EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2014
EMA/CHMP/230414/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pradaxa

International non-proprietary name: dabigatran etexilate

Procedure No. EMEA/H/C/000829/II/0048/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II Group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 3 June 2013 an application for a group of variations.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Pradaxa	Dabigatran etexilate	See Annex A

The following variations were requested in the group:

Variations requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
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The MAH proposed the update of section 4.1 of the SmPC for 150mg strength in order to add the following two new related indications: (1) treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death (a VTEt), (2) prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death (s VTEp). Several sections of the SmPC for 150mg strength were proposed to be modified to include the data relevant for two new indications. The Package Leaflet was proposed to be updated accordingly.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Rapporteur: Jens Heisterberg

1.2. Steps taken for the assessment

Submission date:	3 June 2013
Start of procedure:	21 June 2013
PRAC Rapporteur's preliminary assessment report circulated on:	12 August 2013
Rapporteur's preliminary assessment report circulated on:	14 August 2013
PRAC RMP Advice and assessment overview:	5 September 2013
Rapporteur's updated assessment report circulated on:	13 September 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 September 2013
MAH's responses submitted to the CHMP on:	20 November 2013

PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	2 December 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 December 2013
PRAC Rapporteur's final assessment report on the MAH's responses circulated on:	6 January 2014
PRAC RMP Advice and assessment overview:	9 January 2014
Rapporteur's final assessment report on the MAH's responses circulated on:	17 January 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	23 January 2014
MAH's responses submitted to the CHMP on:	25 March 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	8 April 2014
Rapporteur's final assessment report on the MAH's responses circulated on:	
An Oral explanation took place on:	22 April 2014
CHMP opinion:	25 April 2014

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0228/2012 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

2. Scientific discussion

2.1. Introduction

In 2008, dabigatran etexilate(DE) was approved in the EU for the primary prevention of VTE after total elective hip- or knee-replacement surgery. In 2010, DE was approved in the US and Canada to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF) and subsequently its US package insert has been changed to reflect that DE (150 mg twice daily) is superior in reducing ischemic and hemorrhagic strokes relative to warfarin (W). It was approved for SPAF in the EU, Japan, Australia, and New Zealand in 2011.

Within current grouped variation the results of 4 pivotal studies (1160.53 (RE-COVER), 1160.46 (RE-COVER II), 1160.47 (RE-MEDY), and 1160.63 (RE-SONATE)) were submitted that according to the MAH established the effectiveness and safety of dabigatran etexilate (DE) for the:

1. Treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death ([aVTEt], RE-COVER I and II)

and

2. Prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death ([sVTEp], RE-SONATE and RE-MEDY).

The four pivotal studies in the development program were all randomized, double-blind Phase III studies, three of which were active-controlled (one warfarin- and one placebo- (P) controlled). The replicate studies 1160.53 (1,274 DE and 1,265 W patients treated) and 1160.46 (1,279 DE and 1,289 W patients treated) evaluated the efficacy and safety of DE for the acute treatment of venous thromboembolism (VTE) (DVT with or without PE). The other two studies, 1160.47 (1,430 DE and 1,426 W patients treated) and 1160.63 (681 DE and 662 P patients treated), evaluated the efficacy and safety of DE for the reduction of risk of recurrent VTE. The DE dose regimen was 150 mg b.i.d. for patients in these four studies.

The plan for the aVTEt/sVTEp development program took into account the scientific advice feedback from the French and Swedish health authorities as well as scientific advice given during multiple interactions with the FDA.

2.2. Clinical pharmacology aspects

2.2.1. Introduction

No clinical pharmacology studies or dose-response studies were performed to specifically support the sought indications. The efficacy of DE was demonstrated in four randomized, double-blind Phase III studies; three were active-controlled and one was placebo; two support the aVTEt indication, and two support the sVTEp indication. The figure presented below shows the overall design of the four studies and the patient flow from the acute studies to the prevention studies.

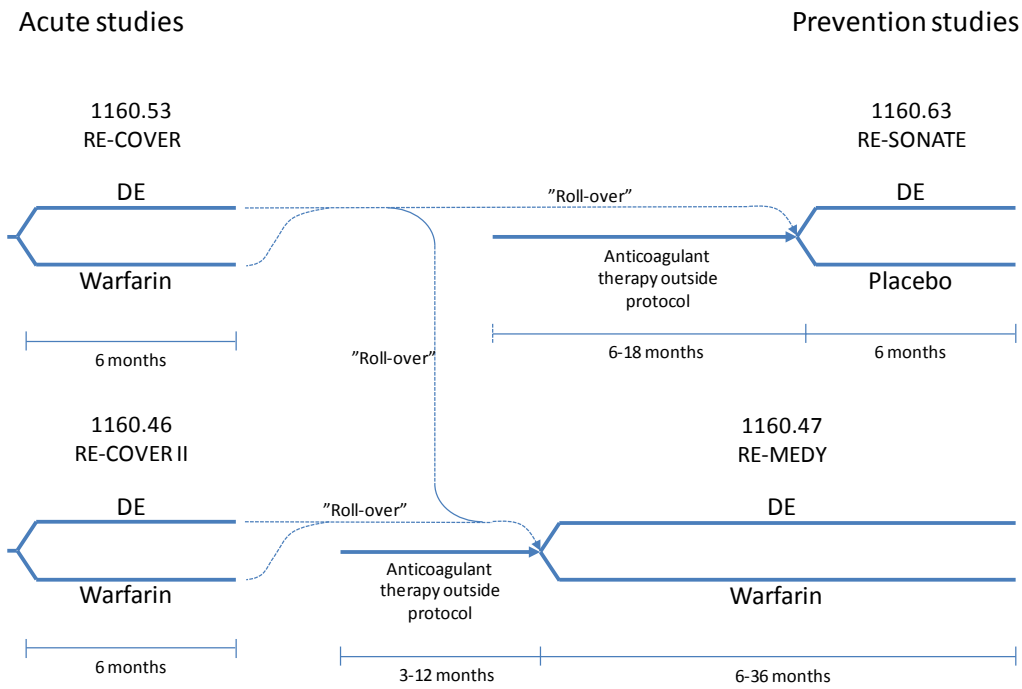
GCP

All clinical trial protocols were approved by institutional review boards or independent ethics committees. The trials followed the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP), conformed to the Declaration of Helsinki and were conducted in accordance with Boehringer Ingelheim (BI) standard operating procedures. Written informed consent was obtained from all patients. The CHMP has during the review of the dossier not identified any issues regarding GCP non-compliance requiring a triggered GCP inspection.

Overview of clinical studies

The efficacy and safety of DE was documented in four randomized, double-blind Phase III studies; three active controlled (warfarin) and one placebo-controlled. Two of the studies support the aVTEt indication, and two of the studies supported the sVTEp indication.

The four studies are depicted below.



2.2.2. Pharmacokinetics

Absorption

There are no new data addressing absorption. No new formulations are introduced.

Distribution

There are no new data addressing distribution.

Elimination

There are no new data addressing elimination.

Dose proportionality and time dependencies

There are no new data addressing dose proportionality. Only one dose was investigated in the clinical trials (150 mg b.i.d.). In the PK/PD analysis of the RE-COVER study, the median trough plasma concentrations of total dabigatran for patients in the dabigatran group were consistent between Visit 4 (58.7 ng/mL) and Visit 9 (60.2 ng/mL). There are no other new data addressing time dependency.

Target population and special populations

Since the PK/PD characteristics of DE in patients with non-valvular AF have been described in the previous submissions, only data from patient studies in the VTE indications sought in the current submission are presented. The review is further limited to one of the four pivotal Phase III studies, 1160.53 (RE-COVER), since only in RE-COVER was PK/PD evaluated.

The RE-COVER study was randomized, double blind (double dummy technique including use of sham INR), parallel-group, active-controlled study comparing two treatment groups (DE vs. warfarin) for 6 months in 2500 patients, evenly randomized to the treatments warfarin (target INR 2.0 - 3.0) or DE 150

mg b.i.d. Patients received 150 mg DE b.i.d. after a minimum of 5 days previous therapy with a parenteral anticoagulant. Trough samples for PK and PD analysis were collected on Day 30 (Visit 4) and Day 180 (Visit 9), the last dosing. In addition to the scheduled sampling, unscheduled PK sampling was performed as soon as a symptomatic DVT, PE, MBE or acute renal failure was suspected. The primary goal of the investigations on pharmacokinetics and pharmacodynamics is the assessment of the PK/PD relationship of dabigatran in patients receiving DE for the treatment of acute symptomatic VTE of the leg or PE.

The number of treated patients overall was 2539. Of those 1274 received DE, and from 850 patients at Visit 4 and 746 at Visit 9 PK/PD samples were taken. The median trough plasma concentrations of total dabigatran for patients in the DE group were consistent between Visit 4 (58.7 ng/mL) and Visit 9 (60.2 ng/mL). The trough concentration of total dabigatran was associated with the creatinine clearance (CLCR), namely those with lower CLCR having higher dabigatran trough concentrations. At Visit 4, the gMean trough concentrations were 170 ng/mL in patients with moderate renal impairment (CLCR of 30 to <50 mL/min), 85.5 ng/mL in patients with mild impairment (CLCR of 50 to < 80 mL/min) and 50.5 ng/mL in patients with normal renal function (CLCR of ≥80 mL/min).

The trough concentration also increased with age, without further consideration of renal function; the lowest age group of 18 to < 40 years had the lowest gMean trough concentration (43.3 ng/mL) while patients of ≥75 years had the highest gMean trough concentration (121 ng/mL). Differences in the trough concentration of total dabigatran were also recorded for sex and body weight, though of clinically unimportant magnitude compared with renal function. The effect of covariates is summarized in Table 2.1: 1, below.

Table 2.1: 1 Trough plasma concentrations of total dabigatran at Visit 4 by demographic characteristics

		Cpre,ss			
	Patients with values (N)	Median [ng/mL]	gMean [ng/mL]	gCV [%]	10^{th} -90^{th} percentile [ng/mL]
CL_{CR} [mL/min]					
< 30	4	177	191	32.7	146-298
30-< 50	32	188	170	83.6	93.1-363
50-<80	181	89.0	85.8	65.2	39.1-165
≥ 80	627	50.7	50.5	73.0	23.9-108
Age [years]					
18-<40	167	45.8	43.3	60.5	22.5-79.6
40-<50	150	47.0	48.2	65.7	24.8-100
50-<65	263	57.6	58.8	76.8	27.7-131
65-<75	186	75.2	70.6	83.7	29.5-150
≥ 75	84	132	121	74.6	52.5-297
BMI [kg/m^2]					
<25	200	53.8	55.9	77.1	25.4-138
25-<30	348	61.3	61.7	85.0	27.1-145
30-<35	189	58.7	59.2	80.7	22.7-150
≥35	112	58.1	61.2	78.4	29.2-146
Race					
White	822	58.6	59.6	82.1	26.1-146
Asian	12	67.0	68.6	68.0	39.1-118
Black	16	67.5	62.5	63.4	28.6-112
Sex					
Male	506	54.7	53.8	79.8	23.1-130
Female	344	66.6	69.6	80.2	30.1-176

In summary, increased trough total dabigatran plasma concentrations were found in patients ≥75 years of age and patients with renal impairment CLCR <50 mL/min.

Comparing CLCR subgroups of the RE-COVER patient population with AF patients from RE-LY, receiving DE at a dose of 150 mg b.i.d., it became apparent that the magnitude of effect by renal impairment was highly comparable between both patient populations (see Table 1.3.1: 1 below).

Table 1.3.1: 1 Total dabigatran trough concentration by renal function (CL_{CR}) in patients with acute symptomatic venous thrombosis (RE-COVER) or with atrial fibrillation (RE-LY) treated with DE 150 mg b.i.d

	RE-COVER		RE-LY	
CL_{CR} mL/min	N	gMean (gCV%)	N	gMean (gCV%)
30 - < 50	32	170 (83.6)	761	144 (80.6)
50 - < 80	181	85.8 (65.2)	1969	95.2 (73.0)
≥ 80	627	50.5 (73.0)	1347	64.8 (71.6)

Pharmacokinetic interaction studies

No dedicated drug-drug interaction study was conducted for the current application. The following results on drug-drug interactions are all from the PK/PD analysis of the RE-COVER study. The influence of proton pump inhibitor (PPI) co-medication on the resulting total dabigatran trough concentrations is outlined in Table 2.1: 2, below. In contrast to the expected effect of a reduced bioavailability, in RE-COVER the dabigatran trough levels were increased in patients on PPI co-medication. However, the effect on median trough levels never exceeded 25% and the 80% confidence interval was almost identical between both subgroups.

B	RE-COVER all P-gp inhibitors					
	Visit 4			Visit 9		
	without P-gp Inh.	with P-gp Inh.	gMean Ratio [(+)- comed ÷ (-)- comed]	without P-gp Inh.	with P-gp Inh.	gMean Ratio [(+)- comed ÷ (-)- comed]
N	823	27		723	23	
gMean (gCV%) [ng/mL]	59.3 (80.0)	76.5 (124)	1.29	58.4 (89.0)	105 (86.5)	1.80
mean (SD) [ng/mL]	75.6 (59.6)	110 (91.8)		77.0 (68.4)	139 (120)	
10th - 90th percentile [ng/mL]	26.0-145	37.7-283		23.8-149	43.9-261	

P-gp inhibitor co-medication usage was relatively uncommon in this patient population. Only 27 treated patients (3.2%) had a P-gp inhibitor comedication at PK Visit 4 with verapamil being the most common P-gp inhibitor used (N = 14 subjects on verapamil at Visit 4 and 11 subjects at Visit 9, respectively). The use of verapamil was associated with increased gMean dabigatran trough concentrations, as observed at Visit 4 and 9 (no verapamil use: 59.4 and 59.1 ng/mL, verapamil use: 82.4 and 97.3 ng/mL). Since only

patients on verapamil represented a sufficiently large sub-group in RE-COVER only effects by verapamil and all P-gp inhibitor co-medication are discussed. Consistent with previous data in RE-LY or from dedicated Phase I studies, verapamil or P-gp inhibitors increased dabigatran trough concentrations. The effects in RE-COVER are displayed in Table 2.1: 3. The verapamil effect also drives the date for all P-gp inhibitors as amiodarone does not (Visit 4, N = 3) or only marginally increase dabigatran troughs by at maximum 26.6% (Visit 9, N = 2). The magnitude of the effect by verapamil co-medication in RE-COVER was larger compared with RE-LY.

It had been shown previously that the magnitude of interaction effect is dependent on relative dosing time (DE in relation to verapamil), the time being on verapamil (first dose different to multiple dosing of verapamil) and the formulation used (immediate- vs. extended release verapamil). With the available data it cannot be clarified whether a higher percentage of patients in RE-COVER had initiated verapamil, more of the verapamil immediate release formulation was used or whether more patients had taken verapamil concomitant or before DE.

The inter-subject variability in the group of patients receiving verapamil or any P-gp inhibitor co-medication is clearly increased (see Table 2.1: 3, below).

Table 2.1: 3 Influence of verapamil (A) or all P-gp inhibitor co-medicat total dabigatran steady-state trough concentrations in patie experienced a venous thrombotic event (VTE)

A	RE-COVER Verapamil					
	Visit 4			Visit 9		
	without Vera	with Vera	gMean Ratio [(+)- comed ÷ (-)- comed]	without Vera	with Vera	gMean Ratio [(+)- comed ÷ (-)- comed]
N	836	14		735	11	
gMean (gCV%) [ng/mL]	59.4 (80.1)	82.4 (170)	1.39	59.1 (89.3)	97.3 (107)	1.65
mean (SD) [ng/mL]	75.9 (60.2)	124 (93.9)		78.0 (69.0)	143 (158)	
10th - 90th percentile [ng/mL]	26.1-145	41.3-283		24.4-155	38.8-234	

B	RE-COVER all P-gp inhibitors					
	Visit 4			Visit 9		
	without P-gp Inh.	with P-gp Inh.	gMean Ratio [(+)- comed ÷ (-)- comed]	without P-gp Inh.	with P-gp Inh.	gMean Ratio [(+)- comed ÷ (-)- comed]
N	823	27		723	23	
gMean (gCV%) [ng/mL]	59.3 (80.0)	76.5 (124)	1.29	58.4 (89.0)	105 (86.5)	1.80
mean (SD) [ng/mL]	75.6 (59.6)	110 (91.8)		77.0 (68.4)	139 (120)	
10th - 90th percentile [ng/mL]	26.0-145	37.7-283		23.8-149	43.9-261	

2.2.3. Pharmacodynamics

Mechanism of action

Dabigatran is a synthetic, non-peptide, competitive, oral direct thrombin inhibitor (oral DTI), that specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. The mechanism of action of dabigatran involves the binding to exosite 1, the active site on thrombin. This binding subsequently prevents cleavage of fibrinogen to fibrin and hence blocks the final step of the coagulation cascade and thrombus development. It reversibly inhibits fibrin-bound thrombin, free circulating thrombin and thrombin-induced platelet aggregation. DE (DE) is the oral pro-drug of the active moiety dabigatran and does not possess any anticoagulant activity. The pro-drug DE is used in its salt form DE mesilate.

No new data on mechanism of action have been submitted with the current application.

Primary and secondary pharmacology

No new data on primary pharmacology have been submitted with the current application.

2.2.4. PK/PD Modelling

No PK/PD modelling was carried out as such. However, to further elucidate the exposure (i.e. total dabigatran trough plasma concentration) response relationship for the target indication, VTE, trough concentrations from Study 1160.53 (RECOVER), were related in a time to event analysis (over an observational period of 174 days) with the following two endpoints:

1. For safety, major bleeding events (MBE)

2. For efficacy, time to first recurrent symptomatic VTE and death related to VTE

The risk of a MBE was dependent on the trough concentration while no correlation could be observed between trough concentration and the prevention of recurrent VTE and VTE related death. The median trough concentration was consistently higher (Visit 4 and 9) in patients with major bleeding events (MBE) (79.9 and 100 ng/mL) than in patients without bleeding event (58.6 and 59.9 ng/mL).

2.2.5. Discussion on clinical pharmacology

The CHMP noted the extensive information about the pharmacokinetic performance of DE and dabigatran from other indications/development programmes. Pharmacokinetic (PK) samples were only obtained in one of the four pivotal studies supporting the sought indication: the RE-COVER study. The timing and frequency of the PK sampling, the selection of subgroups and the overall presentation of the PK data are acceptable.

The PK analysis of the RE-COVER study is largely in line with results from the RE-LY study. Trough dabigatran concentrations by the three categories of renal function are similar to the ones obtained for the 150 mg dose in the RE-LY study. The high dependence of dabigatran clearance on renal function, age and P-gp activity is confirmed. Also the effect of gender and body weight on dabigatran is in line with previous experience. The Applicant has provided a further analysis and discussion of the PK results of the RE-COVER study. There was a more than 2-fold increase in dabigatran exposure in patients aged 80 years or more compared to non-elderly patients, an about 3-fold increase in patients with moderate renal impairment (CrCL 30-50 mL/min) compared to patients without renal impairment, and an about 1.5-fold increase in patients taking verapamil compared to patients not taking verapamil. Based on these PK results and the clinical outcome data, the MAH agreed with reduced dose recommendations (daily dose of 220 mg taken as two 110mg capsules) for patients aged 80 years or above and for patients who receive concomitant verapamil.

Dabigatran is pharmacologically well-characterized with regard to the sought indications. Therefore, the submitted new PK/PD information is very sparse. This was considered acceptable by the CHMP. Unlike the RE-LY study, the RE-COVER study only showed a relationship between trough dabigatran concentrations and safety (major bleeding events). A relationship between dabigatran concentrations and efficacy (recurrent VTE, VTE related death) was not evident.

2.2.6. Conclusions on clinical pharmacology

There is extensive information about the clinical pharmacological properties of DE and dabigatran from other indications/development programmes. Additional information from the current programme is limited. PK samples were only obtained in one of the four pivotal studies supporting the sought indication (RE-COVER study). The PK analysis of the RE-COVER study is consistent with results from the RE-LY study. The high dependence of dabigatran clearance on renal function, age and P-gp activity is confirmed. The study showed a relationship between trough dabigatran concentrations major bleeding events, but a relationship between concentrations and efficacy endpoints (recurrent VTE, VTE related death) could not be shown. The dose recommendations in subgroups were challenged by the CHMP, and subsequently the Applicant accepted to align the dose recommendations for the aVTEt and sVTEp indications with those of the atrial fibrillation indication, i.e. a lower dose (110 mg BID) for patients aged 80 years and over and patients treated with verapamil, and this lower dose should also be considered for other subgroups, e.g. patients with moderate renal impairment. This was accepted by the CHMP.

2.3. Clinical efficacy

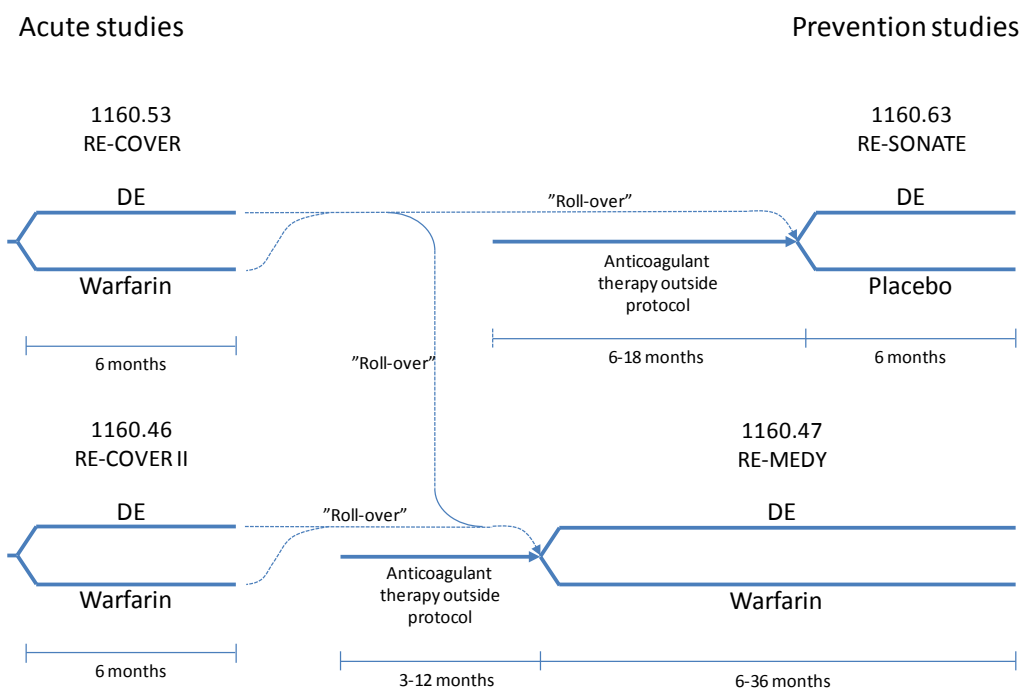
2.3.1. Dose response study

No dedicated dose finding studies were performed.

The clinical efficacy and safety data collected from the studies in orthopaedic surgery and atrial fibrillation (BISTRO-2, PETRO, and PETRO-EX), supplemented with pharmacokinetic and anticoagulation biomarker data, reassured the Applicant that DE at a dose of 150 mg b.i.d. would provide the right balance of efficacy and safety for the acute treatment of VTE and the prevention of its recurrence in the Phase III clinical studies; excessive bleeding had been noted at doses of 225 mg b.i.d. and 300 mg b.i.d in these Phase II studies, while there were no excess thromboembolic events at a dose of 150 mg b.i.d.

2.3.2. Main studies

The efficacy and safety of DE was documented in four randomized, double-blind Phase III studies; three active controlled (W) and one placebo-controlled. Two of the studies support the aVTEt indication (acute studies), and two of the studies supported the sVTEp indication (prevention studies).



Acute studies 1160.53 (RE-COVER) and 1160.46 (RE-COVER II)

Studies 1160.53 and 1160.46 are replicate studies and are described together.

Methods

The pivotal aVTEt studies 1160.53 and 1160.46 (RE-COVER and RE-COVER II, replicate, active-controlled studies) were randomized, double-blind, parallel-group studies of the efficacy and safety of oral DE (150

mg b.i.d.) compared towarfarin(target INR 2.0-3.0) for 6 months of treatment of acute symptomatic venous thromboembolism following initial treatment (5-10 days) with a parenteral anticoagulant approved for this indication. The pivotal aVTEt studies 1160.53 and 1160.46 are replicate studies and will be described together as well as individually described where relevant.

The study design and flowchart for the aVTEt studies are shown graphically below.

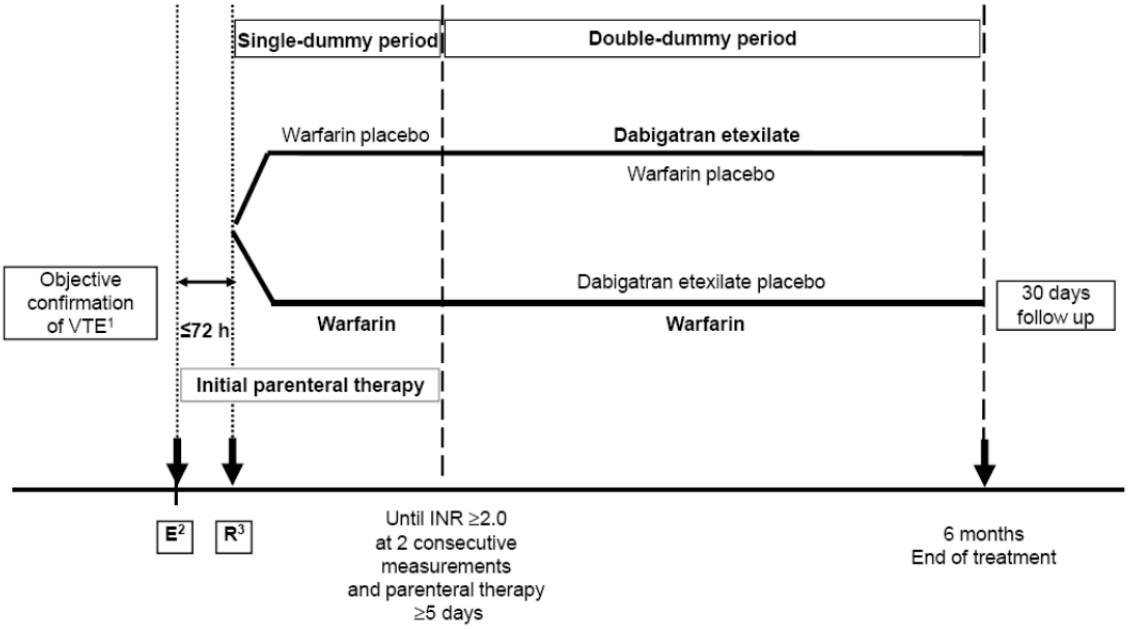


Figure 2.3.3: 1 Study flow chart for aVTEt Studies 1160.53 and 1160.46

Note: Active treatment - starts at randomization for W and oral only treatment (double-dummy treatment) for DE.
Any treatment starts for both W and DE at randomization.
Single-dummy period: patients received open-label parenteral therapy plus blinded oral therapy
Oral only period (double-dummy period): patients received blinded oral therapy only

1 Objective confirmation of VTE was to be obtained prior to enrollment, but not later than 72 hours after enrollment, and prior to randomization.

2 Enrollment

3 Randomization

Study participants

Adult patients (≥ 18 years) with acute symptomatic unilateral or bilateral DVT of the leg involving proximal veins, and/or acute symptomatic PE confirmed by definitive objective clinical testing for whom at least 6 months of anticoagulant therapy was considered appropriate by the investigator and who provided written informed consent.

Treatments

The treatment period included a single-dummy period; patients were to receive parenteral therapy plus either warfarin or warfarin placebo for a planned 5 to 10 days or until INR values were ≥2.0 at 2 consecutive measurements. Patients were then to enter a double-dummy period, during which they were to be randomized to receive either DE/W placebo or DE placebo/W while parenteral therapy was stopped.

Objectives

To compare the safety and efficacy of oral DE (150 mg b.i.d.) and (target INR of 2.0 to 3.0) for 6 month treatment of acute symptomatic venous thromboembolism (VTE) following initial treatment (at least 5 days) with a parenteral anticoagulant approved for this indication in patients with acute symptomatic unilateral or bilateral deep vein thrombosis (DVT) of the leg involving proximal veins and / or pulmonary embolism (PE).

Outcomes / endpoints

Primary efficacy endpoint

Composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined as the composite incidence of DVT (detected by venous compression ultrasonography or venography) and PE (detected by ventilation-perfusion lung scan, pulmonary angiography, or spiral [helical] CT).

A VTE could be a DVT, a PE, both DVT and PE in the same patient, or a death resulting from one of those events. For DVT, diagnosis could be confirmed at autopsy or by either of 2 imaging modalities: a) compression ultrasound (CUS), a non-invasive assessment of venous blood flow in the veins of the pelvis and legs; and b) venography, an invasive technique in which radio-opaque contrast material was injected into the veins to determine if venous blood flow had been impaired or stopped by a thrombus. PE was to be diagnosed at autopsy or by using either non-invasive imaging with spiral computed tomography (CT), ventilation/perfusion radionuclide imaging (V/Q scan), or invasive pulmonary angiography, where radio-opaque contrast material was injected into the pulmonary arterial circulation to determine if an occlusion was present.

Secondary endpoints

For the four pivotal studies, the following were investigated as secondary endpoints:

- Recurrent symptomatic VTE and all-cause deaths
- Recurrent symptomatic VTE excluding unexplained deaths (only for Study 1160.63)
- Symptomatic DVT
- Symptomatic PE
- VTE-related deaths
- All-cause deaths
- Unexplained deaths (only for Study 1160.63)*
- Note: Study 1160.63 excluded unexplained deaths from the key secondary efficacy endpoint “composite of recurrent symptomatic VTE and VTE-related deaths.” Thus, the endpoint “unexplained deaths” was analyzed separately at the study level.

Sample size

For both studies 1160.53 and 1160.46, at least 2550 patients (1275 per treatment group) were to be included to obtain a minimum of 46 patients with confirmed recurrent VTE events. In a time-to-event analysis, the power is dependent on the number of observed events. In a study with a fixed duration of treatment, the number of observed events is dependent on the number of recruited patients, the event rate in the reference group, and the difference between treatment groups. These three factors also determine the power in an analysis of rates. The sample size of 1275 patients per treatment group was originally derived to achieve a sufficient power of at least 90% to claim non-inferiority with a hazard ratio margin of 2.75 for the 2% warfarin hazard rate over 6 months. The warfarin hazard rate of 2% was

based on the recent THRIVE study and similar to the rates observed in Levine et al., 1995 and Schulman et al., 1995. The power was based on one-sided tests with α = 0.025, and the dabigatran hazard rate is also assumed as 2% with an overall drop out of 20% during 6 months. The calculation utilized simulation assuming independent exponential distributions for events and drop-outs.

Randomisation

Patients found to be eligible were to be randomised within 72 hours of enrolment. Randomisation was performed at Visit 2, using an interactive voice response system (IVRS). Patients were randomly assigned to 1 of the 2 treatment groups (W / DE placebo or W placebo /DE); the randomisation ratio was 1:1. Randomisation was stratified by active cancer at baseline and symptomatic PE at baseline (4 strata: 'active cancer and symptomatic PE', 'active cancer, no symptomatic PE', 'no active cancer, symptomatic PE', 'no active cancer, no symptomatic PE') and was to be performed in blocks of 4 to prevent unequal treatment allocation. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before enrolment; any treatment for cancer within 5 years before enrolment; or recurrent or metastatic cancer. During the conduct of the trial, the sponsor received knowledge that 'forced' randomization occurred at individual sites. This occurred when a site contacted IVRS to randomise a patient; however there was not sufficient blinded drug supply in storage at that site for one of the blinded treatment arms. As a result, forced randomisation of the patient to the other treatment group took place using the available study medication. The IVRS provider Almac Clinical Technologies then notified the TCM, but not the site, about the forced randomisation. The sponsor had allowed this process in the IVRS charter, but the IVRS provider was to avoid such cases by following up on the registering of drug supply by the site. Overall, such forced randomisation occurred for 18 patients; a list of these patients and the corresponding sites is stored in the CTMF.

Blinding (masking)

Since the 2 treatments differed in their appearance, blinding was achieved by using a doubledummy design with DE-matching placebo capsules and W-matching placebo tablets. INR values had to be monitored to guide the warfarin therapy; a sham INR procedure was used to prevent unintentional unblinding. INR measurements were to be performed using a point of care (POC) device. Note that in cases where the use of a POC device was not feasible for the monitoring of INR values, the INR could be measured in an unblinded manner by pre-specified individuals who then forwarded the unblinded INR to the IVRS.

Statistical methods

Rationale for the choice of the non-inferiority margins in aVTEt studies

When the initial aVTEt studies were being designed, a superiority study over placebo was deemed unethical in this indication due to the life-threatening consequence of non-treatment. Further, a superiority study over warfarin was impractical as warfarin is known to be very effective. Therefore, non-inferiority studies were planned, although at that time clinically defined non-inferiority margins had not been established in this indication. A non-inferiority margin derived by statistical methods is commonly based on estimates obtained from placebo-controlled studies. For aVTEt, oral anticoagulant therapy following initial therapy with heparin has been established, as evidenced by publications dated as early as 1972. Therefore, due to the lack of placebo-controlled studies, BI decided to use the estimates of the effect of long-term warfarin treatment vs. short-term treatment as a conservative alternative for the aVTEt studies. A confidence interval (CI) from the meta-analysis of short-term warfarin (STW) vs.

placebo, together with CI from the meta-analysis of long-term warfarin (LTW) vs. STW were used to determine an indirect estimate of LTW vs. placebo (Table 1.3.3: 3 presents details for RD and Table 1.3.3: 4 for HR). Short-term was 4-6 weeks with a RD vs. placebo (P – STW) of 15.6% (6.8, 24.5) (Table 1.3.3: 3); long-term was 3-6 months with a RD (STW – LTW) of 8.2% (5.7, 10.7) (Table 1.3.3: 3). The resulting RD for long-term warfarin vs. short-term placebo was indirectly estimated as (P – LTW) 23.8% (14.6, 33.0) (Table 1.3.3: 3). For the HR (and its 95% CI), short-term warfarin vs. placebo was 0.107 (0.013, 0.854) with inverse 9.34 (1.17, 74.5) (Table 1.3.3: 1). Long-term vs. short-term was 0.146 (0.071, 0.300), and the inverse short term/long term: 6.83 (3.34, 14.0) (Table 1.3.3: 2). The HR of long-term vs. placebo was therefore indirectly estimated as 0.082 (95% CI 0.034, 0.195), and for placebo over W, the inverse, as 12.2 (95% CI 5.14, 29.2) (Table 1.3.3: 4). Therefore, using the terminology of the Draft FDA guidance for NI studies, M1=14.6% for RD of placebo minus W, and M1=5.14 for HR of W vs. placebo, for the acute VTE treatment studies, which correspond to the 95-95 fixed-margin approach. Tables 1.3.3: 1 through 1.3.3: 4 below show the historical data and meta-analyses for RD and HR.

Table 1.3.3: 1 Summary of meta-analyses for short-term warfarin vs. placebo

	Hull et al. [R05-0416]	**Lagerstedt et al. [R05-1441]**
Recurrence at week 4 (ST)	warfarin: 0/33 heparin: 8/35 (22.9%)	warfarin: 0/23 placebo: 3/28 (10.7%)
RD (95% CI)	22.9% (8.9, 36.8) for H-$_{ST}$W	10.7% (-0.7, 22.2) for P-$_{ST}$W
	meta analysis[1] 15.6% (6.8, 24.5) for P[2]-$_{ST}$W	
HR (95% CI)	0.066 (0.004, 1.15)	0.203 (0.010, 4.05)
	meta analysis[1] for $_{ST}$W / P[2]: 0.107 (0.013, 0.854) inverse (P[2] / $_{ST}$W): 9.34 (1.17, 74.5)	

Note: HR was estimated assuming exponential distribution; warfarin recurrence was set as 0.5 instead of 0 to obtain the estimate

H=heparin; ST=short term; HR=hazard ratio; RD=risk difference; CI=confidence interval.

1 The weight for each study was given as the inverse of the variance for difference, for HR, the weight was given proportional to the total sample size

2 In this case, heparin is combined with placebo in a meta-analysis

Table 1.3.3: 2 Summary of meta-analysis for LT warfarin vs. ST warfarin

Citation		**Holmgren [R05-1186]/ Schulman [R05-1337][1]**	**Levine [R05-1339]**	**Schulman [R05-0359]**
Result		short trt: 8.9% (7/79) long trt: 3.9% (3/76)	4 week trt: 8.6% (9/105) 3 month trt: 0.9% (1/109)	6 week trt: 10.2% (45/443) 6 month trt: 1.3% (6/454)
RD (95% CI)	$_{ST}$W-$_{LT}$W	4.9% (-2.7, 12.6)	7.7% (2.0, 13.3)	8.8% (5.8, 11.8)
	weight	10.7%	19.7%	69.6%
	meta-analysis[2]	8.2% (5.7, 10.7)		
HR[3] (95% CI)	$_{LT}$W / $_{ST}$W	0.445 (0.115, 1.72)	0.107 (0.014, 0.845)	0.130 (0.056, 0.305)
	weight: total N	12.2%	16.9%	70.9%
	meta-analysis[4]	$_{LT}$W / $_{ST}$W: 0.146 (0.071, 0.300) $_{ST}$W / $_{LT}$W: 6.83 (3.34, 14.0)		

ST=short term; LT=long term; RD=risk difference; HR=hazard ratio, CI=confidence interval.

1 Two studies were combined as an approximation to normal distribution is not appropriate for Schulman study due to a very small number of patients per group (=10).

2 Fixed model approach using a normal approximation; weights are given proportional to either the inverse of the variance or the total sample size

3 Crude approximation assuming exponential distributions as the HR was not reported in any of the references; therefore the variance for log HR was calculated as (d1+d2)/d1/d2 with d1 and d2 denoting the number of events in each group.

4 Fixed model approach using a normal approximation; weights are given proportional to either the inverse of the variance or the total sample size.

Table 1.3.3: 3 Combined analysis (indirect comparisons) in risk difference for LT warfarin vs. placebo

Comparison	RD
ST vs. Placebo (P – $_{ST}$W) (week 4)	15.6% (6.8, 24.5)
LT vs. ST ($_{ST}$W-$_{LT}$W) (3~6 months vs. 4~6 weeks)	8.2% (5.7, 10.7)
LT vs. Placebo (P – $_{LT}$W) (combined)[1]	23.8% (14.6, 33.0)

1 The estimates and variances were obtained by adding the corresponding terms from ST vs. placebo and LT vs. ST.
ST=short term; LT=long term; RD=risk difference; P=placebo; W=warfarin.

Table 1.3.3: 4 Combined analysis (indirect comparisons) of HRs at the end of ST- and LT-treatment in historical data

Comparison	HR estimated from meta analysis	HR for long-term vs. placebo assuming constancy	
		From each period	Indirect comparison[1]
ST: Warfarin vs. placebo (Week 4) [2]	$_{ST}$W / P: 0.107 (0.013, 0.854) (inverse) P / $_{ST}$W: 9.34 (1.17, 74.5)	Same as before assuming constancy	$_{LT}$W / P: 0.082 (0.034, 0.195) (inverse) P / $_{LT}$W: 12.2 (5.14, 29.2)
LT: Warfarin vs. short-term Warfarin (3-6 months vs. 4-6 weeks) [2]	$_{LT}$W / $_{ST}$W: 0.146 (0.071, 0.300) (inverse) $_{ST}$W / $_{LT}$W: 6.83 (3.34, 14.0)	(inverse)[3] 12.9 (5.0, 33.7)	

1 Combined as the weighted average in log scale; the weight was given as the inverse of the variance
2 Estimated from a meta-analysis of the Hull [R05-0416] and Lagerstedt [R05-1441] publications
3 Obtained as (6.83)4/3 assuming constant HR for the ¾ of the time (from the end of ST to the end of LT) and HR of 1 for ¼ of the time (until the end of ST).
ST=short term; LT=long term; HR=hazard ratio; W=warfarin; P=placebo.

Risk difference in aVTEt studies

A margin of 3.6% (=M2) in RD was selected for these studies, preserving at least 75% of the effect of W, anchored at the lower boundary of the 95% CI (14.6%). This non-inferiority margin for the RD was in line with the margins that were used in other clinical studies in the same indication. Indeed, one portion of the analyses (first 4 weeks of warfarin therapy vs. placebo) utilized two studies that had 23 to 35 patients per arm. This small number of patients resulted in a wider CI for the estimate of warfarin effect over placebo. This, together with the fact that the overall effect had to be obtained as a combined estimate over two periods (LT vs. ST and ST vs. placebo), produced what was believed to be an appropriate NI margin at the time of the design of these studies. For example, comparison with putative placebo showed that the number of events being prevented is quite large even by a very low estimate of placebo rate derived from the lower bound of 95% in RD between warfarin and placebo. Another aspect contributing to the belief that a conservative margin was selected stemmed from the characteristics of the two small studies that were used to estimate the effect of ST W. One study compared warfarin over insufficiently effective treatment (heparin), not placebo; the other included distal DVT patients who are known to have a lower risk for recurrence. However, the use of these comparisons resulted in under-estimation of the effect of warfarin and, consequently, a very large sample size. In this sense, 2/3 of the bound, and even 1/2 of the bound, was too conservative and would have led to a sample size which was beyond the feasibility limit for this indication.

Hazard ratio in aVTEt studies

Based on a review of the literature, BI proposed that 57% of the lower bound of the 95% CI in HR would be planned to be preserved. Thus, using the 95-95 fixed margin approach, M1=5.14 and M2=2.75, which

is defined as the non-inferiority margin. This margin required 1275 patients per group (a total of 2550) to have 90% power to declare non-inferiority with a one-sided significance level of 0.025 assuming a 2% event rate and 20% drop-out rate. The total sample size of 2550 patients was at the edge of the feasibility limit and slightly larger than in the THRIVE study, the largest study completed at the time the aVTEt studies were being designed. In addition, this non-inferiority margin for the HR was in line with the margins that were used in other clinical studies in the same indication. Details of the meta-analyses that were consulted, patient populations reviewed, and a summary of published results of relevant studies are provided in Sections 10.2.1 through 10.2.3 of the study protocols for Study 1160.53 and Study 1160.46. Based upon the historical meta-analysis data, which were included in the respective protocols for Studies 1160.53 and 1160.46, and the actual results for these 2 studies, the amount of warfarin effect preserved is presented in Section 3.2.1.9, comparing the actual results with those of the historical meta-analysis.

In conclusion, studies 1160.53 and 1160.46 were designed to demonstrate non-inferiority of DE vs. warfarin and, if non-inferiority could be demonstrated, to allow demonstration of superiority of DE over W. The tests for non-inferiority and superiority were performed in hierarchical order. Both analyses of the primary endpoint - RD at the end of treatment based upon Kaplan-Meier estimates, and HR based upon the Cox regression model - had to have the upper limit of the 2-sided 95% CI less than the pre-specified non-inferiority margin of 2.75 in order to meet non-inferiority according to these pre-defined thresholds. A margin of 3.6% (=M2) in RD was selected for these studies, preserving at least 75% of the effect of W, anchored at the lower boundary of the 95% CI (14.6%).

Results

Participant flow

Study 1160.53 was a multi-centre, multinational study. Overall, 2630 patients were enrolled in 231 centres in 29 countries worldwide; thereof, 228 centres randomised patients. Initially, there were 213 centres in 27 countries. Due to slow recruitment, 37 centres in 3 countries (India, Israel, Turkey) were additionally initiated in 2008. Finland did not enrol any patients and stopped participation in this study in January 2008. The majority of randomised patients came from European countries.

Stduy 1160.46 was an international, multi-centre study. Overall, 2701 patients were enrolled and 2589 patients were randomised in 208 centres in 31 countries worldwide.

Table 3.1.1: 1 Number of patients in analysis datasets for the pivotal studies

	aVTEt Studies		sVTEp Studies	
	1160.53 n (%)	**1160.46 n (%)**	**1160.47 n (%)**	**1160.63 n (%)**
Enrolled	2630	2701	2918	1366
Randomized set	2564 (100.0)	2589 (100.0)	2866 (100.0)	1353 (100.0)
Full analysis set (FAS)[1]	2539 (99.0)	2568 (99.2)	2856 (99.7)	1343 (99.3)
Not treated	25 (1.0)	21 (0.8)	10 (0.3)	10 (0.7)

1 Analyzed as randomized
Source data: SCE appendix, Module 5.3.5.3 [U12-2652], Tables 1.1.5.2 to 1.1.5.5

There were 5331 enrolled patients in the pooled aVTEt studies. Of these, 178 patients (3.3%) were not randomized. Approximately 3 quarters of the 178 did not meet the inclusion or exclusion criteria of their study and were appropriately not randomized; other reasons for not randomizing patients were loss to follow-up, consent withdrawn, adverse event, and “other.” Of the 5107 treated patients, 757 (14.8%)

prematurely discontinued study drug; similar frequencies discontinued in each treatment group. Discontinuations of study drug were most frequently due to AEs. Details are presented in Table 3.1.2.1: 1.

Table 3.1.2.1: 1 Patient disposition at the end of treatment in the pooled aVTEt Studies 1160.53 and 1160.46 - all patients

	DE n (%)	W n (%)	Total n (%)
Enrolled patients			5331
Randomized	2574	2579	5153
Treated patients[1]	2553 (100.0)	2554 (100.0)	5107 (100.0)
Not prematurely discontinued from study drug	2161 (84.6)	2189 (85.7)	4350 (85.2)
Prematurely discontinued from study drug	392 (15.4)	365 (14.3)	757 (14.8)
Adverse events	229 (9.0)	202 (7.9)	431 (8.4)
Worsening of disease under study[2]	63 (2.5)	48 (1.9)	111 (2.2)
Worsening of other pre-existing disease	37 (1.4)	27 (1.1)	64 (1.3)
Other adverse events	129 (5.1)	127 (5.0)	256 (5.0)
Bleeding event[3]	25 (1.0)	40 (1.6)	65 (1.3)
Non-bleeding event	104 (4.1)	87 (3.4)	191 (3.7)
Non-compliant with protocol	60 (2.4)	72 (2.8)	132 (2.6)
Lost to follow-up	15 (0.6)	9 (0.4)	24 (0.5)
Patient refused to continue medication[4]	72 (2.8)	74 (2.9)	146 (2.9)
Other	16 (0.6)	8 (0.3)	24 (0.5)

1 Patients who received at least 1 dose of study drug

2 Symptomatic DVT or PE as based on the assessment of the investigator

3 Including patients who discontinued due to a bleeding event that may or may not have required cessation of treatment

4 Patients who discontinued the intake of study drug could have continued the study without taking study drug, or may have decided to permanently discontinue from the study (i.e., withdrawn their consent).

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Table 1.1.1.1

Roll-over status for aVTEt Studies 1160.53 and 1160.46: Roll-over from the aVTEt studies into a sVTEp study was an option offered to patients whose investigators deemed that they would benefit from continuing anticoagulation therapy in 1 of the sVTEp studies. Of the 5107 patients treated in the pooled aVTEt studies, 1146 (22.4%) rolled over into Study 1160.47, with about equal numbers coming from the 2 different treatment groups. Roll-over patients were re-randomized upon entering Study 1160.47. Of those who rolled over, about half were randomized to the opposite treatment arm in Study 1160.47 and half remained on the same treatment to which they had been randomized in the aVTEt study. A median duration of 1 day for DE patients and 2 days for warfarin patients elapsed between last dose of study drug in the aVTEt study and first dose in Study 1160.47; elapsed time was ≤30 days for > 95% of roll-over patients.

Recruitment

In Study 1160.53, the first patient was entered on 7 April 2006; the last visit date for the last patient was 22 May 2009.

In Study 1160.46 the first patient was randomised on 17 June 2008; the last visit of the last patient was on 5 May 2011.

Conduct of the study

Study 1160.53 (RECOVER)

The original trial protocol (dated 18 November 2005) was amended globally on 4 occasions.

Protocol Amendment 1 allowed alternative means of INR monitoring if use of the POC device was not feasible. In such cases, the INR could be measured in an unblinded manner by authorised personnel who then forwarded the unblinded INR value to the IVRS, while strictly maintaining the blinded status of all study site personnel involved in the conduct of the study (other than those assessing INRs in an unblinded manner); clarified that results of all central assessments by the HRP and ACS / AC were to be provided to the DSMB as soon as the adjudication results were available; and also Protocol Amendment 1 (dated 27 March 2006) clarified that in patients who decided to participate in the RE-MEDY trial, participation in RE-COVER was concluded with the last intake of trial medication. Since Protocol Amendment 1 was issued before the first patient was enrolled (7 Apr 2006), the communication of adjudication results for LFT increases and ACS events followed the specifications made in this amendment.

The main purpose of Protocol Amendment 2 was to contraindicate the concomitant administration of quinidine; If a moderate to strong Pglycoprotein inhibitor was to be concomitantly administered, it was recommended to separate the administration of dabigatran and the P-glycoprotein inhibitor by several hours. A list of Pglycoprotein inhibitors was added to the ISF.

In amendment 3 (18 July 2008) an additional guidance was provided regarding the management of patients who required surgery or invasive procedures during the treatment period.

Protocol Amendment 4 provided guidance on the concomitant administration of verapamil.

Study 1160.46 (RE-COVER II)

The original trial protocol (dated 8 October 2007) was amended globally on 6 occasions.

The protocol amendment 1 clarified that the haematology and biochemistry variables needed to assess the patient's eligibility to participate in the study (serum creatinine, haemoglobin, platelet count, ALT, and AST) were to be obtained from a local laboratory. The results were to be documented on the CRF. This amendment became effective before the first patient was enrolled into the study on 17 June 2008.

The main purpose of Protocol Amendment 2 was to contraindicate the concomitant administration of quinidine; a warning was added with regard to the potential role of P-glycoprotein inhibition on dabigatran plasma levels and subsequent tolerability.

Protocol Amendment 3 was an additional guidance regarding the management of patients who required surgery or invasive procedures during the treatment period.

Protocol Amendment 4 provided guidance on the concomitant administration of verapamil.

Protocol Amendment 5, the systemic use of the P-gp inhibitor ketoconazole was contraindicated and the amendment also provided an updated list of substances tested in drug-drug interaction studies with DE. Further guidance for administration of strong P-gp-inducers was provided, stating that rifampicin and other strong P-gp inhibitors, such as carbamazepine and St. John’s Wart, were to be used with caution and only when no suitable alternative is available.

Following Protocol Amendment 6, the recruitment period was extended by 5 months, hereby changing the planned end of trial date from February 2011 to July 2011.

Baseline data

The demographic characteristics were similar among the 4 pivotal studies and between the treatment groups within studies. About half of the patients in the pivotal studies were male. No important differences were present between studies with regard to mean age (range: 54.6 yrs to 55.8 yrs) or mean BMI (range: 28.4 to 29.1 kg/m2). The percentages of White patients ranged from 77.6% to 94.8%. The highest percentage of Asian patients (20.9%) was in Study 1160.46, the lowest (2.6%) in Study 1160.53. The percentages of Asian patients in sVTEp Studies 1160.47 and 1160.63 were similar (7.9% and 9.3%). About 1.5% to 2.6% of patients per study were Black. Over half of the patients in each study were recruited in Western (17.4% to 55.2%) and Central Europe (25.0% to 34.1%).The demographic characteristics in the pooled aVTEt studies were nearly identical in the DE and warfarin groups.

Table 1.2.1.1 Demographic data for acute VTE treatment studies - FAS

	DE	W	Total
Number of patients [N (%)]	2553 (100.0)	2554 (100.0)	5107 (100.0)
Age [years]			
N	2553	2554	5107
Mean	54.8	54.7	54.8
SD	16.0	16.2	16.1
Min	18	18	18
Q1	43.0	42.0	43.0
Median	56.0	56.0	56.0
Q3	67.0	68.0	67.0
Max	93	97	97
Age category [N (%)]			
18 - < 40 years	495 (19.4)	501 (19.6)	996 (19.5)
40 - < 50 years	449 (17.6)	460 (18.0)	909 (17.8)
50 - < 65 years	825 (32.3)	787 (30.8)	1612 (31.6)
65 - 75 years	531 (20.8)	530 (20.8)	1061 (20.8)
> 75 years	253 (9.9)	276 (10.8)	529 (10.4)
Age category [N (%)]			
<50 years	944 (37.0)	961 (37.6)	1905 (37.3)
>=50 years	1609 (63.0)	1593 (62.4)	3202 (62.7)
Age category [N (%)]			
<65 years	1769 (69.3)	1748 (68.4)	3517 (68.9)
65 - 75 years	531 (20.8)	530 (20.8)	1061 (20.8)
>75 years	253 (9.9)	276 (10.8)	529 (10.4)
Age category [N (%)]			
<70 years	2020 (79.1)	2033 (79.6)	4053 (79.4)
>=70 years	533 (20.9)	521 (20.4)	1054 (20.6)
Age category [N (%)]			
<80 years	2418 (94.7)	2429 (95.1)	4847 (94.9)
>=80 years	135 (5.3)	125 (4.9)	260 (5.1)
Gender [N (%)]			
Male	1520 (59.5)	1521 (59.6)	3041 (59.5)
Female	1033 (40.5)	1033 (40.4)	2066 (40.5)
Race [N (%)]			
White	2206 (86.4)	2193 (85.9)	4399 (86.1)
Black	54 (2.1)	51 (2.0)	105 (2.1)
Asian	292 (11.4)	310 (12.1)	602 (11.8)
Missing	1 (0.0)	0 (0.0)	1 (0.0)

Table 1.2.1.1 Demographic data for acute VTE treatment studies - FAS

	DE	W	Total
Hispanic / Latino [N (%)]			
Non Hispanic	2475 (96.9)	2461 (96.4)	4936 (96.7)
Hispanic	78 (3.1)	93 (3.6)	171 (3.3)
Weight [kg]			
N	2548	2552	5100
Mean	84.3	83.6	84.0
SD	19.4	19.0	19.2
Min	36	35	35
Q1	70.0	70.0	70.0
Median	82.0	82.0	82.0
Q3	95.0	94.0	95.0
Max	185	210	210
Weight category [N (%)]			
< 50 kg	26 (1.0)	31 (1.2)	57 (1.1)
50 - 100 kg	2084 (81.6)	2127 (83.3)	4211 (82.5)
> 100 kg	438 (17.2)	394 (15.4)	832 (16.3)
Missing	5 (0.2)	2 (0.1)	7 (0.1)
Body Mass Index [kg/m²]			
N	2546	2551	5097
Mean	28.6	28.4	28.5
SD	5.7	5.7	5.7
Min	11	13	11
Q1	24.8	24.6	24.7
Median	27.7	27.7	27.7
Q3	31.2	31.1	31.2
Max	59	70	70
BMI category [N (%)]			
<25 kg/m²	665 (26.0)	704 (27.6)	1369 (26.8)
25 - < 30 kg/m²	1035 (40.5)	1043 (40.8)	2078 (40.7)
30 - <= 35 kg/m²	544 (21.3)	527 (20.6)	1071 (21.0)
> 35 kg/m²	302 (11.8)	277 (10.8)	579 (11.3)
Missing	7 (0.3)	3 (0.1)	10 (0.2)
Creatinine Clearance [ml/min]			
N	2525	2533	5058
Mean	107.0	105.8	106.4
SD	42.2	40.5	41.4
Min	17	24	17
Q1	78.8	77.6	78.1
Median	101.9	101.7	101.8
Q3	128.8	127.7	128.3
Max	454	446	454
CrCL category [N (%)]			
< 30 ml/min	12 (0.5)	11 (0.4)	23 (0.5)
30 - < 50 ml/min	114 (4.5)	123 (4.8)	237 (4.6)
50 - < 80 ml/min	539 (21.1)	561 (22.0)	1100 (21.5)
>= 80 ml/min	1860 (72.9)	1838 (72.0)	3698 (72.4)
Missing	28 (1.1)	21 (0.8)	49 (1.0)

In the pooled aVTEt studies, the patients' medical history was similar between the treatment groups. The two most common categories of conditions noted were hypertension (35.5%) and diabetes mellitus (9.0%). There were no important between-group differences for any of the categories.

Concomitant medications in the pooled and individual aVTEt studies 1160.46 and 1160.53

In the pooled aVTEt studies, 28.7% of patients used antithrombotic medication, platelet inhibitors, or NSAIDs concomitantly with study drug (DE: 30.2%, W: 27.3%). The most frequently used concomitant medications were NSAIDs (21.7%) and ASA (9.2%). Cardiovascular medications: In the pooled aVTEt studies, 52.4% of patients used cardiovascular therapy concomitantly; most frequently reported were vasodilators (28.5%), agents acting on the renin-angiotensin system (24.7%), serum lipidreducing agents (19.1%), beta-blocking agents (14.8%), and calcium-channel blockers (9.7%). P-gp inhibitors/inducers: In the pooled aVTEt studies, concomitant use of P-gp inhibitors was reported by few patients (2.0%); most frequent were verapamil (1.2% overall) and amiodarone (0.4% overall). The concomitant use of P-gp inducers (0.7% overall) was less frequent.

The use of concomitant antithrombotic medication, platelet inhibitors, NSAID, cardiovascular medications and P-gp inhibitors/inducers was similar between treatment groups as well as in the individual aVTEt studies.

Risk factors for recurrent VTE

Risk factors for recurrent VTE are presented below in Table 3.1.3.3:1:

Table 3.1.3.3: 1 Risk factors for recurrent VTE in pivotal Studies 1160.53, 1160.46, 1160.47 and 1160.63- FAS

	aVTEt Study		sVTEp Study	
	1160.53	**1160.46**	**1160.47**	**1160.63**
Patients, n (%)	2539 (100.0)	2568 (100.0)	2856 (100.0)	1343 (100.0)
Active cancer at any time	179 (7.1)	156 (6.1)	193 (6.8)	104 (7.7)
At baseline	121 (4.8)	100 (3.9)	119 (4.2)	81 (6.0)
Diagnosed during study	58 (2.3)	56 (2.2)	74 (2.6)	23 (1.7)
Previous VTE (before qualifying event)	649 (25.6)	450 (17.5)[1]	1525 (53.4)	1341 (99.9)
Thrombophilia	236 (9.3)	172 (6.7)	525 (18.4)	155 (11.5)
Factor V Leiden	110 (4.3)	74 (2.9)	268 (9.4)	63 (4.7)
Prothrombin mutation	33 (1.3)	22 (0.9)	63 (2.2)	16 (1.2)
Antithrombotic deficiency	13 (0.5)	8 (0.3)	22 (0.8)	1 (0.1)
Protein C / S deficiency	40 (1.6)	22 (0.9)	54 (1.9)	19 (1.4)
Antiphospholipid antibodies and/or lupus anticoagulant	63 (2.5)	23 (0.9)	92 (3.2)	6 (0.4)
Patients with no available test results for thrombophilia	1611 (63.5)	1750 (68.1)	1491 (52.2)	634 (47.2)
Recent prolonged immobilization	396 (15.6)	351 (13.7)	199 (7.0)	89 (6.6)
Transient immobilization	368 (14.5)	321 (12.5)	184 (6.4)	85 (6.3)
Permanent immobilization	28 (1.1)	30 (1.2)	15 (0.5)	4 (0.3)
History of venous insufficiency[2]	492 (19.4)	405 (15.8)	-	-
Long-distance travel[2]	222 (8.7)	201 (7.8)	-	-
Surgery / trauma[2]	484 (19.1)	442 (17.2)	-	-
Recent use of oestrogens[2,3]	275 (10.8)	197 (7.7)	-	-
Recent pregnancy [2,4]	7 (0.3)	10 (0.4)	-	-
Smoking history				
Never smoked	1298 (51.1)	1372 (53.4)	1643 (57.5)	767 (57.1)
Ex-smoker	699 (27.5)	635 (24.7)	759 (26.6)	353 (26.3)
Current smoker	541 (21.3)	561 (21.8)	454 (15.9)	223 (16.6)

1 In Study 1160.46, the number of previous VTE excludes the qualifying VTE event; for the other pivotal studies the qualifying VTE event may have been included as no separation was performed in the eCRF

2 History of venous insufficiency, long-distance travel, surgery/trauma, recent use of oestrogens, and recent pregnancy as baseline characteristics were specifically queried in the aVTEt but not the sVTEp studies

3 Systemic use of estrogens within last month

4 Pregnancy within last 3 months

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Tables 1.2.4.2 to 1.2.4.5 and 1.2.5.2 to 1.2.5.5

The total number of patients with risk factors for VTEs was similar for Studies 1160.53 (69.4%) and 1160.47 (66.7%). Previous VTE accounted for the greatest proportion of the risk factors in the pivotal studies. The frequency of previous VTE as a risk factor was highest in patients in Study 1160.63 (99.9%), followed by patients in Studies 1160.47 (53.4%) and 1160.53 (25.6%). In total, 17.5% of patients in Study 1160.46 reported previous VTE; however, only in this study did the investigators clearly exclude the qualifying VTE event from the number of previous VTE according to the eCRF. In the other 3 pivotal studies the qualifying event could have been excluded from or included in the number of previous VTEs.

Characteristics of the qualifying VTE event in aVTEt Studies 1160.53 and 1160.46: In the pooled aVTEt studies, 68.5% of patients had only symptomatic DVT as their qualifying VTE event, 22.2% had only symptomatic PE, and 9.1% had both symptomatic DVT and PE. The index event was not confirmed by objective clinical testing by the investigator for 6 patients (0.1%) with symptomatic DVT or symptomatic

PE at baseline. For the individual aVTEt studies, there were no major differences between studies or between treatments within each study.

Compliance

In the pooled aVTEt studies, the rates of non-compliant patients (outside the range of 80% to 120% for at least 2 consecutive visits) were low for patients who received DE and DE-matching placebo (2.1% each). Comparable rates were observed for the individual aVTEt studies.

Warfarin patients had a mean of 1.9 INR measurements per month. The overall mean TTR (INR 2.0-3.0) was 58.0% (median 60.6%) (Table 3.1.7: 1). Periods during which warfarin was withheld (unless the reason was "INR too high or too low") were excluded from the calculation of TTR. For the INR range of 1.8 to 3.2, the overall mean TTR was 72.9% (median 77.2%), and was 90.6% (median 96.2%) for the INR range of 1.5 to 4.0.

Table 3.1.7: 1 Percentage of time in the INR target range of 2.0 to 3.0 in the pooled aVTEt Studies 1160.53 and 1160.46 - FAS, patients in the warfarin group

		Percentage of time (%)								
		INR <2			INR 2 to 3			INR >3		
Time since first warfarin intake	Patients n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Month 0-3	2468	23.4	(23.3)	18.1	54.9	(24.8)	55.8	21.7	(22.1)	15.7
Month 4-6	2286	23.2	(26.6)	14.1	62.4	(28.6)	64.0	14.4	(20.3)	2.9
Month 0-6	2468	23.4	(21.1)	18.6	58.0	(22.7)	60.2	18.7	(18.6)	14.0
Overall	2468	23.4	(21.1)	18.5	58.0	(22.7)	60.6	18.6	(18.6)	14.0

SD=standard deviation
Time categories: 'First month' from 1 week after first warfarin intake to Day 30; 'Month 0-3' from 1 week after first intake of
Time categories: 'First month' from 1 week after first warfarin intake to Day 30; 'Month 0-3' from 1 week after first intake of warfarin to Day 90; 'Month 4-6' from Day 91 to Day 180; 'Month 0-6' from 1 week after first intake of warfarin to Day 180; 'Overall' 1 week after first intake of warfarin to last intake of warfarin.
Number of patients includes all patients who have evaluable data during that time window.
Daily INR calculated using Rosendaal method. One month = 30 days
Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Table 1.5.3.1

Table 3.1.7: 2 Percentage of patients with time in the INR target range of 2.0 to 3.0, by time category (quartiles) in the pooled aVTEt Studies 1160.53 and 1160.46 - FAS, patients in the warfarin treatment group

		Percentage of patients in the INR range 2.0 to 3.0, by time category[1]							
		<45%		45% to <62%		62% to <75%		>75%	
Time since first warfarin intake	Patients n	n	%	n	%	n	%	n	%
Month 0-3	2468	847	34.3	631	25.6	429	17.4	561	22.7
Month 4-6	2286	628	27.5	461	20.2	309	13.5	888	38.8
Month 0-6	2468	656	26.6	650	26.3	565	22.9	597	24.2
Overall	2468	657	26.6	641	26.0	574	23.3	596	24.1

[1] Time categories: 'First month' from 1 week after first warfarin intake to Day 30; 'Month 0-3' from 1 week after first intake of warfarin to Day 90; 'Month 4-6' from Day 91 to Day 180; 'Month 0-6' from 1 week after first intake of warfarin to Day 180; 'Overall' 1 week after first intake of warfarin to last intake of warfarin.
Number of patients includes all patients who have evaluable data during that time window.
Daily INR calculated using Rosendaal method. One month = 30 days
Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Table 1.5.7.1

Outcomes and estimation

The main objectives of the pooled analysis of aVTEt Studies 1160.53 and 1160.46 were the overall estimate of the HR (Cox proportional hazards model) and its 95% CI for the incidence of VTE and VTE-related death between DE and W. Additionally, KM plots were prepared for the primary endpoint, defined as the composite of recurrent symptomatic VTE and VTE-related deaths.

Both analyses of the primary endpoint - RD at the end of treatment based upon Kaplan-Meier estimates, and HR based upon the Cox regression model - had to have the upper limit of the 2-sided 95% CI less than the pre-specified non-inferiority margin in order to meet non-inferiority according to these pre-defined thresholds.

A non-inferiority margin of 2.75 in hazard ratio and 3.6% in RD was selected for these studies, preserving at least 75% of the effect of W, anchored at the lower boundary of the 95% CI (14.6%).

The primary endpoint occurred at a similar rate in both treatment groups (DE: 2.7%; W: 2.4%). The heterogeneity p-value was non-significant; homogeneity was assumed and a common treatment effect was used for both studies. The HR of DE vs. W was 1.09 with an accompanying 95% CI of 0.77 to 1.54. Both treatments were, therefore, assumed to be similar with regard to the primary efficacy endpoint. Results for the ITT analysis and other sensitivity analyses were consistent with those reported here. The KM curves for the primary endpoint were nearly congruent and crossed at multiple points (Figure 3.2.1.2: 1). For both treatment groups, the curves indicated a higher risk of VTE recurrence in the 2-month period immediately after the initial symptomatic VTE. The KM curves for the ITT analysis and other sensitivity analyses were consistent with those presented below. An excess of 0.4 events (VTE and VTE-related deaths) in 100 patient-years of treatment would be expected for patients on DE vs. Warfarin (Table 2.1.5.1 below).

Table 2.1.5.1 Frequency and yearly event rate for centrally adj. VTE and VTE related deaths until the end of the post-treatment period for acute VTE treatment studies - FAS

	DE			W		
	N	Time at risk [pt-yrs]	Rate/ 100pt-yrs	N	Time at risk [pt-yrs]	Rate/ 100pt-yrs
Number of patients	2553			2554		
VTE and VTE related deaths	68	1375.0	(4.9)	62	1368.4	(4.5)

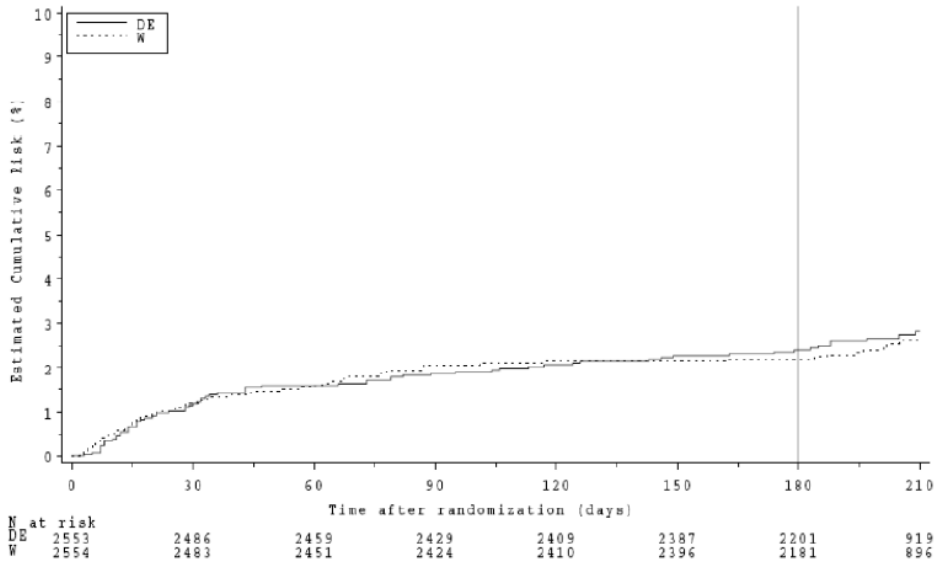


Figure 3.2.1.2: 1 Time to first adjudicated VTE and VTE-related death until the end of post-treatment period for the pooled aVTEt Studies 1160.53 and 1160.46 - FAS

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Figure 2.1.3.1

Table 4.2: 1 Hazard Ratios for efficacy and safety outcome events until the end of planned treatment period in pivotal VTE studies (HRs and 95% CI) - FAS

Study	Pooled aVTEt Studies 1160.53 and 1160.46	1160.47	1160.63
Endpoints	DE 150 mg b.i.d. vs. warfarin HR (95% CI)	DE 150 mg b.i.d. vs. warfarin HR (95% CI)	DE 150 mg b.i.d. vs. placebo HR (95% CI)
VTE and VTE-related death	1.09 (0.77, 1.54)	1.44 (0.78, 2.64)	0.08 (0.02, 0.25)[1]
VTE and all death	1.04 (0.80, 1.37)	1.17 (0.75, 1.84)	0.08 (0.02, 0.25)
MBE	0.60 (0.36, 0.99)[3]	0.54 (0.25, 1.16)	--[2]
MBE or CRBE	0.56 (0.45, 0.71)[3]	0.55 (0.41, 0.72)	2.69 (1.43, 5.07)
Any bleeds	0.67 (0.59, 0.77)[3]	0.71 (0.61, 0.83)	1.77 (1.20, 2.61)

[1] VTE, VTE-related deaths and unexplained deaths.
[2] HR not calculated, 2 MBE for DE vs. 0 MBE for placebo.
[3] HR calculated for bleeding events from start of double dummy period until end of treatment for aVTEt studies 1160.46 and 1160.53.
CRBE= clinically relevant bleeding event, HR=hazard ratio, CI=confidence interval, FAS=full analysis set.
Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Tables 2.1.2.1, 2.1.2.4, 2.1.2.5, 2.2.2.1, 2.2.2.4, and 2.2.2.5; SCS appendix Module 5.35.3 [U12-2653] Tables 4.2.9.1.2.1, 4.2.3.4, 4.2.3.5, 4.4.6.2.1, 4.4.2.4, 4.4.2.5, 4.11.5.1.2.1, 4.11.2.4, 4.11.2.5.

Results from the individual studies 1160.53 and 1160.46 are presented below:

In Study 1160.53, the primary endpoint occurred at a similar rate in both treatment groups (DE: 2.7%; W: 2.5%). The HR was 1.05 with a corresponding p-value for non-inferiority <0.0001. The upper boundary of the CI was well below the pre-defined non-inferiority margin of 2.75 (95% CI: 0.65, 1.70). The KM curves for the primary endpoint were nearly congruent (Figure 3.2.1.3: 1). For both treatment groups, the curves were steeper in the first 2 months and became flatter thereafter. The cumulative risk

for the primary endpoint at 6 months was 2.4% in the DE group and 2.2% in the W group (Table 3.2.1.3: 1). The RD was 0.4% (95% CI −0.7, 1.5). The upper limit of the CI of the RD was below the pre-defined non-inferiority margin of 3.6%. The p-value for the test for non-inferiority was <0.0001. Based on the RD of 0.4, one would expect an excess of 0.2 events (VTE and VTE-related deaths) in 100 patient-years of treatment on DE vs. W.

Table 2.1.1.1 Risk difference at 6 months for centrally adj.VTE and VTE related deaths for study 1160.53 (RE-COVER) - FAS

Strata	DE Patients [N] VTE and VTE related deaths * (cumulative risk %)	W Patients [N] VTE and VTE related deaths * (cumulative risk %)	Risk difference Estimate (95% CI)
At 6 months $ #	1274 30 (2.4)	1265 27 (2.2)	0.4 (-0.7, 1.5)
Minimum important difference ~			3.6
p-value for non-inferiority ^			<.0001
p-value for superiority			0.5017
Without PE	882 19 (2.2)	871 14 (1.7)	0.5 (-0.8, 1.9)
With PE	392 11 (2.9)	394 13 (3.3)	-0.4 (-2.9, 2.0)
Without cancer	1210 28 (2.4)	1208 24 (2.0)	0.3 (-0.8, 1.5)
With cancer	64 2 (3.4)	57 3 (5.4)	-2.0 (-9.5, 5.6)
No PE without cancer	837 18 (2.2)	830 12 (1.5)	0.7 (-0.6, 2.0)
PE without cancer	373 10 (2.7)	378 12 (3.2)	-0.5 (-2.9, 2.0)
No PE with cancer	45 1 (2.4)	41 2 (5.1)	-2.7 (-11.1, 5.7)
PE with cancer	19 1 (5.9)	16 1 (6.3)	-0.4 (-16.7, 15.9)
Overall £	1274 34 (3.0)	1265 32 (3.0)	

*: Number of patients with event
$: Number of patients and cumulative risk computed at Day 180
#: Cumulative risks for each treatment were calculated ignoring strata and risk difference was calculated as the weighted average of KM estimates across strata, four strata from two stratification variables of cancer (yes/no) and symptomatic PE at baseline (yes/no).
~: The choice of MID guarantees that dabigatran preserves, if proven non-inferior, at least 75% of the effect of warfarin over placebo in risk difference (based on the lower bound of the 95% confidence interval for the warfarin effect)
^: one-sided p-value £: Number of patients with event until the end of post treatment period

In Study 1160.46, the primary endpoint, recurrent symptomatic VTE and VTE-related deaths (excluding unexplained deaths) until the end of post-treatment period, occurred at a similar rate in both treatment groups (DE: 2.7%; W: 2.3%). The HR vs W was 1.13 (95% CI: 0.69, 1.85). The p-value for non-inferiority was 0.0002. The cumulative risk for the primary endpoint at 6 months was 2.4% in the DE group and 2.2% in the warfarin group (Table 3.2.1.4: 1). The RD was 0.2% (95% CI -1.0, 1.3). The p-value for the test for non-inferiority was 0.0001. Based on the RD of 0.2, one would expect an excess of 0.6 events (VTE and VTE-related deaths) in 100 patient-years of treatment on DE vs. W.

Table 2.1.1.2 Risk difference at 6 months for centrally adj.VTE and VTE related deaths for study 1160.46 (RE-COVER II) - FAS

Strata	DE Patients [N] VTE and VTE related deaths * (cumulative risk %)	W Patients [N] VTE and VTE related deaths * (cumulative risk %)	Risk difference Estimate (95% CI)
At 6 months $ #	1279 30 (2.4)	1289 28 (2.2)	0.2 (-1.0, 1.3)
Minimum important difference ~			3.6
p-value for non-inferiority ^			<.0001
p-value for superiority			0.7752
Without PE	876 23 (2.7)	876 20 (2.3)	0.4 (-1.1, 1.8)
With PE	403 7 (1.8)	413 8 (2.0)	-0.2 (-2.1, 1.7)
Without cancer	1229 28 (2.3)	1239 26 (2.1)	0.2 (-1.0, 1.4)
With cancer	50 2 (5.2)	50 2 (4.4)	0.8 (-8.4, 10.1)
No PE without cancer	836 21 (2.5)	838 18 (2.2)	0.4 (-1.1, 1.8)
PE without cancer	393 7 (1.8)	401 8 (2.0)	-0.2 (-2.1, 1.7)
No PE with cancer	40 2 (6.7)	38 2 (5.8)	0.9 (-11.0, 12.8)
PE with cancer	10 0 (0.0)	12 0 (0.0)	- (-, -)
Overall £	1279 34 (5.7)	1289 30 (2.4)	

*: Number of patients with event
$: Number of patients and cumulative risk computed at Day 180
#: Cumulative risks for each treatment were calculated ignoring strata and risk difference was calculated as the weighted average of KM estimates across strata, four strata from two stratification variables of cancer (yes/no) and symptomatic PE at baseline (yes/no).
~: The choice of MID guarantees that dabigatran preserves, if proven non-inferior, at least 75% of the effect of warfarin over placebo in risk difference (based on the lower bound of the 95% confidence interval for the warfarin effect)
^: one-sided p-value £: Number of patients with event until the end of post treatment period

Ancillary analyses

With regard to the key secondary endpoint of symptomatic VTE and all-cause death, DE was non-inferior to warfarin in the 3 active-controlled studies and superior to placebo in Study 1160.63.

Pooling of aVTEt Studies 1160.53 and 1160.46

The secondary endpoint, recurrent symptomatic VTE and all-cause deaths (including unexplained deaths), occurred at a similar rate in both treatment groups (DE: 4.3%; W: 4.1%). The HR of DE vs. W was 1.04 with an accompanying 95% CI of 0.80, 1.37. There was no statistically significant treatment difference between DE and warfarin in the pooled aVTEt studies. The test for heterogeneity resulted in a p-value of 0.6049; thus it can be concluded that the effect of treatment was similar in both aVTEt studies.

The KM curves of the 2 treatment groups for the key secondary endpoint were nearly congruent and crossed multiple times (Figure 3.2.2.1: 1). For both treatment groups, the estimated cumulative risk increased slowly and continuously over the course of the study. The composite endpoint of VTE and all-cause deaths was also assessed by incidence of the most severe component. The incidences of each component were similar among the treatment groups. Death accounted for most of the events (DE: 2.00%, W: 2.04%), followed by symptomatic DVT (DE: 1.45%, W: 1.21%) and PE (0.82% each).

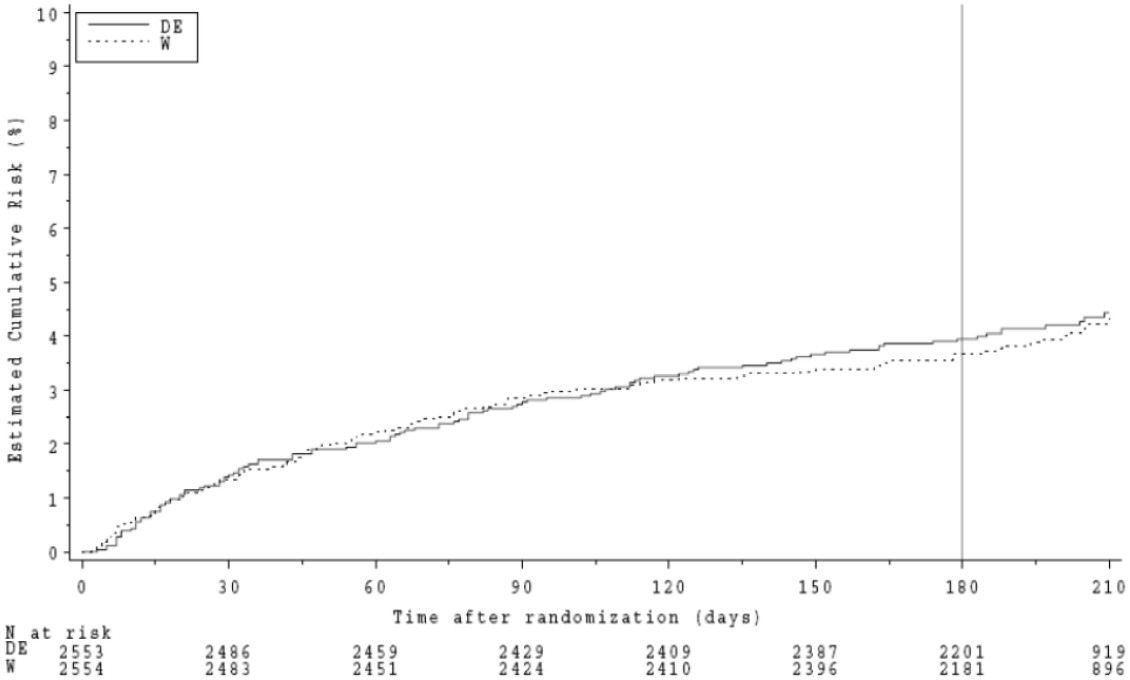


Figure 3.2.2.1: 1 Time to first adjudicated VTE and all-cause deaths until the end of post-treatment period for the pooled aVTEt Studies 1160.53 and 1160.46 - FAS

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Figure 2.2.3.1

In Study 1160.53, the cumulative risks and RDs were also assessed by stratification factor and stratum. As expected, the cumulative risk for the key secondary endpoint was higher for patients with initial symptomatic PE (DE, 5.2%; W, 4.4%) than for patients without PE (3.2% each). Patients with active cancer at baseline had a higher cumulative risk for the key secondary endpoint (DE: 13.0%, W: 14.3%) than patients without active cancer at baseline (3.4% vs. 3.0%), which was also as expected. For the RD between treatment groups in patients with/without initial symptomatic PE and with/without cancer, all CIs included 0, indicating that there was no important statistical difference in cumulative risks between treatment groups.

In Study 1160.46, the cumulative risks and RDs were also assessed by stratification factor and stratum. The cumulative risk for the key secondary endpoint was lower for patients with initial symptomatic PE (DE: 3.5%, W: 3.5%) than for patients without PE (DE: 4.3%, W: 3.9 %). Patients with active cancer at baseline had a higher cumulative risk for the key secondary endpoint (DE: 24.8%, W: 24.9%) than patients without active cancer at baseline (3.2% vs. 2.9%), which was as expected. For the RD between treatment groups in patients with/without initial symptomatic PE and with/without cancer, all CIs included 0, indicating that there was no important statistical between-treatment difference in cumulative risks.

The composite endpoint of VTE and all-cause deaths was also assessed by incidence of the most severe component. The incidences of each component were similar among the treatment groups. Death accounted for most of the events (DE: 2.00%, W: 2.04%), followed by symptomatic DVT (DE: 1.45%, W: 1.21%) and PE (0.82% each), (Table 2.2.5.1):

Table 2.2.5.1 Centrally adj. VTE and all deaths by most severe component until the end of post-treatment period for acute VTE treatment studies - FAS

	DE N(%)	W N(%)
Patients	2553 (100.00)	2554 (100.00)
VTE and all deaths	109 (4.27)	104 (4.07)
Death	51 (2.00)	52 (2.04)
Symptomatic PE	21 (0.82)	21 (0.82)
Symptomatic DVT	37 (1.45)	31 (1.21)

Other secondary endpoints:

- Symptomatic DVT
- Symptomatic fatal and non-fatal PE
- VTE-related deaths
- All-cause deaths

The frequencies of the different secondary endpoints were similar for the DE and warfarin groups in the pooled aVTEt Studies 1160.53 and 1160.46 and in the individual Studies 1160.53 and 1160.46 (Table 3.2.3.1: 1). The CIs widely overlapped for each of the secondary endpoints.

Table 3.2.3.1: 1 Summary of incidence of secondary endpoints until the end of the post-treatment period for the pooled aVTEt Studies 1160.53 and 1160.46, aVTEt Study 1160.53 and 1160.46 - FAS

	DE	W
Pooled aVTEt Studies 1160.53 and 1160.46		
Patients in FAS, n (%)	2553 (100.0)	2554 (100.0)
Recurrent symptomatic VTE and all-cause deaths	109 (4.3)	104 (4.1)
95% CI[1]	3.52, 5.13	3.34, 4.91
Symptomatic DVT	45 (1.8)	39 (1.5)
95% CI[1]	1.29, 2.35	1.09, 2.08
Symptomatic PE	27 (1.1)	26 (1.0)
95% CI[1]	0.70, 1.54	0.67, 1.49
VTE-related deaths	4 (0.2)	3 (0.1)
95% CI[1]	0.04, 0.40	0.02, 0.34
All-cause deaths	51 (2.0)	52 (2.0)
95% CI[1]	1.49, 2.62	1.52, 2.66
aVTEt Study 1160.53		
Patients in FAS, n (%)	1274 (100.0)	1265 (100.0)
Recurrent symptomatic VTE and all-cause deaths	52 (4.1)	53 (4.2)
95% CI[1]	3.06, 5.32	3.15, 5.44
Symptomatic DVT	17 (1.3)	22 (1.7)
95% CI[1]	0.78, 2.13	1.09, 2.62
Symptomatic PE	17 (1.3)	11 (0.9)
95% CI[1]	0.78, 2.13	0.43, 1.55
VTE-related deaths	1 (0.1)	3 (0.2)
95% CI[1]	0.00, 0.44	0.05, 0.69
All-cause deaths	22 (1.7)	26 (2.1)
95% CI[1]	1.09, 2.60	1.35, 3.00
aVTEt Study 1160.46		
Patients in FAS, n (%)	1279 (100.0)	1289 (100.0)
Recurrent symptomatic VTE and all-cause deaths	57 (4.5)	51 (4.0)
95% CI[1]	3.39, 5.74	2.96, 5.17
Symptomatic DVT	28 (2.2)	17 (1.3)
95% CI[1]	1.46, 3.15	0.77, 2.10
Symptomatic PE	10 (0.8)	15 (1.2)
95% CI[1]	0.38, 1.43	0.65, 1.91
VTE-related deaths	3 (0.2)	0 (0)
95% CI[1]	0.05, 0.68	0.00, 0.29
All-cause deaths	29 (2.3)	26 (2.0)
95% CI[1]	1.52, 3.24	1.32, 2.94

[1] Exact 95% Clopper Pearson CI
Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Table 2.2.4.1, Table 2.2.4.2, Table 2.2.4.3

Comparison of results in sub-populations

The analyses of efficacy in pre-specified subgroups were performed for the primary endpoint VTE and VTE-related deaths.

Subgroup analyses were performed to detect interactions between treatment and the following demographic/baseline characteristics:

- Age (<65, 65-75; >75; <75- ≥ 75; <80, ≥80 years)
- Gender (male, female)
- Race (White, Black, Asian)
- Ethnicity (Hispanic vs. non-Hispanic)
- Geographic region (Asia, Central Europe, Latin America, North America, Other and Western Europe)
- BMI (<25, 25 - <30, 30 – ≤35, and >35 kg/m2)
- CrCl (< 30, 30 - <50, 50 - <80, and ≥80 mL/min)
- Smoking history (never smoked, ex-smoker, and current smoker).

Forest Plots for analyses of the primary endpoint by subgroups for pooled aVTEt Studies 1160.53 and 1160.46

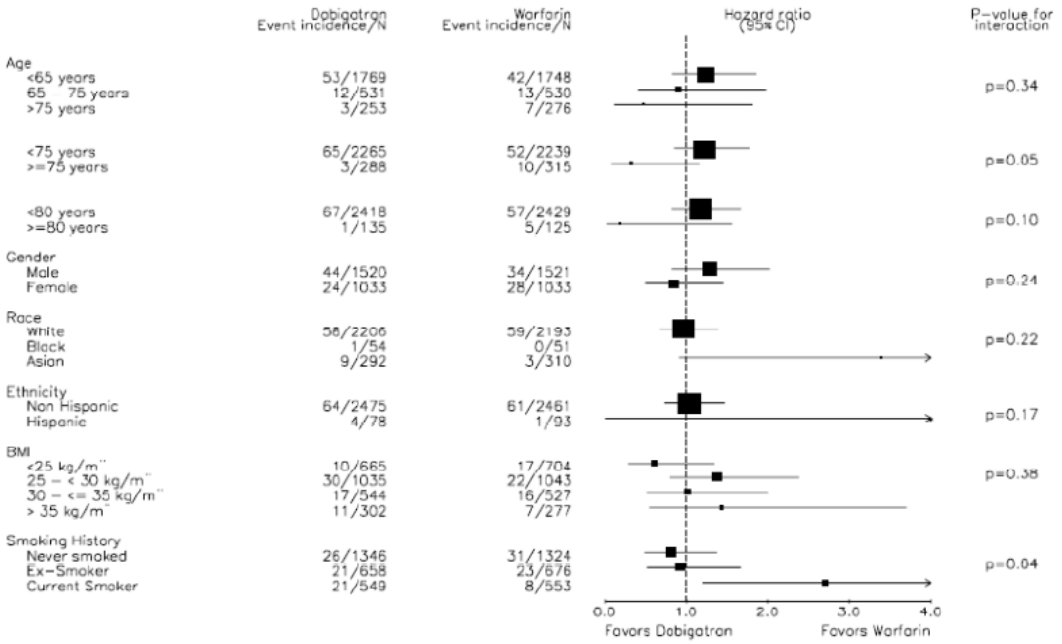


Figure 3.3: 1 Forest plot for centrally adjudicated VTE and VTE-related deaths for subgroups by age, gender, race, ethnicity, BMI, and smoking history; until the end of the post-treatment period for pooled aVTEt Studies 1160.53 and 1160.46 - FAS

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Figure 2.5.55.1.1

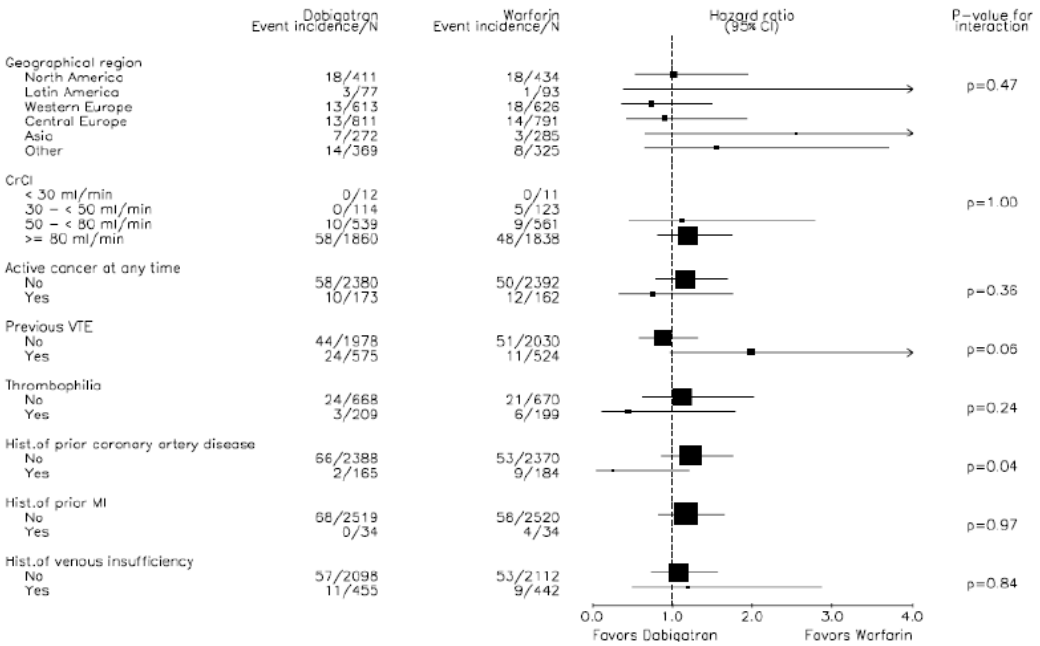


Figure 3.3: 2 Forest plot for centrally adjudicated VTE and VTE-related deaths for subgroups by geographic region, CrCl, presence of cancer, previous VTE, thrombophilia; and history of prior coronary artery disease, MI, and venous insufficiency; until the end of the post-treatment period for pooled aVTEt Studies 1160.53 and 1160.46 - FAS

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Figure 2.5.55.1.1

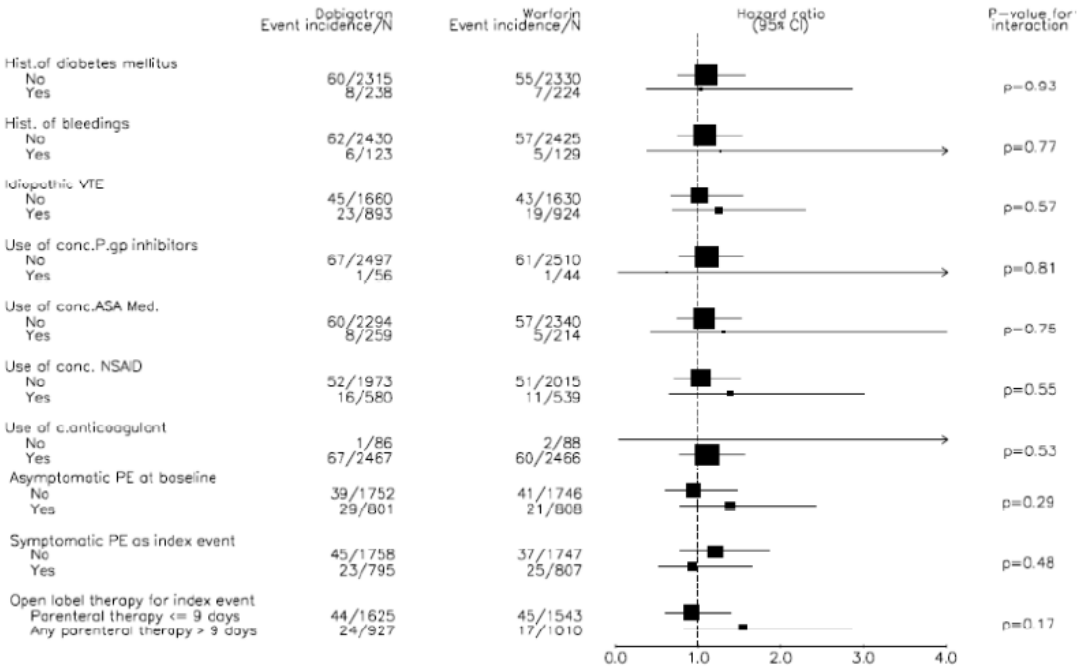


Figure 3.3: 3 Forest plot for centrally adjudicated VTE and VTE-related deaths for subgroups by history of diabetes mellitus, history of bleeding, idiopathic VTE, use of concomitant medications, type of PE at baseline, and by duration of open-label therapy for index event; until the end of the post-treatment period for pooled aVTEt Studies 1160.53 and 1160.46 –FAS

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Figure 2.5.55.1.1

No interactions were detected between treatment and any of the factors analyzed (nominal p-values were all >0.10), except for items 1 through 4 below. None of these exceptions were considered clinically important, and all but item 3 below may be chance findings since multiple comparisons have been made:

1. In pooled aVTEt Studies 1160.53 and 1160.46 a possible interaction was detected between treatment and age <75 vs. ≥75 years for those who experienced VTE or VTE-related death (p=0.0517). Among those <75 years old, 65/2265 (2.9%) DE patients and 52/2239 (2.3%) warfarin patients experienced VTE or VTE-related death. Among those ≥75 years old, 3/288 (1.0%) DE patients and 10/315 (3.2%) warfarin patients experienced VTE or VTE-related death. The same interaction was detected for individual Study 1160.46 (p=0.1046).
2. In pooled aVTEt Studies 1160.53 and 1160.46 a possible interaction was detected between treatment and age <80 vs. ≥80 years for those who experienced VTE or VTE-related death (p=0.0956). Among those <80 years old, 67/2418 (2.8%) DE patients and 57/2429 (2.3%) warfarin patients experienced VTE or VTE-related deaths. Among those ≥80 years old 1/135 (0.7%) DE patients and 5/125 (4.0%) warfarin patients experienced VTE or VTE-related deaths.
3. To confirm that there were no age groups in which the efficacy of warfarin was significantly different from that of DE, age as a continuous variable was also analyzed. In aVTEt Studies 1160.53 and 1160.46 and in sVTEp Study 1160.47 there appeared to be a tendency for DE to have better efficacy at higher ages but it is difficult to draw any definitive conclusions because at all ages, the 95% CIs for the estimated hazard ratio included 1.0, and the interaction was not statistically significant. In the pooled aVTEt studies and in the individual aVTEt studies, when age was analyzed as a continuous

variable, compared with W, the efficacy of DE was lower in younger patients and higher in older patients, with equal efficacy at about age 60 (Figure 3.3.1:1):

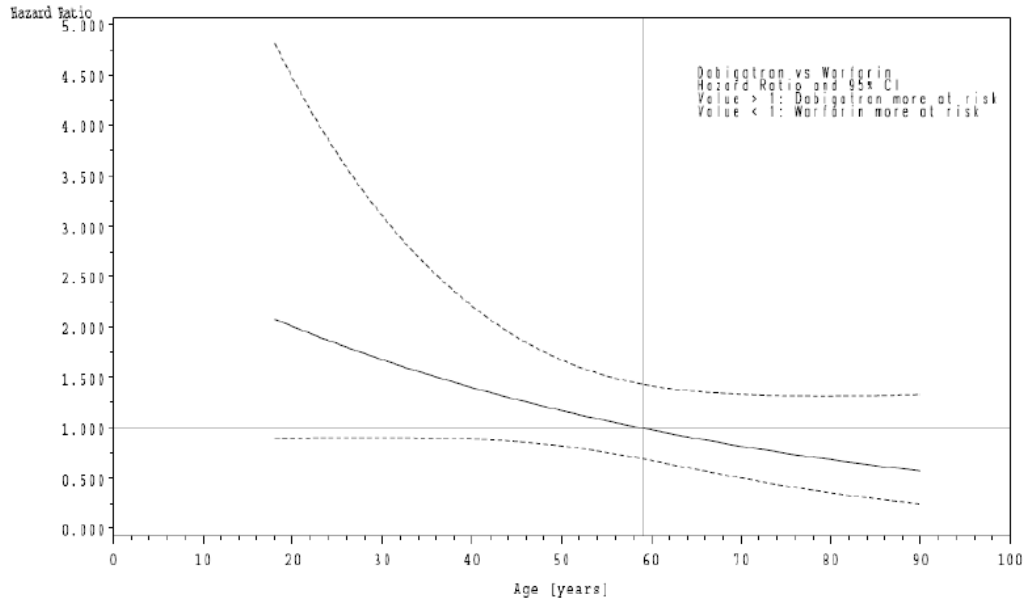


Figure 3.3.1: 1 Hazard ratio for DE vs. warfarin for centrally adjudicated VTE and VTE-related deaths depending on age as a continuous variable for pooled aVTEt Studies 1160.53 and 1160.46 - FAS

Note: Dashed lines represent the upper and lower bounds of Confidence Interval
Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Figure 2.5.57.1.1

4. In pooled aVTEt Studies 1160.53 and 1160.46 a possible interaction was detected between treatment and history of smoking for VTE and VTE-related death (p=0.0430; from Wald Chi square test of treatment-by-smoking-status interaction effect). In this pooling the percentages of DE patients who never smoked, were ex-smokers, or current smokers who had events were 1.9% (26 patients), 3.2% (21 patients), and 3.8% (21 patients) vs. 2.3% (31 patients), 3.4% (23 patients) and 1.4% (8 patients), respectively, for warfarin patients. This finding appears to be driven by Study 1160.46, in which VTE and VTE-related death occurred among current smokers in 4.3% of the DE-treated patients compared to 1.1% of W-treated patients. This finding was not apparent in Studies 1160.63 or 1160.47. Inspection of the frequency data showed no especially high rates of VTE or VTE-related deaths, or of PE, associated either with particular subgroups receiving the same treatment or differences in the occurrence rates in subgroups receiving different treatments. Likewise, the Cox Regression analysis showed no additional interaction factors between treatment and subgroup (all p-values from the Chi-square tests for treatment interaction factor effect were >0.05).

Subgroups based on characteristics associated with the index event

Subgroup analyses were performed to detect potential interactions between the following 4 characteristics associated with the index event and: a) the primary outcome of VTE and VTE-related death, and b) the secondary outcome of PE:

- Asymptomatic PE at baseline
- Symptomatic PE as index event
- Open-label parenteral therapy for the index event (used ≤9 days or > 9 days);

Only one of the analyses detected a possible interaction between treatment and any of the 4 characteristics associated with the index event, either for VTE and VTE-related deaths or for PE; nominal p-values were all >0.10 except for asymptomatic PE at baseline in aVTEt Study 1160.46.

In aVTEt Study 1160.46, a possible interaction was detected between treatment and asymptomatic PE at baseline for those who experienced VTE or VTE-related death (p=0.0580). Among those without symptomatic PE at baseline, 23/881 (2.6%) of DE patients and 20/874 (2.3%) of warfarin patients, experienced VTE or VTE-related death. Among those with asymptomatic PE at baseline, 11/393 (2.8%) of DE patients and 12/391 (3.1%) of warfarin patients, experienced VTE or VTE-related deaths. This may be a chance finding since multiple analyses have been performed.

Risk factors for VTE

Subgroup analyses were conducted to detect potential interactions between treatment and medical histories known to constitute risk factors for recurrent VTE for a) the primary outcome of VTE and VTE-related death; b) the secondary outcome of PE; and c) VTE and VTE-related deaths.

- Active cancer at any time (at baseline or newly diagnosed during study)
- Previous VTE prior to index event
- Thrombophilia (Note: many patients were not tested for thrombophilia)
- History of venous insufficiency (in aVTEt studies only)
- History of prior significant coronary artery disease
- History of prior MI
- History of diabetes mellitus
- History of bleeding events (history of major or clinically relevant bleeding events, history of rectal bleeding, history of frequent nose bleeds, or history of hematuria)
- Idiopathic VTE (no identified risk factors such as active cancer at any time, previous VTE, thrombophilia, history of venous insufficiency, prolonged immobilization, long distance travel, surgery/trauma, recent systemic use of estrogens, and recent pregnancy).

There were no interactions between treatment and the other risk factors analyzed with the following exceptions, none of which were considered clinically important, and all of which may be chance findings since multiple comparisons have been made:

Of the patients without prior VTE, 44/1978 (2.2%) of DE patients and 51/2130 (2.5%) of warfarin patients were reported with the endpoint VTE or VTE-related death. Of those with prior VTE, 24/575 (4.2%) of DE patients and 11/524 (2.1%) of warfarin patients were reported with the endpoint VTE or VTE-related death.

In the pooled aVTEt Studies 1160.53 and 1160.46, a possible interaction was detected between treatment and history of prior coronary artery disease for VTE and VTE-related deaths (p=0.0445). Of those with prior coronary artery disease, 2/165 (1.2%) of DE patients and 9/184 (4.9%) of warfarin patients were reported with the endpoint VTE and VTE-related death.

No drug-drug interactions were detected between treatment and the 4 categories of concomitant medications analyzed:

- P-gp inhibitors
- ASA
- NSAIDS
- Anticoagulants

Nominal p-values were >0.10 for all analyses of drug-drug interactions with one exception. In aVTEt Study 1160.53, a possible interaction was detected between treatment and concomitant use of NSAIDs for those who experienced VTE or VTE-related death (p=0.1070). Among those who did not take NSAIDs concomitantly, 26/980 (2.7%) of DE patients and 30/1018 (2.9%) of warfarin patients, experienced VTE or VTE-related death. Among those who received NSAIDs concomitantly 8/294 (2.7%) of DE patients and 2/247 (0.8%) of warfarin patients experienced VTE-or VTE-related death.

Multivariate subgroup analyses

Multivariate subgroup analyses were conducted for the primary efficacy endpoint, centrally adjudicated VTE and VTE-related deaths, for the pooled aVTEt Studies 1160.46 and 1160.53. A Cox proportional hazards model included the factors age, gender, geographical region, race, BMI, and creatinine clearance as main effects and interaction with treatment. Age, BMI and creatinine clearance were included in the model as continuous variables. The final model was selected using the backward elimination technique with a p-value criterion of 0.2 for the likelihood ratio test. Main effects that had significant interactions were not removed from the model. Gender, BMI and race were eliminated from the final model. Pearson's correlation coefficient was used to assess correlation among age, BMI, and creatinine clearance to validate the variable selection procedure.

The Cox regression analyses indicated no interactions. Within the frequency tables, values over the 10% threshold had only very small numbers of patients in individual data cells, with no apparent trends and minimal difference between the treatment groups. The estimates of the HR for adjudicated VTE and VTE-related deaths for different ages derived from the final model decreased with increasing age, although the 95% CIs included 1.0.

Prevention Study 1160.47 (RE-MEDY)

Methods

Study 1160.47 (RE-MEDEDY, active-controlled study) evaluated the secondary prevention of recurrent VTE (sVTEp) (treatment duration: 6-36 months) and enrolled adult patients with acute symptomatic proximal DVT or PE who had received anticoagulant therapy for 3 to 12 months or who had completed participation in studies 1160.53 or 1160.46.

The study design and flowchart for the study is shown graphically below.

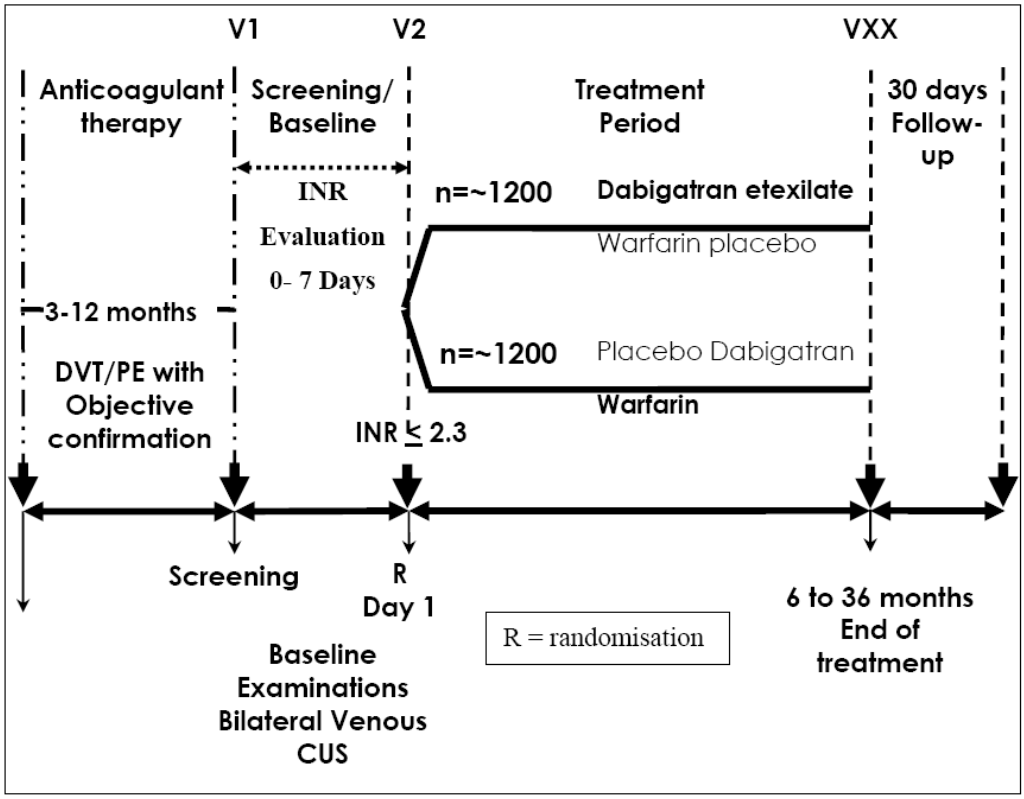


Figure 9.1: 1 Study flow chart of the RE-MEDY trial

Study participants

Adult patients (≥ 18 years) with objectively confirmed symptomatic uni- or bilateral DVT of the leg involving proximal veins or PE, treated with an approved anticoagulant therapy or with study drug taken during participation in the RE-COVER trial for 3 to 6 months at the time of screening, considered at increased risk of recurrent VTE (proximal veins are: trifurcation area, popliteal, superficial femoral, deep femoral, common femoral and iliac vein).

Following Protocol Amendment 2, dated 15 March 2007, the specified duration of prior anticoagulant therapy was changed to 3 to 12 months. Following Protocol Amendment 6, dated 12 December 2008, patients who had completed the RE-COVER II trial were allowed to enter into RE-MEDY.

Treatments

The investigational product in this trial was DE 150 mg b.i.d.. Warfarin was the active comparator. Table 9.4.1.1: 1 summarises the information about the investigational product used in this trial.

Table 9.4.1.1: 1 Dabigatran etexilate (investigational drug) and matching placebo

Name of substance	Dabigatran etexilate (BIBR 1048)	Matching Placebo
Pharmaceutical form	Capsule	Capsule
Source	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength	150 mg[1]	Not applicable
Batch number	Refer to Appendix 16.1.6	Refer to Appendix 16.1.6
Total daily dose	300 mg[1]	Not applicable
Duration of use	6 to 36 months[2]	6 to 36 months[2]
Route of administration	Oral	Oral
Posology	1-0-1	1-0-1

[1] Calculated as free base
[2] The planned treatment duration was 18 months according to the original protocol. The treatment duration was changed through Protocol Amendment 6 (dated 12 December 2008). Patients in Cohort 1 had a planned treatment duration of 18 months, patients in Cohort 2 had a planned treatment duration of >18 months, and patients in Cohort 3 had a planned treatment duration of <18 months.

Table 9.4.1.1: 2 summarises the information about the active comparator used in this trial.

Table 9.4.1.1: 2 Warfarin (active comparator) and matching placebo

Name of substance	Warfarin sodium	Matching Placebo
Pharmaceutical form	Tablet	Tablet
Source	IVAX Pharmaceuticals, Ireland	IVAX Pharmaceuticals, Ireland
Unit strength	1, 3, and 5 mg	Not applicable
Batch number	Refer to Appendix 16.1.6	Refer to Appendix 16.1.6
Total daily dose	Adjusted to maintain a target INR of 2.0 to 3.0	Adjusted to maintain a sham INR of 2.0 to 3.0
Duration of use	6 to 36 months[1]	6 to 36 months[1]
Route of administration	Oral	Oral
Posology	Adjusted to maintain a target INR of 2.0 to 3.0	Adjusted to maintain a sham INR of 2.0 to 3.0

[1] The planned treatment duration was 18 months according to the original protocol. The treatment duration was changed through Protocol Amendment 6 (dated 12 December 2008). Patients in Cohort 1 had a planned treatment duration of 18 months, patients in Cohort 2 had a planned treatment duration of >18 months, and patients in Cohort 3 had a planned treatment duration of <18 months.

Objectives

This trial aimed to demonstrate non-inferiority of DE compared with warfarin for the secondary prevention of symptomatic VTE. If non-inferiority could be demonstrated, this trial also aimed to establish superiority of DE over W.

Outcomes / endpoints

Primary endpoint

The primary efficacy endpoint was a composite of recurrent symptomatic VTE and deaths related to VTE. VTE was defined as the composite incidence of DVT of the leg (including the inferior vena cava) and PE. All recurrent VTEs required objective verification by definitive diagnostic evaluation. All suspected DVTs had to be confirmed by venous compression ultrasonography (CUS) or venography. All suspected PEs

required confirmation by one of the following: ventilation-perfusion (VQ) lung scan, pulmonary angiography, or spiral (helical) CT.

In case of death, autopsy was an additional way to confirm VTE. All objective tests for suspected VTE were to be centrally adjudicated by an Independent Central Adjudication Committee (ICAC/VTE). In addition, all deaths were to be reviewed for evidence of fatal PE or bleeding, and all events that contributed to the primary endpoint (or its components) were adjudicated. Adjudicated results were used in the analyses.

Secondary endpoints

Secondary efficacy endpoints are listed below.

- Composite of recurrent symptomatic VTE (fatal and non-fatal) and all deaths
- Symptomatic DVT
- Symptomatic PE (fatal or non-fatal)
- Deaths related to VTE (i.e. fatal PE)
- All deaths

Statistical methods and sample size

The tests for non-inferiority and superiority were performed in hierarchical order. The non-inferiority margins were chosen to be 2.85 for the hazard ratio (δr) and 2.8% for the risk difference (δd). By requiring fulfilment of both margins, it was assured that DE preserved at least 70% of the warfarin effect versus placebo (based on the point estimate) with regard to the hazard ratio and at least 2/3 with regard to the risk difference (based on the lower bound of 95% confidence interval) if proven to be not inferior to W. This margin required a sample size of 1000 patients per group (a total of 2000) to have a power of at least 85% with one-sided α=0.025.

Please also refer to description of statistical methods for the aVTEt studies.

Randomisation

An IVRS was used to randomly assign patients to one of 2 treatment groups with a randomisation ratio of 1:1. Randomisation was stratified into 4 cells resulting from the combination of 2 stratification factors active cancer (yes/no) and symptomatic PE (yes/no). To prevent unequal treatment allocation, blocks of 4 were used and the blocks were assigned to strata. Active cancer was defined as a diagnosis of cancer (other than basal-cell or squamous-cell carcinoma of the skin) within 5 years before the enrolment; any treatment for cancer within 5 years; or recurrent or metastatic cancer. The randomisation schedule was generated using validated software and verified by a Boehringer Ingelheim statistician who was not involved in the planning or performance of the trial. The access to the randomization code was to be supervised by Clinical Trial Support (Medical Data Services).

Blinding (masking)

Study 1160.47 employed a double-blind design; neither the patient nor the investigator was informed about the allocated treatment. In addition, the personnel involved in the conduct or assessment of the study were unaware of the treatment allocation for the entire duration of the study until the final database was locked. Since the 2 treatments differed in their appearance, blinding was achieved by using a double-dummy design with DE-matching placebo capsules and W-matching placebo tablets. INR values

had to be monitored to guide the warfarin therapy; a sham INR procedure was used to prevent unintentional unblinding. INR measurements were to be performed using a POC device or alternative.

Results

Participant flow

RE-MEDY was an international, multi-centre study. Overall, 2918 patients were enrolled in 261 centres in 33 countries worldwide. The majority of randomized patients came from European countries. Centres in Asian countries joined later in the trial and recruited more patients towards the end of the trial. Of the 2918 patients enrolled, 52 patients (1.8%) were not randomised. The most frequent reason for non-randomisation was a violation of the inclusion or exclusion criteria (1.1%). A total of 2866 patients were randomised to either DE (1435 patients) or warfarin (1431 patients). Of the randomised patients, 10 patients were not treated with study medication (5 patients of each treatment group): 5 patients refused to take study medication and 1 patient was non-compliant with the study protocol (patient no. 9469 took part in a different clinical trial). Four patients were reported with 'other' reasons. Of the 2856 treated patients, 93.8% completed the planned observation time, and there were no between-group differences for those patients who did not (Table 10.1: 2).

Table 10.1: 2 Patient disposition at the end of study participation / all patients

	Dabigatran etexilate n (%)	Warfarin n (%)	Total n (%)
Enrolled patients			2918
Not randomised patients			52
Randomised patients	1435	1431	2866
Patients not treated	5	5	10
Treated patients[1]	1430 (100.0)	1426 (100.0)	2856 (100.0)
Completed planned observation time[2]	1348 (94.3)	1331 (93.3)	2679 (93.8)
Not completed planned observation time[2]	82 (5.7)	95 (6.7)	177 (6.2)
Adverse events	23 (1.6)	22 (1.5)	45 (1.6)
Worsening of disease under study[3]	2 (0.1)	2 (0.1)	4 (0.1)
Worsening of other pre-existing disease	3 (0.2)	4 (0.3)	7 (0.2)
Other AE	18 (1.3)	16 (1.1)	34 (1.2)
Non-compliant with protocol	9 (0.6)	13 (0.9)	22 (0.8)
Lost to follow-up[4]	3 (0.2)	11 (0.8)	14 (0.5)
Consent withdrawn	29 (2.0)	17 (1.2)	46 (1.6)
Other	18 (1.3)	32 (2.2)	50 (1.8)

[1] Patients who received at least 1 dose of study medication
[2] The investigator was to record on the 'Trial completion' page of the CRF if the patient had completed the planned observation time or the reason for non-completion, which was to be selected from a list of pre-defined reasons on this CRF page.
[3] Symptomatic DVT or PE as based on the assessment of the investigator, including an extension of the existing thrombus or a new suspected event
[4] The sponsor became aware of the death of 1 patient (no. 8325) after he had withdrawn his consent to be further followed-up for vital status. This death is not counted towards any efficacy or safety analyses in this trial.

Source data: Table 15.1.1: 5

Recruitment

The first patient was enrolled into this study on 26 July 2006; the last visit of the last patient in this study was on 8 October 2010.

Conduct of the study

The original trial protocol (dated 20 January 2006) was amended globally on 9 occasions. As per original trial protocol, INR measurements during the study were to be performed using a sponsor-supplied POC device, which provided an encryptet INR. Study site personnel had to obtain an unencrypted INR value by calling into an IVRS system (true INR for patients randomized to warfarin / sham INR for patients randomized to warfarin placebo).

Protocol Amendment 1 allowed alternative means of INR monitoring if use of the POC device was not feasible. In such cases, the INR could be measured in an unblinded manner by authorized personnel who then forwarded the unblended INR value to the IVRS, while strictly maintaining the blinded status of all study site personnel involved in the conduct of the study (other than those assessing INRs in an unblinded manner). In addition, Amendment 1 introduced several clarifications and corrections of minor errors.

Protocol Amendment 2 extended the required time period of previous anticoagulant therapy prior to entry into the RE-MEDY trial from 3 to 6 months to 3 to 12 months. This change follows the guidelines of the 7th ACCP Consensus Conference on Antithrombotic Therapy, which state that for patients at highest risk of recurrent VTE, a minimum of 6 to 12 months therapy is recommended. Secondly, the investigator was given the option of using bridging therapy with LMWH for patients who had just completed participation in RE-COVER or RE-COVER II and were beginning participation in RE-MEDY.

Protocol Amendment 3 extended the recruitment period by 7 months, thereby changing the planned end of trial date from December 2009 to July 2010. The schedule of Liver Function Test (LFT) Monitoring was changed, with Mandatory Visits 5, 7 and 8 being replaced by mandatory phone calls.

Protocol Amendment 4 was introduced with the main purpose to contraindicate the concomitant administration of quinidine. A warning was added regarding the potential role of P-glycoprotein (P-gp) inhibition on DE plasma levels and subsequent tolerability.

Protocol Amendment 5 provided additional guidance regarding the management of patients who required surgery or invasive procedures during the treatment period. Clarifications were made regarding the discontinuation of study treatment for patients with severe renal dysfunction.

Protocol Amendment 6 changed the planned treatment duration from 18 months to 6 to 36 months, and the number of patients to be recruited was increased, with recruitment to occur through no later than 31st of December 2009. Based on the protocol-specified review of the overall primary endpoint event rate, this amendment was undertaken to ensure a power of 80 %. As a result, 3 'cohorts' of patients were included in the study. First, patients who completed the trial prior implementation of this amendment or those not willing to consent to participate as per this amendment; such patients had a planned treatment duration of 18 months. Second, patients who were randomised prior to implementation of this amendment and who consented to trial participation as per this amendment; such patients had a planned treatment duration of between 18 and 36 months. Third, patients randomised after implementation of this amendment but enrolled within 18 months of the planned study close-out; these patients had a planned treatment duration of 6 to <18 months. Because of the changes in planned trial duration and patient recruitment, the visit schedule was changed. Protocol Amendment 6 specified the statistical

methods to be used for non-inferiority and superiority testing in this trial given the changes in the planned treatment duration and patient recruitment. The second major change introduced by Protocol Amendment 6 was to allow inclusion of patients of RE-COVER II (Study 1160.46), a replicate trial of RE-COVER. Thirdly, clarifications regarding physical examination requirements were provided.

Protocol Amendment 7, 8 and 9 provided guidance on the concomitant administration of the P-gp inhibitor verapamil (Protocol Amendment 7), contraindication of the systemic use of the P-gp inhibitor ketokonazole and guidance regarding co-administration of the P-gp inducer rifampicin and an updated list of substances tested in drug-drug interaction studies with DE (Amendment 8), and updated guidance for administration of strong P-gp-inducers stating that rifampicin and other strong P-gp inhibitors, such as carbamazepine and St. John's Wort, were to be used with caution and only when no suitable alternative is available (Amendment 9).

Baseline data

The treatment groups were balanced with regard to their demographics and baseline characteristics, with an overall mean age of 54.6 years (range: 18 to 93 years). More than half of all patients (61.0%) were male and most patients (90.1%) were of white ethnicity (Table 11.2.1: 1). Concomitant medication is presented in Tables 11.2.6.2:1-4.

Table 11.2.1: 1 Demographic data / FAS as randomised

	Dabigatran etexilate		Warfarin		Total	
Patients, n (%)	1430	(100.0)	1426	(100.0)	2856	(100.0)
Sex, n (%)						
Male	871	(60.9)	871	(61.1)	1742	(61.0)
Female	559	(39.1)	555	(38.9)	1114	(39.0)
Age, mean (SD) [years]	55.4 (15.0)		53.9 (15.3)		54.6 (15.2)	
Age categories, n (%)						
18 to <40 years	237	(16.6)	269	(18.9)	506	(17.7)
40 to <50 years	250	(17.5)	291	(20.4)	541	(18.9)
50 to <65 years	500	(35.0)	459	(32.2)	959	(33.6)
65 to <75 years	303	(21.2)	288	(20.2)	591	(20.7)
≥75 years	140	(9.8)	119	(8.3)	259	(9.1)
Race, n (%)						
White	1288	(90.1)	1284	(90.0)	2572	(90.1)
Black	29	(2.0)	28	(2.0)	57	(2.0)
Asian	113	(7.9)	114	(8.0)	227	(7.9)
Geographical region, n (%)						
Western Europe[1]	389	(27.2)	395	(27.7)	784	(27.5)
Eastern Europe[2]	476	(33.3)	499	(35.0)	975	(34.1)
North America[3]	165	(11.5)	174	(12.2)	339	(11.9)
Latin America[4]	99	(6.9)	98	(6.9)	197	(6.9)
Asia[5]	107	(7.5)	108	(7.6)	215	(7.5)
Other[6]	194	(13.6)	152	(10.7)	346	(12.1)
Weight, mean (SD) [kg]	86.1 (19.3)		86.0 (18.9)		86.0 (19.1)	
BMI, mean (SD) [kg/m^2]	29.15 (5.65)		29.01 (5.75)		29.08 (5.70)	
Creatinine clearance[7], mean (SD) [mL/min]	104.2 (38.6)		106.6 (37.9)		105.4 (38.3)	
Creatinine clearance categories[7], n (%)						
<30 mL/min	0	(0.0)	4	(0.3)	4	(0.1)
30 to <50 mL/min	59	(4.1)	45	(3.2)	104	(3.6)
50 to <80 mL/min	328	(22.9)	289	(20.3)	617	(21.6)
≥80 mL/min	1031	(72.1)	1072	(75.2)	2103	(73.6)
Smoking history, n (%)						
Never smoked	814	(56.9)	829	(58.1)	1643	(57.5)
Ex-smoker	393	(27.5)	366	(25.7)	759	(26.6)
Current smoker	223	(15.6)	231	(16.2)	454	(15.9)

[1] Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden, UK
[2] Bulgaria, Czech Republic, Hungary, Poland, Russia, Slovakia, Turkey, Ukraine
[3] Canada, USA
[4] Argentina, Brazil, Mexico
[5] China, India
[6] Australia, Israel, New Zealand, South Africa
[7] As assessed by the central laboratory

Source data: Table 15.1.4: 1, Table 15.1.4: 2

Table 11.2.6.2: 1 Platelet inhibitors, ASA, NSAIDs, and other antithrombotic agents used concomitantly with study drug / FAS as randomised

	Dabigatran etexilate		Warfarin		Total	
Patients, n (%)	1430	(100.0)	1426	(100.0)	2856	(100.0)
Patients with at least 1 concomitant antithrombotic medication, platelet inhibitors, or NSAIDs	321	(22.4)	353	(24.8)	674	(23.6)
NSAIDs	236	(16.5)	279	(19.6)	515	(18.0)
ASA	106	(7.4)	86	(6.0)	192	(6.7)
Highest daily dose of ASA[1]						
ASA dose ≤100 mg/day	89	(6.2)	69	(4.8)	158	(5.5)
ASA dose >100 mg/day	12	(0.8)	14	(1.0)	26	(0.9)
ASA with missing dose information	7	(0.5)	3	(0.2)	10	(0.4)
Platelet inhibitors excluding ASA	98	(6.9)	80	(5.6)	178	(6.2)
Other antithrombotic agents	4	(0.3)	5	(0.4)	9	(0.3)

Derived from free-text field entries on the 'Concomitant therapy' page of the CRF
Medication was not considered as concomitant if it was taken during a temporary interruption of study drug
[1] For patients with non-overlapping periods of intake of ASA with different daily doses, the highest daily dose of each ASA intake was considered; thus, patients could be counted more than once in this table

Source data: Table 15.1.4: 7

Table 11.2.6.2: 2 Concomitant use of restricted medication / FAS as randomised

	Dabigatran etexilate		Warfarin		Total	
Patients, n (%)	1430	(100.0)	1426	(100.0)	2856	(100.0)
Patients with any restricted medication	233	(16.3)	200	(14.0)	433	(15.2)
Glycoprotein IIb/IIIa inhibitors	98	(6.9)	80	(5.6)	178	(6.2)
LMWH	60	(4.2)	55	(3.9)	115	(4.0)
NSAIDs with half-life >12h	29	(2.0)	22	(1.5)	51	(1.8)
Corticosteroids	29	(2.0)	14	(1.0)	43	(1.5)
Vitamin K antagonists	19	(1.3)	15	(1.1)	34	(1.2)
UFH	14	(1.0)	17	(1.2)	31	(1.1)
ASA dose >100 mg/day	12	(0.8)	14	(1.0)	26	(0.9)
Clopidogrel or ticlopidine	9	(0.6)	1	(0.1)	10	(0.4)
Other heparins	1	(0.1)	6	(0.4)	7	(0.2)
Systemic ketoconazole	2	(0.1)	0	(0.0)	2	(0.1)
Dextran	1	(0.1)	1	(0.1)	2	(0.1)
Fondaparinux	0	(0.0)	2	(0.1)	2	(0.1)
Direct thrombin inhibitors	0	(0.0)	1	(0.1)	1	(0.0)
Thrombolytics	0	(0.0)	1	(0.1)	1	(0.0)
Quinidine	0	(0.0)	0	(0.0)	0	(0.0)

Derived from free-text field entries on the 'Concomitant therapy' page of the CRF
Medication was not considered as concomitant if it was taken during a temporary interruption of study drug

Source data: Table 15.1.4: 8

Table 11.2.6.2: 3 Use of cardiovascular medication of special interest concomitantly with study drug / FAS as randomised

	Dabigatran etexilate		Warfarin		Total	
Patients, n (%)	1430	(100.0)	1426	(100.0)	2856	(100.0)
Patients with any cardiovascular medication of special interest	758	(53.0)	763	(53.5)	1521	(53.3)
Agents acting on the RAAS	424	(29.7)	369	(25.9)	793	(27.8)
Vasodilators	339	(23.7)	364	(25.5)	703	(24.6)
Serum lipid reducing agents	269	(18.8)	315	(22.1)	584	(20.4)
Beta-blocking agents	242	(16.9)	220	(15.4)	462	(16.2)
Calcium channel blockers	163	(11.4)	153	(10.7)	316	(11.1)
Inotropic agents	44	(3.1)	42	(2.9)	86	(3.0)
Cardiac glycosides	34	(2.4)	36	(2.5)	70	(2.5)
Antiarrhythmic agents	7	(0.5)	5	(0.4)	12	(0.4)

Derived from free-text field entries on the 'Concomitant therapy' page of the CRF
Medication was not considered as concomitant if it was taken during a temporary interruption of study drug
RAAS: renin-angiotensin-aldosterone system

Source data: Table 15.1.4: 9

Table 11.2.6.2: 4 Concomitant use of P-gp inhibitors and P-gp inducers / FAS as randomised

	Dabigatran etexilate		Warfarin		Total	
Patients, n (%)	1430	(100.0)	1426	(100.0)	2856	(100.0)
Patients with any P-gp inhibitor / inducer therapy	50	(3.5)	40	(2.8)	90	(3.2)
Patients with any P-gp inhibitor therapy[1]						
Verapamil	17	(1.2)	18	(1.3)	35	(1.2)
Amiodarone	11	(0.8)	8	(0.6)	19	(0.7)
Cyclosporine A	2	(0.1)	2	(0.1)	4	(0.1)
Tacrolimus	2	(0.1)	2	(0.1)	4	(0.1)
Ketoconazole	2	(0.1)	0	(0.0)	2	(0.1)
Saquinavir	0	(0.0)	1	(0.1)	1	(0.0)
Patients with any P-gp inducer therapy[2]						
Carbamazepine	12	(0.8)	9	(0.6)	21	(0.7)
Rifampicin	4	(0.3)	2	(0.1)	6	(0.2)

Derived from free-text field entries on the 'Concomitant therapy' page of the CRF
Including medication that was taken at least once during the intake of study drug
Medication was not considered as concomitant if it was taken during a temporary interruption of study drug
It was checked for pre-defined P-gp inhibitors / inducers as follows:
[1]P-gp inhibitors (amiodarone, cyclosporine A, dronedarone, itraconazole, ketoconazole, nelfinavir, quinidine, ritonavir, saquinavir, tacrolimus, valspodar, verapamil)
[2] P-gp inducers (carbamazepine, rifampicin, St John's wort, St John's wort plus)

Source data: Table 15.1.4: 10

Compliance: The rates of non-compliance with DE / matching placebo capsules were low in both treatment groups. The percentage of non-compliant patients was 2.0% in the DE treatment group and 1.8% in the warfarin group; the weighted mean compliance for the on-treatment period was 97.1% in the DE group and 96.7% in the warfarin group. Mean TTR during the first month of therapy was 51.9%. The mean percentage of patient time in the INR target range increased over time. The mean and median TTR over the entire study was 61.5% and 65.3%, respectively. For an overview of the percentage of patients' time within TTR in the different time periods refer to Table 11.3: 1.

Table 11.3: 1 Percentage of time in the INR target range of 2.0 to 3.0 / FAS as treated, patients in the warfarin treatment group

		Percentage of time (%)								
		INR <2			2≤ INR ≤3			INR >3		
Time since first warfarin intake	Patients n	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
First month	1216	24.2	(34.89)	0.0	51.9	(38.01)	52.2	23.8	(33.93)	0.0
Month 2	1365	24.8	(34.26)	0.0	58.6	(36.26)	63.3	16.6	(27.65)	0.0
Month 3	1350	24.1	(34.51)	0.0	60.9	(36.88)	66.7	15.0	(26.95)	0.0
Month 4	1341	23.8	(34.69)	0.0	62.1	(37.05)	70.0	14.2	(26.59)	0.0
Month 5	1324	22.6	(33.96)	0.0	62.6	(36.83)	69.2	14.8	(27.56)	0.0
Month 6	1305	22.6	(34.04)	0.0	63.7	(36.68)	73.3	13.7	(26.33)	0.0
Months 7-9	1286	21.2	(26.66)	12.1	65.1	(28.86)	68.9	13.6	(20.59)	0.0
Months 10-12	1108	21.0	(27.50)	9.5	64.3	(30.07)	68.9	14.7	(21.84)	0.0
Months 13-15	930	21.3	(26.84)	11.1	65.7	(28.65)	70.0	13.0	(19.04)	0.0
Months 16-18	859	19.9	(28.17)	4.9	65.8	(30.43)	70.0	14.2	(22.23)	0.0
Months 19-21	309	18.4	(28.00)	0.0	64.9	(32.67)	72.1	16.7	(26.71)	0.0
Months 22-24	196	16.2	(25.18)	1.4	68.8	(28.47)	72.6	15.0	(20.95)	0.0
Months 25-27	137	18.2	(26.10)	5.8	70.5	(27.50)	71.8	11.3	(17.52)	0.0
Months 28-30	67	12.7	(18.01)	0.0	70.0	(24.22)	69.3	17.3	(20.83)	9.5
Months 31-33	21	20.4	(30.25)	0.0	69.8	(30.88)	77.4	9.7	(21.35)	0.0
Overall	1403	23.3	(21.47)	17.3	61.5	(21.84)	65.3	15.2	(14.60)	12.2

Time categories: 'First month' from 1 week after first warfarin intake to Day 30; 'Month 2' from Day 31 to Day 60; 'Month 3' from Day 61 to Day 90; 'Month 4' from Day 91 to Day 120; 'Month 5' from Day 121 to Day 150; 'Month 6' from Day 151 to Day 180; 'Months 7-9' from Day 181 to Day 270; "Months 10-12' from Day 271 to Day 360; 'Months 13-15' from Day 361 to Day 450; 'Months 16-18' from Day 451 to Day 540, 'Months 19-21' from Day 541 to Day 630; 'Months 22-24' from Day 631 to Day 720, 'Months 25-27' from Day 721 to Day 810; 'Months 28-30' from Day 811 to Day 900, 'Months 31-33 from Day 901 to Day 990.

Source data: Table 15.1.5: 3

Outcomes and estimation

The number of patients with events contributing to the primary endpoint during the planned treatment period was 26 in the DE group and 18 in the warfarin group. The primary outcome event was most commonly symptomatic DVT (17 vs. 13 patients), followed by symptomatic PE (10 vs. 5 patients). One DE patient had 2 primary outcome events at the same day (while no warfarin patient did): patient no. 7275 had a symptomatic DVT and a symptomatic PE at the same day. Two patients (1 in each treatment group) were reported with a VTE-related death (i.e. fatal PE): patient no. 7275 (DE group) died 3 days after the onset of the symptomatic DVT and PE; patient no. 9100 (W group) died 1 month after the onset of a symptomatic PE. For both patients, the onset of the symptomatic VTE event (and not the date of death) was counted in the time- to-event analysis of the primary endpoint. A summary of patients with events and events contributing to the primary endpoint is given in Table 11.4.1.1.1: 1.

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with at least 1 event[1], n		
VTE and VTE-related deaths	26	18
Symptomatic DVT	17	13
Symptomatic PE	10	5
Fatal PE	1	1
Events, n		
VTE and VTE-related deaths	27	18
Symptomatic DVT	17	13
Symptomatic PE	10	5
Fatal PE	1	1

[1] Patients who were considered in the primary analysis. For patients with multiple events that were centrally confirmed, only the first event was used for the time-to-event analysis of the primary endpoint. Each event was used independently for the analysis of the components of the composite primary endpoint.

Source data: Table 15.2.1.3.1: 3 and 15.2.1.3.1: 4

The 44 patients with primary outcome events during the planned treatment period were assigned to the cohorts as follows: 32 patients were in Cohort 1 (DE: 18 patients, W: 14 patients), 7 patients were in Cohort 2 (4 vs. 3 patients), and 5 patients were in Cohort 3 (4 vs. 1 patients). Because of the low number of events in Cohorts 2 and 3, not all strata and cohorts were evaluable separately as planned for the meta-analysis approach of the primary analysis. Cohorts 1 and 2 were pooled to obtain the risk differences per stratum; for Cohort 3 the risk difference was estimated overall and not per stratum. The hazard ratio between DE and warfarin was estimated within each cohort (with treatment and symptomatic PE as factors in the Cox regression model) as planned.

The hazard ratio of the primary endpoint of DE versus warfarin was 1.44 (95% CI 0.78, 2.64). Since the upper bound of the confidence interval was below the pre-defined non-inferiority margin of 2.85 (p-value for non-inferiority: 0.0137), the null hypothesis of inferiority of DE versus warfarin could be rejected. Based on the results for the hazard ratio, it was concluded that DE was non-inferior to W. Table 11.4.1.1.1: 2 summarises the results.

Table 11.4.1.1.1: 2 Hazard ratio of dabigatran etexilate vs. warfarin for the composite of recurrent symptomatic VTE and death related to VTE during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	26	18
Hazard ratio vs. warfarin[1] (95% CI)	1.44 (0.78, 2.64)	
p-value (non-inferiority)	0.0137	
p-value (superiority)[2]	0.2424	

Events were taken into account up to the end of the planned treatment period.
[1] The hazard ratio was estimated using a meta-analysis approach: first hazard ratios were estimated within each cohort using a Cox regression model adjusted for the factors treatment and baseline stratification factor (symptomatic PE as qualifying event). The overall hazard ratio was calculated by pooling the hazard ratios across the cohorts with inverse variance weighting of by-cohort hazard ratios.
[2] Two-sided p-value

Source data: Table 15.2.1.1.1: 2

The cumulative risk for the primary endpoint at 18 months was 1.74% in the DE group and 1.38% in the warfarin group (Table 11.4.1.1.1: 3). The risk difference for DE vs. W was 0.38% (95% CI -0.50, 1.25). The upper limit of the confidence interval of the risk difference was below the pre-defined non-inferiority margin of 2.8%; the p-value for the test for non-inferiority was <0.0001. The null hypothesis of inferiority of DE versus warfarin could be rejected based on the evaluation of the risk difference. Thus, it

could be demonstrated based on both the hazard ratio and risk difference that DE was non-inferior to W. Table 11.4.1.1.1: 3 summarizes the results.

Table 11.4.1.1.1: 3 Risk difference of dabigatran etexilate vs. warfarin at 18 months of the composite of recurrent symptomatic VTE and death related to VTE during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	22	17
Cumulative risk (%)[1]	1.74	1.38
Risk difference vs. warfarin (%)[2] (95% CI)	0.38 (-0.50, 1.25)	
p-value (non-inferiority)	<0.0001	
p-value (superiority)[3]	0.4013	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using weighted KM estimate across the 3 cohorts without stratification
[2] The risk difference was estimated using a meta-analysis approach: Cohorts 1 and 2 were pooled because of the low number of events; risk differences were estimated within each stratum (symptomatic PE as qualifying event) using standard KM estimates for the pooled Cohorts 1 and 2; then risk differences were pooled across strata using the weighted average of the KM estimates. The risk difference of Cohort 3 was estimated based on KM estimates of pooled strata. The overall risk difference was calculated as weighted KM estimates across Cohorts 1 and 2, and Cohort 3.
[3] Two-sided p-value

Source data: Table 15.2.1.1.1: 1

Since non-inferiority of DE versus warfarin was demonstrated for both hazard ratio and risk difference, superiority was investigated. Superiority of DE over warfarin for the primary endpoint could not be demonstrated. The KM curves for the primary endpoint together with the number of patients at risk are shown in Figure 11.4.1.1.1: 1.

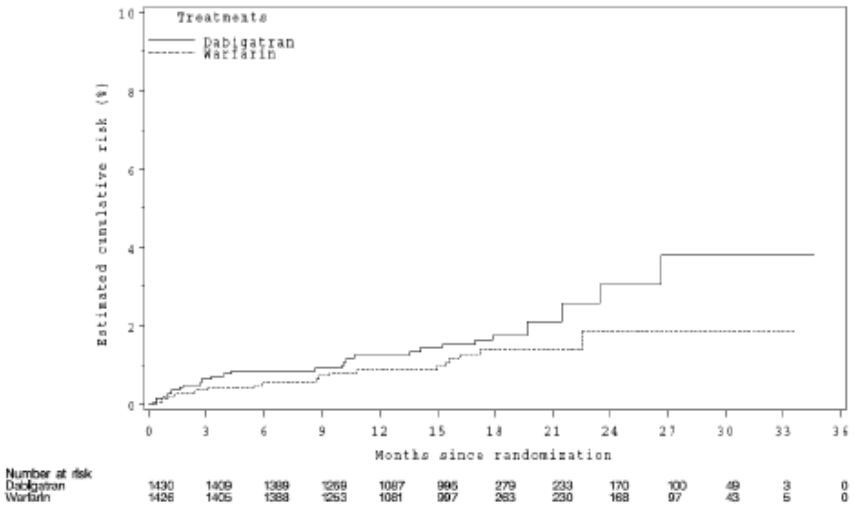


Figure 11.4.1.1.1: 1 Time to the composite of recurrent symptomatic VTE and death related to VTE, based on centrally adjudicated events / FAS as randomised

Events were taken into account up to the end of the planned treatment period

Source data: Figure 15.2.1.1.3: 1

Ancillary analyses

Primary endpoint using pooled cohorts

As a sensitivity analysis, the primary endpoint was analysed after pooling all 3 cohorts. The analysis was performed using the same censoring principles and the same patient set ('FAS as randomised') as for the

primary endpoint. The hazard ratio between DE and warfarin was estimated overall, with treatment, cohort, and baseline stratification factors (cancer at baseline and symptomatic PE) as factors in the Cox regression model. The hazard ratio of DE versus warfarin for the primary endpoint using pooled cohorts was 1.47 (95% CI 0.80, 2.68), see Table 11.4.1.1.2: 1. Both the point estimate and the confidence interval were similar to the results of the primary analysis.

Table 11.4.1.1.2: 1 Hazard ratio of dabigatran etexilate vs. warfarin for the composite of recurrent symptomatic VTE and death related to VTE during the planned treatment period, based on centrally adjudicated events and based on pooled cohorts/ FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	26	18
Hazard ratio vs. warfarin[1] (95% CI)	1.47 (0.80, 2.68)	

Events were taken into account up to the end of the planned treatment period
[1] The Hazard ratio was calculated across pooled cohorts, using a Cox regression model with the factors treatment, cohort, baseline stratification factors (active cancer at baseline, symptomatic PE as qualifying event), and the interaction of active cancer and symptomatic PE.

Source data: Table 15.2.1.1.2: 2

The risk difference between DE and warfarin was first to be estimated for each stratum separately. Because of the low number of events, not all strata were evaluable separately. The stratification variable 'active cancer at baseline' would have resulted in strata without events. Therefore only the 2 strata from the stratification variable 'symptomatic PE as qualifying event' were considered in the analysis. The cumulative risk at 18 months was 1.74% in the DE group and 1.38% in the W group (Table 11.4.1.1.2: 2). The risk difference between DE and W was 0.26% (95% CI -0.72, 1.23). The cumulative risks and risk differences by stratum were comparable with the results by stratum for the primary analysis, again with the confidence interval in both strata including 0.0.

Table 11.4.1.1.2: 2 Risk difference of dabigatran etexilate vs. warfarin at 18 months of the composite of recurrent symptomatic VTE and death related to VTE during the planned treatment period, based on centrally adjudicated events and based on pooled cohorts / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	22	17
Cumulative risk (%)[1]	1.74	1.38
Risk difference vs. warfarin (%)[2] (95% CI)	0.26 (-0.72, 1.23)	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using KM estimate across the 3 cohorts without stratification
[2] The Risk difference was calculated across pooled cohorts, using the weighted average of KM estimates at 18 months across the 2 strata from the stratification variable 'symptomatic PE as qualifying event'. The stratification variable 'active cancer at baseline' could not be used because there would have been strata with no events.

Source data: Table 15.2.1.1.2: 1

Primary endpoint by stratification factor (active cancer at baseline, initial symptomatic PE)

The primary endpoint was also assessed by stratification factor and stratum. As expected, the proportion of patients with a primary VTE event was higher for patients with initial symptomatic PE than for patients without PE. The hazard ratios for the primary endpoint were 2.10 (95% CI 0.85, 5.20) in patients with initial symptomatic PE and 1.07 (95% CI 0.47, 2.43) in patients without PE. The hazard ratios for the primary endpoint were 1.91 (95% CI 0.17, 21.06) in patients with cancer and 1.42 (95% 0.76, 2.64) in patients without cancer at baseline (Table 11.4.1.1.2: 3). For all 4 strata, the 95% confidence intervals

for the hazard ratios included 1, indicating that the observed numerical differences between treatment groups were not statistically significant.

The cumulative risk for the primary endpoint was higher for patients with initial symptomatic PE (DE: 2.9%, W: 1.4%) than for patients without PE (1.3% vs. 1.2%). Patients with active cancer at baseline had a higher cumulative risk for the primary endpoint (DE: 3.3%, W: 1.7%) than patients without active cancer at baseline (1.8% vs. 1.2%), which was also expected. Considering the 4 strata, the cumulative risks were highest in the stratum of patients with initial symptomatic PE and active cancer at baseline, and lowest in patients without PE and cancer, as expected (Table 11.4.1.1.2: 3). Within each stratum, there were numerical between-group differences in the numbers of patients with events and in the cumulative risks.

Table 11.4.1.1.2: 3 Summary of the composite of recurrent symptomatic VTE and death related to VTE by stratification factors and stratum, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate		Warfarin		
	Total n	Incidence[1] n (%)	Total n	Incidence[1] n (%)	HR vs. warfarin (95% CI)
Patients	1430	26 (1.8)	1426	18 (1.3)	
Initial symptomatic PE[2]					
No	939	12 (1.3)	923	11 (1.2)	1.07 (0.47, 2.43)
Yes	491	14 (2.9)	503	7 (1.4)	2.10 (0.85, 5.20)
Active cancer at baseline[3]					
No	1370	24 (1.8)	1367	17 (1.2)	1.42 (0.76, 2.64)
Yes	60	2 (3.3)	59	1 (1.7)	1.91 (0.17, 21.06)
Sympt. PE with cancer[4]	25	1 (4.0)	23	0 (0.0)	
Sympt. PE, no cancer[4]	466	13 (2.8)	480	7 (1.5)	1.95 (0.78, 4.90)
No sympt. PE, with cancer[4]	35	1 (2.9)	36	1 (2.8)	0.98 (0.06, 15.62)
No sympt. PE, no cancer[4]	904	11 (1.2)	887	10 (1.1)	1.08 (0.46, 2.54)

Events were taken into account up to the end of the planned treatment period
Based on the presence of initial symptomatic PE or active cancer at baseline as recorded on the CRF (tick box).
HR = hazard ratio, sympt. PE = symptomatic PE as qualifying event, cancer = active cancer at baseline
[1] Number of patients with events
[2] Cox regression, adjusted for the factor symptomatic PE, treatment interaction, and cohort
[3] Cox regression, adjusted for the factor active cancer at baseline, treatment interaction, and cohort
[4] Cox regression, adjusted for the factors active cancer at baseline, symptomatic PE, treatment interaction, and cohort

Source data: Table 15.2.1.1.2: 2 and 15.2.1.1.2: 3

Primary endpoint using unadjusted models

An unadjusted analysis was performed based on pooled cohorts, using the same censoring principles and the same patient set ('FAS as randomised') as the primary analysis. The hazard ratio between DE and warfarin was estimated overall, using an unadjusted Cox regression model. In addition, the incidence density was calculated as the ratio of the number of patients with an event and the total time at risk. The resulting values between the treatment groups were compared between treatment groups and expressed as relative risk. The hazard ratio of DE versus warfarin for the primary endpoint using pooled cohorts and an unadjusted Cox model was 1.43 (95% CI 0.79, 2.62). Both the point estimate and the confidence interval were similar to the results of the primary analysis. The incidence density was 1.3 events per 100 patient-years in the DE group and 0.91 events per 100 patient-years in the warfarin group. The relative risk for DE vs. warfarin was 1.43 (95% CI 0.79, 2.61).

On-treatment analysis

The on-treatment analysis was performed using the 'FAS as treated' and using the same statistical methodology as for the pooled analysis. However, all patients were censored on the day following the day of last intake of study drug. Twenty patients in the DE group and 15 patients in the warfarin group had a primary outcome event while on-treatment. The on-treatment event was symptomatic DVT in 14 patients in the DE group and in 11 patients in the warfarin group; symptomatic PE in 7 and 4 patients, respectively, and VTE-related death (i.e. fatal PE) in 1 patient in the DE group. The on-treatment hazard ratio of DE versus warfarin for the primary endpoint was 1.35 (95% CI 0.69, 2.64), see Table 11.4.1.1.3: 1. Both the point estimate and the confidence interval were similar to the results of the primary analysis. Note that the upper boundary of the confidence interval was below the non-inferiority margin defined for the primary analysis. Thus, the on-treatment analysis was consistent with the primary analysis.

Table 11.4.1.1.3: 1 Hazard ratio of dabigatran etexilate vs. warfarin for the composite of recurrent symptomatic VTE and death related to VTE during the on-treatment period, based on centrally adjudicated events / FAS as treated (on-treatment analysis)

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	20	15
Hazard ratio vs. warfarin[1] (95% CI)	1.35 (0.69, 2.64)	

Events were taken into account up to the end of the planned treatment period
[1] The Hazard ratio was calculated across pooled cohorts, using a Cox regression model with the factors treatment, cohort, baseline stratification factors (active cancer at baseline, symptomatic PE as qualifying event), and the interaction of active cancer and symptomatic PE.

Source data: Table 15.2.1.2.1: 2

The cumulative risk at 18 months was 1.45% in the DE group and 1.24% in the warfarin group (Table 11.4.1.1.3: 2). The risk difference between DE and warfarin was 0.14% (95% CI -0.81, 1.09) and therefore slightly smaller than in the primary analysis.

Table 11.4.1.1.3: 2 Risk difference of dabigatran etexilate vs. warfarin at 18 months of the composite of recurrent symptomatic VTE and death related to VTE during the on-treatment period, based on centrally adjudicated events / FAS as treated (on-treatment analysis)

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	17	14
Cumulative risk (%)[1]	1.45	1.24
Risk difference vs. warfarin (%)[2] (95% CI)	0.14 (-0.81, 1.09)	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using KM estimate across the 3 cohorts without stratification
[2] The Risk difference was calculated across pooled cohorts, using the weighted average of KM estimates at 18 months across the 2 strata from the stratification variable 'symptomatic PE as qualifying event'. The stratification variable 'active cancer at baseline' could not be used because there would have been strata with no events.

Source data: Table 15.2.1.2.1: 1

Entire study period

The primary analysis was repeated, considering all patient data collected during the entire study period (i.e. up to the date the patient was last contacted to check VTE status). Outcome events were not systematically collected after trial termination. However, all outcome events that were reported to the sponsor until the database was locked on 3 December 2010 were entered into the trial database. The number of patients with a primary outcome event up to the last contact date was 27 in the DE group and

22 in the warfarin group. The primary outcome event was most commonly symptomatic DVT (18 vs. 14 patients), followed by symptomatic, nonfatal PE (10 vs. 8 patients). The additional events after the planned treatment period were 1 DVT in each treatment group and 3 PEs in the warfarin treatment group. All 5 outcome events occurred shortly (4 days to 2 months) after the end of study treatment. All 5 patients did not receive anticoagulant medication between the end of study treatment and the onset of the outcome event. The hazard ratio of DE vs. W was 1.24 (95% CI 0.71, 2.18). The upper limit of the confidence interval was below the non-inferiority margin defined for the primary analysis. The cumulative risk for the primary endpoint at 18 months was 1.73% in the DE group and 1.37% in the warfarin group. The risk difference between treatment groups was 0.25% (95% CI -0.71, 1.22).

Per-protocol analysis

The per-protocol analysis of the primary endpoint included all patients of the FAS who had no major efficacy-related protocol violation. The same statistical methods as for the pooled analyses were applied for the PPS analysis. The hazard ratio on DE vs. W was 1.42 (95% CI 0.77, 2.60). This was almost identical to the result of the primary analysis. The cumulative risks of the primary endpoint in the PPS at 18 months were 1.70% and 1.41% in the DE and warfarin group. The risk difference was 0.16% (95% CI −0.81, 1.14). The results of the perprotocol analyses confirmed the robustness of the primary analysis for the hazard ratio and the risk difference.

Subgroup analysis

Subgroup analyses of the primary endpoint were performed to evaluate the consistency of the treatment effect across a variety of subgroups identified by demographic and baseline characteristics, and risk factors for recurrent VTE. The risk difference at 18 months was estimated using the KM estimate for the pooled cohorts and pooled strata within each subgroup. The hazard ratio was obtained from the Cox model including the subgroup-by-treatment interaction, without the stratification variables due to the small number of events. For all subgroups, the p-values for subgroup-by-treatment interactions were not statistically significant, indicating the lack of statistical evidence to demonstrate that the treatment difference varies across the subgroup categories. For all but 2 subgroups, the confidence intervals for risk differences included 0.0. These were the subgroup of BMI ≥35 kg/m2 (360 patients, RD: 3.11, 95%CI 0.40, 5.81) and the subgroup of CrCl 50 to 80 mL/min (617 patients; RD: 2.04, 95%CI 0.40, 3.67). As the number of patients in these subgroups was relatively low and the p-values for subgroup-by-treatment interactions were close to 1 (BMI: 0.9969, CrCl: 0.9727), these observations were not considered of clinical relevance. In conclusion, because of the small event numbers and the lack of power, the results from the subgroup analyses cannot be considered to provide as robust information as the results from the primary efficacy analyses. Figure 11.4.1.1.6: 1 provides an overview of the analysis of the primary endpoint in key subgroups.

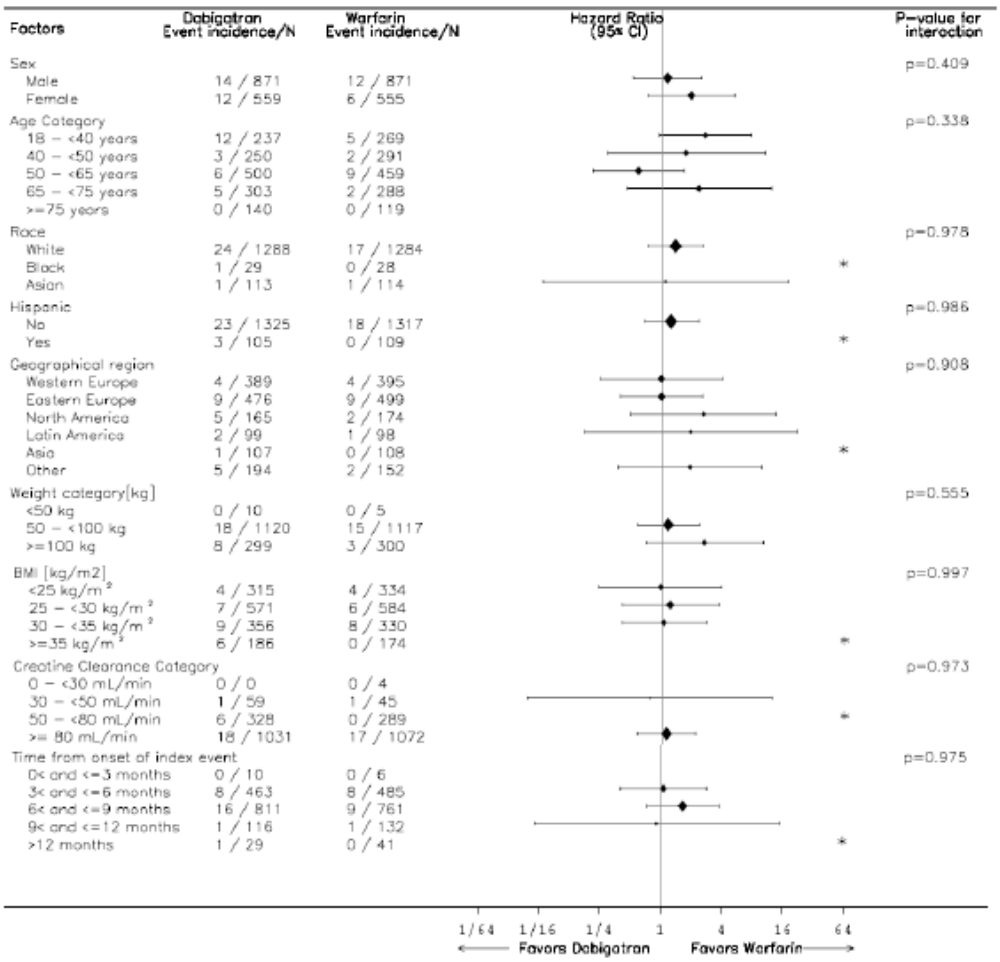


Figure 11.4.1.1.6: 1 Comparison of the treatment effect of dabigatran etexilate vs. warfarin on the primary endpoint in pre-defined subgroups, based on centrally adjudicated events / FAS as randomised

Events were taken into account up to the end of the planned treatment period

Source data: Figure 15.2.1.4.2: 1

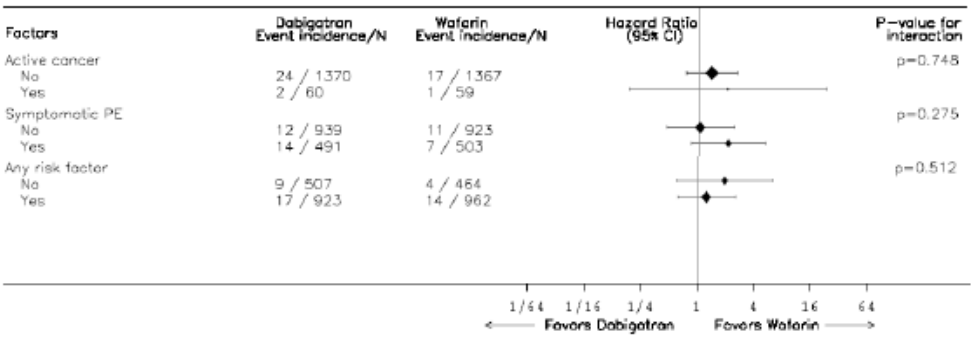


Figure 11.4.1.1.6: 1 Comparison of the treatment effect of dabigatran etexilate vs. warfarin on the primary endpoint in pre-defined subgroups, based on centrally adjudicated events / FAS as randomised (continued)

Events were taken into account up to the end of the planned treatment period

Source data: Figure 15.2.1.4.2: 2

Comparison between central adjudication and local assessment

All outcomes that contributed to the primary endpoint or secondary endpoints were to be adjudicated by the ICAC/VTE which was blinded to the treatment allocation of patients. To characterise the consistency of the endpoint classification, the data as recorded by the investigators on the CRF were compared with the events as classified by the ICAC/VTE. The rate of confirmation by the ICAC/VTE for locally suspected events (i.e. the percentage of events for which the adjudication result was the same as the local assessment) was 90.5% overall. For the different types of outcome events, the confirmation rates were similar to the overall rate (suspected recurrent DVT: 90.4%, suspected recurrent PE: 90.8%). The confirmation rates were similar between treatment groups.

Of those locally suspected events that were also locally confirmed by objective clinical testing, the ICAC/VTE confirmed 63.6% of symptomatic DVTs, 77.8% of symptomatic PEs, and 67.7% of all primary outcome events. The proportion of locally confirmed events which were confirmed by central adjudication was slightly higher in the DE treatment group than in the warfarin group (78.8% vs. 55.1%). One patient (in the DE group) had a suspected recurrent DVT event that was locally confirmed by objective clinical testing but was considered as 'non-evaluable' by central adjudication.

Secondary endpoints

The secondary efficacy endpoints comprised an additional composite endpoint (recurrent symptomatic VTE and all deaths) and separate analyses of the components of the composite endpoints: symptomatic DVT, symptomatic PE (fatal and non-fatal), deaths related to VTE (i.e. fatal PE), and all deaths. Events were taken into account up to the end of the planned treatment period. The analyses of the secondary endpoints were based on all patients randomised and treated; patients were allocated to the treatment groups as randomised, regardless of the actual medication taken ('FAS as randomised'). All 3 cohorts were pooled for these analyses. For all secondary endpoints except the composite endpoint, strata were pooled for the risk difference analysis because of the low number of events.

Composite of recurrent symptomatic VTE and all deaths

The number of patients who experienced recurrent symptomatic VTEs or died due to any reason was 42 patients in the DE group and 36 patients in the warfarin group (Table 11.4.1.2.1: 1). For patients with 2 centrally confirmed events that were components of the composite of recurrent VTE and all deaths, only

the first event was used for the time-to-event analysis. The hazard ratio of DE vs. W for recurrent symptomatic VTE or death due to any reason was 1.18 (95% CI 0.75, 1.84).

Table 11.4.1.2.1: 1 Hazard ratio of dabigatran etexilate vs. warfarin for the composite of recurrent symptomatic VTE and all deaths during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	42	36
Hazard ratio vs. warfarin[1] (95% CI)	1.18 (0.75, 1.84)	

Events were taken into account up to the end of the planned treatment period
[1] The Hazard ratio was calculated across pooled cohorts, using a Cox regression model with the factors treatment, cohort, baseline stratification factors (active cancer at baseline, symptomatic PE as qualifying event), and the interaction of active cancer and symptomatic PE.

Source data: Table 15.2.2.1: 2

The cumulative risk for the composite of recurrent symptomatic VTE and all deaths at 18 months was 2.86% in the DE group and 2.53% in the warfarin group. The risk difference was 0.09% (95% CI -1.11, 1.28), see Table 11.4.1.2.1: 2.

Table 11.4.1.2.1: 2 Risk difference of dabigatran etexilate vs. warfarin at 18 months of the composite of recurrent symptomatic VTE and all deaths during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	36	32
Cumulative risk (%)[1]	2.86	2.53
Risk difference vs. warfarin (%)[2] (95% CI)	0.09 (-1.11, 1.28)	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using KM estimate across the 3 cohorts without stratification
[2] The risk difference was calculated across pooled cohorts, using the weighted average of KM estimates at 18 months across the 4 strata from the 2 stratification variables (active cancer at baseline and symptomatic PE as qualifying event).

Source data: Table 15.2.2.1: 1

The KM curves for the composite of recurrent VTE and all deaths together with the number of patients at risk are shown in Figure 11.4.1.2.1: 1. Events were observed throughout the treatment period, although events seemed to be more frequent between 18 and 24 months of treatment, as indicated by steeper slopes of the KM curves. In the first 9 months, the estimated cumulative risk was slightly higher in the DE group than in the warfarin group. Thereafter, the curves were almost overlapping, until they somewhat diverged again at around 18 months. Note that the number of patients at risk was relatively low after 18 months.

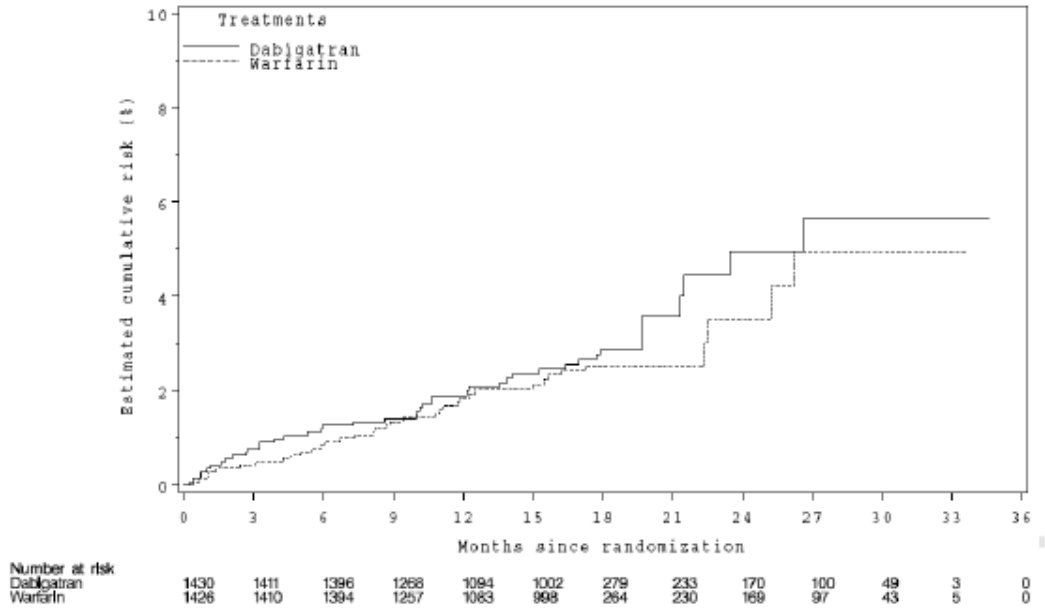


Figure 11.4.1.2.1: 1 Time to the composite of recurrent symptomatic VTE and all deaths, based on centrally adjudicated events / FAS as randomised

Events were taken into account up to the end of the planned treatment period

Source data: Figure 15.2.2.1: 1

The cumulative risks for the composite of VTE and all deaths were highest for patients with initial symptomatic PE and active cancer at baseline (DE: 18.2%, W: 10.0%) and for patients with active cancer but without PE (11.4% vs. 9.1%). Patients with initial symptomatic PE without cancer at baseline had a lower risk for recurrent VTE and death (3.4% vs. 2.0%); patients with neither initial symptomatic PE nor cancer at baseline (1.8% vs. 2.3%) had the lowest risk. Note that the strata of patients with active cancer and with or without PE included a very low numbers of patients. None of the confidence intervals for the risk differences indicated a statistically significant between-treatment difference within any of the strata.

Symptomatic DVT

The number of patients with acute symptomatic DVT was 17 patients in the DE group and 13 patients in the warfarin group. The hazard ratio of DE vs. W for symptomatic DVT was 1.32 (95% CI 0.64, 2.71); see Table 11.4.1.2.2: 1.

Table 11.4.1.2.2: 1 Hazard ratio of dabigatran etexilate vs. warfarin of symptomatic DVT during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	17	13
Hazard ratio vs. warfarin[1] (95% CI)	1.32 (0.64, 2.71)	

Events were taken into account up to the end of the planned treatment period
[1] The Hazard ratio was calculated across pooled cohorts, using a Cox regression model with the factors treatment, cohort, baseline stratification factors (active cancer at baseline, symptomatic PE as qualifying event), and the interaction of active cancer and symptomatic PE.

Source data: Table 15.2.2.2: 2

At 18 months, the number of patients with an acute symptomatic DVT was 15 in the DE group and 12 in the warfarin group. The cumulative risks were 1.17% and 0.98%, respectively. The resulting risk difference was 0.19% (95% CI -0.63, 1.00). A summary of the results is shown in Table 11.4.1.2.2: 2.

Table 11.4.1.2.2: 2 Risk difference of dabigatran etexilate vs. warfarin at 18 months of symptomatic DVT during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	15	12
Cumulative risk (%)[1]	1.17	0.98
Risk difference vs. warfarin (%)[2] (95% CI)	0.19 (-0.63, 1.00)	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using KM estimate across the 3 cohorts without stratification
[2] The risk difference was calculated across pooled cohorts without stratification

Source data: Table 15.2.2.2: 1

Symptomatic PE

The number of patients with a symptomatic, fatal or non-fatal PE was 10 in the DE group and 5 in the warfarin group. The hazard ratio of DE vs. W was 2.04 (95% CI 0.70, 5.98), as shown in Table 11.4.1.2.3: 1.

Table 11.4.1.2.3: 1 Hazard ratio of dabigatran etexilate vs. warfarin of symptomatic PE during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	10	5
Hazard ratio vs. warfarin[1] (95% CI)	2.04 (0.70, 5.98)	

Events were taken into account up to the end of the planned treatment period
[1] The Hazard ratio was calculated across pooled cohorts, using a Cox regression model with the factors treatment, cohort, baseline stratification factors (active cancer at baseline, symptomatic PE as qualifying event), and the interaction of active cancer and symptomatic PE.

Source data: Table 15.2.2.3: 2

At 18 months, the cumulative risks for symptomatic PE were 0.66% in the DE group and 0.40% in the warfarin group (Table 11.4.1.2.3: 2). The risk difference was 0.26% (95% CI -0.32, 0.84).

Table 11.4.1.2.3: 2 Risk difference of dabigatran etexilate vs. warfarin at 18 months of symptomatic PE during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	8	5
Cumulative risk (%)[1]	0.66	0.40
Risk difference vs. warfarin (%)[2] (95% CI)	0.26 (-0.32, 0.84)	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using KM estimate across the 3 cohorts without stratification
[2] The Risk difference was calculated across pooled cohorts without stratification.

Source data: Table 15.2.2.3: 1

Deaths related to VTE

One patient in the DE group and 1 patient in the warfarin group died from PE. The hazard ratio of DE vs. W for VTE-related death was 1.01 (95% CI 0.06, 16.22). The cumulative risks at 18 months were 0.08% and 0.07%, respectively, in the DE group and the warfarin group. The risk difference was 0.01% (95% CI -0.20, 0.23).

All deaths

The number of patients who died during the planned treatment period was comparable between the treatment groups (DE: 17 patients; W: 19 patients). The most frequent adjudicated cause of death was cancer for about half of the patients (DE: 7 patients, W: 9 patients). The hazard ratio of DE vs. W for all deaths was 0.90 (95% CI 0.47, 1.72). Details of the analysis are shown in Table 11.4.1.2.5: 1.

Table 11.4.1.2.5: 1 Hazard ratio of dabigatran etexilate vs. warfarin of death of all causes during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event, n	17	19
Hazard ratio vs. warfarin[1] (95% CI)	0.90 (0.47, 1.72)	

Events were taken into account up to the end of the planned treatment period
[1] The Hazard ratio was calculated across pooled cohorts, using a Cox regression model with the factors treatment, cohort, baseline stratification factors (active cancer at baseline, symptomatic PE as qualifying event), and the interaction of active cancer and symptomatic PE.

Source data: Table 15.2.2.5: 2

The cumulative risks for death at 18 months were 1.22% in the DE group and 1.24% in the warfarin group; the resulting risk difference was -0.02% (95% CI -0.89, 0.84), see Table 11.4.1.2.5: 2.

Table 11.4.1.2.5: 2 Risk difference of dabigatran etexilate vs. warfarin at 18 months of death of all causes during the planned treatment period, based on centrally adjudicated events / FAS as randomised

	Dabigatran etexilate	Warfarin
Patients, n	1430	1426
Patients with event	15	16
Cumulative risk (%)[1]	1.22	1.24
Risk difference vs. warfarin (%)[2] (95% CI)	-0.02 (-0.89, 0.84)	

Events were taken into account up to 18 months of planned treatment
[1] Estimated cumulative risk at 18 months using KM estimate across the 3 cohorts without stratification
[2] The Risk difference was calculated across pooled cohorts without stratification

Source data: Table 15.2.2.5: 1

Prevention Study 1160.63 (RE-SONATE)

Methods

Study 1160.63 (RE-SONATE) evaluated the secondary prevention of recurrent VTE (sVTEp) and was a placebo-controlled study that enrolled patients with acute symptomatic proximal DVT of the leg and/or acute symptomatic PE (treatment duration: 6 months), who had been treated for 6 to 18 months with an oral VKA or study drug in Study 1160.53.

The study design and flowchart for the study is shown graphically below.

Study flow chart for P-controlled pivotal study

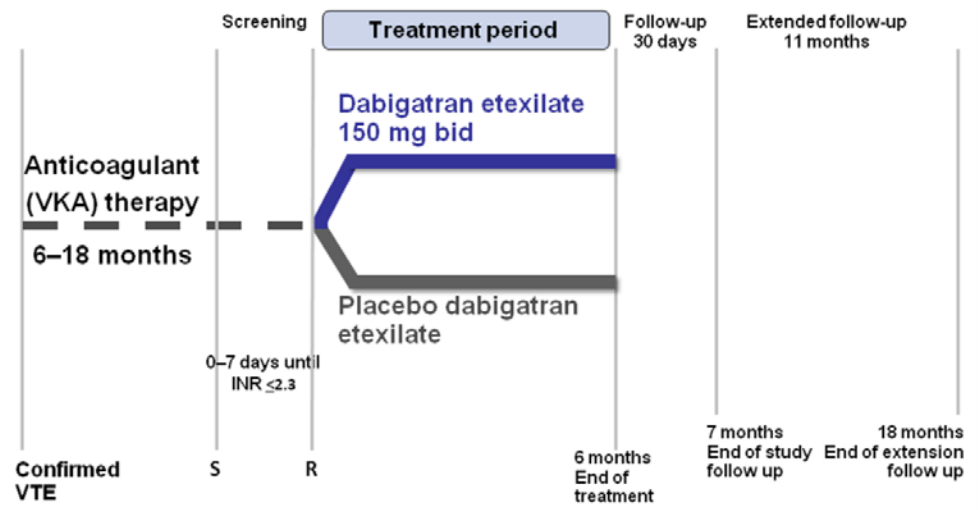


Figure 2.3.3: 3 Study flow chart for sVTEp Study 1160.63

S=screening; R=randomization

Study participants

Adult patients (≥ 18 years) with confirmed symptomatic PE or proximal DVT who had been treated for 6 to 18 months with therapeutic dosages (intended INR between 2-3) of an oral VKA (e.g. W, acenocoumarol, phenprocoumon, or fluindione) up to the moment of randomisation for the current study.

After the implementation of Protocol Amendment 2 (dated 30 May 2008) also patients completing the RE-COVER study could be enrolled.

Treatments

The investigational product in this trial was DE 150 mg b.i.d. Placebo was the control treatment.

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.

Objectives

The primary efficacy objective was to evaluate whether DE 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).

Outcomes / endpoints

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. The primary endpoint was analysed in terms of the time to first occurrence. Secondary efficacy endpoints were:

- The composite of recurrent symptomatic VTE (symptomatic DVT, symptomatic non-fatal PE, and fatal PE). Unexplained deaths were not included in this endpoint.
- The individual components of the primary efficacy endpoint:
    - Symptomatic DVT
    - Symptomatic PE
    - Unexplained death

Statistical methods and sample size

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 DE-to-placebo hazard ratio (HR) and its corresponding 2-sided 95% confidence intervals (CI) were calculated. Superiority of the DE 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 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 DE group compared to the placebo group, a total of 36 events would give a power of 95% to demonstrate that DE 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.

Randomisation

Each eligible patient was randomly assigned to either fixed dose (150 mg b.i.d.) DE or to placebo. Assignment of study treatment was via an IVRS with an allocation ratio of 1:1 for DE : placebo. Randomisation was stratified by centre using permuted blocks (block size: 4) to prevent a series of imbalanced treatment allocations. Randomisation was to take place 6 to 18 months after the index PE or

DVT event. All patients were to continue treatment with an oral VKA or RE-COVER study medication up to randomisation (or until screening, after Protocol Amendment 2 dated 30 May 2008 was implemented). Patients could only be randomised if their INR was ≤2.3.

Blinding (masking)

This study employed a double-blind design; neither the patient nor the investigator was informed about the allocated treatment. To ensure appropriate blinding, an IVRS was used for the assignment of patients to treatment groups.

Results

Participant flow

The patient flow is shown in table below.

Table 3.1.2.1: 3 Patient disposition at the end of treatment in sVTEp Study 1160.63 - all patients

	DE n (%)	P n (%)	Total n (%)
Enrolled patients			1366
Randomized	685	668	1353
Treated patients[1]	681 (100.0)	662 (100.0)	1343 (100.0)
Not prematurely discontinued from study drug	610 (89.6)	563 (85.0)	1173 (87.3)
Prematurely discontinued from study drug	71 (10.4)	99 (15.0)	170 (12.7)
Adverse events	50 (7.3)	81 (12.2)	131 (9.8)
Worsening of disease under study[2]	4 (0.6)	49 (7.4)	53 (3.9)
Worsening of other pre-existing disease	4 (0.6)	4 (0.6)	8 (0.6)
Other adverse events	42 (.2)	28 (4.2)	70 (5.2)
Bleeding event[3]	11 (1.6)	4 (0.6)	15 (1.1)
Non-bleeding event	31 (4.6)	24 (3.6)	55 (4.1)
Non-compliant with protocol	9 (1.3)	5 (0.8)	14 (1.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Patient refused to continue medication[4]	12 (1.8)	13 (2.0)	25 (1.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)

[1] Patients who received at least 1 dose of study drug

[2] Symptomatic DVT or PE as based on the assessment of the investigator

[3] Including patients who discontinued due to a bleeding event that may or may not have required cessation of treatment

[4] Patients who discontinued the intake of study drug could have continued the study without taking study drug, or may have decided to permanently discontinue from the study (i.e., withdrawn their consent).

Source data: SCE appendix, Module 5.3.5.3 [U12-2652] Table 1.1.1.5

Recruitment

The recruitment period was December 2007 to December 2011.

Conduct of the study

There were 7 global amendments to the trial protocol for Study 1160.63.

The main purpose of Protocol Amendment 1 was to contraindicate the concomitant administration of quinidine.

Amendment 2 introduced an extension of the follow-up period and eligibility criteria for roll-over patients from 1160.53.

Amendment 3 updated the information regarding the management of patients requiring surgery.

Amendment 4 updated the guidance concerning the concomitant use of verapamil and Amendment 6 about the administration of ketoconazole and rifampicin and Amendment 7 about concomitant administration of other P-gp inducers (carbamazepine and St. Johns Wort).

Amendment 5 introduced changes to administrative aspects of the trial.

Local amendments in Germany

In Local Protocol Amendment 1 in Germany (dated 24 October 2007), for safety reasons, an exclusion criterion was added to exclude patients with a contraindication to systemic anticoagulation. Local Protocol Amendment 2 in Germany (dated 26 June 2008) was introduced to amend the exclusion criteria regarding excessive risk of bleeding (because of anticipated need for quinidine), to allow previous study medication from the RE-COVER trial to have been used, and to exclude patients with active cancer. These changes were to ensure the protocol was consistent with the changes introduced with the global clinical trial Protocol Amendments 1 (11 February 2008) and 2 (30 May 2008).

Local amendment in Sweden

In Local Protocol Amendment 1 in Sweden (dated 15 October 2007), exclusion criterion 11 was amended because combined systemic hormonal contraceptives were contraindicated in Sweden for women with a history of venous thromboembolism. Combined oral contraceptives were added to the list of restricted concomitant medications. The concomitant use of gestagen-only systemic hormonal contraception required a risk benefit assessment by the investigator.

Only Protocol Amendment 2 had an impact on the statistical analysis of the trial. This amendment, dated 30 May 2008, was implemented for the following reasons:

- To determine whether or not there was an increase in VTE recurrence following discontinuation of study treatment by inclusion of a long term, open label follow-up period
- To clarify patients eligibility if bridging therapy was given during the previous 6 to 18 months of oral VKA therapy
- Clarification of timing of initiation of study medication relative to last dose of VKA
- To allow inclusion of patients after participation in RE-COVER (Study 1160.53)
- Exclusion of patients with known active cancer
- Reducing scheduled LFT monitoring frequency, which was done following a DSMB recommendation.
- Correction of typographical errors

The major changes from the amendment with an impact on the statistical analysis were the inclusion of the extended follow-up period and allowing patients to roll-over into RE-SONATE after participation in RE-COVER (Study 1160.53). Due to inclusion of patients rolling over from RE-COVER, the randomisation was changed in the protocol to allow for stratification within centres of patients by participation in RECOVER. This resulted in a number of changes to the statistical analysis plan (please refer to study report for further details).

Baseline data

Baseline data are tabulated below.

Table 11.2.1: 1 Demographic and baseline characteristics of patients by randomised treatment group - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
Number of patients, n (%)	681	(100.0)	662	(100.0)	1343	(100.0)
Age, mean (SD) [years]	56.1	(15.5)	55.5	(15.1)	55.8	(15.3)
Age ≥70 years, n (%)	143	(21.0)	138	(20.8)	281	(20.9)
Male sex, n (%)	381	(55.9)	364	(55.0)	745	(55.5)
Race, n (%)						
White	610	(89.6)	585	(88.4)	1195	(89.0)
Asian	58	(8.5)	60	(9.1)	118	(8.8)
Black/African Amer.	9	(1.3)	14	(2.1)	23	(1.7)
Amer.Ind./Alaska Nat	4	(0.6)	3	(0.5)	7	(0.5)
Ethnicity, n (%)						
Non-Hispanic/Latino	647	(95.0)	631	(95.3)	1278	(95.2)
Hispanic/Latino	19	(2.8)	21	(3.2)	40	(3.0)
Missing	15	(2.2)	10	(1.5)	25	(1.9)
CrCl at screening, Mean (SD) [mL/min]	99.6	(35.8)	101.2	(37.1)	100.4	(36.4)
By category [mL/min], n (%)[1,2]						
<30	1	(0.1)	0		1	(0.1)
30 to <50	41	(6.0)	30	(4.5)	71	(5.3)
50 to <80	165	(24.2)	169	(25.5)	334	(24.9)
≥80	472	(69.3)	462	(69.8)	934	(69.5)
Missing	2	(0.3)	1	(0.2)	3	(0.2)
BMI, mean (SD) [kg/m^2]	28.45	(5.44)	28.41	(5.56)	28.43	(5.50)
Current smokers, n (%)	106	(15.6)	117	(17.7)	223	(16.6)
Geographical region, n (%)						
Western Europe	374	(54.9)	367	(55.4)	741	(55.2)
Central Europe	170	(25.0)	166	(25.1)	336	(25.0)
Asia	55	(8.1)	58	(8.8)	113	(8.4)
North America	60	(8.8)	49	(7.4)	109	(8.1)
Other [3]	22	(3.2)	22	(3.3)	44	(3.3)
Duration of previous VKA treatment, n (%) [months]						
0 to <6	49	(7.2)	50	(7.6)	99	(7.4)
6 to 12	472	(69.3)	452	(68.3)	924	(68.8)
>12 to 18	154	(22.6)	153	(23.1)	307	(22.9)
>18	6	(0.9)	7	(1.1)	13	(1.0)
Previous acute treatment with dabigatran etexilate [4]	7	(1.0)	8	(1.2)	15	(1.1)

[1] CrCl rate at screening: <30 mL/min = severe renal impairment; 30 to <50 mL/min = moderate renal impairment; 50 to <80 mL/min= mild renal impairment; ≥80 mL/min = normal renal function

[2] No baseline laboratory values were available for 3 patients (2 dabigatran etexilate patients; 1 placebo patient).

[3] Australia, New Zealand, and South Africa

[4] All were patients recruited from the RE-COVER study (Trial 1160.53). Note: Of the 4 patients from RE-COVER II, 3 were treated with warfarin and 1 with dabigatran etexilate during RE-COVER II; these data were not in the RE-SONATE database [U11-2298-01].

Source data: Tables 15.1.4: 1 and 15.1.4: 3

Table 11.2.2: 1 Demographic and baseline characteristics of patients by randomised treatment group - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
Number of patients, n (%)	681	(100.0)	662	(100.0)	1343	(100.0)
Patients with at least 1 risk factor	133	(19.5)	101	(15.3)	234	(17.4)
Coagulation disorder						
No	266	(39.1)	288	(43.5)	554	(41.3)
Not tested	328	(48.2)	306	(46.2)	634	(47.2)
Yes	87	(12.8)	68	(10.3)	155	(11.5)
Factor V Leiden	35	(5.1)	28	(4.2)	63	(4.7)
Protein C/S deficiencies	11	(1.6)	8	(1.2)	19	(1.4)
Prothrombin mutation	10	(1.5)	6	(0.9)	16	(1.2)
Antiphospholipid antibodies and/or Lupus anticoagulant	4	(0.6)	2	(0.3)	6	(0.4)
Antithrombin deficiency	1	(0.1)	0		1	(0.1)
Other coagulation disorders	43	(6.3)	35	(5.3)	78	(5.8)
Recent immobilisation						
No	606	(89.0)	614	(92.7)	1220	(90.8)
Not reported	22	(3.2)	12	(1.8)	34	(2.5)
Yes	53	(7.8)	36	(5.4)	89	(6.6)
Transient	49	(7.2)	36	(5.4)	85	(6.3)
Permanent	4	(0.6)	0		4	(0.3)

Source data: Table 15.1.4: 4

Concomitant medications of particular interest during the treatment period were antithrombotics/anticoagulants (including NSAIDs), certain restricted medications, cardiovascular therapies, and P-gp inducers or inhibitors.

Table 11.2.3.1: 1 Concomitant medications of particular interest during the treatment period by randomised treatment group - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of patients	681	(100.0)	662	(100.0)	1343	(100.0)
Use of at least 1 concomitant medication of particular interest						
During the treatment period	137	(20.1)	123	(18.6)	260	(19.4)
Platelet aggregation inhibitor excluding ASA	4	(0.6)	3	(0.5)	7	(0.5)
ASA	52	(7.6)	52	(7.9)	104	(7.7)
Aspirin ≤100 mg/day [1]	48	(7.0)	47	(7.1)	95	(7.1)
Aspirin >100 mg/day [1]	3	(0.4)	5	(0.8)	8	(0.6)
Aspirin with missing dose	1	(0.1)	0		1	(0.1)
Other antithrombotic agents	1	(0.1)	0		1	(0.1)
NSAIDs	87	(12.8)	73	(11.0)	160	(11.9)

Note: Interruptions of study treatment were not considered. Patients were considered to have received concomitant medication if taken for at least 1 day at any time between the first and penultimate day of receiving study medication.

1 Patients on ASA were counted in the highest ASA dosing category only.

Source data: Table 15.1.4: 12

Table 11.2.3.1: 2 Use of restricted medications reported during the treatment period by randomised treatment group - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of patients	681	(100.0)	662	(100.0)	1343	(100.0)
Use of at least restricted medication	24	(3.5)	24	(3.6)	48	(3.6)
Heparin and heparinoid	16	(2.3)	18	(2.7)	34	(2.5)
VKA	0		1	(0.2)	1	(0.1)
DTI	0		0		0	
Fondaparinux	1	(0.1)	0		1	(0.1)
Acetylsalicylic acid >100 mg/day	3	(0.4)	5	(0.8)	8	(0.6)
Clopidogrel and/or ticlopidine	4	(0.6)	1	(0.2)	5	(0.4)
Glycoprotein IIb−IIIa inhibitors	0		0		0	
Thrombolytics	0		0		0	
Dextrans	0		0		0	
Quinidine	0		0		0	
Ketoconazole (systemic use)	1	(0.1)	0		1	(0.1)

Note: Interruptions of study treatment were not considered. Patients were considered to have received concomitant medication if taken for at least 1 day at any time between the first and penultimate day of receiving study medication. Patients could be counted in more than one category.

Source data: Table 15.1.4: 13

Table 11.2.3.1: 3 Use of cardiovascular medications reported during the treatment period by randomised treatment group - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of patients	681	(100.0)	662	(100.0)	1343	(100.0)
Use of at least 1 cardiovascular medication [1]	354	(52.0)	296	(44.7)	650	(48.4)
Agents affecting the RAS	204	(30.0)	177	(26.7)	381	(28.4)
Beta blocking agents	140	(20.6)	108	(16.3)	248	(18.5)
Vasodilators	147	(21.6)	110	(16.6)	257	(19.1)
Serum lipid reducing agents [2]	132	(19.4)	107	(16.2)	239	(17.8)
Calcium channel blockers	60	(8.8)	59	(8.9)	119	(8.9)
Antiarrhythmic agents	12	(1.8)	11	(1.7)	23	(1.7)
Cardiac glycosides	4	(0.6)	0		4	(0.3)
Inotropic agents	2	(0.3)	1	(0.2)	3	(0.2)

Note: Interruptions of study treatment were not considered. Patients were considered to have received concomitant medication if taken for at least 1 day at any time between the first and penultimate day of receiving study medication.
RAS: renin−angiotensin system
Patients could be counted in more than one category.

1 Vasoprotective agents were not included here, but were included in the overall summary of concomitant medications in Table 15.1.4: 17 as medications of the cardiovascular system. Therefore the incidences of cardiovascular medications differ in the 2 tables.

2 Including statins

Source data: Table 15.1.4: 14

Table 11.2.3.1: 4 Use of P-gp inducers or inhibitors reported during the treatment period by randomised treatment group - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of patients	681	(100.0)	662	(100.0)	1343	(100.0)
Use of at least 1 P-gp inhibitor	13	(1.9)	10	(1.5)	23	(1.7)
Verapamil	8	(1.2)	6	(0.9)	14	(1.0)
Amiodarone	2	(0.3)	2	(0.3)	4	(0.3)
Tacrolimus	1	(0.1)	1	(0.2)	2	(0.1)
Ketoconazole	1	(0.1)	0		1	(0.1)
Ritonavir	0		1	(0.2)	1	(0.1)
Cyclosporine A	1	(0.1)	0		1	(0.1)
Dronedarone	0		0		0	
Itraconazole	0		0		0	
Nelfinavir	0		0		0	
Quinidine	0		0		0	
Saquinavir	0		0		0	
Valspodar	0		0		0	
Use of a P-gp inducer	4	(0.6)	7	(1.1)	11	(0.8)
Carbamazepine	2	(0.3)	6	(0.9)	8	(0.6)
St John's wort	2	(0.3)	1	(0.2)	3	(0.2)
Rifampicin	0		0		0	

Note: Interruptions of study treatment were not considered. Patients were considered to have received concomitant medication if taken for at least 1 day at any time between the first and penultimate day of receiving study medication. Patients could be counted in more than one category.

Source data: Tables 15.1.4: 15 and 15.1.4: 16

Outcomes and estimation

The incidence of the events of the primary endpoint was 0.4% in the DE group compared with 5.6% in the placebo group.

The HR for DE versus placebo was 0.08 (95% CI: 0.02, 0.25). Superiority was therefore demonstrated for DE versus placebo.

Table 11.4.1.1.1: 1 Analysis of symptomatic recurrent VTE (i.e. the composite of recurrent DVT or fatal or non-fatal PE and unexplained deaths) during the intended treatment period - FAS - as randomised

	Dabigatran etexilate	Placebo
FAS - as randomised, n (%)	681 (100.0)	662 (100.0)
Patients with events, n (%)	3 (0.4)	37 (5.6)
Hazard ratio	0.08	
95% CI	0.02, 0.25	
Superiority p-value	<0.0001	

Based on centrally adjudicated events.
Cox proportional hazards model including the main effect of treatment.

Source data: Table 15.2.1.1: 1

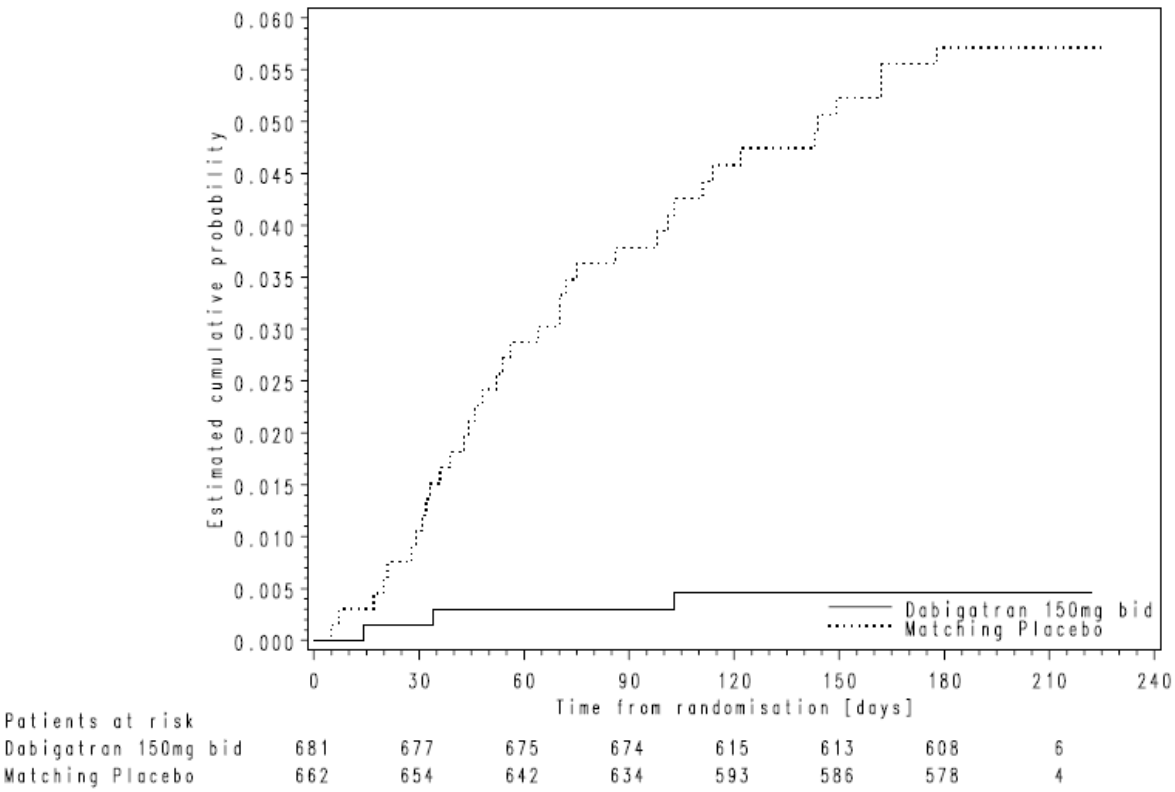


Figure 11.4.1.1.2: 1 Kaplan-Meier estimate of time to first centrally confirmed symptomatic recurrent VTE including unexplained death during the intended treatment period - FAS - as randomised

Based on centrally adjudicated events.

Source data: Figure 15.2.1.2: 1

Secondary endpoints

The composite endpoint of recurrent symptomatic VTE events without unexplained death was analysed in the same way as the primary endpoint. The incidences of recurrent symptomatic VTE excluding unexplained death were 0.4% in the DE group and 5.3% in the placebo group. The HR for time to first occurrence of an event for DE versus placebo was 0.08, (95% CI: 0.03, 0.27). Superiority was therefore demonstrated for DE versus placebo since the upper 95% confidence limit of the HR was less than 1. Since there were only 2 unexplained deaths (both in the placebo group), these findings were similar to the primary analysis of efficacy.

Ancillary analyses

Consistent with the incidence of the composite endpoint, the incidences of DVTs, non-fatal PEs, and unexplained deaths were all lower for the DE group than for the placebo group.

Table 11.4.1.2.2: 2 Analysis of the individual components of the primary efficacy endpoint during the intended treatment period - FAS - as randomised

	Dabigatran etexilate	Placebo
FAS - as randomised, n (%)	681 (100.0)	662 (100.0)
Recurrent symptomatic DVT [1]		
Patients with events, n (%)	2 (0.3)	23 (3.5)
95% CI [2]	0.04, 1.06	2.21, 5.17
p-value [3]	<0.0001	
Recurrent symptomatic PE		
Patients with events, n (%)	1 (0.1)	14 (2.1)
95% CI [2]	0.00, 0.82	1.16, 3.52
p-value [3]	0.0004	
Unexplained death		
Patients with events, n (%)	0 (0.0)	2 (0.3)
95% CI [2]	0.00, 0.54	0.04, 1.09
p-value [3]	0.2428	

Based on centrally adjudicated events.
1 Includes all DVT events, not only the first DVT event.
2 Clopper-Pearson method
3 Fisher's exact test

Source data: Table 15.2.2.2: 1, 15.2.2.3: 1, and 15.2.2.4: 1

The per-protocol analysis of the primary endpoint was consistent with the primary analysis of efficacy.

Table 11.4.1.1.4: 1 Comparative analysis of the primary endpoint during the intended treatment period - PPS

	Dabigatran etexilate	Placebo
PPS, n (%)	603 (100.0)	599 (100.0)
Patients with events, n (%)	2 (0.3)	37 (6.2)
Hazard ratio	0.05	
95% CI	0.01, 0.22	
p-value	<0.0001	

Based on centrally adjudicated events.
Cox proportional hazards model including the main effect of treatment.

Source data: Table 15.2.1.2: 2

Symptomatic recurrent VTE and unexplained deaths stratified by participation in RE-COVER

In total, 27 patients rolled over from the RE-COVER trial (DE: 15 patients; placebo: 12 patients). None of the patients in the DE group and 2 patients in the placebo group who continued into RE-SONATE from the RE-COVER trial had centrally confirmed VTE events during the intended treatment period. Of the 2 placebo patients with events, 1 patient had been treated with DE during RE-COVER (No. 22954) and had the event on Day 72 and 1 patient (No. 22956) previously treated with warfarin had an event on Day 28 of the RE-SONATE trial.

Subgroup analyses

Subgroup analyses were performed for the primary endpoint in an exploratory manner based on the following baseline characteristics: previous participation in the RE-COVER study, age, sex, race, ethnicity, geographical region, type of qualifying VTE event, history of multiple VTEs, and CrCl at baseline. Some subgroups had very small numbers of patients with events and as such, interpretation of these analyses is limited. Incidences of symptomatic recurrent VTE and unexplained deaths, HRs, and 95% CIs are summarised by subgroup in Figure 11.4.1.1.5:1. DE was effective versus placebo in all age subgroups, in males and females, and regardless of whether the qualifying event was DVT, PE, or both DVT and PE.

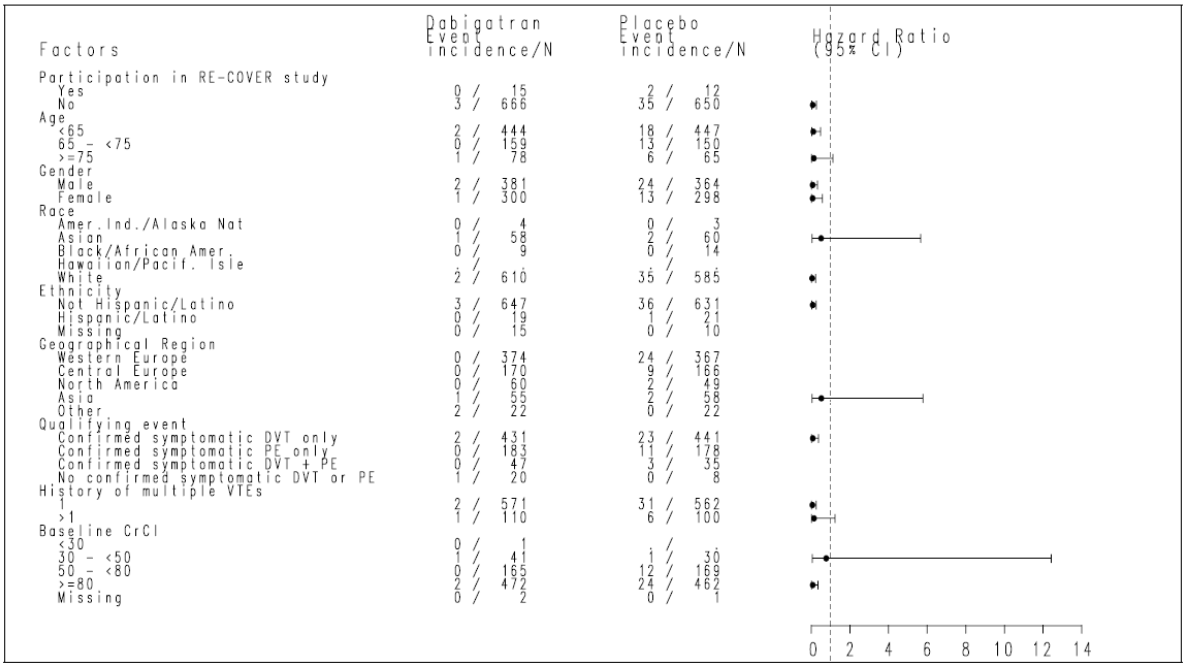


Figure 11.4.1.1.5: 1 Forest plot of HRs and 95% CIs for each subgroup category for the first centrally confirmed symptomatic recurrent VTE including unexplained death during the intended treatment period (based on centrally confirmed events) - FAS - as randomised

Source data: Appendix 16.1.9.2, Figure 6.1.2.1.1

A sensitivity analysis of the primary endpoint was performed, introducing each of the baseline covariates as a main effect (previous participation in the RE-COVER study, age, sex, race, ethnicity, geographical region, type of qualifying VTE event, history of multiple VTEs, and CrCl at baseline) together with the main effect of treatment in separate Cox regression models:

Table 11.4.1.1.5: 1 Hazard ratios and CIs for time to first centrally confirmed symptomatic recurrent VTE including unexplained death during the intended treatment period (Cox regression) adjusting for age, sex, and CrCl - FAS - as randomised

	Hazard ratio	95% CI
Dabigatran etexilate 150 mg b.i.d. vs. placebo	0.077	0.024, 0.251
Age (difference of 10 years)	1.320	1.012, 1.722
Sex (female vs. male)	0.703	0.364, 1.358
Baseline CrCl (difference of 10 mL/min)	1.063	0.981, 1.151

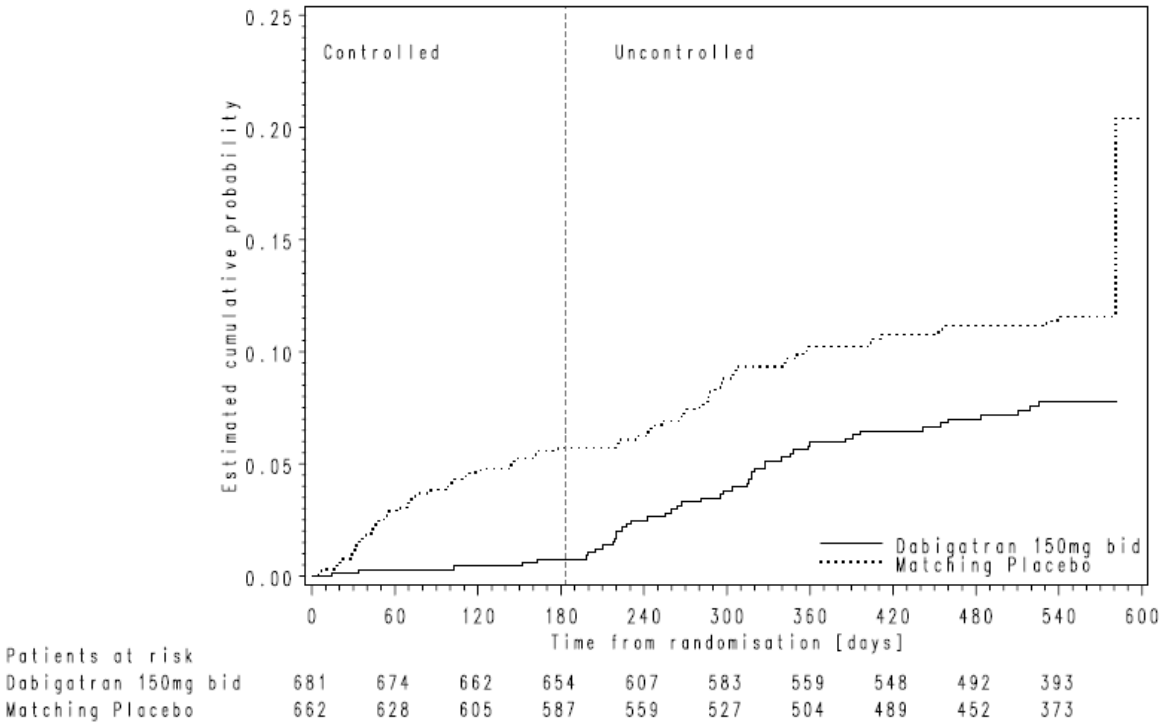
Based on centrally adjudicated events.
The model included treatment, age, sex, and CrCl as covariates. No interactions were included.

Source data: Appendix 16.1.9.2, Table 6.1.3.11

Cumulative symptomatic recurrent VTE events according to duration of previous VKA therapy (0 to ≤6; >6 to ≤12 months, and >12 months) was determined. Kaplan-Meier plots of time to the first centrally confirmed symptomatic recurrent VTE event, including unexplained death, in the intended treatment period indicated no noteworthy difference in the cumulative occurrence, regardless of the duration of previous VKA treatment.

Symptomatic recurrent VTE events in the extended follow-up period

Kaplan-Meier plots of time to the first centrally confirmed symptomatic recurrent VTE events, including unexplained death, in the entire study period indicated no marked rebound in VTE events after discontinuation of DE treatment. In the 3-day washout period immediately after discontinuation of study treatment, the incidence of VTE events was lower in the DE group (0.1%) than in the placebo group (1.5%). Thereafter, during follow-up, there was an increase in the number of events in the DE group, but the HR at the end of the entire study period measured 0.61 (95% CI 0.42, 0.88). Superiority was therefore demonstrated for DE versus placebo at the end of the extended follow-up period.



Patients at risk										
Dabigatran 150mg bid	681	674	662	654	607	583	559	548	492	393
Matching Placebo	662	628	605	587	559	527	504	489	452	373

Figure 11.4.1.3.1: 2 Kaplan-Meier estimate of time to first centrally confirmed symptomatic recurrent VTE event in the entire study period - FAS - as randomised

Patients with no VTE event were censored at the time of using a post treatment nonstudy preventive anticoagulant.
Based on centrally adjudicated events.

Source data: Figure 15.2.2.5: 2

Table 11.2.3.3: 1 Use of concomitant medications preventative of a symptomatic recurrent VTE by randomised treatment group during the extended follow-up - FAS - as randomised

	Dabigatran etexilate		Placebo		Total	
	N	(%)	N	(%)	N	(%)
Number of patients	681	(100.0)	662	(100.0)	1343	(100.0)
Use of at least 1 preventative medication	138	(20.3)	169	(25.5)	307	(22.9)
VKA	96	(14.1)	133	(20.1)	229	(17.1)
LMWH	83	(12.2)	113	(17.1)	196	(14.6)
Unfractionated heparin	27	(4.0)	20	(3.0)	47	(3.5)
DTI	3	(0.4)	1	(0.2)	4	(0.3)
Fondaparinux	6	(0.9)	13	(2.0)	19	(1.4)
Other heparin	1	(0.1)	1	(0.2)	2	(0.1)

Note: In addition, 1 patient (No. 22315) took apixaban or enoxaparin/warfarin in another clinical trial during the follow-up period.
Patients could be counted in more than one category.

Source data: Table 15.1.4: 18

2.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The scope of the application was to evaluate the effect of DE in the treatment of acute VTE (aVTEt) and secondary prevention of recurrent VTE (sVTEp). VTE was defined as a composite of DVT and PE.

No dedicated dose-finding study was performed to support the aVTEt and sVTEp indications. A dose of 150 b.i.d. DE showed a promising benefit risk ratio in several dose finding trials for patients undergoing orthopaedic surgery and patients with NVAF. The similarity in the profile of this regimen to warfarin at the same target INR in another patient population (SPAF) supports the use in patients with VTE. Subgroup analysis of efficacy for the primary and secondary endpoints in patients with VTE did not reveal any subgroup-by-treatment interactions.

In all populations studied with DE 150 mg b.i.d, plasma levels correlated well with the anticoagulant activity. Data from previous studies showed that doses of DE 50 mg bi.d. and DE 150 mg o.d. seemed to be less effective than warfarin with a target INR of 2-3. DE 300 mg b.i.d. resulted in more bleeding events than the comparator in phase II trials in orthopedic surgery patients and patients with NVAF, and the choice of DE 150 mg b.i.d. seemed more reasonable from a safety point of view. An exposure-response analysis was performed in patients in VTE Study 1160.53, which demonstrated that up to a trough DE concentration of 159 ng/mL, the upper bound of the 95% CI DE major bleeding event rate was below the observed major bleeding event rate on warfarin (2%). For most subgroups analysed (age, gender, race, ethnicity, BMI, geographic region, creatinine clearance [CrCl] at baseline, active cancer at any time, and history of bleeding) the incidence of bleedings were similar to warfarin or less.

In conclusion, the dose of DE 150 mg b.i.d. was chosen because a higher dose of 300 mg b.i.d. resulted in increased rates of bleeding events and that dose-finding trials found the dose of 150 mg b.i.d. to be favourable in patients undergoing orthopaedic surgery and NVAF. Similarities in study populations

suggested that the dose could be extrapolated to patients with VTE. The Applicant's rationale for dose selection was largely considered acceptable. However, a lower dose may be more appropriate for certain subpopulations (elderly, patients with moderate renal, patients treated with P-gp inhibitors). The MAH subsequently proposed a posology identical to that of the atrial fibrillation indication. i.e. recommendation of a reduced dose recommendations (daily dose of 220 mg taken as two 110 mg capsules) for patients aged 80 years or above and for patients who receive concomitant verapamil, as well as recommendations to consider this dose for other subgroups.

The effect of DE was demonstrated in four randomized, double-blind Phase III studies; three active controlled (W) and one placebo-controlled. Two of the studies support the aVTEt indication, and two of the studies supported the sVTEp indication. Studies 1160.53 and 1160.46 (RE-COVER and RE-COVER II) were W-controlled 6-month studies enrolling patients with acute symptomatic venous thromboembolism. These aVTEt studies 1160.53 and 1160.46 were replicate studies.

Study 1160.47 (RE-MEDY) was warfarin-controlled and had a treatment duration of 6-36 months. It evaluated the secondary prevention of recurrent VTE (sVTEp) and enrolled adult patients with acute symptomatic proximal DVT or PE who had received anticoagulant therapy for 3 to 12 months or who had completed participation in Study 1160.53 or 1160.46.

Study 1160.63 (RE-SONATE) was placebo-controlled and had a treatment duration of 6 months. It evaluated the secondary prevention of recurrent VTE (sVTEp) and enrolled patients with acute symptomatic proximal DVT of the leg and/or acute symptomatic PE, who had been treated for 6 to 18 months with an oral VKA or study drug in Study 1160.53.

Overall, the studies were well designed to fulfill their objective and according to relevant regulatory guidelines. The number of protocol amendments was quite high in the development programme, but this is acceptable when considering the size and complexity of the programme. Some of the amendments were a result of the decision to include patients completing the aVTEt studies into the sVTEp studies.

The design of the individual studies is discussed further below.

Studies supporting the aVTEt indication: 1160.53 and 1160.46 (RE-COVER and RE-COVER II)

The pivotal aVTEt studies 1160.53 and 1160.46 (RE-COVER and RE-COVER II) were randomized, double-blind, parallel-group studies of the efficacy and safety of oral DE (150 mg b.i.d.) compared to warfarin (target INR 2.0-3.0) for 6 months of treatment of acute symptomatic venous thromboembolism following initial treatment (5-10 days) with a parenteral anticoagulant approved for this indication. The pivotal aVTEt studies 1160.53 and 1160.46 were replicate studies.

The inclusion and exclusion criteria overall reflected the patient population in which DE is intended to be used. The patients were randomized according to active cancer and symptomatic PE at baseline. Baseline characteristics, medical history and concomitant medications were comparable between the treatment groups. Risk factors for VTE were previous VTE, smoking, immobilization, estrogen use and surgery/trauma and were balanced between treatment groups.

The primary endpoint of aVTEt studies (as well as the active-controlled sVTEp Study 1160.47) was the composite of recurrent symptomatic VTE and VTE-related deaths (excluding unexplained deaths, i.e., deaths which could not be attributed to a documented cause and for which PE/DVT could not be ruled out). This composite endpoint is the endpoint recommended for a non-inferiority design in the relevant EMA guidelines (*Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease [CPMP/EWP/563/98]* and *Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients [CPMP/EWP/6235/04]*). The

choice of primary and secondary endpoints is acceptable. The pre-defined non-inferiority margin for the primary endpoint for hazard ratio was 2.75 and for risk difference 3.6%.

Studies supporting the sVTEp indication

Two studies supported the sVTEp indication. One study (1160.47, RE-MEDY) was in patients at high risk of recurrence. The other study (1160.63, RE-SONATE) included patients at presumed low risk of recurrence, hence justifying the placebo control arm.

Study 1160.47 (RE-MEDY)

Study 1160.47 (RE-MEDY) was a randomized, double-blind, double-dummy, parallel-group, active-controlled, multi-centre study to assess whether DE could show non-inferiority to warfarin on long-term prophylaxis after venous thromboembolism. It included patients with acute symptomatic proximal DVT or PE who had received anticoagulant therapy for 3 to 12 months or who had completed participation in the aVTEt studies.

The inclusion and exclusion criteria overall reflect the patient population in which DE is intended to be used. The inclusion and exclusion criteria are considered relevant, sufficient and appropriate.

As indicated above, the primary endpoint was the composite of recurrent symptomatic VTE and VTE-related deaths (excluding unexplained deaths). The choice of primary and secondary endpoints is acceptable. The pre-defined non-inferiority margin for the primary endpoint for hazard ratio was 2.85 and for risk difference 2.80%.

Study 1160.63 (RE-SONATE)

Study 1160.63 (RE-SONATE) was a randomized, double-blind, parallel-group, placebo-controlled, multi-centre study to assess whether DE was superior to warfarin in the prevention of recurrent symptomatic VTE. It included patients who had had a PE or DVT, for which the patients had received treatment with oral VKA in 6-18 months prior to enrolment in Study 1160.63. The patients could also roll-over from Study 1160.53 (RE-COVER), being re-randomised entering Study 1160.63. The planned treatment period was 180 days followed by a 30 day wash-out period (double-blind treatment). The follow-up period was 11 months.

The inclusion and exclusion criteria were different from those of the RE-MEDY study since patients were at low risk of recurrence. This justified the placebo-controlled design. In light of the objective of the study and in the context of the RE-MEDY study, the criteria are deemed acceptable.

The primary endpoint, a composite of symptomatic DVT, non-fatal and fatal PE, was analysed using the Cox proportional hazards model. In contrast to the other three studies, unexplained deaths were defined as fatal PEs. The design and conduct of the study was acceptable.

Efficacy data and additional analyses

Studies supporting the aVTEt indication: 1160.53 and 1160.46 (RE-COVER and RE-COVER II)

The baseline characteristics were comparable between the two aVTEt studies and also across the two treatment arms in the respective studies.

In Study 1160.53, the hazard ratio for the primary endpoint was 1.05 (95% CI: 0.65, 1.70). The p-value for non-inferiority was <0.0001. The cumulative risk for the primary endpoint at 6 months was 2.4% in the DE group and 2.2% in the warfarin group. The RD was 0.4% (95% CI −0.7, 1.5). The upper limit of the CI of the risk difference was below the pre-defined non-inferiority margin of 3.6%.

In Study 1160.46, the hazard ratio for the primary endpoint was 1.13 (95% CI: 0.69, 1.85). The p-value for non-inferiority was 0.0002. The cumulative risk for the primary endpoint at 6 months was 2.4% in the DE group and 2.2% in the warfarin group. The risk difference was 0.2% (95% CI -1.0, 1.3).

Use of DE in the treatment of VTE was non-inferior to warfarin under the conditions given, i.e. a non-inferiority margin (NIM) of 2.75 for the hazard ratio and 3.6% in risk difference. The upper limits of the 95% confidence limits were never above the NIM of 2.75. However, patients treated with DE experienced consistently more events than patients treated with warfarin although the numbers were small (excess VTEs in the DE group of 0.2 events per 100 person years in Study 1160.53 and 0.6 events per 100 person years in Study 1160.46).

The mean time in therapeutic range (TTR) in the aVTEt studies were 58%, and the median TTR was 60.6%. This was a concern since higher levels can probably be achieved in several EU/EEA countries, and suboptimal TTR may present a bias disfavouring W. In its response to these concerns, the Applicant provided a survey of TTR data from a real world setting and from several historical VTE studies. It is accepted that TTR data from a real world setting are scarce and that TTR results may vary considerably depending on indication for VKA treatment and experience. Generally, the TTR in the VKA group of the aVTEt studies for DE was slightly lower than in the corresponding studies for other new oral anticoagulants. However, the mean TTR in the VTE studies for DE was in the same range as other recent VTE studies.

The Applicant also presented the primary efficacy endpoint and one secondary efficacy endpoint (VTE and all death) by five approximately equally sized groups (quintiles) of patients according to their TTR: <40%, 40-<57%, 57-<67%, 67-<78% and ≥78% (see table below). There was no clear relationship between TTR range and the two efficacy endpoints. Somewhat unexpected, the quintile for the aVTEt studies with the highest number of events was the one with the best TTR. In contrast, bleeding events quite clearly occurred more frequently in the quintile with the poorest TTR (please see safety section).

Primary and secondary efficacy endpoint by TTR in quintiles for pooled aVTEt studies and study 1160.47 (RE-MEDY) overall population, warfarin only; n/N (%)

TTR (INR 2.0-3.0)	<40%	40 - < 57%	57-<67%	67-<78%	>=78%
Primary endpoint					
RE-COVER	4/241 (1.7)	7/238 (2.9)	2/219 (0.9)	1/255 (0.4)	13/263 (4.9)
RE-COVER II	5/279 (1.8)	5/282 (1.8)	3/275 (1.1)	1/206 (0.5)	9/205 (4.4)
RE-MEDY	3/239 (1.3)	4 / 238 (1.7)	6/298 (2.0)	2/334 (0.6)	3/306 (1.0)
Secondary endpoint*					
RE-COVER	12/241 (5.0)	9/238 (3.8)	3/219 (1.4)	4/255 (1.6)	14/263 (5.3)
RE-COVER II	18/279 (6.5)	8/282 (2.8)	4/275 (1.5)	2/206 (1.0)	11/205 (5.4)
RE-MEDY	10/239 (4.2)	6/238 (2.5)	9/298 (3.0)	3/334 (0.9)	8/306 (2.6)

*Secondary efficacy endpoint: VTE and all death

In summary, the analysis of the effect of TTR on the efficacy results for warfarin did not reveal any clear impact on efficacy.

It is noteworthy that both aVTEt studies (along with the active-referenced sVTEp study RE-MEDY discussed below) showed warfarin to be numerically superior to DE – although the preset non-inferiority criteria were met.

The key secondary endpoint, recurrent symptomatic VTE and all-cause deaths, occurred at a similar rate in both the DE in warfarin group in the replicate studies 1160.53 and 1160.46. The HR of DE vs. warfarin was 1.04 (95% CI of 0.80, 1.37). In both studies, the differences in the cumulative risks and risk

differences in patients with/without symptomatic PE and with/without cancer in the two treatment groups were not significantly different. The incidences among the treatment groups of the individual components of the composite endpoint (death, symptomatic PE and DVT) were similar, with death as the most frequent event followed by DVT and PE.

Univariate and multivariate subgroups analysis did not show any clinically relevant interactions regarding baseline characteristics variables.

Studies supporting the sVTEp indication

Study 1160.47 (RE-MEDY)

The two treatment arms of the study were comparable with regard to demographic profile and other baseline characteristics. The rate of non-compliance was low in both study arms.

Slightly more patients in the DE treatment arm experienced events contributing to the primary endpoint (26) compared to the warfarin arm (18). However, overall the numbers were low. The upper limit of the confidence interval of the hazard ratio (1.44, 95% CI 0.78-2.64) was below the pre-defined non-inferiority margin of 2.85 (p=0.0137 for non-inferiority), and thus non-inferiority could be claimed. The cumulative risk for the primary endpoint at 18 months were slightly higher in the DE treatment arm (1.74%) compared to the warfarin treatment arm (1.38%).

The upper limit of the confidence interval of the risk difference (0.38, 95% CI -0.50-1.25) was below the pre-defined non-inferiority margin of 2.8% (p<0.0001 for non-inferiority), and thus non-inferiority could be claimed.

The time in therapeutic range (TTR) was low (51.9%) during the first study month increasing gradually during the study. The mean TTR was 61.5% and the median TTR was 65.3%. This was raised as a concern. However, the above discussion on the Applicant's response with regard to TTR for the aVTEt studies is also applicable to the RE-MEDY study.

A number of sensitivity analyses, such as using pooled cohorts and per-protocol analysis, yielded results that were comparable to the primary analysis.

All subgroup analyses of the primary endpoint had p-values that did not indicate statistical significance and thus the data indicate that the treatment does not vary across subgroups. In all subgroups but 2, the confidence intervals for risk differences included 0.0. These were the subgroup of BMI ≥35 kg/m2 (360 patients, RD: 3.11, 95%CI 0.40, 5.81) and the subgroup of CrCl 50 to 80 mL/min (617 patients; RD: 2.04, 95%CI 0.40, 3.67). As the number of patients in these subgroups was relatively low and the p-values for subgroup-by-treatment interactions were close to 1 (BMI: 0.9969, CrCl: 0.9727), these observations were not considered of clinical relevance. In conclusion, because of the small event numbers and the lack of power, the results from the subgroup analyses cannot be considered to provide as robust information as the results from the primary efficacy analyses. This is regarded as acceptable.

All three cohorts were pooled for the analyses of secondary endpoints. 42 patients (DE) compared to 36 patients (W) experienced recurrent VTEs or died due to any reason. The hazard ratio of DE vs. warfarin was 1.18 (95% CI 0.75-1.84). The cumulative risk for the composite of recurrent symptomatic VTE and all deaths at 18 months was 2.86% in the DE group and 2.53% in the warfarin group. The risk difference was 0.09% (95% CI -1.11, 1.28).

The cumulative risks for the composite of VTE and all deaths were highest for patients with initial symptomatic PE and active cancer at baseline (DE: 18.2%, W: 10.0%) and for patients with active cancer but without PE (11.4% vs. 9.1%). This is in accordance with expectations.

Comparable numbers of patients experienced DVT in the two treatment arms (DE: 17, W 13). The hazard ratio of DE vs. W was 1.32 (95% CI 0.64, 2.71). At 18 months, 15 patients (DE) vs. 12 patients (W) had experienced an acute symptomatic DVT. The cumulative risks were 1.17% and 0.98%, respectively. The resulting risk difference was 0.19% (95% CI -0.63, 1.00).

More patients experienced symptomatic, fatal or non-fatal PE in the DE group (10) vs. in the W group (5). The hazard ratio of DE vs. warfarin was 2.04 (95% CI 0.70, 5.98). At 18 months, the cumulative risks for symptomatic PE were 0.66% in the DE group and 0.40% in the warfarin group. The risk difference was 0.26% (95% CI -0.32, 0.84).

One patient in each group died from PE. The hazard ratio of DE vs. W for VTE-related death was 1.01 (95% CI 0.06, 16.22). The cumulative risks at 18 months were 0.08% (DE) and 0.07% (W). The risk difference was 0.01% (95% CI -0.20, 0.23). A comparable number of deaths of all causes during the planned treatment period were observed in the two groups (DE: 17, W: 19).

Study 1160.63 (RE-SONATE)

More patients receiving placebo (15%) discontinued the study compared to patients receiving DE (10.4%). Discontinuations were primarily due to adverse events (n=81 in the placebo group and n=50 in the DE group). Of these adverse events n=49 in the placebo group was symptomatic DVT or PE compared to n=4 in the DE treated group. DE treated patients experienced more bleedings (n=11) compared to the placebo group (n=4). Overall, 85-90% did no discontinue from study drug which is acceptable. The rate of non-compliance was low in both study arms.

Baseline characteristics were comparable between the two treatment groups. The frequencies of baseline conditions were reasonably balanced between treatment groups, with a few exceptions that are not considered to impact the overall results.

Superiority of DE over placebo for the secondary prevention of VTE (composite of recurrent DVT or fatal or non-fatal PE and unexplained deaths) was shown in the study. The DE treated group experienced 3 symptomatic VTEs compared to 37 symptomatic VTEs in the 6 month treatment period. The HR for DE versus placebo was 0.08 (95% CI: 0.02, 0.25). The analysis of the individual components of the primary composite endpoint showed that for all components the frequency was lower in the placebo group. The per-protocol analysis of the primary endpoint was consistent with the primary analysis of efficacy. DE was effective versus placebo in all age subgroups, in males and females, and regardless of whether the qualifying event was DVT, PE, or both DVT and PE. Age, sex and baseline CrCL adjusted Cox regression model did not alter the overall HR (HR 0.07, 95% CI: 0.024, 0.251) compared to the primary analysis. It appears that the effect of DE compared to placebo was sustained in the study-drug free 12 month follow-up period with a HR of 0.61 (95% CI: 0.42, 0.88) at the end of the entire study period.

The results show that at least 25% of patients in the placebo group needed anticoagulant therapy at the end of the study treatment period. This high number of patients is quite remarkable for a placebo-controlled study. This confirms that some patients included still were in need of anticoagulant therapy.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table Summary of main efficacy results RE-COVER study

BI study No. [Report no.] **Study start and completion** **Number of centers / locations**	**Study design and type of control** **Main inclusion criteria**	**Study & control drugs** **Dose regimen** **Planned duration of treatment**	**Study objective**	**No. of randomized [completed][1] patients by treatment arm** **Key demographic characteristics: sex, mean age ± SD**	**Primary endpoint results**
Active-controlled pivotal study 1160.53 [U09-1400] RE-COVER 231 enrolling centers / Europe, North and Latin America, Australia, and Africa Apr-06 to May-09	Randomized, double-blind, double-dummy, parallel-group, active-controlled study Adult patients with acute symptomatic proximal DVT of the leg and/or acute symptomatic PE, for whom at least 6 months anticoagulant therapy was considered appropriate	DE: 150 mg b.i.d., oral W: target INR of 2.0-3.0; oral 6 months	To compare the safety and efficacy of DE and warfarin for a 6-month treatment of acute symptomatic VTE following an initial treatment (5 – 10 days) with a parenteral anticoagulant approved for this indication	Total: 2564 [2341] DE: 1280 [1172] W: 1284 [1169] Sex: 41.6% female Age: 54.7 ± 16.0 year	Composite of recurrent symptomatic VTE and VTE-related death HR DE vs. W: 1.05 (95% CI: 0.65, 1.70) p-value<0.0001 for non-inferiority RD DE vs. W: 0.4 (95% CI: -0.8, 1.5) p-value<0.0001 for non-inferiority

[1]Completed the planned observation time for the study.
HR= HR; RD=RD

Table Summary of main efficacy results RE-COVER II study

BI study No. [Report no.] **Study start and completion**	**Study design and type of control** **Main inclusion criteria**	**Study & control drugs** **Dose regimen**	**Study objective**	**No. of randomized [completed][1] patients by treatment arm**	**Primary endpoint results**

Number of centers / locations		Planned duration of treatment		Key demographic characteristics: sex, mean age ± SD	
Active-controlled pivotal study 1160.46 [U11-2298] RE-COVER II 208 centers / Europe, North and Latin America, Asia, Australia, New Zealand, Israel, and South Africa Jun-08 to May-11	Randomized, double-blind, double-dummy, parallel-group, active-controlled study Adult patients with acute symptomatic proximal DVT of the leg and/or acute symptomatic PE, for whom at least 6 months of anticoagulant therapy was considered appropriate	DE: 150 mg b.i.d., oral W: target INR of 2.0-3.0, oral 6 months	To compare the safety and efficacy of DE and warfarin for a 6-month treatment of acute symptomatic VTE following an initial treatment (at least 5 days) with a parenteral anticoagulant approved for this indication	Total: 2589 [2327] DE: 1294 [1155] W: 1295 [1172] Sex: 39.4% female Age: 54.9 ± 16.2 years	Composite of recurrent symptomatic VTE and VTE-related deaths HR DE vs. W:1.13 (95% CI: 0.69, 1.85) p = 0.0002 for non-inferiority RD DE vs. W: 0.2 (95% CI -1.0, 1.3) p-value <0.0001 for non-inferiority

[1] Completed the planned observation time for the study. HR= HR; RD=RD

Table Summary of main efficacy results RE-MEDY study

BI study No. [Report no.] Study start and completion Number of centers / locations	Study design and type of control Main inclusion criteria	Study & control drugs Dose regimen Planned duration of treatment	Study objective	No. of randomized [completed][1] patients by treatment arm Key demographic characteristics: sex, mean age ± SD	Primary endpoint results
Active-controlled	Randomized,	DE: 150 mg b.i.d., oral	To compare the safety	Total: 2866 [2679]	Composite of recurrent

pivotal study 1160.47 [U10-2533] RE-MEDY 264 centers / Europe, North and Latin America, Asia, Australia, New Zealand, Israel, and South Africa Jul-06 to Oct-10	double-blind, double-dummy, parallel-group, active-controlled study. Adult patients with acute symptomatic proximal DVT or PE who had received anticoagulant therapy for 3 to 12 months or who had completed participation in 1160.53 or 1160.46.	W: target INR of 2.0-3.0, oral 6 to 36 months	and efficacy of DE and warfarin for the long-term treatment and secondary prevention of acute symptomatic VTE following initial treatment (3-12 months) with standard doses of an anticoagulant or completion of participation in Study 1160.53 or Study 1160.46.	DE: 1435 [1348] W: 1431 [1331] Sex: 39.0% female Age: 54.6 ± 15.2 years	symptomatic VTE and VTE-related deaths HR DE vs. W: 1.44 (95% CI 0.78, 2.64) p = 0.0137 for non-inferiority RD: 0.4% (95% CI -0.5, 1.2) p<0.0001 for non-inferiority

[1] Completed the planned observation time for the study. HR= HR; RD=RD

Table Summary of main efficacy results RE-SONATE study

BI study No. [Report no.] **Study start and completion Number of centers / locations**	**Study design and type of control** **Main inclusion criteria**	**Study & control drugs Dose regimen** **Planned duration of treatment**	**Study objective**	**No. of randomized [completed][1] patients by treatment arm** **Key demographic characteristics: sex, mean age ± SD**	**Primary endpoint results**
Active-controlled pivotal study 1160.63 [U11-2267-02]	Randomized, double-blind, placebo-controlled study. Adult patients with	DE: 150 mg b.i.d., ora Placebo: b.i.d., oral 6 months with 12-month study-drug-	To compare the safety and efficacy of DE with placebo in the long-term prevention of recurrent symptomatic	Total: 1353 [1318] DE: 685 [667] P: 668 [651]	Composite of recurrent symptomatic VTE and VTE-related deaths.

RE-SONATE 147 centers / Europe, North America, Asia, Australia, New Zealand, and South Africa Dec-07 to Dec-11	acute symptomatic proximal DVT of the leg and/or acute symptomatic PE, who had been treated for 6 to 18 months with an oral VKA or study drug in Study 1160.53.	free follow-up	VTE following initial treatment (6-18 months) with therapeutic dosages of an oral VKA or completion of participation in Study 1160.53.	Sex: 44.5% female Age: 55.8 ± 15.3 years	HR: DE vs. placebo 0.08 (95% CI 0.02, 0.25) P<0.0001 for superiority

[1] Completed the planned observation time for the study. HR= HR; RD=RD

Uncertainties regarding the results

During the assessment, the CHMP expressed a concern that up to about half of the effect of warfarin may be lost as evidenced by the results of the RE-MEDY study combined with the excess of ACS events and the fact that the advantage over warfarin in terms of bleedings appear to diminish in warfarin-treated patients who are managed reasonably well (i.e. disregarding patients with the poorest INR control). It was acknowledged by the CHMP that the efficacy looks more favourable in the acute treatment studies (RE-COVER and RE-COVER II). The CHMP considered that it would be highly problematic to grant a treatment indication without also granting a prevention indication.

The Applicant further justified the positive benefit-risk balance of DE in both the acute treatment and the prevention indication. The Applicant explained that the three warfarin-controlled studies with DE in (acute) venous thromboembolism (VTE) treatment (RE-COVER, RE-COVER II) and in secondary VTE prevention (RE-MEDY) clearly met the predefined non-inferiority (NI) margins with regard to recurrent VTE for both the hazard ratios (HRs) and risk differences (RDs), demonstrating consistent efficacy for both VTE treatment and prevention of recurrent VTE. In addition, a positive net clinical benefit was demonstrated with DE against warfarin, which was not driven by poor levels of INR control in the warfarin patients. Finally, the placebo-controlled study with DE in long-term prevention of recurrent VTE (RE-SONATE) unequivocally demonstrated the efficacy of DE in the VTE prevention setting.

In clinical studies with very low incidences of efficacy endpoint events, as observed in the RE-MEDY study, the RD was considered statistically more appropriate than the HR to measure any difference in the effect size between the treatment groups. The RDs for the primary efficacy endpoint of recurrent VTE and VTE related deaths events in RE-COVER, RE-COVER II, and RE-MEDY were comparable at 0.4%, 0.2% and 0.4%, respectively. This clearly indicates that there is no clinically meaningful difference in efficacy between treatments for both (acute) VTE treatment and secondary VTE prevention. Retrospective calculations showed that the three warfarin-controlled trials independently demonstrated that more than 85% of the warfarin effect was preserved, demonstrating comparability across trial results which is not as clearly observed when comparing HRs alone. The amount of preserved effect is in line with the literature, which recommends 50% preservation of the effect in terms of the confidence interval (classical 95-95 rule) or 2/3 of the effect.

In addition to comparable efficacy to warfarin, the incidence of all categories of major bleeding events (MBE) was lower for DE patients compared to warfarin for both studies of short (6 months in RE-COVER/RE-COVER II) and longer duration (up to 36 months in RE-MEDY). Based on the study results, one would expect a reduction of 1.5 events less (MBE) in 100 patient-years of treatment with DE vs. warfarin in patients treated for (acute) VTE, and 0.6 events less (MBE) in 100 patient-years in patients treated for secondary VTE prevention. To better represent clinical situations, adding clinically relevant bleeding events (CRBE) to MBE demonstrated a reduction of 7.7 events less (MBE and CRBE) in 100 patient-years of treatment with DE vs. warfarin in patients treated for (acute) VTE, and 3.8 events less (MBE and CRBE) in 100 patient-years in patients treated for secondary VTE prevention. These bleeding reductions were considered clinically meaningful.

To put the rate of ACS events into a broader perspective, a composite net clinical benefit endpoint was applied. The composite endpoint of non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death and MBE was very similar between DE and warfarin for both the pooled RE-COVER/RE-COVER II studies as well as for RE-MEDY, with HRs of 1.02 (95% CI: 0.81-1.27) and 1.05 (95% CI: 0.75-1.46), respectively. Furthermore, when both MBEs and clinically relevant non major bleeding events (CRBEs) were included into this analysis, a statistically significant benefit for DE over warfarin was shown for both the pooled RE-COVER/RE-COVER II studies as well as for RE-MEDY, with HRs of 0.80 (95% CI: 0.68-0.95) and 0.73 (95% CI: 0.59-0.91) respectively.

The benefit of warfarin is dependent on the patient's time in therapeutic range (TTR). Hence, it was questioned whether the positive results in the DE trials were partly driven by poor control of INR in warfarin patients. The MAH therefore analysed the association of the clinical effect of dabigatran to the quality of warfarin control by using the centre TTR (cTTR), which is the mean TTR of all warfarin patients in each centre. In all these analyses for both the pooled RE-COVER/RE-COVER II and RE-MEDY studies, it was shown that there was no clear dependency between the clinical efficacy, clinical safety and the net clinical benefit results of DE to the centre TTR. This demonstrated that the positive results of DE in the VTE programme were not driven by the poor levels of INR control in the warfarin patients.

Consistency of overall efficacy results

The objective of all three warfarin-controlled trials with DE (RE-COVER, RE-COVER II and RE-MEDY) was to show non-inferiority to warfarin in both hazard ratio (HR) and risk difference (RD). For the (acute) VTE treatment studies, RE-COVER and RE-COVER II, based on data from previous published studies in this therapy area, an NI margin of 2.75 in HR and 3.6% in RD was selected, corresponding to preservation of at least 57% and 75% of the effect of full-dose W, respectively. The individual studies, RE-COVER and RE-COVER II, showed comparable HRs, 1.05 (95% CI, 0.65 to 1.70) and 1.13 (95% CI, 0.69 to 1.85) respectively, demonstrating consistent efficacy of DE in two independent studies during the first six months of therapy after an index VTE event. The primary endpoint results of both trials, RE-COVER and RE-COVER II, with regard to the upper limit of the 95% CI of the HR (1.70 and 1.85, respectively) were well below the pre-specified NI margin of 2.75 and it is important to note that these results were also below the more restrictive margin of non-inferiority of 2.0, used in the pivotal trials for rivaroxaban, EINSTEIN-DVT and EINSTEIN-PE. The RDs for both the studies were consistent, and were also well below the pre-specified NI margin of 3.6%. The RDs was 0.4% (95% CI, -0.7 to 1.5) for the RE-COVER study and 0.2% (95% CI, -1.0 to 1.3) for the RE-COVER II study. The results of the HRs and RDs from RE-COVER and RE-COVER II studies indicate a clear relationship between HR and RD.

For the secondary VTE prevention study RE-MEDY, an NI margin of 2.85 in HR and 2.8% in RD was selected, corresponding to preservation of at least 70% and 67% of the effect of full-dose W, respectively. These pre-specified criteria for declaring non-inferiority for the HR and RD were met in the RE-MEDY study: HR 1.44 (95% CI: 0.78, 2.64) and RD 0.4% (95% CI: -0.5, 1.2). Even though the HR was above 1 in RE-MEDY, the effect of low event rates on the HR can be seen, as the between-group RD was still small and similar to the rate seen in the RE-COVER and RE-COVER II studies. Having a relatively large HR (upper limit 95% CI was 2.64) while having a small RD of 0.4% can be explained by the very low rate of recurrent VTEs and VTE-related deaths in this study (22 VTE events (1.7%) in the DE group, 17 VTE events(1.4%) in the warfarin group). As a result, each incremental event had a significant impact on the HR, but the event rates and RD remained low and indicate that both DE and warfarin are effective.

Based on the yearly event rates calculation, one would expect an excess of 0.4 events (VTE and VTE-related deaths) per 100 patient-years of treatment with DE vs. warfarin in patients treated for secondary VTE prevention, and also 0.4 events (VTE and VTE-related deaths) per 100 patient-years of treatment with DE vs. warfarin in patients treated for (acute) VTE. This shows the consistency of results between the three warfarin-controlled studies indicating that there is no clinically meaningful difference between the effect of DE in the treatments for both (acute) VTE treatment and secondary VTE prevention.

From further analyses of the different components of the primary efficacy endpoint one can expect an excess of 0.35 events (symptomatic DVT) and 0.07 events (fatal and non-fatal PE) per 100 patient-years of treatment with DE vs. warfarin patients treated for (acute) VTE. For patients treated for secondary VTE prevention one can expect an excess of 0.15 events (symptomatic DVT) and 0.25 events (fatal and non-fatal PE) per 100 patient-years of treatment with DE vs. warfarin. This again shows the consistency of

results between studies, and confirms that risk differences for more severe events (PE events) are very small in both the (acute) VTE and secondary VTE prevention studies.

In addition, the clinical efficacy of DE in the secondary VTE prevention indication is further supported by the results from the RE-SONATE study. In the RE-SONATE study, which was a placebo-controlled, secondary VTE prevention study, DE was clearly shown to be superior than placebo in terms of the primary endpoint (VTE, VTE-related and unexplained deaths) with a HR of 0.08 (95% CI , 0.02 to 0.25; p<0.001). This result is comparable to the primary efficacy endpoint result from the EINSTEIN-Extension study. (HR 0.18; 95% CI, 0.09 to 0.39).

Efficacy results and association with warfarin INR control

The benefit of warfarin is dependent on the quality of the INR control and this can be deduced from the patient's time in therapeutic range (TTR) (INR between 2.0 and 3.0). It was questioned whether the positive results in the DE trials were partly driven by the poor control of the INR in the warfarin patients. Therefore an analysis on the association of the clinical effect of DE to the quality of the INR control in the warfarin patients was performed. For this analysis, the quality of the INR control is represented by the centre TTR (cTTR), which is the mean TTR of all the individual warfarin patients in each centre. Centers were then divided into five groups (quintiles) according to their mean TTR values. DE patients were assigned to the five groups based on the assignment of their individual center. The quintiles were determined for the pooled RE-COVER/RE-COVER II and RE-MEDY studies separately.

The analysis of the primary clinical efficacy endpoint according to the cTTR, for both the RE-COVER/RE-COVER II and the RE-MEDY studies showed no obvious clear pattern between the clinical efficacy and cTTR quintiles, therefore confirming that the clinical efficacy effect of DE does not diminish when compared to warfarin-treated patients who are managed reasonably well.

Clinical benefit of overall safety results

In addition to comparable efficacy to warfarin, the incidence of all categories of MBEs (consisting of MBEs, adjudicated MBEs with a fatal outcome, TIMI major bleeding, and intracranial MBEs) as well as life-threatening bleeding events, MBEs and CRBEs, and any bleeding events (MBEs, CRBEs, and nuisance/trivial bleeding) were lower for DE patients compared to warfarin for both studies of short (6 months in RE-COVER/RE-COVER II) and longer duration (up to 36 months in RE-MEDY). Based on the study results one would expect a reduction of 1.5 events less (MBE) per 100 patient-years of treatment with DE vs. warfarin in patients treated for (acute) VTE, and 0.6 events less (MBE) per 100 patient-years in patients treated for secondary VTE prevention, and a reduction of 7.7 events less (MBE and CRBE) per 100 patient-years of treatment with DE vs. warfarin in patients treated for (acute) VTE, and 3.8 events less (MBE and CRBE) per 100 patient-years in patients treated for secondary VTE prevention. These bleeding reductions were considered clinically meaningful.

Further analyses were conducted to ascertain the effect of cTTR on the bleeding results (MBE, MBE and CRBE). For both the RE-COVER/RE-COVER II and the RE-MEDY studies no obvious clear pattern could according to the Applicant be observed between the bleeding risk and cTTR quintiles, therefore showing that the advantage over warfarin in terms of bleeding does not appear to diminish when compared to warfarin-treated patients who are managed reasonably well.

Net clinical benefit in RE-COVER/RE-COVER II and RE-MEDY

The benefit-risk balance of DE compared to warfarin in both the (acute) VTE treatment and the secondary VTE prevention indications was further explored by evaluating the net clinical benefit. This was evaluated using two approaches. The first more conservative approach to this composite endpoint includes non-fatal

recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death, and MBE. With the second approach, MBE and CRBE are also included, which gives a comprehensive analysis applicable to real-world clinical practice situations.

The first composite net clinical benefit endpoint (non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death, MBE) calculated for the pooled RE-COVER and RE-COVER II studies is shown in table 1.4.1.1.1.1 below (please note that in the tables, the composite net clinical benefit endpoint is presented as "composite cardiovascular endpoint"). With a HR close to 1, the net clinical benefit is similar for DE and warfarin treatment (HR 1.02 (95% CI: 0.81-1.27)). However, when MBEs and CRBEs were included in the calculation of the net clinical benefit (endpoint non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism, all-cause death, MBE/CRBE), a statistically significant difference was evident favouring DE over warfarin (HR 0.80 (95% CI: 0.68-0.95)) (Table 1.4.1.2.1.1 below).

Table 1.4.1.1.1.1 Hazard ratio for composite cardiovascular endpoint incl. MBE and all death until the end of the post-treatment period for acute VTE treatment studies - FAS

	DE	W
Number of patients	2553	2554
Composite cardiovascular endpoint and MBE (incl. all death) [N(%)] *	155 (6.1)	152 (6.0)
Model 1 #		
Hazard Ratio vs. warfarin		
Estimate (95% CI)	1.02 (0.81, 1.27)	

Table 1.4.1.2.1.1 Hazard ratio for composite cardiovascular endpoint incl. MBE or CRBE and all death until the end of the post-treatment period for acute VTE treatment studies - FAS

	DE	W
Number of patients	2553	2554
Composite cardiovascular endpoint and MBE or CRBE (incl. all death) [N(%)] *	252 (9.9)	308 (12.1)
Model 1 #		
Hazard Ratio vs. warfarin		
Estimate (95% CI)	0.80 (0.68, 0.95)	

The analyses performed for the RE-COVER studies were also applied to the RE-MEDY study. As with the pooled RE-COVER/RE-COVER II studies, the first composite net clinical benefit endpoint analysis showed similar net clinical benefit between DE and warfarin, with a HR close to 1 (HR 1.05 (95% CI: 0.75-1.46)). However, in the second composite net clinical benefit endpoint analysis where MBEs and CRBEs were included, a statistically significant difference was again evident favouring DE over warfarin (HR 0.73 (95% CI: 0.59-0.91)). (Tables 1.4.1.1.1.4 and 1.4.1.2.1.4 below).

Table 1.4.1.1.1.4 Hazard ratio for composite cardiovascular endpoint incl. MBE and all death until the end of the planned treatment period for study 1160.47 (RE-MEDY) - FAS

	DE	W
Patients [N(%)]	1430	1426
Composite cardiovascular endpoint and MBE (incl. all death)*	72 (5.0)	69 (4.8)
Hazard Ratio vs. warfarin		
Estimate (95% CI) #	1.05 (0.75, 1.46)	
p-value for superiority	0.7819	

Table 1.4.1.2.1.4 Hazard ratio for composite cardiovascular endpoint incl. MBE or CRBE and all death until the end of the planned treatment period for study 1160.47 (RE-MEDY) - FAS

	DE	W
Patients [N(%)]	1430	1426
Composite cardiovascular endpoint and MBE or CRBE (incl. all death)*	136 (9.5)	183 (12.8)
Hazard Ratio vs. warfarin		
Estimate (95% CI) #	0.73 (0.59, 0.91)	
p-value for superiority	0.0058	

The results of the net clinical benefit analyses therefore shows that overall, when compared to warfarin, DE has a positive impact to the clinical outcome of the patients treated for acute VTE and also for secondary VTE prevention.

Net Clinical Benefit stratified by cTTR:

For the pooled RE-COVER and RE-COVER II studies, in both the net clinical benefit endpoint analyses, no clear pattern was according to the Applicant obvious between cTTR quintiles and the net clinical benefit, indicating that the positive benefit of DE over warfarin is not dependant on the quality of the INR control in the warfarin patients.

For the RE-MEDY study, the results again showed no clear pattern. For the net clinical benefit including MBEs and CRBEs, it is worth noting that for all the cTTR quintiles, all the HRs are below 1, numerically favouring DE over warfarin.

According to the Applicant, the results of the net clinical benefit analyses according to cTTR therefore showed that overall, when compared to warfarin, the positive impact of DE to the clinical outcome of the patients treated for acute VTE and also for secondary VTE prevention, is not dependant to the quality of INR control in the warfarin treated patients.

The MAH concluded that the three active-controlled studies with DE, two of which in (acute) VTE treatment (RE-COVER, RE-COVER II) and the third in secondary VTE prevention (RE-MEDY) robustly demonstrated therapeutic equivalence compared to warfarin. No clear dependency between clinical efficacy, clinical safety and net clinical benefit and the cTTR levels was detected demonstrating that the positive results were not driven by the poorly controlled warfarin patients. Furthermore, DE in the long-term prevention of recurrent VTE (RE-SONATE) was unequivocally superior to placebo in terms of clinical efficacy. According to the MAH, the totality of the data demonstrates that DE is safe and efficacious and can serve as a valuable alternative to warfarin for both the (acute) treatment of VTE and secondary VTE prevention.

The CHMP largely agreed with the response of the Applicant. The Applicant argued that because of the low number of events in the RE-MEDY study, the risk difference was a more appropriate calculation. The CHMP agreed that the absolute difference between DE and warfarin in the RE-MEDY study was small. Looking at the results of the RE-MEDY study in the perspective of the aVTEt studies and the lack of a plausible explanation as to why the efficacy of DE compared to warfarin would be less in the prevention setting than in the acute setting as well as the convincing placebo-controlled prevention study (RE-SONATE), the CHMP considered that the efficacy also for the prevention indication was acceptable – also in light of the advantages in terms of bleedings. While the CHMP did consider that poorly managed

patients on warfarin had more major bleedings than other warfarin patients, it was agreed that the advantage of DE in terms of major bleeding events was also evident when comparing to warfarin-treated patients in other TTR categories, including patients with TTR levels similar to those typically seen in Europe.

Correlation between DE exposure and clinical events in VTE patients

In addition the CHMP expressed the opinion that no assessment of efficacy results related to exposure was performed in RE-COVER due to the low number of ischaemic events. The Applicant was asked to further assess the correlation between DE exposure in VTE patients and clinical events in order to be able to define the target range of PK values where it is necessary to perform drug monitoring (in a bleeding or emergency setting for example).

The Applicant provided a response were it was argued that in VTE patients, due to the low number of endpoint events and the availability of PK only in the RE-COVER study (N = 850 patients had PK at visit 4), a limited exposure-response analysis (only on MBE, no sub-group analyses [U12-3388]) could be done. Although the correlation was weaker (especially at higher concentrations) in RE-COVER than in the more robust RE-LY analysis these data confirm consistency in the exposure-bleeding relationship across VTE and NVAF (non-valvular atrial fibrillation) patients. Additionally, a high consistency could be observed between RE-LY and RE-COVER patients when comparing dabigatran trough plasma concentrations from patients stratified by age, renal function or verapamil co-medication. The clinical phase III study in NVAF patients, RE-LY, is considered to have a robust and more informative data set in terms of exposure-response. A trough concentration exceeding 200 ng/mL, which is exceeding the 90th percentile in RE-LY, may be associated with a presumably increased risk of bleeding also for VTE patients if the comorbidities and co-medications influencing bleeding risk are also similar. The Applicant clarified that the available information is reflected in the current SmPC for the approved indications. The SmPC was proposed to be changed to reflect this information for both indications, SPAF and DVT/PE treatment and secondary prevention. Assessment of dabigatran plasma concentrations may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors for bleeding. The Applicant pointed out, that this information is included the SmPC, section 4.4 and will also apply to DVT/PE patients:

Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution (see section 5.1).

This information is further detailed in the DVT/PE prescriber guide.

In general, DE does not qualify for a narrow therapeutic index drug (NTI) according to the commonly accepted definitions (see also Am J Health Syst Pharm 1997; 54: 1630-2 [R09-6026]). According to the Applicant, DE has been proven to be safe and efficacious in several fixed dose clinical trials in orthopaedic surgery (OS) patients, patients with non-valvular atrial fibrillation (NVAF) and patients with DVT/PE (VTE) and results of all clinical studies with dabigatran across indications, so far, do not point to the need of regular therapeutic drug monitoring (TDM) and dosing guided by TDM. In terms of safety (major bleeding events, MBE) in VTE patients fixed dose dabigatran was shown to have even less MBEs than INR controlled warfarin. The Applicant was thus, of the opinion that the submitted label contains sufficient

information including quantitative information on dabigatran concentrations and PD to safeguard the therapy with DE. The Applicant concluded that although the determination of the anticoagulation activity may be helpful in some situations (in a bleeding or emergency setting for example), DE does not qualify for a drug which requires regular drug monitoring as has been consistently shown in multiple trials across indications in comparison to INR monitored warfarin. The need for drug monitoring is further limited by the fact that the current label would allow dose adjustment due to patient characteristics such as age and renal function, further mitigating the risk of excessive anticoagulation and bleeding. With respect to any definition of a "target therapeutic range" even the multitude of clinical data in RE-LY did not allow for clearly defined boundaries, making any chosen value questionable. It is, thus, not expected that any further clinical trial in the VTE indication would allow for a more precise estimation of a presumed "therapeutic range". In terms of bleeding, the Applicant considered it reasonable to communicate the dabigatran plasma concentrations which may be indicative of dabigatran-induced bleeding in case of an emergency. As the pathophysiology for bleeding is regarded as not different between the two patient populations of VTE and NVAF patients, the levels already reported in the current SmPC (see Table 2 from the section 4.4 Special Warnings and Precautions) are overall applicable. It is, thus not expected that any further study would provide substantial new information to change the current information based on the data from RE-LY in over 18,000 patients and confirmed by the data from RE-COVER.

The CHMP agreed in general with the conclusions provided by the Applicant. Due to the low number of endpoint events in VTE patients and the availability of PK only in the RE-COVER study (N = 850 patients had PK at visit 4), a limited exposure-response analysis, could be done showing only a dose-response relationship for MBE. It is acknowledged that the PK data from the RELY study are more robust, due to the higher number of included patients in this study. However, this does not preclude, in the future, further PK analyses in smaller studies, in order to collect information from different clinical settings for example, and thus be able to check the consistency of results between studies or no, since it is an important issue with this product. The consistency between RE-COVER and RE-LY was demonstrated as assessed by the CHMP. Therefore, the CHMP endorsed the proposition of the MAH to extend the current information provided in the SmPC for SPAF indication to DVT/PE indication: trough concentration > 200 ng/ml associated with a presumably increased risk of bleeding.

The Applicant assumed that only plasma concentrations which may be indicative of dabigatran-induced bleeding are of value, in case of an emergency for instance. The CHMP considered however that the detection of low plasma concentrations which may indicate insufficient efficacy (and therefore correlated with increased risk ischemic events) are also of value. Such values could be useful indeed, when dabigatran has to be temporarily discontinued, before surgery for instance, in order to check that patients are not under-anticoagulated and may need a switch to parenteral anticoagulation. Therefore, it was recommended that the Applicant should continue to perform PK analyses in the ongoing and upcoming clinical trials to check the consistency of the results between studies on the correlation of PK data to MBE events and ischaemic events and provide the results of these analyses within the upcoming PSURs.

An important concern pertained to the dose recommendations originally proposed by the Applicant. Based on the four pivotal studies forming the basis of the DVT/PE application, the Applicant initially recommended no posology changes based on an age criteria or in the event of concomitant treatment with P-gp inhibitors such as verapamil. While it may be argued that the SPAF population represents a more frail subgroup as compared to the DVT/PE population, posology changes and dose reduction of DE based on an age criterion such as over 80 years might be considered relevant. Similarly, the CHMP assumed that P-gp inhibition with verapamil might in general affect patients equally, irrespective of the presence of a diagnosis of SPAF or DVT/PE.

Thus, even in the DVT/PE population, a different posology recommendation in these subgroups was considered relevant. In contrast, the possible consequence of suboptimal treatment might be perceived as being greater in the SPAF population as compared with the DVT/PE population. Accordingly, a greater risk of bleeds may be accepted in the SPAF population to achieve optimal anticoagulation. Nevertheless, it is within this (SPAF) indication that reduced dosing regimens of DE are recommended.

Finally, following the discussion, the Applicant subsequently accepted a posology identical to that of the SPAF indication. i.e. recommendation of a reduced dose recommendations (daily dose of 220 mg taken as two 110 mg capsules) for patients aged 80 years or above and for patients who receive concomitant verapamil, as well as recommendations to consider this dose for other subgroups. It should noted that this lower dose was not tested in the aVTEt and sVTEp programme, and the low number of patients in these subgroups in the completed studies with 150 mg BID did not allow firm conclusions based on clinical outcomes. However, pharmacokinetic data indicated that alignment with the posology for the SPAF indication was the most appropriate solution, and it was supported by the CHMP.

The percentage of patients with cancer enrolled in warfarin-controlled trials was 4.5% for the pooled RE-COVER trials and 4.2% for RE-MEDY. In all the warfarin-controlled trials, *active cancer* was defined as a diagnosis of cancer, other than basal-cell or squamous-cell carcinoma of the skin, within five years before the enrolment, any treatment for cancer within five years or recurrent or metastatic cancer.

The results show that there was a significantly higher frequency of recurrent VTE or VTE-related mortality among patients who had cancer compared to patients who did not have cancer, independently of the anticoagulation treatment received. Amongst the cancer patients, the efficacy of DE was not different from W. In terms of safety, the incidence of bleeding events in cancer patients treated with dabigatran was comparable to those treated with W.

Given the limitations of the small samples sizes of patients with cancer enrolled in the VTE programme with DE and the heterogeneity of cancer, the Applicant acknowledged that it is adequate to include the warning in the SmPC section 4.4 for Pradaxa 110 mg and 150 mg that the efficacy and safety have not been established for DVT/PE patients with active cancer.

During the assessment the CHMP suggested that the current algorithm in section 4.2 of the SmPC for switching from DE to VKA could be revised as a patient could receive VKA for 5 days without monitoring which may be too long, especially in the case of acenocoumarol.

The MAH explained that the current SmPC wording was driven by the fact that INR testing to assess anticoagulation status when taking DE is unreliable and in some patients false positive INR elevations have been reported. Hence, even a declining, residual effect of dabigatran may still elevate the INR level during the switching period. The Applicant agreed with the comment that the current wording (*Because Pradaxa can contribute to an elevated INR, INR testing should not be performed until Pradaxa has been stopped for at least 2 days*) should be revised.

At the end it was agreed to modify the wording as follows:

Because Pradaxa can increase INR, the INR will better reflect VKA's effect only after Pradaxa has been stopped for at least 2 days. Therefore, INR testing is not recommended until Pradaxa has been stopped for at least 2 days.

2.3.4. Conclusions on the clinical efficacy

As no dedicated dose-finding study was performed to support the aVTEt and sVTEp indications,the dose of DE 150 mg b.i.d. was chosen because a higher dose of 300 mg b.i.d. resulted in increased rates of

bleeding events, and dose-finding trials that were conducted for patients undergoing orthopaedic surgery and NVAF found the dose of 150 mg b.i.d. to be favourable.. Similarities in study populations suggested that the dose could be extrapolated to patients with VTE. The Applicant's rationale for dose selection was largely considered acceptable. The MAH subsequently accepted a posology identical to that of the SPAF indication, i.e. recommendation of a reduced dose recommendations (daily dose of 220 mg taken as two 110 mg capsules) for patients aged 80 years or above and for patients who receive concomitant verapamil, as well as recommendations to consider this dose for other subgroups. This is acceptable.

Overall, all four main studies the studies were well designed and conducted. The warfarin treatment was not optimal in the three active-referenced studies, and time in the therapeutic range (TTR) fell below what can be achieved in some EU/EES countries. This was a concern since it may have presented a bias disfavouring the warfarin treatment arms. However, the TTR levels in the DE studies were comparable to other recent VTE studies. Further, the Applicant also presented the primary efficacy endpoint and one secondary efficacy endpoint (VTE and all death) by five approximately equally sized groups (quintiles) of patients according to their TTR. There was no clear relationship between TTR range and the two efficacy endpoints.

In all three studies, warfarin outperformed DE numerically – although non-inferiority was formally shown in the studies. It has been sufficiently documented that the efficacy of DE is similar to that of warfarin and thus acceptable.

2.4. Clinical safety

2.4.1. Introduction

Brief summary of existing safety profile

In the four actively controlled VTE prevention trials in orthopaedic surgery, more than 5,000 were treated with 150 mg or 220 mg daily of DE (DE), while about 400 received doses less than 150 mg daily and about 1,200 received doses in excess of 220 mg daily. In the pivotal study investigating the prevention of stroke and SEE in patients with atrial fibrillation (the RE-LY study), about 12,000 patients were randomized to DE. About half were treated with 150 mg b.i.d., and about half received 110 mg b.i.d.

About 9 % of patients treated for elective hip or knee surgery (short-term treatment for up to 42 days) and 22 % of patient with atrial fibrillation treated for the prevention of stroke and SEE (long-term treatment for up to 3 years) experienced adverse reactions.

As expected with an anticoagulant, the most commonly reported adverse reactions were bleedings occurring in approximately 14 % of patients treated short-term for elective hip or knee replacement surgery, and 16.5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE.

Bleedings, in particular gastrointestinal bleedings, have been the most prominent adverse effects of DE, also in the post-marketing setting.

In addition to gastrointestinal bleedings, other gastrointestinal adverse effects such as abdominal pain, diarrhoea, dyspepsia and nausea are commonly attributed to treatment with DE.

Safety analyses in the aVTEt and sVTEp programme

All four studies (studies 1160.53 and 1160.46 (RE-COVER and RE-COVER II), Study 1160.47 (RE-MEDY) and Study 1160.63 (RE-SONATE) were combined efficacy and safety studies.

Safety was assessed based on:

1. Incidence of bleeding events
    a. Major Bleeding Events (MBEs)
    b. MBEs and Clinically Relevant Bleeding Events (CRBEs)
    c. any bleeding events (MBEs, CRBEs, and nuisance bleeding events)
2. Adverse Events (AEs; including findings in the physical examination)
3. Discontinuation of study treatment due to Aes
4. Laboratory measures, especially Liver Function Tests (LFTs)
5. Acute Coronary Syndrome (ACS)
6. Vital signs

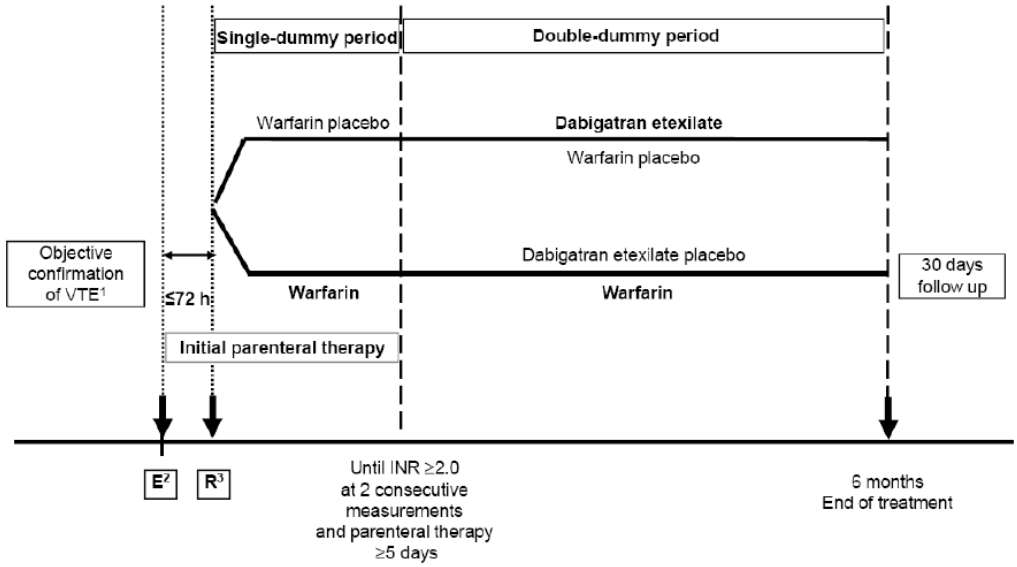
All safety analyses were based on the treated set, which consisted of all randomised patients who were documented to have taken at least 1 dose of study drug. The safety data for these patients were analysed according to the treatment they actually received. In case a patient received more than one treatment in a study, the first medication kit used by the patient determined the treatment group assignment.

The definition for the main safety endpoint, MBEs, followed the recommendations of the International Society on Thrombosis and Haemostasis (ISTH).

All bleeding events were centrally adjudicated by an independent committee that was blinded with regard to the treatment allocation of patients. Adjudicated results were used in the analyses of bleeding events.

The analyses of bleeding events for all four pivotal studies include those reported from the first intake of active study drug in the sVTEp studies (1160.46 and 1160.53) and from the start of oral only treatment (double-dummy treatment) in the aVTEt studies (1160.47 and 1160.63) up to 6 days after the last intake of study drug.

According to clinical practice, oral treatment with warfarin was initiated while receiving parenteral treatment in the aVTEt studies. In contrast, patients randomised to DE, were immediately switched from parenteral anticoagulant therapy to DE (i.e., no overlap between both treatments necessary). To ensure blinding, patients randomised to DE received W-placebo in the overlapping period of parental and oral treatment, and this period is mentioned as the “Single-dummy period”. When parental treatment was stopped, all patients received treatment with study-medication and this period is mentioned as the “Double-dummy period”. Due to this difference, three counting scenarios for adverse events (AEs) are possible (Figure 6.3.1:1).



Counting scenarios	Start counting events from:	Post-treatment
First dose at start of oral only treatment (double-dummy treatment)	DE: first intake of DE to 6 days after last intake of DE W: first intake of W during the oral only period (double-dummy period) to 6 days after last intake of W	
First dose of active treatment	DE: first intake of DE to 6 days after last intake of DE W: first intake of W to 6 days after last intake of W	
First dose of any treatment	DE: first intake of W placebo to 6 days after last intake of DE W: first intake of W to 6 days after last intake of W	

Figure 6.3.1: 1 Counting scenarios for bleeding events

Note: Active treatment - starts at randomization for W and oral only treatment (double-dummy treatment) for DE.
Any treatment starts for both W and DE at randomization.
[1] Objective confirmation of VTE was to be obtained prior to enrollment, but not later than 72 hours after enrollment, and prior to randomization.
[2] Enrollment
[3] Randomization

The MAH states that the preferred analyses of all bleeding events from the aVTEt studies (1160.46 and 1160.53) included those that were reported after first intake of study drug at the start of oral only treatment (double-dummy treatment). This comparison has the advantage of avoiding differences which are created by the nature of uptitration with warfarin (which leads to an overlap with the parenteral drug), which DE does not need. In order to provide a complete analysis, two alternative methods of counting bleeding events (from first intake of any active treatment [DE or W] and from first intake of any

treatment [parenteral, DE or DE-placebo, warfarin or W-placebo]; Table 6.3.1: 1) were also explored for the aVTEt studies. The safety database for DE 150 mg b.i.d. comprises all patients included in the two aVTEt studies (1160.53 and 1160.46) and all patients included in the two sVTEp studies (1160.47 and 1160.63). Including all patients from these studies, provides the ability to assess the safety profile of DE in the two indications for which marketing authorisation is being sought. Furthermore, the safety of DE following continuous treatment from an aVTEt study to a sVTEp study was also evaluated as well as the safety of DE after patients were re-allocated from DE to warfarin or from warfarin to DE.

Patient exposure

All patients included in the pivotal studies and randomised to DE were treated with the dose of 150 mg b.i.d., which is also the dose sought for in both indications.The two aVTEt studies (1160.46 and 1160.53) provide data for the safety of DE used in the acute treatment of VTE, whereas the two sVTEp studies (1160.47 and 1160.63) provide data for the safety of DE used in the prophylactic treatment of recurrence of VTE as well as the long-term safety (12-36 months) for use in the sought indications. Table 1.2.1:1 shows the number of patients randomised and treated in each of the pivotal studies.

Table 1.2.1: 1 Number of patients randomized and treated in each of the pivotal studies - all randomized patients

	1160.53 n	1160.46 n	1160.47 n	1160.63 n
Randomized	2564	2589	2866	1353
Not treated	25	21	10	10
Treated	2539	2568	2856	1343
DE	1273	1280	1430	684
Warfarin	1266	1288	1426	--
Placebo	--	--	--	659

Source data: SCS appendix [Module 5.3.5.3, U12-2653], Tables 1.1.4, 1.1.5, 1.1.7, 1.1.8

A total of 8,197 unique patients were randomised in the four pivotal studies and 8,132 (99.3%) were treated with study drug. Across the studies, a total of 4,667 patients were treated with DE, 3,980 were treated with warfarin and 659 were treated with placebo.

The aVTEt studies (1160.46 and 1160.53) included 5,153 randomised and 5,107 treated patients. A total of 1,175 patients included in one of the aVTEt studies continued into one of the sVTEp studies (1160.47 and 1160.63) and were re-randomised (rollover patients), and 3,044 non-rollover patients were randomised into the sVTEp studies (1160.47 and 1160.63).

Table 1.2.3:1 shows the patients disposition for all four pivotal studies.

Table 1.2.3: 1 Patient disposition - all patients

	DE n	W n	P n	Total n
Total randomized				
Randomized patients in all studies[1]				9372
Unique randomized				8197
aVTEt Studies 1160.53 and 1160.46				
Randomized patients	2574	2579		5153
Not treated	21	25		46
Treated patients[2]	2553	2554		5107
aVTEt patients continuing in sVTEp Studies 1160.47 and 1160.63				
Randomized patients				1175
Not treated				1
Treated patients[2]	609	552	13	1174
Newly randomized patients in sVTEp Studies 1160.47 and 1160.63				
Randomized patients				3044
Not treated				19
Treated patients[2]	1505	874	646	3025

[1] A patient may have been randomized more than once (i.e., in an aVTEt study and an sVTEp study).
[2] Patients who received at least 1 dose of study drug
Source data: SCS appendix [Module 5.3.5.3, U12-2653], Table 1.1.1

Table 1.2.2:1 shows the duration of exposure to study drug after randomisation in the double-dummy period during the treatment period in the four pooled pivotal VTE studies.

Table 1.2.2:2 shows the exposure to study drug during the double-dummy period in the pooled aVTEt studies (1160.46 and 1160.53), and Tables 1.2.2:3 and 1.2.2:5 show the exposure to study drug during the double-dummy period in the two sVTEp studies (1160.47 and 1160.63).

As seen from the tables, median exposure to any study medication was 174 days in the two pivotal aVTEt studies (1160.46 and 1160.53), 534 days in the long-term sVTEp Study 1160.47, and 182 days in the short-term sVTEp Study 1160.63.

Mean treatment duration for the pooled VTE studies was 278 days for DE, 298 days for warfarin and 162 days for placebo. The maximum duration of continuous treatment for any patient treated with DE was 1,210 days (~40 months).

Safety data beyond 6 months were available for 2,214 (67.6%) DE patients, 1,670 (45.0%) warfarin patients and 445 (67.6%) placebo patients. Safety data >12 months were available for 1,043 (23.8%) DE patients, 1,034 (27.9%) warfarin patients and 0 placebo patients (Table 1.2.2:1).

As the safety set is the same as the treated set, patient disposition and patient demographic for patients included in the safety set did not differ from the patients included in the efficacy data set, please refer to relevant efficacy sections. Demographic characteristics were generally similar among the four pivotal studies and also between the treatment groups within those studies.

Table 1.2.2: 1 Exposure to study drug in the double-dummy period during the treatment period in the pooled pivotal VTE Studies 1160.53, 1160.46, 1160.47, and 1160.63 - treated set

	DE	W	P
Patients, n	4387	3707	659
Duration of treatment, mean (SD) [days]	277.6 (211.6)	297.6 (221.4)	162.0 (47.3)
Duration of treatment, median [days]	181.0	179.0	182.0
Duration of treatment categories, n (%)[1]			
≤1 month	141 (3.2)	129 (3.5)	24 (3.6)
>1 and ≤2 months	94 (2.1)	68 (1.8)	24 (3.6)
>2 and ≤3 months	98 (2.2)	52 (1.4)	26 (3.9)
>3 and ≤4 months	101 (2.3)	53 (1.4)	45 (6.8)
>4 and ≤5 months	50 (1.1)	42 (1.1)	10 (1.5)
>5 and ≤6 months	1592 (36.3)	1601 (43.2)	85 (12.9)
>6 and ≤7 months	911 (20.8)	362 (9.8)	442 (67.1)
>7 and ≤9 months	110 (2.5)	113 (3.0)	3 (0.5)
>9 and ≤12 months	150 (3.4)	161 (4.3)	0
>12 and ≤15 months	106 (2.4)	107 (2.9)	0
>15 and ≤18 months	277 (6.3)	283 (7.6)	0
>18 and ≤21 months	305 (7.0)	288 (7.8)	0
>21 and ≤24 months	120 (2.7)	117 (3.2)	0
>24 and ≤27 months	116 (2.6)	113 (3.0)	0
>27 and ≤30 months	47 (1.1)	64 (1.7)	0
>30 and ≤33 months	41 (0.9)	39 (1.1)	0
>33 and ≤36 months	22 (0.5)	14 (0.4)	0
>36 and ≤39 months	8 (0.2)	7 (0.2)	0
>39 months	1 (0)	2 (0.1)	0
Patients who did not enter the double-dummy period	97 (2.2)	92 (2.5)	0
Total exposure [years][2]	3261	2946	292

For the contribution of the aVTEt studies, drug exposure is calculated during the double-blind treatment period only.
Treatment duration = date of last intake of study drug – date of first intake +1

[1] Patients who rolled over from an aVTEt study to a sVTEp study and received the same study drug in both studies were counted only once, with their total exposure calculated as the sum of the 2 exposure durations. Roll−over patients treated with different study drugs in the 2 studies were counted once for each treatment group.

[2] Total exposure was defined as the sum of exposure days across all subjects / 365.25

Source data: SCS appendix [Module 5.3.5.3, U12-2653], Table 3.1.1.1

Table 1.2.2: 2 Exposure to study drug during the double-dummy period in the pooled aVTEt Studies 1160.53 and 1160.46 - treated set

	DE	W
Patients, n	2553 (100.0)	2554 (100.0)
Duration of treatment, mean (SD) [days]	163.4 (38.3)	162.7 (39.5)
Duration of treatment, median [days]	174.0	174.0
Duration of treatment categories, n (%)		
≤1 month	83 (3.3)	97 (3.8)
>1 and ≤2 months	56 (2.2)	55 (2.2)
>2 and ≤3 months	49 (1.9)	36 (1.4)
>3 and ≤4 months	43 (1.7)	35 (1.4)
>4 and ≤5 months	38 (1.5)	33 (1.3)
>5 and ≤6 months	1689 (66.2)	1795 (70.3)
>6 and ≤7 months	493 (19.3)	404 (15.8)
>7 months	5 (0.2)	7 (0.3)
Patients who did not enter the double-dummy period	97 (3.8)	92 (3.6)
Total exposure [years][1]	1099	1097

The double-dummy period was defined as the time from the first intake of DE / DE placebo until the last intake of any study drug, irrespective of temporary interruptions of active study drug.
[1] Total exposure was defined as the sum of exposure days across all subjects / 365.25
Source data: SCS appendix [Module 5.3.5.3, U12-2653], Table 3.1.1.3

Table 1.2.2: 3 Exposure to study drug in sVTEp Study 1160.47 - treated set

	DE	W
Patients, n	1430	1426
Duration of treatment, mean (SD) [days]	473.3 (211.3)	473.5 (206.5)
Duration of treatment, median [days]	534.0	534.0
Duration of treatment categories, n (%)		
≤1 month	37 (2.6)	39 (2.7)
>1 and ≤2 months	27 (1.9)	15 (1.1)
>2 and ≤3 months	24 (1.7)	18 (1.3)
>3 and ≤4 months	16 (1.1)	20 (1.4)
>4 and ≤5 months	10 (0.7)	11 (0.8)
>5 and ≤6 months	21 (1.5)	13 (0.9)
>6 and ≤7 months	27 (1.9)	27 (1.9)
>7 and ≤9 months	114 (8.0)	122 (8.6)
>9 and ≤12 months	163 (11.4)	177 (12.4)
>12 and ≤15 months	101 (7.1)	96 (6.7)
>15 and ≤18 months	312 (21.8)	322 (22.6)
>18 and ≤21 months	354 (24.8)	339 (23.8)
>21 and ≤24 months	61 (4.3)	60 (4.2)
>24 and ≤27 months	68 (4.8)	73 (5.1)
>27 and ≤30 months	49 (3.4)	51 (3.6)
>30 and ≤33 months	43 (3.0)	38 (2.7)
>33 and ≤36 months	3 (0.2)	5 (0.4)
Total exposure [years][1]	1853	1849

Treatment duration = date of last intake of study drug - date of first intake +1, irrespective of temporary interruptions of active study drug.
Total exposure was defined as the sum of exposure days across all subjects / 365.25
Source data: SCS appendix [Module 5.3.5.3, U12-2653], Table 3.1.1.7

Table 1.2.2: 5 Exposure to study drug in sVTEp Study 1160.63 - treated set

	DE	P
Patients, n	684 (100.0)	659 (100.0)
Duration of treatment, mean (SD) [days]	165.3 (44.6)	162.0 (47.3)
Duration of treatment, median [days]	182.0	182.0
Duration of treatment categories, n (%)		
≤1 month	25 (3.7)	24 (3.6)
>1 and ≤2 months	12 (1.8)	24 (3.6)
>2 and ≤3 months	30 (4.4)	26 (3.9)
>3 and ≤4 months	42 (6.1)	45 (6.8)
>4 and ≤5 months	5 (0.7)	10 (1.5)
>5 and ≤6 months	88 (12.9)	85 (12.9)
>6 and ≤7 months	479 (70.0)	442 (67.1)
>7 months	3 (0.4)	3 (0.5)
Total exposure [years][1]	310	292

Exposure in Study 1160.63 was defined as the date of last intake of study drug - date of first intake +1, irrespective of temporary interruptions of study drug.

[1] Total exposure was defined as the sum of exposure days across all subjects / 365.25

Source data: SCS appendix [Module 5.3.5.3, U12-2653], Table 3.1.1.8

Overall, there was no meaningful difference in demographic characteristics between the treatment groups. Moreover, the demographic characteristics were generally similar among the 4 pivotal studies and between the treatment groups within those studies. Mean age in the pivotal studies was approximately 55 years, around 30% of all included patients were >65 years of age and an acceptable amount of patients (8-9%) were >75 years old. Overall, 60% were males and the majority (>85%) of the included patients were white. Most patients (>75%) had a normal kidney function, with mean GRF above 100 ml/min, 72% of all included patients had a GFR ≥80 ml/min and 22% had a GFR 50- <80 ml/min.

The patients' medical history was in general similar between the treatment groups. Slightly more patients in the DE group in Study 1160.47 had hypertension (DE: 40.7%, W: 36.5%), diabetes mellitus (DE: 10.5%, W: 7.6%) and coronary artery disease (DE: 8.4%, W: 6.1%).

Concomitant medication use in the pivotal studies reflected the medical conditions present in the patient populations. Accordingly, cardiovascular medication use was reported for approximately half of all patients for each pooling of the data, with no difference between treatment groups. An exception was Study 1160.63 where concomitant cardiovascular medication was used more often in the DE group (52.5%) than the placebo group (45.1%). In contrast, in Study 1160.47 where more patients in the DE group had concomitant cardiovascular diseases, there was no clinically relevant difference in the percentage of patients with use of any cardiovascular medication of special interest (53.0% vs. 53.5%).

Antithrombotic agents, platelet inhibitors, or NSAIDs use was reported for 19.7% – 29.3% of patients in the four VTE studies, with similar use in both treatment groups. Only few patients reported the use of P-gp inhibitors (around 2% in the different studies) and inducers (<1% in all studies) with no notable difference between the treatment groups.

At least one risk factor for recurrent VTE was reported for the majority (70.7%) of patients in the pooled pivotal VTE studies. The most frequently reported risk factor was previous VTE (41.0%), which, as would be expected, also had a lower incidence in the pooled aVTEt studies (21.5%) versus the individual sVTEp studies (Study 1160.47: 53.4%, Study 1160.63: 99.9%). The high percentage in Study 1160.63 reflects that prior VTE was an inclusion criterion.

The majority of patients (66.2-67.0%) in the four pivotal studies had a qualifying event of DVT only; PE only was the qualifying event in 22.8-27.2% of patients, and DVT+PE was the qualifying event for 6.7-10.3% of patients.

Adverse events

Patients received DE 150 b.i.d. in all 4 pivotal studies, warfarin as a comparator in studies 1160.53, 1160.46 (the two 6-month aVTEt studies), and 1160.47 (one of the two sVTEp studies, treatment duration of up to 36 months), and placebo as a comparator in 1160.63 (the other sVTEp study with treatment duration of 6 months).

An overall summary of AEs in the combined pool of all four VTE studies (aVTEt + sVTEp) is provided in Table 2.3.1.2: 1.

Table 2.3.1.2: 1 Overall summary of investigator-reported adverse events in the pooled pivotal VTE Studies 1160.46, 1160.53, 1160.47, and 1160.63 - treated set

	DE n (%)	W n (%)	P n (%)
Patients	4387 (100.0)	3707 (100.0)	659 (100.0)
Patients with any AE	2929 (66.8)	2646 (71.4)	326 (49.5)
Patients with severe AEs	400 (9.1)	374 (10.1)	30 (4.6)
Patients with investigator-defined drug-related AEs	680 (15.5)	783 (21.1)	43 (6.5)
Patients with other significant AEs (according to ICH E3)	219 (5.0)	165 (4.5)	42 (6.4)
Patients with AEs leading to study drug discontinuation	421 (9.6)	326 (8.8)	81 (12.3)
Patients with SAEs	605 (13.8)	538 (14.5)	62 (9.4)
Patients with SAEs with fatal outcomes	49 (1.1)	55 (1.5)	2 (0.3)

AEs in the treatment period are those that occurred between first intake and 6 days after last intake of any study drug.
Percentages are calculated using total number of patients per treatment as the denominator.
Source data: SCS appendix [Module 5.3.5.3], Table 5.1.1

Across all the active-controlled studies 66-72% of patients treated with DE and 67-72% of patients treated with warfarin experienced an AE. There was a small difference in favour of DE in the percentage of AEs between the two treatment groups across the active controlled studies. In the placebo-controlled Study 1160.63, fewer patients experienced an AE 49-51% in the two treatment groups compared to the active controlled studies, with no difference between the two treatment groups.

In all four studies, AEs most often were within the SOCs of Gastrointestinal disorders, Infections and infestations and Muscoloskeletal and connective tissues disorders. The most frequent reported AEs were headache and pain in extremities.

A summary of the most common (≥1% in any group) AEs in the pooled pivotal studies is presented in Table 2.3.1.2: 2.

Table 2.3.1.2: 2 Adverse events in ≥1% of patients in any treatment group by SOC/PT in pooled Studies 1160.53, 1160.46, 1160.47, 1160.63 - treated set

System organ class Preferred term	DE n (%)	W n (%)	P n (%)
Patients	4387 (100.0)	3707 (100.0)	659 (100.0)
Patients with any AE	2929 (66.8)	2646 (71.4)	326 (49.5)
Gastrointestinal disorders	**1085 (24.7)**	**843 (22.7)**	**60 (9.1)**
Diarrhoea	198 (4.5)	142 (3.8)	9 (1.4)
Dyspepsia	161 (3.7)	50 (1.3)	8 (1.2)
Nausea	145 (3.3)	156 (4.2)	10 (1.5)
Rectal haemorrhage	114 (2.6)	59 (1.6)	2 (0.3)
Vomiting	91 (2.1)	87 (2.3)	1 (0.2)
Constipation	82 (1.9)	108 (2.9)	4 (0.6)
Abdominal pain	57 (1.3)	88 (2.4)	2 (0.3)
Gingival bleeding	54 (1.2)	98 (2.6)	3 (0.5)
Abdominal pain upper	82 (1.9)	53 (1.4)	8 (1.2)
Gastritis	59 (1.3)	29 (0.8)	5 (0.8)
Gastrooesophageal reflux disease	55 (1.3)	30 (0.8)	2 (0.3)
Haemorrhoids	50 (1.1)	30 (0.8)	0
Toothache	43 (1.0)	40 (1.1)	1 (0.2)
Infections and infestations	**1016 (23.2)**	**991 (26.7)**	**87 (13.2)**
Nasopharyngitis	217 (4.9)	227 (6.1)	18 (2.7)
Influenza	125 (2.8)	110 (3.0)	5 (0.8)
Bronchitis	104 (2.4)	98 (2.6)	7 (1.1)
Urinary tract infection	101 (2.3)	100 (2.7)	8 (1.2)
Upper respiratory tract infection	86 (2.0)	85 (2.3)	13 (2.0)
Sinusitis	56 (1.3)	54 (1.5)	3 (0.5)
Gastroenteritis	53 (1.2)	42 (1.1)	1 (0.2)
Lower respiratory tract infection	46 (1.0)	43 (1.2)	0
Pharyngitis	32 (0.7)	42 (1.1)	2 (0.3)
Pneumonia	50 (1.1)	41 (1.1)	6 (0.9)
Cellulitis	41 (0.9)	36 (1.0)	0
Viral infection	32 (0.7)	36 (1.0)	3 (0.5)
Musculoskeletal and connective tissue disorders	**866 (19.7)**	**817 (22.0)**	**78 (11.8)**
Pain in extremity	272 (6.2)	252 (6.8)	24 (3.6)
Back pain	177 (4.0)	171 (4.6)	10 (1.5)
Arthralgia	167 (3.8)	140 (3.8)	11 (1.7)
Muscle spasms	96 (2.2)	95 (2.6)	7 (1.1)
Musculoskeletal pain	52 (1.2)	55 (1.5)	4 (0.6)
Osteoarthritis	52 (1.2)	39 (1.1)	5 (0.8)
Joint swelling	29 (0.7)	37 (1.0)	3 (0.5)
Myalgia	42 (1.0)	36 (1.0)	6 (0.9)
General disorders and administration site condition	**634 (14.5)**	**608 (16.4)**	**49 (7.4)**
Oedema peripheral	185 (4.2)	159 (4.3)	14 (2.1)
Chest pain	135 (3.1)	133 (3.6)	11 (1.7)
Fatigue	94 (2.1)	105 (2.8)	7 (1.1)
Pyrexia	65 (1.5)	94 (2.5)	7 (1.1)

Table 2.3.1.2: 2 (cont'd) Adverse events in ≥1% of patients in any treatment group by SOC/PT in pooled Studies 1160.53, 1160.46, 1160.47, 1160.63 - treated set

System organ class Preferred term	DE n (%)	W n (%)	P n (%)
Respiratory, thoracic and mediastinal disorders	**594 (13.5)**	**618 (16.7)**	**63 (9.6)**
Dyspnoea	131 (3.0)	138 (3.7)	11 (1.7)
Epistaxis	124 (2.8)	227 (6.1)	6 (0.9)
Cough	121 (2.8)	104 (2.8)	6 (0.9)
Pulmonary embolism	43 (1.0)	27 (0.7)	21 (3.2)
Haemoptysis	36 (0.8)	39 (1.1)	4 (0.6)
Oropharyngeal pain	38 (0.9)	37 (1.0)	1 (0.2)
Nervous system disorders	**587 (13.4)**	**545 (14.7)**	**45 (6.8)**
Headache	241 (5.5)	255 (6.9)	20 (3.0)
Dizziness	118 (2.7)	120 (3.2)	9 (1.4)
Paraesthesia	40 (0.9)	43 (1.2)	2 (0.3)
Injury, poisoning and procedural complications	**452 (10.3)**	**498 (13.4)**	**27 (4.1)**
Contusion	118 (2.7)	158 (4.3)	3 (0.5)
Fall	61 (1.4)	66 (1.8)	6 (0.9)
Laceration	44 (1.0)	49 (1.3)	3 (0.5)
Skin and subcutaneous tissue disorders	**440 (10.0)**	**455 (12.3)**	**30 (4.6)**
Rash	89 (2.0)	92 (2.5)	8 (1.2)
Pruritus	55 (1.3)	58 (1.6)	3 (0.5)
Vascular disorders	**429 (9.8)**	**433 (11.7)**	**77 (11.7)**
Hypertension	125 (2.8)	107 (2.9)	15 (2.3)
Haematoma	68 (1.6)	109 (2.9)	3 (0.5)
Deep vein thrombosis	62 (1.4)	60 (1.6)	35 (5.3)
Thrombophlebitis	6 (0.1)	9 (0.2)	7 (1.1)
Investigations	**239 (5.4)**	**362 (9.8)**	**10 (1.5)**
International normalised ratio increased	6 (0.1)	97 (2.6)	0
Alanine aminotransferase increased	49 (1.1)	49 (1.3)	1 (0.2)
Renal and urinary disorders	**185 (4.2)**	**240 (6.5)**	**8 (1.2)**
Haematuria	80 (1.8)	137 (3.7)	3 (0.5)
Psychiatric disorders	**189 (4.3)**	**184 (5.0)**	**9 (1.4)**
Insomnia	60 (1.4)	67 (1.8)	4 (0.6)
Anxiety	47 (1.1)	51 (1.4)	1 (0.2)
Depression	58 (1.3)	42 (1.1)	1 (0.2)
Eye disorders	**181 (4.1)**	**171 (4.6)**	**5 (0.8)**
Conjunctival haemorrhage	23 (0.5)	38 (1.0)	0
Cardiac disorders[1]	**170 (3.9)**	**148 (4.0)**	**15 (2.3)**
Reproductive system and breast disorders	**156 (3.6)**	**171 (4.6)**	**9 (1.4)**
Menorrhagia	30 (0.7)	57 (1.5)	1 (0.2)
Blood and lymphatic system disorders	**101 (2.3)**	**100 (2.7)**	**3 (0.5)**
Anaemia	51 (1.2)	49 (1.3)	2 (0.3)
Ear and labyrinth disorders	**83 (1.9)**	**71 (1.9)**	**7 (1.1)**
Vertigo	41 (0.9)	37 (1.0)	6 (0.9)

AEs in the treatment period are those that occurred between first intake and 6 days after last intake of any study drug.
[1] The SOC 'Cardiac disorders' was included in this table although none of the individual events in this SOC were ≥1%.
Source data: SCS appendix [Module 5.3.5.3], Table 5.2.2.1 and 5.2.1.1

As seen from the table 2.3.1.2:2, more patients treated with warfarin compared to patients treated with DE experienced AEs within the following SOCs:

Respiratory, thoracic and mediastinal disorders (13.5% vs. 16.7%) which was mainly due to more patients with epistaxis in the warfarin group (2.8% vs. 6.1%).

Injury poisoning and procedural complications (10.3% vs. 13.4%) which were mainly due to more patients with contusions in the warfarin group (2.7% vs. 4.3%).

Vascular disorders (9.8% vs. 11.7%) which were mainly due to more patients with haematomas in the warfarin group (1.6% vs. 2.9%).

Renal and urinary tract disorders (4.2% vs. 6.5%) which were mainly due to more patients with haematuria in the warfarin group (1.8% vs. 3.7%).

More patients treated with DE compared to patients treated with warfarin experienced AEs within the following SOC:

Gastrointestinal disorders (24.7% vs. 22.7%) which were mainly due to more patients with dyspepsia (4.5% vs. 3.8%) and rectal haemorrhage (2.7 vs. 4.3%) in the DE group.

Overall, dyspepsia-/gastritis-like symptoms, nausea, vomiting, diarrhea and rectal bleeding were the most frequently reported GI AEs in DE patients and were all (with exception of nausea and vomiting) seen more commonly among patients treated with DE compared with patients treated with warfarin and placebo. Other bleeding disorders including conjuntival haemorrhage, epistaxis, haemopthysis, haematuria, menorhagia and haematomas were all seen more often in the warfarin group compared with the DE group. No difference was seen in the frequency of anaemia (1.2% and 1.3% respectively in the DE and the warfarin groups) and elevated alanine aminotransferase was also reported equally in the two active treatment groups (1.1% and 1.3% respectively in the DE and the warfarin groups).

Pulmonary embolism was reported slightly more frequent in the DE group (1.0%) compared to the warfarin group (0.7%). There was a small difference in the frequency of DVT between the two treatment groups (1.4% vs. 1.6% in the DE and the warfarin group respectively). These results are discussed in the efficacy section of this assessment report.

The GI system was the SOC with the highest incidence of investigator-reported drug-related AEs (DE: 7.0%; W: 5.7%). Also AEs within the SOC of “Infection and infestation” and “Musculoskeletal and connective tissue disorders” were commonly reported. The two most commonly reported AEs were the preferred terms headache and pain in extremities

In the pooled pivotal studies cardiac disorders were reported equally in the two active treatment groups; 3.9% and 4.0% in the DE and warfarin group respectively.

Suspected cardiovascular adverse events occurred more often in the active controlled studies (0.9 - 2.0% in the DE group and 0.6 - 1.3% in the warfarin group) compared to the placebo-controlled study (0.4% and 0.3% in the DE and placebo group respectively). The lower number seen in the placebo-controlled study is probably due to the more restricted inclusion criteria.

Most investigator-reported AEs were mild or moderate in intensity for all treatment groups in all pivotal studies. The proportion of patients with severe AEs was similar in the two active treatment groups (9.1% in the DE group and 10.1% in the warfarin group). Most severe AEs were reported in ≤0.2% of patients in any treatment group. The only severe AEs that occurred in ≥0.5% of patients in any treatment group included investigator-reported AEs of DVT (DE: 0.5%, W: 0.5%, placebo: 1.1%) and PE (DE: 0.5%; W: 0.4%; placebo: 1.4%).

<u>aVTEt studies</u>

The AE profile for the pooled aVTEt studies was generally similar to the profile for all pooled pivotal studies (Table not shown). In the DE group 66.7% of all patients reported any AEs compared with 69.8% in the warfarin group. More patients in the warfarin group (20.3%) had an investigator-defined drug-related AE compared with patients in the DE group (15.3%). Severe AEs were reported for 13.0% in the DE group and 12.4% in the warfarin group.

Overall, the most frequently reported AEs (incidence of at least 5%) in the DE group in the pooled aVTEt studies were extremity pain (5.5%) and headache (5.4%) both of which occurred at a comparable incidence in the warfarin group (extremity pain 4.6% and headache 6.2%). As was the case in the pooled pivotal studies, PE was seen more often in the DE group (1.3% vs. 0.9% in the warfarin group). Dyspepsia, gastritis, gastrointestinal reflux disease and rectal haemorrhage were also reported more often in the DE group compared to the warfarin group. Minor non-GI bleeding disorders including conjuntival haemorrhage, epistaxis, haemopthysis, haematuria, menorhagia and haematomas were all reported more often in the warfarin group compared with the DE group. Anaemia was also reported more often in the DE group compared with the warfarin group (1.0% vs. 1.5%). No difference was seen in the frequency of elevated alanine aminotransferase (1.2% in both treatment groups), whereas INR, as could be expected, was increased more often in the warfarin group compared to the DE group.

sVTEp studies

Reported AEs in the long-term active-controlled sVTEp Study 1160.47 are presented in Table 2.3.1.4:1.

Table 2.3.1.4: 1 Overall summary of reported adverse events in Study 1160.47 - treated set

	DE n (%)	W n (%)
Patients	1430 (100.0)	1426 (100.0)
Patients with any AE	1029 (72.0)	1010 (70.8)
Patients with severe AEs	143 (10.0)	151 (10.6)
Patients with investigator-defined drug-related AEs	229 (16.0)	280 (19.6)
Patients with other significant AEs (according to ICH E3)	75 (5.2)	63 (4.4)
Patients with AEs leading to study drug discontinuation	145 (10.1)	126 (8.8)
Patients with SAEs	227 (15.9)	224 (15.7)
Patients with SAEs with fatal outcomes	12 (0.8)	18 (1.3)

AEs in the treatment period are those that occurred between the first intake and 6 days after last intake of any study drug.
Percentages are calculated using total number of patients per treatment as the denominator.
Source data: SCS appendix [Module 5.3.5.3], Table 5.1.5

Generally more gastritis-like symptoms and rectal haemorrhage were reported in patients treated with DE compared to patients treated with W. Minor non-GI bleeding disorders were reported more often in patients treated with W.

Patients were allowed to roll-over from each of the aVTEt studies (Study 1160.53 or 1160.46) into the active-controlled sVTEp Study 1160.47 but could also enter the study directly. Overall, 1,097 patients randomised patients in Study 1160.47 were roll-over patients from one of the previous aVTEt studies. For these patients, AEs were analysed by prior treatment assignment in an aVTEt study (i.e. previous treatment with DE or W).

The incidence of patients with any AE was similar between the DE and warfarin groups for patients who had previously received DE, patients who had previously received W, and for non-roll-over patients (Table 2.3.1.5: 1).

Table 2.3.1.5: 1 Overall summary of reported adverse events in Study 1160.47 by roll-over status and prior treatment - treated set

	Roll-over patients, n (%)				Non-roll-over patients, n (%)[1]	
Treatment in prior aVTEt study:	**DE**		**W**		**NA**	
Treatment in Study 1160.47:	**DE**	**W**	**DE**	**W**	**DE**	**W**
Patients	266 (100.0)	266 (100.0)	303 (100.0)	262 (100.0)	841 (100.0)	874 (100.0)
Patients with any AE	194 (72.9)	193 (72.6)	225 (74.3)	190 (72.5)	595 (70.7)	611 (69.9)
Patients with severe AEs	18 (6.8)	37 (13.9)	41 (13.5)	26 (9.9)	84 (10.0)	87 (10.0)
Patients with investigator-defined drug-related AEs	48 (18.0)	61 (22.9)	51 (16.8)	45 (17.2)	128 (15.2)	172 (19.7)
Patients with other significant AEs (according to ICH E3)	13 (4.9)	13 (4.9)	13 (4.3)	11 (4.2)	48 (5.7)	39 (4.5)
Patients with AEs leading to study drug discontinuation	22 (8.3)	27 (10.2)	33 (10.9)	21 (8.0)	89 (10.6)	77 (8.8)
Patients with SAEs	38 (14.3)	45 (16.9)	64 (21.1)	34 (13.0)	124 (14.7)	143 (16.4)
Patients with SAEs with fatal outcomes	0	6 (2.3)	7 (2.3)	3 (1.1)	5 (0.6)	9 (1.0)

[1] Newly enrolled in Study 1160.47, no prior participation in aVTEt study
Percentages are calculated using total number of patients per treatment as the denominator.
AEs in the treatment period are those that occurred between first intake and 6 days after last intake of any study drug.
Source data: SCS appendix [Module 5.3.5.3], Table 5.1.7

Patients remaining on the same therapy after rolling over (i.e., DE→DE or W→W) had fewer severe AEs, serious AEs, AEs leading to discontinuation, and AEs with fatal outcomes than patients changing therapies.

The incidence of any AE (70.7% and 69.9% respectively) and severe events was the same (10.0% and 10.6% respectively) between the DE and warfarin groups for non-roll-over patients. The incidence of drug-related AEs was lower in the DE group compared to warfarin for non-roll-over patients.

Patients who were allocated to a different treatment (DE→W or W→DE) exhibited some differences in their patterns of reported AEs. Patients who started with DE and were reallocated to warfarin (DE→W) had more haematomas, ecchymosis, haemarthrosis, menorrhagia, and contusions than W→DE patients. Lower GI bleeding was more common in W→DE patients when compared to DE→W patients.

Study 1160.63 was a placebo-controlled sVTEp study with an intended treatment period of 6 months and a 12-month extended follow-up period after the last intake of study drug. During the treatment period, the incidence of most types of investigator-reported AEs (any AE, severe AEs, and other significant AEs) was similar between the DE and placebo groups in Study 1160.63. The incidence of drug-related AEs was higher in the DE group (11.5%) compared to placebo (6.5%). Conversely, the incidence of patients with AEs leading to study drug discontinuation (7.3% vs. 12.3%) and SAEs (7.3% vs. 9.4%) was lower in the DE group compared to placebo. This was mainly due to a higher incidence of investigator-reported AEs of DVT (5.3% vs. 0.4%) and PE (3.2% vs. 0.3%) in placebo patients compared to DE.

The SOC with the highest incidence of investigator-reported AEs in patients treated with DE was GI disorders. The overall incidence of patients with GI disorders was 16.7% in DE patients and 9.1% in placebo patients. The most frequently reported AEs (incidence of at least 3%) in the DE group were dyspepsia (4.1% vs. 1.2%), back pain (3.1% vs. 1.5%), extremity pain (3.2% vs. 3.6%), and headache (3.1% vs. 3.0%).

The incidence of most of the common non-bleeding GI AEs (dyspepsia, diarrhoea, gastritis, abdominal pain and vomiting) was higher in patients treated with DE compared to placebo. Likewise, the incidence of the most common investigator-reported AEs associated with minor bleeding (haematoma, epistaxis, rectal haemorrhage, and contusion) was also higher in patients treated with DE compared to placebo.

In the pooled pivotal studies as well as in the individual studies, mean systolic and diastolic blood pressure results were generally 1 to 2 mmHg lower than baseline throughout the trials, with no clinically meaningful differences between treatment groups.

Serious adverse event / deaths / other significant events

As the dose of DE in all pivotal was 150 mg b.i.d., all serious adverse events (SAEs) below refer to this dose. In the pooled pivotal VTE studies, SAEs were reported in 13.8% of patients treated with DE, 14.5% of patients treated with warfarin and 9.4% of patients treated with placebo. Across the three active-controlled pivotal studies (1160.46, 1160.53 and 1160.47), 11.8-15.9% patients experienced an SAE. In all three studies slightly more patients in the DE group (12.2-15.9%) experienced an SAE compared to the warfarin group (11.8-15.7%) and in all three studies slightly more patients treated with DE (0.7-1.0%) compared to patients treated with warfarin (0.4-0.8%) experienced DVT. The same pattern was seen for PE, DE: 0.6-1.1% vs. W: 0.2-0.9%. In the placebo-controlled study (1160.63) more patients treated with placebo compared to DE experienced SEAs (6.9% vs. 9.1%). This was mostly due to more patients in the placebo group experienced DVT and PE (DVT: 0.3% vs. 2.3%; PE: 0.1% vs. 2.4%). In all four pivotal studies, the most frequently reported SAEs were gastrointestinal disorders, infections and infestations, neoplasms and DVT and PE. In Study 1160.47, also (acute) myocardial infarctions was frequently reported (see below). Accordingly, SAEs most frequently occurred within the SOCs Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders and also Infections and infestations and Neoplasms.

Bleedings

The risk of bleedings is the most important safety topic related to the use of DE. Bleedings are described and assessed in this section even if some of them are do not fulfill the criteria for being SAEs.This section provides an assessment of adjudicated bleeding events (confirmed MBEs, CRBEs and any bleeding events [includes MBEs, CRBEs and nuisance/trivial bleeding]) for the four pivotal VTE studies. CRBEs generally reflect bleeding events that required medical evaluation/intervention/testing and, thus, in addition to inconveniencing patients by requiring visits to emergency departments or physician's offices also required expenditures of funds.

The site of all bleeding events (for MBEs, CRBEs, and nuisance/trivial bleeding) presented in this assessment are based on the investigator's assessment, except for Study 1160.63 where the bleeding location was categorized by the independent adjudication committee. Four events of minor bleeding with a location of intracranial (the events were, e.g., nose bleeds, all in warfarin patients) did not technically meet the definition of an ICH and were therefore not counted as MBEs. The analyses of bleeding events reported in the aVTEt studies (1160.53 and 1160.46) were performed based on 3 possible counting scenarios, as described previously in section 4.1. For the sVTEp studies, bleeding events are analyzed for the period starting with first intake of active study drug or placebo through 6 days after last intake of any study drug. Different counting scenarios were not investigated for the sVTEp studies as these studies only had one treatment period and patients in both treatment groups started dosing at the same time. The preferred counting scenario is the one including bleeding events from the aVTEt studies that were reported after first intake of study drug at the start of oral only treatment (double-dummy treatment).

Hence, the main focus of the following presentation and assessment of results is bleeding events that were reported after the first intake of study treatment (for the aVTEt studies, from start of doubledummy treatment) or placebo, up to 6 days after last intake of any study drug, except for rollover patients.

aVTE studies – by different counting scenarios

Bleeding events (MBEs, life-threatening MBEs, intracranial MBEs, MBEs/CRBEs, and any bleeding events) were analyzed using all 3 counting methods for the aVTEt studies and are presented in Table 2.1.1: 1.

Using the preferred counting scenario (double-dummy treatment), the DE:W HR for MBEs was in favor of DE (0.60) and was statistically significant. The DE:W HRs also favored DE for both MBEs/CRBEs (0.56) and any bleeding (0.67), and the differences were statistically significant.

However, also when using the two alternative counting scenarios, the DE:W HR was generally in favour of DE with the exception of life-threatening bleedings using the "Any treatment" scenario where the 95% confidence interval was wide.

Table 2.1.1: 1 Analysis of bleeding events by counting scenario for the aVTEt pool of studies – treated set

	Number of Patients N (%)		
Bleeding Event/Counting from start of:	**DE**	**W**	**DE:W HR (95% CI)**
MBE			
Any study treatment	37/2553 (1.4)	51/2554 (2.0)	0.73 (0.48, 1.11)
Double-dummy treatment	24/2456 (1.0)	40/2462 (1.6)	0.60 (0.36, 0.99)
Active study treatment	24/2456 (1.0)	51/2554 (2.0)	0.48 (0.29, 0.78)
Life-threatening bleeding			
Any study treatment	9/2553 (0.4)	8/2554 (0.3)	1.13 (0.43, 2.92)
Double-dummy treatment	4/2456 (0.2)	6/2462 (0.2)	0.66 (0.19, 2.36)
Active study treatment	4/2456 (0.2)	8/2554 (0.3)	0.52 (0.16, 1.71)
Intracranial bleeding			
Any study treatment	2/2553 (0.1)	5/2554 (0.2)	0.40 (0.08, 2.07)
Double-dummy treatment	2/2456 (0.1)	4/2462 (0.2)	0.50 (0.09, 2.74)
Active study treatment	2/2456 (0.1)	5/2554 (0.2)	0.41 (0.08, 2.10)
MBEs or CRBEs			
Any study treatment	136/2553 (5.3)	217/2554 (8.5)	0.62 (0.50, 0.76)
Double-dummy treatment	109/2456 (4.4)	189/2462 (7.7)	0.56 (0.45, 0.71)
Active study treatment	109/2456 (4.4)	217/2554 (8.5)	0.50 (0.40, 0.63)
Any bleeding			
Any study treatment	411/2553 (16.1)	567/2554 (22.2)	0.70 (0.61, 0.79)
Double-dummy treatment	354/2456 (14.4)	503/2462 (20.4)	0.67 (0.59, 0.77)
Active study treatment	354/2456 (14.4)	567/2554 (22.2)	0.60 (0.53, 0.69)

Note: the same censoring rules were used for all 3 scenarios.

Major bleeding events (MBEs)

MBEs are presented for all four studies individually and for the pooled aVTEt studies in Table 6.3.3: 1. MBEs were reported less frequently in DE patients compared to warfarin patients in the pooled aVTEt studies (1.0% vs. 1.6%, respectively from the start of oral only treatment [doubledummy treatment]) and in Study 1160.47 (0.9% vs. 1.8%, respectively). The HR of DE over warfarin for MBEs from the start of oral only treatment (double-dummy treatment) was statistically significant for the pooled aVTEt studies, but only for one of the individual aVTEt studies. While the HRs favored DE over W, in Study 1160.47 the result was not statistically significant. In the placebo-controlled Study 1160.63, there were 2 (0.3%; 2/684) DE-treated patients and 0 (0%; 0/659) P-treated patients with an MBE.

Table 6.3.3: 1 Summary of patients with MBEs for aVTEt and sVTEp studies from the start of oral only treatment (double-dummy treatment) – treated set

	DE	W	P	DE vs. W, HR (95% CI)
MBEs				
Pooled aVTEt, n/N (%)	24/2456 (1.0)	40/2462 (1.6)	--	0.60 (0.36, 0.99)
Study 1160.53, n/N (%)	17/1226 (1.4)	22/1214 (1.8)	--	0.76 (0.40, 1.43)
Study 1160.46, n/N (%)	7/1230 (0.6)	18/1248 (1.4)	--	0.39 (0.16, 0.93)
sVTEp Study 1160.47, n/N (%)	13/1430 (0.9)	25/1426 (1.8)	--	0.54 (0.25, 1.16)
sVTEp Study 1160.63, n/N (%)	2/684 (0.3)	--	0/659 (0.0)	NC

NC = Not Calculable

In the pooled analysis of all four VTE studies, MBEs occurred less frequently in DE patients compared to warfarin patients for all categories of MBEs (MBEs, MBEs with a fatal outcome, intracranial MBEs, and TIMI major bleeding) as well as for life-threatening bleeding in the pooled all pivotal VTE studies (Table 2.1.3.1: 2). The pool of all pivotal trials includes the placebo-controlled Study 1160.63, in which 2 of 684 DE treated patients had an MBE (0.3%) and none of 659 placebo treated patients had an MBE (Table 6.3.3: 1).

Table 2.1.3.1: 2 Overview of MBEs in all 4 pooled VTE studies (1160.53, 1160.46, 1160.47, and 1160.63) from start of double-dummy treatment in the aVTEt studies - treated set

	DE	W	P
Number of patients	4290	3615	659
Time at risk [pt-yrs]	3318.6	2991.9	303.1
MBE rate/100 pt-years	1.2	2.2	0
Patients, n (%)	4290 (100.0)	3615 (100.0)	659 (100.0)
Patients with MBE(s)[1], n (%)	39 (0.9)	65 (1.8)	0
Patients with 1 MBE	34 (0.8)	60 (1.7)	0
Patients with 2 MBEs	5 (0.1)	5 (0.1)	0
Patients with			
TIMI major bleeds[2]	14 (0.3)	17 (0.5)	0
Life-threatening bleeding[3]	5 (0.1)	9 (0.2)	0
Intracranial bleeding[4]	4 (0.1)	8 (0.2)	0
Patients with MBEs with a fatal outcome[5]	1 (0.0)	3 (0.1)	0
Patients with MBEs or CRBEs	224 (5.2)	333 (9.2)	13 (2.0)
Patients with any bleeding event(s), n (%)	689 (16.1)	857 (23.7)	40 (6.1)
Patients who discontinued study drug due to AEs classified as, n (%) [6]			
MBEs	13 (0.3)	43 (1.2)	0
MBEs or CRBEs	38 (0.9)	66 (1.8)	4 (0.6)
Any bleeding	47 (1.1)	70 (1.9)	4 (0.6)

[1] Based on the recommendations of the ISTH
[2] Modified 'TIMI major': any centrally confirmed (any) bleeding event causing a fall in hemoglobin level of 50 g/L (3.1 mmol/L) or more compared to baseline or a fall in hematocrit >15% compared to baseline (considering lab values within a time period of ±7 days around the bleeding event) or intracranial bleeding event.
[3] Life-threatening bleeding: bleeding events classified by central adjudication as any bleeding event and further classified as a serious, life-threatening adverse event by the investigator. All life-threatening bleeding events were adjudicated as MBEs.
[4] Intracranial bleeding: any centrally confirmed MBEs with an intracranial location.
[5] Includes bleeding events adjudicated as an MBE by the ICAC/BE because the bleeding event was fatal (DE: Patient 53-2311; W: Patient 53-3354; Patient 46-4800; Patient 47-8684) (SCS appendix [Module 5.3.5.3], Table 4.2.1.1 and Listing 4.13.2.7.1)

In the pooled aVTEt studies, from the start of double-dummy treatment, the rate of MBEs was lower in DE patients compared to warfarin patients (2.1 vs. 3.6 MBEs/100 pt-years). The incidence of MBEs was lower in the DE group compared to the warfarin group for all categories of MBEs (MBEs, adjudicated MBEs with a fatal outcome, intracranial MBEs, and TIMI major bleeding) and the same for life-threatening bleeding (where there was a difference of 2 patients) (Table 2.1.3.2: 2). The incidence of MBEs/CRBEs was also lower in the DE group (4.4%) than the warfarin group (7.7%).

Table 2.1.3.2: 2 Overview of MBEs in the pooled aVTEt Studies 1160.53 and 1160.46 - from start of double-dummy treatment in the aVTEt studies - treated set

	DE	W	DE/W Hazard Ratio (95% CI)[7]
Number of patients	2456	2462	
Time at risk [pt-yrs]	1127.0	1124.9	--
MBE rate/100 pt-years	2.1	3.6	--
Patients, n (%)	2456 (100.0)	2462 (100.0)	
Patients with MBE(s)[1], n (%)	24 (1.0)	40 (1.6)	0.60 (0.36, 0.99)
Patients with 1 MBE	22 (0.9)	37 (1.5)	--
Patients with 2 MBEs	2 (0.1)	3 (0.1)	--
Patients with			
TIMI major bleeds[2]	9 (0.4)	11 (0.4)	0.82 (0.34, 1.97)
Life-threatening bleedings[3]	4 (0.2)	6 (0.2)	0.66 (0.19, 2.36)
Intracranial bleedings[4]	2 (0.1)	4 (0.2)	0.50 (0.09, 2.74)
Patients with MBEs with a fatal outcome[5]	1 (0.0)	2 (0.1)	--
MBEs or CRBEs	109 (4.4)	189 (7.7)	0.56 (0.45, 0.71)
Patients with any bleeding event(s), n (%)	354 (14.4)	503 (20.4)	0.67 (0.59, 0.77)
Patients who discontinued study drug due to AEs classified as, n (%)[6]			
MBEs	7 (0.3)	24 (1.0)	--
MBEs or CRBEs	14 (0.6)	30 (1.2)	--
Any bleeding	16 (0.7)	32 (1.3)	--

[1] Based on the recommendations of the ISTH
[2] Modified 'TIMI major': any centrally confirmed (any) bleeding event causing a fall in hemoglobin level of 50 g/L (3.1 mmol/L) or more compared to baseline or a fall in hematocrit >15% compared to baseline (considering lab values within a time period of ±7 days around the bleeding event) or intracranial bleeding event.
[3] Life-threatening bleeding: bleeding events classified by central adjudication as any bleeding event and further classified as a serious, life-threatening adverse event by the investigator. All life-threatening bleeding events were adjudicated as MBEs.
[4] Intracranial bleeding: any centrally confirmed MBE with an intracranial location.
[5] Includes bleeding events adjudicated as an MBE by the ICAC/BE because the bleeding event was fatal (SCS appendix [Module 5.3.5.3], Table 4.13.2.7.1)
[6] Patients who discontinued study drug (Action taken = discontinued) due to a bleeding adverse event adjudicated as an MBE, CRBE, or nuisance bleeding event are included (SCS appendix [Module 5.3.5.3], Listing 4.13.2.7.3 and Tables 4.13.2.10.1, 4.13.11.6.1, 4.13.4.8.1)
[7] Cox model (Model #1) regression including the factor treatment. This model assumes different baseline hazards for the individual studies and a common treatment effect.

With regard to bleeding location for MBEs, investigator-reported GI bleeding was the most common MBE bleeding location for patients treated with DE. GI and urogenital bleeding were the most common MBE bleeding locations for patients treated with W. From the start of double-dummy treatment, the incidence of GI MBE bleedings was 0.4% and 0.5%, respectively (Table 2.1.3.2:4). GI bleeding (MBEs and any bleeding) is discussed later.

Table 2.1.3.2: 4 MBEs by bleeding criteria and location in the pooled aVTEt Studies 1160.53 and 1160.46 - from start of double-dummy treatment - treated set

	DE	W
Number of patients (%)	2456 (100.0)	2462 (100.0)
Patients with MBE(s), n (%)	24 (1.0)	40 (1.6)
Patients with MBEs by bleeding criteria[1], n (%)		
Bleeding event with a fatal outcome[2]	1 (0.0)	2 (0.1)
Symptomatic bleeding in a critical area or organ[3]	4 (0.2)	11 (0.4)
Bleeding causing a fall in hemoglobin or leading to transfusion[4]	20 (0.8)	30 (1.2)
Patients with MBEs by bleeding location[5], n (%)		
Gastrointestinal	10 (0.4)	12 (0.5)
Urogenital	6 (0.2)	12 (0.5)
Other bleeding location[6]	3 (0.1)	7 (0.3)
Intracranial*	2 (0.1)	4 (0.2)
Intraarticular*	2 (0.1)	3 (0.1)
Intramuscular*	1 (0.0)	2 (0.1)
Retroperitoneal*	0	0
Intraocular*	0	0
Intraspinal	0	0
Pericardial	0	0

* Indicates bleeding in a critical area or organ
[1] Bleeding events were classified as an MBE if at least one of the criteria applied. Therefore, an MBE could be included in more than 1 category. Criteria as assessed by central adjudication.
[2] All deaths and bleeding events were reviewed independently by two different committees, a listing of all deaths and adjudication results for MBEs and deaths is provided in SCS appendix [Module 5.3.5.3], Listing 5.4.7.2. All deaths are discussed further in Section 2.3.2.
[3] Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.
[4] Bleeding causing a fall in hemoglobin level of ≥20 g/L or leading to transfusion of ≥2 units of whole blood or red blood cells
[5] Bleeding location as documented by the investigator. Patients can have more than one site of bleeding.
[6] MBEs classified as 'other' by the investigator are presented by preferred term and sy stem order class in SCS appendix [Module 5.3.5.3], Listing 4.13.2.7.2 and Table 2.1.3.2: 4.

In the active-referenced sVTEp study (1160.47), investigator-reported GI bleeding was the most common MBE bleeding location for patients treated with W. The most common MBE bleeding locations for patients treated with DE were GI and intraocular. The incidence of patients with GI MBEs was lower in the DE group (0.3%) compared to the warfarin group (0.6%) in this study (Table 2.1.3.3: 3).

Table 2.1.3.3: 3 MBEs by criteria and location in Study 1160.47 - treated set

	DE	W
Number of patients (%)	1430 (100.0)	1426 (100.0)
Patients with MBE(s), n (%)	13 (0.9)	25 (1.8)
Patients with MBEs by bleeding criteria[1], n (%)		
Bleeding event with a fatal outcome[2]	0	1 (0.1)
Symptomatic bleeding in a critical area or organ[3]	7 (0.5)	11 (0.8)
Bleeding causing a fall in hemoglobin or leading to transfusion[4]	7 (0.5)	16 (1.1)
Patients with MBEs by bleeding location[5], n (%)		
Gastrointestinal	4 (0.3)	8 (0.6)
Intraocular*	4 (0.3)	2 (0.1)
Other bleeding location[6]	2 (0.1)	4 (0.3)
Intracranial*	2 (0.1)	4 (0.3)
Urogenital	1 (0.1)	1 (0.1)
Intramuscular*	0	4 (0.3)
Intraarticular*	0	2 (0.1)
Retroperitoneal*	0	1 (0.1)
Intraspinal	0	0
Pericardial	0	0

Includes events that occurred between the first intake of active study drug and 6 days after last intake of active study drug.
Major bleeding based on recommendation of ISTH.
* Indicates bleeding in a critical area or organ
[1] Bleeding events were classified as an MBE if at least one of the criteria applied. Therefore, an MBE could be included in more than 1 category. Criteria as assessed by central adjudication.
[2] All deaths and bleeding events were reviewed independently by two different committees, a listing of all deaths and adjudication results for MBEs and deaths is provided in SCS appendix [Module 5.3.5.3], Listing 5.4.7.2. All deaths are discussed further in Section 2.3.2.
[3] Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome.
[4] Bleeding causing a fall in hemoglobin level of ≥20 g/L or leading to transfusion of ≥2 units of whole blood or red blood cells
[5] Bleeding location as documented by the investigator. Patients can have more than one site of bleeding.
[6] MBEs classified as 'other' by the investigator are presented by preferred term and system order class in [SCS appendix [Module 5.3.5.3], Listing 4.2.7.2] and Table 2.1.3.1: 3.

Clinically relevant bleeding events (MBEs/CRBEs)

MBEs/CRBEs are presented for all four studies individually and for the pooled aVTEt studies in Table 6.3.4: 1. Consistent with the results for MBEs, the incidence of patients with an MBE or a CRBE was also lower in DE patients than warfarin patients in the pooled aVTEt studies (4.4% vs. 7.7%, from the start of oral only treatment [double-dummy treatment]) and in the sVTEp Study 1160.47 (5.6% vs. 10.2%). The DE to warfarin HR for MBEs/CRBEs was 0.56 (95% CI: 0.45, 0.71) from the start of oral only treatment (double-dummy treatment) in the pooled aVTEt studies and was 0.55 (95% CI: 0.41, 0.72) in the sVTEp Study 1160.47. The HR of DE over warfarin for MBEs/CRBEs was statistically significant for both analyses.

Table 6.3.4: 1 Summary of patients with MBEs/CRBEs for aVTEt (from the start of oral only treatment [double-dummy treatment]) and sVTEp studies – treated set

	DE	W	P	DE vs. W or P, HR (95% CI)
MBEs/CRBEs[1]				
Pooled aVTEt, n/N (%)	109/2456 (4.4)	189/2462 (7.7)	--	0.56 (0.45, 0.71)
Study 1160.53, n/N (%)	58/1226 (4.7)	99/1214 (8.2)	--	0.57 (0.41, 0.79)
Study 1160.46, n/N (%)	51/1230 (4.1)	90/1248 (7.2)	--	0.55 (0.39, 0.78)
sVTEp Study 1160.47, n/N (%)	80/1430 (5.6)	145/1426 (10.2)	--	0.55 (0.41, 0.72)
sVTEp Study 1160.63, n/N (%)	36/684 (5.3)	--	13/659 (2.0)	2.69 (1.43, 5.07)

[1] Includes MBEs based on the recommendations of the ISTH and CRBEs as defined in [SCS, U12-2617, Section 1.1.3.2].

Any bleeding events

Any bleeding events are presented for all four studies individually and for the pooled aVTEt studies in Table 6.3.5: 1. Any bleeding events include MBEs, CRBEs, and nuisance/trivial bleeding events. DE-treated patients had fewer any bleeding events than those receiving warfarin and more any bleeding events than placebo. For the pooled aVTEt studies, any bleeding events from the start of oral only treatment (double-dummy treatment) were reported less frequently in patients receiving DE (14.4%), compared to those receiving warfarin (20.4%) with a HR of 0.67 (95% CI 0.59, 0.77). Patients treated with DE in the sVTEp Study 1160.47 also had a lower any bleed rate (19.4%) compared to those receiving warfarin (26.2%), with a DE:W HR for any bleeding of 0.71 (95% CI 0.61, 0.83).

In the placebo-controlled Study 1160.63, any bleeding events were reported more often in patients treated with DE (10.5%) than those treated with placebo (6.1%) with an HR of 1.77 (95% CI, 1.20, 2.61).

Table 6.3.5: 1 Summary of patients with any bleeding events in the aVTEt (from the start of oral only treatment [double-dummy treatment]) and sVTEp studies – treated set

	DE	W	P	DE vs. W or P, HR (95% CI)
Pooled aVTEt, n/N (%)	354/2456 (14.4)	503/2462 (20.4)	--	0.67 (0.59, 0.77)
1160.53, n/N (%)	180/1226 (14.7)	248/1214 (20.4)	--	0.70 (0.57, 0.84)
1160.46, n/N (%)	174/1230 (14.1)	255/1248 (20.4)	--	0.65 (0.54, 0.79)
Study 1160.47, n/N (%)	278/1430 (19.4)	373/1426 (26.2)	--	0.71 (0.61, 0.83)
Study 1160.63, n/N (%)	72/684 (10.5)	--	40/659 (6.1)	1.77 (1.20, 2.61)

Gastrointestinal bleedings

Gastrointestinal (GI) bleedings are of particular interest because DE in other indications have been associated with an excess of GI bleedings. GI bleedings may belong to any of the categories MBE, MBE/CRBE or any bleeding.

GI bleedings are presented for all four studies individually and for the pooled aVTEt studies in Table 2.1.5: 1. The incidence of any bleeding events in the GI system was higher in patients treated with DE compared to warfarin (2.9% vs. 2.2% from start of double-dummy treatment for aVTEt pooled, and 3.1%

vs. 2.2% Study 1160.47). However, the incidence of MBEs in the GI system in DE patients was similar to or lower than patients treated with warfarin for both the aVTEt pooled analysis (0.4% vs. 0.5% from start of double-dummy, for aVTEt studies) and for the sVTEp Study 1160.47 (0.3 vs. 0.6%).

The rate/100 pt-years for GI MBEs was similar for DE and warfarin for the aVTEt pooled (from start of double-dummy treatment, 0.9 vs. 1.1) and sVTEp Study 1160.47 (0.2 vs. 0.4) analyses. For the analysis of any GI bleeding, the rate/100 pt-years was higher in DE patients compared to warfarin patients in the aVTEt pooled (any treatment, 6.7 vs. 5.3 and double-dummy, 6.3 vs. 4.9) and in sVTEp Study 1160.47 (2.4% vs. 1.7%).

The incidence of any GI bleeding events was higher in DE patients compared to placebo (0.7% vs. 0.3%) in the sVTEp Study 1160.63.

Table 2.1.5: 1 Gastrointestinal bleeding for the pooled aVTEt studies, Study 1160.47, and Study 1160.63 - treated set

	DE	W	P	DE vs. W, HR (95% CI)
Pooled aVTEt studies from start of any treatment				
Number of patients, n (%)	2553	2554	--	
GI MBE, n (%)	15 (0.6)	14 (0.5)	--	1.07 (0.52, 2.22)
Time at risk [pt-yrs]	1179.2	1180.9	--	
rate/100 pt-years	1.3	1.2	--	
Any GI bleed, n (%)	78 (3.1)	62 (2.4)	--	1.26 (0.90, 1.76)
Time at risk [pt-yrs]	1160.5	1165.2	--	
rate/100 pt-years	6.7	5.3	--	
Pooled aVTEt studies from start of double-dummy treatment				
Number of patients, n (%)	2456	2462	--	
GI MBE, n (%)	10 (0.4)	12 (0.5)	--	0.83 (0.36, 1.93)
Time at risk [pt-yrs]	1130.1	1128.3	--	
rate/100 pt-years	0.9	1.1	--	
Any GI bleed, n (%)	70 (2.9)	55 (2.2)	--	1.27 (0.90, 1.82)
Time at risk [pt-yrs]	1112.0	1114.7	--	
rate/100 pt-years	6.3	4.9	--	
sVTEp Study 1160.47				
Number of patients, n (%)	1430	1426	--	
GI MBE, n (%)	4 (0.3)	8 (0.6)	--	NC
Time at risk [pt-yrs]	1874.0	1870.6	--	
rate/100 pt-years	0.2	0.4	--	
Any GI bleed, n (%)	45 (3.1)	32 (2.2)	--	1.39 (0.87, 2.20)
Time at risk [pt-yrs]	1836.8	1852.0	--	
rate/100 pt-years	2.4	1.7	--	
sVTEp Study 1160.63				**DE vs. P, HR (95% CI)**
Number of patients, n (%)	684	--	659	
GI MBE, n (%)	2 (0.3)	--	0	NC
Time at risk [pt-yrs]	320.7	--	303.1	
rate/100 pt-years	0.6	--	0	
Any GI bleed, n (%)	5 (0.7)	--	2 (0.3)	2.38 (0.46, 12.27)
Time at risk [pt-yrs]	319.3	--	302.8	
rate/100 pt-years	1.6	--	0.7	

NC = not calculable

Bleeding events in warfarin-treated patients as a function of Time in Therapeutic Range (TTR)

The Applicant also presented major bleeding events and clinically relevant bleeding events (including major) by five approximately equally sized groups (quintiles) of patients according to their TTR: <40%, 40-<57%, 57-<67%, 67-<78% and ≥78%. Bleeding events quite clearly occurred more frequently in the quintile with the poorest TTR (see table below).

Bleeding endpoints by TTR in quintiles for pooled aVTEt studies and study 1160.47 (RE-MEDY) overall population, warfarin only; n/N (%)

TTR (INR 2.0-3.0)	<40%	40 - < 57%	57-<67%	67-<78%	>=78%
MBE					
RE-COVER	12/236 (5.1)	3/262 (1.1)	1/196 (0.5)	2/254 (0.8)	2/260 (0.8)
RE-COVER II	10/276 (3.6)	3/305 (1.0)	4/250 (1.6)	0/207 (0.0)	0/206 (0.0)
RE-MEDY	10/242 (4.1)	7/260 (2.7)	2/271 (0.7)	3/341 (0.9)	3/302 (1.0)
MBE/CRBE					
RE-COVER	44/241 (18.3)	18/244 (7.4)	18/223 (8.1)	6/243 (2.5)	9/255 (3.5)
RE-COVER II	50/277 (18.1)	12/287 (4.2)	10/270 (3.7)	4/200 (2.0)	12/209 (5.7)
RE-MEDY	50/251 (19.9)	21/244 (8.6)	20/280 (7.1)	25/339 (7.4)	28/301 (9.3)

Acute Coronary Syndrome

All suspected Acute Coronary Syndrome (ACS) events were reviewed by independent adjudication committees in a treatment-blinded fashion in each of the 4 pivotal studies and include cardiovascular death, myocardial infarction and coronary ischemia (Study 1160.53, 1160.46, 1160.47, and 1160.63). Table 2.2:1 shows the adjudicated coronary syndrome events for the pivotal studies.

Table 2.2: 1 Adjudicated coronary syndrome events for the pooled aVTEt studies and Studies 1160.47 and 1160.63 - treated set

	DE	W	P
Pooled aVTEt studies			
Patients, n (%)	2553(100.0)	2554 (100.0)	
Patients with definite or likely ACS events by ICAC during intake of study drug,[1] n (%)	10 (0.4)	5 (0.2)	--
Cardiac death, n (%)	0	1 (0.0)	--
Myocardial infarction, n (%)	9 (0.4)	4 (0.2)	--
Ischemia / unstable angina, n (%)	1 (0.0)	1 (0.0)	--
sVTEp Study 1160.47			
Patients, n (%)	1430 (100.0)	1426 (100.0)	--
Patients with definite or likely ACS events by ICAC during intake of study drug,[1] n (%)	14 (1.0)	3 (0.2)	--
Cardiac death, n (%)	0	0	--
Myocardial infarction, n (%)	11 (0.8)	1 (0.1)	--
Ischemia / unstable angina, n (%)	4 (0.3)	2 (0.1)	--
sVTEp Study 1160.63			
Patients, n (%)	684 (100.0)	--	659 (100.0)
Patients with definite or likely ACS events by ICAC during intake of study drug,[1] n (%)	1 (0.1)	--	1 (0.2)
Cardiac death, n (%)	0	--	0
Myocardial infarction, n (%)	1 (0.1)	--	1 (0.2)
Ischemia / unstable angina, n (%)	0	--	0

[1] Includes the day after last intake of study drug.
Note that Patient 005558, Study 1160.53 had an MI with a fatal outcome; both MI and death were adjudicates as definite ACS events.

The incidence of definite or likely MI during intake of study drug (+1 day) was lower in warfarin patients than DE patients in the pooled aVTEt studies (0.2% vs. 0.4%) and in sVTEp Study 1160.47 (0.1% vs. 0.8%). When compared with placebo in Study 1160.63, there was one patient in each treatment group (DE and placebo) with an MI. Across all studies, one patient with a definite or likely cardiac death during intake of study drug (+1 day) was reported, this patient received W

Table 2.2:1 above only refers to adjudicated ACS event during intake of active study drug + one day. The numbers below refer to ACS events reported during the entire study period, thus including events during and after intake of active study medication.

In all four pivotal studies more suspected acute coronary syndrome (ACS) events were seen among patients treated with DE compared to patients treated with warfarin or placebo:

Study 6011.46: DE: 11 (0.9%) patients vs. W: 8 (0.6%) patients
Study 6011.53: DE: 24 (1.9%) patients vs. W: 17 (1.3%) patients
Study 6011.47: DE: 30 (2.0%) patients vs. W: 15 (1.0%) patients
Study 6011.63: DE: 3 (0.4%) patients vs. placebo: 2 (0.3%) patients

Likewise, more patients treated with DE were adjudicated to have a definite ACS event:

Study 6011.46: DE: 5 (0.4%) patients vs. W: 1 (0.1%) patients
Study 6011.53: DE: 11 (0.9%) patients vs. W: 5 (0.4%) patients
Study 6011.47: DE: 12 (0.8%) patients vs. W: 2 (0.1%) patients
Study 6011.63: DE: 3 (0.4%) patients vs. placebo: 2 (0.3%) patients

In the study (116047) where the difference between DE and warfarin was most pronounced, there was a statistically significant difference in the risk of definite ACS events during the on-treatment period, with a HR of DE vs. warfarin of 4.35 (95% CI 1.24, 15.27) and a p-value of 0.0217. There was a greater baseline prevalence of cardiac risk factors in the DE treatment group than in the warfarin treatment group. As a post-hoc analysis, the incidence of ACS events adjudicated as definite was analysed for patient subgroups. No relevant treatment-by-subgroup interaction was observed for the any subgroup evaluated, including history of coronary artery disease, heart failure, hypertension, and diabetes mellitus.

The Applicant was requested to further investigate the cardiovascular benefits and risks of DE using a composite cardiovascular outcome endpoint. The composite consisted of non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism and all-cause death and was a slight adaptation of the one used in the HOKUSAI-VTE study. Consistently across all three warfarin-controlled studies, there was a higher incidence in patients on DE compared to warfarin-treated patients although the hazard ratio was not statistically significantly different from 1.

Deaths

All deaths were adjudicated by the ICAC/VTE/death. The overall incidence of reported AEs with an outcome of death for all VTE studies is presented in Table 2.3.2: 1. In the pooled pivotal VTE studies, the incidence of investigator-reported AEs with an outcome of death during the treatment period was lower in the DE group (1.1%) compared to the warfarin group (1.5%) and was lowest in the placebo group (0.3%).

A summary of investigator-reported AEs with an outcome of death in 2 or more patients in any treatment group during the treatment period is presented in Table 2.3.2.1: 1 for the pooled pivotal VTE studies.

Table 2.3.2.1: 1 Investigator-reported adverse events with an outcome of death in at least 2 patients in any treatment group in the pooled pivotal VTE Studies 1160.46, 1160.53, 1160.47, and 1160.63 - treated set

	DE n (%)	W n (%)	P n (%)
Patients	4387 (100.0)	3707 (100.0)	659 (100.0)
Patients with any AE with an outcome of death	49 (1.1)	55 (1.5)	2 (0.3)
Neoplasms benign, malignant and unspecified	24 (0.5)	28 (0.8)	1 (0.2)
Metastases to liver	3 (0.1)	1 (0.0)	0
Neoplasm malignant	3 (0.1)	2 (0.1)	0
Pancreatic carcinoma	3 (0.1)	1 (0.0)	0
Hepatic neoplasm malignant	2 (0.0)	1 (0.0)	0
Lung neoplasm malignant	2 (0.0)	1 (0.0)	0
Lung adenocarcinoma	2 (0.0)	0	0
Metastatic neoplasm	1 (0.0)	2 (0.1)	0
Ovarian cancer metastatic	0	2 (0.1)	0
Respiratory, thoracic and mediastinal disorders	11 (0.3)	5 (0.1)	0
Pulmonary embolism	5 (0.1)	4 (0.1)	0
Respiratory failure	3 (0.1)	0	0
Infections and infestations	6 (0.1)	4 (0.1)	0
Sepsis	1 (0.0)	2 (0.1)	0
Cardiac disorders	5 (0.1)	7 (0.2)	1 (0.2)
Cardiac arrest	2 (0.0)	1 (0.0)	0
General disorders and administration site conditions	4 (0.1)	6 (0.2)	0
Death	2 (0.0)	3 (0.1)	0
Multi-organ failure	1 (0.0)	2 (0.1)	0
Injury, poisoning and procedural complications	3 (0.1)	1 (0.0)	0
Gastrointestinal disorders	1 (0.0)	2 (0.1)	0
Nervous system disorders	1 (0.0)	5 (0.1)	0

Deaths in the treatment period are those that occurred between first intake and 6 days after the last intake of any study drug.
Source data: SCS appendix [Module 5.3.5.3], Table 5.4.2.1

The incidence of investigator-reported AEs with fatal outcomes was similar between DE and warfarin patients in the pooled aVTEt studies and was lower in DE patients than warfarin patients in Study 1160.47 (0.8% vs. 1.3%). In the placebo-controlled sVTEp study (1160.63), 1 DE patient and 2 placebo patients had an investigator-reported AE with an outcome of death.

Neoplasms were the most frequently reported AEs with an outcome of death. The second most common cause of deaths was respiratory disorders: 11 (0.3%) DE patients including 5 patients with PE and 5 (0.1%) warfarin patients including 4 patients with PE. Overall, PE was the most frequent investigator-reported AE with an outcome of death in the DE group. Four of the five PE in the DE patients and three of the four PE in the warfarin patients occurred in the two aVTEt studies.

Overall, 2 DE patients and 5 warfarin patients had bleeding events with a fatal outcome during the treatment period (onset of bleeding event was within 6 days of the last intake of study drug). Four of these patients (1 DE and 3 W) had adjudicated major bleeding events (MBEs) with a fatal outcome according to the ICAC/BE during the treatment period and 2 additional warfarin patients had MBEs with a fatal outcome according to the ICAC/VTE/Death.

Investigator-reported AEs of cardiac disorders with an outcome of death were rare (DE: 0.1%, W: 0.2%, P: 0.2%) in the pooled VTE studies, and only one adjudicated ACS event had a fatal outcome.

For the roll-over patients in Study 1160.47, there appeared to be a higher incidence of investigator-reported AEs with an outcome of death for patients who were allocated to a different treatment in Study 1160.47 compared to those who continued with the same treatment (DE→W: 2.3%, W→DE: 2.3% compared to DE→DE: 0%, W→W: 1.1%).

Laboratory findings

Laboratory parameters, introduction

All analyses of laboratory data were based on normalised values. Safety laboratory parameters were analysed by descriptive statistics (each visit, categorised time windows, last value on treatment, worst value on treatment, and changes from baseline), by transitions relative to reference range (low, normal, high) at baseline and last value on treatment (and worst value on treatment for liver function test results), and by possible clinically significant abnormalities (increase or decrease from baseline).

In the following, analysis of liver parameters is described separately.

Laboratory parameters, liver function parameters

Analyses of liver function tests results (ALT, AST, total bilirubin, and alkaline phosphatase (ALP)) were periodically performed to evaluate the potential for drug-induced liver injury according to the FDA Guidance for Industry, Drug-Induced Liver Injury: pre-marketing clinical evaluation. Liver function parameters and transitions relative to the reference range from baseline to worst and last value on treatment and possibly clinically significant abnormalities including the number of patients whose laboratory parameters returned to a normal range were summarised based on actual local or central laboratory results and reference ranges.

Results from the early registration studies as well as post marketing experience do not indicate any hepatotoxic effect of DE.

Mean changes from baseline and transitions relative to reference range

In all four pivotal studies, no clinically relevant treatment differences were observed for the means of the baseline value, last value on treatment, and the maximum post-baseline value for ALT, AST, ALP and bilirubin. Neither did analysis of the transitions relative to reference ranges from baseline to the last value of treatment and the maximum value on treatment reveal any meaningful differences between the treatment groups in any of the four pivotal studies.

For ALT, AST, and ALP the incidence of transitions to above the reference range from baseline to the last on-treatment value and to the worst on-treatment value were higher in the DE and warfarin groups compared with the placebo group. For bilirubin, the incidence of transitions to above the reference range from baseline to the last on-treatment value was similar among the three treatment groups whereas the incidence of transitions to above the reference range from baseline to the worst on-treatment value was higher in the DE and warfarin groups compared with the placebo group.

Additional analyses of LFT elevations of individual parameters and review of cases with ALT >3 x ULN by Hepatic Review Panel

The majority of patients with elevated LFT values had only minor elevations in ALT and/or AST and values of ≥2 x upper limit of normal (ULN) were infrequent in all four studies. Table 3.1.4: 1 shows the frequencies and magnitudes of LFT values elevation >3 x ULN for the pooled pivotal studies.

Table 3.1.4: 1 Frequency of patients with liver function test value elevations in the pooled pivotal VTE Studies 1160.46, 1160.53, 1160.47 and 1160.63 - treated set

Treatment Parameter, n (%)	>3 × ULN	>5 × ULN	>10 × ULN	>20 × ULN
DE				
With ALT elevation (n = 4666)	61 (1.31)	28 (0.60)	7 (0.15)	2 (0.04)
With AST elevation (n = 4666)	51 (1.09)	22 (0.47)	1 (0.02)	0
With AST or ALT elevation (n= 4666)	76 (1.63)	39 (0.84)	7 (0.15)	2 (0.04)
W				
With ALT elevation (n = 3980)	64 (1.61)	40 (1.01)	8 (0.20)	3 (0.08)
With AST elevation (n = 3980)	36 (0.90)	23 (0.58)	5 (0.13)	1 (0.03)
With AST or ALT elevation (n = 3980)	69 (1.73)	42 (1.06)	11 (0.28)	3 (0.08)
P				
With ALT elevation (n = 659)	3 (0.46)	1 (0.15)	0	0
With AST elevation (n = 658)	1 (0.15)	1 (0.15)	0	0
With AST or ALT elevation (n = 659)	4 (0.61)	1 (0.15)	0	0
	>1.5 x ULN		>2 x ULN	
DE				
With ALP elevation (n = 4664)	109 (2.34)		NA	
With total bilirubin elevation (n = 4664)	71 (1.52)		25 (0.54)	
W				
With ALP elevation (n = 3974)	118 (2.97)		NA	
With total bilirubin elevation (n = 3973)	53 (1.33)		29 (0.73)	
P				
With ALP elevation (n = 658)	5 (0.76)		NA	
With total bilirubin elevation (n = 657)	7 (1.07)		2 (0.30)	

The table is based on the number of patients with at least 1 post-baseline value for the respective parameter.
NA = not assessed
Source data: SCS appendix [Module 5.3.5.3], Tables 6.1.1.1, 6.1.2.1, 6.1.3.1, 6.1.4.1, and 6.1.5.1

As seen, LFT elevations in the different ULN categories were reported more frequently for the DE and warfarin groups compared with the placebo group. Numerically more patients treated with warfarin had ALT and AST values elevation >5 x ULN.

In Study 1160.47 and 1160.53, cases with ALT >3 x ULN were reviewed by a Hepatic Review Panel (HRP). In these two studies, a total of 68 patients treated with DE and 82 patients treated with warfarin were assessed by the HRP for their causal relationship of the ALT elevations with any study drug. In 4 DE treated and 2 warfarin treated patients the assessment was “probably related” (defined as a good temporal relationship with study drug intake was present and no other obvious potential cause for the elevations was identified).

Possible clinically significant abnormalities and potential Hy’s law cases

Possible clinically significant abnormalities (PCSAs) were specified by the Investigator applying MAH (BI)’s standard definitions of PCSAs.

No relevant differences in the frequencies of PCSAs between the treatment groups were observed for any of the four liver function parameters in any of the four pivotal studies. In all four studies, PCSAs were most frequently reported for ALT, followed by AST.

Overall, PCSAs were reported at similar or slightly lower frequencies in the DE group (0.6%-2.3% within the different liver function test results [LFT] results) compared with warfarin (0.7%-2.9% within the different LFTs), but more frequently than placebo (0%-0.8% within the different LFTs) for all LFT results (Table 3.1.3: 1).

Table 3.1.3: 1 Frequency of patients with possibly clinically significant liver function test value elevations in the pooled pivotal VTE Studies 1160.46, 1160.53, 1160.47, and 1160.63 - treated set

Parameter	DE n/N (%)	W n/N (%)	P n/N (%)
ALT	103/4559 (2.3)	113/3869 (2.9)	5/638 (0.8)
AST	90/4558 (2.0)	74/3869 (1.9)	3/638 (0.5)
ALP	41/4559 (0.9)	58/3868 (1.5)	0/638 (0.0)
Total bilirubin	26/4560 (0.6)	29/3869 (0.7)	1/637 (0.2)

n is the number of patients with possibly clinically significant abnormalities, N is the number of (non-unique - could be counted twice if, e.g., re-randomized) patients with at least 1 post-baseline assessment of the respective parameter; a patient is counted twice if re-randomized as a rollover patient.
Possibly clinically significant increases were specified by the Investigator. Only patients with a baseline value that was not possibly clinically significant (or without any baseline value) could have a possibly clinically significant abnormality.
Source data: SCS appendix [Module 5.3.5.3], Table 6.3.3.1

Possible clinically significant abnormalities in LFT values resolved in 44% (ALP) to 77% (ALT) among patients treated with DE and for 47% (ALP) to 70% (ALT) among patients treated with W.

Hy's law is (a prognostic indicator of a pure drug-induced liver injury) is defined as patients with elevations of ALT or AST >3 x upper limit of normal (ULN) who had also elevations of total bilirubin of >2 x ULN ± 30 days of the transaminase elevation. In the four pivotal studies, 6 patients treated with DE, 7 patients treated with warfarin and 0 patients treated with placebo experienced elevation in liver function test values fulfilling the criteria for potential Hy's law cases. For all patients treated with DE and 6 of the 7 patients treated with warfarin there was a good explanation for the elevation of ALT and bilirubin. The last patient (included in Study 1160.46) treated with warfarin had concomitant disease (MRCP confirmed cholecystolithiasis) as well as he was treated with medication also know to be able to induced elevated liver parameters (atorvastatin and ampicillin/sulbactam) thus, overall, there was no strong evidence of a Hy's law case in any of the pivotal studies.

Abnormal laboratory liver function parameters reported as adverse events

Only few cases of abnormal laboratory liver function parameters were reported as adverse events. The most frequently reported AE was increase in ALT, which was reported in less than 1% of the patients in all four studies and with no difference between treatment groups. Increased AST levels were reported in 0.2%-0.5% in all patients groups also with no clinically meaningful difference between treatment groups. Only in very few cases, the AEs were leading to study drug discontinuation or reported as SAEs.

Liver function parameters, conclusion

Mean changes from baseline were small and no clinically relevant difference between DE and warfarin was seen. Most changes from baseline were not considered to be clinically relevant and there were no differences in the frequencies of possible clinically significant abnormalities (PCSAs) between the treatment groups in any of the 4 liver function parameters in any of the four pivotal studies. The most frequent reported PCSA was elevated ALT followed by elevated AST. In total less than 20 cases fulfilled the criteria for potential Hy's law cases however, review of the cases showed other more likely explanations for the elevated LFT values, thus there was no strong evidence of a Hy's law case in any of the pivotal studies. Only few cases of abnormal laboratory liver function parameters were reported as (serious) adverse events.

Laboratory parameters other than liver function parameters

Standard haematology and clinical chemistry parameters were analysed descriptively for changes from baseline to the last on treatment value and for the worst value on treatment for studies 1160.53, 1160.46, and 1160.47. Transitions relative to the reference range from baseline to worst and last value on treatment and possibly clinically significant abnormalities including the number of patients whose laboratory parameters returned to a normal range were summarised based on normalised values. Regarding creatinine clearance, the Cockcroft-Gault formula was used to estimate creatinine clearance in all four pivotal studies.

Due to the few patients having other parameters than liver function parameters tested during the trial of 1160.63, comparison of DE with placebo is not possible.

There were no clinically relevant important differences in median haematology, electrolyte, creatinine, and urea values between the DE and warfarin groups.

Changes in the median values from baseline to the last on-treatment value and to the worst on-treatment value were generally small and did not show any clinically important differences between the DE and warfarin groups. Specifically, no differences were seen in creatinine.

Possible clinically significant abnormalities (PCSAs) in laboratory values (other than liver function parameters) were in general low in all studies (1160.46, 1160.47 and 1160.53) and with no clinically relevant difference between the DE and the warfarin groups. Decrease in haematocrit was the most often reported PCSA and was reported in 3.5% (Study 1160.53) – 4.4% (Study 1160.46) of patients in the DE-groups and in 4.6% (Study 1160.47) – 4.9% (Study 1160.46) of patients in the W-groups.

Increase in creatinine was reported in 1.6% (Study 1160.46) – 2.5% (Study 1160.47) of DE treated patients with no difference as compared with warfarin (1.7% - 2.9%).

Changes in white blood cell counts, platelets, sodium and potassium considered as PCSAs was reported in <1% of all patients in both treatment groups.

Safety in special populations

The intrinsic factors of primary interest for DE are renal function and age. Also gender, ethnicity and BMI are briefly presented. Further analyses of intrinsic factors were investigated for bleedings. These are summarised at the end of this section.

Renal function

A summary of bleeding events by renal impairment category is presented in Table 6.3.6: 1. All presented data are from the start of oral only treatment (double-dummy treatment).

Few patients had CrCl <30 mL/min at baseline in the pooled aVTEt studies or in Study 1160.47. None of these patients had MBEs. Administration of DE to patients with CrCl <30 mL/min is contraindicated.

In VTE patients with moderate renal impairment (CrCl of 30 to <50 mL/min), the incidence of MBEs in the pooled aVTEt studies was higher for DE patients (6/106; 5.7%) compared to warfarin (5/114; 4.4%). The difference between the groups is 1 patient. Additionally, DE-treated patients had a higher percentage of MBEs/CRBEs in VTE patients with moderate renal impairment compared to W, although numerically they were the same. The incidence of bleeding events in VTE patients with moderate renal impairment was lower in DE patients compared to warfarin patients in all other instances (MBEs and MBEs/CRBEs in Study 1160.47, and any bleeding in aVTEt pooled and Study 1160.47).

For patients with CrCl of 50 to <80 mL/min and ≥80 mL/min, the incidence of patients with MBEs, MBEs/CRBEs, and any bleeding events was lower in DE patients compared to warfarin patients in the pooled aVTEt studies and sVTEp Study 1160.47.

Table 6.3.6: 1 Summary of bleeding events (MBEs, MBEs/CRBEs, and any bleeding) by creatinine clearance category from the start of oral only treatment (double-dummy treatment) in the pooled aVTEt studies and sVTEp Study 1160.47 – treated set

Creatinine clearance categories, n/N (%)*	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs	**DE**	**W**	
Pooled aVTEt studies			
<30 mL/min	0/8 (0)	0/10 (0)	NC
30 to <50 mL/min	6/106 (5.7)	5/114 (4.4)	1.32 (0.40, 4.31)
50 to <80 mL/min	9/504 (1.8)	16/536 (3.0)	0.58 (0.26, 1.31)
≥80 mL/min	9/1811 (0.5)	19/1783 (1.1)	0.47 (0.21, 1.03)
sVTEp Study 1160.47			
<30 mL/min	0/0 (0)	0/4 (0)	NC
30 to <50 mL/min	2/59 (3.4)	3/45 (6.7)	0.51 (0.09, 3.09)
50 to <80 mL/min	3/328 (0.9)	8/289 (2.8)	0.32 (0.09, 1.21)
≥80 mL/min	8/1031 (0.8)	14/1072 (1.3)	0.60 (0.25, 1.42)
MBEs/CRBEs	**DE**	**W**	
Pooled aVTEt studies			
<30 mL/min	1/8 (12.5)	0/10 (0)	NC
30 to <50 mL/min	12/106 (11.3)	12/114 (10.5)	1.10 (0.49, 2.45)
50 to <80 mL/min	36/504 (7.1)	66/536 (12.3)	0.55 (0.36, 0.82)
≥80 mL/min	59/1811 (3.3)	110/1783 (6.2)	0.52 (0.38, 0.71)
sVTEp Study 1160.47			
<30 mL/min	0/0 (0.0)	0/4 (0.0)	NC
30 to <50 mL/min	3/59 (5.1)	5/45 (11.1)	0.46 (0.11, 1.91)
50 to <80 mL/min	23/328 (7.0)	33/289 (11.4)	0.60 (0.35, 1.02)
≥80 mL/min	54/1031 (5.2)	107/1072 (10.0)	0.52 (0.37, 0.72)
Any bleeding	**DE**	**W**	
Pooled aVTEt studies			
<30 mL/min	2/8 (25.0)	2/10 (20.0)	1.47 (0.21, 10.47)
30 to <50 mL/min	21/106 (19.8)	29/114 (25.4)	0.79 (0.45, 1.38)
50 to <80 mL/min	97/504 (19.2)	125/536 (23.3)	0.78 (0.63, 1.02)
≥80 mL/min	231/1811 (12.8)	342/1783 (19.2)	0.64 (0.54, 0.75)
sVTEp Study 1160.47			
<30 mL/min	0/0 (0)	1/4 (25.0)	NC
30 to <50 mL/min	16/59 (27.1)	15/45 (33.3)	0.87 (0.43, 1.78)
50 to <80 mL/min	67/328 (20.4)	79/289 (27.3)	0.70 (0.51, 0.97)
≥80 mL/min	194/1031 (18.8)	275/1072 (25.7)	0.70 (0.58, 0.84)

NC = Not Calculable
* In the VTE studies, patients with CrCl <30 mL/min were not to be enrolled.

Age

A summary of bleeding events by renal impairment category is presented in Table 5.1.1.2: 1. Data from start of any treatment as well as from the start of oral only treatment (double-dummy treatment) are presented.

The incidence of bleeding events appears to increase with age for both DE and warfarin patients. The incidence of bleeding (MBEs, MBE/CRBEs, and any bleeding) was lower in DE patients compared with warfarin in the pooled aVTEt studied and sVTEp Study 1160.47, in most age subgroups analyzed – with the exception of MBEs in patients more than 75 years (aVTEt) and in MBEs and MBEs/CRBEs in patients in the age range 65-75 years (sVTEp Study 1160.47).

Table 5.1.1.2: 1 Bleeding events (MBEs, MBEs/CRBEs, and any bleeding) by age categories in the pivotal aVTEt and sVTEp studies - treated set

Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
MBEs			
Pooled aVTEt studies	**DE**	**W**	
Pooled aVTEt studies, from start of any treatment			
<65 years	14/1771 (0.8)	24/1746 (1.4)	0.57 (0.30, 1.11)
65 to 75 years	12/529 (2.3)	15/532 (2.8)	0.76 (0.36, 1.64)
>75 years	11/253 (4.3)	12/276 (4.3)	1.03 (0.45, 2.33)
≥80 years	6/135 (4.4)	3/125 (2.4)	1.99 (0.50, 7.95)

Table 5.1.1.2: 1 (cont.) Bleeding events (MBEs, MBEs/CRBEs, and any bleeding) by age categories in the pivotal aVTEt and sVTEp studies - treated set

Age categories, n/N (%)	Treatment No. events/no. of patients (%)		DE/W Hazard Ratio (95% CI)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	11/1722 (0.6)	19/1685 (1.1)	0.57 (0.27, 1.20)
65 to 75 years	5/503 (1.0)	11/515 (2.1)	0.43 (0.15, 1.24)
>75 years	8/231 (3.5)	10/262 (3.8)	0.90 (0.35, 2.28)
≥80 years	4/122 (3.3)	3/121 (2.5)	1.31 (0.29, 5.86)
sVTEp Study 1160.47	**DE**	**W**	
<65 years	3/987 (0.3)	14/1019 (1.4)	0.22 (0.06, 0.78)
65 to 75 years	9/329 (2.7)	3/307 (1.0)	2.70 (0.73, 9.96)
>75 years	1/114 (0.9)	8/100 (8.0)	0.10 (0.01, 0.82)
≥80 years	0/52 (0)	4/47 (8.5)	--
MBEs/CRBEs			
Pooled aVTEt studies, from start of any treatment			
<65 years	65/1771 (3.7)	117/1746 (6.7)	0.54 (0.40, 0.73)
65 to 75 years	42/529 (7.9)	63/532 (11.8)	0.66 (0.44, 0.97
>75 years	29/253 (11.5)	37/276 (13.4)	0.88 (0.54, 1.43)
≥80 years	16/135 (11.9)	17/125 (13.6)	0.95 (0.48, 1.88)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	58/1722 (3.4)	102/1685 (6.1)	0.55 (0.40, 0.76)
65 to 75 years	29/503 (5.8)	54/515 (10.5)	0.52 (0.33, 0.82)
>75 years	22/231 (9.5)	33/262 (12.6)	0.74 (0.43, 1.26)
≥80 years	11/122 (9.0)	16/121 (13.2)	0.69 (0.32, 1.48)
sVTEp Study 1160.47	DE	W	
<65 years	40/987 (4.1)	101/1019 (9.9)	0.40 (0.28, 0.58)
65 to 75 years	33/329 (10.0)	23/307 (7.5)	1.35 (0.79, 2.30)
>75 years	7/114 (6.1)	21/100 (21.0)	0.28 (0.12, 0.65)
≥80 years	4/52 (7.7)	10/47 (21.3)	0.39 (0.12, 1.27)
Any bleeding			
Pooled aVTEt studies, from start of any treatment			
<65 years	256/1771 (14.5)	363/1746 (20.8)	0.66 (0.56, 0.78)
65 to 75 years	100/529 (18.9)	133/532 (25.0)	0.73 (0.56, 0.95)
>75 years	55/253 (21.7)	71/276 (25.7)	0.87 (0.61, 1.24)
≥80 years	33/135 (24.4)	33/125 (26.4)	0.99 (0.61, 1.60)
Pooled aVTEt studies, from start of double-dummy treatment			
<65 years	229/1722 (13.3)	324/1685 (19.2)	0.66 (0.56, 0.78)
65 to 75 years	81/503 (16.1)	115/515 (22.3)	0.68 (0.51, 0.91)
>75 years	44/231 (19.0)	64/262 (24.4)	0.76 (0.52, 1.12)
≥80 years	25/122 (20.5)	31/121 (25.6)	0.79 (0.47, 1.34)
sVTEp Study 1160.47	**DE**	**W**	
<65 years	176/987 (17.8)	261/1019 (25.6)	0.67 (0.55, 0.81)
65 to 75 years	70/329 (21.3)	75/307 (24.4)	0.84 (0.60, 1.16)
>75 years	32/114 (28.1)	37/100 (37.0)	0.74 (0.46, 1.19)
≥80 years	13/52 (25.0)	18/47 (38.3)	0.66 (0.32, 1.35)

Gender

Overall, 59.2% of patients were men in the pooled pivotal VTE studies. Women tended to have a slightly higher frequency of investigator-reported AEs compared with men in the DE (70.6% and 64.1%, respectively) and warfarin groups (74.1% and 69.6%). Conversely, men had a higher frequency of

investigator-reported AEs compared with women in the placebo group (51.4% and 47.1%, respectively). The overall frequency of investigator-reported AEs was higher in active treatment groups compared with the placebo group for both genders.

The overall pattern of AE frequencies by gender was mostly similar to those reported in the overall assessment of investigator-reported AEs. However, GI disorders were reported at a higher frequency in women than men for both the DE group and the warfarin group, and the difference was more pronounced in the DE group.

Ethnicity

The overall frequency of investigator-reported AEs appeared to be higher in African patients compared with Caucasian or Asian patients. However, the majority of patients (86.8%) were Caucasian and there were fewer than 100 African patients per treatment group. Similarly, the majority of patients were non-Hispanic (95.4%) and there were fewer than 200 Hispanic patients per treatment group. These small numbers of patients precluded an accurate assessment of potential differences by race or ethnicity.

BMI

The BMI category with the most patients was 25 to 30 kg/m2. Patients with a BMI >35 kg/m2 had a higher frequency of investigator-reported AEs in the DE and warfarin groups compared with the lower BMI categories. The overall pattern of AE frequencies by BMI category was mostly similar to those reported in the overall assessment of investigator-reported AEs. For all categories of BMI the reported overall AE frequencies were always numerically lower for the DE group compared with the warfarin group.

Further analyses of intrinsic factors for bleedings

There were generally fewer MBEs reported for patients treated with DE compared with those treated with warfarin in the pooled aVTEt studies, across all subgroups of patients. In the pooled aVTEt studies, from the start of doubledummy treatment, the incidence of MBEs in DE patients was lower compared with warfarin patients for the intrinsic risk factors of all age categories except 80 years or more, creatinine clearance categories >50 mL/min (i.e. not severe and moderate renal impairment), patients of non-Hispanic ethnicity or Asian race, and patients in regions other than Asia and "other", regardless of gender.

Also in the sVTEp Study 1160.47, there were generally fewer MBEs reported for patients treated with DE compared with those treated with W. The incidence of MBEs in DE patients was lower compared with warfarin patients for most age categories (but not for the age range 65-75 years), creatinine clearance categories >50 mL/min (i.e. not severe and moderate renal impairment), and patients of non-Hispanic ethnicity and Caucasian race, regardless of gender.

The Applicant was requested to analyse the influence of a combination of risk factors. The only meaningful analysis was the combination of age over 75 years and moderate renal impairment. The incidence of bleedings was numerically higher in patients on DE with this combination of risk factors compared to patients on DE not having this combination of risk factors. This was particularly true for major bleeding events.

Safety related to drug-drug interactions and other interactions

P-gp inhibitors

In the VTE program, few patients reported concomitant use of P-gp inhibitors in the pooled aVTEt studies (DE: 2.2%, W: 1.7%) or in sVTEp Study 1160.47 (DE: 2.8%, W: 2.5%). The most frequently reported P-

gp inhibitors taken concomitantly with DE were verapamil (1.3% and 1.2%) followed by amiodarone (0.3% and 0.8%) in the aVTEt studies and sVTEp Study 1160.47, respectively.

Overall, a smaller proportion of patients were taking P-gp inhibitors in the VTE studies than in the SPAF studies with DE.

Major bleeding events were reported for no DE patients and 1 (2.7%) warfarin patient who concomitantly used a P-gp inhibitor. In 1160.47, major bleeding events were reported for no patients in the DE group and 1 patient (3.6%) in the warfarin group who concomitantly used a P-gp inhibitor. The incidence of MBEs/CRBEs for patients who took concomitant P-gp inhibitors was lower in DE patients compared to warfarin patients in the pooled aVTEt studies and in sVTEp Study 1160.47. Further, DE patients taking concomitant P-gp inhibitors did not experience more bleeding events (MBEs or MBEs/CRBEs) than DE patients not receiving P-gp inhibitors.

In the aVTEt studies and in 1160.47, the incidence of any bleeding events was similar between the DE and warfarin groups with concomitant use of P-gp inhibitors.

Antithrombotic/anticoagulant agents and NSAIDs

In the VTE studies, the incidence of bleeding events (MBEs, MBEs/CRBEs, any bleeding) did not generally increase in DE-treated patients with co-administration of ASA, NSAIDs, or anticoagulants. The incidence of MBEs was lower for DE patients than warfarin patients with concomitant use of ASA, but the difference in incidences varied depending on the time of starting to count the bleeding events (from start of any treatment vs. double-dummy treatment), with slightly more DE-treated patients than warfarin patients having an event with concomitant use of an NSAID, an anticoagulant, or parenteral therapy for the index event > 9 days. These subgroups were small as was the number of events. The 2 DE patients in Study 1160.63 who had MBEs did not use ASA, NSAIDs, or anticoagulants concomitantly.

Discontinuation due to adverse events

In general, AEs were the cause of discontinuation in 7-12% in the four pivotal studies. Most common AEs causing discontinuation of study drug were related to vascular disorders, respiratory disorders and GI disorders.

In the pooled pivotal studies, discontinuations of study drug due to AEs were more common among DE patients (9.6%) compared to warfarin patients (8.8%). The highest frequency was seen among the placebo-treated patients (12.3%).

Overall DVT caused discontinuation in 0.4-1.4% of patients treated with DE and in 1.1-1.3% in patients treated with W. PE caused discontinuation in 0.6-1.2% of patients treated with DE compared to 0.2-0.6% in patients treated with W. The discontinuation rates due to investigator-reported cardiac disorder AEs were low across all treatment groups: 0.6% for DE patients, 0.3% for warfarin and 0.5% for placebo.

As presented in the tables in the bleeding subsection (in 4.4), discontinuations due to MBEs, MBEs/CRBEs and any bleeding were consistently fewer in patients treated with DE compared to patients receiving W.

In the pooled aVTEt studies, investigator-reported AEs were the cause of discontinuation of study drug in 8.9% of patients in the DE group vs. 7.8% of patients in the warfarin group. PE led more often to discontinuation in patients treated with DE (26 patients; 1.0%) than those receiving warfarin (15 patients; 0.6%). Investigator-reported AEs of DVT leading to discontinuation occurred at the same rate (1.4%) in both treatment groups. More patients treated with DE compared with patients treated with warfarin discontinued treatment due to infections and infestations (16 (0.6%) patients and 6 (0.2%) patients respectively) and due to blood and lymphatic disorders (9 (0.4%) patients and 2 (0.1%)

respectively). In both treatment groups, discontinuation due to cardiac disorders was infrequent (0.4% in both study groups).

Fewer DE patients than warfarin patients discontinued study drug due to adjudicated bleeding events in the pooled aVTEt studies: MBE (0.3% vs. 1.0%), combined MBEs or CRBEs (MBEs/CRBEs) (0.6% vs. 1.2%), any bleeding (0.7% vs. 1.3%).

In Study 1160.47, 10.1% of patients treated with DE experienced an investigator-reported AE leading to discontinuation of the study drug compared to 8.8% of those receiving W. There was a higher incidence of investigator-reported cardiac disorders leading to discontinuation in the DE group (1.0%) than in the warfarin group (0.2%) largely resulting from more frequent instances of acute MI, MI, coronary artery occlusion, and coronary artery stenosis in the DE treatment group compared to those receiving W.

Investigator-reported AEs of PE leading to discontinuation were infrequent, but occurred at a higher rate in those receiving DE (0.4%) compared to those receiving warfarin (0.1%). There were slightly fewer investigator-reported AEs of DVT leading to discontinuation of study drug in patients receiving DE (0.8%) compared to those receiving warfarin (1.1%).

Infections and infestations led to discontinuation in 0.3% and 0.6% of patients treated with DE and warfarin respectively.

Fewer DE patients than warfarin patients discontinued study drug due to adjudicated bleeding events in Study 1160.47: MBE (0.3% vs. 1.3%), MBE/CRBE (1.0% vs. 2.5%), any bleeding (1.3% vs. 2.7%).

When assessed by roll-over status in Study 1160.47, there appeared to be a tendency for patients to be more likely to experience an AE leading to discontinuation of the study medication if they were allocated to a different treatment in Study 1160.47 (frequencies of 8.3% for the DE→DE treatment sequence group, 8.0% for the W→W group, 10.2% for the DE→W group, and 10.9% for the W→DE group).

In Study 1160.63, more patients in the placebo group (12.3%) discontinued study medication due to AEs compared with patients in the DE group (7.3%). Investigator-reported PE and DVT was more often leading to discontinuation of study drug in the placebo group (2.9% and 4.9% respectively) compared to the DE group (0.1% and 0.4% respectively). For most other AEs leading to discontinuation the incidence was comparable between the DE and placebo groups; cardiac disorders caused discontinuation of study drug in 0.4% and 0.5% treated with DE and warfarin respectively.

Discontinuations due to bleeding events were higher in DE patients than P patients: MBE 0.1% vs. 0.0%, MBE/CRBE 1.5% vs. 0.6%, and any bleeding 1.8% vs. 0.6%.

Post marketing experience

DE (DE) was first authorised on 18 March 2008 in all member states of the European Economic Area (EEA) via the centralised procedure. The indication obtained was “Prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery”, and in 2011 the indication of “Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with AF” was approved in EU.

Outside Europe, DE is approved in the US and Canada since 2010 and in Japan, Australia, and New Zealand since 2011. Overall, marketing authorisation for DE has been received in more than 90 countries worldwide.

Post-authorisation (non-trial) cumulative exposure data until 31 Jan 2013 is estimated to be approximately 1,556,379 patient years. Data derives from the MAH's Global Drug Safety Database (GDSD).

Since the first marketing authorisation, the cumulative most common reported ADRs from post-marketing sources are within the SOC "Gastrointestinal disorders" (26,882 spontaneous reports) and "Nervous system disorders" (8,113 spontaneous reports) followed by "General disorders" (7.352 spontaneous reports). Table 1 shows ADRs (preferred terms) that have been reported in >1000 cases.

Table 1: ADRs reported in >1000 cases

Preferred term	Cummulative spontaneous reports
GI haemorrhage	3,987
Dyspepsia	3,656
Haemorrhage	2,280
Diarrhoea	1,787
Abdominal discomfort	1,786
Nausea	1,645
Rectal haemorrhage	1,579
Epistaxis	1,542
Haematuria	1,439
Dizziness	1,348
Abdominal pain, upper	1,332
Contusion	1,226
Rash	1,065
Cerebrovascular accident	1,063
Headache	1,050

Source: The Cumulative and Interval Summary Tabulation of ADRs from post-marketing sources; PSUR #9, cut-off date 18 Mar 2013.

In general, the most common reported preferred terms ADRs are related to bleedings several of these with a potential serious outcome (e.g. GI haemorrhages and cerebrovascular accidents). Other common reported ARDs are GI-related and general disorders.

During the reporting period for the last PSUR (PSUR #9, reporting interval of 19 Sep 2012 to 18 Mar 2013), relevant safety findings were obtained from a subgroup analysis from the RE-LY trial. The findings showed that patients with major bleedings on DE were older, had a lower creatinine clearance and more frequently used aspirin or non-steroid anti-inflammatory agents than those on W. Though subgroups at increased risk are in line with previous knowledge and not unexpected, the results from the study confirmed that certain patient categories have an increased risk of major bleeding events when treated with DE.

These findings from clinical trials and a number of post-marketing reports resulted in updates of the SmPC including a recommendation that in all patients renal function should be assessed, a more detailed

specification of contraindications in section 4.3, and an update of section 4.4 “Special warnings and precautions for use”, specifying that use of ASA, clopidogrel or non steroidal anti-inflammatory drugs, as well as the presence of oesophagitis, gastritis or gastroesophageal reflux increases the risk of GI haemorrhages. Furthermore, with the purpose to include more detailed instruction for prevention of clinically relevant bleeding, Section 4.4 “Special warnings and precautions for use” was also updated to include with the information that “Close clinical surveillance (looking for signs of bleeding or anaemia) is recommended throughout the treatment period, especially if risk factors are combined”.

Due to an imbalance in thromboembolic and total (mainly minor) bleeding events in disfavour of DE in the RE-ALIGN trials (1160.113 and 1160.138), several actions were taken including trial discontinuation and addition of “prosthetic heart valves requiring anticoagulant treatment” as a new contraindication in the EU SmPC. Also a warning that concomitant use of DE and ticagrelor may increase the risk of bleeding has been included in the newly updated European SmPC (mechanism: concomitant use of DE and ticagrelor increase the AUC of ticagrelor).

Important identified risks in the RMP include haemorrhage, various gastrointestinal disorders, hypersensitivity (including pruritus, rash, urticaria, angioedema and anaphylactic reactions) and off-label use in patients with prosthetic heart valves. Furthermore, following a request from the EMA (assessment report regarding the submission in the indication SPAF, December 2010), MI has also been classified as potential risk in the RMP.

Overall, the post marketing experience with DE shows that the most commonly reported ADRs are related to the GI system, central nervous system and general disorders. Due to the risk of bleedings, especially an increased risk of GI bleedings, the European SmPC has been updated to include specific warnings and precautions. As the risk of bleedings has been shown to be partly related to decreased kidney function, the EU SmPC recommends that kidney function should be monitored in all patients treated with DE. Furthermore, “prosthetic heart valves requiring anticoagulant treatment” has been added as a contraindication due to an increased risk of bleeding and thromboembolic events.

For risks that are associated with long-duration exposure and having a high baseline incidence (e.g. malignancies and osteoporotic fractures), analyses of individual case safety reports are unlikely to provide the necessary information. In the latest PSUR, the MAH is asked to discuss and propose suitable additional pharmacovigilance activities that can be applied when potential risks have these characteristics.

2.4.2. Discussion on clinical safety

The safety data is based on four randomised double-blinded active- or placebo-controlled studies. The definition for the main safety endpoint, MBEs, followed the recommendations of the International Society on Thrombosis and Haemostasis (ISTH), and furthermore all bleeding events were centrally adjudicated by an independent committee that was blinded with regard to the treatment allocation of patients. Adjudicated results were used in the analyses of bleeding events. This is endorsed.

The choice of analysing all bleeding events from the aVTEt studies with data reported after first intake of study drug at the start of oral only treatment (double-dummy treatment) is not considered to produce a bias in favour of DE and is therefore supported.

Many of the provided safety analyses are based on a pooled dataset comprising all four studies. There are a number of advantages of including all four studies, but there could also be some drawbacks. The patients included in the aVTEt studies may be different from the patients in the sVTEp studies. Further,

the patients in the two sVTEp studies differ in terms of VTE recurrence risk. However, where relevant, the Applicant has also provided pooled analyses of the aVTEt studies and the three W-controlled studies.

Patient exposure

In the pooled pivotal studies, 8,132 patients were treated with study drug, of these 4,667 patients were treated with DE. Mean treatment duration for the pooled VTE studies was 278 days for DE, 298 days for warfarin and 162 days for placebo. The maximum duration of continuous treatment for any patient treated with DE was 1,210 days (~40 months).

Safety data for more than 6 months were available for 2,214 DE patients, 1,670 warfarin patients and 445 placebo patients. Safety data for more than 12 months were available for 1,043 DE patients, 1,034 warfarin patients and no placebo patients.

In general, demographic characteristics were equally distributed across treatment groups, and the included patients are considered to be representative for the target patient group. An acceptable amount of patients above the age of 75 years are included, likewise the studies also included patients with cardiac disorders (approximately 8% of all included patients) and patients with moderate renal impairment (37% of the included patients had GFR <80 ml/min).

It is considered that the number of patients and the extent of exposure fulfil the ICH guidelines. A significant number of patients have been exposed to DE in an acceptable timeframe of 6 to 12 months. Overall, there were no marked differences in baseline demographics. In Study 1160.47, slightly more patients in the DE group had cardiovascular diseases at baseline; however, there was no difference in use of cardiovascular medication between the two study groups.

AEs

Across all the active-controlled studies, 66-72% of patients treated with DE and 67-72% of patients treated with warfarin experienced an AE. Overall, dyspepsia-/gastritis-like symptoms, nausea, vomiting, diarrhea and rectal bleeding were the most commonly reported GI AEs in DE patients and were generally (but not exclusively) seen more frequently among patients treated with DE compared to patients treated with warfarin and placebo. Other bleeding disorders including conjunctival haemorrhage, epistaxis, haemopthysis, haematuria, menorhhagia and haematomas were all seen more often in the warfarin group compared with the DE group.

Pulmonary embolism was reported slightly more frequently in the DE group (1.0%) compared to the warfarin group (0.7%).

Most investigator-reported AEs were mild or moderate in intensity for all treatment groups in all pivotal studies.

Suspected cardiovascular adverse events occurred more often in the active-controlled studies (0.9-2.0% in the DE group and 0.6-1.3% in the warfarin group) compared to the placebo-controlled study (0.4% and 0.3% in the DE and placebo group respectively). The lower number seen in the placebo-controlled study is probably due to the more restrictive inclusion criteria. A more appropriate way of comparing the two active treatment groups would be only to include data from the active-controlled studies (studies 1160.46, 116053 and 1160.47) as including all four pivotal studies might dilute the percentage of cardiovascular events in the DE group. The Applicant presented the result of cardiovascular AEs for the individual studies and for the pooled active-controlled studies, and the concern was resolved during the procedure.

Gastrointestinal adverse events including dyspepsia-/gastritis-like symptoms and rectal bleeding were recorded more often in patients receiving DE compared to W. The Applicant was asked to provide data for the proportions of the rectal bleedings which presented as passage of fresh blood, melena or presence of occult blood in the stool. Further, the Applicant provided information about the reversibility of the GI adverse effects, including the proportion of the GERD-like adverse effects and rectal haemorrhages which resolved spontaneously and how many patients needed treatment. This was accepted by the CHMP.

SAEs

Across the three active-controlled pivotal studies, 11.8-15.9% of patients experienced a serious adverse event (SAE) during the treatment period. In all three active-controlled studies, slightly more patients in the DE group (12.2-15.9%) experienced an SAE compared to the warfarin group (11.8-15.7%), and in all three studies slightly more patients treated with DE (0.7-1.0%) compared to patients treated with warfarin (0.4-0.8%) experienced DVT. The same pattern was seen for PE: DE 0.6-1.1% vs. W 0.2-0.9%.

In the placebo-controlled study, more patients treated with placebo compared to DE (9.1% vs. 6.9%) experienced SAEs which is not surprising. The difference was mostly due to more SAEs of DVT and PE in the placebo-treated group, indicating a better prophylactic effect of DE compared to placebo.

In all four pivotal studies, most frequently reported SAEs included gastrointestinal disorders, DVT and PE.

Bleedings

Major bleeding events (MBEs) were fewer among DE-treated patients than in patients treated with W, but more frequent than in patients on placebo. This pattern of more events in patients receiving warfarin is consistent when looking at the pooled data sets and the studies individually.

There was generally also a higher incidence of MBEs in the warfarin group when breaking down MBEs by bleeding criteria or by bleeding location. One exception was intraocular bleedings; however, the number of events was low.

The results are not surprising when considering the results of the RE-LY study in atrial fibrillation patients where the 150 mg b.i.d. was tested against W.

As expected, there were more MBEs on DE than on placebo in the placebo-controlled sVTEp study.

Clinically relevant bleeding events (MBEs/CRBEs) followed the pattern seen with MBEs. The hazard ratios DE vs. W were statistically significant in each individual study and in the pooled aVTEt dataset. As expected, there were more events on DE in the placebo-controlled sVTEp study.

All bleeding events (MBEs/CRBEs) also followed the pattern seen with MBEs.

The incidence of bleedings in the W-treated patients appeared to be dependent on the quality of the INR control (Time in Therapeutic Range, TTR). Bleeding events quite clearly occurred more frequently in patients with the poorest TTR (<40%). In relation to the overall benefit-risk balance of DE, the Applicant addressed the influence on major bleeding events when disregarding poorly managed warfarin patients. Analyses suggested that the advantage of DE in terms of major bleeding events was also evident when comparing to warfarin-treated patients across other TTR ranges, including patients with TTR levels similar to those typically seen in Europe.

Acute coronary syndrome

ACS events appear to occur more frequently in DE-treated patients than in patients receiving W.

The topic of a possible causal relation between DE and myocardial infarction has previously been extensively reviewed by the CHMP - in particular in variation Pradaxa II-31 which followed a meta-analysis by Ken Uchino and Adrian V Hernandez (Circulation. 2011; 124: A15500). In the RE-LY study supporting the indication in atrial fibrillation patients, a slightly higher rate of myocardial infarction (MI) was noted in patients treated with either of the DE doses than in patients treated with W. This finding inspired the meta-analysis by Uchino and Hernandez. The objective of the meta-analysis was to systematically evaluate the risk of MI or acute coronary syndrome (ACS) with the use of DE for several indications. Control arms included W, enoxaparin or placebo. The result of the meta-analysis was that DE was significantly associated with a higher risk for MI or ACS than the control group (DE 1.23% vs. control 0.88%; OR 1.31, 95% CI 1.03-1.67). As a response, the Applicant provided an extensive review and conducted its own meta-analysis which addressed some of the weaknesses of the Uchino and Hernandez meta-analysis. This meta-analysis included all the studies included in the current application. It showed that from randomization to study termination, the odds ratios (OR) for MI (95% CI) were 1.30 (0.96, 1.76) and 1.42 (1.07, 1.88), for DE 110 mg b.i.d. and 150 mg b.i.d., compared to W, respectively. The odds ratios (OR) for MI (95% CI) were 1.07 (0.36, 3.20) and 1.37 (0.50, 3.70), for DE 110 mg b.i.d. or 150 mg b.i.d., compared to placebo, respectively. When looking at the studies with warfarin as a comparator individually and from the meta-analysis, it appeared to be a consistent and relatively robust finding that the incidence of MI in patients treated with DE was higher than in patients treated with W. The absolute differences were small, and it was agreed by the CHMP that the difference was counterbalanced by DE's beneficial effects in terms of stroke reduction and lower observed rates of CV mortality and overall mortality by a solid margin. It was not finally established whether the difference in MI rates between DE and warfarin represent a true adverse effect of DE or is caused by a protective effect of warfarin (or both).

The current application has not provided much new information about the topic. However, given the efficacy results in the aVTEt and sVTEp indications where warfarin consistently performed better than DE (in contrast to the SPAF population), the results on ACS have implications for the benefit-risk balance in these indications. To further address these implications, the Applicant provided an analysis using a composite cardiovascular endpoint consisting of non-fatal recurrent VTE, non-fatal MI, non-fatal stroke, non-fatal systemic embolism and all-cause death. In all three warfarin-controlled studies, there was a higher incidence in patients on DE compared to warfarin-treated patients although the hazard ratio was close to and not statistically significantly different from 1.

Deaths

The frequency of deaths was slightly higher in the warfarin group compared to the DE group. No remarkable differences in the pattern of adverse events leading to death are noted.

Patients switching treatment when "rolling over" to Study 1160.47 had a higher mortality than patients who stayed on the same treatment.

Laboratory findings

Liver function tests:

Overall the mean changes from baseline were small and without any clinically relevant difference between treatment groups in all four pivotal studies. For ALT, AST and ALP the changes were higher in the DE and warfarin groups compared with the placebo group. For all liver parameters, no clinically relevant difference between DE and warfarin was seen for transitions to above the reference range from baseline to the last on-treatment value and to the worst on-treatment value.

No relevant differences in the frequencies of possible clinically significant abnormalities (PCSAs) between the treatment groups were observed for any of the four liver function parameters in any of the four pivotal studies. In all four studies, the PCSAs were most frequently reported for ALT, followed by AST. PCSAs were in general seen in less than 2.5% within each treatment group and liver function test, more often among patients treated with DE and warfarin compared with patients treated with placebo. There was no clinically relevant difference in the frequency of PCSAs between the DE and the warfarin group.

Only few cases of abnormal laboratory liver function parameters were reported as adverse events; most commonly increase in ALT or AST. The numbers of cases where the AEs were leading to study drug discontinuation or reported as SAEs are too few to draw any conclusion. However, there was no indication of differences between treatment groups.

The results of the liver function parameters of DE treated patients in the four pivotal studies are in line with results from previous studies and post marketing experiences with the same dose as applied for. In general, slightly more elevated liver function parameters were seen in the DE and the warfarin groups compared with the placebo group. However, no clinically relevant differences in liver function parameters were seen between DE and W. Results from the studies do not indicate any hepatotoxicity.

Other laboratory parameters:

There were no clinically relevant important differences in median haematology, electrolyte, creatinine, and urea values between the DE and warfarin groups. Changes in the median values from baseline to the last on-treatment value and to the worst on-treatment value were generally small and did not show any clinically important differences between the DE and warfarin groups. Decrease in haematocrit was the most often reported possible clinically significant abnormality and was reported in up to 4.4% in patients treated with DE and up to 4.9% of patients treated with W. This adverse event is likely (partly) to be related to bleedings during the treatments, and anaemia is already mentioned as a common possible adverse event in the SmPC. Increase in creatinine was reported with a similar incidence in the DE and the warfarin treatment groups.

Safety in special populations

In the aVTEt studies, in patients with moderate renal impairment, MBEs and MBEs/CRBEs were more frequent in the DE treatment group than in the warfarin group. However, this was not seen in the W-controlled sVTEp study (1160.47).

Generally, the bleeding risk increased with age, and the relative advantage of DE compared to warfarin generally diminished with age – with a few exceptions for some categories where patient numbers were low.

Only one dose (150 mg BID) was investigated in the aVTEt and sVTEp studies. However, the MAH was requested to discuss and reconsider the posology in special populations with regard to age, kidney function and P-gp inhibition. The number of patients of high age, patients with moderate renal impairment or receiving P-gp inhibitors in the pivotal studies was limited and did not allow firm conclusions based on clinical outcome, but pharmacokinetic considerations indicated that a lower dose may be more appropriate in some subgroups. The MAH subsequently proposed a posology identical to that of the SPAF indication. i.e. recommendation of a reduced dose (daily dose of 220 mg taken as two 110 mg capsules) for patients aged 80 years or above and for patients who receive concomitant verapamil, as well as recommendations to consider this dose for other subgroups.

Safety related to drug-drug interactions and other interactions

The number of patients taking P-gp inhibitors in the VTE studies is lower than in the RE-LY study. Considering the differences in the study populations and the fact that a number of antiarrythmic agents are P-gp inhibitors, this is expected.

Even if the concomitant use of P-gp inhibitors was not associated with an increased bleeding risk compared to W, it is difficult to draw firm conclusions because of the low number of patients taking P-gp inhibitors.

Generally, there were fewer bleedings with DE than with warfarin in patients concomitantly using antithrombotic/anticoagulant agents and NSAIDs. However, in the aVTEt studies, MBEs were slightly more frequent in the DE group than in the warfarin group in patients receiving concomitant NSAID. But the number of events was very small.

Discontinuation due to AEs

In both the pooled pivotal studies, the pooled aVTEt studies and the active-controlled prevention Study 1160.47, discontinuations due to AEs occurred slightly more frequently in the DE groups (7.8–10.1%) compared to the warfarin groups (6.8%–8.8%). In the placebo-controlled sVTEp study, more patients in the placebo group (12.3%) compared with the DE group (7.3%) discontinued treatment. AEs that resulted in discontinuation of treatment mirrored the types of SAEs that were reported most frequently in this study: vascular disorders, respiratory disorders and gastrointestinal disorders.

Discontinuations due to MBEs, MBEs/CRBEs and any bleeding were consistently fewer in patients treated with DE compared to patients receiving W.

Both in the pooled pivotal studies, the pooled aVTEt studies and the active-controlled prevention Study 1160.47, PE leading to discontinuation was reported more often in the DE group compared with the warfarin group. This is in accordance with the overall findings of (S)AEs, where PE was reported more often in patients treated with DE compared with W. There was no significant difference in percentage of DVT leading to discontinuation between the two active treatment groups. Results of recurrence of VTE are discussed in the efficacy section.

In the pooled aVTEt studies, more patients treated with DE compared with patients treated with warfarin discontinued treatment due to infections and infestations and due to blood and lymphatic disorders. The Applicant provided on request additional information about the nature of the infections and infestations leading to discontinuation among the DE treated patients and likewise more information about the blood and lymphatic disorders that caused discontinuation of study drug.

In the active-controlled long-term Study 1160.47, there was a higher incidence of investigator-reported cardiac disorders leading to discontinuation of study medication in the DE group (1.0%) compared to the warfarin group (0.2%), largely resulting from more frequent instances of acute MI, MI, coronary artery occlusion, and coronary artery stenosis, in the DE treatment group compared to those receiving W. This was not observed in the short-term aVTEt studies.

2.4.3. Conclusions on clinical safety

The safety results from the aVTEt and sVTEp clinical development programme are very much in line with the experience from the atrial fibrillation indication. The bleeding risks with the 150 mg b.i.d. dose are less than observed with W. However, the difference in bleeding risk appear to diminish in certain subpopulations and when comparing to patients who are reasonably well managed on warfarin in terms of INR control. Events of acute coronary syndrome appear to occur more frequently in DE-treated patients than in patients receiving W, although absolute numbers are low. This excess has to be factored into the

benefit-risk balance. Gastrointestinal adverse events occur more frequently with DE than with W. However, in contrast to the RE-LY study (supporting the SPAF indication), major GI bleedings were not more frequent in DE patients compared to warfarin patients.

No major objections relating specifically to safety have been identified, but the excess of acute coronary events has to be factored into the benefit-risk balance.

The MAH accepted dose recommendations for the aVTEt and sVTEp identical to those of the SPAF indication. This was accepted by the CHMP.

2.5. Risk management plan

The applicant submitted a risk management plan. Please, see the Summary of the Risk Management Plan tables below:

Table Summary table of safety concerns

Important identified risks	Haemorrhage
	Gastrointestinal disorders
	Hypersensitivity
Important potential risks	Hepatotoxicity
	Myocardial infarction
	Pulmonary embolism
	Off-label use in patients with prosthetic heart valves
Important missing information	Patients with renal impairment (creatinine clearance ≤30 mL/min)
	Patients with liver impairment (liver enzymes >2x upper limit of normal)
	Pregnant and lactating women
	Patients under 18 years
	Patients with low body weight

Table of ongoing and planned studies in the post-authorisation pharmacovigilance development plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Planned date for submission of (interim and) final results[3]
Substudies of RELY-ABLE long-term multicenter extension of dabigatran treatment in patients with atrial fibrillation who completed the RE-LY trial and a cluster randomised trial to assess the effect of a knowledge translation intervention on patient outcomes (1160.71),	Long-term extension study in patients with atrial fibrillation	Haemorrhage Hepatotoxocity Myocardial infarction Pulmonary embolism	Started	Interim trial report submitted June 2012
An open label, non-comparative, pharmacokinetic and pharmacodynamic study to evaluate the effect of dabigatran etexilate on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min) undergoing primary unilateral elective total knee or hip replacement surgery (1160.86),	Effect on coagulation parameters in patients with orthopaedic surgery	Haemorrhage	Started	Planned Final study report expected December 2013
GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients with Atrial Fibrillation (Phase II/III – European Union [EU]/European Economic Area [EEA] Member States) (1160.136),	Long-term safety	Haemorrhage Myocardial infarction Pulmonary embolism	Started	Planned Final study report expected November 2015
1160.84 - Observational cohort study to evaluate safety and efficacy of Pradaxa (dabigatran etexilate) in patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min) undergoing elective total hip replacement surgery or total knee replacement surgery; Phase IV,	Safety and efficacy in patients with moderate renal impairment	Haemorrhage	Started	Planned Final study report expected Q2 2015

Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
1160.144 - Descriptive, observational, multicountry European cross-sectional database study of new users of dabigatran etexilate that will characterise on-and off-label use status and other medical characteristics at the time of the first prescription,	Characterisation of on-and off-label use status and other medical characteristics	Off-label use	Planned	Planned Final study report expected Q1 2015
1160.149 - Post-authorisation study to evaluate the effectiveness of the risk minimisation activities in the prevention of stroke in patients with atrial fibrillation (SPAF), Phase IV,	Effectiveness of risk minimisation with prescribed guide and patient alert card (SPAF)	Haemorrhage	Planned	Planned Final study report expected June 2014
1160.102 - Observational cohort study on the prevention of venous thromboembolic events after elective orthopaedic surgery in patients treated with Pradaxa, Phase IV,	Prevention of VTE after elective surgery	Haemorrhage	Started	Planned Final study report expected Q2 2013
1160.118 - Observational cohort study to evaluate the safety and efficacy of switching from Lovenox (enoxaparin) 40 mg to Pradaxa (dabigatran etexilate) 220 mg in patients undergoing elective total hip or knee replacement surgery, Phase IV,	Prevention of VTE after elective surgery	Haemorrhage	Started	Planned Final study report expected Q2 2013
1160.124 - Stimulated post-marketing adverse reaction reporting: dabigatran etexilate (Pradaxa), post-marketing study (PMS),	Patients with AF	Haemorrhage	Started	Planned Final study report expected Q3 2013

Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
1160.128 - A prospective, open label study evaluating the efficacy of two management strategies (pantoprazole 40 mg q.a.m. and taking Pradaxa with food (within 30 minutes after a meal) on gastrointestinal symptoms in patients newly on treatment with Pradaxa 150 mg bid or 75 mg bid for the prevention of stroke and systemic embolism in patients with non-valvular AF, Phase IV,	Evaluation of management strategies on gastrointestinal symptoms	Gastrointestinal adverse events	Started	Planned Final study report expected 2015
1160.130 - Post-marketing surveillance on the long-term use of Prazaxa capsules in patients with non-valvular AF, Phase IV,	Long-term use in Japanese patients (SPAF)	Haemorrhage	Started	Planned Final study report expected Q4 2016
1160.157 - comparative effectiveness of oral anticoagulants: a cohort study, Phase IV,	Effectiveness of oral anticoagulants	Haemorrhage	Started	Planned Final study report expected Q4 2013
1160.162 - An observational study assessing the management of gastrointestinal and urogenital bleeding events in patients with AF treated with dabigatran etexilate, Phase IV,	Management of gastrointestinal and urogenital haemorrhage in patients with AF	Haemorrhage	Planned	Planned Final study report expected Q1 2014
1160.166 - An exploratory study to investigate the pharmacokinetics and effects of DABIgatran etexilate in patients with stable severe RENAL disease: DabiRenal, Phase I,	Pharmaokinetics in patients with severe renal impairment	Haemorrhage	Started	Planned Final study report expected Q2 2014
1160.173 - A prospective, open label study to evaluate the pharmacokinetics of dabigatran in non-valvular AF patients with severely impaired renal function on dabigatran etexilate 75 mg bid therapy, Phase IV,	Pharmaokinetics in patients with severe renal impairment	Haemorrhage	Planned	Planned Final study report expected 2014

Table of ongoing and planned additional pharmacovigilance studies/activities in the pharmacovigilance plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
1160.142 - Investigation of drug-drug interaction of dabigatran and ticagrelor under steady state conditions in healthy male subjects, Phase I,	Drug-drug interaction with ticagrelor	Drug-drug interaction	Started	Planned Final study report expected Q2 2013
1160.129 - GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients with Atrial Fibrillation (Phase II/III), Phase IV,	Registry	Haemorrhage	Started	Planned Final study report expected Q2 2020
1160.171 - GLORIA-AF: Global Registry on Long-Term Oral Anti-thrombotic Treatment In Patients with Atrial Fibrillation (Phase II/III-India and Switzerland), Phase IV,	Registry	Haemorrhage	Planned	Planned Final study report expected Q2 2020

[1] Type, title and category (1-3). Note that the categories were not in place when the follow-up measures listed in this table were first imposed.
[2] Planned or started.
[3] Planned or actual.

Table Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Haemorrhage	Summary of product characteristics (SmPC) sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9	Prescriber guide for each indication, patient alert card, clinical and observational studies (1160.84, 1160.85, 1160.71, 1160.86, 1160.136)
Gastrointestinal disorders	SmPC section 4.8	None
Hypersensitivity	SmPC section 4.8	None
Important potential risks		
Hepatotoxicity	SmPC sections 4.3, 4.4, and 4.8	None
Myocardial infarction	SmPC 4.4, 4.8, and 5.1	None
Pulmonary embolism	Not applicable	None
Off-label use in patients with prosthetic heart valves	SmPC sections 4.3 and 5.1	None
Important missing information		
Patients with renal impairment	SmPC sections 4.2 and 4.	None
Patients with liver impairment	SmPC sections 4.3, 4.4, and 4.8	None
Pregnant and lactating women	SmPC section 4.6	None
Patients under 18 years	SmPC section 4.2	None
Patients with low body weight	SmPC section 4.2	None

2.5.1. PRAC advice

Based on the PRAC review of the Risk Management Plan version 26 and 27, the PRAC considers by consensus that the risk management system for dabigatran (PRADAXA) in the treatment of proposed/approved indication(s)

Current

Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic elective total hip replacement surgery or total knee replacement surgery

Prevention of stroke, and systemic embolism, and reduction of vascular mortality in adult patients with non-valvular atrial fibrillation (SPAF) with 1 or more of the following risk factors:

- *Previous stroke, transient ischaemic attack, or systemic embolism*
- *Left ventricular ejection fraction <40%*
- *Symptomatic heart failure, New York Heart Association Class 2*
- *Age ≥75 years*

- *Age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension*

Proposed

- *Treatment of acute deep venous thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death*
- *Prevention of recurrent DVT and/or PE and related death*

is acceptable provided that the MAH answerers sufficient to the LoQ raised.

The MAH has sufficiently responded to the list of questions raised and the RMP is approved.

In the next RMP update the MAH should clarify a remaining minor issue and follow the suggestion in relation to Q18 (In a clinical trial the rate of heart attacks with DE was numerically higher than with W. The overall occurrence was low. The wording of the second sentence is not optimal and might be changed to "In a clinical trial the rate of heart attacks was numerically higher in the group treated with DE than in the group treated with Warfarin.") and also revise the category from 1 to 3 for the following studies since none of them are in fact included in the Annex II: 1160.136 GLORIA –AF, 1160.130, 1160.139.

Additional risk minimisation measures

The PRAC considers that no additional risk minimisation measures will be necessary for the safe and effective use of the medicinal product.

Pharmacovigilance Plan

The PRAC considers that the existing obligations in the MA are sufficient.

The CHMP has endorsed the PRAC advice without changes

2.6. Changes to the Product Information

As a consequence of the new indications, sections 4.2 and 5.3 of the SmPC for the 75 mg strength, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC for the 110 mg and 150 strengths have been updated. The Package Leaflet has been updated accordingly. A large number of further requests for modifications of the SmPC have been made by the CHMP. Please refer to the annotated Product Information included in Annex 1.

3. Benefit-risk balance

Benefits

Beneficial effects

The efficacy of dabigatran etexilate (DE) in the treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) has been documented in two replicate, warfarin-controlled 6-months studies (RE-COVER and RE-COVER II). In both studies non-inferiority was formally shown against the pre-set non-inferiority margin for the primary endpoint (recurrent symptomatic VTE and deaths related to VTE). Numerically, warfarin was superior to DE in both studies and hence also in the pooled analysis.

The efficacy of DE in the prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) was documented in a long-term warfarin-controlled study (RE-MEDY) and a 6-month placebo-controlled study (RE-SONATE). In the latter study, the baseline risk of VTE was significantly lower than in the former study. Non-inferiority was formally shown against the pre-set non-inferiority margin in the RE-MEDY study for the primary endpoint (recurrent symptomatic VTE and deaths related to VTE) although warfarin was numerically superior to DE. In the RE-SONATE study, DE was clearly superior to placebo.

Uncertainty in the knowledge about the beneficial effects

The uncertainty with regard to the suboptimal warfarin treatment in all three warfarin-controlled studies and its impact on the efficacy evaluation of DE has largely and to a satisfactory extent been resolved. The efficacy of warfarin in the studies did not appear to depend on the Time in Therapeutic Range (TTR).

There was uncertainty about the efficacy of DE. While the aVTEt studies showed comparable (although numerically inferior) efficacy to W, the RE-MEDY study suggested that when using the hazard ratio as basis for the calculation up to about half of the effect of warfarin may have been lost with DE. However, when using the risk difference as basis for the calculation, about 85% of the effect of warfarin was preserved. The Applicant argued that because of the low number of events in the RE-MEDY study, the latter was a more appropriate calculation. The CHMP agreed that the absolute difference between DE and warfarin in the RE-MEDY study was small. Looking at the results of the RE-MEDY study in the perspective of the aVTEt studies and the lack of a plausible explanation as to why the efficacy of DE compared to warfarin would be less in the prevention setting than in the acute setting as well as the convincing placebo-controlled prevention study (RE-SONATE), the CHMP considered that the efficacy also for the prevention indication was acceptable – also in light of the advantages in terms of bleedings (see later).

Risks

Unfavourable effects

The risk profile of DE in the aVTEt and sVTEp clinical development programme is consistent with the profile in the atrial fibrillation indication. The bleeding risk profile with DE was generally favourable compared to W. However, in the aVTEt studies, in patients with moderate renal impairment, MBEs and MBEs/CRBEs were more frequent with DE than in the warfarin group. Further, the relative advantage of DE compared to warfarin generally diminished with age. The posology in subgroups of patients with high age, patients with moderate renal impairment and patients receiving P-gp inhibitors was challenged, and the MAH accepted to align the dose recommendations for the aVTEt and sVTEp indications with those of the atrial fibrillation indication. This was accepted by the CHMP and will entail a lower dose (110 mg BID) for patients aged 80 years and over and patients treated with verapamil, and this lower dose should also be considered for other subgroups, e.g. patients with moderate renal impairment.

Events of acute coronary syndrome appear to occur more frequently in DE-treated patients than in patients receiving W, although absolute numbers are low. This is consistent with experience from the atrial fibrillation indication.

Also in line with previous experience, gastrointestinal adverse events occur more frequently with DE than with W.

Uncertainty in the knowledge about the unfavourable effects

The uncertainty with regard to the suboptimal quality of the warfarin treatment in the active-controlled studies and its impact on the advantage of DE over warfarin in terms of bleedings has been resolved to a satisfactory extent. Analyses show that poorly managed patients on warfarin (TTR<40%) had more major bleedings than other warfarin patients. However, analyses suggested that the advantage of DE in terms of major bleeding events was also evident when comparing to warfarin-treated patients with TTR levels similar to those typically seen in Europe.

It remains uncertain whether the difference in rates of acute coronary syndrome between DE and warfarin represents a real adverse effect associated with the use of DE or it is caused by a protective effect of warfarin. This uncertainty was however considered acceptable by the CHMP.

Besides, the optimal dose for patients with renal impairment, high age and/or concomitant treatment with P-gp inhibitors is still uncertain. Given the alignment with the posology of the SPAF indication, this was also considered as acceptable by the CHMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

In all warfarin-controlled studies (both aVTEt studies and one sVTEp study), non-inferiority was shown. Warfarin was nominally superior to DE in all studies, but the absolute differences were small.

In the placebo-controlled prevention study, DE was statistically and clinically clearly superior to placebo. The efficacy of DE in both aVTEt and sVTEp is considered clinically relevant, robust and generally on par with warfarin.

Overall, the differences in bleeding risk between DE and warfarin are considered to be clinically significant. The differences appear smaller when disregarding poorly managed warfarin patients. For patients with renal impairment and to some extent with high age, the differences with the tested dose (150 mg BID) do not seem clinically relevant.

The absolute increase in acute coronary syndrome events observed with DE compared to warfarin is small and was not observed in the comparison to placebo, but given the nature of these events still important.

Benefit-risk balance

Non-inferiority was shown in the warfarin-controlled studies, although DE was nominally inferior all three studies. However, overall the efficacy of DE is considered comparable to that of warfarin.

The advantages of DE over warfarin with regard to bleedings are evident from the results, also when disregarding poorly managed warfarin patients.

The excess of events of acute coronary syndrome observed with DE compared to warfarin (but not to placebo) is considered to be important, but the number of the events was low and should be seen in the context of the advantages in terms of major bleedings.

Discussion on the benefit-risk balance

The benefit of DE in the aVTEt and sVTEp indications is considered comparable to that of warfarin, even though it may be marginally less. However, this should be seen in the perspective of the advantages in terms of major bleedings and other bleeding events. The excess of acute coronary syndrome with DE

compared to warfarin (but not to placebo) is small and is not considered to outweigh the advantages associated with DE.

Consequently, the benefit-risk balance is considered positive in the aVTEt and sVTEp indications.

4. Overall conclusion

Based on the review of the data on clinical efficacy and safety, the CHMP consider that the application for DE in aVTEt and sVTEp is approvable.

An important other concern related to dose recommendations for patients with renal impairment, high age and/or concomitant treatment with P-gp inhibitors as well as other remaining issues concerning the SmPC were satisfactorily resolved by the MAH during the procedure.

5. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of section 4.1 of the SmPC for 110mg and 150mg strengths in order to add the following two new related indications: (1) treatment of acute deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and prevention of related death (aVTEt), (2) prevention of recurrent deep vein thrombosis (DVT) and/or pulmonary embolism (PE) and related death (sVTEp). Several sections of the SmPC for 75, 110 and 150mg strengths were proposed to be modified to include the data relevant for two new indications. The Package Leaflet was proposed to be updated accordingly.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following new conditions (addition **in bold underlined**, deletion **in bold ~~strikethrough~~**):

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use Pradaxa. This educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Pradaxa and providing guidance on how to manage that risk.

The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution for ~~**both**~~ **all** therapeutic indications prior to launch ~~**of the new indication (prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors))**~~ in the Member State.

The physician educational pack should contain:
- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:
- Details of populations potentially at higher risk of bleeding
- Information on medicinal products that are contraindicated or which should be used with caution due to an increased risk of bleeding and/or increased dabigatran exposure
- Contraindication for patients with prosthetic heart valves requiring anticoagulant treatment
- Recommendation for kidney function measurement
- Recommendations for dose reduction in at risk populations
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
  - Signs or symptoms of bleeding and when to seek attention from a health care provider.
  - Importance of treatment compliance
  - Necessity to carry the Patient alert card with them at all times
  - The need to inform Health Care Professionals about all medicines they are currently taking
  - The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure.
- An instruction how to take Pradaxa

The MAH shall also provide a patient alert card in each medication pack, the text of which is included in Annex III.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.