* The analyses of mean changes from baseline to last value on treatment and of transitions relative to the reference ranges did not reveal any meaningful differences between the treatment groups. Regarding possible clinically significant abnormalities (PCSAs), no noteworthy differences between the treatment groups were noted. Among the LFTs, abnormalities of possible clinical significance were most frequently observed for GGT, followed by ALT and AST. PCSAs for the other safety parameters were most frequently documented for eosinophil cell count (increase), haematocrit (decrease), and haemoglobin (decrease). Two patients (both DE 110) had ALT or AST >3x ULN accompanied by elevations of bilirubin ≥2x ULN (potential Hy's law cases); these events were caused by a case of metastatic pancreatic cancer and a case of hepatitis C infection. For vital signs, no meaningful differences between treatment groups were observed.
Conclusions:	This was a placebo-controlled, adaptive design, dose-finding study investigating 4 doses of DE (twice daily 50 mg, 75 mg, 110 mg, or 150 mg) in ACS patients post index event with additional risk factors for cardiovascular complications on a background dual antiplatelet medication. A modest dose-dependent increase in the incidences of MBEs/CRBEs (primary endpoint) among the DE groups was observed. The increase in the incidence of MBEs in the DE groups was reasonably low, with a maximum increase of 1.5% (ISTH definition) and 0.9% (TIMI definition) compared with placebo. D-dimer and F1.2 concentrations were reduced in all treatment groups at 1 and 4 weeks of treatment; the reductions were greater in all DE groups than in the placebo group. The incidences of the 2 composite endpoints of adjudicated efficacy OEs were low and did not reveal clinically significant differences between treatment groups. The risk for bleeding events, but not for efficacy OEs, seemed to increase with the plasma concentration of dabigatran. The incidences of AEs were similar in all treatment groups. Overall, treatment with DE up to 150 mg b.i.d. was well tolerated in patients with ACS on dual antiplatelet therapy.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the complete disposition results and results of additional secondary endpoints, as summarised below. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format; therefore, results for a total of 10 endpoints are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Descriptive statistics of D−dimer concentration (Secondary endpoint)	Table 15.7.1: 1
Change from baseline in D−dimer concentration at Week 4 (Secondary endpoint)	Table 15.7.1: 2
Change from baseline in D-dimer concentration at Week 1 (Secondary endpoint)	Table 15.7.1: 4
Descriptive statistics of F1.2 concentration (Secondary endpoint)	Table 15.7.2: 1
Change from baseline in F1.2 concentration at Week 4 (Secondary endpoint)	Table 15.7.2: 3
Change from baseline in F1.2 concentration at Week 1 (Secondary endpoint)	Table 15.7.2: 4
Number of patients with any reduction in D−dimer concentration at Week 1 or Week 4 (Secondary endpoint)	Table 15.7.1: 5
Number of patients by bleed type and treatment group (Primary endpoint)	Table 15.2.1.1: 1
Time to first adjudicated major or clinically relevant minor bleed (Primary endpoint)	Table 15.2.1.4: 1
Adverse event overall summary	Table 15.3.2: 2

Table 15.1.1: 1 Summary of patient disposition (trial completion)

	Placebo N (%)	DE 50mg bid N (%)	DE 75mg bid N (%)	DE 110mg bid N (%)
Enrolled				
Not entered/randomised				
Entered/randomised	373	372	371	411
Not treated	2	3	3	5
Treated	371 (100.0)	369 (100.0)	368 (100.0)	406 (100.0)
Patient completed planned observation time	318 (85.7)	297 (80.5)	309 (84.0)	330 (81.3)
Patient did not complete planned observation time	53 (14.3)	72 (19.5)	59 (16.0)	76 (18.7)
Adverse event	30 (8.1)	28 (7.6)	30 (8.2)	46 (11.3)
Worsening of disease/condition under study	10 (2.7)	4 (1.1)	1 (0.3)	3 (0.7)
Worsening of other pre-existing disease/condition	4 (1.1)	2 (0.5)	3 (0.8)	4 (1.0)
Other adverse event	16 (4.3)	22 (6.0)	26 (7.1)	39 (9.6)
Non compliant with protocol	8 (2.2)	17 (4.6)	8 (2.2)	6 (1.5)
Lost to follow-up	1 (0.3)	1 (0.3)	1 (0.3)	4 (1.0)
Consent withdrawn, not due to adverse event	5 (1.3)	6 (1.6)	4 (1.1)	3 (0.7)
Other	9 (2.4)	20 (5.4)	16 (4.3)	17 (4.2)

Table 15.7.1: 1 Descriptive statistics of D-dimer concentration (mg/L)
full analysis set

D-dimer [mg/L]	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set	356	358	358	388	332	1436
Baseline						
N	341	338	342	375	324	1379
Mean	260.10	259.42	311.76	309.90	294.20	294.30
SD	369.54	357.15	947.23	624.11	649.83	677.03
Min	15.0	15.0	15.0	15.0	15.0	15.0
Median	169.00	163.00	152.00	163.00	158.00	160.00
Max	4160.0	2954.0	13456.0	8730.0	6995.0	13456.0
IQR	212.30	213.20	216.10	223.10	212.30	217.50
CV [%]	142.1	137.7	303.8	201.4	220.9	230.0
gMean	146.72	143.60	136.08	156.23	146.02	145.55
gSD	3.1	3.1	3.3	3.1	3.0	3.1
gCV [%]	159.7	161.3	180.3	160.3	155.3	164.2
Week 1						
N	351	353	354	377	325	1409
Mean	243.77	153.89	169.53	182.71	161.17	167.21
SD	477.99	218.65	470.94	641.25	257.22	438.98
Min	15.0	15.0	15.0	15.0	15.0	15.0
Median	131.00	97.50	79.90	88.40	90.50	89.00
Max	6727.0	2333.0	6236.0	11878.0	2422.0	11878.0
IQR	195.60	160.70	171.00	141.20	158.10	156.20
CV [%]	196.1	142.1	277.8	351.0	159.6	262.5
gMean	122.47	80.24	70.14	82.26	80.97	78.25
gSD	3.2	3.3	3.5	3.2	3.2	3.3
gCV [%]	171.4	174.0	196.9	166.2	168.1	176.2

D-dimer is being evaluated as a possible indicator of clinical efficacy with a reduction in D-dimer concentration suggestive of an improvement in clinical outcome.

Source data: Appendix 16.2, Listing 6.2.1 biomark.sas 24FEB2010

Table 15.7.1: 1 Descriptive statistics of D-dimer concentration (mg/L)
full analysis set

D-dimer [mg/L]	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Week 4						
N	345	335	347	374	314	1370
Mean	177.04	106.30	99.34	90.33	81.04	94.39
SD	456.42	297.48	203.59	164.03	167.11	214.17
Min	15.0	15.0	15.0	15.0	15.0	15.0
Median	78.90	41.40	31.40	39.25	36.20	37.15
Max	7050.0	4332.0	2049.0	1388.0	2333.0	4332.0
IQR	143.60	88.00	75.00	78.10	82.50	80.40
CV [%]	257.8	279.8	205.0	181.6	206.2	226.9
gMean	79.02	46.46	42.53	45.13	43.36	44.36
gSD	3.3	3.1	3.2	2.9	2.7	3.0
gCV [%]	174.6	157.3	166.8	144.0	132.9	150.1
Week 26						
N	322	288	310	334	280	1212
Mean	112.60	59.99	101.03	87.59	44.56	74.53
SD	180.19	89.07	621.62	377.11	57.93	375.28
Min	15.0	15.0	15.0	15.0	15.0	15.0
Median	63.90	25.15	20.70	23.75	21.15	22.35
Max	2341.0	763.0	10369.0	5858.0	576.0	10369.0
IQR	109.00	51.60	51.20	52.30	34.10	43.40
CV [%]	160.0	148.5	615.3	430.5	130.0	503.6
gMean	61.89	34.74	33.54	34.49	29.38	33.06
gSD	2.9	2.6	2.8	2.8	2.2	2.6
gCV [%]	143.7	118.9	137.6	133.7	95.8	122.5

D-dimer is being evaluated as a possible indicator of clinical efficacy with a reduction in D-dimer concentration suggestive of an improvement in clinical outcome.

Source data: Appendix 16.2, Listing 6.2.1 biomark.sas 24FEB2010

Table 15.7.1: 1 Descriptive statistics of D-dimer concentration (mg/L)
full analysis set

D-dimer [mg/L]	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Week 28						
N	324	305	312	348	292	1257
Mean	112.19	117.25	123.42	123.98	88.97	114.08
SD	192.78	409.41	310.38	311.89	159.15	312.03
Min	15.0	15.0	15.0	15.0	15.0	15.0
Median	59.45	56.60	46.15	59.15	49.55	52.10
Max	2022.0	6850.0	4060.0	4912.0	2200.0	6850.0
IQR	104.10	82.30	104.35	104.60	76.50	92.70
CV [%]	171.8	349.2	251.5	251.6	178.9	273.5
gMean	60.61	56.13	52.73	60.49	50.57	55.07
gSD	2.9	2.8	3.1	2.9	2.7	2.9
gCV [%]	141.3	139.4	164.7	146.8	127.5	145.0

D-dimer is being evaluated as a possible indicator of clinical efficacy with a reduction in D-dimer concentration suggestive of an improvement in clinical outcome.

Source data: Appendix 16.2, Listing 6.2.1 biomark.sas 24FEB2010

Table 15.7.1: 2 Change from baseline in log10 D-dimer concentration at Week 4 (observed cases)
full analysis set

	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set	356	358	358	388	332	1436
Total number of patients analysed	331	318	335	363	308	1324
Baseline [mg/L], geometric mean (gSD)	146.7 (3.1)	143.6 (3.1)	136.1 (3.3)	156.2 (3.1)	146.0 (3.0)	145.6 (3.1)
Week 4 [mg/L], geometric mean (gSD)	79.0 (3.3)	46.5 (3.1)	42.5 (3.2)	45.1 (2.9)	43.4 (2.7)	44.4 (3.0)
Ratio of Week 4 to baseline						
Geometric mean (gSD)	0.57 (3.01)	0.33 (3.04)	0.31 (3.30)	0.29 (3.14)	0.31 (3.02)	0.31 (3.13)
Adjusted* geometric mean	0.56	0.33	0.31	0.31	0.31	0.31
95% confidence interval	(0.51, 0.63)	(0.30, 0.37)	(0.28, 0.34)	(0.28, 0.34)	(0.28, 0.34)	(0.30, 0.33)
Ratio to placebo*						
Adjusted geometric mean		0.58	0.54	0.54	0.54	0.55
95% confidence interval		(0.50, 0.68)	(0.47, 0.63)	(0.47, 0.62)	(0.47, 0.63)	(0.49, 0.62)
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

* ANCOVA on difference in log10 D-dimer concentrations adjusting for log10 baseline D-dimer concentration
D-dimer is being evaluated as a possible indicator of clinical efficacy with a reduction in
D-dimer concentration suggestive of an improvement in clinical outcome

Table 15.7.1: 4 Change from baseline in log10 D-dimer concentration at Week 1 (observed cases)
full analysis set

	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set	356	358	358	388	332	1436
Total number of patients analysed	337	333	339	366	319	1357
Baseline [mg/L], geometric mean (gSD)	146.7 (3.1)	143.6 (3.1)	136.1 (3.3)	156.2 (3.1)	146.0 (3.0)	145.6 (3.1)
Week 1 [mg/L], geometric mean (gSD)	122.5 (3.2)	80.2 (3.3)	70.1 (3.5)	82.3 (3.2)	81.0 (3.2)	78.3 (3.3)
Ratio of Week 1 to baseline						
Geometric mean (gSD)	0.87 (2.45)	0.58 (2.60)	0.52 (2.81)	0.52 (2.54)	0.55 (2.58)	0.54 (2.63)
Adjusted* geometric mean	0.87	0.58	0.51	0.54	0.55	0.54
95% confidence interval	(0.79, 0.96)	(0.53, 0.64)	(0.47, 0.56)	(0.49, 0.59)	(0.50, 0.61)	(0.52, 0.57)
Ratio to placebo*						
Adjusted geometric mean		0.67	0.59	0.61	0.64	0.62
95% confidence interval		(0.58, 0.76)	(0.51, 0.67)	(0.54, 0.70)	(0.55, 0.73)	(0.56, 0.69)
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

* ANCOVA on difference in log10 D-dimer concentrations adjusting for log10 baseline D-dimer concentration
D-dimer is being evaluated as a possible indicator of clinical efficacy with a reduction in
D-dimer concentration suggestive of an improvement in clinical outcome

Table 15.7.2: 1 Descriptive statistics of F1.2 concentration (pmol/L)
full analysis set

Pro-thrombin fragment 1 and 2 [pmol/L]	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set	356	358	358	388	332	1436
Baseline						
N	341	338	342	375	324	1379
Mean	717.57	859.75	844.84	627.66	1073.40	843.14
SD	2929.90	3000.43	3402.27	2555.37	4001.26	3258.26
Min	52.7	30.2	42.7	41.9	37.4	30.2
Median	178.00	181.50	183.00	188.00	179.00	182.00
Max	24000.0	24000.0	24000.0	24000.0	24000.0	24000.0
IQR	116.00	139.00	133.00	145.00	166.00	146.00
CV [%]	408.3	349.0	402.7	407.1	372.8	386.4
gMean	213.61	236.55	220.72	216.51	229.47	225.38
gSD	2.6	3.0	2.7	2.5	3.1	2.8
gCV [%]	118.4	152.6	132.6	113.5	164.5	139.3
Week 1						
N	351	353	354	377	325	1409
Mean	672.95	860.22	761.33	941.64	708.70	822.21
SD	2595.99	3251.07	3120.07	3819.04	3012.03	3327.70
Min	50.8	24.5	51.9	48.6	50.6	24.5
Median	172.00	140.00	136.00	138.00	124.00	135.00
Max	24000.0	24000.0	24000.0	24000.0	24000.0	24000.0
IQR	105.00	97.00	78.00	90.00	85.10	88.00
CV [%]	385.8	377.9	409.8	405.6	425.0	404.7
gMean	207.18	189.94	176.92	182.87	165.42	178.90
gSD	2.6	3.1	2.9	3.0	2.8	3.0
gCV [%]	120.9	162.5	143.6	155.5	138.9	150.3

Pro-thrombin fragment 1 and 2 is being evaluated as a possible indicator of clinical efficacy with a reduction in Pro-thrombin fragment concentration suggestive of an improvement in clinical outcome.

Source data: Appendix 16.2, Listing 6.2.1 biomark.sas 24FEB2010

Table 15.7.2: 1 Descriptive statistics of F1.2 concentration (pmol/L)
full analysis set

Pro-thrombin fragment 1 and 2 [pmol/L]	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Week 4						
N	345	335	347	374	314	1370
Mean	549.93	715.54	845.75	516.20	734.39	698.43
SD	2034.33	2789.60	3475.21	2464.48	3125.41	2975.58
Min	49.3	57.2	51.2	41.5	50.1	41.5
Median	169.00	143.00	132.00	135.00	135.50	136.00
Max	24000.0	24000.0	24000.0	24000.0	24000.0	24000.0
IQR	99.00	101.00	91.00	77.00	102.00	92.00
CV [%]	369.9	389.9	410.9	477.4	425.6	426.0
gMean	200.03	188.32	172.43	157.24	171.30	171.55
gSD	2.4	2.8	2.9	2.4	2.8	2.7
gCV [%]	108.5	137.2	148.1	104.3	136.0	130.7
Week 26						
N	322	288	310	334	280	1212
Mean	1325.17	1323.56	794.56	770.24	621.22	873.51
SD	4639.28	4516.03	3357.45	3299.23	3154.08	3614.17
Min	47.6	48.5	39.7	42.9	50.4	39.7
Median	169.50	135.00	134.00	138.00	124.50	133.00
Max	24000.0	24000.0	24000.0	24000.0	24000.0	24000.0
IQR	102.00	102.00	79.00	99.00	80.15	91.00
CV [%]	350.1	341.2	422.6	428.3	507.7	413.8
gMean	225.58	201.95	167.25	172.92	149.67	172.06
gSD	3.4	3.8	2.9	2.8	2.5	3.0
gCV [%]	184.4	221.5	146.7	138.5	112.3	153.1

Pro-thrombin fragment 1 and 2 is being evaluated as a possible indicator of clinical efficacy with a reduction in Pro-thrombin fragment concentration suggestive of an improvement in clinical outcome.

Source data: Appendix 16.2, Listing 6.2.1 biomark.sas 24FEB2010

Table 15.7.2: 1 Descriptive statistics of F1.2 concentration (pmol/L)
full analysis set

Pro-thrombin fragment 1 and 2 [pmol/L]	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Week 28						
N	324	305	312	348	292	1257
Mean	919.94	1213.31	755.31	1144.49	589.21	935.60
SD	3593.36	4314.04	3211.08	4292.75	2711.67	3730.85
Min	30.8	33.0	44.2	26.6	43.4	26.6
Median	169.00	165.00	154.00	168.00	148.50	159.00
Max	24000.0	24000.0	24000.0	24000.0	24000.0	24000.0
IQR	94.50	127.00	106.50	108.00	113.00	112.00
CV [%]	390.6	355.6	425.1	375.1	460.2	398.8
gMean	204.21	225.35	193.46	213.75	182.86	203.69
gSD	2.9	3.4	2.7	3.2	2.5	3.0
gCV [%]	145.4	190.3	127.0	167.1	113.3	149.5

Pro-thrombin fragment 1 and 2 is being evaluated as a possible indicator of clinical efficacy with a reduction in Pro-thrombin fragment concentration suggestive of an improvement in clinical outcome.

Source data: Appendix 16.2, Listing 6.2.1 biomark.sas 24FEB2010

Table 15.7.2: 3 Change from baseline in log10 F1.2 concentration at Week 4 (last observation carried forward)
full analysis set

	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set	356	358	358	388	332	1436
Total number of patients analysed	341	338	342	374	324	1378
Baseline [pmol/L], geometric mean (gSD)	213.6 (2.6)	236.6 (3.0)	220.7 (2.7)	216.5 (2.5)	229.5 (3.1)	225.4 (2.8)
Week 4 [pmol/L], geometric mean (gSD)	199.7 (2.4)	185.7 (2.7)	174.5 (3.0)	159.1 (2.4)	172.3 (2.8)	172.4 (2.7)
Ratio of Week 4 to baseline						
Geometric mean (gSD)	0.94 (2.57)	0.79 (3.10)	0.80 (3.28)	0.73 (2.57)	0.75 (2.75)	0.76 (2.92)
Adjusted* geometric mean	0.92	0.81	0.79	0.72	0.76	0.77
95% confidence interval	(0.84, 1.01)	(0.74, 0.89)	(0.72, 0.87)	(0.66, 0.78)	(0.69, 0.83)	(0.73, 0.80)
Ratio to placebo*						
Adjusted geometric mean		0.89	0.86	0.78	0.83	0.84
95% confidence interval		(0.78, 1.01)	(0.76, 0.98)	(0.69, 0.89)	(0.72, 0.94)	(0.75, 0.93)
p-value		0.071	0.027	< 0.001	0.005	< 0.001

* ANCOVA on difference in log10 Prothrombin fragment (F1.2) concentrations adjusting for log10 baseline Prothrombin fragment (F1.2) concentration
Prothrombin fragment (F1.2) is being evaluated as a possible indicator of clinical efficacy with a reduction in Prothrombin fragment (F1.2) concentration suggestive of an improvement in clinical outcome

Table 15.7.2: 4 Change from baseline in log10 F1.2 concentration at Week 1 (observed cases)
full analysis set

	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set	356	358	358	388	332	1436
Total number of patients analysed	337	333	339	366	319	1357
Baseline [pmol/L], geometric mean (gSD)	213.6 (2.6)	236.6 (3.0)	220.7 (2.7)	216.5 (2.5)	229.5 (3.1)	225.4 (2.8)
Week 1 [pmol/L], geometric mean (gSD)	207.2 (2.6)	189.9 (3.1)	176.9 (2.9)	182.9 (3.0)	165.4 (2.8)	178.9 (3.0)
Ratio of Week 1 to baseline						
Geometric mean (gSD)	0.95 (2.44)	0.80 (3.23)	0.82 (2.56)	0.84 (3.14)	0.70 (2.75)	0.79 (2.93)
Adjusted* geometric mean	0.93	0.82	0.81	0.83	0.71	0.79
95% confidence interval	(0.85, 1.03)	(0.75, 0.91)	(0.74, 0.90)	(0.75, 0.91)	(0.65, 0.79)	(0.76, 0.83)
Ratio to placebo*						
Adjusted geometric mean		0.88	0.87	0.89	0.76	0.85
95% confidence interval		(0.77, 1.01)	(0.76, 1.00)	(0.77, 1.01)	(0.66, 0.88)	(0.76, 0.95)
p-value		0.079	0.047	0.081	< 0.001	0.004

* ANCOVA on difference in log10 Prothrombin fragment (F1.2) concentrations adjusting for log10 baseline Prothrombin fragment (F1.2) concentration

Prothrombin fragment (F1.2) is being evaluated as a possible indicator of clinical efficacy with a reduction in Prothrombin fragment (F1.2) concentration suggestive of an improvement in clinical outcome

Table 15.7.1: 5 Number (%) of patients with any reduction in D-dimer concentration at Week 1 or Week 4
full analysis set

	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set [N (%)]	356 (100.00)	358 (100.00)	358 (100.00)	388 (100.00)	332 (100.00)	1436 (100.00)
Number of patients with any reduction [N (%)]	264 (74.16)	290 (81.01)	293 (81.84)	333 (85.82)	296 (89.16)	1212 (84.40)
Number of patients with no reduction [N (%)]	77 (21.63)	48 (13.41)	49 (13.69)	41 (10.57)	28 (8.43)	166 (11.56)
Number of patients without baseline, week 1 or week 4 data [N (%)]	15 (4.21)	20 (5.59)	16 (4.47)	14 (3.61)	8 (2.41)	58 (4.04)
Comparison to placebo*						
Odds ratio		1.762	1.744	2.369	3.083	2.130
95% Confidence interval		(1.185, 2.621)	(1.175, 2.589)	(1.569, 3.576)	(1.940, 4.900)	(1.576, 2.878)
Cochran-Armitage linear trend test						
p-value	< 0.001					

* Patients with missing baseline, week 1 or week 4 data have been excluded from the analysis

Table 15.2.1.1: 1 Number (%) of patients by adjudicated bleed type (RE-DEEM definition) and treatment group treated set (on-trt, off-trt and follow-up bleeds)

	Placebo N (%)	DE 50mg bid N (%)	DE 75mg bid N (%)	DE 110mg bid N (%)	DE 150mg bid N (%)	DE combined N (%)
Total number of patients in analysis set	371 (100.00)	369 (100.00)	368 (100.00)	406 (100.00)	347 (100.00)	1490 (100.00)
Number of patients with any type of bleed	25 (6.74)	42 (11.38)	45 (12.23)	60 (14.78)	42 (12.10)	189 (12.68)
Number of patients with major bleed	2 (0.54)	3 (0.81)	1 (0.27)	8 (1.97)	4 (1.15)	16 (1.07)
Number of patients with minor bleed (clinically relevant)	6 (1.62)	10 (2.71)	16 (4.35)	24 (5.91)	23 (6.63)	73 (4.90)
Number of patients with minor bleed (not clinically relevant)	17 (4.58)	32 (8.67)	29 (7.88)	35 (8.62)	20 (5.76)	116 (7.79)
Number of patients with major or clinically relevant minor bleed	8 (2.16)	13 (3.52)	16 (4.35)	32 (7.88)	27 (7.78)	88 (5.91)

Table 15.2.1.4: 1 Time to first adjudicated major or clinically relevant minor bleed (RE-DEEM definition) treated set (on-trt and off-trt bleeds)

	Placebo	DE 50mg bid	DE 75mg bid	DE 110mg bid	DE 150mg bid	DE combined
Total number of patients in analysis set [N (%)]	371 (100.00)	369 (100.00)	368 (100.00)	406 (100.00)	347 (100.00)	1490 (100.00)
Patients with a major or clinically relevant minor bleed [N (%)]	7 (1.89)	12 (3.25)	15 (4.08)	29 (7.14)	27 (7.78)	83 (5.57)
Patients censored [N (%)]	364 (98.11)	357 (96.75)	353 (95.92)	377 (92.86)	320 (92.22)	1407 (94.43)
Comparison to placebo						
Hazard ratio		1.77	2.17	3.92	4.27	3.02
95% confidence interval		0.70, 4.50	0.88, 5.31	1.72, 8.95	1.86, 9.81	1.40, 6.53
p-value*		0.222	0.084	< 0.001	< 0.001	0.003

* - Log-rank test

Table 15.3.2: 2 Adverse event overall summary - treated set

Dose adjusted patients analysed at adjusted dose level

	Screening N (%)	Placebo N (%)	DE 50mg bid N (%)	DE 75mg bid N (%)	DE 110mg bid N (%)	DE 150mg bid N (%)
Number of patients	1861 (100.0)	371 (100.0)	416 (100.0)	372 (100.0)	385 (100.0)	317 (100.0)
Patients with any AE	118 (6.3)	203 (54.7)	240 (57.7)	216 (58.1)	225 (58.4)	172 (54.3)
Patients with severe AEs	2 (0.1)	30 (8.1)	32 (7.7)	23 (6.2)	25 (6.5)	14 (4.4)
Patients with investigator defined drug-related AEs	0 (0.0)	18 (4.9)	34 (8.2)	42 (11.3)	42 (10.9)	40 (12.6)
Patients with AEs leading to discontinuation of trial drug	2 (0.1)	31 (8.4)	41 (9.9)	31 (8.3)	43 (11.2)	31 (9.8)
Patients with other significant AEs (according to ICH E3)	0 (0.0)	24 (6.5)	31 (7.5)	26 (7.0)	38 (9.9)	29 (9.1)
Patients with serious AEs	6 (0.3)	32 (8.6)	38 (9.1)	28 (7.5)	36 (9.4)	18 (5.7)
Fatal	0 (0.0)	2 (0.5)	4 (1.0)	2 (0.5)	0 (0.0)	2 (0.6)
Imm life-threatening	0 (0.0)	3 (0.8)	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.3)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	2 (0.1)	27 (7.3)	31 (7.5)	22 (5.9)	34 (8.8)	15 (4.7)
Prol.hospitalisation	3 (0.2)	3 (0.8)	2 (0.5)	3 (0.8)	2 (0.5)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.1)	1 (0.3)	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 12.0