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.

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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..

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Name of active ingredient: Dabigatran etexilate mesilate		**Page:** 1 of 11	
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Title of trial:	Twice-daily oral direct thrombin inhibitor dabigatran etexilate in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism **RE-SONATE**
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study conducted in 147 centres in 21 countries worldwide (in Asia, Central Europe, Western Europe, and North America, and others [Australia, New Zealand, and South Africa]).
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objective:	The primary efficacy objective was to evaluate whether dabigatran etexilate was superior to placebo in the long-term prevention of recurrent symptomatic venous thromboembolism (VTE) in patients with symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) who had completed 6 to 18 months of treatment with a vitamin K antagonist (VKA).
Methodology:	This was a Phase III, randomised, double-blind, placebo-controlled, event-driven, superiority study for efficacy evaluating both the efficacy and safety of oral dabigatran. When the required number of centrally confirmed recurrent symptomatic VTE events was reached (i.e. at least 36 events), as pre-specified, the trial close-out process was initiated, including termination of patient recruitment. Patients who had not completed the 3-month visit at trial close-out (on 30 September 2010) ended treatment at the 3-month visit. All other patients were to continue double-blind treatment for the intended (planned) treatment period of 6 months. All patients, including those randomised but not treated, were to be followed up for the intended treatment period. There was to be a follow-up visit 30 days later for all patients. With the introduction of Protocol Amendment 2 (dated 30 May 2008) the follow-up period was extended to 12 months for all patients. This report includes the data that were collected up to the end of the extended follow-up period of this trial.

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No. of patients:	
planned:	Entered: 1800 (900 randomised into each treatment group) This number could vary based on the actual incidence of symptomatic recurrent VTE in this event driven study (36 events were needed).
actual:	Enrolled: 1366, entered: 1353, treated: 1343 Dabigatran etexilate: entered: 685, treated: 681, analysed (for primary endpoint): 681, analysed (for safety): 684, analysed for extended follow-up: 672 (efficacy); 675 (safety) Placebo: entered: 668, treated: 662, analysed (for primary endpoint): 662, analysed (for safety): 659, analysed for extended follow-up: 651 (efficacy); 648 (safety)
Diagnosis and main criteria for inclusion:	Patients with confirmed symptomatic PE or proximal DVT of the legs who had been treated for 6 to 18 months with therapeutic dosages (target INR 2.0 - 3.0) of an oral VKA or RE-COVER study medication (study 1160.53) up to screening for the RE-SONATE study.
Test product:	Dabigatran etexilate capsules
dose:	150 mg twice daily (b.i.d.)
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Placebo capsules
dose:	Not applicable; administered twice daily
mode of admin.:	Oral
batch no.:	Refer to Appendix 16.1.6
Duration of treatment:	The intended (planned) treatment period was 6 months. After trial close-out started, the intended treatment period was approximately 3 months for patients who had not already completed their 3-month visit and 6 months for those who had already completed this visit.

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Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was symptomatic recurrent VTE, defined as the composite of symptomatic DVT, non-fatal and fatal PE during the intended treatment period. Deaths that were unexplained were considered as fatal PEs for the evaluation of the primary endpoint.

Secondary endpoints were the composite of recurrent symptomatic VTE (symptomatic DVT, symptomatic non-fatal PE, and fatal PE, excluding unexplained deaths) and the individual components of the primary efficacy endpoint.

All VTE events and deaths were adjudicated by an independent central adjudication committee.

Safety:

Safety endpoints included:

- adjudicated bleeding events (major bleeding events [MBEs], clinically relevant bleeding (MBEs and clinically relevant non-major bleeding events [CRBEs]), and all bleeding events (MBEs, CRBEs, and trivial bleeding events)
- adjudicated cardiovascular events (acute coronary syndrome), ischaemic stroke, non-central nervous system systemic embolism, transient ischaemic attacks [TIAs], and vascular [cardiac] death)
- adverse events (AEs), coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1; during the extended follow-up period only serious AEs (SAEs) were reported
- deaths
- liver function tests (LFTs) and other laboratory parameters

Statistical methods:

The primary efficacy endpoint was analysed in terms of the time to first occurrence using a Cox proportional hazards model including the main effect of treatment. The dabigatran etexilate-to-placebo hazard ratio (HR) and its corresponding 2-sided 95% confidence intervals (CI) were calculated. Superiority of the dabigatran etexilate group over placebo was to be concluded if the upper 95% confidence limit of the HR was less than 1. Kaplan-Meier plots stratified by treatment were produced for efficacy endpoints that occurred during the intended treatment period. Patients who did not experience an event were censored. The log-rank test was performed as a sensitivity analysis. The

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Statistical methods (continued):

composite endpoint of recurrent symptomatic VTE without unexplained death was analysed as described for the primary efficacy analysis. The frequencies of the individual components contributing to the primary efficacy endpoint were summarised by treatment group, 95% CIs were calculated using the Clopper-Pearson method, and Fisher's exact test was used to compare the 2 treatment groups.

The cumulative incidence of recurrent symptomatic VTE events (with and without unexplained deaths) from randomisation up to the end of the 12-month extended follow-up period, after the intended treatment period, was determined. Kaplan-Meier plots stratified by treatment were produced, and log rank p-values and HRs were determined. Also, risk differences for recurrent symptomatic VTE events were estimated at 180, 220, 365, and 540 days after randomisation. Kaplan-Meier curves, log rank p-value, and HR were also determined for recurrent symptomatic VTEs including unexplained death and including use of non-study anticoagulant medication during follow-up as an event.

Assuming a 70% risk reduction in the dabigatran etexilate group compared to the placebo group, a total of 36 events would give a power of 95% to demonstrate that dabigatran etexilate was superior to placebo (two-sided type I error = 0.05). Assuming a 3% frequency for the placebo group, approximately 900 patients per group were needed.

Safety endpoints were summarised using descriptive statistics. Bleeding events were analysed as described for the primary analysis of efficacy. If there were too few events, 95% CIs were calculated using the Clopper-Pearson method and Fisher's exact test was used to compare the 2 treatment groups. The time to first elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x the upper limit of normal (ULN) or total bilirubin >2 x ULN and the cumulative incidences were determined using the Kaplan-Meier method and compared using the log rank test.

SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 1343 randomised and treated patients, 1248 had an intended treatment period of 6 months (622 dabigatran etexilate; 626 placebo); the remainder (95 patients) had an intended treatment period of 3 months (59 dabigatran etexilate patients; 36 placebo patients).

In total, 170 patients (12.7%) discontinued treatment prematurely (dabigatran etexilate: 10.4%; placebo: 15.0%). Discontinuation of study medication due to

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Efficacy results (continued):

occurrence of an AE was less frequent on dabigatran etexilate (7.2%) than on placebo (12.4%), predominantly due to fewer dabigatran etexilate (0.6%) than placebo patients (7.4%) discontinuing due to worsening of the disease under study (symptomatic DVT/PE). In total, 1330 patients (treated and untreated) continued into the extended follow-up period, comprising 1323 (98.5%) of the 1343 randomised and treated patients (dabigatran etexilate: 98.7%; placebo: 98.3%) and 7 of the 10 patients who were randomised but not treated. In total, 1283 (95.5%) treated patients (dabigatran etexilate: 95.7%; placebo: 95.3%) and 4 patients who were not treated completed this follow-up period.

The treatment groups were generally balanced with respect to demographic and baseline characteristics. The patient population was predominantly White (89.0%), and just over half were male (55.5%). The majority were from Western or Central Europe (80.2%). The mean age was 55.8 years and there was a high percentage of young patients (66.3% below 65 years and 35.1% below 50 years). The most frequent baseline condition of particular interest was hypertension, reported in 38.8% of patients, followed by diabetes mellitus (8.0%) and heart failure (4.6%). Hypertension was more common in dabigatran etexilate patients (41.3%) than in placebo patients (36.3%). A baseline history of prior myocardial infarction was more common in dabigatran etexilate patients (2.1%) than in placebo patients (0.8%). The frequencies of other baseline conditions were balanced between treatment groups.

Based on local assessments, the qualifying event was symptomatic DVT alone for 64.6% of patients, symptomatic PE alone for 27.8% of patient, and both symptomatic DVT and PE for 7.7% of patients. For 91.7% of patients, the duration of previous VKA treatment was 6 to 18 months. The characteristics of the qualifying events were balanced between the treatment groups.

Concomitant medications of particular interest were used by 19.4% of patients, including NSAIDs (11.9%) and ASA (7.7%). The concomitant use of P-gp inhibitors or inducers was uncommon (measuring 1.7% and 0.8%, respectively). Restricted medications (including restricted anticoagulants) were used concomitantly with study drug by 3.6% of patients. Heparin and heparinoids were the most frequently reported restricted medication (incidence: 2.5%). During the extended follow-up period, the use of anticoagulant medications considered to be preventative of a symptomatic recurrent VTE was less frequent for dabigatran etexilate patients (20.3%) than for placebo patients (25.5%). Both VKAs and low molecular weight heparins were less commonly reported for

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Efficacy results (continued):

dabigatran etexilate patients (14.1% and 12.2%, respectively) than for placebo patients (20.1% and 17.1%, respectively).

Compliance rates were high and identical in both treatment groups (96.5%) while blinded study drug was administered.

Primary endpoint

The incidences of the primary endpoint (symptomatic recurrent VTE including unexplained deaths) was 0.4% in the dabigatran etexilate group and 5.6% in the placebo group. The HR for dabigatran etexilate versus placebo was 0.08, 95% CI 0.02, 0.25. Superiority was demonstrated for dabigatran etexilate versus placebo since the upper 95% confidence limit of the HR was well below 1 ($p<0.0001$). The upper limit of the confidence interval was 0.25, indicating that there was 95% confidence that dabigatran etexilate reduced the risk of recurrent symptomatic VTE events by at least 75% compared to placebo. All secondary and sensitivity analyses of the primary endpoint confirmed the robustness of the primary analysis, with confidence intervals the same or very similar to the primary analysis. Kaplan-Meier curves for dabigatran etexilate and placebo for the primary endpoint diverged soon after the start of treatment and continued to diverge throughout the treatment period.

Secondary endpoints

All analyses of secondary endpoints supported the primary analysis of efficacy. For the endpoint recurrent symptomatic VTE excluding unexplained deaths, the HR was 0.08, 95% CI 0.03, 0.27. All individual components of the composite primary endpoint were less frequent on dabigatran etexilate than on placebo and all differences between treatment groups were significant.

With the onset of the extended follow-up period, and the cessation of anticoagulation in those subjects allocated to dabigatran etexilate, there was an increase in the rate of recurrent VTE events. Nevertheless, the cumulative incidence of symptomatic recurrent VTE events was consistently lower for the dabigatran etexilate group than for the placebo group: at the end of the extended follow-up period, the cumulative incidence of recurrent VTE was 6.9% for the dabigatran etexilate group versus 10.7% for the placebo group. The HR for time to first occurrence of a symptomatic recurrent VTE for dabigatran etexilate versus placebo for the entire study period was 0.61, 95% CI 0.42, 0.88. When including unexplained deaths, the difference was also significant, with an HR for the entire study period of 0.63, 95% CI 0.43, 0.90 ($p=0.0127$). Risk differences

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Efficacy results (continued):	for the cumulative occurrences of recurrent symptomatic VTEs including unexplained deaths demonstrated that dabigatran etexilate was superior to placebo up to 180, 220, 365, and 540 days after randomisation. The HR for time to first occurrence of a symptomatic recurrent VTE including unexplained deaths or additional anticoagulant therapy for dabigatran etexilate versus placebo for the entire study period was 0.76, 95% CI 0.61, 0.95 (p=0.0148).
Safety results:	The mean duration of exposure was similar in both treatment groups (dabigatran etexilate: 165.3 days; placebo: 162.0 days). In both groups the majority of patients were treated with study medication for at least 170 days (82.2% of dabigatran etexilate patients and 79.5% of placebo patients). The total exposure to active treatment was 309.6 patient years for dabigatran etexilate and 292.3 patient years for placebo. Patients were not treated with study medication during the follow-up period. The mean duration of the post-treatment period was 352.0 days (SD 63.8) and was similar in both treatment groups (dabigatran etexilate: 350.8 days, SD 59.7; placebo: 353.3 days, SD 67.9). <u>Bleeding events</u> The incidence of MBEs on treatment was very low in this trial. MBEs were reported for only 2 patients (0.3%) on dabigatran etexilate and none on placebo. The 95% CI (Clopper-Pearson method) for dabigatran etexilate were 0.04 to 1.05 compared with 0.00 to 0.56 for placebo (p=0.4998, Fisher's exact test). The incidences of CRBEs and of any bleeding event were significantly higher for patients on dabigatran etexilate (5.3% and 10.5%, respectively) than for patients on placebo (1.8% and 5.9%, respectively). The HR for CRBEs was 2.92 (95% CI: 1.52, 5.60; p=0.0013), indicating a significantly higher risk of an event on dabigatran etexilate compared with placebo. For any bleeding event HR was 1.82 (95% CI: 1.23, 2.68; p=0.0027). Kaplan-Meier curves for the time to first CRBE and for time to first bleeding event of any kind for dabigatran etexilate and placebo diverged immediately after the start of treatment. The incidence of bleeding events leading to discontinuation of study medication was 1.6% for dabigatran etexilate patients and 0.6% for placebo patients. <u>Cardiovascular events</u> The overall incidence of cardiovascular events during the treatment period was low and comparable for the dabigatran etexilate (0.4%) and placebo (0.3%) treatment groups. Note: there was 1 myocardial infarction event in each

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Safety results (continued):

treatment group.

Adverse events

The overall incidence of AEs was comparable in the dabigatran etexilate (50.6%) and placebo treatment groups (49.2%), as were the frequencies of AEs within most MedDRA system organ classes (SOCs) and for most preferred terms. The most frequently reported AEs for patients on dabigatran etexilate by SOC were gastrointestinal disorders (16.5%), with a lower incidence for placebo patients (8.8%). Gastrointestinal AEs with the most marked difference in incidence between groups (>1%) were dyspepsia and rectal haemorrhage, which were more frequent for patients on dabigatran etexilate than for patients on placebo (dyspepsia: 4.1% for dabigatran etexilate vs. 1.2% for placebo; rectal haemorrhage: 2.2% vs. 0.3%). Vascular disorders were less frequently reported for patients on dabigatran etexilate (6.4%) than for patients on placebo (11.5%). The difference in incidence was predominantly due to the higher incidence of DVT for patients on placebo (5.2%) compared with patients on dabigatran etexilate (0.4%).

The overall incidence of AEs that were considered by investigators to be drug-related was higher for patients on dabigatran etexilate (11.5%) than for the patients on placebo (6.5%). Drug-related gastrointestinal disorders were more frequent in patients on dabigatran etexilate (5.8%) than in patients on placebo (3.5%). AEs (preferred terms) considered to be drug-related that were more frequently reported for patients in 1 treatment than in the other group (difference between treatment groups >0.5%) were dyspepsia (dabigatran etexilate: 1.5%, placebo: 0.5%), rectal haemorrhage (1.3%; 0.2%), and contusion (1.0%; 0.2%).

The incidence of AEs that led to discontinuation of study medication was lower for patients on dabigatran etexilate (7.3%) than for patients on placebo (12.3%) predominantly due to a lower incidence of DVT leading to discontinuation for patients on dabigatran etexilate vs. placebo (0.4% vs. 4.9%) and of PE leading to discontinuation (0.1% vs.2.9%).

Similarly, the incidence of SAEs was lower for patients on dabigatran etexilate (6.9%) than for patients on placebo (9.1%) and the difference was predominantly due to higher incidences in the placebo group of DVT and PE reported as SAEs. Three patients died presumably as a result of an SAE with an onset during the treatment period (dabigatran etexilate: 1 patient; placebo: 2 patients). The dabigatran etexilate patient was diagnosed with a lung adenocarcinoma during the washout period and died during the extended follow-up. In the placebo

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Safety results (continued):

group, 1 patient died on the last day of treatment due to hypertensive heart disease and 1 patient was diagnosed with chronic lymphocytic leukaemia during the treatment period and died during the extended follow-up. None of the fatal SAEs were considered related to study medication. Two patients on dabigatran etexilate (0.3%) had an immediately life-threatening SAE (1 diabetic hyperglycaemic coma, 1 acute myocardial infarction; both considered unrelated to study medication). One placebo patient (0.2%) had an SAE that resulted in persistent or significant disability or incapacity (lung neoplasm diagnosed on 3 days after start of treatment; unrelated to study medication). SAEs that were considered to be drug-related were reported for 2 patients on dabigatran etexilate (in total, 4 events) and 4 patients on placebo (in total, 5 events).

During the 12-month post treatment period nonserious and serious AEs were reported during the 30-day follow-up. Thereafter, only SAEs were reported. The overall incidence of post-treatment SAEs was similar in both treatment groups during the 30-day follow-up period (dabigatran etexilate: 3.4%; placebo: 2.1%) and during the extended follow-up period (dabigatran etexilate: 9.6%; placebo: 10.1%). Almost all SAEs reported during the 30-day follow-up, were reported for only 1 patient in either treatment group. The most common post-treatment SAEs were DVT and PE. During the 30-day follow-up, PE was reported for 0.4% of patients on dabigatran etexilate vs. 0.5% of patients on placebo and DVT for 0.4% vs. 0.2%. During the extended follow-up period, the incidences for PE were 3.3% vs. 2.2% and for DVT they were 1.9% vs. 1.7%. During the extended follow-up, all other SAEs were reported by ≤3 patients in either treatment group.

Twelve patients died presumably as a result of SAEs with an onset in the post-treatment period (dabigatran etexilate: 5 patients; placebo: 7 patients). In the dabigatran etexilate group, 1 patient each was reported with a fatal case of lung carcinoma (unspecified cell type), cerebrovascular accident, PE, and 1 patient was reported with fatal cases of DVT and a PE. For 1 patient, the reported SAE was 'death', which followed a severe intestinal infarction. In the placebo group, 1 patient each was reported with a fatal case of PE, myocardial infarction, and mesenteric vessel thrombosis, and 4 patients died due to neoplasms (1 patient with a rectal neoplasm and 3 patients with a malignant lung neoplasm).

Immediately life-threatening SAEs were reported for 1 patient on placebo during the 30-day follow-up period (acute myocardial infarction) and for 3 patients on dabigatran etexilate during the extended follow-up period (intracranial

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Safety results (continued):	aneurysm, PE, and ventricular fibrillation). SAEs that resulted in persistent or significant disability or incapacity were reported for 2 dabigatran etexilate patients, 1 during the 30-day follow-up (oesophageal neoplasm) and 1 during the extended follow-up period (cerebrovascular accident). Clinical laboratory data and vital signs For all laboratory values including LFTs, there were no clinically meaningful differences between the two treatment groups for mean and outlier values. Kaplan-Meier estimates of ALT or AST >3 x ULN or bilirubin >2 x ULN showed no significant differences between treatment groups. No potential Hy's Law cases were identified. There were no noteworthy changes in vital signs during this trial in either treatment group.
Conclusions:	Dabigatran etexilate was superior to placebo for the prevention of recurrent symptomatic VTE events including unexplained deaths, with a risk reduction of 92% during the treatment period. All secondary and sensitivity analyses of the primary endpoint and all analyses of secondary endpoints, during the treatment period, showed superiority of dabigatran etexilate over placebo and confirmed the robustness of the primary efficacy analysis. Patients in this study received 6-18 months of prior non-study drug anticoagulant therapy for a VTE and then were randomised to 6 months of dabigatran etexilate or placebo. When evaluating cumulative VTE rates over the 6 months blinded study treatment period plus 12 months of additional observation, dabigatran etexilate treated patients had significantly fewer recurrent VTE events than placebo treated patients. This suggests that a short duration of dabigatran etexilate treatment has persistent benefit in preventing recurrent symptomatic VTEs. Additionally, patients had a recurrent VTE rate of about 5-6% over the 12 months following completion of their study treatment, a rate that was about half of the annualised placebo VTE rate during the study treatment period of RE-SONATE. However, a 6% annual VTE occurrence rate is such that continuing anticoagulant treatment is justified, especially if there would be a modest rate of bleeding associated with the continuing use of an oral anticoagulant. The safety profile of dabigatran etexilate was consistent with the known safety profile of dabigatran etexilate. There were few MBEs in either treatment group during the treatment and follow up periods. Dabigatran etexilate resulted in 2 to 3 times as many CRBEs and bleeding events compared to placebo, during the

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treatment period. There were fewer reported SAEs and fewer discontinuations due to AEs or SAEs on dabigatran etexilate compared to placebo, during the treatment period. During the post-treatment period, the overall incidences of reported SAEs and the incidences of DVT and PE were similar in patients previously treated with dabigatran etexilate and those previously treated with placebo.

Six months of dabigatran etexilate treatment was extremely effective and well tolerated in patients at risk of recurrent symptomatic VTE at equipoise with respect to the need for continued anticoagulation treatment. Given the persistent VTE recurrence rate in patients believed at equipoise for the need for further anticoagulant therapy and the low rate of major bleeding observed with the tested dabigatran etexilate regimen in this study, prolonged treatment with dabigatran etexilate for patients at equipoise for the use of warfarin (VKAs) could potentially benefit (i.e. with reduced VTE rates) from sustained therapy with dabigatran etexilate with a limited risk of major bleeding events.

Trial Synopsis - Appendix

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

Results for	presented in
Patient disposition	Table 15.1.1: 1
Frequency of patients with any symptomatic DVT (secondary endpoint)	Table 15.2.2.2: 1
Frequency of patients with any symptomatic fatal and non-fatal PE (secondary endpoint)	Table 15.2.2.3: 1

Table 15.1.1: 1 Summary of patient disposition at the end of treatment
As Randomised Assignment

	Dabigatran 150mg bid N (%)		Matching Placebo N (%)		Total N (%)	
Entered (randomised)	685		668		1353	
Not treated	4		6		10	
Treated	681	(100.0)	662	(100.0)	1343	(100.0)
Not prematurely discontinued from trial medication	610	(89.6)	563	(85.0)	1173	(87.3)
Prematurely discontinued from trial medication	71	(10.4)	99	(15.0)	170	(12.7)
AE	50	(7.3)	81	(12.2)	131	(9.8)
AE: Worsening of disease/condition under study (i.e. DVT or PE)	4	(0.6)	49	(7.4)	53	(3.9)
AE: Worsening of other pre-existing disease/condition	4	(0.6)	4	(0.6)	8	(0.6)
AE: Other adverse event	42	(6.2)	28	(4.2)	70	(5.2)
Bleeding event	11	(1.6)	4	(0.6)	15	(1.1)
Other event (no bleeding)	31	(4.6)	24	(3.6)	55	(4.1)
Non compliant with protocol	9	(1.3)	5	(0.8)	14	(1.0)
Patient refused to continue study medication	12	(1.8)	13	(2.0)	25	(1.9)

The planned treatment duration is 6 months. Once 36 patients were confirmed as having a centrally confirmed recurrent VTE event during intended treatment period, all patients completed their participation in the study at their next 3-month visit (month 3 or month 6) so that the last patients randomised were treated for approximately 3 months.
Patients discontinuing due to a bleeding and non-bleeding AE are categorised under discontinuation due to bleeding.

Source data: Appendix 16.2.1, Listing 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7 scs\t_s1x.sas 16MAR2012

Table 15.2.2.2: 1 Frequency of patients with any centrally confirmed symptomatic DVT during the intended treatment period
FAS - As Randomised Assignment

	Dabigatran 150mg bid	Matching Placebo
Full analysis set N (%)	681 (100.0)	662 (100.0)
Number of patients with any@ recurrent DVT confirmed N (%)	2 (0.3)	23 (3.5)
95% CI#	0.04, 1.06	2.21, 5.17
P-value*	<.0001	
Number of events N	2	23

Clopper Pearson
* Fisher Exact Test
@ This table includes all symptomatic recurrent events that occurred in the intended treatment period, not just the first event.
Source data: Appendix 16.2.6, Listing 1.2, 1.3, 1.4 sce\t_xbe.sas 16MAR2012

Table 15.2.2.3: 1 Frequency of patients with any centrally confirmed symptomatic PE during the intended treatment period
FAS - As Randomised Assignment

	Dabigatran 150mg bid	Matching Placebo
Full analysis set N (%)	681 (100.0)	662 (100.0)
Number of patients with any@ recurrent PE confirmed N (%)	1 (0.1)	14 (2.1)
95% CI#	0.00, 0.82	1.16, 3.52
P-value*	0.0004	
Number of events N	1	14

Clopper Pearson
* Fisher Exact Test
This table includes both fatal and non-fatal PE.
@ This table includes all symptomatic recurrent events that occurred in the intended treatment period, not just the first event.
Source data: Appendix 16.2.6, Listing 1.5, 1.6, 1.7 sce\t_xbe.sas 16MAR2012