12 November 2020
EMA/145360/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pradaxa

International non-proprietary name: dabigatran etexilate

Procedure No. EMEA/H/C/000829/X/0122/G

Note

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

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Administrative information

Name of the medicinal product:	Pradaxa
MAH:	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim GERMANY
Active substance:	dabigatran etexilate mesilate
International Non-proprietary Name/Common Name:	dabigatran etexilate
Pharmaco-therapeutic group (ATC Code):	antithrombotic agents, direct thrombin inhibitors (B01AE07)
Therapeutic indication(s):	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: - Previous stroke, transient ischemic attack, or systemic embolism (SEE) - Left ventricular ejection fraction < 40 % - Symptomatic heart failure, - > New York Heart Association (NYHA) Class 2 - Age - > 75 years - Age - > 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

	Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age. **For age appropriate dose forms, see section 4.2.**
Pharmaceutical form(s):	Capsule, hard; Coated granules; Powder and solvent for oral solution
Strength(s):	*Capsule, hard:* 75 mg, 110 mg 150 mg *Coated granules:* 20 mg, 30 mg, 40 mg, 50 mg, *Powder and solvent for oral solution:* 6.25 mg/mL,
Route(s) of administration:	Oral use
Packaging:	*Capsule, hard:* blister (alu/alu), bottle (PP) and white blister (alu/alu) *Coated granules:* Sachet (PET/alu/LDPE) *Powder and solvent for oral solution:* Powder: sachet (PET/alu/LDPE); Solvent: bottle (glass); Sucralose powder: sachet (PET/alu/LDPE),
Package size(s):	*Capsule, hard:* 10 x 1 capsules (unit dose), 100 (2 x 50 x 1) capsules (unit dose) (multipack), 180 (3 x 60 x 1) capsules (unit dose) (multipack), 30 x 1 capsules (unit dose), 60 x 1 capsules (unit dose), 60 capsules *Coated granules:* 60 sachets *Powder and solvent for oral solution:* 30 sachets (powder) + 30 preparation packs (1 bottle + 1 sachet (sucralose powder) + 2 dosing pipettes (3 mL) + 2 dosing pipettes (12 mL) + 1 bottle adapter)

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List of abbreviations

AE	Adverse event
Alu	aluminium
aPTT	Activated partial thromboplastin time
AS	active substance
aVTEt	Acute VTE treatment
BI	Boehringer Ingelheim
CAPAs	corrective actions and preventive measures
CI	Confidence interval
C_{max}	Maximum measured concentration
CLT	Central Line Thrombosis
CMAs	critical material attributes
CQAs	critical quality attributes
CPPs	critical process parameters
CRNM	Clinically relevant non-major bleeding event
CT	Computed tomography
CTP	Clinical trial protocol
CTR	Clinical trial report
CVST	Cerebral Venous Thrombosis and/or Sinus Thrombosis
DE	Dabigatran etexilate
DMC	Data monitoring committee
dTT	Diluted thrombin time
DVT	Deep vein thrombosis
ECT	Ecarin clotting time
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMS	ethyl methanesulfonate
EU	European Union
FDA	Food and Drug Administration
GS(-MSD)	gas chromatography (mass spectrometry detector)
Granules	Coated granules in sachets
HDPE	high density polyethylene
HMS	N-hexyl methanesulfonate
HPLC	high pressure liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDBL	Interim database lock
iFF	Intended final formulation
IMS	isopropyl methanesulfonate
IPCs	in-process controls
IR	infrared spectroscopy
LDPE	low density polyethylene
LMWH	Low molecular weight heparin
MAH	Marketing authorisation holder
MBE	Major bleeding event
MMS	methyl methanesulfonates
MRI	Magnetic resonance imaging
OLF	Oral liquid solution
OOS	out-of-specification
PBRER	Periodic benefit risk evaluation report
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PDE	permitted daily exposure
PE	Pulmonary embolism
PE	polyethylene
PET	polyester

P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric investigational plan
PK	Pharmacokinetic(s)
PP	polypropylene
PPI	Proton pump inhibitor
PT	MedDRA preferred term
PTS	Post-thrombotic syndrome
pVTEp	Primary VTE prevention
QTPP	quality target product profile
REC	recommendation
RH	relative humidity
SAE	Serious adverse event
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	standard deviation
SoC	Standard of care
SPAF	Stroke prevention in atrial fibrillation
sVTEp	Secondary VTE prevention
TF II	Trial formulation II
TT	Thrombin time
UFH	Unfractionated heparin
USP	United States Pharmacopoeia
UV	ultraviolet spectrometry
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
y	Year(s)

Definition of age strata
Stratum 1: from 12 to <18 years of age
Stratum 2: from 2 to <12 years of age
Stratum 3: from birth to <2 years of age

1. Background information on the procedure

1.1. Submission of the dossier

Boehringer Ingelheim International GmbH submitted on 11 October 2019 a group of variations consisting of extensions of the marketing authorisation and the following variations:

Variation(s) requested		Type
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	IA
B.I.b.1.c	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	IB
B.I.b.1.d	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	IB
B.I.b.1.d	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	IA
B.I.b.2.a	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	IA
B.I.d.1.a.1	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	IA
B.II.c.1.c	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	IA
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	IA
B.II.d.1.d	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	IB
B.II.d.2.a	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	IA
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

Extension application to add two new pharmaceutical forms for PRADAXA (coated granules (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg) and powder and solvent for oral solution (6.25 mg/mL)) and five new strengths (related to the coated granules), grouped with:
-A type II variation (C.I.6.a) - Extension of Indication to include new indication for Pradaxa 75 mg, 110 mg,

150 mg capsules based on the paediatric trials 1160.106 and 1160.108.
As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 37.0 has also been submitted.

The MAH applied for the following indication for Pradaxa the new strengths and new pharmaceutical forms:

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dosage forms, see section 4.2.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0399/2018 on the agreement of a paediatric investigation plan.

At the time of submission of the application, the PIP/0399/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0399/2018.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The CHMP (EMA/SAWP/148452/1/2012/PED/II) advice on clinical and quality development of products for treatment of paediatric patients aged from 0-18 years was requested in 2013 (see below section 2.1.5).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kirstine Moll Harboe Co-Rapporteur: Jean-Michel Race

The application was received by the EMA on	11 October 2019

The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 January 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 January 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 January 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 February 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	12 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 June 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	23 July 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	14 September 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 September 2020
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the MAH on	15 October 2020
The MAH submitted the responses to the 2nd CHMP List of Outstanding Issues on	20 October 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 October 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pradaxa on	12 November 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Venous thromboembolism (VTE) is a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a thrombus that forms in a deep vein, e.g. in the leg, the renal vein or in any other deep vein in the body. This is likely to occur when for any reason the blood is in a state of hypercoagulability, when there is stasis of the venous blood flow and/or when the endothelium is diseased and dysfunctional. PE occurs when a deep venous thrombus, or a part of it breaks free from the vein wall, travels to the lungs and then blocks some or all of the pulmonary blood supply.

While the VTE pathophysiology of hypercoagulability, blood flow stasis and endothelial dysfunction are similar in children and adults and would be receptive to the same type of treatment, the risk factors and triggers of VTE in children are different from those in adults. Consequently, the epidemiology, clinical picture and outcomes are different in children compared to adults, see below.

In addition, children are a challenging patient population to treat because VTE most often occurs in the context of another serious diagnosis that also must be treated.

Paediatric VTE has a significant impact on both immediate and long-term health outcomes. Immediate complications of VTE include death from pulmonary embolism (PE) and non-lethal PE. Long-term consequences involve recurrent VTE, bleeding associated with anticoagulation therapy, and post-thrombotic syndrome (PTS). PTS is a burdensome condition that can lead to severe disability and poor quality of life in affected children.

2.1.2. Epidemiology

Venous thromboembolism is a relatively rare disease in the paediatric population with an estimated population prevalence of about 0.6 to 1.1 per 10 000 children. Among hospitalised children, the incidence is with ≥58 per 10 000 paediatric admissions significantly higher than in the paediatric population overall. A dramatic increase of 70% has been noted over less than one decade; most likely due to better survival of acutely ill patients and increased use of central venous access devices. VTE is now among hospitalised children the second most common cause of preventable harm.

2.1.3. Aetiology and pathogenesis

The common pathophysiology of venous thromboembolism involves the triad of hypercoagulability, stasis and endothelial injury, which is historically named Virchow's triad.

The risk of VTE is significantly lower in the paediatric population compared to adults. Children and adolescents are less exposed to the range of prothrombotic risk factors that are frequently associated with adult venous thromboembolism, e.g. diabetes and cardiovascular disease involving endothelial dysfunction, prothrombotic medications, pregnancy, smoking, malignancy, surgery and other factors.

In addition, there are physiologic differences in the haemostatic system as children have lower levels of vitamin K dependent factors, and increased plasma concentrations of the thrombin inhibitor alpha-2-macroglobulin, both resulting in lower thrombin generation (Spentzouris G et al. Pediatric venous thromboembolism in relation to adults. J Vasc Surg. 2012; 55:1785–1793)

Most paediatric VTEs constitute a secondary complication of other clinical conditions such as venous catheterisation, malignancy, infection/sepsis, congenital heart disease, trauma/surgery, renal disease, and inherited thrombophilia (e.g. Factor V Leiden mutation and others) or acquired thrombophilia. Among these, the most common etiologic factor for VTE in paediatric patients is the presence of a central venous access device

2.1.4. Clinical presentation, diagnosis

The clinical presentation of VTE will depend on the location and the extension of the thrombus. A few examples are given:

The most frequent trigger of VTE in children is the presence of a central venous catheter. The clinical presentations range from asymptomatic, chronic symptoms, e.g. with frequent clotting of the catheter, development of collateral venous circulation, recurrent sepsis, to acute symptoms with pain, swelling, discolouration of the affected area or limb and possible PE.

DVT in the lower limb may be located distally or proximally in the deep veins of limb, causing pain, swelling, and discolouration. Proximal DVT is generally associated with higher risk for PE, but in the presence of other concomitant risk factors even distal (below the knee) DVT may be associated with PE.

PE can present with chest pain, dyspnoea, pleuritis, cough, haemoptysis, but it can also present in children with non-specific symptoms depending on the underlying disease.

Renal vein thrombosis is relatively common compared to other VTE presentations in children. It can cause flank pain and haematuria and impaired kidney function.

There is no specific diagnostic biomarker for PE. Imaging with ultrasound, e.g. compression ultrasound, is the most frequently used method if the location of the suspected thrombus is accessible, e.g. in a limb. However, for the diagnosis of a more centrally located thrombus, contrast venography (cMRV), contrast magnetic resonance venography or computed tomography (CT) venography may be used. For the diagnosis of PE, computed tomographic pulmonary angiography (CTPA) have largely replaced ventilation/perfusion scan with medical isotopes although the latter may still be used in some cases.

2.1.5. Management

The standard of care (SoC) for the treatment of VTE in children is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administered for generally 5 to 7 days followed by LMWH or a vitamin K antagonist (VKA). A further treatment option is the injectable factor Xa inhibitor fondaparinux. There are frequent challenges with the therapeutic agents commonly used in children, including the need for venous access or subcutaneous injection, the risk of thrombocytopenia and bleeding, the need for frequent monitoring, variable PK of UFH, and drug-drug and drug-food interactions with VKA. These clinical challenges warrant the development of easier to use treatment modalities with a comparable safety and efficacy profile to current SoC treatments. DE may provide such an option; it is effective and safe for treating VTEs in adults.

Pradaxa is indicated for the prevention and treatment of the below mentioned diseases. The indication applied for this extension procedure is listed below:

Indication

75 mg, 110mg, 150mg hard capsules:

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.
For age appropriate dosage forms, see section 4.2.

20 mg coated granules in sachets
30 mg coated granules in sachets
40 mg coated granules in sachets
50 mg coated granules in sachets
110 mg coated granules in sachets
150 mg coated granules in sachets:

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.
For age appropriate dosage forms, see section 4.2.

6.25 mg/mL oral solution:

Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.
For age appropriate dosage forms, see section 4.2.

About the product

Dabigatran etexilate (DE) is the oral pro-drug of the active moiety dabigatran. The dabigatran etexilate pro-drug was developed due to the limited oral availability of dabigatran, and it is converted into dabigatran in vivo via esterases. The drug substance is the mesilate salt form of the pro-drug, called dabigatran etexilate mesilate. Dabigatran is a potent, synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. DE does not inhibit thrombin or factor Xa, respectively, demonstrating that the pro drug does not possess anticoagulant activity.

An ATC code B01AE07 (Oral direct thrombin inhibitors) had been assigned by the WHO to dabigatran etexilate.

PRADAXA 75 mg, 110 mg and 150 mg are available as hard, hydroxypropylmethylcellulose capsule. It is presented in aluminium/aluminium blister strips (packs with 10, 30. 60, 100 and 180 capsules) as well as in polypropylene bottles with 60 capsules.

In the EU dabigatran etexilate was submitted in 2007 under the Centralized Procedure and approved with the brand name PRADAXA on 18 March 2008 (EU/1/08/442/0001-0019) for the indication "Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp). "

The recommended dose of Pradaxa is 220 mg once daily taken as 2 capsules of 110 mg.
Treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.
For the following groups the recommended daily dose of Pradaxa is 150 mg taken once daily as 2 capsules of 75 mg:

- Patients with moderate renal impairment (creatinine clearance (CrCL) 30-50 mL/min)
- Patients who receive concomitant verapamil, amiodarone, quinidine
- Patients aged 75 or above

In August 2011 dabigatran etexilate was furthermore approved in the indication
"Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (SPAF) with one or more of the following risk factors:

- Previous stroke, transient ischemic attack, or systemic embolism (SEE)
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension"

and in June 2014 the additional indication "Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults" was approved.

The currently recommended daily dose of dabigatran etexilate in the SPAF indication is 300 mg taken as one 150 mg capsule twice daily.

For the following two groups the recommended daily dose of Pradaxa is 220 mg taken as one 110 mg capsule twice daily:

- Patients aged 80 years or above
- Patients who receive concomitant verapamil

For the following groups, the daily dose of Pradaxa of 300 mg or 220 mg should be selected based on an individual assessment of the thromboembolic risk and the risk of bleeding:

- Patients between 75-80 years
- Patients with moderate renal impairment
- Patients with gastritis, esophagitis or gastroesophageal reflux
- Other patients at increased risk of bleeding

Globally PRADAXA is currently approved in more than 112 countries.

Type of Application and aspects on development

This application is submitted upon completion of the dabigatran EU PIP (EMEA-000081-PIP01-07-M11) and proposes the following paediatric indication for Pradaxa®:

- Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

It is intended to treat the paediatric population with already registered capsules and the two new paediatric pharmaceutical forms according to the following scheme:

- Pradaxa® powder and solvent for oral solution (6.25 mg/mL after reconstitution) for children less than 1 year;
- Pradaxa® coated granules (20/30/40/50/110/150 mg per sachet) for children below 12 years as soon as the child is able to swallow soft food;
- Pradaxa® hard capsules (75/110/150 mg) for children from 8 years to below 18 years.

Paediatric clinical development programme

The EU Paediatric Investigation Plan (PIP) for dabigatran etexilate was adopted with EMA decision P/76/2008 on 14 Sep 2008 (EMEA-000081-PIP01-07). Since then, the PIP was modified 11 times (EMEA-000081-PIP01-07-M11) with the latest decision adopted on 07 Dec 2018 (P/399/2018).

The dabigatran PIP contains waivers for the indications pVTEp and SPAF and requires a total of 6 clinical studies in the paediatric population aged 0 to less than 18 years or healthy volunteers ((see Table 1 below) to investigate the PIP condition "Treatment of thromboembolic events". Furthermore, the PIP requires the development of an age-appropriate formulation.

Compliance with the PIP
In accordance with the PIP, this grouped extension application is based on data of several Phase I to Phase III trials. Five trials (1160.87, 1160.194, 1160.88, 1160.89, and 1160.105) have already been completed. For the completed trials that are part of the PIP (all except 1160.194), the partial compliance checks by the PDCO were successful and confirmed compliance with the key binding elements.

Trials included in the grouped extension application

Trial no.	Objectives	Formulation of DE[1]	Age group
Phase I			
1160.87	Bioavailability	Oral solution, granules, and capsules	Adults
1160.194[2]	Bioavailability	Oral solution, granules, and capsules	Adults
Phase IIa			
1160.88	PK, PD, safety, tolerability	Capsules	12 to <18 years
1160.89	PK, PD, safety, tolerability	Oral solution	1 to <12 years
1160.105	PK, PD, safety, tolerability	Oral solution	0 to <1 year
Phase IIb/III			
1160.106, final	PK, PD, efficacy, safety, tolerability	Oral solution, granules, and capsules	0 to <18 years
1160.108, final	PK, PD, safety, tolerability	Oral solution, granules, and capsules	0 to <18 years

Two trials (1160.106 and 1160.108) were still ongoing at the initial submission based on an interim analysis and CTR. These trials have both been completed in the meantime. An updated dossier with the final CTRs for both trials has been provided. As agreed with the EMA, the interim CTRs covered all key binding elements as per PIP.

At the time of submission of the application, the PIP P/0399/2018 was completed. The PDCO issued an opinion on compliance for the PIP P/0399/2018 on 23 Aug 2019 (EMEA-C-000081-PIP01-07-M11) based on draft interim clinical trial reports for 1160.106 and 1160.108.

The interim analysis from trials 1160.106 and 1160.108 included data from the following patient population:

- All patients who already completed either trial
- Ongoing patients who were recruited after 1 Nov 2018 and attended at least Visit 3 (i.e. Day 4). This visit corresponds to the time point when the first PK measurement of dabigatran was performed

Recruitment in trials 1160.106 and 1160.108 continued until April 2019 for 1160.108 and July 2019 for 1160.106 in order to comply with the FDA post marketing requirements and as part of the written request that has been issued by the FDA. The resulting final CTRs with the complete data set for trials 1160.106 and 1160.108 have been provided within current procedure.

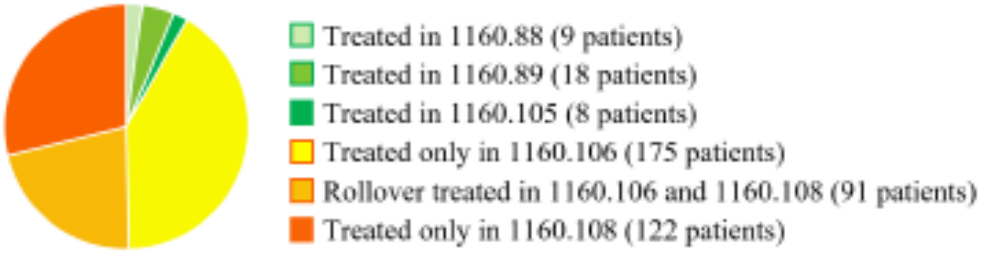
No relevant changes exist between these draft CTR versions and the finalized interim CTR versions, which were submitted as part of this grouped extension application. Specifically, no relevant changes were made, which relate to the key binding elements.

All trials are/were being performed in compliance with GCP and in accordance with applicable regulatory requirements and BI standard operating procedures. All CTPs were approved by institutional review boards or independent ethics committees. In accordance with GCP and according to the local regulatory and legal requirements, informed consent/assent was obtained from all patients/parent(s) or the patient's legally accepted representative.

Trials included in the analysis of efficacy and safety

The efficacy and/or safety of DE in paediatric patients have been investigated in 5 trials, with trials 1160.106 and 1160.108 contributing the majority of patients to the programme. Of these 5 trials, 3 Phase IIa trials have been completed with each trial covering a different age range from adolescents to infants. The patients in all 3 Phase IIa trials received DE either as single intake or for 3 days.

The Phase IIb/III trials have a twice daily dosing for DE and a treatment duration of 3 months (1160.106) or up to 12 months (1160.108). Trial 1160.106 is a Phase IIb/III trial with the objective to document the appropriateness of the proposed dosing algorithm, in addition to efficacy and safety analyses. Trial 1160.108 is a Phase III trial with the objective to collect safety data with a considerably longer trial duration than for 1160.106.



Source data: [U12-3378, Table 15.1.1: 1; c09069268, Table 15.1.1: 1; c09085437, Table 15.1.1: 1; c29773859, Tables 15.1.1: 1 and 3]

Figure 1 Number of treated patients by trial

Overview of trials included in the evaluation of efficacy/safety

Table 2 Overview of trials included in the evaluation of efficacy/safety

Trial no. (Phase) [Reference]	Trial design	N[1]	Formulation of DE	DE dose; duration of treatment	Trial population
1160.88 (IIa) [U12-3378]	Open label, single arm	9	Capsules	Weight-adjusted dose; 3 days bid	Adolescents (12 to <18 years)
1160.89 (IIa) [c09069268]	Open label, single arm	18	Oral solution	Age- and weight-adjusted dose; single dose/ 3 days bid[2]	1 to <12 years
1160.105 (IIa) [c09085437]	Open label, single arm	8	Oral solution	Age- and weight-adjusted dose; single dose	0 to <1 year
1160.106 (IIb/III), [c29773859]	Open label, randomised, active-controlled (standard of care)	266	Oral solution, granules[3], capsules	Age- and weight-adjusted dose and formulation; 3 months	0 to <18 years
1160.108 (III), [c29754273]	Open label, single arm	213	Oral solution, granules[3], capsules	Age- and weight-adjusted dose and formulation; treatment until resolution of clinical risk factor (max.: 12 months)	0 to <18 years

[1] Number of treated patients. Rollover patients are counted in each trial where they participated.
[2] As agreed with the PDCO, the multiple dosing schedule was changed to a single dose of DE during the trial.
[3] For consistency with the CTPs, the term 'pellets' is used in the CTRs. It refers to 'coated granules in sachets' or short 'granules', see Section 1.5.

The first trial investigating DE capsules in adolescents was 1160.88 and started in August 2009. The patients were treated for 3 days twice daily. The subsequent trial 1160.89 analysed DE as oral solution when given to paediatric patients aged 1 to 12 years. As agreed with the PDCO, the dosing scheme was changed during the trial from 3 days twice daily to a single dose. Most patients in this trial were treated with a single instead of

multiple dose of DE. In trial 1160.105, the youngest age group (<1 year) received a single dose of DE as oral solution.

The 2 trials with the largest number of treated patients in the paediatric programme are trials 1160.106 and 1160.108. They recruited patients until April 2019 (1160.106) and July 2019 (1160.108). The resulting final CTRs with the complete data set for trials 1160.106 and 1160.108 have been provided within current procedure. The Phase IIb/III trial 1160.106 is an open-label, randomised, active-controlled non-inferiority trial comparing DE with standard of care i.e. low molecular weight heparins or vitamin K antagonists or fondaparinux. Trial 1160.106 has a planned patient participation of 3 months, beyond the initial parenteral therapy (at least 5 days and at most 21 days). The dosing algorithm, which was investigated in trial 1160.106, was also applied in the Phase III trial 1160.108. The latter is a safety trial and investigated DE as single treatment in patients requiring secondary prevention of VTE. Patients from trial 1160.106 who were in continued need for anticoagulation could also participate in trial 1160.108. The treatment duration in trial 1160.108 with up to 12 months is longer than the planned treatment duration in trial 1160.106.

Bioavailability trials with paediatric formulations in adults
The Phase I trials 1160.87 and 1160.194 were performed in adult healthy volunteers and investigated the bioavailability of different formulations of DE. The tested formulations were then used in the paediatric clinical trials. Both bioavailability trials in adults analysed the formulations oral solution, coated granules, and capsules which were given either as single dose (1160.87) or for 3 days (1160.194). Individual $C_{max,ss}$ and $AUC_{\tau,ss}$ values observed for the 3 formulations were within the range of exposure seen in previous trials in adults. The noted increase in exposure was small enough to consider the formulations interchangeable for trials with dose-finding/dose-confirmation character like trials 1160.106 and 1160.108. Furthermore, trough levels were similar for the 3 formulations. Thus, it was concluded that a conversion factor does not need to be applied for dosing purposes in children for dose finding/confirmation trials. These 2 trials are included in the summary of biopharmaceutical studies and associated analytical methods to support the formulation development but are excluded from the analyses in the SCE and SCS.

Rationale for open-label design
For trial 1160.106, an open-label design was chosen for several reasons. The different paediatric formulations of DE and the s.c. administration of some of the SoC treatments would have required an unethical number of dummy treatments in a blinded trial, especially considering the vulnerability of a paediatric trial population. Similarly, the constant INR monitoring required for some SoC treatments would also have had to be simulated for the DE group in a blinded trial. However, important efficacy and safety outcomes of the trial were adjudicated in a blinded fashion by an independent committee.

An open-label design was also chosen for trial 1160.108 to enable ongoing DMC review of outcomes within the trial, as well as other related trials with DE in paediatric patients. It ensured the safety of the patients in the trial. Furthermore, it allowed modifications of the trial design, sequential inclusion of younger patients, and, if warranted, recruitment of further patients. The single-arm design was considered adequate for this safety trial, especially since results from the controlled trial 1160.106 added to the interpretation of the results.

Scientific (EMA/SAWP/148452/1/2012/PED/II) advice on clinical and quality development of products for treatment of paediatric patients aged from 0-18 years was requested in 2013.

The Applicant's initial position was to develop 2 dosage forms for paediatric use, i.e. a capsule and an oral liquid form.

The capsules were initially intended for use in children from 8 years, but it was questioned whether the acceptability results obtained for the 12 years old could be directly applied to the 8 years old children.

The oral solution, which was prepared from granules and solvent, was initially intended for use in children up to the age of 8 years, but several problems were encountered with the initial formulation as follows:

- Prolonged shaking (5 min) upon reconstitution
- Short in-use shelf-life of 2 hours due to stability issues requires that caretakers must prepare oral solution twice a day for 3-6 months or longer periods. The volume in one bottle may be enough for an additional dose in the evening and it is thus tempting to store the remaining solution and use it in the evening. Storage for 1 or 2 days seems more optimal in relation to wastage and usefulness to carers.
- Potential palatability issues due to administration of large volumes twice a day for prolonged periods.
- High dosing volumes due to dilute solution (higher concentrations would cause a more bitter taste and even longer reconstitution times).
- Measuring/dosing devices were not fully described; five different sizes were mentioned at that time but their dosing accuracy and acceptability were not elucidated.

During the SA procedure the CHMP concluded that the oral solution was a rather deficient dosage form and an improved formulation or strategies to overcome acceptability issues should be suggested.

The CHMP encouraged the Applicant to consider an additional dosage form such as mixing granules (pellets) with food in order to address acceptability issues with either the liquid or capsule formulations. The rationale was that capsules are likely to be opened, anyway, and their content of pellet mixed with food. Additional dosage forms should be explored, i.e. sachets containing capsule content, which could be useful for children not able to swallow capsules.

In accordance with the advice given, the Applicant has developed all 3 dosage forms, i.e. capsules, coated granules and oral liquid formulation and re-defined the age-groups for which the respective dosage forms are intended as age-appropriate.

In addition, the oral liquid formulation has been further optimised as regards stability, and the target age-group has been re-defined to 0-1 years old. This considers that the impurity specification limits only allow maximum doses of 300 mg dabigatran etexilate. The complexity of reconstitution has been increased, since two different sachets with granules (one containing the active substance and one with a sweetener) are required to be dissolved in the solvent before administration in the proposed formulation.

The advice given has been followed with respect to the points discussed above.

It is noted that the scientific advice raised an issue regarding the bioavailability of granules from the capsules when it was opened and the granules sprinkled on food. The bioavailability was higher than for the intact capsules, see excerpt from the Final Advice Letter:

"At the meeting with the Applicant the mixing of capsule contents with food was discussed. The Applicant provided details of BI trial No, 1160.87, which considers the relative bioavailability of dabigatran after administration of a single oral dose of 150 mg dabigatran etexilate (capsule, powder for reconstitution into solution, and coated granules on food) in healthy male and female volunteers. BI states that the coated granules were sprinkled on a teaspoon of the baby food (GERBER® Cereal for Baby, RICE single grain) and administered immediately (within a period of 10 minutes) with about 240 mL of water. For the sprinkle the AUC0-inf was 175.1 % compared to the intact capsule. From this study it was also noted that AUC0-inf was

154.8 % for Test 2 (solution reconstituted from powder). It is noted that the oral solution is more bioavailable than the capsules. Also, the capsules opened and mixed with food are more bioavailable that the capsules. This increase in bioavailability of capsules opened and sprinkled on food seemed unexpected." (Final Advice Letter, 21 March 2013)

In the meantime, the Applicant has conducted a series of pharmacology studies to inform the dosing algorithm in the paediatric population. As described in the CTR section 7.2 on the Drug Profile, subheading Bioavailability of DE formulations used in the paediatric trials: "two Phase I trials in healthy adult volunteers (trials 1160.87 [U09-1839-01] and 1160.194 [c02248557-02; not part of the PIP]) were conducted to investigate the bioavailability of the formulations to be used in the paediatric clinical trials. Individual $C_{max,ss}$ and $AUC_{\tau,ss}$ values observed for the 3 formulations (capsules, reconstituted solution from DE powder, and DE coated granules sprinkled on food) were within the range of exposure seen in previous trials. The noted increase in exposure was small enough to consider the formulations interchangeable. Furthermore, trough levels were similar for the 3 formulations. Thus, no conversion factor needs to be applied for dosing purposes in children for dose finding/confirmation trials."

However, in the clinical paediatric studies the apparent relative bioavailability paradoxically turned out to be lower for oral solution and coated granules than for capsules. Having discussed this extensively with the Applicant during the current procedure, the Applicant is not able to explain this opposite bioavailability in children and adults. The dosing algorithm is taking the lower bioavailability into account and the issue will not be further pursued. Please refer to the section on Clinical Pharmacology in this report for details.

2.2. Quality aspects

2.2.1. Introduction

This application concerned a line extension for the addition of two new pharmaceutical forms and new strengths intended for paediatric patients grouped with a number of type IA and IB variations to update the information regarding the active substance and the currently authorised hard capsules. The type IA and IB variations are related to, or are a consequence of, the introduction of the two new pharmaceutical forms. The two new pharmaceutical forms are Powder and solvent for oral solution and Coated granules. The Powder and solvent for oral solution is 6.25 mg/mL; the new strengths in relation to the Coated granules are 20 mg, 30 mg, 40 mg and 50 mg, 110 mg and 150 mg.

Pradaxa 6.25 mg/mL powder and solvent for oral solution comprises three components for reconstitution:

- Pradaxa powder for oral solution in sachets, containing 180.4 mg of dabigatran etexilate (as mesilate) per sachet;
- Solvent for Pradaxa oral solution in a bottle, containing 28 mL of a clear, colourless solution;
- Sucralose powder for Pradaxa oral solution in sachets, containing 70 mg of sucralose per sachet.

Other ingredients in Pradaxa powder for oral solution are: mannitol and hydroxypropylcellulose.

Other ingredients in Solvent for Pradaxa oral solution are: tartaric acid, hydrochloric acid (for pH-adjustment), and purified water.

The Sucralose powder for Pradaxa oral solution contains only sucralose.

Pradaxa powder and solvent for oral solution is supplied as a medication kit that contains:

- 1 carton box containing an aluminium bag that contains 30 PET/Alu/LDPE sachets of Pradaxa powder for oral solution and a desiccant.
- 30 carton boxes which are referred to as individual preparation packs. Each pack contains:
    - one PET/Alu/LDPE sachet containing Sucralose powder for Pradaxa oral solution,
    - one amber glass bottle containing Solvent for Pradaxa oral solution,
    - two dosing pipettes (12 mL) and
    - one adapter for the bottle.

The co-packaged dosing pipettes and the adapter are CE marked medical devices.

Pradaxa Coated granules is presented as single dose sachets for oral use containing 20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg of dabigatran etexilate (as mesilate) per sachet.

Other ingredients are: Tartaric acid, acacia, hypromellose, dimeticone 350, talc and hydroxypropylcellulose.

Pradaxa Coated granules are packaged in sachets made of PET/Alu/LDPE foil.

2.2.2. Active Substance

The active substance used in the finished product is the same as in the already approved product Hard capsules. As a consequence, no evaluation is required for the active substance sections, except for the evaluation of the some proposed changes for the control of the active substance for the use in the oral solution, and the changes introduced with the variations grouped with this extension application (e.g. change of the acceptance limits for some of the parameters in the specification).

The specification of the active substance, dabigatran etexilate mesilate , used for capsules and coated granules is identical. The active substance specification used for granules for oral solution includes updated limits for polymorphism and the degradation products compared to the active substance used for capsules and coated granules. The updated limits are necessary to ensure the desired quality of the granules for oral solution.

The following quality variations were applied for:

B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method;

B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits;

B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter);

B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure;

B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter);

B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period – Reduction.

The addition of testing parameter chromatographic purity to the specification for the raw material toluene-4-sulfonic acid is justified and acceptable.

The active substance specification was evaluated with respect to the paediatric dosing algorithm which includes a maximum daily dose of 660mg dabigatran etexilate (free base) for dosage forms capsules and coated granules and maximum daily dose of 300 mg for the granules and solvent for oral solution. Therefore, the specified impurities were re-evaluated with respect to toxicologically qualified levels and impurities with mutagenic potential were re-evaluated according to ICH M7. The re-evaluations did not impact the specified degradation products since the acceptance levels are still below the toxicologically qualified limits. However, the ICH M7 re-evaluation did result in a change of specification for alkyl methanesulfonates in the active substance and finished product and also to warnings in the SmPC that the oral solution is only to be used for neonates up to 12 months and that dosing volume is not to exceed 12 mL.

A complete testing of the methane sulfonates was performed. All the results were below the reporting threshold. The proposed deletion of the testing for alkyl methanesulfonates impurities and the sum of all specified impurities are from the specification of the active substance has been sufficiently justified and is acceptable.

The updated limit for an alkylsulfonate impurity in dabigatran etexilate mesilate active substance specification is accepted. The consequential update of the purity method for an alkylsulfonate impurity is accepted too. The replacement of the heavy metal test in the specification of the active substance by the provided risk assessment according to ICH Q3D(R1) is also accepted. The active substance reduced retest period is not dependent on its intended use (oral solution, coated granules or capsules). The new retest period and the proposed storage conditions are acceptable.

The changes in the active substance specification do not require additional validation of the analytical methods, with the exception of the method used for the determination of the desired polymorphic form, which was adequately revalidated.

Batch results were provided from release testing of the active substance obtained using both synthesis routes. The testing was performed in accordance to the proposed specification. All the results were compliant with the acceptance criteria in the specification.

All the applied variations are accepted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Pradaxa Hard capsules

The following quality variations related to the authorised finished product hard capsules were applied:

B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits;

B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter;

B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure;

B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter).

The specifications for dabigatran etexilate hard capsules (all strengths) are updated since the control strategy for alkyl methanesulfonates was re-assessed in accordance with ICH M7 in the context of the expansion into the paediatric population which leads to a higher maximum daily dose i.e. 660 mg (dabigatran etexilate (free base)).

It has been sufficiently justified why alkylmethanesulfonate impurities are omitted in the hard capsules specification. It is considered acceptable, based on presented batch results and the presented stability data that a single alkylsulfonate impurity is only tested on pellets (intermediate) and hard capsules finished product during shelf-life with the proposed tightened limit. The proposed change to the analytical procedure for purity is acceptable. The deletion of heavy metal test and the Japan-specific parameters Characters from the specification for the excipient HPMC capsule shells is also acceptable.

All the applied variations are accepted.

Pradaxa Powder and solvent for oral solution

Description of the product and pharmaceutical development

The finished product is supplied as a medication kit comprising three components, to be mixed before administration of the oral solution:

- Dabigatran etexilate powder for oral solution, 180.4 mg/ sachet: a yellowish-white powder in sachets;
- Solvent for dabigatran etexilate oral solution, 28 mL/ bottle: a clear, colourless solution;
- Sucralose powder for dabigatran etexilate oral solution, 70 mg/ sachet: a white to almost white powder in sachets.

The qualitative composition of each of the three components is shown in paragraph 2.2.1 of this report and in section 6.1 of the SmPC. The oral solution is prepared prior to administration by dissolving dabigatran etexilate powder for oral solution and sucralose powder for oral solution in the solvent for dabigatran etexilate oral solution. The concentration of dabigatran etexilate (free base) in the oral solution is 6.25 mg/mL. The dose ranges from 6.25 to 143.75 mg corresponding to dosing volumes of 1 to 23 mL, administered by the oral syringes.

Pradaxa powder for oral solution, is packaged in a sachet made of a three-ply foil composed of an outer polyester film, an aluminium foil layer and an inner low-density polyethylene (PET/Alu/LDPE). The aluminium bag that contains the Pradaxa powder for oral solution sachets and the desiccant is also made of PET/Alu/LDPE foil; the desiccant is labelled with "DO NOT EAT" including pictogram and "SILICA GEL". The Solvent for Pradaxa oral solution, is packaged in an amber glass bottle with a polypropylene/ high-density polyethylene (PP/HDPE) screw-cap with a nominal volume 60 mL and a 2-piece plastic closure. The Sucralose powder for Pradaxa oral solution is packaged in a sachet made of a three-ply PET/Alu/LDPE foil.

Pharmaceutical development

A quality target product profile (QTPP) was established for dabigatran etexilate oral solution, describing requirements of the medicinal product to be developed, and critical quality attributes (CQA) were defined. Critical process parameters and critical (in-process) material attributes were identified.

The selected oral solution formulation was designed to meet the quality targets concerning age appropriateness, specifically dosing flexibility and accuracy (two dosing syringes provided, 12 mL), acceptable taste, acceptable excipients for paediatric use and acceptable stability particularly during the in-use period.

Excipients selected for dabigatran etexilate powder and co-supplied solvent for oral solution and the excipient sucralose are commonly used in oral formulations. These excipients are soluble in water to be able to provide a clear oral solution after solubilisation in the co-supplied solvent. All except the peach flavour are described in Ph. Eur. The choice and function of the excipients in the formulation has been described. Compatibility of excipients has been demonstrated.

The maximum intake of all excipients has been evaluated from a toxicological perspective as outlined in the Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2. Based on present knowledge mannitol, hydroxypropyl cellulose, tartaric acid, propylene glycol in peach flavour, and sucralose at the maximum intended dose in the oral solution are considered to have no adverse effect when orally administered at the intended dose in the oral solution formulation.

The active substance' solubility is pH dependent (high solubility at low pH and low solubility at pH 5 and above). In order to maintain adequate solubility, leading to a clear solution, a low pH was required for the formulation. As the active substance is sensitive to hydrolysis at low pH, the active had to be separated from the acidic aqueous solvent until the moment of the preparation for administration of the finished product. Moreover, in order to ensure patients compliance, the bitter taste of the active substance had to be masked. This was achieved by using sweeteners and a flavouring agent.

It was established by relevant studies that a preservative was not needed in the formulation of dabigatran etexilate powder for oral solution which is anyway intended to be used within a short period of time. The choice of sucralose as sweetener has been justified on stability and palatability grounds. A major objection was raised relating to the development of three components which need to be combined to produce the final oral solution, because the complexity of reconstitution steps could increase the risk of medication errors occurring. However, the presented stability data justified the need for the three-component system. In addition, as discussed below, the results of a usability study showed that the probability of medication errors is low. The major objection was therefore considered resolved from a quality perspective. See also further discussion below in Clinical aspects.

Several studies were performed to evaluate the time needed for the dissolution of the active substance in the solvent and the type of solvent. Based on these studies, the optimum composition and pH of the solvent were determined.

A formulation with a flavouring agent was preferred, based on the presumably better acceptability by the patients and the acceptable risk from the intake of additional excipients, such as propylene glycol.
An adequate discussion, supported by relevant, data, of the related substances that could be formed under the conditions of the manufacturing process or preparation of the oral solution was provided especially in relation to alkyl methane sulfonates, degradation impurity as well as the active substance polymorphic form; appropriate controls were introduced in the specification of either the active substance or the finished product.

Manufacturing process development
The manufacturing process for dabigatran etexilate powder for oral solution consists of the two main process steps: granulation and sachet filling (primary packaging), followed by subsequent steps for bulk packaging, and protective secondary packaging of the final product. Granulation optimisation was driven by the need for an adequately short reconstitution time for preparation of the oral solution and the chemical stability of the active substance. The process was successfully transferred to the proposed commercial site and scale.

The manufacturing process for the solvent consists of two main process steps: preparation of solvent solution, and filling of the solution into bottles and closing of the bottles. The process was successfully transferred to the proposed commercial site and scale. The manufacturing process for the solution is a series of mixing steps with a filtration step at the end. The filtered solution is filled into bottles, so that each bottle is a single dose unit, containing the amount of solvent required for dissolving the contents of one dabigatran etexilate sachet and one sucralose sachet.

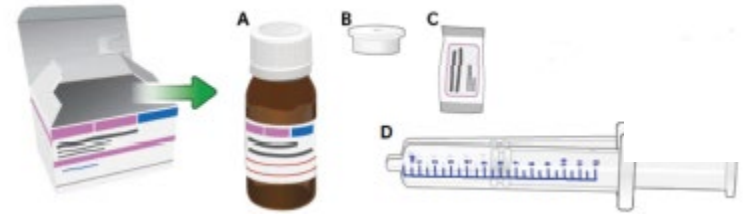
The manufacturing process for sucralose consists of the process for packaging of sucralose granules into sachets to yield the unit doses of sucralose powder for dabigatran etexilate oral solution (70 mg/ sachet). It was developed at the commercial manufacturing site directly.

The changes of the composition of the dabigatran etexilate powder and of the solvent during clinical development have been clearly presented. Also, a short overview of the history of the development of the manufacturing process for each of the components was provided.

Potentially critical in-process material attributes and process parameters were investigated during the process development of the granules and the solvent. Sucralose did not require an initial risk assessment since it only involves a packaging operation. Potential relationships between the in-process material attributes, process parameters and the Critical Quality Attributes (CQAs) were investigated, to evaluate suitable process settings or proven acceptable ranges (PARs). These ranges were used to gain process knowledge to ensure adequate process performance during routine production. No Design Space (DS) is claimed. The PARs and recommended process parameter settings intended for commercial scale for every individual step of the processes for dabigatran etexilate powder, for the solvent and for the sucralose powder were provided.

Medication kit

The oral solution has to be prepared by the caregiver before administration. Each medication kit is composed of an inner box (*medication box*) containing 30 sachets with the powder for the oral solution, packed with a desiccant, and 30 individual *preparation packs*, each of them containing the solvent for the oral solution, a sachet containing the sucralose and the syringes for the administration (2 syringes for oral administration (dosing pipette) for dosing up to 12 mL, as well as a bottle adaptor) as shown in Figure 1. In order to avoid a mix-up of dabigatran etexilate powder and sucralose, the sachets are different in colour (silver and white respectively) and size. The desiccant pouch is a white plastic fibre pouch distinguishable from the aluminium dabigatran etexilate powder sachets.



A: Amber bottle with 28 mL solvent

B: adaptor for bottle/syringe

C: white sachet with 70 mg sucralose

D: 2 x 12 mL syringes

Preparation pack

Medication box

Figure 1. Contents of medication kit

In a usability study with representative samples of the market presentation, all test participants, lay caregivers and healthcare professionals (HCPs), were aware that two different sachets are needed for preparation of the oral solution. All test participants (lay caregivers and HCPs) were able to locate the medication granules and the sweetener needed for the preparation of the oral solution. Thus, the probability

of medication errors due to the presence of two different sachets to be used for preparation of the final formulation before use is considered as low.

Compatibility
The solution is not compatible with any beverages or food, and should not be co-administered, because a risk of precipitation due to pH differences, which would not guarantee the correct dosing.

The oral solution was shown to be compatible with nasal tubes of the following materials: PVC, polyurethane and silicone. Compatibility study were performed using nasal tubes in polyvinyl chloride (PVC), polyurethane and silicone with different lengths (from 110 to 38 cm). Water is recommended as a flushing liquid, based on the results of the compatibility studies performed with water, apple juice and the solvent solution. Studies of the volume of liquid needed for flushing were also performed, and it was concluded that a volume equal to the volume of product administered is necessary for the flushing from short and small nasal tube, whereas a volume twice the one administered is required for flushing the product from wider and long tubes.

Container closure system and medical devices
The container closure system of the powder for the oral solution comprises an aluminium sachet as primary packaging and an aluminium bag with desiccant as secondary protective packaging to protect dabigatran etexilate powder for oral solution in sachets from moisture. The sachets are manufactured from three-ply foil composed of an outer polyester (PET) film, an aluminium foil (Alu) layer and an inner polyethylene (PE) film. The polyethylene (PE) film layer is the layer in contact with the dabigatran etexilate powder. A similar three-ply aluminium foil is used for the secondary protective package. Compliance of the materials with the EU food legislation on materials intended to come into contact with food is declared. The sachets have been tested as child resistant packaging according to US 16 CFR§1700.20. Compatibility between dabigatran etexilate powder and the aluminium sachet has been demonstrated during formal stability studies.

The container closure system for solvent consists of an amber glass bottle, glass nominal volume 60 mL and a 2-piece plastic closure. The bottle contains 28 mL solvent. The container closure system is child resistant according to 16 CFR part 1700 and tamper evident. Although the reconstituted oral solution is not photosensitive an amber glass bottle was selected as a conservative measure. However, although the amber glass bottle obscures some light, differentiation between air bubbles and undissolved powder can be observed visually through the bottle during the preparation of the oral solution.

The container closure system for the sucralose powder consists of an aluminium sachet as primary packaging. The sachets are manufactured from a white three-ply foil composed of an outer polyester (PET) film, an aluminium foil layer and an inner polyethylene (PE) film. The polyethylene (PE) film layer is the layer in contact with the sucralose. Compliance of the materials with the EU food legislation on materials intended to come into contact with food, is declared. The container closure system is compatible with sucralose as demonstrated through stability testing of the sucralose in sachets under long term and accelerated testing conditions. The sachets have been tested as child resistant packaging according to US 16 CFR§1700.20.

CE marked dosing syringes (2x12 mL) are provided for the administration of the product. On the 12 mL dosing pipette, a scale from 0 to 12 mL with 0.25 mL graduation is printed. With regard to the dosing accuracy of the syringe a validation study was conducted in order to show compliance with the requirements of Ph. Eur. method of analysis 2.9.27 Uniformity of mass of delivered doses from multidose containers. The enclosed adaptor is also CE marked. Compliance with the food legislation on plastic materials intended to come into contact with food has been declared by the medical device manufacturers.

Manufacture of the product and process controls

Dabigatran etexilate powder for oral solution

The manufacturing process is a standard process, comprising the following main steps: wet-granulation, screening and drying, filling into sachets, secondary packaging into an aluminium bulk bag together with a desiccant pouch. The granules are moisture sensitive and packaging is performed in controlled low-humidity environment.

During the packaging process, each sachet is labelled and the correct number of labelled sachets appropriate to the pack size is placed in an aluminium bag for secondary protective packaging together with a desiccant. The filled aluminium bag is heat-sealed, labelled and placed into a folding carton, together with a package insert. The packaging process sis also performed under controlled environmental conditions.

The aluminium bag is then combined with the preparation packs, containing the solvent for oral solution, 28 mL/ bottle, the sucralose powder for oral solution, 70 mg/sachet, the adapter and oral syringes (2x12 mL), and package insert into the medication kit.

The controls of the critical steps during the manufacture of the granules were presented, with suitable acceptance criteria. The specification used for the control of the granules, considered to be the intermediate obtained during the process, as well as details on the methods used for the controls and their validations were provided.
The proposed holding time for the intermediate granulate and bulk storage of sachets with granules is supported by stability data. During storage periods an increase in the content of a specified genotoxic impurity is observed; however, results are still well within the release specification limits. Satisfactory information and specifications of the packaging material used for bulk storage were provided, including specifications for the desiccant.

The process validation was performed on three production full scale batches manufactured at the proposed manufacturing site. The validation covered the manufacturing of the granules, their filling into sachets and packaging of the sachets into the bulk bags containing the desiccant and included extensive monitoring.

Solvent for oral solution

The manufacturing process for the solvent is a standard process, including the preparation of solvent solution (through a series of steps for dissolving the excipients, pH adjustment, and filtration) and filling into bottles.

Critical steps have been indicated and acceptable in-process controls are applied during the manufacture of the solvent.

The manufacturing process was evaluated on two batches manufactured at the intended batch size and site. In addition to the in-process controls proposed for the manufacture of the commercial batches, the validation batches were subjected to more extensive monitoring. The results obtained show compliance with the acceptance criteria and are similar between batches.

Sucralose powder for oral solution

The manufacturing process for the sucralose is a standard process involving simply the filling of sucralose as supplied by the supplier into sachets.

Critical steps were identified and acceptable in-process controls are applied. A process validation study was performed on three batches at the proposed batch size and site. The results confirmed the reliability of the packaging process.

Conclusion
The manufacturing processes for each of the three components of the medicinal product, the dabigatran etexilate granules, the solvent for the oral solution and the sucralose powder, have been described in sufficient detail. The overall control strategy for the three components of the medicinal product is considered adequate. Process validation at commercial scale has been performed for all three components. It is considered that all processes are adequately under control in order to consistently obtain a product that complies with the specifications.

Product specification

The Pradaxa powder for oral solution release and shelf life specifications include appropriate tests and limits for description (visual), water content (Karl-Fischer), identification (HPLC-UV), assay (HPLC-UV), degradation products (HPLC-UV), uniformity of dosage units-content uniformity (Ph. Eur.), purity (GC-MSD) and microbiological quality (Ph. Eur.), reconstitution time and description of oral solution.

The Solvent for Pradaxa oral solution release and shelf life specifications include appropriate tests and limits for description (visual), pH (Ph. Eur.), identification of tartaric acid (colour reaction), volume of contents (gravimetry), loss of mass (gravimetry), microbiological quality (Ph. Eur.) and microbiological quality BCC (USP).

The Sucralose powder for Pradaxa oral solution release and shelf life specifications include appropriate tests and limits for description (visual), identification (IR), weight of contents (gravimetry), assay (Ph. Eur.), impurities H and I (Ph. Eur.), specific optical rotation (polarimetry), water content (Karl-Fischer) and microbiological quality (Ph. Eur.).

The proposed specifications of the three components of the product are acceptable and the proposed tests are relevant for each of the components. The specification limits have been set in line with ICH Q3B(R2), Q3C(R7), Q6A and ICH M7, as well as batch results and relevant pharmacopoeial standards.

The proposed limits for specified and total degradation products are qualified conservatively at a maximum daily dose of 660 mg/day proposed for the paediatric population and inside the safety margin established by toxicology studies. For oral solution the maximum daily dose is 287.5 mg (conservatively rounded to 300 mg).

The proposed limits for specified and total degradation products in the specification of dabigatran etexilate powder are set based on the maximum daily dose of 287.5 mg/day (conservatively rounded up to 300 mg /day in the calculations for an alkylsulfonate impurity), proposed for the paediatric population and inside the safety margin established by toxicology studies.

The omission of polymorphic form testing has been justified since the polymorphic form does not change during manufacture and storage of the finished product. Polymorphism is controlled in the active substance specification. The amount of isopropanol was found to be < 50 ppm in the intermediate granulate during development and process validation. Thus, testing in the finished product is not warranted.

A risk assessment for the oral solution was performed as per ICH Q3D guideline to evaluate the potential presence of elemental impurities. The same maximum daily dose of 660 mg was used as for Hard capsules and Coated granules, to calculate the maximum intake of each of the excipients and the active substance. Elemental impurity data show levels well below the corresponding control threshold of 30% of the permitted

daily exposure (PDE). The controls already in place for the active substance and finished product (oral solution) ensure that elemental impurities in the finished product will be maintained below the respective PDE levels and thus no controls are warranted.

Risk assessments, in line with the "Questions and answers on Information on nitrosamines for marketing authorisation holders" and the "Information on nitrosamines for marketing authorisation holders" published on the EMA website, have been presented for both the finished product manufacturing process and the active substance with respect to potential formation of nitrosamine impurities. The outcome of the risk assessment confirms that there is no risk for nitrosamine impurities formation and no risk for cross-contamination with other products.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. The same analytical methods as used for the control of the capsules are used for the control of the granules. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analysis

Dabigatran etexilate powder: Batch analysis results from 13 commercial size batches of dabigatran etexilate powder for oral solution, including the process validation batches and primary stability batches/clinical batches. Results comply with the proposed specifications and therefore indicate consistent manufacture of this finished product component.

Solvent for oral solution: batch analysis of 25 batches supplied for clinical trials, stability studies and process evaluation were presented. Batches that are representative of the commercial product are also included, including one of the evaluation batches. Results comply with the specifications and therefore indicate consistent manufacture of this finished product component.

Sucralose powder: Batch information was provided for six production scale batches used for stability and/or clinical studies. No batch analysis were presented because it was demonstrated that the packaging of sucralose granules into sachets has no influence on the stability, as no relevant changes were observed for any of the test parameters and the original control strategy justified full release of the excipient along with manufacturing controls performed according to GMPs to ensure the suitability of the filling and packaging process. However, CHMP recommends that the applicant will generate batch release data for future batches as per the specification (REC3). Until new batches of sucralose powder are generated, the presented process validation data and stability data can be viewed in lieu of release data to demonstrate the proposed release test parameters comply with the specifications and therefore are reassuring of consistent manufacture of this finished product component.

Stability of the product

Pradaxa powder for oral solution:

Stability data from three commercial scale batches of this product component stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches were manufactured by the proposed manufacturer and were packed in the primary packaging proposed for marketing.

Samples were analysed for description, water content, assay, degradation products, purity: alkyl methanesulfonates, reconstitution time (oral solution), description (oral solution) and microbiological quality

(annually) and polymorphic purity. The polymorphic form was monitored by Raman spectroscopy for information.

At the long-term condition, only a slight increase in the degradation product is observed. An increase of a specified alkylmethanesulfonate impurity over time was observed at long term and accelerated storage conditions for one of the batches. At the accelerated storage condition, an increase in the degradation products is observed in all three stability batches. However, under both storage conditions all results meet the proposed shelf life specifications.

Stress studies
Stress stability studies were performed assess the influence of light and open storage on the stability of dabigatran etexilate powder. Data were presented for one production scale primary stability batch manufactured at the commercial site, according to the proposed commercial manufacturing process. The following stress conditions were evaluated: photo stability testing according to ICH guideline Q1, open storage stress testing. Parameters investigated were description, water content, assay, degradation products, purity: alkylmethanesulfonates, reconstitution time (oral solution), description (oral solution). During stress stability testing, individual alkylmethanesulfonate impurities, and the sum of all specified alkyl methanesulfonates were determined. For the commercial product, only one alkylmethanesulfonate impurity is specified. All results remained within the specification limits; it is concluded that dabigatran etexilate powder is not sensitive to light but that it is sensitive to open storage at elevated temperature.

In-use stability
Pradaxa powder for oral solution: An in-use stability study was performed on one commercial scale batch at 25°C/60 % RH by opening the outer bag and removing the desiccant. Data up to 4 months were presented. Parameters investigated: description, water content, assay, degradation products, purity: alkylmethanesulfonates, reconstitution time (oral solution), description (oral solution) and microbiological quality (annually) and polymorphic purity (for information). All results comply with the specifications. In addition, CHMP recommends (and the applicant has committed) to perform the in-use stability studies for batches close to the end of shelf-life (REC1).

Based on the results the SmPC 6.3 recommends: "Once the aluminium bag containing the sachets is opened, the medicinal product must be used within 4 months. The sachets should not be opened prior to use.", "The opened sachet cannot be stored and must be used immediately after opening."

Based on the overall stability data the proposed shelf life of 2 years with storage conditions "The aluminium bag containing the sachets with the powder for oral solution should only be opened immediately prior to use of the first sachet in order to protect from moisture" and "After opening of the aluminium bag, the individual sachets should be kept unopened until immediately prior to use in order to protect from moisture", is acceptable.

Reconstituted oral solution: The study was undertaken to investigate the quality of oral solution for an in-use period of up to 48 hours on two commercial scale bathes. The batches of dabigatran etexilate powder for oral solution were previously stored for 12 months at 25°C/60% RH storage conditions. Parameters investigated: description, assay, degradation products, microbiological. All results comply with the specifications.

A freeze/thaw study was performed on reconstituted dabigatran etexilate oral solution. The bottle containing dabigatran etexilate oral solution was stored upright during freezing. After the period of frozen storage, the bottle was allowed to thaw at room temperature for 4 hours until the oral solution was completely thawed. Assay, degradation products, description, and pH were tested before and after storage. Results indicated no negative impact on dabigatran etexilate oral solution occurred upon freezing.

In-use stability study was performed at 25°C/60% RH for 6 hours and at 2-8°C for 48 hours mimicking the practical use of the product. Parameters investigated: description, assay, degradation products, microbiological quality. All results comply with the specifications.

In addition, CHMP recommends (and the applicant has committed) to repeat the practical in-use study using the slightly modified method of preparation (REC2).

The photostability of the oral solution has been assessed during early development. Data confirm that the oral solution is not light sensitive during the in-use period. Protection of the oral solution from light is not required, but an amber glass bottle was selected as a conservative measure.

Based on the results the SmPC 6.3 recommends: "Once reconstituted, the oral solution in the bottle can be stored for 2 hours below 25°C, or for 18 hours at 2-8°C (refrigerator). The bottles must be stored in an upright position.", and the PL "Do not give the oral solution if it has been stored for more than 2 hours at room temperature. Discard the oral solution if it has been stored for more than 2 hours at room temperature." These storage conditions and recommendations for the reconstituted oral solution are justified firstly on the basis of the submitted stability data; and secondly to prevent medication errors during use of the reconstituted oral solution. The proposed in-use storage times as set in the SPC are considered justified.

Solvent for oral solution:

Stability data from three commercial scale batches of this product component stored for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches were manufactured by the proposed manufacturer and were packed in the primary packaging proposed for marketing and simulate the commercial product. Samples were stored upright and horizontally. Horizontal storage orientation shows slightly higher loss in solvent volume over time compared to upright storage at the same storage condition.

Samples were analysed for description, pH, volume of contents, microbiological quality (annually). Some out-of-specification (OOS) findings triggered a thorough, cross product root cause investigation resulting in appropriate corrective actions and preventive measures (CAPAs), which were identified and implemented at the supplier of the glass bottles introducing bottles of improved quality.

Additional stability studies on three batches of solvent filled into the improved quality bottles have been performed and results were presented after 12 months at 25°C/60% RH and 6 months at 40°C/75% RH. No glass particles have been identified, thereby demonstrating the suitability of the CAPA measures and ruling out compatibility problems. For market supply, the improved quality glass bottles will be used.

For upright storage orientation, no relevant change in volume of contents was observed at any storage temperature condition. As expected, horizontal storage orientation shows a slightly higher loss in solvent volume over time compared to upright storage. An OOS result for volume of content for one solvent bottle stored in horizontal orientation was observed after 6 months storage at accelerated storage conditions. The result of the OOS investigation attributed the cause to a manufacturing issue in the bottle closing process rather than a stability issue. An optimised bottle closing process will be implemented for future market supply and a test for loss of mass has been included in the stability protocol for the solvent bottles.

Stress studies

Stress studies were performed on one commercial scale batch to assess the influence of light and temperature on the stability of solvent for oral solution. Samples were irradiated as per ICH Q1B conditions

and subjected to elevated temperature stress testing and were tested for description, pH, volume content. No changes in any of the tested parameters was observed at either condition. Based on the stability data the following shelf-life/ storage conditions are proposed: 24 months/ do not freeze.

A freeze/thaw studies was performed to evaluate the appearance of the solvent and the integrity of the container closure system. The closed bottles were frozen in upright and inverted positions and then thawed at room temperature in the same positions. After storage, the bottles were inspected for cracks, damage, or leaking blue dye solution. No damage or leakage occurred. Hence, the bottle and closure combination remain tight after it has been frozen and thawed at room temperature, either in upright or inverted storage orientation, and with or without the inserted adapter. No change in appearance was observed either.

Based on the overall stability data the proposed shelf life of 24 months without special storage conditions is acceptable.

Sucralose powder:

Stability data from three commercial scale batches of this product component stored for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches were manufactured by the proposed manufacturer and were packed in the primary packaging proposed for marketing with the exception that sachets were printed instead labelled.

Samples were tested for appearance, assay of sucralose, impurities, specific optical rotation, and water content. Microbiological quality and a visual assessment of the packaging material have been performed for information only. Although assay values fluctuate all results comply with the specifications and no special trends are observed at either storage condition.

The results from stability studies support the proposed shelf-life of 36 months without special storage conditions.

Adventitious agents

There are no materials of human or animal origin in any of the three components of the finished product.

Pradaxa Coated granules

Description of the product and pharmaceutical development

The finished product is yellowish coated granules in sachets for oral use. The dabigatran etexilate granules are filled into single dose PET/Alu/LDPE sachets in order to achieve strengths of 20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg of dabigatran etexilate (free base) per sachet. The mesylate salt of dabigatran etexilate is used.

This dosage form, coated granules, was developed for paediatric patients and is intended to be mixed with soft food prior to administration. The dabigatran etexilate granules used to fill the sachets is essentially the same intermediate granules used to fill the authorised hard capsules by corresponding adjustments in fill

weight. Different sachet labels with different colour markings were selected to support differentiation of the dose strengths to ensure correct dosing and to avoid medication errors.

After opening the sachet, the entire content of the sachet is to be mixed with the recommended soft food and ingested together with the food. The composition of the finished product is presented in paragraph 2.2.1 and in section 6.21 of the SmPC.

Development of coated granules for paediatric patients focused on an age appropriate formulation for oral use following PDCO request as oral solution was not considered to be the optimal formulation for all age groups. The aim was to provide a dosage form available over a range of dosage strengths for paediatric patients that are not able to swallow capsules but able to swallow coated granules mixed with soft food.

The selected coated granules formulation is designed as appropriate to meet the quality targets concerning age-appropriateness, i.e., acceptability and ability to meet the desired administration scheme of the dosage form is given from a formulation design and a control strategy perspective

Patient acceptability surveys for coated granules in sachets have been evaluated in clinical studies. Therefore, the administration approach to mix coated granules with soft foods is feasible for patients that can swallow soft food.

In addition to the coated granules for the dosing of children aged 0 to <12 years, two alternative dosage forms are available: the already authorised capsules and a powder for oral solution (see above) was developed to specifically provide an age appropriate formulation for children <12 months.

The coated granules comprise a spherical starter cores upon which the active substance layer is spayed. After ingestion, gastric fluids penetrate the active substance layer and (depending on the pH of the gastric fluids) partly dissolve the active substance layer. The composition facilitates the dissolution of the active substance. As the composition of the coated granules is identical to the composition of the granules in the authorised hard capsules, it is agreed that no further development work on the formulation of the product was necessary, as long as the excipients are demonstrated to be safe for the administration to paediatric patients.

All excipients in the coated granules are commonly used and described in the European Pharmacopoeia. Approved excipient specifications for dabigatran etexilate capsules are referenced in the excipients section for the coated granules drug product. It is stated, that toxicological assessment was performed for each excipient; according to the procedure outlined in Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2.

Compatibilities studies of the product with food were performed with specified food and the provided results support the recommended administration instructions. The studies on food compatibility are representative of all dosing scenarios.

The results from the stability study demonstrate compatibility of dabigatran etexilate coated granules when mixed with either rice cereal (prepared with water), apple sauce, carrot mush, banana mush, or apple juice for 30 minutes at room temperature. The recommended in-use period after mixing with food is 30 min. The results also demonstrated suitable compatibility of dabigatran etexilate coated granules when mixed with either rice cereal (prepared with water), apple sauce, carrot mush, banana mush, or apple juice for up to 30 minutes at room temperature. Due to the increase of the unspecified degradation product for coated granules in contact with milk products (e.g. yoghurt, vanilla pudding, or milk), it is not recommended to use milk products for administration purpose in the Product Information.

It has been shown that chewing the coated granules has no negative impact, as there is no functional release coating on the surface of the coated granules that could be damaged by chewing. During the clinical trials, chewing of the soft food mixed with the coated granules was not contraindicated nor required and no specific instructions on how to swallow the granules were provided. The applicant's conclusion that no further instructions are required is considered justified.

The method proposed for the dissolution is the same as for capsules.

At 15 min the active substance layer was sufficiently dissolved. The dissolution of the coated granules was found to be strength independent. Representative dissolution profiles for all the granules strengths (20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg) were provided and show very similar dissolution profiles.

The manufacturing process applied to manufacture the dabigatran etexilate coated granules for the commercial authorised capsule is used for the paediatric coated granules finished product. No further process development was required. The manufacturing process is a robust and well understood standard packaging process. The filling process of the sachets has been assessed during several evaluation runs. The focus of the process development of sachet filling was set on fill weight and tightness. Dabigatran etexilate is sensitive to moisture, therefore the room temperature and humidity conditions are considered critical and are controlled during the packaging process. The tightness of the sachets is critical in order to keep the low moisture content over the shelf life.

In-process controls ensure that the specifications for the CQA 'drug content' and 'drug content uniformity' are met for each filled sachet. The accuracy of the net fill weight under production conditions has been verified in development runs and during process qualification.

The container closure system consists of an aluminium sachet as primary packaging to protect the dabigatran etexilate coated granules from moisture. Each sachet contains the amount of coated granules that are required for the dose strengths. The sachets are manufactured from three-ply foil composed of an outer polyester (PET) film, an aluminium (Alu) foil layer and an inner low-density polyethylene (LDPE) film. The LDPE film layer is the layer in contact with the dabigatran etixilate coated granules. The aluminium bag and the desiccant pouch are not in direct contact with the finished product. It has been justified by stability data that the sachets alone do not provide sufficient protection against degradation and formation of the known degradation product. However, when stored in a secondary bag with desiccant the product is stable with no storage restrictions and a shelf-life of 36 months can be proposed. The PET film complies with the requirements of the food stuff regulation (EU) 10/2011 (as amended). The Alu foil complies with the requirements of the food stuff regulation EN 602:2004-07 (as amended). The LDPE film fulfils the requirements of the food stuff regulation (EU) 10/2011 (as amended) and of the Ph. Eur. monograph 3.1.3. for polyolefins.

The functional secondary container closure system is an aluminium bag composed of an outer polyester (PET) film, an aluminium foil layer (Alu) and an inner linear low-density polyethylene (LLDPE) film. PET, Alu and LLDPE film layers of the secondary packaging also comply with the above-mentioned EC regulations and Ph. Eur. requirements as applicable. The bag additionally contains a desiccant cylinder to maintain a low moisture content of the coated granules in sachets throughout the storage period. The desiccant cylinder comprises Silica Gel with low density polyethylene (LDPE) as a binder and hydroxypropylmethylcellulose (HPMC) and titanium dioxide as coating. The quantity and the quality of the desiccant in the secondary packaging were considered to be critical for the quality of the finished product. The introduction of the desiccant is performed under controlled conditions. The desiccant cylinder fulfils the requirements of the food stuff regulation (EU) 10/2011 (as amended).

The sachets have been tested on the basis of the desiccant method for packaging systems for oral dosage forms as described in USP <671> Containers – Performance Testing. The sachets have been tested as child resistant according to US 16 CFR§1700.20.

Compatibility between dabigatran etexilate coated granules and the aluminium sachet has been established through stability testing of the finished product under long term and accelerated storage conditions as described in section Stability of the product below.

Manufacture of the product and process controls

The manufacturing process comprises the following main stages and final secondary packaging:

Preparation of spherical starter cores, coating of starter cores, drying and screening of coated pellets and packaging into sachets.

The last stage of the process is the secondary packaging process, during which each sachet is labelled and the correct number of labelled sachets appropriate to the pack size is placed in an aluminium bag for secondary protective packaging together with a desiccant cylinder. The filled aluminium bag is heat-sealed, labelled and placed into a folding carton, together with a package insert.

Each stage consists of a number of steps which were adequately described concerning process parameter settings. Four intermediate products are defined and are controlled by acceptable specifications.

Critical process parameters (CPPs) and critical material attributes (CMAs) were identified. For the dabigatran etexilate coated granules the same in-process controls (IPCs) are in place as described for the intermediate dabigatran etexilate coated granules used for the manufacture of capsules. Holding times for the four intermediates have been established and are justified.

Process validation covers the filling of dabigatran etexilate pellets into sachets and packaging of dabigatran etexilate coated granules in sachets into bulk bags that contain desiccant. For the process validation, an acceptable bracketing design was used. The holding times used for the 4 intermediates were also studied during process validation studies.

The results of the process validation met the pre-defined analytical specifications and demonstrate that the manufacturing process will consistently produce dabigatran etexilate coated granules in sachets at the proposed strengths. Therefore, the primary and bulk packaging process has been successfully validated. The packaging process into the final secondary container has been assessed in 3 packaging runs. In addition, it has been sufficiently justified that bulk packaging and secondary packaging (final packaging) have no influence on the product quality for release.

Overall, the process is considered successfully validated and that it is adequately under control in order to consistently obtain a product that complies with the specifications.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), loss on drying (gravimetry), identification (HPLC-UV), assay (HPLC-UV), degradation products (HPLC-UV), uniformity of dosage units-content uniformity (Ph. Eur.), dissolution (Ph. Eur., UV), purity (GC-MSD) and microbiological quality (Ph. Eur.),

The same specification applied to the coated granules in sachets is used for the coated granules intermediate for the authorised capsules. The specification limit for the controls of alkyl mesilates was adjusted based on the dosing increase for the intended paediatric population and compliance to ICH M7.

The proposed specification is acceptable, and the proposed tests are relevant for this type of product. The specification limits have been set in line with ICH Q3B(R2), Q3C(R7), and Q6A as well as batch results and relevant pharmacopoeial standards. The maximum daily dose for paediatric population is up to 660 mg. The impurities have been qualified in the adult formulation and dosage form of a daily dose of 300 mg/day. However, the results from toxicity studies performed in order to support the adult formulation also support the higher dose regimen of 660 mg/day.

It has been adequately justified that the elemental impurity risk assessment performed for the dabigatran etexilate capsules in line with the ICH Q3D is valid and applicable for the dabigatran etexilate coated granules in sachets too. It is concluded that the potential daily intake of class 1 and class 2A elements as well as the intentionally added class 2B elements is consistently far below the 30% control threshold of the oral PDEs. Thus, no additional controls have to be implemented in the finished product specification.

Risk assessments, in line with the "Questions and answers on Information on nitrosamines for marketing authorisation holders" and the "Information on nitrosamines for marketing authorisation holders" published on the EMA website, have been presented for both the finished product manufacturing process and the active substance with respect to potential formation of nitrosamine impurities. The outcome of the risk assessment confirms that there is no risk for nitrosamine impurities formation and no risk for cross-contamination with other products.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. The same analytical methods as used for the control of the capsules are used for the control of the granules. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch results for the all the product strengths were provided for a total of 49 batches covering all strengths. These batches were used for clinical studies, process validation and stability studies.
The results comply with the specification and therefore indicate consistent manufacture of the finished product.

Stability of the product

The stability studies were carried out on three batches of each tested strength manufactured at the proposed manufacturing site stored packaged in the proposed commercial container closure system (sachets in an aluminium bag with desiccant) under long term conditions (25 °C ± 2 °C / 60 % ± 5 % RH) for 24 months and under accelerated conditions (40 °C ± 2 °C / 75 % ± 5 % RH) for 6 months according to the ICH guidelines. An acceptable bracketing approach between lowest and highest strengths has been applied.

Samples were tested for description, loss on drying, assay, degradation products, dissolution, purity: alkyl methanesulfonates, and microbiological quality. The analytical methods used for testing the stability samples are the same as those used for release testing. An increase in degradation products was observed under both long term and accelerated conditions and assay values fluctuated with no clear trend for some batches or with a decreasing trend in other batches. At both storage conditions, a change over time is observed for the test parameter alkylmethanesulfonate towards lower values. In all cases the reported results complied with the specification under long term and accelerated conditions.

In-use stability study was conducted for 6 months long-term storage at 25°C/60% RH on one batch from the 20 mg, 30 mg and 150 mg strengths. The study was undertaken to investigate the quality of the product (sachets) stored in an opened aluminium bag without desiccant over a subsequent in-use period of 6 months to demonstrate the cumulative effect of long-term storage and patient handling.

During the 6 months in-use testing, a slight increase on loss on drying and in the content of a degradation impurity was observed but the results were still well within acceptance criteria. For all other test parameters, no change was observed. Based on the results of this study the SmPC and PL instructions have been included in SmPC 6.3 and PL section 5 respectively.

Stress stability studies were performed to assess the influence of light, elevated temperature and humidity on the stability of the finished product. Data were presented for two production scale primary stability batches, 20 mg/ sachet and 150 mg/ sachet, manufactured at the commercial site, according to the proposed commercial manufacturing process. The following stress conditions were evaluated: photo stability testing according to ICH guideline Q1, elevated temperature stress testing, and humidity stress testing. Parameters investigated were description, loss on drying, assay, degradation products, dissolution, alkyl methanesulfonates, and microbiological quality. The results indicated that the finished product is not light sensitive and can withstand storage at the elevated temperature studied, when stored in the primary packaging material. The finished product was found sensitive to moisture. After open storage in the humidity stress study, a significant increase in the test parameters loss on drying and degradation products and a significant decrease in assay and dissolution was observed. The description of the coated granules changed to pellets, liquefied. No changes observed for the results for alkylmethanesulfonate impurities.

Stability of the product has also been studied when mixed with different food for 30 min as discussed above in Pharmaceutical development and appropriate recommendations for administration of the dose were introduced in the SmPC (6.3) and PL.

Based on the available data, the proposed shelf life of 3 years and storage conditions: "After first opening of the aluminium bag: Once the aluminium bag containing the sachets with the coated granules and the desiccant is opened, the medicinal product must be used within 6 months.", "After first opening of the sachet: The opened sachet cannot be stored and must be used immediately after opening.", "After preparation: After mixing with soft food or apple juice, the medicinal product has to be administered within 30 minutes.", as per SmPC sections 6.3 and 6.4 can be accepted.

Adventitious agents

None of the excipients is of animal or human origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The present application concerned a line extension for the addition of two new pharmaceutical forms and five new strengths (related to the Coated granules) intended for paediatric patients and one Type II variation introducing the paediatric indication, grouped with a number of type IA and IB variations to update the information regarding the active substance and the currently authorised hard capsules related to, or as a consequence, of the introduction of the two new pharmaceutical forms. The two new pharmaceutical forms are Powder and solvent for oral solution and Coated granules. The Powder and solvent for oral solution is 6.25 mg/mL; the new strengths in relation to the Coated granules are 20 mg, 30 mg, 40 mg and 50 mg 110 mg and 150 mg.

The information on the control and retest period of the active substance has been satisfactorily updated by six Type IB/IA variations. The quality of the active substance used for capsules and coated granules is identical. The active substance quality for intended for the oral solution includes tighter limits for polymorphic purity and the degradation products, necessary to ensure the desired physicochemical and pharmaceutical properties for the reconstituted oral solution.

The information on the control of the authorised hard capsules was updated by four Type IB/IA acceptable variations.

The Pradaxa powder and solvent for oral solution has been developed as a three component product that requires reconstitution before administration. The granules for oral solution come as a separate sachet that needs to be combined with the solvent in the bottle and the sucralose powder sachet in order to prepare the oral solution which requires special storage conditions and dosing via a measuring oral syringe. A major objection was raised relating to the development of three components which need to be combined to produce the final oral solution, because the complexity of reconstitution steps could increase the risk of medication errors occurring. However, stability data justifying the need for this three-component system as opposed to a two-component system with granules and solvent have been provided. The major objection was therefore considered resolved from a quality perspective. See also further discussion below in Clinical aspects.

The excipients are suitable for paediatric patients. Toxicological assessment was performed for each excipient in line with the Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2.

Satisfactory information regarding the development, the manufacturing process, stability and the overall control strategy for all three components of the finished product and the reconstituted oral solution has been provided. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance. Three recommendation are proposed having no impact on the B/R balance.

The Pradaxa Coated granules are essentially the same granules that are filled into the authorized hard capsules. However Hard capsule and Coated granules are administered based on different dosing tables for each pharmaceutical form as per the SmPC, see below in Clinical aspects. The coated granules are intended to be mixed with selected soft foods, for which compatibility has been demonstrated and are specified in the labelling. The excipients are suitable for paediatric patients and were toxicologically assessed in line with the Guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 2.

The presented information for the development, the manufacturing process, stability and the overall control strategy is considered satisfactory. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Pradaxa powder and solvent for oral solution:

1. to perform the in-use stability studies for batches close to the end of shelf-life for Pradaxa Powder for oral solution.

2. to perform a practical in-use study of the reconstituted oral solution according to the final approved Instructions for Use (IFU) prior to market launch. The oral solution will be reconstituted according to the final approved IFU and sample withdrawal for analysis will be done using the bottle adapter and oral syringe provided in the medication kit. Samples will be tested for assay and degradation products initially after preparation of the reconstituted oral solution, after 18 hours storage at 2-8°C and after subsequent warming up for 90 minutes and 120 minutes at room temperature.

3. to generate batch analysis data for future batches Sucralose powder as per the respective specification.

2.3. Non-clinical aspects

2.3.1. Introduction

Two nonclinical juvenile studies have been submitted and assessed previously (EMEA/H/C/000829/P46/046). A summary of the previous assessment is presented below.

2.3.2. Pharmacology

No new data has been submitted.

2.3.3. Pharmacokinetics

No new data has been submitted.

2.3.4. Toxicology

The juvenile rat toxicity studies were already evaluated in procedure EMA/H/C/000829/P46/046. The following conclusions were drawn:

"The juvenile toxicity studies presented by the Applicant were requested by the FDA and included a preliminary dose-range finding study and a pivotal toxicology study in neonate (7 day old) and juvenile (28 day old) Han Wistar rats. Toxicological findings were seen primarily at doses above 70 mg/kg/day and were considered to be related to the pharmacology of dabigatran etexilate, i.e. haemorrhage-related. In the youngest animals, an approximately 5-fold increase in exposure was seen, which by the Applicant was proposed to be related to reduced activity of P-gp and carboxylesterase in neonate rats, in addition to pH-dependent saturation of absorption due to high gastric pH in neonates. These explanations are considered

plausible. According to the Applicant, mortality in the juvenile toxicity study was associated with bleeding events at similar exposures at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in nor any toxicity specific to juvenile animals."

Impurities

The paediatric formulations of capsules and granulate have been capped at 22.2 mg/kg. Therefore, a maximum daily dose of up to 660 mg is proposed. The impurities have been qualified in the adult formulation and dosage form of a daily dose of 300 mg/day. However, the toxicity studies performed in order to support the adult formulation, also support the higher dose regimen of 660 mg/day. Please refer to the tables 8.2: 1 through 5 in the nonclinical summary submitted in sequence 0282. In these tables, the presented exposure to the impurities identified in the nonclinical studies, exceed the possible exposure from the proposed specifications.

For the oral solution formulation of 287.5 mg/day (rounded up to 300 mg /day in the calculations provided by the Applicant), the proposed impurity specifications are also within the limits qualified in the original studies. However, with regards to a specified genotoxic alkylmethanesulfonate impurity, the specifications are based on a maximum daily dose of 300 mg, hence the oral solution formulation is not suitable for infants with high bodyweights resulting in a daily dose above 300 mg/day.

There is an observed alkylmethanesulfonate impurity in the active substance and finished product. According to ICH M7(R1), this is a class 3 impurity (positive in the (Q)SAR system for prediction of mutagenicity, DEREK Nexus, version 6.0.1 and Sarah Nexus, version 3.0.0) with an allowable daily intake of 1.5 µg for a treatment duration for > 10 years or lifetime.

Table 8.2: 6 Proposed acceptance criteria for HMS in dabigatran etexilate mesilate drug substance and dabigatran etexilate drug products

Drug Product	Specified Mutagenic Impurity	ICH M7 classification (allowed daily intake for treatment > 10 years to lifetime)	Acceptance criteria			Maximum daily dose	Maximum daily intake of HMS
			DS*	DP Release**	DP Shelf life**		
Capsules and Coated Granules	HMS	Class 3 (1.5 µg/day)	1.9 ppm	2.2 ppm	2.2 ppm	660 mg	1.5 µg
Powder for Oral Solution				2.6 ppm	5.0 ppm	300 mg***	1.5 µg

* The acceptance criterion for DS of 1.9 ppm is calculated with respect to the salt form. If calculated with respect to the free base the limit is 2.2 ppm and identical to the DP release limit for capsules and coated granules.

** The acceptance criteria for DP are calculated with respect to the free base.

*** The oral solution is dosed in paediatric patients to levels of 287.5 mg/day dabigatran etexilate (conservatively rounded to 300 mg/day).

2.3.5. Ecotoxicity/environmental risk assessment

The Applicant calculated the respective PEC/PNEC ratios of the various compartments, taking into consideration the multiple indications of dabigatran etexilate, i.e. the paediatric indication, which is the subject of the present application and the indications currently approved in adults as follows.

PEC/PNEC ratios for Dabigatran etexilate

Table 156:1 shows the maximum daily doses of Dabigatran etexilate of all approved indications as well as for the new indication, which is subject of the present application.

Table 156:1 Maximum daily doses of Dabigatran etexilate (DE)

Treatment	Maximum daily dose of DE
Prevention of DVT after knee and hip replacement surgery	**220 mg** (2x 110 mg once a day) or 150 mg (2x 75 mg once a day)
Prevention of thromboembolic stroke and systemic embolism (SPAF)	**300 mg** (150 mg twice a day) or 220 mg (110 mg twice a day)
Treatment of acute venous thromboembolism (aVTEt)	**300 mg** (150 mg twice a day) or 220 mg (110 mg twice a day)
Extended treatment after an acute VTE (sVTEp)	**300 mg** (150 mg twice a day) or 220 mg (110 mg twice a day)
Treatment of venous thromboembolic events (VTE) and prevention of recurrent VTE in paediatric patients*	**660 mg** (330 mg twice a day)

* New indication

The Applicant provided updated PEC and PNEC values for the various compartments considering all indications (daily dose representing the sum of the highest recommended daily doses for each indication) and default Fpen (0.01). This resulted in PEC/PNEC ratios lower than trigger values for all compartments, except sediment with a value slightly above 1. For the latter compartment, it is indicated that the PEC/PNEC ratio may actually be lower in view of the experimental conditions used in the OECD 218 study. In addition, this approach is considered as very conservative since the Fpen was not refined, notably for the paediatric VTE indication with the highest daily dose but whose incidence is reported in literature as below the EU orphan definition of 5:10,000. This has likely shifted the PECsed/PNECsed ratio from 0.71 (ratio without paediatric indication) to 1.12 (with paediatric indication) in a non-realistic manner.

Table 156:2 PEC and PNEC values and PEC/PNEC ratios for Dabigatran etexilate

Compartment	PEC	PNEC	PEC/PNEC ratio	Trigger value
Surface water	8.9 µg/L	100 µg/L	0.089	1
Microorganisms	8.9 µg/L	100000 µg/L	0.000089	0.1
Groundwater	2.2 µg/L	120 µg/L	0.018	1
Sediment	1121 µg/kg	≥ 1000 µg/kg	≤ 1,12	1

The assessor calculated a refined PECsw value of 0.165 µg/L for the new paediatric indication considering a Fpen equal to the incidence rate for orphan drugs of 5:10,000 (10-fold higher than the reported incidence rate of paediatric VTE), with a subsequent PECsed value of 20.79 µg/kg. The addition of this additional parameter to those calculated for the already approved indications result in a global PEC/PNEC ratio of 0.73 for the sediment compartment. This confirms that the approval of the new paediatric indication is unlikely to represent an additional risk to the environment.

Table 156:3 Refined PEC and PNEC values and PEC/PNEC ratios for Dabigatran etexilate

Compartment	PEC	PNEC	PEC/PNEC ratio	Trigger value
Surface water	5.6 µg/L	100 µg/L	0.056	1
Microorganisms	5.6 µg/L	100000 µg/L	0.000056	0.1
Groundwater	1.4 µg/L	120 µg/L	0.012	1
Sediment	705 µg/kg	≥ 1000 µg/kg	≤ 0,71	1

2.3.6. Discussion on non-clinical aspects

To support the paediatric extension of PRADAXA to patients from birth to 18 years of age, the applicant has conducted toxicity studies in rats at the request of the FDA. These studies were already evaluated in the context of an Art.46 submission (see EMA/H/C/000829/P46/046), and conclusions drawn at that time are endorsed. It is particularly noted that toxicological findings were seen primarily at doses above 70 mg/kg/day and were considered to be related to the pharmacology of dabigatran etexilate, i.e. haemorrhage- related. Mortality in the juvenile toxicity study was associated with bleeding events at similar exposures at which bleeding was seen in adult animals. In both adult and juvenile rats, mortality is considered to be related to the exaggerated pharmacological activity of dabigatran in association with the exertion of mechanical forces during dosing and handling. Data of the juvenile toxicity study did neither indicate an increased sensitivity in nor any toxicity specific to juvenile animals.

No new impurity was identified in the drug products developed for paediatric use. The applicant has used the same reasoning as that used for qualification of these impurities in the drug substance and drug product already on the market and has adapted the specifications according to the doses recommended for children. Although from a toxicological point of view, the proposed limits for the specified genotoxic alkylmethanesulfonate impurity, for the two different formulation types are acceptable, the practicality of the two separate specifications for powder for solution and capsules and coated granules respectively are questioned. See also the quality assessment report for further discussion, and other concern raised. The daily intake of the ICH M7 class 3 methanesulfonate impurity has to be limited to 1.5 µg/day, therefore the use of the oral solution should be restricted to patients below 1 year of age.

The applicant has provided additional discussion related to the environmental risk assessment. It is concluded that new paediatric indication is unlikely to represent an additional risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

From a nonclinical point of view, the application was considered approvable. Overall, no new pharmacology data have been submitted.

To support the paediatric extension of PRADAXA to patients from birth to 18 years of age, toxicity studies in rats have been conducted. These studies were already evaluated in the context of an Art.46 EMA/H/C/000829/P46/046 which concluded that data of the juvenile toxicity study did neither indicate an increased sensitivity in nor any toxicity specific to juvenile animals. This information has been included in the SmPC section 5.3.

The applicant has provided additional discussion related to the environmental risk assessment. It is concluded that new paediatric indication is unlikely to represent an additional risk to the environment. From a nonclinical perspective, there is no remaining nonclinical issue and the application was considered approvable.

2.4. Clinical aspects

2.4.1. Introduction

The pharmacokinetics of dabigatran etexilate (DE) is well characterised in adults. The Applicant has conducted a clinical development programme in paediatric patients with venous thromboembolic events (VTE) in order to apply for an extension of indication.

The clinical pharmacology study program of dabigatran in paediatric patients is comprised of three phase IIa trials and two phase IIb/III trials. Number of trial subjects with observations, age, and number of dabigatran observations in these trials are presented in Table 1. Matching PK and PD samples were collected from paediatric patients in all five clinical trials. Several population PK/PKPD analyses were conducted to confirm the dosing algorithms and to estimate the PK/PD responses in the paediatric population and compare it to adults. The initial pop PK models were based on the phase II studies whereas the following refined models included the larger dataset from the phase IIb/III studies.

Three different formulations were employed in the dabigatran paediatric clinical development program: capsules, coated granules in sachets (coated granules), and oral liquid solution (OLF). The latter two were developed for the paediatric programme. In addition, a new 50 mg capsule was developed but based on an updated dosing algorithm this capsule strength was abandoned again. Prior to the paediatric studies, the bioavailability of the different formulations was examined in an adult trial population.

The PK of DE in the paediatric population was examined in relation to impaired renal function, body weight, age, sex, and race. Also, effects of extrinsic factors in the form of drug-drug interactions with concomitant pantoprazole (gastric acid reduction) on PK was examined. Further, the effect of dabigatran on the PD endpoints aPTT, dTT, and ECT in paediatric patients was determined and compared to the adult study results.

Table 1: Number of individuals with observations, age, and number of dabigatran observations in the analysis data set

Study	Number of subjects	Age (Y)	Number of PK observations
1160.88	9	12-<18 y	33
1160.80	18	1-<12 y	82

1160.105	8	0-<1 y	16
1160.106	139	0-<18 y	940
1160.108	203	0-<18 y	1377
1160.194	32	20-53 y	1523
All	424		3971

A total of 59 patients in study 1160.106 treated with dabigatran etexilate were also enrolled to study 1160.108. In this analysis they were treated as separate subjects.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

TABULAR LISTING OF CLINICAL TRIALS

Type of trial	Trial identifier	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of sub-jects[1]	Healthy subjects or diagnosis of patients	Duration of treatment	Trial status; type of report
BA	1160.87 [U09-1839] submitted in the eCTD Sequence 0000	Relative BA	Open-label, randomised, uncontrolled, 3-way crossover	3 doses of 150 mg DE, with 1 dose per formulation (capsules, coated granules, oral solution). Oral intake.	30	Healthy male and female adult subjects	Single dose; at least 7 days washout between treatment periods	Complete, full
BA	1160.194[2] [c02248557] submitted as part of the eCTD Sequence 192	Relative BA	Open-label, randomised, uncontrolled, 3-way crossover	5 doses of 150 mg DE (Day 1+2: bid, Day 3: single dose) per formulation (capsules, coated granules, oral solution). Oral intake.	54	Healthy male adult subjects	Multiple dose for 3 days; at least 5 days washout between treatment periods	Complete, full
PK, PD, safety	1160.88 [U12-3378]	PK, PD, tolerability, safety	Open-label, uncontrolled	DE capsules for 3 days bid. Weight-adjusted dose (max. 150 mg). Oral intake.	9	Male and female patients with primary VTE (aged 12 to <18 years)	3 days	Complete, full
PK, PD, safety	1160.89 [c09069268] submitted as part of the eCTD Sequence 230	PK, PD, tolerability, safety	Open-label, uncontrolled	6 DE doses of oral solution (3 days bid) before global amendment 5, thereafter single dose. Age- and weight-adjusted dose, equivalent to 150 mg DE. Oral intake.	18	Male and female patients with VTE (aged 1 to <12 years)	3 days before global amendment 5, thereafter single dose on 1 day	Complete, full
PK, PD, safety	1160.105 [c09085437] submitted as part of the eCTD Sequence 229	Appropriate-ness of dosing algorithm, safety, tolerability	Open-label, uncontrolled	Single dose of DE oral solution. Age- and weight-adjusted dose, equivalent to 150 mg DE. Oral intake.	8	Male and female patients with VTE (aged <1 year)	Single dose	Complete, full

Type of trial	Trial identifier	Objective(s) of the trial	Trial design and type of control	Test product(s); dosage regimen; route of administration	Number of sub-jects[1]	Healthy subjects or diagnosis of patients	Duration of treatment	Trial status; type of report
PK, PD, efficacy, safety	1160.106 [c29773859]	Appropriate-ness of dosing algorithm, efficacy, safety	Active-controlled, open-label, randomised, parallel-group, non-inferiority	-Age- and weight-adjusted DE for 3 months bid (capsules, coated granules, oral solution). Oral intake. -SoC: LMWH or fonda-parinux (subcutaneously) or VKA (oral)	267	Male and female patients with acute VTE (birth to <18 years)	Up to 3 months	Complete, full
PK, PD, safety	1160.108 [c29754273]	Safety	Open-label, uncontrolled	Age- and weight-adjusted DE for up to 12 months bid (capsules, coated granules, oral solution). Oral intake.	214	Male and female patients with need of secondary prevention of VTE (birth to <18 years)	Up to 12 months	Complete, full

BA = bioavailability; bid = twice daily; DE = dabigatran etexilate; eCTD = electronic common technical document; LMWH = low molecular weight heparin; max. = at maximum; PK = pharmacokinetics; PD = pharmacodynamics; SoC = standard of care; VKA = vitamin K antagonist; VTE = venous thromboembolism

[1] Entered/randomised
[2] This trial is not part of the EU paediatric investigational plan.

2.4.2. Pharmacokinetics

Methods

Analysis of dabigatran

Specific and highly sensitive HPLC-MS/MS (high performance liquid chromatography coupled to tandem mass spectrometry) methods for the quantitation of dabigatran were developed and validated for the human biological matrices plasma and urine to support the clinical dabigatran etexilate development program. Methods were applied for the quantitation of non-conjugated dabigatran and of total dabigatran. Total dabigatran represents the sum of non-conjugated drug plus glucuronic acid conjugated dabigatran. As it was shown that the glucuronic acid conjugates of dabigatran do have similar pharmacodynamic activity as the active moiety dabigatran itself, total dabigatran was considered the primary "bio-relevant" pharmacokinetic measure.

During the development program, two distinct bioanalytical LC-MS/MS methods were used to measure total dabigatran, non-conjugated dabigatran, dabigatran etexilate and intermediate semi-prodrugs in human plasma. According to the applicant, the second bioanalytical methods used for quantification of total plasma dabigatran (method n00239283) and for quantification of non-conjugated dabigatran, dabigatran etexilate, and intermediate semi-prodrugs (n00238725), respectively, were adequately validated. However, the full validation reports for these bioanalytical methods (n00239283 and n00238725) were not provided.

PK parameters

The PK properties of dabigatran were examined using both non-compartmental PK parameters (clinical studies) and a two-compartment disposition model (pop PK analyses) of standard PK endpoints (plasma conc. of total dabigatran, AUC, Cmax, Ctrough, Tmax, Cl/F, Vd/F, T½).

Population PK and PKPD analyses

Several pop PK/PKPD models were constructed during the program. These models were used to confirm the dosing algorithms, to evaluate the effects of selected covariates, to estimate the PK/PD responses in the paediatric population and compare it to adults. In the PK models, all disposition parameters were a priori allometrically scaled by body weight. The data set used in the pop PK analysis is seen in Table 1 above. In

the final pop PKPD analysis, model predictions of dabigatran concentration-response for the aPTT, ECT and dTT clotting time in healthy adult subjects were used as a reference, for comparison with the paediatric data.

The PK of dabigatran is best described by a 2-compartment model with first order absorption.

The disposition parameters increased with rising body weight in accordance with allometric scaling.

The population PK model parameter estimates of the final model for dabigatran are presented in

Table 7.

Table 7. Parameter estimates of the final model for dabigatran

Table 7: Parameter estimates of the final model for dabigatran.

		Final model for dabigatran		
	Unit	Value	RSE (%)	SHR (%)
CL/F	L/h	110	2.70	
V_c/F	L	1090	5.11	
Q/F	L/h	47.8	7.93	
V_p/F	L	496	10.8	
$k_{a\,capsules}$	h^{-1}	0.939	15.3	
$k_{a\,oral\ solution}$	h^{-1}	1.84	14.8	
$k_{a\,coated\ granules\ in\ sachets}$	h^{-1}	1.56	18.9	
$FR_{paediatric\ capsules}$		1.00		
$FR_{paediatric\ oral\ solution}$		0.686	7.44	
$FR_{paediatric\ coated\ granules\ in\ sachets}$		0.619	7.52	
$FR_{adult\ capsules}$		1.00		
$FR_{adult\ oral\ solution}$		1.16	11.3	
$FR_{adult\ coated\ granules\ in\ sachets}$		1.25	15.3	
$T_{lag\,capsules}$	h	0.431	1.96	
$T_{lag\,oral\ solution}$	h	0.300	3.48	
$T_{lag\,coated\ granules\ in\ sachets}$	h	0.408	1.30	
HILLCL		2.12	22.2	
PMACL50	weeks	45.5	8.00	
WT on CL/F		0.750		
WT on Q/F		0.750		
WT on V_c/F		1.00		
WT on V_p/F		1.00		
Factor of V_c/F for adults		0.555	16.9	
eGFR on CL/F		0.223	10.3	
SEX on CL/F		-0.104	23.2	
Prop. $RUV_{capsules}$		0.0878	29.1	
Prop. $RUV_{oral\ solution\ \&\ coated\ granules\ in\ sachets}$		0.0193	33.7	
Prop. $RUV_{capsules\ in\ study\ 106\ \&\ 108}$		0.280	2.88	
Prop. $RUV_{oral\ solution\ \&\ coated\ granules\ in\ sachets\ in\ study\ 106\ \&\ 108}$		0.309	5.73	
Add. RUV	ug/L	6.47	4.64	
IIV CL	(CV)	0		
IIV V_c	(CV)	0.276	12.8	43.8
IIV Q	(CV)	0		
IIV V_p	(CV)	0		
IIV $k_{a\,capsules}$	(CV)	0.818	13.7	58.1
IIV $k_{a\,oral\ solution}$	(CV)	0.560	16.4	64.3
IIV $k_{a\,coated\ granules\ in\ sachets}$	(CV)	0.605	23.8	69.2
IIV $FR_{capsules}$	(CV)	0.302	6.03	23.3
IIV $FR_{oral\ solution}$	(CV)	0.285	15.2	59.3
IIV $FR_{coated\ granules\ in\ sachets}$	(CV)	0.433	9.82	62.5
IIV $FR_{adult\ coated\ granules\ in\ sachets}$	(CV)	0.319	16.8	71.5
IIV Prop. RUV	(CV)	1.15	27.7	73.8
IIV Prop. RUV in study 106 & 108	(CV)	0.306	8.47	31.2
IIV Add. RUV	(CV)	0.206	21.8	66.9
RUV		1.00		3.63

The RSE for IIV and RUV parameters are reported on the approximate SD scale. Disposition parameters are expressed for a male paediatric patient with reference body weight of 70 kg, eGFR of 100 mL/min/1.73m^2 and fully age matured CL. CL/F: apparent clearance; V_c/F: apparent central volume of distribution; Q/F: apparent inter-compartmental clearance; V_p/F: apparent peripheral volume of distribution; k_a: first-order absorption rate constant; FR: apparent relative bioavailability; T_{lag}: lag time; HILLCL: maturation parameters Hill factor; PMACL50: postmenstrual age achieving 50% maturation of clearance; WT on CL/F, WT on V_c/F, WT on Q/F, & WT on V_p/F are the allometric scaling parameters; eGFR on CL/F: exponent for eGFR-CL relationship; SEX on CL/F: factor for CL/F in females relative to males; OFV: objective function value; RSE: relative standard error; RUV: residual unexplained variability; SD: standard deviation; SHR: shrinkage; CV: coefficient of variation. Parameters without any associated RSE were fixed. Values were rounded to 3 significant digits.

The models are adequately described and validated. A VPC for the final population PK model is shown in **Figure 25**.

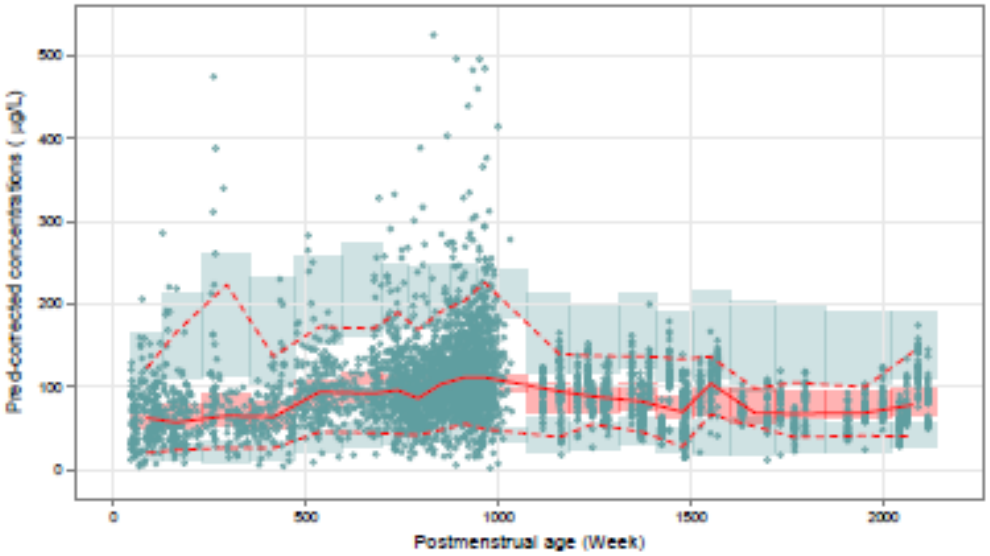


Figure 25: Prediction corrected visual predictive check for the final population PK model of dabigatran concentrations versus patient's time-varying postmenstrual age. The solid and dashed red lines represent the median, 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th and 95th percentiles predicted by the model. The observed data are indicated by open circles.

Dosing regimen

The initial dosing algorithms were developed on the basis of an allometric relationship. This allometric method calculates glomerular filtration rate (GFR) in children as a function of age and body weight, and enables the calculation of paediatric doses by scaling down dosage from an adult reference patient. The intended paediatric exposure was the same as in the adult studies with a dabigatran reference trough exposure range of 26-250 ng/mL. Dose could be adjusted guided by dabigatran concentrations. Doses in the clinical studies ranged between 12.5 mg and 330 mg of DE twice daily.

Absorption and Distribution

Following an oral administration of DE to paediatric VTE patients, dabigatran etexilate was rapidly absorbed with peak plasma concentrations of dabigatran reached approximately within 2.5 hours of administration. This was followed by a rapid distribution phase and a terminal phase, with the typical elimination half-life in paediatric patients of approximately 10–16 hours.

In pop PK analyses, the apparent volume of distribution was predicted to increase with age from 277 L in a 6 months old child to 1598 L in an 18-year-old.

Bioavailability

In adults, the absolute bioavailability of dabigatran following oral administration of DE capsules is about 6.5%.

Observed and projected steady state trough concentrations of DE stratified by age and mode of administration are depicted below in Table 3.2:4. For comparison, data from the adult study RE-COVER (1160.53) are shown as well.

Comparison of exposures across studies

The trough exposures of paediatric by studies, age group, and formulation are shown in Table 3.2: 4.

Table 3.2: 4 Comparisons of projected steady-state (1160.89 and 1160.105) and observed steady-state trough (1160.106, 1160.108, and RE-COVER) plasma total dabigatran concentrations by age groups or formulations across studies

	0 to <1y[1] 1160.105	1 to <2y[2] 1160.89	2 to <12y[2] 1160.89	0 to 6m 1160.106 1160.108 pooled[3]	6m to 2 y 1160.106 1160.108 pooled[3]	0 to 2 y 1160.106 1160.108 pooled[3]	2 to 12 1160.106 1160.108 pooled [3]
N	8	6	9	9	19	28	66
gMean [ng/mL]	74.5 -107	53.1-87.6	40.8-67.3	52.9	54.4	53.9	63.0
gCV%	--	--	--	49.1	65.0	59.0	52.7
Median	--	--	--	51.8	62.6	59.5	65.8
Q1	--	--	--	41.3	43.5	42.4	55.2
Q3	--	--	--	60.8	78.6	78.5	83.5
P10	--	--	--	22.7	19.8	22.7	35.2
P90	--	--	--	108	110	108	109

Source: [1]Table 13:2 of 1160.105 [c09085437], [2]Table 13:1of 1160.89 [c09069268]. [3] Table 6.1.2: 3-4 [c31614469] ; [4]Visit 4 data in RE-COVER [U09-1400, Table 15.6.1.1:1].

	12 to <18 y[3] 1160.106/ 1160. 108 pooled	Oral Solution 1160.106/ 108 pooled[3]	Coated Granules 1160.106 /1160.108 pooled [3]	Capsules 1160.106/ 1160.108 pooled[3]	1160.106/ 1160.108 pooled (ALL)[3]	Adults RE-COVER 1160.53[4]
N	184	12	63	203	278	850
gMean [ng/mL]	99.1	54.7	54.7	97.9	83.7	59.7
gCV%	35.3	44.1	58.6	34.5	49.9	81.6
Median	98.9	55.7	60.0	98.1	88.0	58.7
Q1	78.2	42.4	49.1	77.9	65.2	38.6
Q3	127	72.0	76.0	125	115	94.5
P10	63.7	40.5	25.9	63.7	51.2	26.3
P90	152	92.1	88.3	151	145	146

Source: [1]Table 13:2 of 1160.105 [c09085437], [2]Table 13:1of 1160.89 [c09069268]. [3] Table 6.1.2: 3-4 [c31614469] ; [4]Visit 4 data in RE-COVER [U09-1400, Table 15.6.1.1:1].

The observed steady-state trough exposure in the paediatric phase IIb/III trials (pooled PK analysis of 1160.106 and 1160.108, Table 3.2:4 or Table 3.2: 5) was largely between the 10th and 90th percentile of the observed dabigatran plasma exposure of the adult VTE program [RE-COVER].

Bioequivalence

Two adult phase I bioavailability studies (a single dose and a multiple dose study) with the new developed formulations were conducted. In the adults receiving oral solution and the coated granules in sachets, the apparent relative bioavailability of dabigatran was 1.17 and 1.26 times that for capsules, respectively. In contrast, in children receiving the oral solution and the coated granules in sachets, the apparent relative bioavailability of dabigatran was 0.705 and 0.649 times that for capsules, respectively.

Influence of food

In the adult development programme, it was shown that food does not affect the bioavailability of DE but delays the time to peak plasma concentrations by about 2 h. Influence of food was not evaluated in the paediatric population but the same effects as in adults are expected.

Elimination

The apparent clearance increases with age. The pop PK analysis demonstrated that clearance increases steadily from 18-20 L/h in 6 months old children to 96-108 L/h in 18 years old adolescents. The typical elimination half-life in paediatric patients was approximately 10–16 hours in all age groups. Dabigatran is eliminated primarily (approx. 85%) in the unchanged form by renal excretion. Only minor metabolism takes place; dabigatran is subject to conjugation forming pharmacologically active acylglucuronides (1-O, 2-O, 3-O, and 4-O-acylglucuronide), each account for less than 10 % of total dabigatran in plasma.

Dose proportionality and time dependencies

As clearance is independent of dose in the final population PK model, dabigatran is expected to exhibit linear pharmacokinetics with dose-proportional increases in maximum plasma concentrations and area under the plasma concentration-time curves after single or multiple oral administrations in paediatric VTE patients. Multiple administrations of oral doses of dabigatran etexilate in paediatric patients resulted in an accumulation of dabigatran that is approximately 1.5- to 1.9- fold in the plasma and steady state was reached after approximately 2-3 days of dosing.

Intra- and interindividual variability

The intersubject variability (gCV%) based on trough concentrations was approximately 50% across all patients (0-<18 years old) in the pooled phase IIb/III paediatric studies, which is smaller than the 82% variability observed for adult VTE patients given fixed dose of 150 mg BID.

Special populations

The PK of dabigatran has been investigated in paediatric populations with different age, weight, race, gender, and renal function. The PK of dabigatran is affected by age, weight, and renal function. Accordingly, the dosing algorithm of DE has to take these factors into account. No dose adjustment seems warranted with eGFR >=50 mL/min/1.73m^2. Patients with impaired renal function below 50 mL/min/1.73 m^2 was excluded from the paediatric studies. The PK of dabigatran in patients with impaired hepatic function has not been

investigated. Based on the final population model, disposition parameters increased with increasing body weight in accordance with allometric scaling. The apparent clearance increased with increasing age (independent of body weight); with half the maturation is reached at 52 weeks and 90% at around 125 weeks postmenstrual age (corresponding to a postnatal age of 3 and 21 months, respectively). Clearance was on average 11% lower in females than in males, irrespective of the dabigatran formulation given. No dose adjustment is needed for sex. Based on the final population PK model, race or ethnic origin did not have any statistically significant influence on the PK parameters; however, the proportions of paediatric patients with these characteristics were low (Black n = 8; Asian n = 21).

Pharmacokinetic interaction studies

Dabigatran etexilate is poorly soluble in aqueous media at neutral pH, and its solubility is best at low gastric pH. It was, therefore, expected that effective elevation of gastric pH by proton pump inhibitors (PPIs) would affect the bioavailability of dabigatran etexilate. In adult studies, systemic exposure of dabigatran was reduced by approximately 30% when dabigatran etexilate was co-administered with the PPI pantoprazole. The paediatric pop PK analysis of the phase IIb/III data suggested that PPIs had no effect on exposure of dabigatran. No dedicated drug-drug interaction studies have been conducted in the paediatric program.

Dabigatran etexilate is a substrate for intestinal P-glycoprotein (P-gp); when given together with a P-gp inhibitor, exposure to dabigatran is expected to increase. *In vitro* studies on human intestinal tissues indicate that the P-gp transporter function may be fully developed from birth. The data on interactions between P-gp and dabigatran for adults may thus be applicable to the paediatric patients. No dedicated P-gp inhibitor studies with dabigatran have been conducted in children.

2.4.3. Pharmacodynamics

Dabigatran etexilate is a well-known drug from the many years of adult use. Dabigatran is a potent, non-peptide, competitive, oral direct thrombin inhibitor (DTI) that specifically and reversibly inhibits thrombin, the penultimate enzyme in the coagulation cascade. The pharmacodynamic endpoints in the clinical studies were the usual blood coagulation parameters - activated thromboplastin time (aPTT), ecarin clotting time (ECT), and diluted thrombin time (dTT).

Relationship between plasma concentration and effect

The PD evaluation showed that the parameters dTT and ECT increased in direct linear proportion to the plasma concentration of dabigatran, whereas aPTT prolongation was not linearly related, but best described by an Emax model.

A comparison of the resulting PKPD curves with the final aPTT model in typical paediatric and adult healthy subjects are shown in Figure 23. The PKPD relationships are similar between the children and the healthy adults. Much of the difference appears to be related to the difference in baseline. Generally, when correcting for baseline differences, the younger children achieve a somewhat higher response to dabigatran whereas the adolescents above 15 years achieve a slightly lower response than what was seen in healthy adults.

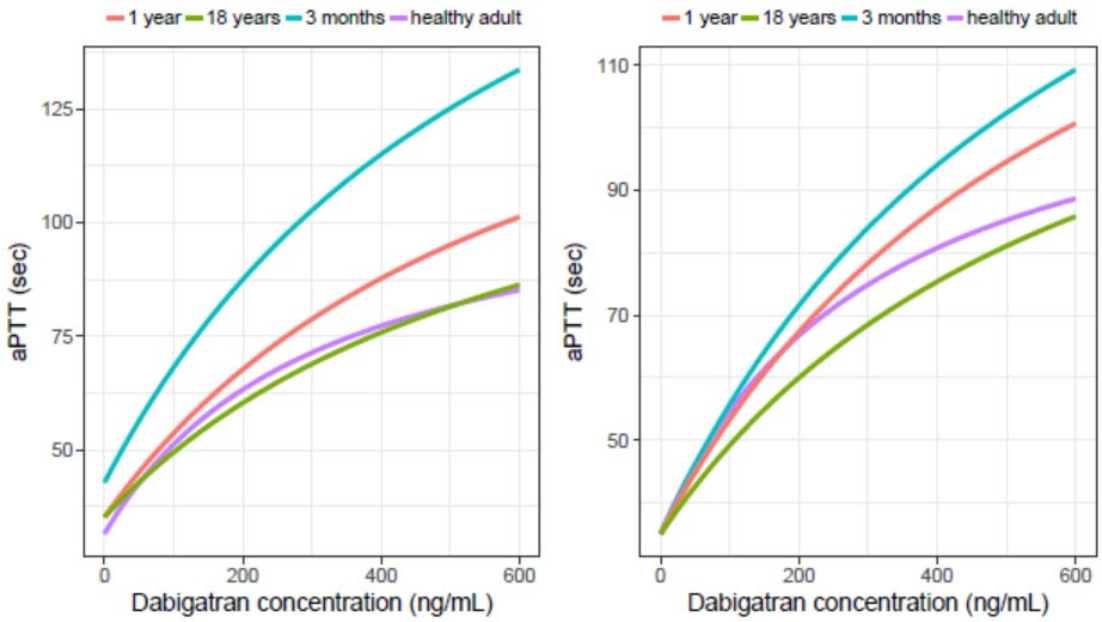


Figure 23: Typical population model predictions for the final aPTT model by age group. The left plot includes the observed baseline differences. In the right plot a baseline of 35 seconds was assumed for all groups.

A comparison of the resulting PKPD curves with the final dTT model in typical paediatric and adult healthy subjects are shown in Figure 29. The PKPD relationships are similar between the children and the healthy adults. The observed baseline was similar in the healthy adult and the pediatric populations with no identified age-related differences between the children.

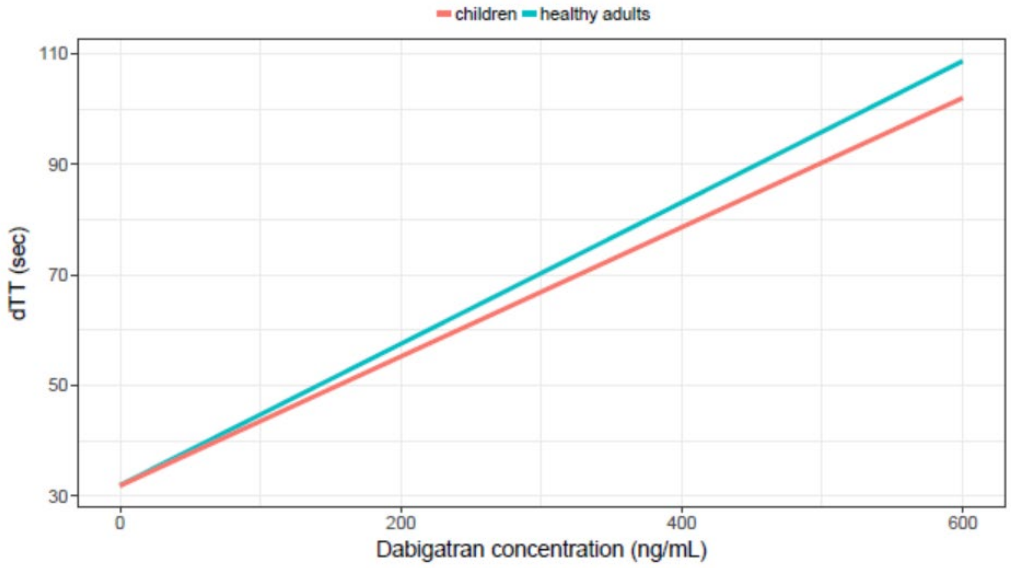


Figure 29: Typical population model predictions for the final dTT model by age group. Baseline was similar for the adults and children (31.9 in adults and 31.8 in children).

A comparison of the resulting PKPD curves with the final ECT model in typical paediatric and adult healthy subjects are shown in Figure 35. The PKPD relationships are similar between the children and the healthy

adults. Much of the difference appear to be related to the difference in baseline. Generally, when correcting for baseline differences, the very youngest children achieve a slightly higher response to dabigatran whereas children above 1 year of age appear to achieve a lower response, gradually decreasing with age, than what was seen in a typical healthy adult.

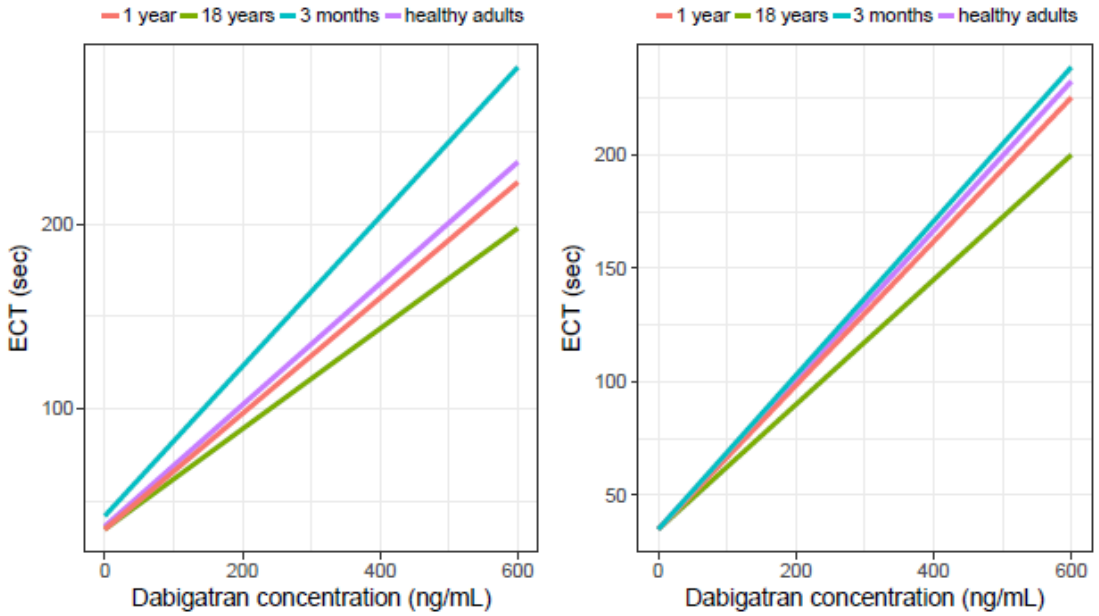


Figure 35: Typical population model predictions for the final ECT model by age group. The left plot includes the observed baseline differences. In the right plot a baseline of 35 seconds was assumed for all groups.

When assessing the relative change of aPTT, ECT, and dTT from baseline, the exposure-response relationship was similar between the youngest children and the healthy adults. However, among the very young children below 3 months, a somewhat higher response than seen in the healthy adults was still present after correcting for baseline differences.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of DE in the paediatric development programme has been studied in children aged 0 to <18 years. The analytical methods used during the programme are described in details.

Five clinical paediatric studies (three phase IIa trials and two phase IIb/III trials) have been conducted, all being part of the paediatric program for DE in compliance with the EU PIP. Several pop PK/PKPD models were part of the development program. The first models were constructed based on phase II data and the later models were built upon these initial models and included new data from the phase IIb/III studies. The models were used to confirm the dosing algorithms and to estimate the PK/PD responses in the paediatric population and compare it to adults. In the PK models, all disposition parameters were a priori allometrically scaled by body weight. The models are considered valid and suitable for the intended purposes. Prior to the clinical studies, two studies in adults investigating the bioavailability of two new formulations compared to capsules were undertaken. PK data from 450 individual children and adolescent subjects have been analysed. Matching PK and PD samples were collected from paediatric patients in all five clinical trials. The dosing

regimen in the clinical studies was based on the children`s age and weight according to a predefined algorithm. The intended paediatric exposure was the same as in the adult studies with a dabigatran reference trough exposure range of 26-250 ng/mL. In the clinical trial, dabigatran concentrations were monitored and one dose adjustment allowed. More than one third had a dose adjustment. The PK of DE in the paediatric population was examined in patients with different renal function, body weight, age, sex, and race. Also, the effect of concomitant pantoprazole (gastric acid reduction) on PK was examined. The PK of dabigatran in the therapeutic dose range is expected to be linear in paediatric subjects.

In the adult bioavailability studies, the bioavailability of capsules was lower than for both oral solution and coated granules in sachets. Thus, the different formulations are not bioequivalent. The relative bioavailability of the formulations was used to qualify the dosing regimen in the paediatric studies. However, in the clinical paediatric studies the apparent relative bioavailability paradoxically turned out to be lower for oral solution and coated granules than for capsules. The applicant was not able to explain this opposite bioavailability in children and adults. It was agreed that the dosing algorithm is taking the lower bioavailability into account.

The youngest patients in studies 1160.106/1160.108 aged 0 to < 1 year (n=8 on oral solution) had the same trough exposure as the patients administered coated granules as well as the adults.

For the typical paediatric VTE patient the half-life of DE is estimated to be relatively equal in paediatric subjects from 6 months to 18 years of age.

The PK of dabigatran is affected by age, weight, and renal function. This is reflected adequately in section 4.2 of the proposed SmPC. In adults, DE may be used with reduced doses in patients with eGFR > 30 mL/min. In contrast, renal GFR should be > 50 mL/min in paediatric patients.

Gender or race do not seem to affect the PK of DE. According to normal procedure, no clinical drug-drug interaction studies have been conducted in the paediatric development programme. In the clinical studies, the use of pantoprazole was allowed. The PK of dabigatran in patients with impaired hepatic function has not been investigated; this is acceptable since 85% of dabigatran is excreted unchanged in the urine. According to the adult product information, dabigatran is subject to conjugation forming pharmacologically active acylglucuronides (1-O, 2-O, 3-O, and 4-O-acylglucuronide), with each accounting for less than 10 % of total dabigatran in plasma. The same metabolism is expected to occur in the paediatric population.

The pharmacodynamic endpoints examined in the paediatric patients comprised aPTT, dTT, and ECT, and these results have been compared to the effects in the adult population.

Doses in the clinical studies ranged between 12.5 mg and 330 mg of DE twice daily dosing. The dosing was based on weight and age in order to reach comparable exposure to that in adults.

The clinical studies demonstrated a linear relationship between the plasma concentration of dabigatran and the PD endpoints ECT and dTT. For aPTT, a non-linear relationship was considered most appropriate.

The PKPD relationships were examined in several pop PK and pop PKPD analyses. The PKPD relationships for dTT were similar between healthy adults and children of all age groups. For aPTT, the analysis showed higher values the younger the child. For ECT, the same tendency of higher values in the youngest children was found. For both aPTT and ECT, the differences could be explained by differences in baseline values since the exposure-response relationship was similar between the young children and the healthy adults when assessing the relative change of aPTT, ECT, and dTT from baseline. However, in the youngest patients below 2-3 months of age, a higher PD response than seen in the healthy adults was still present after correcting for

baseline differences. The PKPD relationships for dTT seem similar between healthy adults and children of all age groups supporting the dosing strategy to achieve comparable exposure across age groups.

Overall, the trials in children and adolescents have shown that DE, except in the smallest children from 3 months to 1 year, has a comparable PKPD relationship to that in adults. The PKPD analyses have demonstrated that the measured clotting parameters (aPTT, dTT, and ECT) generally respond in a similar way to dabigatran exposure in children and adults. The proposed dosing recommendations of the three formulations in children and the rationale and relevance of the proposed target range of 26- <250 ng/mL have been sufficiently justified.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology program conducted was comprehensive and adequate in terms of number of enrolled subjects and type of studies performed. There were no remaining concerns regarding PK/PD and the proposed dosing algorithms for different age groups and formulations was considered acceptable.

2.5. Clinical efficacy

Table 1 shows the trials included in this grouped extension application for DE in paediatrics.

Table 1 Overview of clinical trials included in the grouped extension application

Trial no.	Objectives	Formulation of dabigatran etexilate	Age group
Phase I			
1160.87 [U09-1839]	Bioavailablity	Oral solution, granules, and capsules	Adults
1160.194 [c02248557][1]	Bioavailablity	Oral solution, granules, and capsules	Adults
Phase IIa			
1160.88 [U12-3378]	PK, PD, safety, tolerability	Capsules	12 to <18 years
1160.89 [c09069268]	PK, PD, safety, tolerability	Oral solution	1 to <12 years
1160.105 [c09085437]	PK, PD, safety, tolerability	Oral solution	0 to <1 year
Phase IIb/III			
1160.106, interim [c26571231]	PK, PD, efficacy, safety, tolerability	Oral solution, granules, and capsules	0 to <18 years
Phase III			
1160.108, interim [c26496086]	PK, PD, safety, tolerability	Oral solution, granules, and capsules	0 to <18 years

[1] This trial is not part of the PIP.

2.5.1. Dose response studies and main studies

In accordance with the PIP, this grouped extension application is based on data of several Phase I to Phase III trials (Table 1). All trials were performed in compliance with GCP and in accordance with applicable regulatory requirements and BI standard operating procedures.

Of these, five trials (1160.87, 1160.194, 1160.88, 1160.89, and 1160.105) have investigated the bioavailability, PK, PD safety and tolerability.

No formal dose phase II studies have been performed to identify the accurate dose regimen for each paediatric age categories. Dosing appropriateness and efficacy and safety were evaluated in parallel as per trial design (Phase IIb/III).

As highlighted above, dosing rational is based on a PK/PD exploration targeting plasma dabigatran concentrations estimated for adults receiving approved doses for dabigatran.

The two large Phase IIb/III trials (1160.106 and 1160.108) were still ongoing at the initial submission based on interim analysis results for this grouped extension application. These trials have both been completed in the meantime. An updated dossier with the final CTRs for both trials has been provided. Within the paediatric programme of DE, only trial 1160.106 was designed to evaluate the efficacy of DE versus a comparator while the remaining trials were single arm trials with DE.

The interim CTRs covered all key binding elements as per PIP. Trial 1160.106 is an open-label, randomised, active-controlled non-inferiority trial comparing DE with standard of care (low molecular weight heparin [LMWH], vitamin K antagonist [VKA], or fondaparinux). It has a planned treatment duration of 3 months after initial parenteral therapy (at least 5 days and at most 21 days). While not clear in the initial submission, it has been clarified in the present submission that the course of the initial parental therapy is not included in the treatment period of 3 months with the randomised treatment of DE vs. SoC in study 1160.106. The Phase III trial 1160.108 with DE as single treatment arm is considered a safety trial and has a considerably longer planned treatment duration than trial 1160.106, i.e. up to a maximum of 12 months. The trial aims to provide critical information regarding the safety of DE for secondary prevention of VTE. Patients from trial 1160.106 who were in continued need for anticoagulation could also participate in trial 1160.108.

Recruitment in trials 1160.106 and 1160.108 continued until April 2019 for 1160.108 and July 2019 for 1160.106 in order to comply with the FDA post marketing requirements and as part of the written request that has been issued by the FDA. The resulting final CTRs with the complete data set for trials 1160.106 and 1160.108 have been provided and assessed within current procedure.

2.5.2. Main studies

Within the paediatric programme of DE, only trial 1160.106 was designed to evaluate the efficacy of DE versus a comparator while the remaining trials were single arm trials with DE. Therefore, the clinical efficacy assessment is based on this trial only.

However, reference is also made to Trial 1160.108 with DE as single treatment arm, which is considered a safety trial with a longer planned treatment duration than trial 1160.106, i.e. up to a maximum of 12 months. This trial aims to provide critical information regarding the safety of DE for secondary prevention of VTE.

Of note, patients from trial 1160.106 who were in continued need for anticoagulation could also roll over to participate in trial 1160.108. At the time of the interim analysis, 88 patients had rolled over. In the final analysis overall, 91 patients (34.1% of the randomised patients in trial 1160.106) rolled over into trial 1160.108. In addition, 122 patients were newly recruited and treated in trial 1160.108.

The initial evaluation of efficacy was based on interim data of trial 1160.106. The interim database snapshot was created on 28 Mar 2019, when the required number of paediatric patients, as agreed in the PIP, had been reached:

- At least 140 patients evaluable for the primary efficacy endpoint in 1160.106, including at least 60 patients in age stratum 1 (patients from 12 years to <18 years), and at least 18 patients in age stratum 2 (patients from 2 years to <12 years)
- At least 100 treated patients in 1160.108
- At least 10 patients in age stratum 3 (patients from birth to <2 years) from both trials 1160.106 and 1160.108 together (counting roll-over patients from 1160.106 to 1160.108 only once)

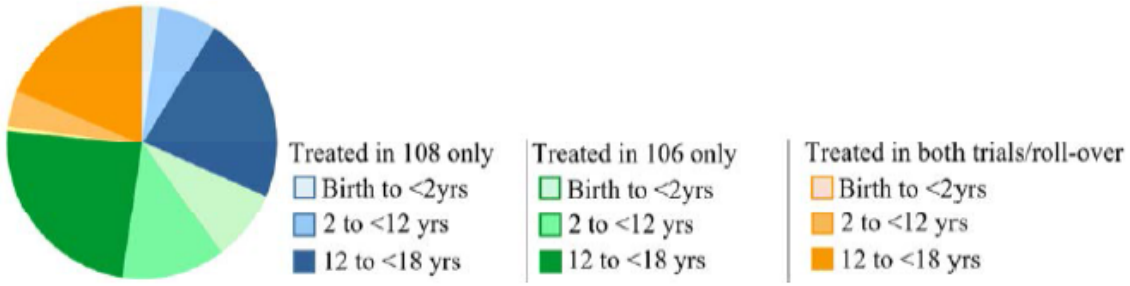
All patients who had either completed trial 1160.106, had an early End of Treatment (eEOT) visit, or were still ongoing and had reached at least the time point of Visit 3 by 28 Feb 2019 (cut-off date for the interim analysis) were included in the interim analysis. For these patients, data from all visits that took place on or before 28 Feb 2019 were considered (see exception below for adjudicated data). Between the cut-off date for the interim analysis and the interim database snapshot date, data were cleaned and source data verified as complete as possible. Investigators were able to enter new data during this time (i.e. new visits occurring after 28 Feb 2019) or change existing data (i.e. based on the ongoing cleaning process). However, data from visits occurring after 28 Feb 2019 were disregarded for analysis. All outcome events were to be adjudicated and included, if possible. For a number of outcome events reported before the cut-off date for interim analysis, adjudication was not completed in time for the interim database snapshot, because source data or replies to clarification questions had reached the adjudication committee too late to provide a result on time. The primary efficacy analyses were performed on evaluable patients who had completed treatment or discontinued treatment prematurely and had the full set of adjudicated data available.

The final analysis has now been provided with the following full data sets:

Table 10.1: 3 Number of patients in trials 1160.106 and 1160.108 by age group – RS, TS

	DE			SoC		
Age stratum	Birth to <2 years	2 to <12 years	12 to <18 years	Birth to <2 years	2 to <12 years	12 to <18 years
Randomised in 1160.106	22	43	112	13	21	56
Treated in 1160.106	22	43	111	13	21	56
Treated in 1160.106 only	21	31	63	12	17	31
Treated in both trials (roll-over)	1	12	48	1	4	25
Treated in 1160.108 only	8	27	87	--	--	--
Total of treated patients	30	70	198	13	21	56

Source data: Tables 15.1.1: 1 and 3



Source data: Tables 15.1.1: 1 and 3

Figure 10.1: 2 Source of patients in trials 1160.106 and 1160.108 by age group – TS

As a general remark, while the initial list of questions was asked during the assessment of the interim analysis, the Applicant's responses to these questions are based on the final analysis of the full data sets.

Study 1160.106 DIVERSITY

Methods

Trial 1160.106 was a multicentre, open-label, randomised, parallel-group, active-controlled, non-inferiority trial of DE versus standard of care (SoC) in children from birth to less than 18 years of age. The design of this trial (including the definition of endpoints and the choice of SoC comparators) has been agreed with the PDCO. This committee has previously endorsed the principal design elements and endpoints of the trial.

An open-label design was chosen for several reasons. The different paediatric formulations of DE and the subcutaneous administration of some of the SoC treatments would have required an unethical number of dummy treatments in a blinded trial, especially considering the vulnerability of a paediatric trial population. Similarly, the constant international normalised ratio (INR) monitoring required for some SoC treatments would also have had to be simulated for the DE group in a blinded trial. Important efficacy and safety outcomes of the trial were adjudicated in a blinded fashion by an independent committee.

A specific comparator was not provided by the sponsor; instead, investigators were able to choose from several SoC treatments based on local practice. This was considered to reflect a real-world situation but does not allow for the comparison of DE against a distinct SoC comparator class or compound. Available options were LMWH, VKA, or fondaparinux; doses had to be monitored and adjusted regularly.

The trial has been completed. Recruitment was first initiated in the adolescent group (12 to <18 years) and was consecutively opened to younger age groups (2 to <12 years of age; 0 to <2 years) based on the DMC recommendations. It was planned to include a minimum of 141 evaluable patients for the primary efficacy endpoint, including a target of 60 patients in the age group from 12 to <18 years of age, 18 patients in the age group from 2 to <12 years of age and 10 patients in the age stratum from birth to <2 years of age. The minimum number in the lowest age group could be included from either trial 1160.106 or trial 1160.108. Randomisation was 2:1 (DE:SoC). At the interim cut-off date, the planned number of patients was already exceeded.

The trial consisted of 3 periods: a screening period, an open-label treatment period, and a follow-up period. After consent (and assent, if applicable), the patients entered a screening period while they were completing their initial phase of VTE treatment. At the latest after 21 days of initial VTE treatment, patients were randomised in a 2:1 ratio to DE or SoC. The intended SoC (LMWH, or VKA, or fondaparinux) was required to be specified at randomisation. Once eligibility had been confirmed, patients received either daily DE or SoC for 3 months beyond the initial parental therapy.

Patients requiring discontinuation of DE per CTP were switched to an appropriate SoC therapy and followed up until the end of the trial, based on an intent-to-treat principle. Patients requiring VTE therapy beyond 3 months were switched at Visit 8 (Day 84) to SoC treatment (if randomised to DE) or continued SoC treatment (if randomised to SoC). The follow-up period was 4 weeks after last administration of DE (as implemented with Global Amendment 5 dated 29 Nov 2016; the initial follow-up period had been 9 months). Patients requiring further anticoagulation for secondary VTE prevention due to an unresolved clinical risk factor were offered to enrol in the open-label secondary prevention trial 1160.108 and their follow-up visits were performed within this separate trial.

Study Participants

Trial sites and investigators in Trial 1160.106

This multinational, multicentre trial was conducted in 63 sites (with screened patients) in 25 countries in Asia, Europe, North America, and South America.

Patient selection

Trial 1160.106 included male and female patients from birth to <18 years of age (at the time of informed consent) with a documented diagnosis of clinically stable VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis) based on investigator judgement. The VTE was initially treated (minimum of 5 to 7 days but not longer than 21 days) with parenteral anticoagulation therapy, such as unfractionated heparin (UFH) or LMWH. Short-term pre-treatment with VKAs was permitted if the INR had not yet reached a therapeutic level (i.e. the INR was still <2.0). Patients were eligible if they needed anti-thrombotic treatment for an anticipated duration of at least 3 months beyond the initial parental therapy.

Inclusion criteria

1) Male or female patients from birth to <18 years of age at the time of informed consent/assent

2) Documented diagnosis of clinically stable VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis) per investigator judgement, initially treated (minimum of 5 to 7 days, but not longer than 21 days) with parenteral anticoagulation therapy, such as UFH or LMWH. Short-term pre-treatment with VKAs was permitted if the INR had not yet reached a therapeutic level (i.e. the INR was still <2.0)

3) Anticipated treatment duration with anticoagulants for the VTE episode (under inclusion criterion 2) for at least 3 months, inclusive of the initial parenteral therapy

4) Written informed consent provided by the patient's parent or legal representative and assent provided by the patient (if applicable) at the time of informed consent signature according to local regulations

Exclusion criteria

1) Conditions associated with an increased risk of bleeding:

   a) Any prior intracranial haemorrhage, classified as a macrobleed. Any intracranial anatomical abnormality or intracranial aneurysm. Active meningitis, encephalitis, or intracranial abscess at randomisation. Patients with asymptomatic petechial or microbleeds could be included into the trial as per investigator`s judgement. As a general recommendation, an intracranial microbleed was considered to be ≤0.5 cm in greatest diameter on gradient recalled echo, or T2*MRI sequences (criteria could vary depending on MRI imaging modalities; [R15-2999]). Irrespective of size, any cerebral bleed that caused focal neurologic signs or symptoms did not constitute a microbleed. Further, any blood visualised on a CT was to be classified as a microbleed

   b) Intracranial or intraspinal surgeries within 6 months of Visit 2 (randomisation) or any other major surgery within 4 weeks of Visit 2. Major surgeries included an invasive operation upon an organ within the cranium, chest, abdomen, pelvic cavity, or any other procedure regarded as major surgery per investigator judgement. In general, major surgery involved the opening of a mesenchymal barrier (pleural cavity, peritoneum, meninges). Removal or insertion of a central venous line was not considered a major surgery provided haemostasis was achieved after the procedure

   c) Any major planned procedure that might have put the patient at an increased risk of a bleed per investigator judgement within 5 days prior to taking trial medication

   d) History of intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding, unless the causative factor had been permanently treated (e.g. by surgery)

   e) Gastrointestinal haemorrhage within the past year prior to screening unless the cause had been permanently eliminated (e.g. by surgery)

   f) History of gastroduodenal ulcer disease

   g) History of haemorrhagic disorder or bleeding diathesis (e.g. von Willebrand disease, haemophilia A or B or other hereditary bleeding disorder, history of spontaneous intra-articular bleeding, history of prolonged bleeding after surgery/intervention)

   h) Administration of fibrinolytic agents within 48 hours of DE administration (note that the use of tissue plasminogen activators, e.g. alteplase, or any other thrombolytic agents to re-establish patency of an obstructed central venous line were allowed as long as the used dose was devoid of relevant systemic effects)

   i) Uncontrolled hypertension on antihypertensive medication (systolic or diastolic blood pressure above ULN for age and sustained over 24 hours)

j) Any other disease, health condition or intervention that exposed the patient to a higher risk for bleeding in the investigator's opinion

2) Renal dysfunction (eGFR <50 mL/min/1.73m2 using the Schwartz formula) or requirement for dialysis. Retesting the eGFR during the screening period was allowed (once). The threshold was decreased stepwise from <80 mL/min/1.73 m2 with Global Amendment 5 and Global Amendment 9. However, at the time of this interim analysis, Global Amendment 9 had been implemented only in a few countries.

3) Active infective endocarditis

4) Patients with a heart valve prosthesis requiring anticoagulation

5) Hepatic disease:

   a) Active liver disease, including known active hepatitis A, B, or C, or

   b) Persistent ALT or AST or AP >3x ULN within 3 months of screening. Transient increases of these parameters were acceptable, if retesting demonstrated results within these limits

6) Pregnant or breast-feeding female patients. Female patients who had reached menarche and were not using a medically accepted contraceptive method per local guidelines. Acceptable methods of birth control are listed below and must have been used in a correct and consistent manner:

   a) Oral or parenteral (patch, injection, implant) hormonal contraception which has been used continuously for at least 1 month prior to the first dose of trial medication

   b) Intrauterine device or intrauterine system

   c) Double-Barrier method of contraception: condom and spermicidal agent

   d) Complete sexual abstinence. Note: Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception

7) Patients in stratum 3 (0 to <2 years) with gestational age at birth <37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards [provided in the ISF]). Note that this exclusion criterion was added with Global Amendment 2

8) Anaemia (haemoglobin <80 g/L) or thrombocytopenia (platelet count <80x109/L) at screening. Transfusions during the screening period were allowed, provided that a satisfactory haemoglobin or platelet level was attained prior to Visit 2 (randomisation) Patients who had taken prohibited or restricted medication within 1 week of the first dose of trial medication, other than medication for prior VTE treatment and P-glycoprotein inhibitors. For trial restrictions, see Section 9.4.2.2

9) Patients who had received an investigational drug in the past 30 days prior to screening

10) Patients who were allergic/sensitive to any component of the trial medication including solvent

11) Patients or parents/legal representatives considered unreliable to participate in the trial per investigator judgement or any condition which would present a safety hazard to the patient based on investigator judgement

12) Patients or parents/legal representatives who are unwilling or unable to undergo or permit the repeat of the baseline imaging tests required to confirm thrombus resolution at Day 84/Week 12 (or at eEOT, whichever came first) or in whom repeating such imaging tests at these pre-specified time points may not have been in the patient's best medical interest. Examples included unwarranted radiation exposure

as a result of a repeat CT scan for a patient with an isolated case of PE evaluated at baseline solely by a CT scan. In such cases, the baseline radiological assessment (e.g. CT) could be supplemented with an acceptable non-radiological assessment at baseline (e.g. MRI) which could then be repeated at Day 84/Week 12 (or eEOT), hence alleviating any potential unwarranted radiation exposure

Treatments

The investigational medicinal product DE was supplied by Boehringer Ingelheim (study sponsor). The active comparator used as SoC (e.g. LMWHs or VKAs, or fondaparinux) was **not** supplied as part of the investigational medicinal product by the sponsor.

Identity of BI investigational product

Dabigatran etexilate capsules. Unit strengths: 50 mg, 75 mg, 110 mg and 150 mg. Total daily dose: The administered dose was based on an age and weight adjusted nomogram (see below). Posology: Twice daily. Route of administration: Oral

Dabigatran Etexilate coated granules. Unit strength: coated granules to be sprinkled on food (for the available strengths. Total Daily dose: The administered dose was based on an age and weight adjusted nomogram (see below). Posology Twice daily. Route of administration: Oral

Dabigatran etexilate oral liquid formulation (OLF). Dabigatran etexilate granules (180.4 mg) and flavoured or unflavoured solvent for reconstitution (28 mL). Pharmaceutical formulation: Oral liquid formulation. Unit strength: Granules for oral solution (6.25 mg/mL after reconstitution). Total Daily dose: A specific volume of a 6.25 mg/mL solution after reconstitution was administered based on an age and weight adjusted nomogram (see below).

Posology Twice daily.

Route of administration: Oral

Dosing of dabigatran etexilate

Patients aged ≥ 8 years: Age and weight adjusted dabigatran etexilate capsules.

Patients aged < 8 years or for patients who cannot take capsules even if older than 8 (but below 12 years of age): Age and weight adjusted dabigatran etexilate coated granules.

Patients aged < 12 months: Age and weight adjusted dabigatran etexilate OLF or any other alternative age-appropriate formulation. For patients < 12 months of age, OLF is preferred over coated granules provided that OLF supplies are available to the site.

Dabigatran etexilate is taken twice daily (BID). Estimated age and weight adjusted starting doses are outlined in the following nomograms, which refer to the total amount of dabigatran etexilate to be taken at a single time-point.

10.3.1 Dosing nomogram (starting doses)

- dabigatran etexilate capsules - 50, 75, 110 and 150 mg

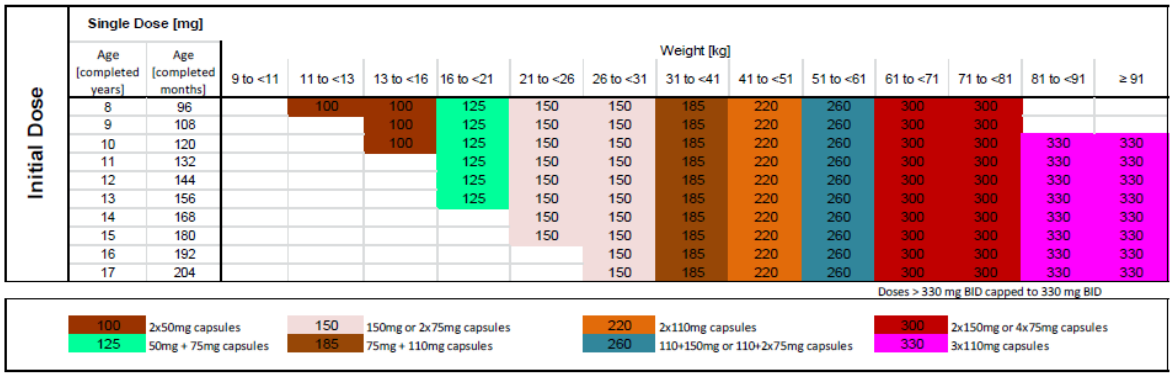


Figure 10.3.1: 1 Age and weight adjusted starting doses using capsules

- *dabigatran etexilate pellets*

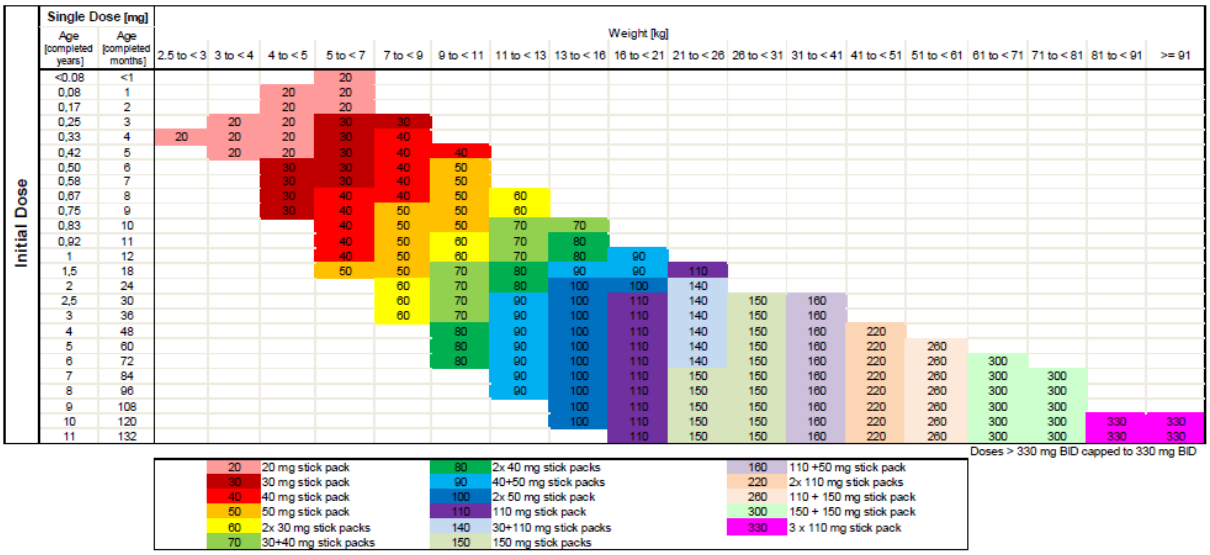


Figure 10.3.1: 2 Age and weight adjusted starting doses using pellets

- dabigatran etexilate OLF - 6.25 mg per mL

Initial Dose	Single Dose [mg]		Weight [kg]									
	Age [completed years]	Age [completed months]	2.5 <3	3 to <4	4 to <5	5 to <7	7 to <9	9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31
	<0.08	<1	12.50	12.50	12.50	18.75							
	0.08	1	12.50	12.50	18.75	18.75							
	0.17	2	12.50	18.75	18.75	25.00							
	0.25	3	12.50	18.75	25.00	25.00	31.25						
	0.33	4	18.75	18.75	25.00	31.25	37.50						
	0.42	5		18.75	25.00	31.25	37.50	43.75					
	0.50	6			25.00	31.25	43.75	43.75					
	0.58	7			25.00	31.25	43.75	50.00					
	0.67	8			31.25	37.50	43.75	50.00	62.50				
	0.75	9			31.25	37.50	43.75	56.25	62.50				
	0.83	10				37.50	50.00	56.25	62.50	75.00			
	0.92	11				43.75	50.00	56.25	68.75	75.00			

12.50	2 mL	31.25	5 mL	50.00	8 mL	68.75	11 mL
18.75	3 mL	37.50	6 mL	56.25	9 mL	75.00	12 mL
25.00	4 mL	43.75	7 mL	62.50	10 mL		

Figure 10.3.1: 3 Age and weight adjusted starting doses using OLF

Note: In addition to these starting dose nomograms, there are Dose Adjustment nomograms for up- and down-titration, respectively (not shown):

Up-titration: In case patients have trough concentrations below 50 ng/mL, the dose may be increased by 15 to 100% as outlined in the relevant nomograms for capsules, coated granules and LOF, respectively

Down-titration: Whenever a trough concentration is greater than or equal to 250 ng/mL, the dose may be reduced by 40 to 50% as outlined in the relevant nomograms for capsules, coated granules and LOF, respectively.

Dosing of the SoC comparator

Patients assigned to take SoC were to follow the investigator's recommendation for adequate dosing and administration based on the product's locally approved label and in consideration of local treatment guidelines. The SoC dose was to be monitored regularly as appropriate (e.g. INR for VKAs).

Rationale for the dose selection for DE

Dose selection for DE was based on dabigatran's linear PK with renal function (GFR) being the most important determinant of dabigatran PK. Allometric models were considered appropriate in determining doses in paediatric patients. To adjust for the on average lower body weight and hence lower absolute GFR in children aged <1 year, the dose estimation procedure according to Hayton was used. For renally eliminated drugs like dabigatran, this model can be used to estimate dosing regimens based on the adult dose with adjustment to the age and weight of the child. In this way, doses and resulting nomograms can be used in clinical practice without the need for regular laboratory measurements. The dosing was intended to achieve trough plasma dabigatran concentrations between 50 and 250 ng/mL, which have generally been proven to be safe and effective in adult populations, mainly RE-COVER and RE-LY, see also rationale below.

Based on the calculated target DE doses and the available formulation strengths, age- and weight-adjusted nomograms were provided for each formulation. Dosing of patients was only to occur according to the adjusted nomograms, which were updated with Global Amendments 3, 4, 5, and 8 to reflect the addition of the younger age strata and respective formulations to the trial. The dose regimen was also regularly reviewed by the DMC, which could have revised it as data on trough dabigatran levels, PD, efficacy, and

safety data from this and other studies became available. No such revision was done until the cut-off date for the interim analysis.

Rationale for the target plasma dabigatran concentration

A dabigatran trough concentration of ≥50 to <250 ng/mL was defined as target in trial 1160.106 because of the additional dose finding/confirmation character of the trial. In the RE-LY trial a relationship between total dabigatran exposure and efficacy (i.e. ischemic stroke) has been established; a total dabigatran trough concentration above 28 ng/mL (10th percentile) was associated with appropriate efficacy for the prevention of stroke. In the RE-COVER trial, the correlation between efficacy and total dabigatran trough concentration was weak. Efficacy could be considered as adequate at concentrations above the 10th percentile (26 ng/mL) of the trough concentrations observed in RE-COVER. Based on the anticipated similarity of the pathophysiology of thrombotic events in the populations of these two trials, a trough concentration ≥50 ng/mL was expected to provide the most favourable efficacy and was therefore proposed for paediatric patients in this trial. In addition, 50 ng/mL had to be chosen as this was the limit of quantification of the dTT assay used in the trial initially. Based on a low risk of major bleeding events with rising total dabigatran trough concentrations even beyond 250 ng/mL, it was considered that maintaining a trough concentration between 50 to <250 ng/mL has a reasonable likelihood to be effective and safe with a positive benefit/risk ratio in children of all ages, as seen in adults. This range constituted a rather conservative safeguard in this trial, where dosing appropriateness and efficacy and safety were evaluated in parallel as per trial design (Phase IIb/III).

The DMC could recommend further refinement of the target trough steady state dabigatran concentration based on data from ongoing paediatric trials or if emerging data from other DE trials in other populations suggested that a wider or narrower total dabigatran trough concentration range is associated with better benefit/risk ratio.

Adjustments to reach target plasma dabigatran concentrations

The dose of DE had to be adjusted during the trial to ensure that a steady state trough plasma concentration between ≥50 to <250 ng/mL was achieved (see above). Steady state is reached within first week of dosing, after 6 consecutive doses were taken. Patients who had a total steady state trough concentration between 50 and <250 ng/mL were advised to continue on the same dose until the following visit. If the trough concentration was below 50 ng/mL the concentration was greater than or equal to 250 ng/mL, the dose had to be reduced by 25 to 50%. During the regulatory procedure, the Applicant has provided additional descriptive statistics for steady state plasma concentrations of total dabigatran at Visit 3 (after at least 6 consecutive dabigatran doses), post-titration (at least 3 days after a dabigatran dose adjustment), and over all visits – PK Set by age stratum as follows:

	Visit 3			Post-titration			Trough gMean over visits		
	N	gMean [ng/mL]	gCV [%]	N	gMean [ng/mL]	gCV [%]	N	gMean [ng/mL]	gCV [%]
				Age Group					
Total	139	79.8	68.6	49	81.7	54.7	164	83.3	51.5
Birth to <2 years	16	50.6	57.7	11	72.6	44.5	20	58.9	44.8
Birth to <6 months	8	44.8	64.2	6	73.4	62.3	9	52.9	49.1
6 months to <2 years	8	57.1	51.7	5	71.6	20.6	11	64.4	41.0
2 to <12 years	35	49.0	71.8	23	75.2	54.0	42	61.0	58.8
12 to 18 years	88	105	45.6	15	101	58.3	102	101	35.9

Only valid trough values and uncapped doses from the PK Set are included, thus Ns for individual visits differ from the overall N. The 49 patients in the column 'post-titration' were those patients who were titrated, and the concentrations shown were the concentrations at least 3 days after the dose adjustment. Not all 49 patients may have a valid PK sample at visit 3 as they may not be within the time window during Visit 3.

Furthermore, the Applicant has provided a comparison of trough gMean values in 1160.106 over all visits and trough gMean values over all visits normalised to dose before adjustment – PK Set by age stratum and formulation as follows:

	Trough gMean over all visits[ng/mL]	Trough gMean over all visits normalised to target dose [ng/mL]	Difference [%][1]
Age stratum			
Birth to <2 years (N = 20)	58.9 (44.8)	52.2 (49.5)	-11.4
Birth to <6 months (N = 9)	52.9 (49.1)	46.0 (54.7)	-13.0
6 months to <2 years (N = 11)	64.4 (41.0)	58.0 (44.4)	-9.93
2 to <12 years (N = 42)	61.0 (58.8)	53.8 (61.7)	-11.8
12 to 18 years (N = 102)	101 (35.9)	101 (40.8)	0.00
Formulation			
Capsules (N = 111)	99.9 (35.5)	99.2 (40.4)	-0.70
Pellets (N = 41)	57.7 (59.2)	50.3 (61.4)	-12.8
OLF (N = 12)	54.7 (44.1)	48.5 (49.7)	-11.3

[1] Difference in % = 100%* (gMean over visits normalised to target dose –gMean over visits)/gMean over visits
Only valid trough values and uncapped doses from PKS included, thus Ns for individual visits differ from the overall N.

It can be seen that the difference in exposure over the full treatment period when a dose titration had taken place compared with the expected exposure had it not taken place is <15% difference for all subgroups.

Objectives

This trial was a prospective, multicentre, international, open-label, randomised, parallel-group, non-inferiority trial comparing DE to SoC. It was designed to assess the efficacy and safety of DE relative to SoC for the treatment of secondary prevention of VTE in patients from birth to less than 18 years of age and to document the appropriateness of the proposed DE dosing algorithm.

Hypothesis testing

The non-inferiority hypothesis for the primary endpoint (proportion of patients with complete thrombus resolution, with no recurrent VTE and no VTE-related death) was:

H01: p1C – p1D ≥δ1 vs. H11: p1C – p1D <δ1 for the primary endpoint (δ1 = 20%) *

* The letter D stands for DE and the letter C for SoC.

The non-inferiority margin was based on 11 trials with SoC in paediatric patients. A complete thrombus resolution rate without treatment cannot be established from recent publications. It is uncommon to see patient completely without treatment, and the rate of complete thrombus resolution is believed to be low. In the absence of solid evidence of spontaneous thrombus resolution, a precise effect size was difficult to be determined. By using a wide range of plausible complete thrombus resolution rates without treatment, it was demonstrated that the 20% non-inferiority margin (concerning the rate difference) can preserve at least 62% and up to 70% of the effect size under SoC treatment.

Upon showing significance of non-inferiority for the primary endpoint (using a 90% confidence interval), a test of superiority was performed subsequently (with a one-sided significance level of 0.05), in the following order:

H03: p1C – p1D ≥0 vs. H13: p1C – p1D <0 for the primary endpoint

* The letter D stands for DE and the letter C for SoC.

Refer to Section 9.7.2 of the interim CTR [c26571231] for further details regarding the non-inferiority margin, the significance level for superiority, the sample size, and power calculations.

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint was the combined endpoint of the proportion of patients with:

- Complete thrombus resolution
- Freedom from recurrent VTE (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, DVT, PE and PDE, thrombus progression)
- Freedom from mortality related to VTE

The events outlined in the above combined primary endpoint were assessed by radiologists or other such qualified clinicians using an appropriate method such as ultrasound, echocardiography, venography, or CT scan, based on the location of the thrombus and the test used to perform the baseline assessment.

Secondary endpoints

Freedom from major bleeding events (MBEs), defined as either fatal bleeding; clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L in a 24-hour period; bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system; or bleeding that requires intervention in an operating suite

PK and PD assessments at Visit 3 (after at least 6 consecutive DE doses) and after at least 3 days following any DE dose adjustment

Frequency of dose adjustments (i.e. number of patients with dose adjustment), temporary and permanent discontinuation from therapy, and number of patients with laboratory monitoring requirements for dose adjustment during the treatment phase

Frequency of switch of type of anti-coagulation therapy (including DE to SoC), i.e. frequency of patients switching the type of anti-coagulation therapy including DE to SoC and switching from an intended SoC treatment to another

Freedom from thrombus progression at end of therapy (Day 84 after randomisation (Visit 8) or eEOT whichever came first), compared with baseline

Assessment of the acceptability of an age-appropriate formulation at end of therapy

All bleeding events

All-cause mortality

All individual components of the primary efficacy endpoints

All components of the primary efficacy endpoint as well as all bleeding and all fatal events were centrally adjudicated by an independent blinded committee

Randomisation and blinding (masking)

The randomization was performed in blocks of six and stratified by age groups (age<2, 2≤age<12, 12≤age<18), with allocation ratio of 2:1 for dabigatran to SOC. The correct assignment to trial medication kits was managed via an IRT based on the estimated dose. The randomization list was generated using a validated system.

The trial is an open-labelled trial. Different paediatric formulations of DE and the s.c. administration of some of the SoC treatments would have required an unethical number of dummy treatments in a blinded trial, especially considering the vulnerability of a paediatric trial population. In addition, the constant international normalised ratio (INR) monitoring required for some SoC treatments would also have had to be simulated for the DE group in a blinded trial.

Important efficacy and safety outcomes of the trial were adjudicated in a blinded fashion by an independent Data Monitoring Committee (DMC).

Investigators, patients, and trial members will be unblinded. The only party blinded to treatment assignment are members of the adjudication committee.

Statistical methods

Primary analysis

The analysis of the primary efficacy endpoint and its individual components was based on the randomised set (RS), which included all randomised patients in the treatment groups to which they were randomised, regardless whether they took trial medication.

As range of sensitivity analyses were based on either the RS or the treated set (TS), please refer to the table below. The treated set (TS) included all patients who were dispensed trial medication and were documented to have taken at least 1 dose of trial medication.

The following treatment periods were defined for the evaluation of efficacy:

- On-treatment period: time of first administration of trial medication to 6 days after last administration of trial medication (6 days was the defined residual effect period [REP])
- Intention-to-treat period: day of randomisation to Day 84 (+ 7 day visit window), including all observed time on and off trial medication
- Full follow-up period (i.e. complete observation period): day of randomisation to day of the last follow-up visit, lost to follow-up, death, or consent withdrawn

The primary efficacy endpoint contained 3 components. Each component was evaluated separately, and only if the criteria for all 3 components were satisfied, the primary endpoint was considered achieved.

Component 1: free from VTE-related mortality

Patients with VTE-related death occurring between randomization to Day 84 + 7 days will be considered as NOT meeting the endpoint in terms of the component of "freedom from mortality related to VTE", and therefore will not contribute to the proportion of patients achieving the primary efficacy endpoint.

Component 2: free from recurrent VTE

For patients with recurrent VTE(s) from randomization to Day 84 + 7 days, the component of "free from recurrent VTE" will be considered as NOT satisfied.

For patients WITHOUT ANY recurrent VTE records:

- If the entire treatment period is completed (Day 84 visit available), the component of "free from recurrent VTE" will be considered as satisfied.
- Patients who die (not VTE-related) or withdraw consent prior to Day 84 - 7 days without record of recurrent VTE will be considered as "free from recurrent VTE".
- For patients who discontinue treatment prematurely (before Day 84 + 7) this component will be considered as missing. In the primary analysis, we use LOCF, so no record of recurrent VTE will be considered as "free from recurrent VTE".

Component 3: complete thrombus resolution

Assessment of index VTE status (best overall response) was scheduled on Day 84 ± 7 days (Visit 8) for patients who were alive without consent withdrawn, regardless of the treatment status (completion or premature discontinuation) at that time.

- The thrombus status assessed at Day 84 ± 7 days will be used for evaluation of this component. If

more than one thrombus assessment is available within this time window, the one closest to and before Day 84+7 will be adopted.

- For patients completing the treatment period OR patients terminating treatment early, if the index thrombus assessment during Day 84 ± 7 days is missing, but an early VTE assessment was performed, for instance, at an unscheduled visit or an eEOT visit, the latest available thrombus status will be carried forward (LOCF) in the primary analysis.
- If not any index VTE assessment was performed until Day 84 + 7 days, these patients will be considered as having missing data and NOT meeting the criterion of "complete thrombus resolution"
- Patients with index VTE assessment performed only once after Day 84 + 7 days will be considered to have missing data and to not achieve the complete thrombus resolution in the primary analysis

Patients who are still being treated and have not yet reached Day 84 ± 7 days at time of EMA interim data cut-off will not be included in the analysis.

The primary analysis of the primary efficacy endpoint used the randomised set, following the intention-to-treat principle. Age group was used as stratification factor using a Mantel-Haenszel type weighted average of differences with weights as proposed by Greenland and Robins [R09-1299]. The analyses only included adjudicated events.

Sensitivity analyses

An analysis of the adjudicated primary endpoint was also performed on the RS with a logistic regression model using the fixed effect terms: treatment, age group, and the interaction of treatment by age group. Profile likelihood estimates were used to calculate the confidence intervals. The significance of the interaction term was assessed by this model. A Hosmer-Lemeshow test was performed to check the appropriateness of the analysis model.

The following sensitivity analyses were performed for the primary endpoint:

SCE Table 2 Overview of primary and sensitivity analyses of the primary endpoint

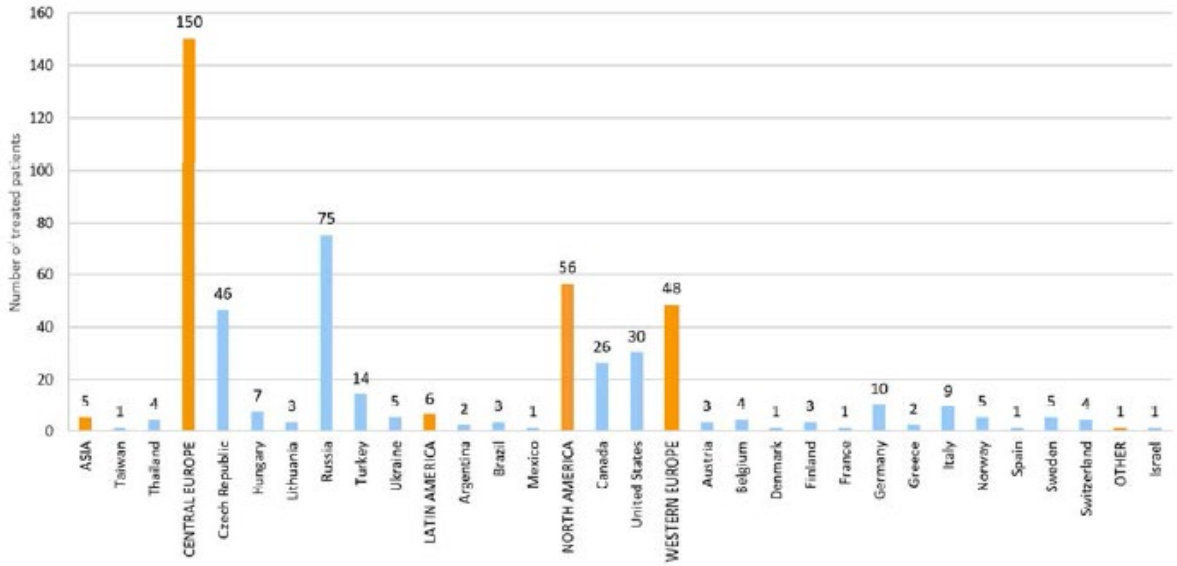
Analysis type	Event type	Patient set	Analysis period		Imputation rule
			Start	End	
Primary analysis	Adjudicated	RS	Randomisation	To the time point of interest	Missing VTE recurrence: LOCF Missing index thrombus assessment: LOCF
Sensitivity: on-treatment	Adjudicated	TS	First intake of trial medication	To the end of on-treatment period	Same as primary analysis
Sensitivity: full follow-up	Adjudicated	RS	Randomisation	To the end of full follow-up period	Same as primary analysis
Sensitivity: with imputation	Adjudicated	RS	Randomisation	To the time point of interest	Missing VTE recurrence: not free from recurrent VTE Missing thrombus assessment: not achieving complete thrombus resolution
Sensitivity: investigator-reported	Investigator-reported	RS	Randomisation	To the time point of interest	Same as primary analysis
Sensitivity: investigator-reported and on-treatment	Investigator-reported	TS	First intake of trial medication	To the end of on-treatment period	Same as primary analysis

RS, randomised set. TS, treated set

Results

Participant flow

A total of 328 patients were screened/enrolled, at 65 sites in 26 countries. The largest proportions of treated patients overall and across age groups were from Central Europe (56.4%), followed by North America (21.1%) and Western Europe (18.0%). At country level, Russia contributed the most patients (28.2%); the next largest contributions came from the Czech Republic (17.3%), and United States (11.3%).



Source data: Appendix 16.1.13.1, Table 1.2

Number of treated patients by region and country – Treated Set (TS)

Of the 328 screened patients, 267 patients were randomised. The main reasons why screened patients were not randomised were not meeting the in-/exclusion criteria (44 patients) and other reasons (11 patients). All randomised patients were treated, apart from 1 patient in the oldest age group, who had been randomised to DE. This patient withdrew consent after randomisation. At the end of the trial, 253 patients (95.1%) had completed the planned observation time (defined as attendance of the Follow-up Visit 9 or roll over into trial 1160.108 after Visit 8 [Week 12]). Thirteen patients (4.9%) had prematurely discontinued from the trial, with the most frequent reasons being 'other' (1.9%). The proportion of patients who prematurely discontinued was similar in both treatment groups (DE: 4.5%, SoC: 5.6%); see Table 4.

Table 4 Disposition of patients – enrolled set

	DE N (%)	SoC N (%)	Total N (%)
Screened/enrolled[1]			328
Randomised	177	90	267
Not treated	1	0	1
Treated	176 (100.0)	90 (100.0)	266 (100.0)
Completed planned observation time[2]	168 (95.5)	85 (94.4)	253 (95.1)
Premature trial discontinuation	8 (4.5)	5 (5.6)	13 (4.9)
Other	3 (1.7)	2 (2.2)	5 (1.9)
Non-compliance with the CTP	2 (1.1)	1 (1.1)	3 (1.1)
Other AE	1 (0.6)	2 (2.2)	3 (1.1)
Lost to follow-up	2 (1.1)	0	2 (0.8)
Consent withdrawn[3]	0	0	0
No premature discontinuation of trial medication	135 (76.7)	80 (88.9)	215 (80.8)
Completed assessment at Week 12 (Visit 8)	135 (76.7)	80 (88.9)	215 (80.8)
Missing assessment at Week 12 (Visit 8)	41 (23.3)	10 (11.1)	51 (19.2)
Premature discontinuation of trial medication	41 (23.3)	10 (11.1)	51 (19.2)

1 A total of 61 patients were not randomised.
2 Planned observation time starts from the last intake of trial medication until the Follow-up Visit 9. Patients who discontinued from treatment prematurely but underwent Visit 9 were considered as having completed the planned observation time. Patients who rolled over to trial 1160.108 after Visit 8 were also considered as having completed the planned observation time.
3 Consent withdrawn regarding trial participation

Source data: [c29773859, Tables 15.1.1: 1 and 15.1.1: 2]

Fifty-one patients (19.2%) in total prematurely (and permanently) discontinued trial medication, with the most frequent reasons being 'other' (10.5%) and AEs (other than recurrence of VTE or worsening of other pre-existing diseases; 5.6%) (Table 5). The most common 'other' reason for discontinuation was 'failure to obtain target dabigatran concentration', as the CTP only allowed 1 dose adjustment (after Global Amendment 2). In addition, other reasons included thrombus resolution, investigator judgement, and parents' unwillingness to continue. The proportion of patients who prematurely discontinued trial medication was higher in the DE group (23.3%) than in the SoC group (11.1%), which was mainly driven by the high number of 'other' discontinuations connected with not reaching the target dabigatran concentration as described above. In addition, patients who switched from DE to SoC were regarded as permanently discontinued, while patients in the SoC group who switched the SoC type were still regarded as on-treatment for SoC.

Table 5 Summary of temporary and permanent treatment discontinuation – TS

	DE	SoC
Number of patients treated, N (%)	176 (100.0)	90 (100.0)
Prematurely discontinued permanently from trial medication, N (%)	41 (23.3)	10 (11.1)
Reason for permanent interruption, N (%)		
Other[1]	22 (12.5)	6 (6.7)
Other AE	13 (7.4)	2 (2.2)
Non-compliance with the CTP	5 (2.8)	1 (1.1)
Recurrence of VTE	1 (0.6)	1 (1.1)
Worsening of other pre-existing disease	0	0
Lack of efficacy	0	0
Lost to follow-up	0	0
Consent withdrawn[2], not due to an AE	0	0
Temporary interruption from trial medication, N (%)	25 (14.2)	6 (6.7)
Total duration of temporary interruption, mean (SD), [days]	3.5 (2.2)	4.6 (3.7)
Reason for temporary interruption, N (%)		
Other	10 (5.7)	4 (4.4)
Non−surgical intervention	6 (3.4)	0
Non−serious AE	3 (1.7)	3 (3.3)
Bleed	5 (2.8)	0
Surgery	5 (2.8)	0
Serious AE	3 (1.7)	0

1 For patients on DE, in eCRF versions 1 and 2: 'failure to obtain target dabigatran concentration after 2 consecutive titrations' was mapped to 'other' in eCRF versions 3 and 4.

2 Consent withdrawn regarding intake of trial medication

Source data: [c29773859, Tables 15.1.1: 1 and 15.2.2.2: 2]

Further details on discontinuations by age-group in the DE treated patient group is provided in the following table:

Table A.1: 1 Disposition of patients by age group and treatment duration on dabigatran etexilate - discontinuation from the treatment of dabigatran etexilate

	Birth to <2 years		2 to <12 years		12 to <18 years		Birth to <18 years	
	>=12 weeks	Total	>=12 weeks	Total	>=12 weeks	Total	>=12 weeks	Total
Treated	22 (100.0)	30 (100.0)	52 (100.0)	74 (100.0)	195 (100.0)	224 (100.0)	269 (100.0)	328 (100.0)
Not prematurely discontinued from trial medication	14 (63.6)	14 (46.7)	39 (75.0)	43 (58.1)	148 (75.9)	149 (66.5)	201 (74.7)	206 (62.8)
Prematurely discontinued from trial medication	8 (36.4)	16 (53.3)	13 (25.0)	31 (41.9)	47 (24.1)	75 (33.5)	68 (25.3)	122 (37.2)
Recurrence of VTE	1 (4.5)	1 (3.3)	0 (0.0)	0 (0.0)	3 (1.5)	5 (2.2)	4 (1.5)	6 (1.8)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.4)	1 (0.5)	1 (0.4)	2 (0.7)	2 (0.6)
Other adverse event	1 (4.5)	3 (10.0)	1 (1.9)	4 (5.4)	3 (1.5)	11 (4.9)	5 (1.9)	18 (5.5)
Failure to obtain target dabigatran concentration	2 (9.1)	3 (10.0)	3 (5.8)	6 (8.1)	13 (6.7)	18 (8.0)	18 (6.7)	27 (8.2)
Non-compliant with protocol	1 (4.5)	3 (10.0)	2 (3.8)	3 (4.1)	1 (0.5)	5 (2.2)	4 (1.5)	11 (3.4)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Consent withdrawn, not due to adverse event [1]	0 (0.0)	0 (0.0)	1 (1.9)	2 (2.7)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.6)
Other	3 (13.6)	6 (20.0)	5 (9.6)	15 (20.3)	26 (13.3)	35 (15.6)	34 (12.6)	56 (17.1)

The proportions who were prematurely discontinued from trial DE medication were 53.3%, 41.9% and 33.5% in the age-groups Birth to <2 years, 2 to <12 years and 12 to <18 years, respectively.

Patients from trial 1160.106 who had completed the treatment period in trial 1160.106 and required further anticoagulation for secondary prevention of VTE due to presence of a clinical risk factor could roll over into trial 1160.108.

Overall, 91 patients (34.1% of the randomised patients in trial 1160.106) rolled over into trial 1160.108. In addition, 122 patients were newly recruited and treated in trial 1160.108 (Table 6 and Figure 2). In total, 388 distinct patients were treated in both trials 1160.106 and 1160.108 (birth to <2 years: 43 patients; 2 to <12 years: 91 patients; 12 to <18 years: 254 patients).

Table 6 Number of patients in trials 1160.106 and 1160.108 by age group – RS, TS

	DE			SoC		
Age stratum	Birth to <2 years	2 to <12 years	12 to <18 years	Birth to <2 years	2 to <12 years	12 to <18 years
Randomised in 1160.106	22	43	112	13	21	56
Treated in 1160.106	22	43	111	13	21	56
Treated in 1160.106 only	21	31	63	12	17	31
Treated in both trials (roll-over)	1	12	48	1	4	25
Treated in 1160.108 only	8	27	87	--	--	--
Total of treated patients	30	70	198	13	21	56

Source data: [c29773859, Tables 15.1.1: 1 and 15.1.1: 3]

Datasets analysed

The enrolled set comprised 328 patients. The RS included 267 patients (DE: 177 patients; SoC: 90 patients) and the TS comprised 266 patients (DE: 176 patients; SoC: 90 patients).

No per protocol set was defined for this trial. However, important protocol deviations (IPDs) were documented. The only IPD that could have led to exclusion from all analysis sets was 'informed consent not available', which did not occur in this trial.

Baseline data

Baseline refers to the last available measurement taken prior to first administration of DE or SoC in the trial.

Demographic characteristics

Overall, demographic characteristics were balanced between the 2 treatment groups (Table 7). About half of the randomised patients (49.8%) were male. The majority of patients were White (91.8%). Most of the patients were treated in trial centres in Central Europe (56.6%), North America (21.0%), and Western Europe (18.0%). The mean age at screening was 11.1 years (SD 6.1 years); see Table 7.

There were no relevant differences between age groups regarding sex, race, ethnicity, and region. Overall, 168 patients were 12 to <18 years old (mean age: 15.3 years [SD 1.6 years]), 64 patients 2 to <12 years old (mean age: 5.9 years [SD 3.1 years]), and 35 patients were younger than 2 years (mean age: 8.1 months [SD 6.7 months]). Of those, 21 patients were 6 months to <2 years old and 14 patients were <6 months old. Note that age information in the statistical analysis is not based on exact birth dates. Age at screening was stored in the database either in months or in years. Thus, a more precise age than '0 months' is not available for the youngest patients.

The mean/median BMI was in the normal range across age groups. The BMI ranged from 11.0 to 43.7 kg/m2 in 12 to <18 years old patients, from 10.7 to 23.3 kg/m2 in 2 to <12 years old patients, and from 12.1 to 19.9 kg/m2 in the youngest age group.

The eGFR was calculated using the Schwartz formula for children (see [c29773859, Section 9.5.3.3]). The overall mean eGFR was 116 mL/min/1.73 m^2 (SD 33 mL/min/1.73 m^2). and ranged from 67 to 238 mL/min/1.73 m^2 in 12 to <18 years old patients, from 89 to 219 mL/min/1.73 m^2 in 2 to <12 years old patients, and from 52 to 215 mL/min/1.73 m^2 in the youngest age group.-Note: At the beginning of the trial, patients with an eGFR <80 mL/min/1.73 m^2 were not eligible. During the trial, the eGFR threshold for exclusion from the trial was reduced to <60 mL/min/1.73m^2 for patients aged 12 to <18 years but remained unchanged for patients aged 0 to <12 years.

Table 7 Demographic data – RS

	DE	SoC	Total
Randomised patients, N (%)	177 (100.0)	90 (100.0)	267 (100.0)
Sex, N (%)			
Male	81 (45.8)	52 (57.8)	133 (49.8)
Female	96 (54.2)	38 (42.2)	134 (50.2)
Race, N (%)[1]			
White	163 (92.1)	82 (91.1)	245 (91.8)
Asian	10 (5.6)	3 (3.3)	13 (4.9)
Black or African American	1 (0.6)	3 (3.3)	4 (1.5)
Multiple	2 (1.1)	0	2 (0.7)
Missing[2]	1 (0.6)	2 (2.2)	3 (1.1)
Ethnicity, N (%)			
Not Hispanic/Latino	169 (95.5)	86 (95.6)	255 (95.5)
Hispanic/Latino	8 (4.5)	3 (3.3)	11 (4.1)
Missing[2]	0	1 (1.1)	1 (0.4)
Region, N (%)[3]			
Central Europe	100 (56.5)	51 (56.7)	151 (56.6)
North America	39 (22.0)	17 (18.9)	56 (21.0)
Western Europe	28 (15.8)	20 (22.2)	48 (18.0)
Latin America	4 (2.3)	2 (2.2)	6 (2.2)
Asia	5 (2.8)	0	5 (1.9)
Other	1 (0.6)	0	1 (0.4)
Age [years]			
Mean (SD)	11.1 (6.1)	11.0 (6.1)	11.1 (6.1)
Median (range)	14.0 (0 – 17)	14.0 (0 – 17)	14.0 (0 – 17)

1 None of the patients were American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander

2 Information on race and ethnicity could not be collected in certain countries because of legal requirements

3 Asia: Taiwan, Thailand; Central Europe: Czech Republic, Hungary, Lithuania, Russia, Turkey, Ukraine; Latin America: Argentina, Brazil, Mexico; North America: Canada, United States; Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Norway, Spain, Sweden, Switzerland; Other: Israel.

Source data: [c29773859, Table 15.1.4: 1]

Baseline disease characteristics

Characterisation of leading index VTE

In both treatment groups, most patients (63.7%) had DVT as leading index VTE (Table 8). More patients in the DE group (11.3%) than in the SoC group (4.4%) had PE as leading index VTE. The main imaging method used to confirm the VTE assessment was compression ultrasound (72.3%). The mean time from first diagnosis of the index VTE until randomisation was similar in both treatment groups (overall 16.2 days, SD: 6.3 days).

Table 8 Leading index VTE – RS

	DE	SoC	Total
Randomised patients, N (%)	177 (100.0)	90 (100.0)	267 (100.0)
Type of leading index VTE[1], N (%)			
Deep vein thrombosis (DVT)	110 (62.1)	60 (66.7)	170 (63.7)
Central line thrombosis	27 (15.3)	20 (22.2)	47 (17.6)
Cerebral venous thrombosis or sinus thrombosis	20 (11.3)	6 (6.7)	26 (9.7)
Pulmonary embolism (PE)	20 (11.3)	4 (4.4)	24 (9.0)
Imaging method confirming VTE assessment[2], N (%)			
Compression ultrasound	118 (66.7)	75 (83.3)	193 (72.3)
CT scan	31 (17.5)	11 (12.2)	42 (15.7)
MRI scan	25 (14.1)	7 (7.8)	32 (12.0)
Other	14 (7.9)	3 (3.3)	17 (6.4)
Contrast venography	2 (1.1)	2 (2.2)	4 (1.5)
Pulmonary angiography	2 (1.1)	1 (1.1)	3 (1.1)
V/Q scan	1 (0.6)	1 (1.1)	2 (0.7)
Days since first diagnosis of index VTE			
Mean (SD)	16.1 (6.5)	16.4 (5.8)	16.2 (6.3)
Median (range)	16.0 (5 – 55)	16.0 (6 – 33)	16.0 (5 – 55)
Duration of parenteral anticoagulant treatment (prior to randomisation), days			
Mean (SD)	14.8 (5.3)	15.7 (5.2)	15.1 (5.3)
Median (range)	15.0 (5 – 28)	16.0 (5 – 31)	16.0 (5 – 31)
Initial parenteral anticoagulant therapy, N (%)[3]			
Low molecular weight heparin	165 (93.2)	83 (92.2)	248 (92.9)
Unfractionated heparin	32 (18.1)	16 (17.8)	48 (18.0)
Fondaparinux	0	1 (1.1)	1 (0.4)
Other parenteral anticoagulation	7 (4.0)	2 (2.2)	9 (3.4)
Other non-anticoagulation therapy (clopidogrel)	0	1 (1.1)	1 (0.4)

1 With eCRF Version 3, tick boxes were introduced for the subcategories. For the analyses, information provided in the free text field of eCRF Versions 1 and 2 were mapped to the subcategories.

2 Patients could be assessed with more than 1 imaging method.

3 Patients could be treated with more than 1 initial therapy. All patients received at least 1 initial parenteral anticoagulant for the leading index VTE [c29773859, Appendix 16.2.4, Listing 3].

Source data: [c29773859, Table 15.1.4: 2]

Further details on location and symptomatology of DVT and PE are provided in the source data for the above table:

Table 15.1.4: 2 Baseline disease characteristics
randomised set

	Dabigatran etexilate	Standard of care	Total
Location of DVT [2] [N (%)]			
Distal	0 (0.0)	0 (0.0)	0 (0.0)
Proximal	0 (0.0)	0 (0.0)	0 (0.0)
Arm	14 (7.9)	5 (5.6)	19 (7.1)
Leg	57 (32.2)	33 (36.7)	90 (33.7)
Other	41 (23.2)	15 (16.7)	56 (21.0)
Location not specified	45 (25.4)	33 (36.7)	78 (29.2)
Is the DVT symptomatic? [2] [N (%)]			
Yes	89 (50.3)	46 (51.1)	135 (50.6)
No	37 (20.9)	22 (24.4)	59 (22.1)
Missing	31 (17.5)	18 (20.0)	49 (18.4)
Pulmonary embolism [3] [N (%)]			
Left side	9 (5.1)	3 (3.3)	12 (4.5)
Pulmonary embolism size [N (%)]			
Small	3 (1.7)	1 (1.1)	4 (1.5)
Moderate	4 (2.3)	1 (1.1)	5 (1.9)
Large	2 (1.1)	1 (1.1)	3 (1.1)
Right side	15 (8.5)	2 (2.2)	17 (6.4)
Pulmonary embolism size [N (%)]			
Small	7 (4.0)	1 (1.1)	8 (3.0)
Moderate	6 (3.4)	0 (0.0)	6 (2.2)
Large	2 (1.1)	1 (1.1)	3 (1.1)
Missing	4 (2.3)	1 (1.1)	5 (1.9)
Was PE symptomatic? [N(%)]			
Yes	14 (7.9)	3 (3.3)	17 (6.4)
No	2 (1.1)	0 (0.0)	2 (0.7)
Missing	4 (2.3)	1 (1.1)	5 (1.9)

#= VKA, NOAC, or Non-anticoagulant therapy prior to randomization was taken by the following patient: 20005101

[1] Patients can be assessed by more than one imaging methods.
[2] For patients with leading index VTE as deep vein thrombosis, central line thrombosis, and cerebral venous thrombosis and/or sinus thrombosis.
[3] Patients may be counted in more than one category.
[4] Sum of durations if more than one parenteral anticoagulant received.
[5] All parenteral anticoagulant therapy is provided if more than one type was received.

Please note that "DVT" in the above table includes deep vein thrombosis, central line thrombosis, and cerebral venous thrombosis and/or sinus thrombosis. It is noted that 50.6% of total are symptomatic, 22.1% of total are asymptomatic and 18.4% are missing symptomatology.

Further details on the most recent VTE in the DE treated patients across study 1160.106 and 1160.108 by age-group is provided in the following table:

Table A.2: 4 Baseline disease characteristics by age group and treatment duration on dabigatran etexilate
unique DE treated set in 1160.106 and 1160.108

	Birth to <2 years		2 to <12 years		12 to <18 years		Birth to <18 years	
	>=12 weeks	Total	>=12 weeks	Total	>=12 weeks	Total	>=12 weeks	Total
Number of patients [N(%)]	22 (100.0)	30 (100.0)	52 (100.0)	74 (100.0)	195 (100.0)	224 (100.0)	269 (100.0)	328 (100.0)
Type of most recent VTE [N(%)]								
Deep Vein Thrombosis (DVT)	7 (31.8)	12 (40.0)	27 (51.9)	38 (51.4)	156 (80.0)	177 (79.0)	190 (70.6)	227 (69.2)
Pulmonary Embolism (PE)	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.4)	25 (12.8)	32 (14.3)	26 (9.7)	33 (10.1)
Central Line Thrombosis	10 (45.5)	12 (40.0)	13 (25.0)	15 (20.3)	4 (2.1)	5 (2.2)	27 (10.0)	32 (9.8)
Cerebral Venous Thrombosis and/or Sinus Thrombosis	5 (22.7)	6 (20.0)	11 (21.2)	20 (27.0)	12 (6.2)	12 (5.4)	28 (10.4)	38 (11.6)

It is noted that the proportions with Central Line Thrombosis (CLT) are 40.0%, 20.3% and 2.2% in the age-groups Birth to <2 years, 2 to <12 years and 12 to <18 years, respectively. The proportions with Cerebral Venous Thrombosis and/or Sinus Thrombosis (CVST) are 20.0%, 27.0% and 5.4% in the age-groups Birth to <2 years, 2 to <12 years and 12 to <18 years, respectively.

Previous thromboembolic events

Overall, 28 patients (10.5%) had a history of VTEs other than the index VTE. For most of the patients (5.6%), the previous VTE was a DVT and the majority of patients had not more than 1 previous VTE (9.4%); see Table 9.

Table 9 History of previous thromboembolic events – RS

	DE N (%)	SoC N (%)	Total N (%)
Randomised patients	177	90	267
Number of patients with medical history collected	176 (100.0)	90 (100.0)	266 (100.0)
Previous VTE (other than the index VTE)	14 (8.0)	14 (15.6)	28 (10.5)
Number of confirmed previous VTEs			
1	13 (7.4)	12 (13.3)	25 (9.4)
2	1 (0.6)	2 (2.2)	3 (1.1)
≥3	0	0	0
Previous VTE[1]			
Deep vein thrombosis	7 (4.0)	8 (8.9)	15 (5.6)
Pulmonary embolism	3 (1.7)	6 (6.7)	9 (3.4)
Other	4 (2.3)	0	4 (1.5)
Cerebral venous thrombosis and/or sinus thrombosis	1 (0.6)	1 (1.1)	2 (0.8)
Paradoxical embolism	0	0	0
Central line thrombosis	0	0	0
Previous VTE classification[1]			
Unprovoked/idiopathic	10 (5.7)	5 (5.6)	15 (5.6)
Provoked	4 (2.3)	9 (10.0)	13 (4.9)

[1] Patients may be counted in more than 1 category

Source data: [c29773859, Table 15.1.4: 6]

Medical history

Medical history was fairly balanced across both treatment groups, with the exception of cancer, which was mainly reported for patients in the DE group, and heart failure and congenital heart disease, which was mainly reported for the SoC group. About a third of the patients (30.5%) tested positive for at least 1 inherited coagulation disorder, most of them Factor V Leiden (9.8%). Other relevant medical history included congenital heart disease (18.0%), heart failure (8.3%), and history of cancer (7.1%); see Table 10.

Table 10 Medical history – RS

	DE N (%)	SoC N (%)	Total N (%)
Randomised patients	177	90	267
Number of patients with medical history collected	176 (100.0)	90 (100.0)	266 (100.0)
Inherited thrombophilia or coagulation disorder[1, 2]	51 (29.0)	30 (33.3)	81 (30.5)
Factor V Leiden	18 (10.2)	8 (8.9)	26 (9.8)
Anatomical thrombophilia	14 (8.0)	9 (10.0)	23 (8.6)
Protein C/S deficiency	7 (4.0)	7 (7.8)	14 (5.3)
Other coagulation disorder	9 (5.1)	3 (3.3)	12 (4.5)
Prothrombin mutation	9 (5.1)	3 (3.3)	12 (4.5)
Antiphospholipid antibodies or Lupus anticoagulant	4 (2.3)	7 (7.8)	11 (4.1)
Antithrombin deficiency	6 (3.4)	3 (3.3)	9 (3.4)
Other medical history[1]			
Congenital heart disease	21 (11.9)	27 (30.0)	48 (18.0)
Heart failure	6 (3.4)	16 (17.8)	22 (8.3)
History of cancer	18 (10.2)	1 (1.1)	19 (7.1)
Diabetes mellitus	4 (2.3)	1 (1.1)	5 (1.9)
Hypertension	1 (0.6)	1 (1.1)	2 (0.8)
History of major or clinical relevant bleeding event	1 (0.6)	0	1 (0.4)
Medical circumstances that increase the risk of thrombosis[1]			
Other medical circumstances	39 (22.2)	24 (26.7)	63 (23.7)
Presence of central venous line/catheter	40 (22.7)	24 (26.7)	64 (24.1)
Recent immobilisation	22 (12.5)	9 (10.0)	31 (11.7)
Presence of other venous or arterial catheter	10 (5.7)	2 (2.2)	12 (4.5)
Total parenteral nutrition–dependency	1 (0.6)	0	1 (0.4)

1 Patients may be counted in more than 1 category.

2 Not all patients were tested for all disorders; results are only shown for patients who were tested (and tested positive).

Source data: [c29773859, Table 15.1.4: 6]

For general baseline conditions, refer to [c29773859, Table 15.1.4: 5].

Numbers analysed

Study 1160.106:

Table 10.2: 1 Data analysis sets – enrolled set

	DE N (%)	SoC N (%)	Total N (%)
Enrolled set			328
Randomised set	177 (100.0)	90 (100.0)	267 (100.0)
TS	176 (99.4)	90 (100.0)	266 (99.6)
PKS	174 (98.3)	NA	174 (65.2)
PDS	176 (99.4)	NA	176 (65.9)
PK/PD set	169 (95.5)	NA	169 (63.3)

Source data: Table 15.1.2: 1 and 15.6.1.1: 1, Listings 16.1.13.5.1: 2 and 16.1.13.6.1: 2

RS: Randomized set. TS: Treated set. PKS: PK set. PDS: PD set.

Outcomes and estimation

Primary endpoint

Primary analysis

Of the 267 randomised patients, 81 patients (45.8%) in the DE group and 38 patients (42.2%) in the SoC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The corresponding rate difference and 90% CI was −0.038 (−0.141, 0.066) and thus demonstrated non-inferiority of DE to SoC, since the upper bound of the 90% CI was lower than the predefined non-inferiority margin of 20%. Superiority of DE over SoC could not be demonstrated, as the upper bound of the 90% CI was above 0; see Table 13.

Table 13 Composite primary endpoint, intention-to-treat period, adjudicated data – RS

	DE		SoC	
Number of patients randomised	177 (100.0)		90 (100.0)	
Complete thrombus resolution	81	(45.8)	38	(42.2)
Freedom from recurrent VTE	170	(96.0)	83	(92.2)
Freedom from mortality related to VTE	177	(100.0)	89	(98.9)
Composite endpoint met	81	(45.8)	38	(42.2)
Difference in rate (90% CI)[1]	−0.038 (−0.141, 0.066)			
Difference in rate (95% CI)[1]	−0.038 (−0.161, 0.086)			
p-value for non-inferiority	<0.0001			
p-value for superiority	0.2739			

[1] Mantel-Haenszel weighted difference with age group as stratification factor

Source data: [c29773859, Table 15.2.1.1: 1]

Secondary endpoints

Freedom from major bleeding events

Primary analysis

An adjudication-confirmed major bleed was reported for 4 patients (2.3%) in the DE group and 2 patients (2.2%) in the SoC group. There was no statistically significant difference in the risk for major bleeding between treatment with DE and SoC (Table 14).

Table 14 Time to first major bleeding event, on-treatment period, adjudicated data – TS

	DE		SoC	
Number of patients treated, N (%)	176	(100.0)	90	(100.0)
Patients with major bleeding, N (%)	4	(2.3)	2	(2.2)
Kaplan-Meier estimate for the probability of freedom from major bleeding at Day 84 (90% CI)[1]	0.977 (0.948, 0.990)		0.977 (0.929, 0.993)	
Kaplan-Meier estimate of the difference in rate (90% CI)	0.000 (−0.032, 0.032)			

[1] Age group stratification factor not considered because of the low number of events

Source data: [c29773859, Table 15.2.2.1.1: 1]

The results of the sensitivity analysis, using the intention-to-treat period instead of the on-treatment period, confirmed the results of the primary analysis. A total of 5 patients (2.8%) with events in the DE arm and 2 patients (2.2%) with events in the SoC arm were included, resulting in a rate difference (90% CI) of 0.006 (−0.027, 0.039).

All-cause mortality

One patient (treatment group: SoC; age: 15 years) had died on-treatment because of an adjudication-confirmed major bleed. None of the patients in the DE arm died during the on-treatment period.

All individual components of the primary efficacy endpoints

In line with the primary endpoint, individual components of the primary endpoint occurred in comparable frequencies across treatment groups (see Table 15) except for recurrent VTE, which was less frequent with DE (4.0%) than with SoC (7.8%). The most common recurrent VTE was DVT.

Table 15 Summary of individual components of the primary endpoint, intention-to-treat period, adjudicated data – RS

	DE N (%)	SoC N (%)
Number of patients randomised	177 (100.0)	90 (100.0)
Complete thrombus resolution by Day 84	81 (45.8)	38 (42.2)
Recurrent VTE by Day 84	7 (4.0)	7 (7.8)
VTE-related death by Day 84	0	1 (1.1)

Source data: [c29773859, Tables 15.2.2.7: 1 to 15.2.2.7: 3]

Freedom from thrombus progression at end of therapy

Eleven patients were reported with thrombus progression during the intention-to-treat period (DE: 6 patients, 3.4%; SoC: 5 patients, 5.6%). In total 13.1% of patients were missing a VTE assessment at the end of the trial, therefore the proportion of patients confirmed free from thrombus progression at the end of the intention to treat period was 83.6% in the DE arm and 81.1% in the SoC arm.

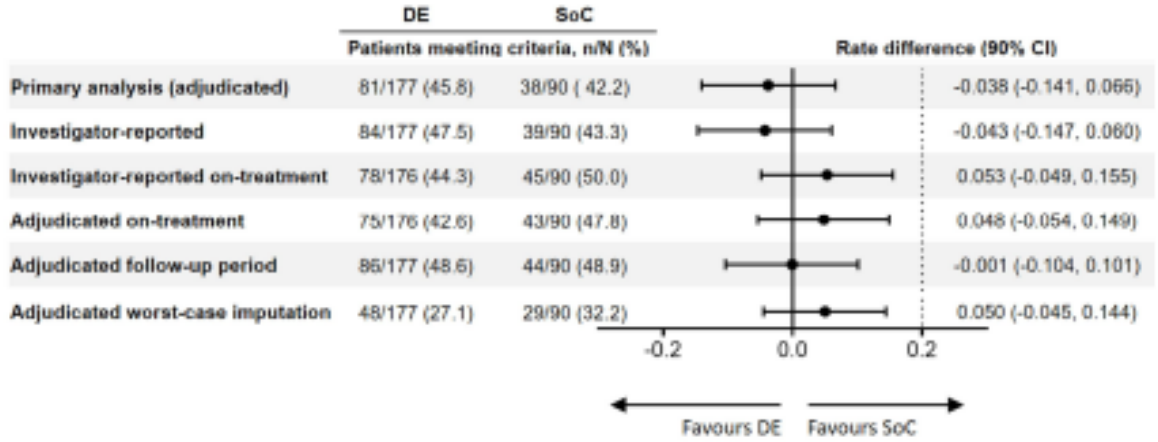
Ancillary analyses

Sensitivity analyses for the primary endpoint

The results of the sensitivity analyses were consistent with the result of the primary endpoint. Independent of the data source (adjudicated vs. investigator-reported), analysis period (on-treatment vs. intention-to-treat vs. full follow-up), and missing data imputation (LOCF vs. worst case), the upper bounds of the 90% CIs were consistently lower than the predefined non-inferiority margin of 20% (Figure 3). The same was true for the 95% CIs, demonstrating non-inferiority of DE to SoC at 1-sided alpha of 0.025 (Figure 3 and 3A).

Note: LOCF in this context means that missing VTE recurrence was considered as being free from recurrent VTE, and the last thrombus assessment was carried forward for the component of complete thrombus resolution. Worst case means that a missing VTE recurrence was imputed as being not free from recurrent VTE for early discontinued patients, and missing thrombus assessment at Visit 8 was imputed as not achieving complete thrombus resolution.

Figure 3 Summary of primary endpoint sensitivity analyses RS/TS



Source data: [c29773859, Tables 15.2.1.1: 1; 15.2.1.2: 2 to 15.2.1.2: 6]

When analysing the primary endpoint with a logistic regression by age group, the results showed that there was no treatment by age group interaction [c29773859, Table 15.2.1.2: 1], see also subgroup analyses in Section 2.2.2.

Additional sensitivity analyses with 95% CI were reported with the final study results:

Figure 3 A:

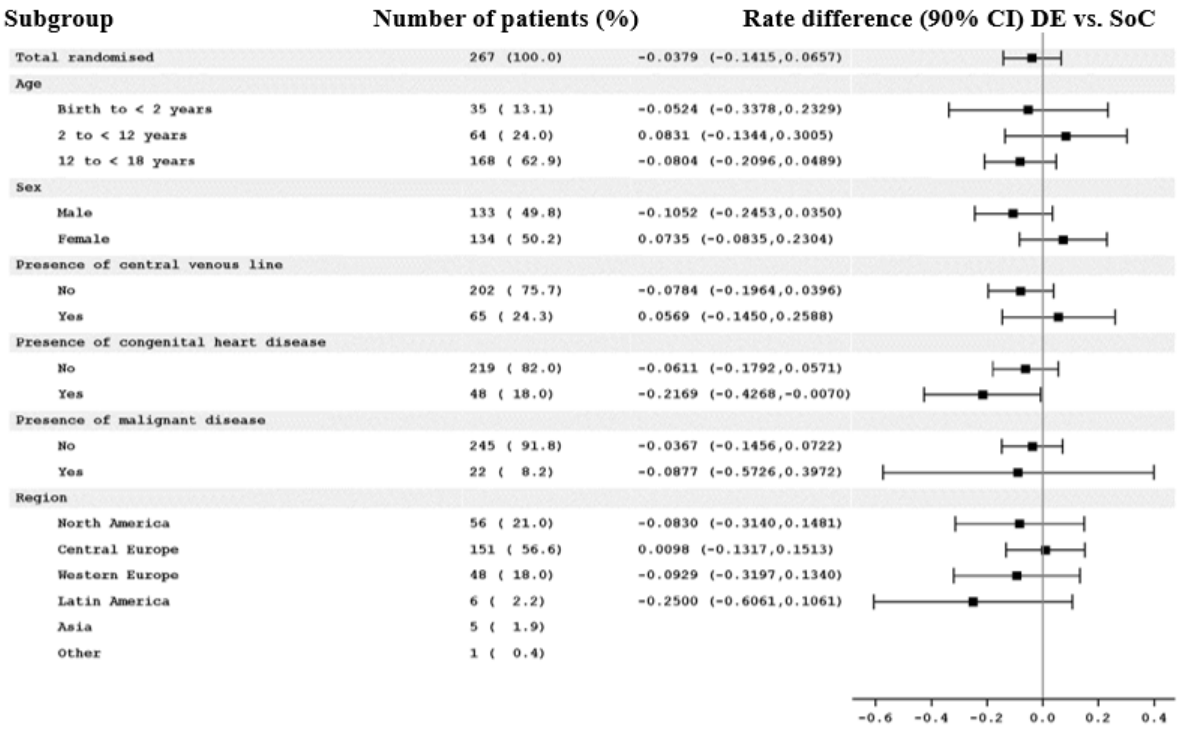
Table 175: 1 Summary of primary and sensitivity analyses with 95% CI for the efficacy endpoint

	DE	SoC	
	Patients meeting criteria, n/N (%)		Rate difference (95% CI)
Primary analysis (adjudicated)	81/177 (45.8)	38/90 (42.2)	-0.038 (-0.161, 0.086)
Investigator-reported	84/177 (47.5)	39/90 (43.3)	-0.043 (-0.167, 0.080)
Investigator-reported on-treatment	78/176 (44.3)	45/90 (50.0)	0.053 (-0.068, 0.174)
Adjudicated on-treatment	75/176 (42.6)	43/90 (47.8)	0.048 (-0.073, 0.169)
Adjudicated full follow-up	86/177 (48.6)	44/90 (48.9)	-0.001 (-0.123, 0.121)
Adjudicated worst-case imputation	48/177 (27.1)	29/90 (32.2)	0.050 (-0.063, 0.163)

Source data: [c29773859, Tables 15.2.1.1: 1, and 15.2.1.2: 2 to 15.2.1.2: 6]

Subgroup analyses

Consistent results were generally observed across subgroups. (Figure 4) Some small subgroups showed very wide confidence intervals, but there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors (central venous line, congenital heart disease, malignant disease).



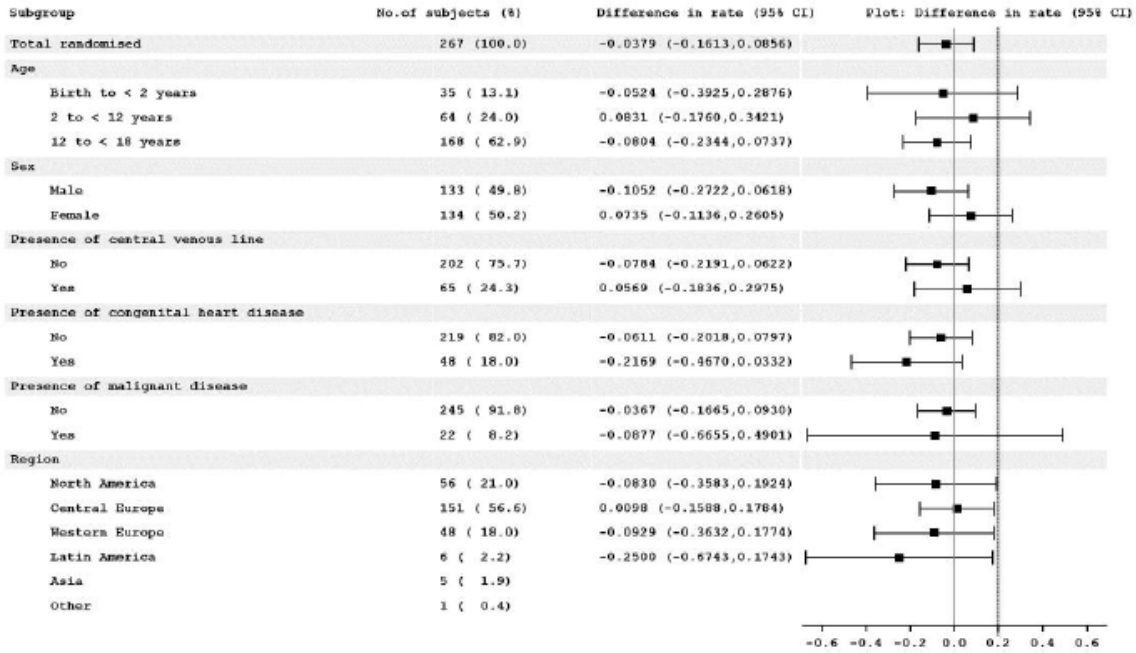
For the definition of subgroups, refer to Table 3.

Source data: [c29773859, Figure 15.2.1.3: 1]

Figure 4 Forest plot of the primary endpoint by subgroups, intention-to-treat period, adjudicated data – RS

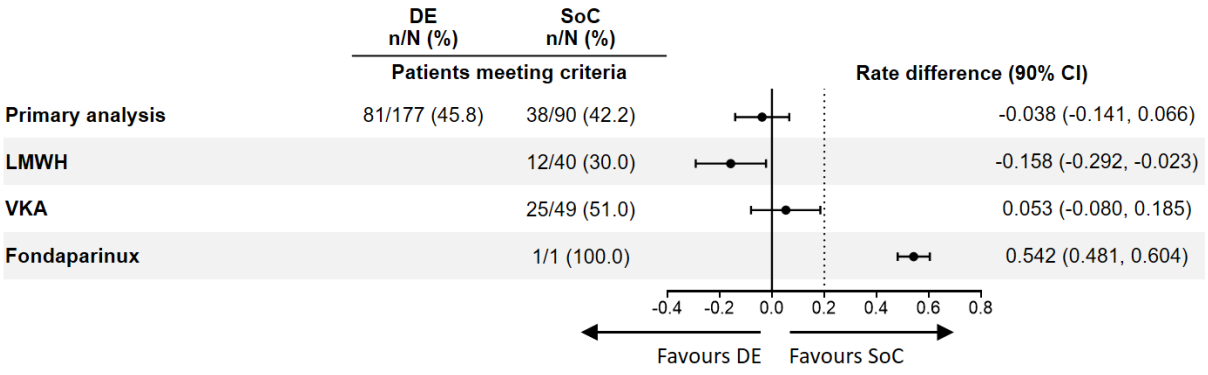
Additional subgroup analyses with 95% CI were reported with the final study results:

Figure 175: 1 Forest plot of rate difference with 95% CI for the efficacy endpoint by subgroup – adjudicated data in randomized set during ITT period



Source data: [c29773859, Figure 15.2.1.3: 1]

An analysis by type of control treatment (LMWH, VKA, or fondaparinux) showed differing results by treatment (see Figure 5); however, results have to be interpreted with caution, as the choice of control treatment was not randomised and the number of patients in the groups was unbalanced (i.e. 1 patient on fondaparinux vs. 177 patients on DE).



Source data: [c29773859, Tables 15.2.1.1: 1 and 15.2.1.3: 3]

Forest plot of the primary endpoint by type of control treatment, intention-to-treat period, adjudicated data – RS

Additional details on the VKA treatment is provided in the following table:

Table 198: 1 Shift table of reference range categories for laboratory values– treated set PT–INR

Treatment/ Visit	# Pts (%) with value at visit				Pts (%) with value at visit compared to baseline			
	N***	< LLN	[LLN, ULN]	> ULN	N at risk*	>= LLN to < LLN	N at risk**	<= ULN to > ULN
Standard of care (N= 46)								
Baseline	22	22 (100.0)	0	0				
Visit1/2 pre-treatment	22	22 (100.0)	0	0				
VISIT 2	2	2 (100.0)	0	0	0	0	0	0
VISIT 3	4	2 (50.0)	1 (25.0)	1 (25.0)	0	0	2	1 (50.0)
VISIT 4	34	9 (26.5)	7 (20.6)	18 (52.9)	0	0	16	9 (56.3)
VISIT 5	37	7 (18.9)	16 (43.2)	14 (37.8)	0	0	19	8 (42.1)
VISIT 6	40	16 (40.0)	17 (42.5)	7 (17.5)	0	0	19	1 (5.3)
VISIT 7	40	20 (50.0)	10 (25.0)	10 (25.0)	0	0	20	5 (25.0)
SOC TITRATION	15	8 (53.3)	3 (20.0)	4 (26.7)	0	0	9	2 (22.2)
EEOT	1	0	1 (100.0)	0	0	0	0	0
VISIT 8	42	19 (45.2)	16 (38.1)	7 (16.7)	0	0	22	4 (18.2)
Min value on treatment	46	37 (80.4)	6 (13.0)	3 (6.5)	0	0	22	1 (4.5)
Max value on treatment	46	1 (2.2)	16 (34.8)	29 (63.0)	0	0	22	14 (63.6)
Last value on treatment	46	20 (43.5)	18 (39.1)	8 (17.4)	0	0	22	4 (18.2)

Source: [attachment 1 to Question 198]

Summary of main study(ies)

The following tables summarise the efficacy results from the main efficacy study supporting the present application. The first table summarises the efficacy results in the overall patient population. The second table summarises the results according to the primary efficacy endpoint and its individual components, and on-treatment bleeding events and fatal events by treatment group and age strata. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for trial 1160.106: Overall and by treatment and age strata

Table 1 Summary of efficacy for trial 1160.106

Open-label, randomised, parallel-group, active-controlled, multicentre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study		
Study identifier	1160.106	
Design	Open-label, randomised, parallel-group, active-controlled, multicentre non-inferiority trial of DE vs. SoC in children from birth to less than 18 years • Recruitment in consecutive age strata (stratum 1: from 12 to <18 years of age; stratum 2: from 2 to <12 years of age; stratum 3: from birth to <2 years of age), based on recommendations of the Data Safety Monitoring Board that take into account analysis of data on PK, PD, dose adjustment from current stratum (percentage of dabigatran PK trough results within the predefined range); exposure-response PK/PD data and efficacy and safety data for consecutive stratum. • Randomisation ratio 2:1	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	The planned duration of treatment was 3 months after randomisation. Not applicable There was no extension phase in the trial. Patients from trial 1160.106 who had completed the treatment period in trial 1160.106 and required further anticoagulation for secondary prevention of VTE due to presence of a clinical risk factor could roll over into trial 1160.108
Hypothesis	The primary efficacy endpoint was tested for non-inferiority using a non-inferiority margin of 20% at a one-sided level of 0.05. Upon showing non-inferiority for the primary endpoint, the primary endpoint was subsequently tested for superiority at a one-sided level of 0.05.	
Treatments groups	DE	*Formulation and dose* Patients aged ≥8 years: age- and weight-adjusted DE dosing via capsules using 50 mg, 75 mg, 110 mg, and 150 mg capsules. Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): age- and weight-adjusted dosing via DE granules. Patients aged <12 months: age- and weight-adjusted dosing via DE oral solution *Treatment duration*: 3 months after randomisation *Number of patients randomized*: 177 patients

Treatments groups (continued)	SoC		A comparator product was not provided for this trial by the sponsor. Investigators decided on SoC treatment at time of randomisation: either LMWH or vitamin K antagonists (VKA) or fondaparinux. *Treatment duration:* 3 months after randomisation *Number of patients randomized:* 90 patients
Endpoints and definitions	Primary endpoint	Composite primary endpoint	Composite endpoint of • Complete thrombus resolution • Freedom from recurrent venous thromboembolic event (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism, thrombus progression) • Freedom from mortality related to venous thromboembolic event
	Main secondary endpoint	Freedom from MBE	Freedom from major bleeding events
	Main secondary endpoint	All-cause mortality	All-cause mortality
	Main secondary endpoint	Complete thrombus resolution	Complete thrombus resolution
	Main secondary endpoint	Recurrent VTE	Recurrent VTE
	Main secondary endpoint	VTE-related death	VTE-related death
Final database lock	18 Dec 2019		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intention-to-treat		

Descriptive statistics and estimate variability	Treatment group	DE	SoC
	Composite primary endpoint Patients randomised, N (%) Endpoint met, N (%)	 177 (100.0) 81 (45.8)	 90 (100.0) 38 (42.2)
	Freedom from MBE Patients treated, N (%) Patients with MBE, N (%) Probability of freedom from at Day 84 (90% CI) [2]	 176 (100.0) 4 (2.3) 0.977 (0.948, 0.990)	 90 (100.0) 2 (2.2) 0.977 (0.929, 0.993)
	All-cause mortality Patients treated, N (%) Number of patients died, N (%) Kaplan-Meier estimate of survival at Day 84 (90% CI) [3]	 176 (100.0) 0 1.000 (1.000, 1.000)	 90 (100.0) 1 (1.1) 0.989 (0.942, 0.998)
	Individual components of the primary endpoint Patients randomised, N (%) Complete thrombus resolution by Day 84, N (%) Recurrent VTE by Day 84, N (%) VTE-related death by Day 84, N (%)	 177 (100.0) 81 (45.8) 7 (4.0) 0	 90 (100.0) 38 (42.2) 7 (7.8) 1 (1.1)
Effect estimate per comparison	Composite primary endpoint	Comparison groups	DE vs. SoC
		Difference in rate [1]	−0.038
		90% CI 95% CI	(−0.141, 0.066) (−0.161, 0.086)
		p-value for non-inferiority p-value for superiority	<0.0001 0.2739
	Main secondary endpoint: Freedom from MBE	Comparison groups	DE vs. SoC
		Difference in rate [2]	0.000
		90%CI	(−0.032, 0.032)
	Main secondary endpoint: All-cause mortality	Comparison groups	DE vs. SoC
		Difference in rate [3]	−0.011
		90% CI	(−0.030, 0.007)
Note	Only results for primary and main secondary endpoints are included in this table.		

[1] Mantel-Haenszel weighted difference with age group as stratification factor

[2] Kaplan-Meier estimate; age group stratification factor not considered because of the low number of events

[3] Kaplan-Meier estimate pooling all age groups (age group not considered as stratification factor)

Table 161: 2 Adjudicated outcomes by treatment group and age strata according to the primary efficacy endpoint and its individual components, and on-treatment bleeding events and fatal events

	Dabigatran*			Standard of care†		
	12 to <18 years	2 to <12 years	0 to <2 years	12 to <18 years	2 to <12 years	0 to <2 years
Primary efficacy endpoint and its individual components (randomised set)						
No. of children	**112**	**43**	**22**	**56**	**21**	**13**
Composite primary endpoint‡ met, n (%)	47 (42·0)	21 (48·8)	13 (59·1)	19 (33·9)	12 (57·1)	7 (53·8)
Complete thrombus resolution	47 (42·0)	21 (48·8)	13 (59·1)	19 (33·9)	12 (57·1)	7 (53·8)
Freedom from recurrent VTE	106 (94·6)	42 (97·7)	22 (100·0)	50 (89·3)	20 (95·2)	13 (100·0)
Freedom from VTE-related death	112 (100·0)	43 (100·0)	22 (100·0)	55 (98·2)	21 (100·0)	13 (100·0)
On-treatment bleeding events and fatal events (treated set)						
No. of children	**111**	**43**	**22**	**56**	**21**	**13**
Bleeding events, n (%)	24 (21·6)	8 (18·6)	6 (27·3)	20 (35·7)	2 (9·5)	0
Major	2 (1·8)	1 (2·3)	1 (4·5)	2 (3·6)	0	0
CRNM	2 (1·8)	0	0	1 (1·8)	0	0
Minor	21 (18·9)	7 (16·3)	5 (22·7)	19 (33·9)	2 (9·5)	0
Bleeding-related deaths, n (%)	0	0	0	1 (1·8)	0	0
All-cause deaths, n (%)	0	0	0	1 (1·8)	0	0

*One adolescent patient randomised to dabigatran was not treated. In total, 119 children were treated with capsules alone, 42 were treated with pellets alone, 13 were treated with oral solution alone, one switched from capsules to pellets, and one switched from oral solution to pellets.
†LMWH, VKA, or fondaparinux.
‡Complete thrombus resolution, freedom from recurrent VTE, and freedom from VTE-related death.
CRNM=clinically relevant non-major. LMWH=low-molecular-weight heparin. VKA=vitamin K antagonist. VTE=venous thromboembolism

Source data: [c29773859, Tables 15.2.1.3: 1, 15.2.2.6: 1, and 15.2.2.6: 6]

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

Dosing recommendation

Number of patients with dose adjustments in the pooled population Phase IIb/III

The number of patients with DE dose adjustments during the on-treatment period was analysed. Since only one dose adjustment was allowed, this is equivalent to the number of DE dose adjustments. Overall, the DE dose was adjusted in 118 patients (36.0%) during the on-treatment period. In the majority of these patients, the DE dose was increased. DE dose adjustments were more frequent in the younger age groups than in the oldest age group (Table 16). There was no difference regarding treatment duration (i.e. ≥12 weeks vs. total.).

Table 16 Number of patients with DE dose adjustment during the on-treatment period by age group and treatment duration on DE – unique DE treated set in trials 1160.106 and 1160.108

	Birth to <2 years	2 to <12 years	12 to <18 years	Birth to <18 years
	Total	Total	Total	Total
Patients treated	30 (100.0)	74 (100.0)	224 (100.0)	328 (100.0)
Patients with dose adjustment [1]	20 (66.7)	42 (56.8)	56 (25.0)	118 (36.0)
Patients with DE up-titration	20 (66.7)	41 (55.4)	43 (19.2)	104 (31.7)
Patients with DE down-titration	0	2 (2.7)	15 (6.7)	17 (5.2)

[1] One patient had an up-titration in both trials and is counted only once for up-titration. Three additional patients had an up- and down-titration.

Source data: [c31325825, Table A.4: 2]

Additional details on dose adjustments in the study population receiving DE in the controlled 1160.106 study is provided in the following table:

Stratum	Birth to <2 years	2 to <12 years	12 to 18 years	Total
Treated patients, N	22	43	111	176
Patients with DE dose adjustment, N	14	26	23	63
Patients who discontinued DE due to failure to reach target range, N	4	8	5	17
Patients able to reach DE target range after 1 dose adjustment, N (%)	10 (45.5)	18 (41.9)	18 (16.2)	46 (26.1)

The percentage of patients able to reach DE target range after dose adjustment = (number of patients with DE dose adjustment - number of patients discontinued DE due to failure to reach target range) / number of treated patients

Appropriateness of dosing algorithm

The dosing algorithm for trials 1160.106 and 1160.108 was developed based on RE COVER [U09-1400], which was a Phase III trial with DE in adults diagnosed with acute VTE. In RE-COVER, dosing was fixed (150 mg bid) and efficacy was demonstrated without titration or considering dabigatran plasma concentrations. Efficacy was assumed to be adequate at dabigatran concentrations above the 10th percentile (26 ng/mL) of the trough concentrations observed in RE COVER. Since the RE COVER trial showed a favourable treatment effect of DE in

adults, the predefined trough concentration had a reasonable likelihood to be effective and safe with a positive benefit/risk ratio in children of all ages.

For this submission, data from all available paediatric trials (1160.88, 1160.89, 1160.105, 1160.106, and 1160.108) were used to refine the dosing algorithm for paediatric patients. Refer to Module 2.7.2 for details.

Acceptability of an age-appropriate formulation

Studies of acceptability of DE new formulations have been done in all trials.

In trials 1160.106 and 1160.108, questionnaires were available for the investigator/site staff, patients, and parents/caretakers. Responses were provided based on tick boxes in the questionnaire. Trials 1160.88, 1160.89, and 1160.105 had an investigator assessment only.

Granules and capsules

In trial 1160.106, the administration of capsules and granules was generally assessed as good or acceptable by investigators, parents, and patients. In trial 1160.108, the capsules were generally well accepted by investigators, parents, and patients. From Visit 4 to 11, the percentage of patients stating that they could not take the capsules for a longer time was not greater than 5%. Granules were generally assessed as good or acceptable by investigators, parents, and patients. In trial 1160.88, all 9 treated patients had good tolerability of the capsules, as per investigator assessment.

Oral solution

The acceptability of the oral solution was assessed in trials 1160.89 (Phase IIa, single dose or 3 day bid dosing), 1160.105 (Phase IIa with single dose), and 1160.106 (Phase IIb/III, treatment up to 3 months). The oral solution was either available with or without peach flavour.

Acceptability of the flavoured oral solution in 1160.89 – TS

Table 17 Acceptability of the flavoured oral solution in 1160.89 – TS

	Single dose		Multiple dose	All patients
	1 to <2 years N (%)	2 to <12 years N (%)	2 to <12 years N (%)	N (%)
Treated patients in 1160.89	6 (100.0)	9 (100.0)	3 (100.0)	18 (100.0)
Tolerability				
Good	2 (33.3)	1 (11.11)	3 (100.0)	6 (33.33)
Satisfactory	1 (16.67)	2 (22.22)	0	3 (16.67)
Not satisfactory	2 (33.33)	4 (44.44)	0	6 (33.33)
Bad	0	2 (22.22)	0	2 (11.11)
Not assessable	1 (16.67)	0	0	1 (5.56)

Source data: [c09069268, Table 15.3.3.2: 2]

Acceptability of the oral solution (flavoured or unflavoured) in 1160.105 for patients <12 months of age

Acceptability of the oral solution in 1160.105 – TS

Table 18 Acceptability of the oral solution in 1160.105 – TS

Patient #	Tolerability
Flavoured oral solution	
subject #	Good
Subject #	Good
Subject #	Satisfactory
Subject #	Bad
Unflavoured oral solution	
Subject #	Good
Subject #	Good
Subject #	Good
Subject #	Good

Source data: [c09085437, Appendix 16.2.8, Listing 3.2, Appendix 16.1.6 and Appendix 16.2.4, Listing 1]

Acceptability of the oral solution (flavoured or unflavoured) in 1160.106 for patients <12 months of age

A total of 14 patients were treated with oral solution in trial 1160.106. Of these, 13 patients provided data on tolerability: 8 for the flavoured and 5 for the unflavoured oral solution. One of the 8 patients receiving flavoured oral solution switched to granules.

Overall, the investigators assessed the patient's acceptability of the oral solution mostly as good or satisfactory across visits. To map the different questionnaires across CRF versions for a combined analysis, scores were assigned to the acceptability questions. Thus, a lower score number indicates better acceptability. The mean score at the end of treatment for the overall acceptability question was 1.2 (SD 0.4) for the unflavoured and 1.6 (SD 0.8) for the flavoured oral solution. For the unflavoured oral solution, 2 of 5 patients had difficulties to swallow the oral solution because of its taste and thus did not always take the oral solution: 1 patient reported the difficulties only at the first assessment (Day 3) and 1 patient had the difficulties for all 3 assessments. The other 3 patients on unflavoured oral solution did not have difficulties to swallow because of the taste. For the flavoured oral solution, 1 of 8 patients reported difficulties to swallow because of the taste at the first assessment. Other reasons for missed intake were having forgotten to take the medication or surgery. The intake was possible all the time (for the majority of patients) or very often (a few instances).

Study 1160.108

An open label, single arm safety prospective cohort, multi-centre, phase III study (1160.108) was conducted to assess the safety of dabigatran etexilate for the prevention of recurrent VTE in paediatric patients from birth to less than 18 years. Patients who required further anticoagulation due to the presence of a clinical risk factor after completing the initial treatment for confirmed VTE (for at least 3 months) or after completing the DIVERSITY study were allowed to be included in the study. Eligible patients received age and weight adjusted doses of an age-appropriate formulation (capsules, coated granules or oral solution) of dabigatran etexilate until the clinical risk factor resolved, or up to a maximum of 12 months. The primary endpoints of the study included the recurrence of VTE, major and minor bleeding events and the mortality (overall and related to

thrombotic or thromboembolic events) at 6 and 12 months. Outcome events were adjudicated by an independent blinded adjudication committee.

Overall, 214 patients entered the study; among them 162 patients in age stratum 1 (from 12 to less than 18 years of age), 43 patients in age stratum 2 (from 2 to less than 12 years of age) and 9 patients in age stratum 3 (from birth to less than 2 years of age). During the on-treatment period, 3 patients (1.4%) had an adjudication-confirmed recurrent VTE within the first 12 months after treatment start. Adjudication-confirmed bleeding events during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. The majority of the bleeding events were minor. In 3 patients (1.4%), an adjudication-confirmed major bleeding event occurred within the first 12 months. For 3 patients (1.4%), adjudication-confirmed CRNM bleeding was reported within the first 12 months. No on-treatment deaths occurred. During the on-treatment period, 3 patients (1.4%) developed post-thrombotic syndrome (PTS) or had worsening of PTS within the first 12 months.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of DE in the paediatric population was investigated in a single randomised controlled phase IIB/III trial, i.e. trial 1160.106. This trial had 2 primary objectives. The one primary objective was to estimate the effect of 3 months intervention comprising oral DE treatment following 5-21 days initial parenteral treatment versus Standard of Care (SoC) on survival with recurrence-free complete thrombus resolution in paediatric patients 0- <18 years with VTE. The other primary objective was to document the appropriateness of the proposed DE dosing algorithm.

Six other trials in this line extension application dossier were single-arm bioavailability, PK, PD, safety and tolerability trials, i.e. the phase I trials 1160.87 and 1160.194; the phase IIa trials 1160.88; 1160.89, and 1160.105; and the phase 2B/III 12-months safety trial 1160.108. Data from these trials are discussed in details in the sections on Clinical Pharmacology and Clinical Safety, respectively.

Based on the interim analysis, the Applicant was requested to confirm that patients disposition between DE and Soc arms are statically similar, especially regarding the youngest age category of infant aged less than 2 years of age. Based on the final CTR, randomization between both arms and different age strata are equivalent and there is no difference between treated number of children according to the distribution 2 DE / 1 SOC. This is true also for the youngest category [Stratum 3 from birth to < 2 years (DE: 22 patients, SOC: 13 patients)].

In the PIP for the interim analysis for the youngest age-group with the fewest number of patients enrolled, it is was accepted to pool the numbers from trial 1160.106 and 1160.108 to meet the requirement. The patient populations in the two trials are similar and the pooling is acceptable for the analysis of safety, PK and PD endpoints in this group, while only the patients in trial 1160.106 may contribute to the efficacy endpoints. It is noted that the primary efficacy analyses were done on the total patient population in trial 1160.106 as the trial was not powered for analysing each age-group separately.

However, according to the *CHMP Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease (Draft -*

EMA/CHMP/763438/2017), since "*similarities between younger children and adults in clinical factors for VTE, course and response to VTE treatment are not entirely straightforward, an extrapolation of efficacy and safety data from adults only based on similar exposure and PD data is not supported, and some extent of efficacy and safety data in children are needed*". For the patient selection for clinical studies "*an adequate representation of paediatric patients of different age ranges is necessary*" (…). "*In particular, it is of importance to study paediatric patients < 2 yrs. due to differences in underlying aetiologies and thrombus location, as well as a not fully matured coagulation/fibrinolysis system*."

The final analysis has provided updated numbers of patients within the **youngest age-group Birth to <2 years**, including the numbers of patients <1 year and <6 months, respectively. There were **30 patients** in this age-group receiving DE in study 1160.106, of whom roughly half discontinued from trial medication prematurely. According to the final pooled analysis of all patients exposed to DE in the paediatric program, i.e. studies 1160.88, 1160.89, 1160.105, 1160.106 and 1160.108, there was a total of 27 patients <1 year of age exposed to DE in these studies. Of those, 8 patients were exposed to a single dose of DE in the Phase IIa single-dose study 1160.105. A total of 19 patients <1 year of age was exposed to multiple doses of DE in the two Phase II/III studies 1160.106 and 1160.108 combined. There seems to be 11 patients < 6 months of age treated with DE in study 1160.106.

However, there continue to be limitations of patient numbers and treatment exposures in the Birth to <2 years age-group considering the differences in terms of immaturity of coagulation system and renal function and leading index VTE types compared to the older age-groups and adults.

Therefore, a **SAG meeting was convened** to discuss the adequacy of relying on efficacy and safety data from adults in the youngest children, to discuss the safety profile in this age-group considering the limitations of patient numbers and treatment exposures, and to discuss whether particular precautions should be applied in the youngest children if dabigatran is approved in all age-groups.

Additional expert consultation

Upon request from the CHMP, this SAG CVS meeting was convened on 07 September 2020.

FINAL PRADAXA SAG CVS ANSWERS

1. **The MAH is proposing an indication including children of all ages. However, the experience of using dabigatran in children younger than 2 years is limited and safety in this age group is currently questioned.**

    a. **Please discuss the adequacy of relying on efficacy and safety data from adults in the youngest children in light of the known age-related development of haemostasis.**

    b. **Please discuss the acceptability of the safety profile in this age-group considering the limitations of patient numbers and treatment exposures: While the overall frequencies of major and CRNM bleedings were low to moderate, there was an imbalance with on-treatment bleeding events occurring in 6/22 (27.3%) children aged 0 to < 2 years in the dabigatran group, and 0 (N=13) in the SoC group. This is of concern considering the apparently low exposure as reflected in the high rates for dose adjustment and discontinuations, and the mean DE trough values towards the lower limits of the recommended range.**

    c. **Should particular precautions be applied in the youngest children if dabigatran is approved in all age groups?**

The experts acknowledged that evidence of safety and efficacy with regards to Standard of Care (SoC) comes mainly from studies in adults and data generated from RCT in children is lacking. However, there is a relatively large amount of long-term experience with the use of SoC in the treatment and prevention of venous thromboembolism (VTE) in children.

The experts did not consider that relying solely on efficacy and safety data from adults would be appropriate to draw conclusions regarding the use of dabigatran in children below 2 years old. The experts found the efficacy and safety results in studies in children of all ages reassuring. Overall similar PK data have been observed in children as measured in the adult studies (i.e. values within Cmax, AUC, Cthrough adult ranges). The scarcity of data in the youngest age category was noted (a total of 30 patients below 2 years old in both trials 106 and 108) but the existence of some evidence in this group was welcomed given the known difficulties in recruiting children into the clinical trials with anticoagulants.

Most experts agreed that the safety profile of dabigatran in the treatment and prevention of VTE in children is acceptable also in children below 2 years old. Most of the observed bleedings were only minor and bleedings are also a known complication of the anticoagulant treatment in general. The experts found it reassuring that there was only one major bleeding event recorded in both studies in the dabigatran group (ICH in a subject with meningitis with full recovery). A possibility of underreporting of minor bleedings for SoC in the open trial was suggested based on historical experience.

The group did not recommend specific precautions for the youngest children. One expert suggested the need for monitoring of plasma concentrations in some very specific paediatric groups to establish anti-coagulation ranges in e.g. small bowel disease.

One expert was of opinion that treatment with dabigatran of children below 2 years old is not acceptable considering the limited number of patients studied, and the relatively high number of bleedings observed in dabigatran group compared to SoC (even if only minor) without additional benefit in efficacy. The expert believed this to be of concern given the observed dabigatran exposure was on the lower limits of the recommended range and suggested a further clinical study in the youngest group of children to address these concerns.

Some concerns were expressed regarding the proposed 20% increase in the final dosing algorithm for the new pellet formulation due to low exposure of dabigatran observed in clinical studies as reflected in the high rates of per protocol dose adjustments, discontinuations and the mean dabigatran etexilate trough values tending towards the lower limits of the recommended range. The concern was that the proposal is based on modelling and has not been tested in clinical trials.

Furthermore, the group emphasized the need for post-authorisation data collection to better characterise the safety profile of dabigatran as the only way of further characterising the use of dabigatran etexilate in the very young children.

2. **The proposed paediatric target population includes some types of VTE for which evidence of efficacy and safety in adults is not available, and thus the evidence relies more heavily on the observed pediatric data from the phase IIb/III studies alone. This is of particular concern for cerebral vein and sinus thrombosis (CVST) and central line thrombosis (CLT).**

    a. **Concerning CVST, considering that this is a condition which is generally known to be associated with intracerebral haemorrhage, please discuss if there are subpopulations (age, disease states, underlying disease conditions) or instances of**

CVST where the risk of bleeding may be too high? In the study 1160.106 there was one case with ICH in the context of meningitis. This led to an amendment to implement an exclusion criterion of active ongoing meningitis, encephalitis and intracranial abscess in the study.

b. Is the proposed treatment duration adequate? (at least 3 months in the study 1160.106, possibility for extension in 1160.108). Is there a need for particular precautions/monitoring? Based on what is known about paediatric CVST, please discuss the adequacy of extrapolating data on efficacy and safety of treatment with pradaxa in older children with CVST to children < 2 years of age, for whom there is very little data in the phase III study

c. As reflected in the literature the overall benefits of anticoagulation are generally less clear for CLT than for other pediatric VTE-subtypes. Considering this please, discuss the relevance of the duration of VTE anticoagulation stated in the current Pradaxa SmPC "short duration at least 3 months". Are there particular subpopulations or instances of CLT where the risk of bleeding is considered too high? Please discuss the relevance of data on efficacy and safety in subjects with chronic or sub-acute CLT for the proposed target indication.

The experts admitted that both CVST and CLT are observed mainly in children. The fact that there are only limited data available supporting efficacy and safety of dabigatran by type of VTE subgroup was noted. However, it was felt that the available evidence doesn't give rise to any particular concern and therefore the group recommended dabigatran to be available also for treatment of children in these two conditions.

Moreover, it was noted that the guidelines support the need for anticoagulant treatment in CVST despite the known risk of bleeding, especially intracranial bleeding. In fact, CVST with intracranial bleeding is an indication for anticoagulants, since the bleeding usually diminishes if the thrombus resolves. In the paediatric studies with dabigatran in CVST the rate of bleeding events was as expected and comparable to the SoC arm (5 bleeds in 20 patients with dabigatran [with 1 ICH and 4 minor] vs 4 bleeds in 6 patients with SoC [with 1 ICH and 3 minor]). In line with the exclusion of patients with meningitis, encephalitis and intracranial abscess in the clinical study the experts suggested a contraindication regarding these conditions. It was challenging to provide any precise recommendation in case these inflammatory conditions develop during treatment with dabigatran and treatment should be considered on case-by -case basis.

The potential benefits of anticoagulant therapy may be less clear for CLT than for other types of VTE due to additional contributing factors, namely lack of timely recognition of symptoms, the different degrees of occlusion and different local or systemic prothrombotic states. It was noted that anticoagulation treatment is not effective in the resolution of an already formed thrombus but the expert highlighted the importance of preserving catheters in these very sick children and hence the need for treating the thrombosis. Thrombus resolution rates in CLT group were similar in dabigatran and SoC groups (74% in DE vs 75% in SoC).

Regarding the duration of treatment in CVST and CLT types the experts indicated that this depends on the presence of underlying risk factors and should follow the clinical practice guidelines: for CVST up to 3 months or longer, if the index thrombotic risk factor remains even in the presence of bleeding. For CLT treatment duration is not clearly specified. There is one study ongoing comparing VTE regimens of different duration (6 weeks vs 3 months; The Kids-DOTT trial [NCT00687882]) with results available in 2021 that should further inform the guidelines).

It is agreed that very young children have physiologically lower circulating antithrombin levels and lower coagulation factor levels. As discussed at the SAG meeting, the experts did not consider that relying solely on efficacy and safety data from adults would be appropriate to draw conclusions regarding the use of dabigatran in children below 2 years old. With respect to the PK/PD relationship in the youngest children,

both aPPT and ECT showed higher values, but the differences could be explained by higher baseline values, whereas the PK/PD relationship was similar between the young children and the healthy adults when assessing the relative change of aPTT, ECT, and dTT from baseline. Please refer to the pharmacology section of this report for details. The experts found that overall similar PK data have been observed in children as measured in the adult studies (i.e. values within Cmax, AUC, Cthrough adult ranges). The scarcity of data in the youngest age category was noted (see numbers above), but the existence of some evidence in this group was welcomed given the known difficulties in recruiting children into the clinical trials with anticoagulants.

A comparison of DE and SoC treatment groups in trial 1160.106 showed discontinuation rates for other AEs of 13.6% and 0% for DE and SoC, respectively. Discontinuation for protocol non- compliance occurred in 4.5% of patients on DE and 0% of patients on SoC. Thus, while discontinuation for tolerability was infrequent, it was more frequent for DE than SoC. However, the discontinuations caused by AEs in the DE group do not reveal any specific pattern. It is acknowledged that it should be considered that patients who switched from DE to SoC were regarded as permanently discontinued, while patients in the SoC group who switched the SoC type were still regarded as on treatment for SoC.

To justify that routine laboratory monitoring of dabigatran therapy should not be routine practice, the MAH argued based on the generally predictable PK/PD profile of dabigatran that the age- and weight adjusted dosing regimen in children resulted in expected dabigatran concentrations that do not require careful laboratory monitoring in routine clinical setting. After modelled revision of the dosing algorithm, which involves increase of the coated granules dosing by 20%, it is expected that more patients will reach the target therapeutic range.

Furthermore, to elaborate on the impact of dose adjustments, the Applicant has provided data on comparison between the achieved trough geometric Mean (gMean) over all visits following no more than 1 dose titration, and the trough gMean overall visits normalised to the nomogram-based target dose, as well as following any dose titrations (please see section on Adjustments to reach target plasma dabigatran concentrations above). The Applicant's interpretation of the gMean plasma concentration before versus after the titration is that the effect of dose adjustment was minimal, i.e. increase from 79.8 ng/mL to 81.7 ng/mL. However, this may only be true for the overall gMean. In the age-groups Birth to <2 years, Birth to <6 months, 6 months to >2 years and 2 to >12 years the effect of dose adjustment is more pronounced. It is only in the oldest age group 12 to 18 years there is minimal effect of dose adjustment. Since that group is the largest, i.e. 88/139 (63.3%) it adds most weight to the overall gMean. It is acknowledged that the revised dosing algorithm, derived from simulation of the phase II/III study results, prescribes higher doses of coated granules. These are intended as age-appropriate dosage form in the younger age-groups 1 – <8 years of age. This largely correspond to the age-groups with pronounced effect of dose adjustment in the study. It is expected that more patients in these age-groups will reach the target therapeutic range without need for dose adjustment. The observed pronounced effect of dose adjustment in the younger age-groups seen in the study may then become less relevant. The bleeding safety aspect of the increased dose of coated granules in the modelled revision of the dosing algorithm will be addressed with a requested post-authorisation safety surveillance (PASS) study, see below.

As discussed at the SAG meeting, the group of experts did not recommend specific precautions such as routine plasma concentration monitoring for the youngest children. However, one expert suggested the need for plasma concentration monitoring in some very specific paediatric groups to establish anti-coagulation ranges in e.g. small bowel disease. The Applicant argued that clinical characteristics of the patient have been proven to be most reliable to support dosing decisions by HCPs and proposed to add a statement in section 4.4 of the SmPC to that effect instead of plasma concentration monitoring in these patients. It was agreed

that the clinical characteristics of the patients with potential absorption impairment, e.g. because of small bowel disease, may support the dosing decision by the prescriber including considerations to use an anticoagulant with parenteral route of administration. This is reflected in section 4.4 of the SmPC.

There was an imbalance in the number of treatment emergent bleedings in the youngest cohort. On-treatment bleeding events occurred in 6/22 (27.3%) children aged 0 to < 2 years in the dabigatran group, one of which was a major bleed, and 0 (N=13) in the SoC group. In light of the apparently low exposure, with a large proportion discontinuing treatment early and/or doses that were initially too low to be accepted based on laboratory monitoring of dabigatran concentration, and with mean dabigatran trough values in this age group just above the lower limit of the recommended range, these data were of concern to the CHMP. In addition, as discussed in the SAG meeting, as the study has shown non-inferiority with respect to efficacy, but not superiority, the observed imbalance of mostly minor bleeding should be investigated further. Therefore, in line with the recommendations from the SAG experts, it was agreed that there is a need for post-authorisation data collection to characterise better the safety profile of dabigatran. This was considered as the only way of further characterising the use of dabigatran etexilate in the very young children. The Applicant has provided a draft synopsis for non-interventional European multinational multi-centre cohort study based on newly collected data of patients administered dabigatran for VTE treatment or prevention of recurrent VTE (for details please, see the discussion on Clinical Safety).

In contrast to the adult patient population with VTE, the paediatric patient population with VTE include a high proportion of patients with central line thrombosis (CLT), and a tangible proportion with cerebral venous sinus thrombosis (CVST). Central venous line thrombosis (CLT) as Index type VTE was more frequent in the younger age-groups Birth to <2 years and 2 to <12 years than in the older age-group12 to <18 years. This is expected. Within the age-group Birth to <2 years, the break-down on the smaller age-groups Birth to <6 months, 6 to <12 months and 1 to <2 years did not show any clear distribution pattern as the numbers in each group was small. Data from the literature show that, in general, the majority of patients with CLT are asymptomatic. This is explained by the fact that this VTE type is primordially hospital acquired and difficult for the clinician to distinguish from the underlying condition causing the hospitalisation. In the trials 1160.106 and 1160.108, an objective diagnosis of the VTE by an imaging technique was required for enrolment and therefore, symptomatic and asymptomatic patients were included as the inclusion criterion was based on a positive imaging of a VTE. This approach was accepted. As expected, the underlying conditions in patients with CLT were most frequently cancer (only in the DE arm) and congenital heart disease, including heart failure.

It was acknowledged that for CLT treatment duration is not clearly specified. It is noted that there is one study ongoing comparing VTE regimens of different duration (6 weeks vs 3 months; The Kids-DOTT trial [NCT00687882]) with results available in 2021 that should further inform the guidelines). The Applicant has provided adequate justification for the required treatment duration of 3 months in study 1160.106. The actual treatment duration in the CLT group was shorter in the DE arm, mean 75.3 days, than in the SoC arm, mean 90.1 days, and in the DE arm it was shorter in the youngest age-groups: Birth to 6 months: mean 57.0 days, 6 to <12 months: mean 68.5 days, 1 to <2 years 84.0 days, 2 to < 12 years: mean 76.3 days and 12 to <18 years: mean 83.5 days. In the SoC arm treatment duration was overall in the range of 90 days, with slightly longer duration in the youngest age-group Birth to <2 years, mean: 96.2 days (with no clear trend in the smaller age-groups within this group), than in the older age-groups, 2 to <12 years, mean 85.8 days, and 12 to <18 years, mean 87.0 days. The overall bleeding rate in patients with symptomatic, asymptomatic and chronic CLT thrombosis was low with one major bleeding in the DE arm, age-group 2- <12 years, and one minor bleedings, age-group 0 – 6 months in study 1160.106 and one patients with several minor bleedings in study 1160.108. These incidences do not suggest a different bleeding pattern in CLT patients

compared to the overall patient population. The treatment durations in the CLT group did not differ from the treatment durations of the overall study population in total and broken down on age- and treatment groups. It is accepted that a different length of therapy for children with catheter-related VTE is not recommended.

The proportions of patients with CVST was greater in the lower age-groups Birth to <2 years (with no clear pattern in the smaller age-groups within this group) and 2 to <12 years, than in the older age-group 12 to <18 years. This is as expected. The patient selection excluded patients with CVST accompanied with intracranial bleeding. For patients with CVST, the frequencies of any bleeding were 5 of 20 patients (25%) on DE and 4 of 6 patients (66.7%) on SoC. No dependency on age was observed. There was one major bleed in each treatment group and no clinically relevant non-major bleed. Because of a major bleeding in the DE group in a subject with meningitis, an exclusion criterion on CVST with intracranial infection was implemented in the study. As discussed with the experts at the SAG, the guidelines support the need for anticoagulant treatment in CVST despite the known risk of bleeding, especially intracranial bleeding. In fact, according to the SAG experts, CVST with intracranial bleeding is an indication for anticoagulants, since the bleeding usually diminishes if the thrombus resolves. In the paediatric studies with dabigatran in CVST the rate of bleeding events was as expected and comparable to the SoC arm (5 bleeds in 20 patients with dabigatran [with 1 ICH and 4 minors] vs 4 bleeds in 6 patients with SoC [with 1 ICH and 3 minors]). In line with the exclusion of patients with meningitis, encephalitis and intracranial abscess in the clinical study the experts suggested a contraindication regarding these conditions. However, it was challenging to provide any precise recommendation in case these inflammatory conditions develop during treatment with dabigatran and treatment should be considered on case-by -case basis. Therefore, a warning statement in section 4.4 on haemorrhagic risk has been updated with active meningitis, encephalitis and intracranial abscess added to the haemorrhagic risk factors, and the exclusion criterion on these conditions has been added to the description of study 1160.106 in section 5.1 of the SmPC.

Both study 1160.106 and 1160.108 included symptomatic as well as asymptomatic patients with respect to the VTE. In particular, it is noted that patients with CTL are often asymptomatic with respect to the VTE, which is acknowledged. For patients with acute VTE, the VTE recurrence rate at 3 months was slightly higher (4.0%) than in patients with chronic VTE (0.9%) treated with DE and an approximate pre-treatment of 3 months. The bleeding risk at 3 months was higher in patients with acute VTE (21.6%) than in patients with chronic VTE (18.6%), treated with DE. But this analyse cannot be done without considering the very important difficulties to include patients less than 18 years, and above all the youngest ages in clinical trials. In addition, VTE in children remains a rare condition. The most difficult challenge in this paediatric extension procedure was the recruitment of subjects. In trials 1160.106 and 1160.108 the main objectives were to assess the efficacy and safety of DE relative to SoC and to document the appropriateness of the proposed DE dosing algorithm for use in patients from birth to less than 18 years of age. No sub groups analysis in symptomatic versus asymptomatic patients had been planned. As discussed at the SAG meeting, while recognizing the scarcity of data in the youngest age category was noted, "*the existence of some evidence in this group was welcomed given the known difficulties in recruiting children into the clinical trials with anticoagulants*".

Though the analyses (interim and final) were not consistent with a sequential design as this should have been, the Applicant's has justified this approach as it was agreed in the context of the PIP approved by the PDCO. The submitted final analysis including all participants in the trial confirms and fully supports the interim analysis outcome previously provided. At the time of the interim analysis, the 10% type-I error was not fully justified in the context of also using a much wider 20% non-inferiority margin. With the final analysis, additional 95% CIs have been provided for analyses including sensitivity analyses on the final population analysis (267 patients). The 95% confidence limits of the treatment effect in the primary and

sensitivity analyses show consistency with the non-inferiority conclusion. Same consistency is noticed in subgroups analyses and except for female subgroup, only small size subgroups display confidence limits exceeding the non-inferiority margin, which is understandable.

The design of trial 1160.106 was an open-label, randomised, controlled, non-inferiority trial of DE versus Standard of Care (SoC), which included UFH, LMWH, VKA, or fondaparinux according to clinical practice. It appears that 46 patients in the SoC arm received VKA treatment. This is more than half the total of 90 patients enrolled in the SoC arm. However, the TTR was not recorded or calculated for patients on VKA nor was there a pre-specified target TTR that had to be achieved. Among 22 patients with INR values at baseline and pretreatment visit 1 and 2, all were below 2. At visits 4 through visit 8 between 34/46 (73.9%) to 42/46 (91.3%) had INR values measured. At these visits, between 26.5% to 50% had values below 2, 20.6% to 42.5% had values between 2-3, and 6.5% to 52.9% had values above 3. The Applicant argues that TTR is known to be low in children and the observation time in trial 1160.106 was limited. However, it is noted that a Forest plot of the primary endpoint by type of control treatment seems to favor VKA treatment although not statistically significant and still within the NI conclusion of the primary analysis (see subgroup analyses above). Given the known difficulties with VKA treatment in children, the lack of data on TTR and a defined INR target for the VKA treatment it is surprising that more than half of the children in study 1160.106 were treated with VKA. In current clinical guidelines on treatment of paediatric VTE, LMWH is generally preferred over VKA (Albisetti M et al., UpToDate 2020). However, the Applicant argues that the SoC was reflecting clinical practice as it was up to the investigator to choose from several SoC treatments based on local practice. The Applicant did not supply the SoC treatments, only the dabigatran in the respective age-appropriate dosage forms. Therefore, the distribution of VKA and LMWH, respectively, observed in the main study is reflecting the investigators clinical preferences:

- Children 2 to 18 years, VKA (53,3%) and LMWH (45,4%)
- Children birth to 2years, VKA (61,5) and LMWH (38,5%)

The difference between VKA and LMWH is more pronounced in the youngest age-group, possibly because the VKA is available as oral solution. The Applicant argued that the on INR observed in patients treated with VKA in study is similar to what has been reported for VKA control in children in the literature (Bergman Santos B 217). Despite the ACCP guidelines recommend monitoring of anti-Xa activity to guide dosing for LMWH, and the protocol stating*: "patients assigned to take SoC were to follow the investigator's recommendation for adequate dosing and administration based on the products locally approved and in consideration of local treatment guidelines. The SoC dose was to be monitored regularly as appropriate (e.g. INR for VKAs)"*, anti-Xa monitoring in patients on LMWH was not done routinely by the investigator. It is acknowledged, that monitoring of the anti-Xa activity is only really required in case of *"careful biological monitoring by anti-Xa activity measurement in renally impaired patients"* (Lovenox Art 30 referral 2016 EMEA/H/A-30/1429). It has to be noted that *"Renal dysfunction (eGFR <50 mL/min/1.73m2 using the Schwartz formula) or requirement for dialysis"* was an exclusion criterion. Consequently, this can explain that no data have been presented to justify that anti-Xa monitoring and dose adjustments were done in children receiving LWMH. In conclusion all this underlines that all presented data are from the real-life clinical setting despite of official guidelines or recommendations. The demonstration of non-inferiority of DE as compared to SoC is not questioned. Just one patient 12 years old received as SoC fondaparinux. Fondaparinux product is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy. This has been specified in the description of the SoC treatment in section 5.1 as follows: *"… fondaparinux (1 patient 12 years old)"*. The development of the new treatment in VTE for children based on a direct oral anticoagulant (DOAC) seems well justified as current standard of care with UFH, LMWH and VKA is based on data obtained in adults.

The justification for the open-label design was that different paediatric formulations of DE and the i.v./s.c. administration of some of the SoC treatments would have required an unethical number of dummy treatments in a blinded trial, especially considering the vulnerability of a paediatric trial population. Investigators, patients, and trial members will be unblinded. The only party blinded to treatment assignment are members of the Adjudication Committee. The Applicant has provided all versions (3 in total) of the trial statistical analysis plan (TSAP) and the following table with all the changes. It is noted that the open-label trial design was agreed within the PIP. The changes to the TSAP during the course of the trial are reflecting protocol amendments that have been agreed with the PDCO within the PIP and/or the FDA. The primary endpoint analysis has remained stable since the first revision 28-AUG-2015, when only 8 patients were randomized in the study. The key endpoints have been adjudicated in a blinded fashion. The Applicant's assurance that the changes to the TSAP during the course of the study was not data driven was accepted.

While not clear in the initial submission, it has been clarified in the present submission that the course of the initial parental therapy is not included in the treatment period of 3 months with the randomised treatment of DE vs. SoC in study 1160.106.

The exclusion criteria were generally in line with the known safety profile of DE, but the exclusion criterion on reduced kidney function are different from the current contraindication in adults with reduced kidney function. This exclusion criterion has evolved during the course of the study as new PK data have become available. This approach was chosen to apply a conservative criterion knowing that new-borns renal function is immature. This approach is acknowledged and sufficiently explains the rationale for the stepwise decrease of the eGFR threshold in the clinical studies. It appears that with Global amendment 9 (dated 6 Feb 2019) the eGFR threshold in exclusion criterion 2 was lowered to <50 mL/min/1.73 m^2 using the Schwartz formula for all patients, irrespective of their age. The threshold in the current SmPC for adults is CrCL < 30 mL/min. Based on the following considerations: (1) the reasons for the exclusion criterion for eGFR, (2) a pharmacokinetic rationale for expecting that impaired renal function (for any reason) will affect the PK/excretion of DE, (3) the experience with DE treatment in adults with renal impairment *("In phase I studies the exposure (AUC) of dabigatran after the oral administration of Pradaxa is approximately 2.7-fold higher in adult volunteers with moderate renal insufficiency (CrCL between 30 and 50 mL/min) than in those without renal insufficiency. In a small number of adult volunteers with severe renal insufficiency (CrCL 10-30 mL/min), the exposure (AUC) to dabigatran was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency"* (from the DE SmPC) and (4) the physiology of the renal function development in infants a contraindication of renal impairment in children in the SmPC has been added to section 4.3. The SmPC section 4.2 and 4.4 have been aligned with the information in section 4.3.

The DE treatment consisted of 3 different age-appropriate formulations: capsules, coated granules and oral liquid formulation (OLF). The dosing algorithm recommended the following use of the 3 formulation:

Patients aged ≥8 years: Age and weight adjusted dabigatran etexilate capsules.

Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but below 12 years of age): Age and weight adjusted dabigatran etexilate coated granules.

Patients aged <12 months: Age and weight adjusted dabigatran etexilate OLF or any other alternative age-appropriate formulation. For patients <12 months of age, OLF is preferred over coated granules provided that OLF supplies are available to the site.

The dosing algorithm, which was developed on the basis of the RECOVER trial and the phase 1 and 2a PK trials in the paediatric program was targeting a dabigatran trough concentration of ≥50 to <250 ng/mL.

As discussed in the section on pharmacology, the different formulations are not bioequivalent. The relative bioavailability of the formulations was used to qualify the dosing regimen in the paediatric studies. However, in the clinical paediatric studies the apparent relative bioavailability paradoxically turned out to be lower for oral solution and coated granules than for capsules. The following statement is, therefore, added to the SmPC section 4.2: *"When changing between the formulations, the prescribed dose may need to be altered. The dose stated in the relevant dosing table of a formulation should be prescribed for the age and weight of the child."*

The dosing algorithm included an option for up-titration once during the trial. A high proportion of subjects had a dose adjustment during treatment in study 1160.106. Furthermore, more patients on DE than SoC discontinued study treatment prematurely. A major reason for premature discontinuation of DE was failure to achieve a trough concentration within the target therapeutic range of 50-250 ng/mL. Only one dose adjustment was allowed according to Global amendment no. 2 implemented early in the study (28 January 2015). It appears that the younger patients (mean age 6.0 years) taking oral solution or coated granules were more likely not to reach the target therapeutic range after titration than the older paediatric patients (mean age 11.6 years) taking capsules. Steady-state dabigatran trough exposures for younger patients treated with coated granules or oral solution were lower than that of older patients treated with capsules. As has been discussed in the pharmacology section of this report, the bioavailability of the coated granules seems to be lower in children, which could be part of the explanation. It meant that the probability of reaching the target therapeutic range of 50 to - <250 ng/mL was lower in the younger patients receiving oral solution or coated granules (pellets). It is noted that the target therapeutic range's lower limit of 50 ng/mL was defined for technical reasons alone (LLOQ of Hemoclot®). However, a lower limit of 26 ng/mL, i.e. a range of 26 to <250 ng/mL would be therapeutically justified based on the RE-COVER study. With the lower limit of 26 ng/mL more patients would have reached the target therapeutic range and not needing dose adjustment and potential discontinuation. The revised dosing algorithm, which is discussed elsewhere in this report including in the pharmacology section, has been modelled to increase the likelihood of reaching the target therapeutic range in the younger patients taking coated granules.

The eGFR summarized across all age-groups was higher in those who did not (N=17) versus those who did (N=159) reach the therapeutic range: Mean eGFR 151.758 versus 111.827 mL/min/1.73m^2, median eGFR 156.655 versus 105.728 mL/min/1.73m^2. This is consistent with dabigatran clearance properties; plasma levels of dabigatran would be lower in those with higher renal clearance. This is also consistent with the predominant renal excretion of dabigatran and renal capacity being highest in children up to 14 years (Schwartz GJ Pediatr Nephrol 2007;22:1839-1848).

In addition, within the birth to <2 years age-group 3/7 on flavored oral solution only failed to reach the target therapeutic range compared to 0/6 on unflavored oral solution only and 1/8 on coated granules only. As the acceptability studies indicate similar acceptance of flavored and unflavored solution, the use of flavoured solvent is no longer required for acceptable tolerability of the oral solution. Therefore, the Applicant proposed to register the unflavoured solvent only.

Overall, 63/176 (35.8%) had a dose-adjustment. The majority of these, 46/63 (73.0%), reached the target therapeutic range, whereas 17/63 (27.0%) of these or 17/176 (9.6%) of all did not. Interestingly, the data suggests that patients, who discontinued treatment due to failure to reach target range had higher rate of thrombus resolution 9/17 (52.9%) vs. 72/160 (45.0%), and lower rate of recurrent VTE 0/17 (0%) vs. 7/160 (4.4%) than patients who continued treatment. The Applicant explained the apparent paradoxical observation as a play of chance based on small numbers. The change of status of only one patient with or without a

thrombus resolution or a recurrent VTE under DE would almost eliminate or even reverse the numerical differences:

- One patient less having a thrombus resolution (8/17 instead of 9/17) would lead to a rate of 47% instead of 52.9%, compared to 72/160 (45.0%).
- One patient more with a recurrent VTE (1/17 instead of 0/17) would lead to a rate of 5.9% instead of 0%, compared to 7/160 (4.4%).

This explanation was accepted. As requested, the Applicant has discussed the need for dose titration/monitoring because of the concern that the target concentration for a considerable proportion of the paediatric patient is not easily and fast obtained. This is a concern because it may compromise the efficacy and safety of the treatment. The Applicant has provided additional descriptive statistics for steady state plasma concentrations of total dabigatran at Visit 3 (after at least 6 consecutive dabigatran doses), post-titration (at least 3 days after a dabigatran dose adjustment), and over all visits, please see section on *"Adjustments to reach target plasma dabigatran concentrations"* above in this report. It can be seen that the difference in exposure over the full treatment period when a dose titration had taken place compared with the expected exposure had it not taken place is <15% difference for all subgroups. Furthermore, the Applicant refers to simulation data based on the final PK model, which is the basis for the revised dosing algorithm. It shows that most of the patients in Trial 1160.106 were actually within the target range of 26 - <250 ng/mL, which is therapeutically justified based on the RE-COVER study.

Regarding the patients switching from DE to SoC, as complete thrombus resolution and recurrent VTE were similar to the DE only group at day 84, it appears that switching from DE to SoC did not incur loss of chance in these patients. There is higher frequency of bleeding events and adverse and serious adverse events in the patients switching from DE to SoC. The Applicant has confirmed that the bleeding events occurred before switching while patients were on-treatment with DE. With respect to the bleeding events during the on-treatment period showing higher frequencies in patients switching from DE to SoC, the Applicant suggests the difference is mainly driven by the major imbalance in the sample size of these subgroups and offered no other explanation. It was acknowledged that it is not statistically significant, so even if it would be of interest to know if there had been a link between bleeding and discontinuation in these cases, it seemed to remain speculative and will not be pursued further. With respect to adverse events while patients were still taking DE or during the 6-day residual effect period showing higher frequencies in patients switching from DE to SoC, the Applicant suggested that due to the large imbalance in total numbers of each group and the missing option for SOC to switch to dabigatran, any comparisons are inconclusive, and offers no other explanation. Although it would be of interest to understand better if and how there had been a link between AEs and discontinuations, it seems to remain speculative, except for 7 cases reported as discontinuations because of AEs, and will not be pursued further.

Treatment discontinuation considered as a treatment failure corresponds to the sensitivity analysis using the "worst-case imputation" rule. The 95% confidence interval of the treatment effect provided by this sensitivity analysis performed in the final population, is consistent with the non-inferiority conclusion (d=0.05, 95%CI: [-0.063, +0.163], cf. CSR 1160-06 final analysis, page 300).

In response to a question on the worst-case sensitivity analyses, where the same imputation rule is applied in both treatment groups, which is not considered a conservative approach in a non-inferiority setting, the Applicant has provided clarifications on the tipping point and "worst case" (assumed treatment failure in all switch patients) sensitivity analyses. In the tipping point analysis, missing observations of the primary combined endpoint were imputed from binominal distributions with fixed response rates ranging from 0 –

100% evenly spaced by 20% for the combination of DE and SoC arms. The analysis showed that for all imputation scenarios with the SoC response rate equal to or lower than the DE response rat, the NI test p-value was 0.01 or lower. In the scenario with a SoC response rate up to 20% higher than the DE response rate would still yield a NI test p-value within the range 0.01 – 0.05.

In the DE switch to SoC analysis, all 22 patients who switched from dabigatran to SoC were considered to have failed meeting the primary endpoint of survival with complete thrombus resolution and no recurrent VTE. In that analysis the point estimate is numerically slightly in disfavour of dabigatran: 0.013, 95% CI -0.110, 0.136. However, it is not statistically significant and the 95% CI upper bound is still within the NI margin. It was accepted that the range of sensitivity analyses performed support the primary NI result.

From a methodological perspective, it is noted that the power calculation is based on simulations of Newcombe-Wilson confidence intervals using a 10% significance level, and an assumption of a resolution rate of 72% for both DE and SoC arms. When using a non-inferiority margin of 20% the power to demonstrate non-inferiority is 82%. The non-inferiority margin of 20%, the significance level of 10% and the sample and strata size were agreed with PDCO.

In the final CTR, submitted together with this response document, efficacy was summarized based on the complete randomized set including patients covered in the interim CTRs, as well as new patients recruited after interim database snapshot on 28 Mar 2020. Of the 267 randomized patients, 81 patients (45.8%) in the DE group and 38 patients (42.2%) in the SOC group met the criteria for efficacy endpoint. The point estimate of Mantel-Haenszel weighted rate difference −0.038 showed a favourable treatment effect of DE over SOC, and the corresponding 95% CI (−0.161, 0.086) demonstrated non-inferiority of DE to SOC ($p<0.0001$). Considering the potential for unintentional bias in this open-label trial, each component of the primary efficacy endpoint and bleeding and fatal events were assessed centrally by a blinded, independent adjudication committee, which assured the quality and comparability of the endpoints.

The 1160.106 trial treatment was foreseen to be administered for 12 weeks. Inclusion criterion #3 ensured that only patients with an anticipated treatment duration of at least 3 months with anticoagulants for the VTE episode were included into the trial. However, if a patient did not require treatment with anticoagulants any longer due to complete thrombus resolution as confirmed by appropriate imaging modalities prior to 12 weeks of treatment the patient had to be discontinued from trial treatment

It is noted that the open-label trial design was agreed within the PIP. The changes to the TSAP during the course of the trial are reflecting protocol amendments that have been agreed with the PDCO within the PIP and/or the FDA. The primary endpoint analysis has remained stable since the first revision 28-AUG-2015, when only 8 patients were randomized in the study, see the history table above. The key endpoints have been adjudicated in a blinded fashion.

Regarding the 22 patients who switched from DE to SoC, the Applicant has provided detailed information on continued anticoagulant exposure after discontinuation of DE in the 22 patients, who switched from DE to SoC. It proves that continued exposure to anticoagulant treatment (SoC) after switching from DE was present in the vast majority of patients. Nevertheless, as discussed elsewhere, a sensitivity analysis counting all 22 switch patients as treatment failures still showed non-inferiority, although the point estimate numerically shifted in disfavour of dabigatran. This was considered acceptable.

Efficacy data and additional analyses

A total of 328 patients were screened/enrolled, at 65 sites in 26 countries. The largest proportions of treated patients overall and across age groups were from Central Europe (56.4%), followed by North America (21.1%) and Western Europe (18.0%). At country level, Russia contributed the most patients (28.2%); the next largest contributions came from the Czech Republic (17.3%), and United States (11.3%). Although the Number of treated patients by region and country seems skewed towards Central Europe, a subgroup analysis of the primary endpoints by regions defined as Central Europe, Western Europe, North America, Latin America, Asia, Other, respectively, did not indicate heterogeneity.

The sequence of global amendments, 9 in total, reflects that the dosing algorithm and posology of the different dosage forms in the 3 age strata have evolved in the course of the study. This combined phase II/III approach has been taking in agreement with the PDCO and the study has been conducted according to the KBE, please see the PDCO compliance report.

The amendments also indicate that recruitment may have been challenging. The target number of patients has been reduced twice during the course of the study. This is not unexpected in a study in a relatively rare disease in children. The reductions of target number of patients have been agreed with the PDCO in PIP modifications.

A higher frequency of important protocol deviations (iPD) in the DE arm (28.2%) vs. the SoC arm (12.2%) in the final analysis appears to be driven by imbalances related to medication handling/compliance rules and concomitant medication. These procedures were more applicable to the DE than the SoC treated patients because of the different requirements for the DE and SoC randomized patient groups related to medication handling and dosing. In this study a series of sensitivity analyses, including worst-case scenarios have been conducted, which are all consistent with the NI conclusion. Therefore, it is not likely the impact of the iPD imbalances will change this conclusion.

At the time of the interim analysis, regulatory GCP inspections had been conducted at 6 sites in 3 countries. It is noted that no critical GCP violations were observed in the course of the audits that have been conducted.

Some imbalances were identified in the baseline data on demography, leading index VTE and history of VTE. To evaluate the impact of the imbalance between the DE and SoC arm with respect previous VTE besides the index VTE, the Applicant has performed a sensitivity analysis in those patients with a history of VTE, 14 in each group. The overall frequency of complete thrombus resolution is lower in patients with previous VTE than in patients with no previous VTE besides the index VTE. There is a numerical higher frequency of complete thrombus resolution in the DE arm 4/14 (28.6%) than in the SoC arm 2/14 (14.3%), and the difference in rates (SoC – DE) is -0.143, which is numerically lower than the primary analysis result of -0.038. However, like the primary analysis result, the difference is not statistically significant as both the 90% CI and 95% CI are crossing 0. The upper limit of both these Cis are below the NI margin of 20%. It is accepted that the baseline imbalance with respect to the history of previous VTE does not seem to impact the NI conclusion in any significant way. The imbalance with respect to the proportions of patients with cancer is significant in the final analysis. As cancer is associated with high risk of recurrence of VTE this imbalance is to the disfavour of DE. Despite, the primary endpoint demonstrated NI of DE vs. SoC there were consistent and numerically better results on the components of the combined endpoint. This was considered reassuring. However, since there were other imbalances of baseline characteristics to the disfavor of SoC, e.g. congenital heart disease and heart failure, which may also be associated with increased risk of recurrence of VTE, it was not possible to draw strong conclusions from these observations beyond what is shown in the primary analysis.

The secondary endpoint of major bleeding suggests no difference between treatment arms, and low overall bleeding rate. The sensitivity analysis using the intention-to-treat period seems to confirm that. All-cause mortality is very low.

The results for the individual component of the combined endpoints seem consistent with the overall outcome.

The Applicant have conducted a series of acceptability studies with the capsules, coated granules and OLF. Studies have been done in all trials. In trial 1160.106, the administration of capsules and granules was generally assessed as good or acceptable by investigators, parents, and patients. The acceptability of capsules has been confirmed in trial 1160.108. The acceptability of pellets or granules is confirmed in trial 1160.108 considering that some of the patients treated with coated granules were very young.

When considering the full data from the completed phase IIb/III trials in addition to the previously completed Phase IIa trials, the use of flavoured solvent was considered no longer required for acceptable tolerability of the oral solution. Therefore, it was agreed to register the unflavoured solvent as a replacement for the flavoured solvent and to adapt the set of annexes accordingly.

Compatibility

Compatibility of the oral solution with nasal tubes in different materials was evaluated and data demonstrating compatibility and recovery of doses has been provided. However, administration of the reconstituted oral solution in feeding tubes is not recommended in the SmPC and PL since the oral syringe does not fit with marketed nasal tubes.

2.5.4. Conclusions on the clinical efficacy

In the final CTR for study 1160.106, efficacy was summarized based on the complete randomized set including patients covered in the interim CTRs, as well as new patients recruited after interim database snapshot on 28 Mar 2020. Of the 267 randomized patients, 81 patients (45.8%) in the DE group and 38 patients (42.2%) in the SOC group met the criteria for efficacy endpoint. The point estimate of Mantel-Haenszel weighted rate difference −0.038 showed a favourable treatment effect of DE over SOC, and the corresponding 95% CI (−0.161, 0.086) demonstrated non-inferiority of DE to SOC ($p<0.0001$).

However, although the final analysis provided some clarity on the patients <1 year of age there continued to be limitations of patient numbers and treatment exposures in the Birth to <2 years age-group considering the differences in terms of immaturity of coagulation system and renal function and leading index VTE types compared to the older age-groups and adults.

Furthermore, the benefit of anticoagulant therapy was less clear for CLT than for other types of VTE. In addition, the risk of bleeding, especially intracranial bleeding, could be different in subjects with CVST as compared to other types of VTE, in particular for acute CVST. The reliance on data from adults may not be applicable in these types of thrombosis.

These issues were discussed with independent experts at a SAG meeting on 7 September 2020 and addressed by the Applicant in their responses during the procedure. The scarcity of data in the youngest age category was noted by the independent experts but the existence of some evidence in this group was

welcomed given the known difficulties in recruiting children into the clinical trials with anticoagulants. Because there is an imbalance in mostly minor bleedings in the youngest age-groups on dabigatran compared to SoC in this non-inferiority study, the CHMP concluded that there is a need for post-authorisation data collection to characterise better the safety profile of dabigatran. The Applicant has provided a draft synopsis for non-interventional European multinational multi-center cohort study based on newly collected data of patients administered dabigatran for VTE treatment or prevention of recurrent VTE (see discussion in Clinical Safety section below). The fact that there are only limited data available supporting efficacy and safety of dabigatran by type of VTE subgroup, including CLT and CVST was noted. However, it was felt that the available evidence does not give rise to any particular concern and therefore the SAG experts recommended dabigatran to be available also for treatment of children in these two conditions. In line with the exclusion of patients with meningitis, encephalitis and intracranial abscess in the clinical study the experts suggested a contraindication regarding these conditions. However, it was challenging to provide any precise recommendation in case these inflammatory conditions develop during treatment with dabigatran and treatment should be considered on case-by -case basis. Therefore, the warning statement in section 4.4 on haemorrhagic risk has been updated with active meningitis, encephalitis and intracranial abscess added to the haemorrhagic risk factors, and the exclusion criterion on these conditions has been added to the description of study 1160.106 in section 5.1 of the SmPC.

The line extension for the use of DE in treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age was considered acceptable from efficacy point of view.

2.6. Clinical safety

This safety data encompass data from 5 clinical trials that investigated DE in paediatric patients; three phase IIa trials in children of different age groups, a 'standard of care'-controlled phase III trial, and an open-label single arm safety study. An overview of all 5 trials is provided in Table 1 below.

Table 1 Overview of clinical trials included in the evaluation of safety

Trial no.	Objectives	Formulation of dabigatran etexilate	Age group
Phase IIa			
1160.88 [U12-3378]	PK, PD, safety, tolerability	Capsules	12 to <18 years
1160.89 [c09069268]	PK, PD, safety, tolerability	Oral solution	1 to <12 years
1160.105 [c09085437]	PK, PD, safety, tolerability	Oral solution	0 to <1 year
Phase IIb/III			
1160.106, interim [c26571231]	PK, PD, efficacy, safety, tolerability	Oral solution, coated granules in sachets, and capsules	0 to <18 years
1160.108, interim [c26496086]	PK, PD, safety, tolerability	Oral solution, coated granules in sachets, and capsules	0 to <18 years

[1] The term 'oral solution' used in this document corresponds to 'oral liquid formulation' in the CTRs. The term 'granules' is an abbreviation for 'coated granules in sachets' and corresponds to 'pellet stick pack' or 'pellets' used in the CTRs. The oral solution was always prepared using DE as 'powder' for reconstitution into solution although the term 'granules' might have been used in the respective CTRs.

The three phase IIa studies included 9, 18, and 8 patients. At the time of the interim analysis the 1160.106 study included 234 patients, 88 rolled over to the 1160.108 study. The 1160.108 study included 203 patients. The individual studies and specific requirements for conducting interim analyses to be included in the application have been agreed with the PDCO. Data cut-off for the interim analyses of studies 1160.106 and 1160.108 was 28 Feb 2019.

The final CSRs for study 1160.106 included 267 patients, for study 1160.108 214 patients (91 patients rolled over from study 1160.106 to 1160.80).

Patient exposure

A summary of the overall exposure in the full safety population is given below:

Table 4 Extent of exposure - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Patients treated with DE, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
DE exposure [weeks]				
Mean (SD)	9.3 (10.0)	20.7 (20.5)	31.1 (21.2)	26.0 (21.3)
Median (range)	10.4 (0.1 – 51.0)	12.4 (0.1 - 66.3)	28.4 (0.1 - 68.7)	14.0 (0.1 - 68.7)
DE exposure categories, N (%)				
1 day	15 (34.1)	9 (10.5)	1 (0.4)	25 (6.9)
3 days	0	4 (4.7)	9 (3.9)	13 (3.6)
≥4 days	29 (65.9)	73 (84.9)	223 (95.7)	325 (89.5)
DE formulation, N (%)				
Treated with capsules only	0	21 (24.4)	233 (100.0)	254 (70.0)
Treated with granules only	16 (36.4)	51 (59.3)	0	67 (18.5)
Treated with oral solution only	27 (61.4)	12 (14.0)	0	39 (10.7)
Treated with granules and capsules	0	2 (2.3)	0	2 (0.6)
Treated with oral solution and granules	1 (2.3)	0	0	1 (0.3)

The time when treatment was temporarily interrupted was included in the calculation of exposure, except for the time between trials 1160.106 and 1160.108.

Source data: [c31325825, Tables B.2: 1 and B.3: 1]

However, the majority of the patients were exposed in the phase IIb/III trials which had a planned treatment duration between 12 and 64 weeks. Overall, 300 patients aged 0-<18 years were exposed to DE in the phase IIb/III trials. Approximately 30% (87 patients) were exposed between 0 and 12 weeks, 20% (58 patients) were exposed for 12-18 weeks, while 32% (97 patients) were exposed for more than 42 weeks. The exposure dose was calculated based on weight and age.

Demographics and disease characteristics

The demographics of the full safety population is shown in the table below. The included patients were balanced with regard to gender, comprised mainly Caucasian (approx. 90%) with the majority living in

Europe (70%) or America (24%). The age of the population reflects the inclusion of patients 0-18 years. The majority of the patients suffered from DVT (approx. 63%) while both pulmonary embolism (10%) and cerebral venous or sinus thrombosis (9%) were the second most common types of VTE.

More adolescents than other children suffered from PE, while the frequency of cerebral venous or sinus thrombosis was increased in patients aged 2-12 years (21%). The time since diagnosis of VTE was longer in patients aged 2-18 years than in patients younger than 2 years. The mean eGFRs were well above the recommended 50 mL/min/1.73m^2, with only a few patients in the phase IIa trials with eGFRs slightly below 50 mL/min/1.73m^2

Table 6 Demographic data - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Patients treated with DE, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Sex, N (%)				
Male	19 (43.2)	47 (54.7)	118 (50.6)	184 (50.7)
Female	25 (56.8)	39 (45.3)	115 (49.4)	179 (49.3)
Race, N (%)[1]				
White	38 (86.4)	77 (89.5)	216 (92.7)	331 (91.2)
Asian	3 (6.8)	5 (5.8)	10 (4.3)	18 (5.0)
Black or African American	1 (2.3)	3 (3.5)	4 (1.7)	8 (2.2)
Multiple	1 (2.3)	1 (1.2)	2 (0.9)	4 (1.1)
Missing[2]	1 (2.3)	0	1 (0.4)	2 (0.6)
Region, N (%)[3]				
Central Europe	30 (68.2)	40 (46.5)	115 (49.4)	185 (51.0)
North America	9 (20.5)	11 (12.8)	64 (27.5)	84 (23.1)
Western Europe	4 (9.1)	22 (25.6)	44 (18.9)	70 (19.3)
Latin America	0	6 (7.0)	5 (2.1)	11 (3.0)
Asia	1 (2.3)	5 (5.8)	3 (1.3)	9 (2.5)
Other	0	2 (2.3)	2 (0.9)	4 (1.1)
Age [years]				
Mean (SD)	0.4 (0.5)	6.2 (3.0)	15.2 (1.6)	11.2 (5.8)
Median (range)	0.0 (0 - 1)	6.0 (2 - 11)	16.0 (12 - 17)	14.0 (0 - 17)
Body mass index [kg/m^2]				
Mean (SD)	15.6 (2.0)	17.3 (2.7)	23.7 (5.5)	21.2 (5.7)
Median (range)	15.4 (11.4 - 19.9)	16.7 (11.3 - 23.6)	22.6 (11.0 - 43.7)	20.2 (11.0 - 43.7)
eGFR Schwartz [mL/min/1.73m^2]				
Mean (SD)	115.9 (35.0)	134.1 (29.3)	103.9 (26.6)	112.5 (31.0)
Median (range)	113.6 (48.3 - 233.1)	125.8 (78.5 - 218. 7)	99.8 (67.2 - 326.3)	106.4 (48.3 - 326.3)

1 None of the patients were American Indian, Alaska Native, Native Hawaiian, or Other Pacific Islander
2 Information on race and ethnicity could not be collected in certain countries because of legal requirements
3 Asia: Taiwan, Thailand; Central Europe: Bulgaria, Czech Republic, Hungary, Lithuania, Russia, Turkey, Ukraine; Latin America: Argentina, Brazil, Mexico; North America: Canada, United States; Western Europe: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Norway, Spain, Sweden, Switzerland: Other: Israel.

Source data: [c31325825, Table B.2: 1]

Table 7 Baseline characteristics - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Patients treated with DE, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Type of leading index VTE, N (%)				
Deep vein thrombosis (DVT)	12 (27.3)	38 (44.2)	177 (76.0)	227 (62.5)
Cerebral venous thrombosis or sinus thrombosis	6 (13.6)	20 (23.3)	12 (5.2)	38 (10.5)
Missing	14 (31.8)	12 (14.0)	9 (3.9)	35 (9.6)
Pulmonary embolism (PE)	0	1 (1.2)	32 (13.7)	33 (9.1)
Central line thrombosis	12 (27.3)	15 (17.4)	5 (2.1)	32 (8.8)
Imaging method confirming VTE assessment[1], N (%)				
Compression ultrasound	20 (45.5)	45 (52.3)	157 (67.4)	222 (61.2)
CT scan	3 (6.8)	12 (14.0)	49 (21.0)	64 (17.6)
MRI scan	4 (9.1)	19 (22.1)	18 (7.7)	41 (11.3)
Other	3 (6.8)	3 (3.5)	20 (8.6)	26 (7.2)
Contrast venography	0	3 (3.5)	4 (1.7)	7 (1.9)
Pulmonary angiography	0	0	4 (1.7)	4 (1.1)
V/Q scan	0	0	1 (0.4)	1 (0.3)
Days since first diagnosis of index VTE				
Mean (SD)	57.0 (71.6)	138.7 (331.9)	172.4 (403.4)	154.2 (370.3)
Median (range)	22.0 (5 - 290)	22.0 (5 - 2273)	55.5 (6 - 3798)	22.0 (5 - 3798)

[1] Patients could be assessed with more than one imaging method.

Source data: [c31325825, Table B.2: 4]

Patient disposition

The patient disposition of the full safety population is shown below. Overall, approximately 10% of the children discontinued the studies prematurely. However, as patients in the phase IIa trials were treated for a shorter period (1-3 doses of DE), the discontinuation rates were higher in the phase IIb/III studies, where the planned treatment phase was three months or longer (for disposition in the phase IIa/III studies, please refer to the AR). More patients in the younger age groups discontinued the phase IIb/III studies prematurely than adolescents (50% 0-<2 years, 37% 2-<12 years, 26% 12-<18 years).

Table 2 Disposition of patients - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Treated, N (%)	44 (100.0)	86 (100.0)	233 (100.0)	363 (100.0)
Completed planned observation time[1]	41 (93.2)	81 (94.2)	219 (94.0)	341 (93.9)
Premature trial discontinuation	3 (6.8)	5 (5.8)	14 (6.0)	22 (6.1)
Other	1 (2.3)	2 (2.3)	7 (3.0)	10 (2.8)
Non−compliant with protocol	2 (4.5)	0	2 (0.9)	4 (1.1)
Consent withdrawn	0	2 (2.3)	2 (0.9)	4 (1.1)
Lost to follow−up	0	1 (1.2)	1 (0.4)	2 (0.6)
AE other	0	0	2 (0.9)	2 (0.6)
Source of patients, N (%)				
Participated in 1160.88	0	0	9 (3.9)	9 (2.5)
Participated in 1160.89	6 (13.6)	12 (14.0)	0	18 (5.0)
Participated in 1160.105	8 (18.2)	0	0	8 (2.2)
Participated in 1160.108 only	8 (18.2)	27 (31.4)	87 (37.3)	122 (33.6)
Participated in 1160.106 only	21 (47.7)	31 (36.0)	63 (27.0)	115 (31.7)
Rollover patients from 1160.106 to 1160.108[2]	1 (2.3)	16 (18.6)	74 (31.8)	91 (25.1)

[1] Planned observation time: the time from the last intake of trial medication until the planned follow-up visit.
[2] For patients treated with SoC in trial 1160.106 and with DE in trial 1160.108, age at informed consent in trial 1160.108 was taken for the assignment to age strata. Therefore, patient numbers differ from the 1160.106 CTR, which took age at informed consent in trial 1160.106 as basis for age group assignment.

Source data: [c31325825, Tables B.1: 1 and B.2: 1]

Adverse events

Any AE was reported in 70% of the full safety population. The number was slightly higher (77%) in the phase IIb/III studies, probably due to patients being included for a longer time. In these studies, 26% experienced adverse events assessed as being drug-related.

The incidence of AEs assessed as being drug-related appeared higher in the older age groups, with approximately 15-20% of patients <12 years and 29% of patients aged 12-<18 years experiencing drug-related AEs. Similarly, there was an increased incidence of serious AEs (SAEs) in the older age groups, although the numbers are small and must be interpreted cautiously.

An overview of the occurrence of AEs in the phase IIb/III studies is given in the table below. The results for the full safety population are not shown but resembled the results for the full population, although the frequencies of AEs were lower (i.e. appeared diluted by the patients included in the phase IIa studies).

Adverse event overall summary on-treatment - unique DE treated set of the Phase IIb/III paediatric trials

	Birth to <2 years	**2 to <12 years**	**12 to <18 years**	**Total**
Treated patients, N (%)	16 (100.0)	68 (100.0)	216 (100.0)	300 (100.0)
Patients with any AE	12 (75.0)	48 (70.6)	170 (78.7)	230 (76.7)
Patients with severe AEs	2 (12.5)	6 (8.8)	20 (9.3)	28 (9.3)
Patients with investigator defined drug-related AEs	3 (18.8)	10 (14.7)	63 (29.2)	76 (25.3)
Patients with other significant AEs (according to ICH E3)	2 (12.5)	3 (4.4)	12 (5.6)	17 (5.7)

Patients with AEs leading to discontinuation of trial treatment	3 (18.8)	5 (7.4)	17 (7.9)	25 (8.3)
Patients with protocol-specified AEs of special interest	0	0	1 (0.5)	1 (0.3)
Patients with serious AEs[1]	2 (12.5)	10 (14.7)	36 (16.7)	48 (16.0)
Fatal	0	0	0	0
Immediately life-threatening	0	0	4 (1.9)	4 (1.3)
Disability/incapacity	0	0	0	0
Required hospitalisation	1 (6.3)	9 (13.2)	29 (13.4)	39 (13.0)
Prolonged hospitalisation	1 (6.3)	1 (1.5)	6 (2.8)	8 (2.7)
Congenital anomaly	0	0	0	0
Other	1 (6.3)	4 (5.9)	6 (2.8)	11 (3.7)

The most frequent AEs in the full safety population are shown in the table below and included headache (14.7%), nasopharyngitis (14.0%), and vomiting (9.0%) as the single most common AEs. Of note, approximately half of the reported cases of headache was attributable to baseline conditions (e.g. headache, mastoiditis, intracranial hypertension, cerebral venous thrombosis, and only one case of headache was considered by the investigator to be related to the study drug. Bleeding events are shown as bleedings at specific sites in the table below but a summary of all bleeding events is provided in the section of AESIs.

Table 14 Most frequent adverse events on-treatment (PT overall frequency ≥3.0%) - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Treated patients, N (%)	30 (100.0)	80 (100.0)	225 (100.0)	335 (100.0)
Patients with any AE	12 (40.0)	50 (62.5)	172 (76.4)	234 (69.9)
Headache	0	9 (11.3)	35 (15.6)	44 (13.1)
Nasopharyngitis	2 (6.7)	8 (10.0)	32 (14.2)	42 (12.5)
Vomiting	2 (6.7)	9 (11.3)	16 (7.1)	27 (8.1)
Nausea	0	4 (5.0)	19 (8.4)	23 (6.9)
Dyspepsia	0	1 (1.3)	21 (9.3)	22 (6.6)
Cough	1 (3.3)	7 (8.8)	13 (5.8)	21 (6.3)
Pyrexia	0	4 (5.0)	17 (7.6)	21 (6.3)
Upper abdominal pain	0	2 (2.5)	18 (8.0)	20 (6.0)
Diarrhoea	0	2 (2.5)	18 (8.0)	20 (6.0)
Epistaxis	1 (3.3)	3 (3.8)	14 (6.2)	18 (5.4)
Upper respiratory tract infection	0	2 (2.5)	15 (6.7)	17 (5.1)
Oropharyngeal pain	0	0	17 (7.6)	17 (5.1)
Alopecia	1 (3.3)	2 (2.5)	13 (5.8)	16 (4.8)
Pain in extremity	0	3 (3.8)	13 (5.8)	16 (4.8)
Rhinitis	2 (6.7)	4 (5.0)	8 (3.6)	14 (4.2)
Gastroenteritis	0	5 (6.3)	8 (3.6)	13 (3.9)
Arthralgia	0	1 (1.3)	12 (5.3)	13 (3.9)
Abdominal pain	0	1 (1.3)	11 (4.9)	12 (3.6)
Contusion	0	2 (2.5)	9 (4.0)	11 (3.3)
Haematoma	0	0	11 (4.9)	11 (3.3)
Chest pain	0	1 (1.3)	9 (4.0)	10 (3.0)

The standard of care' (SoC)-controlled phase III study provides the only comparison of AEs in the DE group with AEs in patients receiving other regimens of anticoagulant therapy (SoC). These are shown in the table below. Post thrombotic syndrome was more common in the DE group (4%) as compared to the SoC group (1%).

Table 12.1.2.1: 1 Most frequent adverse events during the on-treatment period (PT overall frequency ≥3.0%) - TS

	DE	Total SoC
Treated patients, N (%)	156 (100.0)	97 (100.0)
Patients with any AE	112 (71.8)	70 (72.2)
Headache	15 (9.6)	4 (4.1)
Nasopharyngitis	9 (5.8)	10 (10.3)
Vomiting	13 (8.3)	2 (2.1)
Epistaxis	7 (4.5)	7 (7.2)
Pyrexia	9 (5.8)	4 (4.1)
Oropharyngeal pain	7 (4.5)	5 (5.2)
Pain in extremity	6 (3.8)	6 (6.2)
Dyspepsia	10 (6.4)	1 (1.0)
Nausea	8 (5.1)	3 (3.1)
Cough	8 (5.1)	2 (2.1)
Upper abdominal pain	8 (5.1)	1 (1.0)
Increased alanine aminotransferase	5 (3.2)	4 (4.1)
Contusion	3 (1.9)	6 (6.2)
Diarrhoea	7 (4.5)	1 (1.0)
Menorrhagia	3 (1.9)	5 (5.2)
Rhinitis	7 (4.5)	2 (2.1)
Upper respiratory tract infection	7 (4.5)	1 (1.0)
Post thrombotic syndrome	6 (3.8)	1 (1.0)

Adverse events of special interest, AESIs

AESIs included recurrent VTE, bleeding events and changes in hepatocellular or renal function.

VTE and Bleeding events

Expected AEs included bleedings, these were categorised as follows:

Major bleeding (MBE)

- Fatal bleeding
- Clinically overt bleeding associated with a decrease in haemoglobin of at least 2 g/dL (20 g/L) in a 24-hour period
- Bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system
- Bleeding that required surgical intervention in an operating suite

Clinically relevant non-major (CRNM) bleeding

- Overt bleeding for which a blood product was administered and which was not directly attributable to the patient's underlying medical condition

- Bleeding that required medical or surgical intervention to restore haemostasis, other than in an operating suite

Minor bleeding

- Any overt or macroscopic evidence of bleeding that did not fulfil the criteria for either MBE or CRNM.

Observed VTE and bleedings in the full safety population are summarised below. Twenty percent (20%) of the total population experienced a bleeding. The incidence of any bleeding increased with increasing age, however, this was not reflected in the incidence of major bleeding events but mainly driven by the incidence of minor bleedings.

Recurrent VTEs and bleeding events on-treatment - unique DE treated set of the combined paediatric trials

	Birth to <2 years	**2 to <12 years**	**12 to <18 years**	**Total**
Treated patients, N (%)	30 (100.0)	80 (100.0)	225 (100.0)	335 (100.0)
Patients with recurrent VTE [1]	0	0	8 (3.6)	8 (2.4)
Patients with bleeding events [1, 2]	3 (10.0)	9 (11.3)	56 (24.9)	68 (20.3)
Major	1 (3.3)	1 (1.3)	5 (2.2)	7 (2.1)
CRNM	0	1 (1.3)	2 (0.9)	3 (0.9)
Minor	2 (6.7)	8 (10.0)	52 (23.1)	62 (18.5)

[1] Data based on adjudicated events (trials 1160.106 and 1160.108) or investigator-reported events (trials 1160.88, 1160.89, and 1160.105)

[2] A patient may be counted in more than bleeding category

The comparison of DE treatment and SoC in the phase III-controlled trial showed a similar incidence of major bleedings in the two treatment groups, all in all indicating a risk of bleeding events in patients in anticoagulant therapy (please refer to the table below).

Table 11.1.2.1: 1 Time to first major bleeding event, on-treatment period, adjudicated data – TS

	DE		SoC	
Number of patients treated, N (%)	156	(100.0)	78	(100.0)
Patients with major bleeding, N (%)	4	(2.6)	2	(2.6)
Kaplan-Meier estimate for the probability of freedom from major bleeding at Day 84 (90% CI)[1]	0.974 (0.942, 0.988)		0.974 (0.918, 0.992)	
Kaplan-Meier estimate of the difference in rate (90% CI)	−0.000 (−0.037, 0.037)			

[1] Age group stratification factor not considered because of the low number of events

No specific analysis on freedom from major bleeding event + clinically relevant but non-major events have been provided. A table of comparison for bleeding events on-treatment period for study 1160.106 vs. 1160.108 has not been provided either.

Additional details on the regional pattern was provided in the 1160.108 study, final report:

Estimates of freedom from bleeding events at 12 months (95% CI) in the 3 regions with most patients, i.e. Western Europe (N=49), North America (N=44) and Central Europe (N=107) are as follows: Western Europe 57.3% (39.0%, 71.9%), North America 45.3% (25.9%, 62.9%) and Central Europe 91.3 (82.1%, 95.9%). The estimated rate and 95% CI for freedom from bleeding in Central Europe do not overlap with the other regions (see later in this section).

Hepatocellular function

Hepatic injury was defined as an AESI. Hepatocellular injury was defined by the following alterations of liver parameters: An elevation of AST and/or ALT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood draw sample. No patients met the Hy's law criteria. However, this is also expected to occur very rarely. According to the listing of laboratory values, some patients experienced increases of transaminases but the possible incidences of AEs and/or laboratory changes related to changes in hepatocellular function have not been adequately summarised by the Applicant.

Increased blood creatinine

A creatinine value above the ULN and ≥2-fold increased from baseline was pre-defined as an AESI. In the controlled phase III study one patient (1%) in the DE group experienced increased blood creatinine as compared to none in the SoC group. Further, three patients (2%) were diagnosed with renal impairment and one (1%) with decreased glomerular filtration rate, while no patients experienced such AE in the SoC group.

Serious adverse event/deaths/other significant events

Deaths

No patient died on-treatment with DE. Six patients died 6-241 days post-treatment. The narratives all indicate that the deaths were not related to the study medication or SoC (please refer to AR for further details regarding the deaths post-treatment).

SAEs

Serious AEs during the on-treatment period were reported for 48 patients (14.3%), all of them in the Phase IIb/III trials. In the Phase IIa trials, no SAE was reported on-treatment; 2 SAEs occurred post-treatment but appeared not related to the study medication.

The main SAE was worsening of the underlying disease, which included DVT and PE. In the controlled phase III-study, there was no difference in the frequency of reported SAEs in the DE-group (N=21, 14%) and the SoC-group (N=19, 20%) (data not shown in tables).

As mentioned earlier in this AR, there may be a tendency of increasing frequency of SAEs with age; N=2, 13% in patients aged <2 years, N=10, 15% in patients aged 2-<12 years, and N=36, 17% in patients aged 12-<18 years.

SAEs occurring in more than one patient are summarised in the table below.

Serious adverse events on-treatment reported overall for more than 1 patient - unique DE treated set of the combined paediatric trials

	Birth to <2 years	2 to <12 years	12 to <18 years	Total
Treated patients, N (%)	30 (100.0)	80 (100.0)	225 (100.0)	335 (100.0)
Patients with any SAE	2 (6.7)	10 (12.5)	36 (16.0)	48 (14.3)
Deep vein thrombosis	0	0	3 (1.3)	3 (0.9)
Febrile neutropenia	0	1 (1.3)	1 (0.4)	2 (0.6)
Tonsillitis	0	1 (1.3)	1 (0.4)	2 (0.6)
Pain in extremity	0	0	2 (0.9)	2 (0.6)
Pneumonia	0	0	2 (0.9)	2 (0.6)
Upper abdominal pain	0	0	2 (0.9)	2 (0.6)

Laboratory findings

In the Phase IIb/III trials with 12 to 52 weeks of treatment, for most safety laboratory parameters, there were no relevant changes from baseline to end of treatment. In shift-tables for haematological parameters, electrolytes, liver enzymes and renal parameters only small changes were observed in mean values. In accordance with this, only few patients reported AEs within the SOC 'Investigations'. More patients were reported to have Possibly clinically significant changes in haematological parameters and liver enzymes. Similarly, no clinically relevant ECG changes have been reported but the description of the ECGs could be elaborated to ascertain that no clinically relevant changes occurred.

Safety in special populations

For a summary of the number of AEs, SAEs, and patients who discontinued the studies early, please refer to the patient disposition presented in the section of Exposure.

Age, gender, race

The possibility of a difference in the risk of AEs including bleeding events in patients of different age groups have been evaluated earlier in this AR, please refer to the sections of AEs and AESIs.

Overall, the risk of bleedings or need for dose modification appeared to be similar in males and females. The proportion of patients with minor bleeding events was lower in Central Europe (5 patients, 5.0%) than in the other main regions (North America: 12 patients, 27.9%; Western Europe: 15 patients, 31.9%; Latin America: 5 patients, 71.4%). Data of the bleedings reported in the different regions show that in the SoC treatment group, a similar pattern was not observed as for this treatment group, the frequencies of bleedings were similar in Eastern Europe and Western Europe but a higher proportion of bleedings were reported in Northern America. Of note, all bleeding events (minor and major) were centrally adjudicated and the Applicant has submitted data showing that whereas the frequency of major bleedings were overall low (<4%), the differences between the regions are attributed to differences in minor bleedings. Taken together, the observed differences are not of major concern and are most likely due to regional differences in reporting of minor bleedings.

Renal impairment

Neither the CSRs, the clinical overview nor the Summary of clinical safety provide any information regarding the safety in patients with renal impairment.

In both pivotal phase III trials, patients with an eGFR <50 mL/min/1.73m^2 (using the Schwartz formula) or requirement for dialysis were excluded. Accordingly, mean GFR was 107-115 mL/min/1.73 m^2, with the lowest

eGFR values being approximately 67 mL/min/1.73 m^2. There is no specific information regarding the safety profile in patients with mild renal impairment (eGFR >60 – 89 mL/min/1.73 m^2). The SmPC has been updated with information regarding use of dabigatran etexilate in children with renal impairment including a contraindication for use in paediatric patients with an eGFR <50 mL/min/1.73m^2.

Hepatic impairment

Neither the CSRs, the clinical overview nor the Summary of clinical safety provide any information regarding the safety in patients with impaired hepatic function.

According to the study protocols for trials 1160.106 and 1160.108, the following exclusion criteria applied: *"a. Active liver disease, including known active hepatitis A, B or C or, b. Persistent ALT or AST or AP >3x ULN within 3 months of screening. Transient increases of these parameters were acceptable, if retesting demonstrated results within these limits."*

According to the CSRs for the pivotal phase III trials (Trials 1160-0106 and 1160-0108), there are no protocol deviations related to inclusion of patients with active liver disease or persistent increase in ALT or AST as defined in the study protocol.

Pregnancy and lactation

According to the current SmPC, there is limited amount of data of use of DE during pregnancy however, studies in animals have shown reproductive toxicity. The potential risk for humans is unknown but it is recommended that women of childbearing potential should avoid pregnancy during treatment with DE, and DE should not be used during pregnancy unless clearly necessary. In the paediatric trials, one pregnancy was reported, DE was discontinued as the pregnancy was discovered. It appears that the foetus could have been exposed in 0-6 weeks; thus, at the initial part of the pregnancy which is most vulnerable for toxic exposure. Nevertheless, it is reported that the patient gave birth to a healthy newborn at Week 32.

Overdose

A single paediatric patient in the clinical trial program for DE was documented with an overdose. Although the patient (1160.108, 12 to <18 years old) took the correct daily dose, the dosing for 3 days was once daily in the evening instead of twice daily. The event overdose (non-serious, mild intensity, recovered) occurred directly before Visit 11 (last on-treatment visit) on Day 355 of treatment. Idarucizumab (Praxbind®) is a specific reversal agent which immediately reverses the antithrombotic activity of dabigatran. It has only been tested in adults but is currently under investigation in a paediatric population. The currently ongoing trial 1321.7 aims to demonstrate the safety of idarucizumab in paediatric VTE patients who receive DE in clinical trials and have life-threatening or uncontrolled bleeding necessitating urgent intervention to rapidly reverse the anticoagulant effects of dabigatran. Praxbind® was first authorised in adult patients on 16 Oct 2015 in the USA and is now approved in adult patients in numerous countries worldwide including the EU and Japan. Trial sites of 1160.106 and 1160.108 were offered to participate in trial 1321.7, if regulatory conditions allowed for this. The information that there is no experience with use of idarucizumab in the paediatric population is correctly and sufficiently included in the updated SmPC.

Vital signs

It is stated that in the Phase IIb/III trials with 12 to 52 weeks of treatment, there were no relevant changes in vital signs and ECGs from baseline to end of treatment, which may be inconsistent with regard to AEs reported in this period of the studies.

Immunological events

Immunological events are not described in neither Clinical overview nor in Summary of Clinical safety. In the Phase III trials, two cases of immunological events are described.

In Trial 1160-0106, one patient (aged 2 – >12 years) developed Hypersensitivity after switch from DE to SoC. This is not considered related to DE. In Trial 1160-0108, one patient (aged 12 – >18 years) developed Drug hypersensitivity. Further, in the same study, one patient is reported with Hypersensitivity. However, no details on these cases have been provided.

Safety related to drug-drug interactions and other interactions

For the two-Phase III trials (1160.106 and 1160.108), the following restrictions were applied:

"The following treatments were not to be taken prior to DE administration: Fibrinolytic agents (within 48 hours prior to DE administration), P-glycoprotein inducers (within one week prior to DE administration), Asparaginase (within one week (or within 2 weeks in case of PEG-asparaginase) prior to DE administration). The following treatments were not to be taken together with DE: Any VKAs, Therapeutic unfractionated heparin or LMWH, Fibrinolytic agents, Asparaginase, P-glycoprotein inhibitors, P-glycoprotein inducers or any other investigational drug."

Trial 1160-0108: Overall, 153 patients (75.4%) took concomitant medications. The main concomitant medications, taken by more than 15% of patients based on the ATC3 code, were other analgesics and antipyretics (69 patients, 34.0%), decongestants and other nasal preparations for topical use (35 patients, 17.2%), topical products for joint and muscular pain (35 patients, 17.2%), stomatological preparations (33 patients, 16.3%), throat preparations (33 patients, 16.3%), and anti-inflammatory and antirheumatic products - non-steroids (32 patients, 15.8%).

Trial 1160-0106: Concomitant medications included all medications taken prior to informed consent and continued during the trial as well as all medications started after informed consent. Concomitant medications included also medications taken up to 6 days after the last intake of trial medication. Patients could use SoC after Visit 8.

Overall, 180 patients (76.6%) took concomitant medications with similar frequencies in both treatment groups (DE: 75.2%; SoC: 79.5%). The main concomitant medications were paracetamol (23.4%), ibuprofen (7.7%), and spironolactone (7.2%).

In Trial 1160-0108, use of prohibited medication was reported in 14 (8.9%) of patients treated with DE (vs. 0 patients in the SoC group). No information regarding the safety or reported AEs in patients with concomitant use of prohibited medication has been presented.

Discontinuation due to adverse events

As shown in the patient disposition, 10% of the full safety population discontinued the studies early. However, the frequency was higher in the phase IIb/III studies with a planned duration of 12 weeks or more. The discontinuations in these studies appeared to be age dependent; 50% among patients 0 – <2 years, 37% among patients 2 – <12 years, and 26% among patients 12 – <18 years.

However, neither the CSRs, the clinical overview nor the Summary of clinical safety provide an overview of AEs that led to early study discontinuation. From a combination of the SCS and the study reports it may be deduced that the most common reason for discontinuation was 'other' but otherwise that impaired renal function and coagulopathy related conditions seemed to be the most often the causes of discontinuation.

Post marketing experience

There is no post-marketing experience in children.

2.6.1. Discussion on clinical safety

Safety data

Overall, 335 patients aged 0 – <18 years were treated with DE, 30 patients aged <2 years, 80 patients aged 2 – <12 years, and 225 patients aged 12-<18 years. Of these, 300 patients aged 0 – <18 years were exposed to DE in either a 'standard of care'-controlled phase III study or/and a long-term safety study. Approximately 30% (87 patients) were exposed between 0 and 12 weeks, 20% (58 patients) were exposed for 12-18 weeks, while 32% (97 patients) were exposed for more than 42 weeks to the proposed dose (individually defined by the chosen dosing algorithm). The size of the safety database, including the number of patients of the different age groups, was agreed with the PDCO before the choice of data cut-off for the presented interim analyses. The cut-off data was 28 Feb 2019.

Deaths, SAEs and Discontinuations

Six patients died 6-241 days post-treatment. Narratives all indicate that the deaths were not related to the study medication or SoC. About 15% of patients had SAEs, which were mostly categorized as serious because they necessitated hospitalization of the patient. Four patients with immediately life-threatening events were registered.

Among all patients, approximately 10% of the children discontinued the studies prematurely. However, in the phase IIb/III studies the frequency of discontinuations was higher; 50% in patients aged 0 – <2 years, 37% in patients aged 2 – <12 years, and 26% in patients aged 12 – <18 years. Further, in the controlled study, the discontinuations appeared to be more common in the DE group than in the 'standard of care' group. Overall, it appears that more patients in the youngest age group (0 – <2 years) discontinue, often due to failure to obtain target DE concentration.

The Applicant has provided a draft synopsis for **non-interventional European multinational multi-center cohort study** based on newly collected data of patients administered dabigatran for VTE treatment or prevention of recurrent VTE. This was considered overall acceptable at this stage however the protocol of the study will be assessed post-authorization.

Adverse events

Generally, the safety profile known from the adult population was confirmed; the most significant AEs being bleeding events and/or risk of VTE. However, overall the reported frequencies of AEs, including bleeding events, were higher in the paediatric than in the adult population. This may indicate either that children are

more sensitive to DE or that the dosing is relatively higher in children than in adults. Approximately 2% of the total population experienced major bleeding events, the frequency was similar in the DE and SoC groups.

A regional pattern of bleeding events was observed. Data of the bleedings reported in the different regions show that in the SoC treatment group, a similar pattern was not observed as for this treatment group, the frequencies of bleedings were similar in Eastern Europe and Western Europe but a higher proportion of bleedings were reported in Northern America. Of note, all bleeding events (minor and major) were centrally adjudicated and the Applicant has submitted data showing that whereas the frequency of major bleedings were overall low (<4%), the differences between the regions are attributed to differences in minor bleedings. Taken together, the observed differences are not of major concern and are most likely due to regional differences in reporting of minor bleedings.

Apart from bleeding events, two other AESIs were defined, namely reduced hepatic and renal function. Such events appeared to have occurred in a smaller number of patients but with a higher frequency in DE-treated patients than in patients receiving SoC. The Applicant has adequately presented or discussed these observations, and the SmPC has adequately been updated with information regarding the posology for paediatric patients with renal impairment including a contraindication for use in paediatric patients with an eGFR <50 mL/min/1.73m^2.

Commonly reported AEs comprised headache, nasopharyngitis, vomiting, nausea, and dyspepsia. Approximately half of the reported cases of headache was attributable to baseline conditions (e.g. headache, mastoiditis, intracranial hypertension, cerebral venous thrombosis, and only one case of headache was considered by the investigator to be related to the study drug thus, an update to include headache in the tabulated list of adverse reactions (paediatric population) is not considered necessary. GI-related AEs have correctly been included in the SmPC. Several AEs are infectious disorders however, this is expectable considered the population of paediatric patients who often suffered from infections. It is not considered that the high frequency of these disorders is due to an effect of DE on the immune system.

Of note, the frequency of AEs assessed as being drug-related seemed to increase with increasing age, which seemed not be caused by a more severely ill population of adolescents being included in the studies. It is speculated that the reason is that the older population is better able to express their experience/observation of (S)AEs. If this holds true, it may be speculated that the number of (S)AEs may be under-estimated among the youngest age-group.

The evaluation of immunological reactions indicates that hypersensitivity reactions were observed in a few patients; hypersensitivity reaction is adequately included in the tabulated list of adverse reaction as an uncommon AE in the paediatric population.

Additional expert consultations

For details regarding SAG meeting 7 September 2020 please, see Discussion on clinical Efficacy section.

2.6.2. Conclusions on the clinical safety

The size of the safety database has been agreed with the PDCO. It comprises 335 patients aged 0 – <18 years; 30 patients aged <2 years, 80 patients aged 2 – <12 years, and 225 patients aged 12 –<18 years. Of these, 30% were exposed to DE for more than 42 weeks.

The safety profile known from the adult population was generally confirmed with the most significant AEs being bleeding events and/or risk of thrombosis. However, it is unknown if children tolerate the treatment as well as adults, and AEs appear to occur more often in the paediatric as compared to the adult population.

Overall, the safety related outstanding issues are considered solved. A PASS is required to collection to characterise better the safety profile of dabigatran with focus on the youngest age group (0 – <2 years) where data are sparse. The Applicant has provided a draft synopsis for non-interventional European multinational multi-centre cohort study based on newly collected data of patients administered dabigatran for VTE treatment or prevention of recurrent VTE. This was considered overall acceptable and the protocol will be subject to assessment post-authorization.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Haemorrhage Gastrointestinal disorders Hypersensitivity Off-label use in patients with prosthetic heart valves Off-label use in patients with severe renal impairment
Important potential risks	Hepatotoxicity Myocardial infarction (adult patients only) Pulmonary embolism Medication error due to complexity of reconstitution of and dosing with the oral solution (paediatric population below 1 year of age)
Important missing information	Patients with liver impairment (liver enzymes >2x upper limit of normal) Pregnant and lactating women Patients aged 0 to 2 years who were born prematurely Paediatric patients with renal dysfunction (eGFR <50ml/min)

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Ongoing				
GLORIA-AF: Global Registry on Long-term Oral Antithrombotic Treatment In Patients with Atrial Fibrillation (Phase II/III –EU/ EEA Member States), category 3 Interim 1160.136 GLORIA–AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (Phase II/III – Europe); Baseline data for all Phase II patients following enrolment completion (GLORIA)	Long-term safety	Haemorrhage Myocardial infarction Pulmonary embolism	Interim report Final study report	05 Jul 2016 Expected 31 Mar 2021
Planned				

1160.XXX: Safety of dabigatran etexilate for treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 2 years of age: a European noninterventional cohort study based on new data collection.	Safety in patients under 2 years of age	Haemorrhage	Protocol submission Final study report	Estimated Q2 2021 Estimated Q2 2025
Human factors study to assess effectiveness of a training video to mitigate potential medication errors during the reconstitution and dosing of the dabigatran etexilate paediatric oral solution	Assessment of effectiveness of training using a video to mitigate potential medication errors during the reconstitution and dosing of the dabigatran etexilate paediatric oral solution	Medication error (paediatric oral solution only)	Protocol submission Final study report	Estimated April 2021 Estimated January 2022

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Haemorrhage	SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 PL Sections 2, 3, and 4 *Other risk minimisation measures:* Praxbind (idarucizumab) has been approved in adult patients as a specific reversal agent for rapid reversal of the anticoagulation	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form *Additional pharmacovigilance activities:* Study 1160.136 (GLORIA-AF)

	effect of dabigatran case of emergency surgery or urgent procedures for situations of life threatening or uncontrolled bleeding. For paediatric patients, haemodialysis can remove dabigatran. *Additional risk minimisation measures:* Prescriber guide and patient alert card	Study 1160.XXX
Gastrointestinal disorders	SmPC Sections 4.2 and 4.8 PL Sections 3 and 4	Routine pharmacovigilance activities
Hypersensitivity	SmPC Sections 4.3 and 4.8 PL Sections 2 and 4	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form (SCAR)
Off-label use in patients with prosthetic heart valves	SmPC Sections 4.3 and 5.1 PL Section 2	Routine pharmacovigilance activities
Off-label use in patients with severe renal impairment	SmPC Sections 4.2 and 4.3 PL Sections 2 and 3	Routine pharmacovigilance activities
Important potential risks		
Hepatotoxicity	SmPC Sections 4.3, 4.4, and 4.8 PL Sections 2 and 4	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* AE follow-up form
Myocardial infarction (adult patients only)	SmPC Sections 4.4 and 5.1 PL Section 2	Routine pharmacovigilance activities
Pulmonary embolism	No risk minimisation measures	Routine pharmacovigilance activities
Medication error due to complexity of reconstitution of and dosing with the oral solution (paediatric population below 1 year of age)	SmPC Section 4.2 PL Sections 3 and 7 *Other risk minimisation measures:*	Routine pharmacovigilance activities *Additional pharmacovigilance activities:*

	• Reconstitution by HCPs with caregiver reconstitution if the treating physician deems it is appropriate • Instructions for use and administration in each medication kit *Additional risk minimisation measures:* • Prescriber Guide for the paediatric indication with special section for the oral • Training video for healthcare professionals and caregivers for reconstitution and use of the oral solution with mandatory training • Technical support via phone	Human factors study
Missing information		
Patients with liver impairment (liver enzymes >2x upper limit of normal)	SmPC Sections 4.3, 4.4, and 4.8 PL Sections 2 and 4	Routine pharmacovigilance activities
Pregnant and lactating women	SmPC Section 4.6 PL Section 2	Routine pharmacovigilance activities
Patients aged 0 to 2 years who were born prematurely	No risk minimisation measures	Routine pharmacovigilance activities
Paediatric patients with renal dysfunction (eGFR <50ml/min)	SmPC Sections 4.2 and 4.4 PL Section 2	Routine pharmacovigilance activities

Conclusion

The CHMP and PRAC considered that the risk management plan version 38.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the MAH and has been found acceptable by the QRD Group for the following reasons:

The QRD Group agreed that the Applicant should comply with the established QRD template for 'minimum particulars to appear on small immediate packaging units'. The Group agreed that the Applicant needed to rework the immediate packaging of both new pharmaceutical forms (coated granules and oral solution) in order to include the route of administration. The active substance should also be included on the immediate packaging for the oral solution. The Group agreed that the method of administration could be omitted due to the inclusion of the route of administration.

In order to have additional space on the immediate packing, the Group suggested to remove the MAH name (not as critical as the route of administration).

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Venous thromboembolism (VTE) is a disease that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a thrombus that forms in a deep vein, e.g. in the leg, the renal vein or in any other deep vein in the body. This is likely to occur when for any reason the blood is in a state of hypercoagulability, when there is stasis of the venous blood flow and/or when the endothelium is diseased and dysfunctional. PE occurs when a deep venous thrombus, or a part of it breaks free from the vein wall, travels to the lungs and then blocks some or all of the pulmonary blood supply.

While the VTE pathophysiology of hypercoagulability, blood flow stasis and endothelial dysfunction are similar in children and adults and would be receptive to the same type of treatment, the risk factors and triggers of VTE in children are different from those in adults. Consequently, the epidemiology, clinical picture and outcomes are different in children compared to adults.

Venous thromboembolism is a relatively rare disease in the paediatric population with an estimated population prevalence of about 0.6 to 1.1 per 10 000 children. Among hospitalised children, the incidence is with ≥58 per 10 000 paediatric admissions significantly higher than in the paediatric population overall. A dramatic increase of 70% has been noted over less than one decade; most likely due to better survival of acutely ill patients and increased use of central venous access devices. VTE is now among hospitalised children the second most common cause of preventable harm.

Most paediatric VTEs constitute a secondary complication of other clinical conditions such as venous catheterisation, malignancy, infection/sepsis, congenital heart disease, trauma/surgery, renal disease, and inherited thrombophilia (e.g. Factor V Leiden mutation and others) or acquired thrombophilia. Among these, the most common etiologic factor for VTE in paediatric patients is the presence of a central venous access device.

Paediatric VTE has a significant impact on both immediate and long-term health outcomes. Immediate complications of VTE include death from pulmonary embolism (PE) and non-lethal PE. Long-term consequences involve recurrent VTE, bleeding associated with anticoagulation therapy, and post-thrombotic syndrome (PTS). PTS is a burdensome condition that can lead to severe disability and poor quality of life in affected children.

3.1.2. Available therapies and unmet medical need

The standard of care (SoC) for the treatment of VTE in children is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administered for generally 5 to 7 days followed by LMWH or a vitamin K antagonist (VKA). A further treatment option is the injectable factor Xa inhibitor fondaparinux. There are frequent challenges with the therapeutic agents commonly used in children, including the need for venous access or subcutaneous injection, the risk of thrombocytopenia and bleeding, the need for frequent monitoring, variable PK of UFH, and drug-drug and drug-food interactions with VKA. These clinical challenges warrant the development of easier to use treatment modalities with a comparable safety and efficacy profile

to current SoC treatments. DE may provide such an option as it is effective and safe for treating VTEs in adults.

3.1.3. Main clinical studies

Within the paediatric programme of DE, only trial 1160.106 was designed to evaluate the efficacy of DE versus a comparator while the remaining trials were single arm trials with DE. While the initial submission was based on an interim analysis, the final analysis has now been provided with the full data sets.

Trial 1160.106 was a multicentre, open-label, randomised, parallel-group, active-controlled, non-inferiority trial of DE versus standard of care (SoC) in children from birth to less than 18 years of age. The design of this trial (including the definition of endpoints and the choice of SoC comparators) has been agreed with the PDCO. This committee has previously endorsed the principal design elements and endpoints of the trial.

Patients had to have documented diagnosis of clinically stable VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis) per investigator judgement, initially treated (minimum of 5 to 7 days, but not longer than 21 days) with parenteral anticoagulation therapy, such as UFH or LMWH. Short-term pre-treatment with VKAs was permitted if the INR had not yet reached a therapeutic level (i.e. the INR was still <2.0).

The trial consisted of 3 periods: a screening period, an open-label treatment period and a follow-up period. After consent (and assent, if applicable), the patients entered a screening period while they were completing their initial phase of VTE treatment. At the latest after 21 days of initial VTE treatment, patients were randomised in a 2:1 ratio to DE or SoC. The intended SoC (LMWH, or VKA, or fondaparinux) was required to be specified at randomisation. Once eligibility had been confirmed, patients received either daily DE or SoC for up to 3 months beyond the initial parental therapy.

Patients in the DE group received treatment according to a treatment algorithm that was designed to target a dabigatran trough concentration of ≥50 to <250 ng/mL. The dosing was adjusted based on age and weight and specified in nomograms for each of 3 different age-appropriate dosage forms as follows:

Patients aged ≥8 years: Age and weight adjusted dabigatran etexilate capsules.

Patients aged <8 years or for patients who cannot take capsules even if older than 8 (but <12 years of age): Age and weight adjusted dabigatran etexilate coated granules.

Patients aged <12 months: Age and weight adjusted dabigatran etexilate oral liquid formulation (OLF) or any other alternative age-appropriate formulation. For patients < 12 months of age, OLF is preferred over coated granules provided that OLF supplies are available to the site.

DE dose could be adjusted once based on dabigatran concentrations.

Patients assigned to take SoC were to follow the investigator's recommendation for adequate dosing and administration based on the product's locally approved label and in consideration of local treatment guidelines. The SoC dose was to be monitored regularly as appropriate (e.g. INR for VKAs).

3.2. Favourable effects

The randomised controlled trial 1160.106 in children and adolescents aged 0- <18 years with documented diagnosis of clinically stable VTE met its primary objective of non-inferiority of 12 weeks DE oral age-appropriate age and weight adjusted dosing algorithm versus standard of care (UFH, LMWH, fondaparinux,

VKA) with respect to the combined primary endpoint of complete thrombus resolution, freedom from recurrent VTE and freedom for mortality related to VTE.

In study 1160.106 of the 267 randomised patients, 81 patients (45.8%) in the dabigatran etexilate group and 38 patients (42.2%) in the SOC group met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The favourable effect in terms of non-inferiority against established SoC on this highly clinically relevant endpoint is important.

Consistent results were also generally observed across subgroups: there were no significant differences in the treatment effect for the subgroups by age, sex, region, and presence of certain risk factors. For the 3 different age strata, the proportions of patients that met the primary efficacy endpoint in the dabigatran etexilate and SOC groups, respectively, were 13/22 (59.1%) and 7/13 (53.8%) for patients from birth to <2 years, 21/43 (48.8%) and 12/21 (57.1%) for patients aged 2 to <12 years, and 47/112 (42.0%) and 19/56 (33.9%) for patients aged 12 to <18 years.

Furthermore, the adjudicated secondary safety endpoint of time to first major bleeding event showed low event rate in both treatment groups and no difference between the groups. Adjudicated major bleeds were reported for 4 patients (2.3%) in the dabigatran etexilate group and 2 patients (2.2%) in the SOC group.

3.3. Uncertainties and limitations about favourable effects

There continue to be limitations of patient numbers and treatment exposures in the Birth to <2 years age-group considering the differences in terms of immaturity of coagulation system and renal function and leading index VTE types compared to the older age-groups and adults.

Furthermore, the benefit of anticoagulant therapy is less clear for catheter-related thrombosis than for other types of VTE. It is noted that a large proportion of subjects who did not have a symptomatic VTE were included in the study.

The risk of bleeding, especially intracranial bleeding, could be different in subjects with CVST as compared to other types of VTE, in particular for acute CVST.

These major issues regarding the benefit-risk assessment were discussed at a SAG meeting and also addressed by the Applicant in their responses during the procedure.

The scarcity of data in the youngest age category was noted, but the existence of some evidence in this group was welcomed given the known difficulties in recruiting children into the clinical trials with anticoagulants.

The fact that there are only limited data available supporting efficacy and safety of dabigatran by type of VTE subgroup, including central line thrombosis and cerebral venous sinus thrombosis was noted. The limited available evidence did not give rise to any particular concern and therefore the CHMP agreed dabigatran to be available also for treatment of children in these two conditions.

A per-protocol analysis was not done, but a range of sensitivity analyses were done instead. Of note, one of these sensitivity analyses was done assuming all missing data after intercurrent events were not meeting the primary endpoint, i.e. a worst-case scenario, confirmed non-inferiority, which is reassuring. In addition, a

tipping point analysis showed that in the scenario with a SoC response rate up to 20% higher than the DE response rate would still yield a NI test p-value within the range 0.01 – 0.05.

The discontinuation rate in the DE arm is considered high, which is to a large extent because of inability to reach the therapeutic trough level with the dosing algorithm used in the trial; this is however not expected to constitute a problem in clinical practise as part of the inability to reach the therapeutic trough level was related to the sensitivity of the laboratory kit meaning the lower end of the range was set higher for technical reasons than was therapeutically justified. In addition, the revised dosing algorithms are modelled to address a lower bioavailability of the coated granules.

The lack of data on time in therapeutic range (TTR) and a defined INR target for the VKA treatment and the apparent lack of monitoring of anti-factor Xa activity in LMWH treatment as part of the SoC, constitute some uncertainty, but it is acknowledged this reflects clinical practice and the low level of evidence of the SoC medications in the pediatric population.

3.4. Unfavourable effects

Generally, the undesirable events known for DE in the adult population also apply to the paediatric population. The most significant types of AEs being bleeding events and/or worsening of VTE. However, overall the reported frequencies of AEs, including bleeding events, were higher in the paediatric than in the adult population. Bleeding events occurred in 20% of the paediatric population but are reported to occur in 14% of the adult population. Major bleeding events occurred in 2,1% of children, with another 1% experiencing clinically relevant non-major bleeding events, as compared to less than 2% in adults.

Overall 10% of the paediatric population discontinued the studies. However, the frequency of discontinuations was higher in phase IIb/III studies, where the treatment was planned to be 12 weeks or longer. In these studies, combined, the overall incidence of discontinuations was as follows, N (%): <2 years: 16 (53.3%), 2-<12 years: 31 (41.9%), 12-<18 years: 75 (33.5%). The number of discontinuations was higher in the DE group (23.3%) than the SoC group (11.1%) in the controlled phase III study. Patients with AEs leading to discontinuation of trial treatment in the phase IIb/III trials combined was Birth to <2 years 13.3%, 2 to <12 years 6.8%, 12 to <18 years 8.0%, total 8.2%.

Because of the exclusion of patients with meningitis, encephalitis and intracranial abscess in the clinical study the experts suggested a contraindication regarding these conditions.

However, it was challenging to provide any precise recommendation in case these inflammatory conditions develop during treatment with dabigatran and treatment should be considered on case-by -case basis.

Therefore, the warning statement in section 4.4 on haemorrhagic risk has been updated with active meningitis, encephalitis and intracranial abscess added to the haemorrhagic risk factors, and the exclusion criterion on these conditions has been added to the description of study 1160.106 in section 5.1.

3.5. Uncertainties and limitations about unfavourable effects

Children may tolerate DE less well than other regimens of SoC; In the SoC-controlled trial, the proportion of patients, who prematurely discontinued trial medication, was higher in the DE group (23.3%) than in the SoC group (11.1%).

An exact extrapolation of the safety profile from the adult population to the paediatric population is questioned by the generally higher frequencies of AEs, including bleeding events, in children.

The degree of possibly deteriorated safety profile and whether it pertains to all subgroups of the paediatric population remain to be clarified.

Furthermore, because there is an imbalance in mostly minor bleedings in the youngest age-groups on dabigatran compared to SoC in this non-inferiority study, the CHMP agreed that there is a need for post-authorisation data collection to characterise better the safety profile of dabigatran. A draft synopsis of a PASS has been provided and the final protocol will be submitted for assessment post-authorisation.

The actual impact of DE on renal and hepatic function is not known and therefore a contraindication for use in paediatric patients with an eGFR <50 mL/min/1.73m^2 has been included in the SmPC.

Lack of understanding of the opposite bioavailability in children and adults was considered of concern as it could not be explained.

3.6. Effects Table

Table 1. Effects Table for Pradaxa paediatric indication: Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

Effect	Short Description	Unit	Dabigatran (n=267 patient)	SoC	Uncertainties/ Strength of evidence	References
Favourable Effects						
Complete thrombus resolution, freedom from recurrence, freedom from VTE death	Primary composite endpoint	N (%)	81 (45.8%) RS, ITT	38 (42.2%) RS, ITT	NI (20% margin) met Difference in rate (90% CI): -0.038 (-0.141, 0.066) P-value for noninferiority: <0.0001 p-value for superiority: 0.2739	Study 1160.106
Sensitivity worst case analysis	Adjudicated worst-case imputation	N (%)	48 (27.1%)	29 (32.2%)	NI (20% margin) still met in worst-case imputation Rate difference: 0.050 (90% CI: -0.045, 0.144)	

Effect	Short Description	Unit	Dabigatran (n=267 patient)	SoC	Uncertainties/ Strength of evidence	References
Complete thrombus resolution	Fist component of primary endpoint	N (%)	81 (45.8%)	38 (42.2)	Combined primary endpoint driven by complete thrombus resolution	
Key secondary endpoint	Time to first MBE	N (%)	4 (2.3%) TS, on treatment	2 (2.2%) TS, on treatment	Low number of events, no difference between treatment groups	
Unfavourable Effects						
Major bleeding events	Bleedings that were either fatal/clinically overt with a decrease in Hgb of at least 2g/dL in a 24h period/Retroperitoneal, pulmonary, intracranial, or otherwise CNS/requiring surgical intervention in an operating suite	N (%)	Unique DE treated set: 7 (2.1%)	Adult population reported in the SmPC of DE: Less than 2%	Low number of events	Studies: 1160.106 and 1160.108 SmPC
Total bleeding events	All reported bleeding events	N (%)	83 (25.3%) <2 years: 7 (23.3%) 2<12 years: 12 (16.2%) 12<18 years: 64 (28.6%)		Low number of events in younger age groups	

Effect	Short Description	Unit	Dabigatran (n=267 patient)	SoC	Uncertainties/ Strength of evidence	References
Discontinuations	Patients with premature trial medication discontinuation	N (%)	Unique DE treated set Overall: 122 (37.2%) <2 years: 16 (53.3%) 2<12 years: 31 (41.9%) 12<18 years: 75 (33.5%)			

Abbreviations: VTE: Venous thromboembolism, MBE: major bleeding events, SOC: Standard of Care; DE: Dabigatran etexilate

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Overall, the trials in children and adolescents have shown that DE, except in the smallest children, has a comparable PKPD relationship to that in adults. The PKPD analyses have demonstrated that the measured clotting parameters (aPTT, dTT, and ECT) generally respond in a similar way to dabigatran exposure in children and adults. Lack of understanding of the opposite bioavailability in children and adults remains as no explanation to this was found despite extensive discussions with the Applicant. However, it is addressed in the revised dosing algorithms. Information has been included in the SmPC that the appropriate dosing algorithm should be used for each dosage form.

Although there was a single incidence of ICH in a patient with CVST and meningitis, it was challenging to provide any precise recommendation in case these inflammatory conditions develop during treatment with dabigatran and treatment should be considered on case-by -case basis. Therefore, the warning statement in section 4.4 on haemorrhagic risk has been updated with active meningitis, encephalitis and intracranial abscess added to the haemorrhagic risk factors, and the exclusion criterion on these conditions has been added to the description of study 1160.106 in section 5.1.

Following the outcome of the SAG CVS meeting held on 07 September 2020, the experts emphasised the need for post-authorisation data collection to characterise better the safety profile of dabigatran as the only way of further characterising the use of DE in very young children. The Applicant has provided a draft synopsis for non-interventional European multinational multi-centre cohort study based on newly collected data of patients administered dabigatran for VTE treatment or prevention of recurrent VTE. This was considered overall acceptable but the protocol of the study will be assessed by the CHMP post-authorisation.

The clinical trial comparing DE to SoC indicated that efficacy of DE was non-inferior to that of SoC in terms of reaching the primary endpoint of a combination of 1) Free from VTE-related mortality, 2) Free from recurrent events and 3) Complete thrombus resolution. Such an effect is considered clinically relevant.

The favourable effect on VTE-related mortality, recurrent events and complete thrombus resolution is considered important in the proposed indication including severely ill children and adolescents, who often have significant co-morbidities.

In terms of types of AEs, DE in children and adolescents does not appear to differ from what is observed in adults. The most significant AE being bleeding episodes. However, an apparent increased incidence of bleeding events in paediatric patients compared to adults need to be clarified through the PASS study.

3.7.2. Balance of benefits and risks

The benefit/risk of Pradaxa outweighs the risks in the proposed extended paediatric indication.

3.7.3. Additional considerations on the benefit-risk balance

In main study 1160.106 the exclusion criterion on reduced kidney function were different from the current contraindication in adults with reduced kidney function. This exclusion criterion has evolved during the course of the study as new PK data have become available. This approach was chosen to apply a conservative criterion knowing that new-borns renal function is immature. A contraindication of renal impairment (eGFR threshold in <50 mL/min/1.73 m^2) in children has been added to section 4.3 of the SmPC.

Human factors study will be performed to assess effectiveness of a training video to mitigate potential medication errors during the reconstitution and dosing of the DE paediatric oral solution.

3.8. Conclusions

The overall B/R of Pradaxa is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Pradaxa:

Pradaxa 6.25 mg/mL powder and solvent for oral solution

Pradaxa 20 mg coated granules

Pradaxa 30 mg coated granules

Pradaxa 40 mg coated granules

Pradaxa 50 mg coated granules

Pradaxa 110 mg coated granules

Pradaxa 150 mg coated granules

as well as:

Pradaxa 75 mg, 110mg and 150mg hard capsules

is favourable in the following indication:

Treatment of VTE and prevention of recurrent VTE in paediatric patients from birth to less than 18 years of age.

For age appropriate dose forms, see section 4.2.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Pradaxa subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

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 all therapeutic indications prior to launch) in the Member State.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guides
- Patient Alert Cards
- A mandatory training video for Pradaxa powder and solvent for oral solution
- Ad hoc technical support via phone for Pradaxa powder and solvent for oral solution

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
- Dosing tables for the different dosage forms (only for paediatric VTE)
- Recommendation for kidney function measurement
- Recommendations for dose reduction in at risk populations (only for adult indications)
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients/carers 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 the patient is 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
- Recommendation that all parents/caregivers of paediatric patients administered Pradaxa powder and solvent for oral solution should be counselled about the reconstitution and dosing of the oral solution

The MAH shall also provide a patient alert card in each pack of the medicinal product, the text of which is included in Annex III.

A digital training video for reconstitution and dosing of the oral solution should contain the following key messages:

- Reconstitution of the oral solution
- Administration of the prepared oral solution and correct use of the devices
- Storage and disposal of the prepared oral solution

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0399/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
B.II.d.1.d	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	Type IB	None
B.II.d.1.a	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	Type IA	None
B.I.b.1.c	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	Type IB	None
B.I.b.2.a	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	Type IA	None
B.II.d.2.a	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	Type IA	None
B.I.b.1.b	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	Type IA	None
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extensio n	I, IIIA, IIIB and A
B.I.d.1.a.1	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction	Type IA	None
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extensio	I, IIIA, IIIB and A

		n	
B.I.b.1.d	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	Type IA	None
B.I.b.1.d	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	Type IB	None
B.II.c.1.c	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	Type IA	None
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	Type II	I, II, IIIA and IIIB

Extension application to add two new pharmaceutical forms for PRADAXA (coated granules (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg) and powder and solvent for oral solution (6.25 mg/mL)) and four new strengths related to the coated granules (i.e. 20 mg, 30 mg, 40 mg, 50 mg) and one new strength related to the powder and solvent for oral solution (6.25 mg/mL), grouped with:

-A type II variation (C.I.6.a) - Extension of Indication to include new indication for Pradaxa 75 mg, 110 mg, 150 mg capsules based on the paediatric trials. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The RMP version 38.3 has also been approved. Small editorial changes were included in Annex I, II and III.

- The IA and IB changes in the quality documentation mentioned in the table above.