Clinical Trial Protocol

Doc. No.: c02154816-11

EudraCT No.:	2014-000583-18
BI Trial No.:	1160.108
BI Investigational Product:	Dabigatran etexilate, BIBR 1048 MS
Title:	Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
Clinical Phase:	III
Trial Clinical Monitor:	Telephone: Fax:
Co-ordinating Investigator:	Telephone: Fax:
Status:	Final Protocol (Revised protocol (based on Global Amendment 8))
Version and Date:	**Version: 9.0** **Date: 07 Feb 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Pradaxa®			
Name of active ingredient: Dabigatran etexilate, BIBR 1048 MS			
Protocol date: 08 Apr 2014	**Trial number:** 1160.108		**Revision date:** **07 Feb 2019**

Title of trial:	Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
Co-ordinating Investigator:	Telephone: Fax:
Trial sites:	Multi-centre trial
Clinical phase:	III
Objective:	To assess the safety of dabigatran etexilate for secondary prevention of venous thromboembolism
Methodology:	An open label, single arm prospective cohort study designed to assess the safety of dabigatran etexilate for secondary prevention of paediatric venous thromboembolism.
No. of patients:	
total entered:	A minimum of 100 patients. Thereafter, the Data Monitoring Committee (DMC) or Sponsor may decide to keep recruitment open in case additional safety data needs to be generated. Patients from the 1160.106 trial who completed study treatment and require anticoagulation for secondary VTE prevention may be rolled-over into this study.
each treatment:	Not applicable
Diagnosis :	Completed course of initial treatment for confirmed venous thromboembolism (for at least 3 months) and requirement for further anticoagulation due to the presence of a clinical risk factor
Main criteria for inclusion:	Patients diagnosed with acute venous thromboembolism who either - completed initial course of anticoagulation therapy (for at least 3 months), or - completed the 1160.106 study treatment , and require anticoagulation therapy for secondary prevention of venous thromboembolism due to presence of a persistent (unresolved) clinical risk factor.
Test product:	Dabigatran etexilate

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dose:	Patients aged ≥ 8 years: Age and weight adjusted dabigatran etexilate capsules using 50 mg, 75 mg, 110 mg and 150 mg doses. Patients aged < 8 years and for patients who cannot take capsules even if older than 8 years (but below 12 years of age): Age and weight adjusted dabigatran etexilate pellets. Patients aged < 12 months: Age and weight adjusted dabigatran etexilate oral liquid formulation (OLF) or any other alternative age-appropriate formulation. Recruitment will be initiated in adolescent group first (12 to <18 years.) and consecutively opened to the second age group (2 to<12 years.) and then to youngest age group (0 to <2 years.) based on Data Monitoring Committee (DMC) recommendations that take into account information from all ongoing dabigatran etexilate paediatric studies; safety aspects, data analyses of PK, PD, exposure-response model updated with relevant paediatric and adult data as well as the appropriateness of dosing algorithm for consecutive age group.
mode of admin.:	Oral
Comparator products:	None
dose:	Not applicable
mode of admin.:	Not applicable
Duration of treatment:	Patients will be treated with dabigatran etexilate until the clinical risk factor has resolved, or up to a maximum of 12 months. At the end of the study all patients need to discontinue dabigatran etexilate, or switch to standard of care, if there is continued need for anticoagulant treatment.

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Criteria for and pharmacodynamics:	• • • Pharmacodynamic parameters: Central measurement of aPTT and ECT		
Criteria for efficacy:	All criteria in this study will be considered as safety endpoints.		
Criteria for safety:	Primary endpoints: • Recurrence of venous thromboembolism (VTE) at 6 and 12 months • Major and minor (including clinically relevant non-major (CRNM)) bleeding events at 6 and 12 months • Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months Secondary endpoints: • Occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months • Pharmacodynamic assessments (central measurement of dTT (Anti-Factor IIa activity), aPTT and ECT) at Visit 3 (after at least six consecutive dabigatran etexilate doses) and after at least 3 days following any dabigatran etexilate dose adjustment • Number of dabigatran etexilate dose adjustments during treatment period (i.e. Number of patients with dabigatran dose adjustments during treatment period) Other safety assessments: • Incidence of adverse events, protocol-specified AESI and serious adverse events •		
Statistical methods:	Overall assessment of safety will be based on descriptive statistics.		

FLOW CHART

Trial Period	Screening	Treatment Period (open-label) with Dabigatran Etexilate													Follow-up
Visit (V) #:	**1** [1,2]	**2** [2]	**3** [3]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**Titration Visit (if needed)** [3]	**Unscheduled Visit (if needed)** [4]	**eEOT** [5]	**12**
Study week	**-1**	**1**	**1**	**3**	**6**	**12**	**18**	**26**	**34**	**42**	**52**			**If medication is discontinued before Visit 11**	
Day *visit window*	**-14 to 1**	**1**	**4** *+3*	**22** *±7*	**43** *±7*	**85** *±7*	**127** *±7*	**183** *±7*	**239** *±7*	**295** *±7*	**365** *±7*				**V11 or eEOT + 28 days** *+7*
Informed consent / assent[6]	X														
Inclusion / exclusion criteria	X	X													
Medical history / demographics	X														
Physical examination[7]	X							X			X			X	X
Assessment of Index VTE and clinical risk factor	X														
Vital signs (BP and HR) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X							X			X			X	
12-lead resting-ECG (5 min supine)[8]	X							X			X			X	
Evaluate signs / symptoms of recurrent VTE and clinical risk factor		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of PTS								X			X				
Evaluation of bleeding events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Objective diagnosis of recurrent VTE or bleeding		In case of suspected recurrent VTE, PTS or bleeding													
Pregnancy test[9]	X							X			X			X	
Laboratory tests (blood)[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PD sample (aPTT and ECT)[11]		X	X	X	X	X	X	X	X	X	X	X		X	
dTT (or alternative method) sample[11]			X	X	X	X	X	X	X	X	X	X		X	
First administration of dabigatran etexilate[12]		X													
Dispense dabigatran etexilate		X	X	X	X	X	X	X	X	X			X		
Adverse events and Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication compliance			X	X	X	X	X	X	X	X	X	X	X	X	
Patient treatment assessment[13]			X	X		X		X			X			X	
Investigator treatment evaluation			X	X		X		X			X			X	
Termination of trial medication											X			X	
Conclusion of Patient Participation															X

1. Screening Visit and Visit 8 of 1160.106 trial may be combined for patients who have completed the treatment period of 1160.106 trial (tests will be done only once)
2. Visit 1 and Visit 2 may occur on the same day provided that results of the local lab are available to confirm eligibility and INR is ≤ 2.3 (for patients who have been treated with VKA). Local lab results will be recorded under Visit 1, central lab results will be recorded under Visit 2 in the eCRF.
3. Visit 3 is not applicable for patients who have previously completed the treatment period in the dabigatran etexilate arm of the 1160.106 study and who continue taking the same dose of dabigatran etexilate in this trial. For all other patients, during Visit 3 the trough dabigatran concentration will be determined

   The first concentration assessment will be done at Visit 3 (after at least 6 consecutive dabigatran etexilate doses are taken). If target trough exposure of 50 to < 250 ng/mL is not achieved, an Unscheduled Visit must be performed in order to adjust the dabigatran etexilate dose (refer to Appendix 10.4.2). A Titration Visit must be scheduled preferably after at least 3 days have elapsed (or at least 6 new doses have been taken) since a dose adjustment to reassess if the new trough dabigatran concentration is within the target range. Trough is achieved 10 to 16 hours after the last intake of dabigatran etexilate. Patients must not be dosed at home prior to attending a Titration Visit; dosing will be done after a trough plasma sample is collected.
4. Unscheduled Visits are to be conducted in all cases of suspected recurrent VTE, paradoxical embolism (PDE), occurrence of post-thrombotic syndrome (PTS), major or clinically-relevant bleeding events (MBEs/CRBEs) or other AESI or SAE. The Unscheduled Visit should be performed as soon as possible, preferably within 24 hours after the site first becomes aware of a suspected event.
   Unscheduled Visit is also to be performed in case a dose adjustment is needed.
5. The early End Of Treatment (eEOT) Visit will be required for all patients who have taken a dose of dabigatran etexilate but the study medication was discontinued early for any reason (e.g. the clinical risk factor has resolved) before Visit 11. For transition recommendation from dabigatran etexilate to a non-study antithrombotic treatment see Appendix 10.3
6. The informed consent (and if applicable assent) should be obtained per local legislations and guidelines from the patient's parent(s) or legal guardian and patient (where applicable) before any study procedures are performed. Should patients reach legal age during the trial they must personally sign and date the informed consent form as soon as possible and, at the latest, at the next visit.
7. A complete physical examination is required at Visit 1, Visit 8, Visit 11, eEOT Visit and Visit 12. At any point during the trial, a comprehensive physical examination should be performed if indicated based on the clinical presentation of the patient (reported symptoms and the findings on the basis of the vital signs). Relevant findings should be recorded in source notes and captured in the trial eCRF.
8. The required ECGs should be performed as noted in the flow chart, additional ECGs should be performed in cases of cardiac symptoms (example: rhythm disorders) or per PI judgment when medically required.
9. A pregnancy test will be done centrally in female adolescents of child bearing potential (subjects who have reached menarche). Menstrual period must be confirmed prior to inclusion in the trial. More frequent testing can be done if required by the local regulation and / or authority or per investigator judgment. Alternatively serum or urine pregnancy testing may be performed locally at screening, see protocol Section 5.2.3.
10. Laboratory tests will be performed according to protocol Section 5.2.3.

The approximate blood volumes (in ml) to be collected for planned central safety laboratory assessments and /PD are outlined in Appendix 10.1.1. An additional blood sample could be collected at screening for local measurement of INR, serum creatinine, HCT, Hb, Platelet count, ALT and AST in order to facilitate the eligibility assessment.

In case of infants and when medically required per Investigator judgment and / or per local guidelines, reduced blood collection will be implemented after consultation with the Sponsor (e.g. omission of exploratory coagulation markers, reduced frequency of safety labs during the treatment period, etc.). The decision for the reduced blood collection in those cases will be documented in the ISF.

11. Collection of pre-dose trough PD samples will be done as indicated in the flow chart. Pre-dose trough PD samples should be taken at approximately 10 to 16 hours after the last dose. Date and exact time of study drug administration on the three days before the samples are taken are to be captured using patient / parent / legal guardian diary (must be distributed during the previous visit). Dabigatran etexilate doses must not be delayed to accommodate a preferred pre-dose collection time point. More frequent plasma level evaluations may be warranted per investigator judgment for infants and in cases where the patient's weight is expected to fluctuate in a short timeframe due to patient age, physiology and other factors.
12. The appropriate dabigatran etexilate starting dose must be based on the latest age and weight-based nomogram provided in Appendix 10.4.1. Patients who completed the treatment period of the 1160.106 study and who are still being treated with dabigatran etexilate may continue taking the same dose also in this trial.
13. This assessment will be completed by the patient (if old enough per investigator judgment) or by the parent / legal guardian. The aim of this evaluation will be to obtain additional information about the experience of taking dabigatran etexilate as capsules, pellets or oral liquid formulation (reconstituted with flavoured or unflavoured solvent). The assessment should be preferably completed by the same person at all defined time points.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine-Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate-Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval 0 to infinity
aPTT	Activated partial thromboplastin time
APCC	Activated prothrombin complex concentrates
aVTEt	Acute Venous thromboembolism treatment
BI	Boehringer Ingelheim
BIBR 1048	Dabigatran etexilate
BIBR 1048 MS	Indicates the mesylate salt of dabigatran etexilate. Unless otherwise specified BIBR1048 MS has been used interchangeably with BIBR 1048
b.i.d.	Twice daily
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Centigrade / Celsius
CA	Competent Authority
CI	Confidence Interval
C_{max}	Maximum Measured Concentration
CML	Clinical Monitor Local
CPMP	Committee for Proprietary Medicinal Products
$C_{pre,ss}$	Pre-dose concentration of the analyte in plasma at steady-state immediately before administration of the next dose
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CRNM	Clinically relevant non-major
CRO	Contract Research Organisation
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CT	Computed Tomography
CVL	Central venous Line
DILI	Drug-Induced Liver Injury
DMC	Data Monitoring Committee
dTT	Diluted Thrombin Time
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECT	Ecarin clotting time
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment

eEOT	Early End of Treatment
F	Fahrenheit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEIBA	Factor Eight Inhibitor Bypassing Activity
FRAC	Fraction of Adult Dose
GCP	Good Clinical Practice
gMean	Geometric Mean
h	Hour
HCT	Haematocrit
HPLC	High Pressure Liquid Chromatography
HR	Heart Rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRT	Interactive Response Technology
IRB	Institutional Review Board
ISF	Investigator Site File
ISTH	International Society on Thrombosis and Haemostasis
LMWH	Low Molecular Weight Heparin
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
mL	Millilitre
mg	Milligram
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
Na	Sodium
ng	Nanogram
No.	Number
OLF	Oral Liquid Formulation
OPU	Operative Unit
p.o.	per os (oral)
PE	Pulmonary embolism
PD	Pharmacodynamic
PDCO	Paediatric Committee (of the European Medicines Agency)
PDE	Paradoxical Embolism
PK	Pharmacokinetic
PPI	Proton Pump Inhibitor
PTS	Post-Thrombotic Syndrome
REP	Residual Effect Period
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamate Pyruvate Transaminase

SI	International System of Units
SOC	Standard of Care
SOP	Standard Operating Procedure
SPAF	Stroke Prevention in Atrial Fibrillation
SUSAR	Suspected Unexpected Serious Adverse Reaction
sVTEp	Secondary Venous thromboembolism Prevention
$t_{1/2}$	Terminal Half-Life
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t_{max}	Time From Dosing to Maximum Measured Concentration
THR	Total hip replacement
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TT	Thrombin Time
UFH	Unfractionated Heparin
ULN	Upper Limit of Normal
VKA	Vitamin K Antagonist
VTE	Venous thrombotic event / Venous Thromboembolism
W	Weight

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

In contrast to adults, venous thromboembolism (VTE) in children is a rare event with an overall annual incidence of approximately 0.07-0.14 events per 10,000 children (R06-2301). Nevertheless it represents a significant management challenge that requires therapeutic intervention (R06-2301, R06-2150, R07-2959). The most common etiologic factor for VTE in children is the presence of a central venous line (CVL) (R06-2305, R06-2150). Immediate complications of VTE include death from pulmonary embolism (PE) and non-lethal PE. Long-term complications involve recurrent VTE, post-thrombotic syndrome (PTS), and bleeding associated with anticoagulation therapy (R07-2959, R07-2954, R07-2962, R06-2305).

The recommendations on antithrombotic therapy in children are based on extrapolation of adult data from randomized controlled studies or on small randomized or non-controlled studies in children (P98-11480, R07-2940). The current 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 3 to 6 months of LMWH or vitamin K antagonists (VKAs) (R07-2939).

There are frequent challenges with the use of UFH and oral anticoagulants (OAC) in children (P06-06652, R07-2938, R07-2956). For UFH, these include variable pharmacokinetics, need for venous access for both administration and monitoring and heparin-induced thrombocytopenia. For VKA, problematic issues with dosing include the significant influences of age, diet, medications and underlying diseases, which result in a need for frequent monitoring (R07-2964). Low molecular weight heparin has several potential advantages in children over UFH/VKAs for the treatment of VTE, which has prompted it becoming the preferred product in children despite the lack of adequate and well-controlled clinical trials. However, the use of LMWH requires subcutaneous administration with a needle poke causing pain in the child and anxiety for the parent or guardian which may translate into non-compliance. These problems with conventional anticoagulation provide the rationale for investigations of novel anticoagulants.

An open-label multicentre randomized study (the REVIVE study) comparing the efficacy and safety of a low molecular weight heparin (reviparin-sodium) to UFH/VKA for the treatment of VTE in children, showed that at 3 months post-therapy, 2/36 patients (5.6%) treated with reviparin-sodium had recurrent VTE or death compared to 4/40 patients (10.0%) receiving UFH/VKA (odds ratio = 0.53; 95% CI=(0.05, 4.00); Fisher's exact test: 2P= 0.677). There were 7 major bleeds reported, 2/36 (5.6%) in the reviparin-sodium group and 5/40 (12.5%) in UFH/VKA group (odds ratio = 0.41; 95% confidence interval 0.04, 2.76); Fisher's exact test: P=0.435). There were 5 deaths reported during the study period, 1 (2.8%) in the reviparin-sodium group and 4 (10.0%) in the UFH/VKA group. All five deaths were considered unrelated to VTE but one was due to an intracranial haemorrhage in the UFH/VKA group. Due to challenges with patient recruitment, REVIVE was closed prematurely. The REVIVE study provides valuable information on the incidence of recurrent VTE, major bleeding and problematic issues associated with therapy of VTE in children (R06-2304).

Paediatric VTE has a significant impact on both immediate and long-term health outcomes (R13-4251, P94-81556; R12-5109). There are two major consequences of VTE that could affect the long-term health status: recurrence of VTE and post-thrombotic syndrome (PTS). The risk of recurrent VTE in children is estimated to be approximately 5-10%. However the risk may be even higher in patients with one or more persisting risk factors (e.g. central venous line (CVL), chronic disease, thrombophilia, etc.) (R07-2936; P09-03357; P12-03887). Data from a recent survey conducted in the USA suggested that approximately 14% of children develop recurrent VTE with the likelihood of recurrence being the highest in adolescent group (19%) (R13-4251). The incidence of clinically significant childhood PTS is estimated to be 10% (P09-03357). Up to date, there are no randomized controlled trials that investigate secondary VTE prevention in paediatric patients.

In a prospective cohort study conducted by and colleagues at the Hospital for Sick Children (Canada), the use of LMWH for treatment and prevention was evaluated in a cohort of 173 patients. There were 146 courses of LMWH administered for treatment and 30 courses for prophylaxis of VTE (R14-1031). Of the 30 patients who received prophylactic doses of LMWH, 11 (37%) patients received LMWH for the prevention of CVL-related thrombosis. Of these 30 patients who received prophylactic doses of LMWH, one (3.3%) patients had symptomatic recurrence of VTE, and died due to extension of old VTE and coronary heart disease. There were no major bleeds.

In another long-term safety and efficacy prospective cohort study conducted by Schobess and colleagues, 80 children aged > 3 months to < 18 years diagnosed with DVT were consecutively recruited to be treated with a LMWH and stratified to once-daily or twice-daily enoxaparin administration, with median treatment duration of 4-5 months (R14-1032). The median follow-up time was 24 months, during the follow-up period 6.3% of children developed PTS and 5% developed recurrent DVT.

A Canadian Paediatric Registry followed 137 consecutive paediatric VTE patients from 6 months to up to 3 years (P94-81556). The registry reported that out of 137 patients, 2.2% died as a direct result of thrombotic complications, 18.5% developed recurrent VTE or PE, of which 70% occurred on anticoagulation therapy. In addition, 21% had evidence of post-thrombotic syndrome.

In summary, patients who suffered from VTE may remain at risk for recurrent thrombosis and thromboembolism after completion of initial anticoagulation treatment course, especially those with CVL, prothrombotic risk factors, etc. Long-term DVT consequences (e.g. post-thrombotic syndrome) are important causes of morbidity and mortality in children and require further investigation.

1.2 DRUG PROFILE

Dabigatran etexilate (BIBR 1048) is an oral pro-drug of the active direct thrombin inhibitor dabigatran (BIBR 953). Dabigatran is a low molecular weight, reversible thrombin inhibitor, which binds to thrombin with a high affinity and specificity. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. The pro-drug itself has no anticoagulant activity.

The efficacy and safety of dabigatran etexilate have been evaluated in Phase III trials that involved over 38,000 adult patients, thereof more than 23,350 dabigatran patients were investigated.

These trials investigated primary VTE prevention after hip and knee surgery, acute VTE treatment (aVTEt), secondary VTE prevention (sVTEp) and stroke prevention in atrial fibrillation (P09-11669).

The aVTEt adult study program with RE-COVER (1160.53, U09-1400-01) and RE-COVER II (1160.46, U11-2298-01) and the two sVTEp studies (RE-MEDY: 1160.47, U10-2533-01 and RE-SONATE: 1160.63, U11-2267-02) have been completed.

Dabigatran etexilate is approved for prevention of VTE following total hip or knee replacement surgery and for prevention of stroke and systemic embolism in patients with atrial fibrillation. At the time this protocol was written, approval was still pending for aVTEt and sVTEp in major markets.

For full details on drug profile, please refer to the latest version of the Investigator's Brochure (IB) (U98-3208).

PK/PD data from adult studies:

Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. It inhibits thrombin-dependent conversion of fibrinogen to fibrin, thus preventing the formation of thrombi.

The clinical pharmacology study program of dabigatran etexilate is comprised of more than 45 individual Phase I studies and the collection of pharmacokinetic and pharmacodynamic data from seven Phase II studies and four Phase III studies (RE-LY, RE-NOVATE, RE-NOVATE-2, and RE-COVER).

Overall, dabigatran plasma concentration increased proportional to the increasing oral dose of the prodrug dabigatran etexilate and there was no time or dose dependency in dabigatran distribution and elimination indicating linear pharmacokinetics (U09-2262-01).

The pharmacokinetic profile of dabigatran is characterized by maximum plasma concentrations at approximately 2 hours after oral administration, a bi-exponential distribution phase and a terminal half-life of 11-17 hours in young (U06-1614-01, U00-1856) and 12 - 13 hours in elderly healthy volunteers (U03-1878), respectively.

Steady state is generally attained by the third day of treatment with dabigatran etexilate administered b.i.d.

There is a clear relationship between dabigatran plasma concentrations and its pharmacodynamic effects (e.g. changes in ecarin clotting time (ECT), thrombin time (TT), diluted thrombin time (dTT), and activated partial thromboplastin time (aPTT)) in all populations studied, resulting in reproducible dose-dependent prolongation in clotting times with rapid onset and offset of these effects. The PK/PD (i.e. prolongation of coagulation

time) was consistent between various patient populations and healthy volunteers and not affected by age, sex, or co-medication (U09-1399-02).

In the RE-LY study (U09-3249-02), a relationship between total dabigatran exposure and efficacy (i.e. ischemic stroke) has been established; a total dabigatran trough concentration above 50 ng/mL was associated with appropriate efficacy for the prevention of stroke and even lower concentrations appeared to provide benefit. In the RE-COVER study, the correlation between efficacy and total dabigatran trough concentration was weak. Efficacy could be considered as adequate at concentrations above the 10^{th} 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 is expected to provide the most favourable efficacy and is therefore proposed for paediatric patients in this trial. Furthermore, based on a low risk of major bleeding events with rising total dabigatran trough concentrations even beyond 250 ng/mL, it is therefore considered that maintaining a trough concentration between 50 and < 250 ng/mL as planned in this study, has a reasonable likelihood to be effective, safe and thus have a positive benefit / risk ratio in children of all ages.

A Phase I study (1160.87) was conducted in 30 healthy adult volunteers to investigate the relative bioavailability of single doses of two formulations: reconstituted solution from powder and pellets sprinkled on food in comparison to the standard adult capsule formulation (U09-1839-01). The two test formulations (pellets and solution reconstituted from powder) had a significantly higher relative bioavailability compared to the reference capsule formulation. The average treatment ratio for the comparison between solution reconstituted from powder and capsules were 154.8 % and 166.6 % for $AUC_{0-\infty}$ and Cmax, respectively. The corresponding 90% confidence intervals for the ratios of $AUC_{0-\infty}$ and Cmax were 127.4 % to 188.2 % and 133.2 % to 208.3 %, respectively. The average treatment ratio for the comparison between pellets and capsules were 175.1 % and 186.9 % for $AUC_{0-\infty}$ and Cmax, respectively. The corresponding 90% confidence intervals for the ratios of $AUC_{0-\infty}$ and Cmax were 141.9 % to 216.1 % and 147.7 % to 236.7 %, respectively.

Another larger phase I study (1160.194; 54 healthy subjects) further examined the bioavailability of steady-state dabigatran etexilate as pellets on food and dabigatran etexilate as granules resolved in reconstitution solution in healthy adult volunteers (c02248557). The examined test formulations resulted in a higher average relative bioavailability compared with the dabigatran etexilate as hard capsule reference formulation (30% for DE as granules resolved in reconstitution solution, and 37% for DE as pellets on food). However, individual $C_{max,ss}$ and $AUC_{\tau,ss}$ values observed for the 3 formulations were within the range of exposure seen with previous dabigatran studies using capsules and reconstitution solution. The increase in exposure is considered small enough to consider the formulations interchangeable. Furthermore, trough levels were similar for the 3 formulations. Based on the results of this study, no conversion factor needs to be applied for dosing purposes in children.

The starting dose may be amended based on further data from phase IIa studies in children.

It is worth mentioning that the goal of the dosing algorithm is to reach the pre-defined target exposure for dabigatran (i.e. a trough plasma concentration of 50-250 ng/mL). This will be achieved by dose adjustments based on plasma level measurements in steady state.

PK/PD in-vitro paediatric data:

Prior to administering dabigatran etexilate to any children, its activity was assessed in the plasma of children *ex vivo* to determine whether there were any age-dependent differences in the effects of dabigatran on the haemostatic system of children of different ages (P08-09073). Cord blood and blood samples were collected from 9-11 children in each age group (0 to <1yr; 1 to <5 yrs.; 5 to <10 yrs. and 10 to 16 years) and compared to pooled adult plasma. This study demonstrated that there was no remarkable difference in the response to dabigatran concentrations ranging from 50-450 ng/ml between adult and paediatric plasma (ages 0-16 years) using standard coagulation assays. The only differences in response were seen with cord plasma, which was more sensitively prolonged than children's plasma of all ages and adult plasma. Both the TT and ECT were linearly and sensitively correlated with dabigatran plasma concentrations.

Evaluation of dabigatran in patients from 12 to less than 18 years of age (study 1160.88):

Eight adolescent patients have successfully completed the three day treatment safety and tolerability Phase IIa study 1160.88 as required per protocol (U12-3378-01) with dabigatran etexilate capsules. No drug-related serious adverse events or bleeds were observed in the 1160.88 study (U12-3378-01). In this small population of patients, dabigatran etexilate capsules were well tolerated with only three mild and transient gastrointestinal adverse events reported by two patients. The PK/PD relationship in this population was similar to the relationship seen in adult VTE patients; as expected, the PK/PD analysis showed linear relationship with ECT and dTT.

From these data it seems justified to apply the adapted adult population pharmacokinetic model to simulate total dabigatran plasma concentration-time profiles in paediatric populations.

Evaluation of dabigatran in patients from 1 to less than 12 years of age (study 1160.89):

Eighteen patients with VTE aged from 1 to < 12 years of age were entered in a safety and tolerability Phase IIa study (1160.89) with dabigatran etexilate oral liquid formulation (c09069268). Six patients received multiple doses (3 days twice daily) and fifteen patients received a single dose. The dose was adjusted according to an algorithm based on Hayton's estimation for renal function taking into account age and weight. Dabigatran etexilate oral liquid formulation was well tolerated, with no study drug-related serious adverse events, no study drug-related adverse events, VTE or bleeds observed. The PK/PD relationships were similar to those observed in adult and adolescent patients with VTE. A linear PK/PD relationship was observed for ECT and dTT whereas the PK/PD relationship was non-linear for aPTT. The projected steady-state dabigatran trough concentrations of this study were largely comparable to those observed in adult patients with VTE.

Evaluation of dabigatran in patients from birth to less than 1 year of age (study 1160.105):

Eight patients with VTE aged from 0 to < 1 year of age were entered in a single dose safety and tolerability Phase IIa study (1160.105) with dabigatran etexilate oral liquid formulation (c09085437). The dose was adjusted according to an algorithm based on Hayton's estimation for renal function taking into account age and weight. Dabigatran etexilate oral liquid formulation was well tolerated, with no study drug-related serious adverse events, no study drug-related adverse events, VTE or bleeds observed. The PK/PD relationships were similar to those observed in adult and adolescent patients with VTE. A linear PK/PD relationship was observed for ECT and dTT whereas the PK/PD relationship was non-linear for aPTT. The projected steady-state dabigatran trough concentrations of this study were largely comparable to those observed in adult patients with VTE.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

VTE treatment and secondary prevention using current standard of care therapies such as LMWH and VKA continues to present some challenges in clinical practice. With VKA use, frequent INR monitoring is required due to a narrow therapeutic range which is often complicated by age, changing diet, medication interactions and underlying disease. LMWH has several benefits in children over VKA and it is currently considered as the preferred agent for paediatric VTE treatment and secondary prevention. However, the anxiety that patients and parents often feel, which is sparked by the requirement of subcutaneous administration, may lead to compliance issues. As well, the use of LMWH for paediatric VTE treatment and secondary prevention is not sufficiently studied and characterised in well-controlled clinical trials. Clinical challenges observed with VKA and LMWH usage warrant the development of easier to use treatment modalities with a comparable safety and efficacy profile to current standard of care treatments. Dabigatran etexilate may provide such an option.

The present study is a safety trial of dabigatran etexilate for secondary prevention of VTE in children from 0 to less than 18 years of age. The design of this study has been agreed with the European Medicines Agency's Paediatric Committee. This study is part of the paediatric dabigatran clinical development program for VTE treatment. This trial has the potential to provide critical information regarding the safety of dabigatran etexilate for secondary prevention of VTE and hence help pave the way for validation of dabigatran etexilate as a potential novel therapy in this indication.

2.2 TRIAL OBJECTIVES

The main objective of this paediatric prospective cohort study is to assess the safety of dabigatran etexilate used for secondary prevention of venous thromboembolism in children from 0 to less than 18 years of age.

2.3 BENEFIT - RISK ASSESSMENT

Individuals participating in this trial may benefit from receiving a drug which was evaluated in preventing secondary VTE in adult patients and demonstrated to be safe and effective in that population. The secondary VTE prevention trials conducted in over 4200 adult patients demonstrated that dabigatran etexilate was non-inferior to very well controlled warfarin (RE-MEDY, U10-2533-01) and superior to placebo in preventing recurrent VTE compared to placebo (RE-SONATE, U11-2267-02).
In the RE-MEDY trial, the primary endpoint event (VTE or VTE-related death) occurred in 26 patients in the dabigatran etexilate treatment group and in 18 patients in the warfarin group (HR 1.44 (95% CI 0.78-2.74, p = 0.0137 for non-inferiority)). The frequency of major bleeding events was numerically lower for the dabigatran etexilate group (0.9%) than for the warfarin group (1.8%). However, this difference did not reach statistical significance (HR 0.52 (95% CI 0.27-1.02, p = 0.0577)).
The RE-SONATE trial demonstrated that dabigatran etexilate was superior to placebo for the

primary endpoint, i.e., the composite of recurrent symptomatic VTE and unexplained death (HR 0.08 (95% CI 0.02, 0.25, p <0.0001 for superiority)). There were only two patients (0.3%) in the dabigatran etexilate treatment group, and none in the placebo group, who had confirmed major bleeding events (HR could not be calculated because of the absence of MBE events in the placebo group). The hazard ratios comparing dabigatran etexilate to placebo for centrally adjudicated clinically relevant bleeding events, measured 2.92 (95% CI, 1.52, 5.60), and any bleed events, measured 1.82 for dabigatran etexilate versus placebo are 2.92 and 1.82 (1.23, 2.68), with p values for both being <0.003.

Based on the adult VTE treatment trials (RE-COVER and RE-COVER II) conducted in over 5000 patients, the incidence of major bleeding events was lower in the dabigatran arms relative to warfarin (hazard ratio DE/W 0.48; 95% CI 0.29 to 0.78) with similar efficacy; primary efficacy endpoint hazard ratio DE/W 1.09; 95% CI 0.77-1.53 (U09-1400-01 and U11-2298-01). Therefore, this study may have the potential to provide a real therapeutic benefit to participating patients at an individual level.

The planned study may also help to bring new and innovative therapy to paediatric patients with risk of secondary VTE, providing a general benefit to society and to the paediatric patient population.

The tolerability and PK/PD profile of dabigatran has been evaluated in a limited number of paediatric patients. Data obtained from 8 adolescent patients in trial 1160.88 (U12-3378-01) demonstrated that dabigatran etexilate capsules were apparently safe and well tolerated. Data obtained from 18 patients aged 1 to < 12 years in trial 1160.89 (c09069268) and in 8 patients aged 0 to < 1 year in trial 1160.105 (c09085437) demonstrated that dabigatran oral liquid formulation was apparently safe and well tolerated. According to the PK data from study 1160.89 in the age group of patients aged 1 to less than 12 years, and from study 1160.105 in the age group of patients from 0 to less than 1 year, a dosing algorithm based on Hayton's estimation for renal function seems to be appropriate.

A twice daily (BID) dosing nomogram was developed to achieve the steady state trough concentrations of dabigatran etexilate between 50 and < 250 ng/ml. Doses in the nomogram were estimated using a scaling method according to Hayton, which is considered applicable for drugs, like dabigatran etexilate, with predominantly renal clearance (R06-2299). The method scales an adult dose which is expected to result in a therapeutically beneficial exposure range down to a child's expected renal function (which Hayton defines based on age and weight).

At the start of study 1160.108, the maximum daily dose of dabigatran etexilate for patients with body weight > 40 kg was capped at 440 mg (given as 220 mg twice daily) instead of using actual calculated dosages in order to avoid high peak concentrations predicted with higher dosages in comparison to expected peak levels in a typical adult VTE patient. The initial experience from 5 adolescents in study 1160.106 using a capped dabigatran dose regimen in patients with a body weight > 40 kg, has observed dabigatran trough concentrations below or close to the lower target cut-off of 50 ng/ml and well below the higher end of the target plasma range (250 ng/ml) as measured by the Hemoclot assay. PK modelling has projected that the percentage of patients with trough plasma levels < 50 ng/ml

is up to 40% depending on the degree of capping (higher dose reductions compared to the actual calculated dose will increase the probability).

With protocol version 3.0, a BID regimen using actual calculated dosages (according to Hayton equation) rather than any capped dosages has been implemented. This dosing regimen will also include the additional safeguard of dose up- or down-titration to achieve a trough plasma level of 50 to < 250 ng/ml. Dose adjustments may occur as early as approximately 5 -12 days after first medication intake based on results from Visit 3 plasma level measurements.

According to PK simulations, a BID regimen using actual calculated dosages according to Hayton will reduce the probability of trough levels to be below 50 ng/ml to approximately 18%. The probability to have levels < 25 ng/ml with the BID uncapped regimen is projected to be as low as 3%, which means that exposure will most likely be sufficient in the vast majority of patients, when risk of VTE recurrence is highest (i.e. within the first 30 days after the index VTE event). Based on the experience from the adult RE-LY and RE-COVER studies dabigatran levels between 25 and 50 ng/mL may still be considered adequate.

In selected patients receiving single dosages greater than 220 mg BID (i.e. up to 330 mg single dose at maximum) in an uncapped regimen, peak levels are projected to be higher than those predicted for the typical adult patient in VTE study RE-COVER. Higher peak levels correspond to high trough levels, for which a down-titration of the dose will occur early in the trial (i.e. after approximately 5-12 days), if the trough level is > 250 ng/ml.

According to the literature, the risk of bleeding tends to be in general lower in children than in adults (R12-0738; P10-09826). In paediatric studies, the rate of major bleeding reported while receiving anticoagulant medication ranged from 0.5% - 1.7% of patients (R12-0738), whereas major bleeding rates in adult patients requiring oral anticoagulant therapy range from 1.3% to 8.3% per year (P04-10723). The proposed BID dosing regimen for dabigatran also appears favourable in comparison to the current standard of treatment with Vitamin K antagonists (VKAs). With VKAs, the risk of not being within the therapeutic INR range has been reported to be much higher than with this proposed dabigatran dosing regimen: published studies describe a mean or median time in therapeutic range between 39% and 81.7% (R12-0738), which means that patients are under- or overdosed for up to 60% of the time with VKA treatment.

A BID regimen with removal of capping (up to a dose of 330 mg BID) is considered favourable. In addition, risks associated with this regimen resulting from low exposure have been projected to be uncommon. Potential risks associated with higher trough exposure are transient and considered acceptable in a paediatric population in the context of less favourable treatment alternatives, specifically when comparing to the large percentage of time out of the therapeutic range with the current standard of care treatment (VKAs).

In summary, the bleeding risk in the paediatric patient population is considered to be lower than that in adult populations (e.g. in the adult SPAF and VTE indications). Based on an overall benefit-risk assessment including the fact that the risk of thrombotic events is highest

in the first 30 days, the predicted exposure in an uncapped BID regimen is considered acceptable.

The efficacy and safety profile of dabigatran etexilate in paediatric patients as well as the appropriateness of proposed dosing algorithm will be evaluated in the phase IIb/III 1160.106 trial. The data will be closely monitored by an independent Data Monitoring Committee (DMC), which will also be utilized to monitor participants' safety during this trial.

The study recruitment will be done similar to that in the 1160.106 trial. The recruitment will be initiated in adolescent patients first (12 to < 18 yrs.) and consecutively opened to the next age group (2 yrs to < 12 yrs.) and then to youngest patients (0 to < 2 yrs.) based on DMC recommendations that take into account information from the current age group in this trial and the 1160.106 trial, as well as data from other dabigatran etexilate paediatric studies. This approach ensures that the younger age groups will only be evaluated after the dosing algorithm is confirmed, age-appropriate formulations are available, and preliminary PK, PD, efficacy and safety data are obtained from older age group(s) from this trial, the1160.106 trial and other phase IIa studies. These measures are expected to provide adequate safety protection for all study participants.

A specific reversal agent antagonising the pharmacodynamic effect of dabigatran in children is not available yet; however, a development program is ongoing (P15-06362).

As protein binding is low, dabigatran is dialyzable, however, there is limited clinical experience in using dialysis in this setting. Clearance of dabigatran by haemodialysis was investigated in patients with end-stage renal disease. Dialysis was conducted with 700 mL/min dialysate flow rate, four hour duration, a blood flow rate of either 200 mL/min or 350-390 mL/min. This resulted in a removal of 50% or 60% of free- or total dabigatran concentrations, respectively. The amount of drug cleared by dialysis is proportional to the blood flow rate.

Although dabigatran etexilate treatment was not associated with any increase in drug-induced liver injury (DILI) in adults, DILI is under constant surveillance by sponsors and regulators. Therefore, as in all Boehringer-Ingelheim sponsored studies, this study requires timely detection, evaluation, and follow up of laboratory alterations of selected liver laboratory parameters to monitor patient safety.

Overall, dabigatran etexilate may reduce the need for frequent blood samples for therapeutic drug monitoring as is the case with currently available oral anticoagulants (VKAs). This study has the potential to offer to the participating subjects close medical care and an alternative therapy which has been evaluated in adults and demonstrated to be safe and effective, hence potentially providing an alternative therapeutic option for secondary VTE prevention in the paediatric patient population.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multinational, open-label, single arm prospective cohort study of dabigatran etexilate to evaluate safety in the secondary prevention of venous thromboembolism in children from 0 to less than 18 years. This study is planned to be conducted in approximately 100 sites located worldwide.

After a signed consent form (and assent, if applicable) has been obtained and if all eligibility criteria are met, patients will initiate or continue treatment with dabigatran etexilate (Visit 2). Detailed guidance on how to switch from standard VTE treatment to dabigatran etexilate is provided in Section 4.1.4.

Patients will be treated with dabigatran etexilate until the clinical risk factor requiring secondary VTE prevention has resolved, or up to a maximum of 12 months. The clinical risk factor must be specified at screening and evaluated at every visit. At the end of the study all patients need to discontinue dabigatran etexilate, or switch to standard of care, if there is continued need for anticoagulant treatment (see Appendix 10.3).

Please refer to Section 4.1.3 for information on dose selection.

Study visits and procedures will be performed as outlined in the Flow Chart. Collection and processing of PD samples is described in Section 5.7.2.

All patients who have taken dabigatran etexilate will have a follow-up period of 28 days after termination of trial medication (Visit 11). Subject participation is concluded when the Follow-up Visit is completed.

Patients who stop study treatment earlier than 12 months (risk factor resolved or early treatment discontinuation) will be asked to perform an eEOT Visit and will be followed up according to the remaining visit schedule until the end of the study. Prior to entering the trial, patients and their parents / legal guardians will be made aware of this requirement.

The end of the trial is defined as “last subject out”, i.e. last visit completed by the last subject.

3.1.1 Administrative structure of the trial

This trial is sponsored by Boehringer Ingelheim (BI).

BI has appointed a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct, and reporting of the trial, ordering the materials as needed for the trial, ensuring appropriate training and information of local clinical monitors (CMLs), clinical research associates (CRAs), and investigators.

Data Management and Statistical evaluation will be performed by BI according to BI SOPs. For these activities, a Trial Data Manager and a Trial Statistician have been appointed.

Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs as appropriate. A list of responsible persons will be given in the Clinical Trial Master File (CTMF) document.

The local organisation of the trial will be done by the respective local BI-organisation (Operating Unit (OPU)) or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. In general, a CML has been appointed in each participating country or OPU. The CML will be responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs.

Trial sites consist of specialised referral centres experienced in the management of venous thromboembolism in the paediatric population. Documents on the participating (Principal) investigator(s) and other important participants, especially their curricula vitae, will be filed in the CTMF.

Details on handling of the trial supplies including responsible institutions are given in Section 4 of this protocol.

The Investigator Site File (ISF) will be kept at sites as required by local regulation and BI SOP. A copy of the ISF documents will be kept as an electronic CTMF document according to BI SOPs.

3.1.1.1 Data Monitoring Committee

Safety and tolerability will be monitored by the same independent DMC responsible for 1160.106 trial. A detailed DMC charter will govern the activities of this committee. The recommendations of the DMC will be maintained in the CTMF.

The committee will review safety on an ongoing basis and will advise the Sponsor on recommendations to continue, modify or terminate the study per the Charter. The DMC will review study results as well as monitor the overall paediatric program results to ensure patient safety. The DMC will recommend whether (and when) it is appropriate to open the trial to younger age groups (from 2 to <12 years of age and then 0 to <2 years of age) based on available safety and efficacy data from this trial and the 1160.106 trial including but not limited to PK and PD analyses, dose adjustment data; exposure-response model updated with all relevant paediatric and adult data and the appropriateness of dosing algorithm for consecutive age groups. The DMC may implement a partial release of the youngest age group (0 to <2 years of age) depending on the availability of PK/PD data from respective age groups studied in the phase IIa studies.

In addition, the DMC will recommend modifications of the target dabigatran plasma concentration range, if required, based on available data from 1160.106 trial. The dose regimen will be reviewed on an ongoing basis by the committee and can be further revised as data on trough dabigatran levels and safety data become available during the course of this

study or if emerging data from other dabigatran etexilate studies in other populations could suggest that wider or narrower total dabigatran trough concentration range is associated with a better benefit / risk ratio.

The DMC may also decide to keep recruitment open after 100 patients have been recruited, in case additional safety data needs to be generated.

3.1.1.2 Central Independent Adjudication Committee

All elements of the primary endpoints will be evaluated by an independent adjudication committee that will confirm or refute outcome events.

3.1.1.3 Central laboratory

All planned safety samples will be analysed at a central laboratory, local safety lab assessment is acceptable in emergency cases (e.g. bleeding event or emergency surgery). If approved by the Sponsor, a local laboratory may alternatively be used for dTT evaluation, as well as for serum or urine pregnancy test, INR, serum creatinine, HCT, Hb, platelet count, ALT and AST measurement at screening (to facilitate the eligibility assessment). If other assays for the quantitative measurement of dabigatran will become available, they may be used after consultation with the Sponsor. pharmacodynamic plasma samples may be analysed at contract research laboratories.

3.1.1.4 Steering Committee

A Steering Committee will provide scientific leadership regarding the design and conduct of the study. It will be composed of one Coordinating Investigator and other representatives. The Sponsor will be represented on this committee.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This is an open-label, single arm prospective cohort study of dabigatran etexilate evaluating safety and tolerability in secondary prevention of venous thromboembolism in paediatric patients. Children from 0 to less than 18 years of age will be eligible to participate.

The design of this study (including the definition of endpoints) has been agreed with the European Medicines Agency's Paediatric Committee. This committee has previously endorsed the outline of the design and endpoints of this trial. Several safety primary endpoints will be used in this study. For details refer to Section 5.2.1. These primary endpoints will be centrally adjudicated.

3.3 SELECTION OF TRIAL POPULATION

The trial population will consist of male and female paediatric patients who require anticoagulation for secondary VTE prevention. Patients who have completed the treatment period (i.e. have reached Visit 8) in 1160.106 study may be rolled-over into this study.

The trial recruitment goal is to have at least 100 patients participating in this study.

Recruitment will be initiated in the adolescent group first (12 yrs. to <18 yrs.) and may be consecutively opened to younger age group (2 yrs. to <12 yrs.), and then to youngest group (0 to <2 yrs.) based on the DMC recommendations. Patients in age group 2 yrs. to <12 yrs. will be included and treated in accordance to the availability of the age appropriate dabigatran etexilate formulations.

A log of all patients included into the study (i.e. having given informed consent / assent (if applicable)) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

Patients from 0 to less than 18 years of age with previously confirmed venous thromboembolism who have completed initial anticoagulation therapy (for at least 3 months) or patients who have completed the 1160.106 treatment period and who require further anticoagulation for secondary prevention of venous thromboembolism due to presence of a clinical risk factor.

3.3.2 Inclusion criteria

1. Male or female subjects from 0 to less than 18 years of age at the time of informed consent / assent.
2. Previously documented objective diagnosis of VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis), followed by completed course of initial VTE treatment for at least 3 months[1] (in case of VKA - intended INR between 2 and 3) or completed study treatment (i.e. reached Visit 8) in the 1160.106 trial. Patients, who during the treatment phase of 1160.106 trial were switched from dabigatran etexilate to SOC arm for any reason, are not eligible for this study.
3. Presence of an unresolved clinical risk factor requiring further anticoagulation for secondary VTE prevention (e.g. central venous line, underlying disease, thrombophilia, etc.)
4. Written informed consent provided by the patient's parent or legal guardian and assent provided by the patient (if applicable) at the time of ICF signature according to local regulations.

[1] A temporary interruption of the anticoagulant therapy for the index VTE event or prior to the start of secondary VTE prophylaxis is acceptable, if one of the following pre-requisites is fulfilled and documented:

- Interruption of anticoagulant treatment due to surgery or intervention, or other medically justifiable reason
- A risk factor requiring secondary VTE prevention has been newly identified only after the completion of initial VTE treatment
- Reappearance of a risk factor

3.3.3 Exclusion criteria

1. Conditions associated with an increased risk of bleeding:

   a. Any prior intracranial haemorrhage, classified as a macrobleed[2]. Any intracranial anatomical abnormality or intracranial aneurysm. Active meningitis, encephalitis, or intracranial abscess at Visit 2.

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

   c. Any major planned procedure that might put the patient at an increased risk of a bleed per investigator judgment within 5 days prior to taking study medication

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

   e. Gastrointestinal haemorrhage within the past year prior to screening unless the cause has 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 a fibrinolytic agents within 48 hours of dabigatran etexilate administration (Please note the following exception: use of tissue plasminogen activator (t-PA) e.g. alteplase, or any other thrombolytic agents to re-establish patency of an obstructed central venous line are allowed as long as the used dose is devoid of relevant systemic effects)

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[2] Patients with history of asymptomatic petechial or microbleeds may be included into the study as per investigator`s judgment. As a general recommendation, an intracranial microbleed is considered to be ≤0.5 cm in greatest diameter on gradient recalled echo (GRE), or T2* MRI sequences (criteria may vary depending on MRI imaging modalities; R15-2999). Irrespective of size, any cerebral bleed that causes focal neurologic symptoms and/or signs does not constitute a microbleed. Further, any blood visualized on a CT should be classified as a macrobleed, which is an exclusion criterion for the trial.

i. Uncontrolled hypertension on antihypertensive medication (systolic and / or diastolic above the upper limit of normal for age and sustained over 24 hours)

j. Any other disease, health condition or intervention which in the investigator's opinion exposes the patient to a higher risk for bleeding

2. Renal dysfunction (eGFR < 50 mL/min/1.73m^2 using the Schwartz formula, refer to Appendix 10.1) or requirement for dialysis. eGFR retesting during the screening period is allowed (once).

3. Active infective endocarditis

4. Subjects 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 alanine aminotransferase (ALT) or aspartate transaminase (AST) or alkaline phosphatase (AP) > 3 × upper limit of normal (ULN) within 3 months of screening. Transient increases of these parameters are acceptable, if retesting demonstrates results within these limits.

6. Pregnant or breast feeding females. Females who have reached menarche and are not using an acceptable method of birth control, or do not plan to continue using this method throughout the study and / or do not agree to adhere to pregnancy testing required by this protocol . Acceptable methods of birth control are listed below and must be used in a correct and consistent manner:

   i. Oral or parenteral (patch, injection, implant) hormonal contraception which has been used continuously for at least one (1) month prior to the first dose of study medication
   ii. Intrauterine device (IUD) or intrauterine system (IUS)
   iii. Double-Barrier method of contraception: condom and spermicidal agent
   iv. Complete sexual abstinence. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

7. Patients in age group 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 - will be provided in the ISF)

8. Anaemia (haemoglobin < 80g/L) or thrombocytopenia (platelet count < 80 x 10^9/L) at screening. Transfusions during the screening period are allowed, provided that a satisfactory haemoglobin or platelet level is attained prior to Visit 2

9. Patients who have taken restricted medication prior to first dose of study medication. For trial restrictions please see Section 4.2.2

10. Patients who have received an investigational drug in the past 30 days prior to screening, except patients who have completed the treatment period (up to Visit 8) in 1160.106 trial

11. Patients who are allergic / sensitive to any component of the study medication including solvent

12. Patients or parents / legal guardians considered unreliable to participate in the trial per investigator judgment or any condition which would present a safety hazard to the patient based on investigator judgment

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An individual patient is to be withdrawn from the trial if:

- The patient / parent / legal guardian withdraws consent, without the need to justify the decision.

An individual patient is to be discontinued from trial treatment, but will remain part of the study and analysis population:

- If the patient is no longer able to take trial medication for other medical reasons (e.g. surgery, AEs, other diseases or concomitant therapies).
- If the patient is noncompliant with study drug administration despite all possible efforts.
- If, in the opinion of the Investigator, continuation on the study drug is not in the patient's best interest, if eligibility criteria are being violated, or if the patient fails to comply with the protocol (e.g. non-attendance at trial assessments).
- In the event that a recurrent thromboembolic event as assessed by appropriate imaging modalities is observed or if the patient experiences a drug-related significant or drug-related serious AE or if drug toxicity is observed.
- If the patient does not reach a total dabigatran plasma trough concentration within the pre-specified therapeutic range after one dose adjustment.
- If the patient becomes pregnant or a pregnancy is suspected during the trial the patient will be discontinued from the dabigatran treatment and will be put on an appropriate therapy per investigator judgment. The patient will be followed up until the end of the study and until the birth or otherwise termination of the pregnancy. For further information, including the process for follow up on the outcome of the pregnancy please see Section 5.2.2.2.

- If a patient develops an active meningitis, encephalitis, or intracranial abscess.

- If the patient develops renal dysfunction anytime during the course of the study (eGFR < 50 mL/min/1.73m^2 using the Schwartz formula, confirmed by one retesting within the next 14 calendar days). If a patient develops eGFR < 50 mL/min/1.73m^2 using the Schwartz formula for a second time during the course of the study, treatment with dabigatran etexilate must be stopped without further retesting
- If the patient does not require treatment with anticoagulants any longer due to resolution of the underlying clinical risk factor prior to 12 months of planned anticoagulation treatment. In such cases, an early EOT Visit is to be performed and the patient should still be followed up according to the remaining visit schedule until the end of the study.

In order to protect patient safety, measurements of dabigatran trough plasma levels will be performed in a central laboratory

If a patient has a dabigatran plasma level of < 50 ng/mL or ≥ 250 ng/mL confirmed despite a dose adjustment, they will be discontinued from trial treatment and must be switched to an appropriate alternative therapy at investigator's discretion.

Dabigatran is predominantly excreted by the kidney; special attention should be given to the kidney function of these patients when needed. As stated above, any patient with confirmed eGFR < 50 mL/min/1.73m^2 using the Schwartz formula at any time during the treatment period will be discontinued from trial treatment. Any suspected worsening of renal function during the study should be investigated by eGFR evaluation.

Patients who discontinue study drug or withdraw from the trial after being entered (Visit 2) will be considered as “early discontinuations” and will not be replaced. The reason for premature discontinuation must be recorded in the eCRF. The data will be included in the trial database and will be reported.

Patients who discontinue study drug prior to 12 months of planned treatment due to resolution of the underlying clinical risk factor will not be considered as “early discontinuations”.

All patients that prematurely discontinue dabigatran etexilate for various reasons as outlined above and in cases where consent / assent is not withdrawn, will be invited to perform an eEOT Visit and will be followed up according to the remaining visit schedule until the end of the study. Procedures to be followed are outlined in Section 6.2.3.

Patients who drop out during screening (i.e. prior to receiving trial medication) will be considered a screening failure. These cases have to be recorded as a screening failure in the electronic case report form (eCRF) and no further follow up visit is required.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Advice of the independent DMC, decision by an independent ethics committee / institutional review board (IEC/IRB) or Competent Authority (CA)
- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy / safety information that could significantly affect continuation of the trial and / or invalidate the earlier positive benefit-risk assessment
- Violation of GCP, the CTP, or the contract by a trial site or investigator

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product dabigatran etexilate will be supplied by Boehringer Ingelheim.

4.1.1 Identity of BI investigational product and comparator product(s)

All patients will be treated with dabigatran etexilate in this trial; there is no comparator product.

The composition of dabigatran etexilate formulations is detailed below:

Dabigatran etexilate capsules:

- Substance: Dabigatran etexilate
- Pharmaceutical formulation: Capsule
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
- Unit strengths: 50 mg, 75 mg, 110 mg and 150 mg
- Total Daily dose: The administered dose (b.i.d.) is based on an age and weight adjusted nomogram included in Appendix 10.4.1.This nomogram has been generated to estimate a yield and exposure comparable to the exposure observed in previously completed adult VTEt/sVTEp and AF populations.
- Route of administration: p.o.
- List of excipients: The most up to date list will be provided in the ISF

Dabigatran etexilate pellets:

- Substance: Dabigatran etexilate
- Pharmaceutical formulation: pellets
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
- Unit strength: pellets stick packs to be sprinkled on food (for the available strengths please refer to the nomogram in Appendix 10.4.1). Detailed preparation and administration instructions will be included in the ISF.
- Total Daily dose: The administered dose (b.i.d.) is based on an age and weight adjusted nomogram included in Appendix 10.4.1. This nomogram has been generated to estimate a yield and exposure comparable to the exposure observed in previously completed adult VTEt/sVTEp and AF populations
- Route of administration: p.o.
- List of excipients: The most up to date list will be provided in the ISF

Dabigatran etexilate oral liquid formulation:

- Substance: Dabigatran etexilate granules (180.4 mg) and flavoured or unflavoured solvent for reconstitution (28 ml)
- Pharmaceutical formulation: oral liquid formulation
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
- 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 is administered (b.i.d.) based on an age and weight adjusted nomogram included in Appendix 10.4.1. This nomogram has been generated to estimate a yield and exposure comparable to the exposure observed in previously completed adult VTEt/sVTEp and AF populations, particularly in patients whose observed exposure was generally associated with the most favourable balance between efficacy and safety.
- Route of administration: p.o.
- List of excipients: The most up to date list will be provided in the ISF.

4.1.2 Method of assigning patients to treatment groups

After obtaining signed informed consent and if applicable assent, patients should complete the screening (Visit 1) procedures and laboratory assessments. Inclusion and exclusion criteria should be assessed to ensure inclusion of eligible patients. The unresolved clinical risk factor requiring longer duration anticoagulation for the secondary prevention of VTE must be specified at screening (e.g. central venous line).

All eligible patients who fulfil all inclusion and exclusion criteria will be assigned to receive dabigatran etexilate. Patients assigned to OLF will be randomized based on 1:1 ratio to receive flavoured or unflavoured solvent for reconstitution. The correct trial medication kit assignment will be managed by Interactive Response Technology (IRT) based on the estimated dose - see Section 4.1.3. All necessary instructions for using the IRT system will be described in a user guide / manual, a copy of which will be available in the ISF. In this trial, IRT will be used for medication assignments (including dose adjustments) and to control aspects of the medication supply chain.

Recruitment will first be initiated in the adolescent group (12 yrs. to <18 yrs.) and may be consecutively opened to younger age groups (2 to <12 years of age); and then to the youngest patients (0 to <2 yrs.) based on the DMC recommendations.

4.1.3 Selection of doses in the trial

Estimated doses for paediatric patients assigned to take dabigatran etexilate will be based on age and weight according to a nomogram (please refer to Appendix 10.4). Patients able to swallow capsules (aged ≥ 8 years) will be assigned to take capsules. If a patient aged ≥ 8

years but below 12 years of age is unable to take capsules, they will be assigned to take the pellets sprinkled on food. Patients < 8 years of age are scheduled to receive pellets sprinkled on food. OLF may be used for patients who are < 12 months of age. For patients < 12 months of age OLF is preferred over pellets provided that OLF supplies are available to the site.

Switching between different dabigatran etexilate formulations during the study is not recommended, but could be considered in special cases following discussion with the Sponsor, provided that the steady state has been reached with the currently assigned formulation (i.e. at least 6 consecutive dabigatran etexilate doses have been taken). A titration visit should be performed 3 days (6 consecutive dabigatran etexilate doses are taken) after the formulation switch.

The dose of dabigatran etexilate must be adjusted throughout the study period to ensure that a steady state plasma concentration between 50 and < 250 ng/mL is achieved. Assigned dosing in this study will be intended to target plasma dabigatran concentrations that have generally been proven to be safe and effective in multiple adult populations. The dose regimen will be reviewed on an ongoing basis by the DMC and can be further revised as data on trough dabigatran levels and safety and efficacy data are obtained.

Dose selection is based on dabigatran's linear PK (U09-2262-01) and renal function (glomerular filtration rate (GFR)) being the most important determinants of dabigatran PK.

Allometric models are considered appropriate in determining drug doses in paediatrics (R08-4306). In order to adjust for the on average lower body weight and hence lower absolute glomerular filtration rate in children aged below 1 year, the dose estimation procedure according to Hayton (R06-2299) seems appropriate. Hayton's model characterized the maturation and growth of renal function parameters based on data obtained from 63 healthy children between the ages of 2 days and 12 years.

For renally eliminated drugs like dabigatran, this model can be used to estimate dosing regimens based on the adult dose and adjusted 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.

Compared to the adult VTE study RECOVER (mean age 55.0), the general paediatric population is characterized by better renal function. To yield total dabigatran exposure at trough comparable to the trough exposure observed in the adult VTE program (i.e. RECOVER: dose 150 mg BID) and to be able to scale down the doses for the paediatric population within the confines of Hayton's model (i.e., GFR predictions up to age of 20 years, at which normal GFR is assumed to be 136 mL/min), a 20 year old adult reference patient weighing 70 kg was chosen. Since this reference patient is younger and has a higher dabigatran clearance due to the better renal function, the dose of 150 mg BID would result in an average trough exposure lower than the trough exposure seen in RE-COVER.

Therefore, this reference patient would receive higher dabigatran etexilate doses, i.e. 300 mg dabigatran etexilate BID or 4.3 mg/kg dabigatran etexilate BID and doses are scaled down to paediatric doses accordingly (fractional dose).

For the reference patient, the equation giving the fractional dose is derived by taking the allometric equation for the GFR (equation 4 in R06-2299):

$$GFR(age,W) = 2.60\ W^{0.662}\ e^{-0.0822*age} + 8.14\ W^{0.662}\ (1 - e^{-0.0822*age}),$$

and subsequently dividing by weight (W) and by the weight-adjusted GFR of the comparator, 136mL/min / 70kg=1.94mL/min/kg. After rearranging, this results in the following equation for the fraction of the adult comparator mg/kg dose:

$$FRAC = W^{-0.338}\ (4.20 - 2.85\ e^{-0.0822*age})$$

FRAC = fraction of adult comparator mg/kg dose

W = weight (kg)

Age (months)

The FRAC was further multiplied by 4.3 mg/kg (adult comparator BID mg/kg dose) and by the child's weight to obtain the absolute dose in mg. For weight groups (e.g. 5 and 6 kg) the average of the derived doses was used.

The derived dabigatran etexilate target doses based on Hayton calculations are displayed in Table 4.1.3: 1. Please note that Table 4.1.3: 1 does not contain information about age-appropriate formulations and available dose strengths. This information is given in the adjusted nomogram provided in Appendix 10.4.1. Dosing of patients should only occur according to the adjusted nomogram provided in Appendix 10.4.1.

Table 4.1.3: 1 Target dabigatran etexilate doses (given in mg) based on Hayton calculations for paediatric patients

Reference Adult dose:	300 mg/70 kg = 4.3 mg/kg																	
Single Dose [mg]																		
Age [completed years]	Age [completed months]	Weight [kg]																
		2.5	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	31 to <41	41 to <51	51 to <61	61 to <71	71 to <81	81 to <91	>=91
0,02083333	0,25	11,1	12,5	15,2	18,7													
0,08333333	1	12,4	14,0	17,0	20,9													
0,16666667	2	14,1	15,9	19,2	23,7													
0,25	3	15,6	17,6	21,2	26,2	32,2												
0,33333333	4	16,9	19,1	23,1	28,5	35,0												
0,41666667	5		20,6	24,9	30,7	37,7	44,1											
0,500	6			26,5	32,7	40,1	46,9											
0,583	7			28,0	34,5	42,4	49,5											
0,667	8			29,3	36,2	44,4	52,0	59,0										
0,750	9			30,6	37,7	46,3	54,2	61,5										
0,833	10				39,1	48,1	56,2	63,8	72,7									
0,917	11				40,5	49,7	58,1	66,0	75,1									
1	12				41,7	51,2	59,9	67,9	77,4	91,3								
1,5	18				47,2	57,9	67,8	76,9	87,6	103,3	121,6							
2	24					62,0	72,6	82,4	93,8	110,7	130,2							
2,5	30					64,6	75,5	85,7	97,6	115,2	135,5	154,4	180,5					
3	36					66,1	77,3	87,7	99,9	117,9	138,8	158,1	184,8					
4	48						79,1	89,8	102,2	120,6	141,9	161,7	189,0	222,9				
5	60						79,7	90,5	103,1	121,6	143,1	163,1	190,6	224,8	256,4			
6	72						80,0	90,8	103,4	122,0	143,6	163,6	191,2	225,5	257,2	287,1		
7	84							90,9	103,5	122,1	143,7	163,8	191,4	225,7	257,5	287,4	315,8	
8	96							90,9	103,5	122,2	143,8	163,8	191,5	225,8	257,6	287,6	316,0	
9	108								103,6	122,2	143,8	163,9	191,5	225,8	257,7	287,6	316,0	
10	120								103,6	122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
11	132									122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
12	144									122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
13	156									122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
14	168										143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
15	180										143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
16	192											163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
17	204											163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8

Patients who have a total dabigatran steady state trough concentration between 50 and < 250 ng/mL will be advised to continue the same dose until the following visit. In case patients have trough concentrations at the first measurement (within first week of dosing, after 6 consecutive doses are taken) below 50 ng/mL the dose must be increased by 10 to 100% according to the dosing nomogram. Assuming dose proportionality, a doubling of the dose would, in the extreme case, not lead to trough concentration > 100 ng/mL and is, hence, considered appropriate. The maximal allowed dose in this study is age and weight adjusted and will neither exceed a daily dose level of 22.2 mg/kg (dabigatran etexilate limit, based on excipient acceptable daily intake) nor a single dose of 330 mg. In the higher age / body weight group this results in a maximal daily dose of 660 mg. Whenever a trough concentration is greater than or equal to 250 ng/mL, the dose must be reduced by 25 to 50%. This dosing decision algorithm is summarized in the Table 4.1.3: 2. For the detailed dosing decision algorithm please refer to Appendix 10.4.2.

Table 4.1.3: 2 Summary of dose adjustments based on trough dabigatran plasma concentration

Steady State Dose Range	Corresponding Action
Between 50 and < 250 ng/mL	Continue on same dose
Less than 50 ng/mL	Dose may be increased by 10-100%. Maximal allowed single dose in this study is 330 mg.
Greater than or equal to 250 ng/mL	Dose may be reduced by 25-50%

The reduction of a dose is not expected to result in concentrations < 75 ng/mL, but should be sufficient to avoid high concentration of ≥ 250 ng/mL. Blood sampling to measure trough dabigatran concentration (derived from dTT or alternative method) will be repeated at least 3 days (after at least 6 adjusted consecutive dabigatran etexilate doses have been taken), but no later than 6 days after dose adjustment, to confirm the new dose. After dose adjustment, the total dabigatran trough concentration should be between 50 and < 250 ng/mL.

If a patient cannot reach trough plasma concentrations between 50 and < 250 ng/mL after one dose adjustment, they must discontinue the study medication.

Due to the dabigatran etexilate limit of 22.2 mg/kg/day (based on excipient acceptable daily intake) as well as the maximal dabigatran etexilate single dose of 330 mg, up-titration will not be feasible in all instances. Likewise down-titration will not be possible in all cases due to unavailability of required dosages, see Appendix 10.4.2. Affected patients have to be discontinued from dabigatran etexilate once the defined plasma trough concentration between 50 and < 250 ng/mL is not reached.

During the course of the study, the DMC can recommend further refinement of the target therapeutic trough steady state dabigatran concentrations based on data from ongoing paediatric studies or if emerging data from other dabigatran etexilate studies in other populations suggest that wider or narrower total dabigatran trough concentration range is associated with better benefit / risk ratio.

4.1.4 Drug assignment and administration of doses for each patient

At Visit 2 patients who meet all eligibility criteria will be assigned to receive dabigatran etexilate (as capsules or pellets to be sprinkled on food or oral liquid formulation based on age and weight and ability to swallow capsules or pellets).

For patients who have been treated with VKA, Visit 2 should take place only if INR is ≤ 2.3 otherwise it should be postponed. The patient will start the study medication on the day of Visit 2 if INR is below 2.0 or on the next day if the INR is between 2.0 and 2.3.

Patients who have been treated with parenteral anticoagulants should start the study medication 0-2 hours prior to the time that the next dose of the alternate therapy (e.g. LMWH) would be due, or at the time of discontinuation in case of continuous treatment (e.g. UFH).

The estimated dosages of dabigatran etexilate (as capsules, pellets to be sprinkled on food or oral liquid formulation) will be based on age and weight according to a nomogram provided in Appendix 10.4.1. Patients who completed the treatment period of study 1160.106 receiving dabigatran etexilate may continue taking the same dose and formulation also in this trial.

Patients aged ≥ 8 years will be assigned to take capsules. In case a patient aged ≥ 8 years but below 12 years of age is unable to take capsules (per investigator judgment), they will be assigned to take pellets sprinkled on food. Patients < 8 years of age are scheduled to receive pellets sprinkled on food. OLF may be used for patients who are < 12 months of age. For patients < 12 months of age OLF is preferred over pellets provided that OLF supplies are available to the site.

Dabigatran etexilate should be taken in the morning and in the evening, at approximately the same time every day. The capsules must not be crushed, not opened and can be taken with or without food. Dabigatran etexilate should be taken with a glass of water to facilitate delivery to the stomach. If gastrointestinal symptoms develop it is recommended to take dabigatran etexilate with a meal and/or a proton pump inhibitor according to the locally approved labelling recommendations. For paediatric patients receiving dabigatran and who suffer from dyspeptic symptoms, it should be taken into account that the local approval status as specified in the Prescribing Information or Product Information may vary between proton pump inhibitors and across countries. Therefore, the local standard of care in accordance with local labelling recommendations for proton pump inhibitors should be followed when treating gastrointestinal symptoms in paediatric patients treated with dabigatran. Alternative measures, such as taking dabigatran with a meal, should be considered if the local labelling recommendations and standard of care do not allow for the use of proton pump inhibitors in certain age groups and/or individual patients.

Pellets should be mixed with food (examples may include baby rice cereal, carrot mush, banana mush, strawberry jam, apple juice or apple sauce) and should be taken in its entirety (pellets and food) at every dose. The volume of the OLF must be taken in its entirety at every dose. The instructions for preparation of the OLF and pellets will be provided in the ISF. Younger patients must be assisted by the parent / legal guardian or an appropriate caregiver to ensure that the dabigatran etexilate dose is properly taken.

The interval between dabigatran etexilate doses should be as close to 12 hours as possible. If a dose of dabigatran etexilate is missed for any reason, the forgotten dose may still be taken up to six hours prior to the next scheduled dose otherwise the missed dose should be omitted and the next dose should be taken as scheduled. A double dose to make up for missed individual doses must never be taken. In addition, if a dose has only been taken partially, there should be no attempt to administer a second dose at that time-point, and the next dose should be taken as scheduled approximately 12 hours later.

Patients will be treated with dabigatran etexilate until the clinical risk factor that necessitated further anticoagulant use has resolved, however for a maximum of 12 months. At the end of the study, all patients need to discontinue dabigatran etexilate, or switch to standard of care, if there is continued need for anticoagulant treatment (see Appendix 10.3 for recommendations for transition to a non-study antithrombotic treatment with early study drug discontinuation or at the end of the trial).

In the event that a patient decides to discontinue dabigatran etexilate and has to be switched to non-study treatment according to the local practice, the Investigator should plan this transition taking into consideration the patient's risk profile and previous experience with anticoagulants. As patients have different risk profiles, optimal approaches might differ between patients and not all possible approaches can be fully outlined.

The transition plan will be up to the Investigator's judgment based on the patient's medical history and prior therapy experience (see Appendix 10.3 for further guidance). Close monitoring of the patient's coagulation profile during the transition period must be implemented to optimize safety. In general, dabigatran etexilate therapy should not overlap with other anticoagulation therapy.

Investigators should recognise that the presence of dabigatran etexilate could elevate the INR. Once dabigatran etexilate has been stopped for >2 days, the INR will better reflect the effect of VKA therapy alone.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label, single arm prospective cohort study.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labelling, and re-supply

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Dabigatran etexilate should be kept out of the reach of children and be stored protected from moisture and direct sunlight. Dabigatran etexilate capsules should be kept in their supplied container and the bottle lid must be kept closed. Dabigatran etexilate capsules must not be transferred to other types of containers.
The medication stick packs containing the dabigatran etexilate pellets should be kept sealed until just prior to intake.
The medication stick packs containing the dabigatran etexilate granules should be kept sealed until just prior to reconstitution, once reconstituted, the oral solution is stable for two hours at room temperature.

Patients / parents / legal guardians should be instructed to keep medication containers tightly closed and not to remove capsules from original package material until immediately prior to the time of intake. Dabigatran etexilate may only be dispensed to trial patients (under supervision of their parent / legal guardian) fulfilling the inclusion and exclusion criteria by authorised study personnel as documented in the ISF. Receipt, usage, and return of the study medication must also be documented on the respective forms in the ISF. All unused medication including bottles and outer boxes (empty or filled) must be either returned to the Sponsor, or, following written authorisation from the Sponsor, may be destroyed at site if applicable. Receipt, usage and return must be documented on the respective forms. Reasons for any discrepancies must be thoroughly documented.

A temperature log must be maintained at the site to make certain that the drug supplies are stored at the correct temperature. For storage conditions refer to the locally approved medication label and the STORM document in the ISF.

Detailed instructions for the preparation and / or reconstitution of dabigatran etexilate (when applicable) and for dispensing and intake of dabigatran etexilate formulations (capsules, pellets and OLF) will be placed in the ISF.

4.1.8 Drug accountability

Drug supplies, which will be provided by the Sponsor, must be kept in a secure, limited access storage area under the storage conditions defined by the Sponsor.

The Investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

- approval of the study protocol by the IRB / ethics committee,
- availability of a signed and dated clinical trial contract between the Sponsor and the Head of Trial Centre,
- approval / notification of the regulatory authority, e.g. competent authority,
- availability of the curriculum vitae of the principal investigator,
- availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol,
- if applicable, availability of the Form 1572.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposition of unused medication.

These records will include dates, quantities, batch / serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational product received from the Sponsor. At the time of return to the Sponsor / appointed CRO, the investigator / pharmacist / investigational drug storage

manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

Any additional drugs considered necessary for the patient's welfare may be given at the discretion of the investigator and with due consideration of the information provided in this protocol and the IB.

Details of concomitant medication administered to the patient during the course of the study should be recorded in the eCRF. This includes all concomitant therapies from time of patient screening until the patient completes follow up.

Certain concomitant therapies or surgery / intervention may require the temporary discontinuation of dabigatran etexilate. Study medication should be restarted as soon as safely possible.

At the Screening Visit, the site must document details of the anticoagulant therapy given for the treatment of the acute VTE.

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

The Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study (also refer to Section 5.2).

Major bleeds for patients on dabigatran:

If a patient experiences a major bleed, dabigatran etexilate should be stopped and the source of bleeding investigated and treated. This will generally involve coagulation testing (e.g. activated partial thromboplastin time (aPTT), TT, dTT (where available), ecarin clotting time (ECT), platelet count), and possibly transfusion, diagnostic procedures and / or surgical haemostasis.

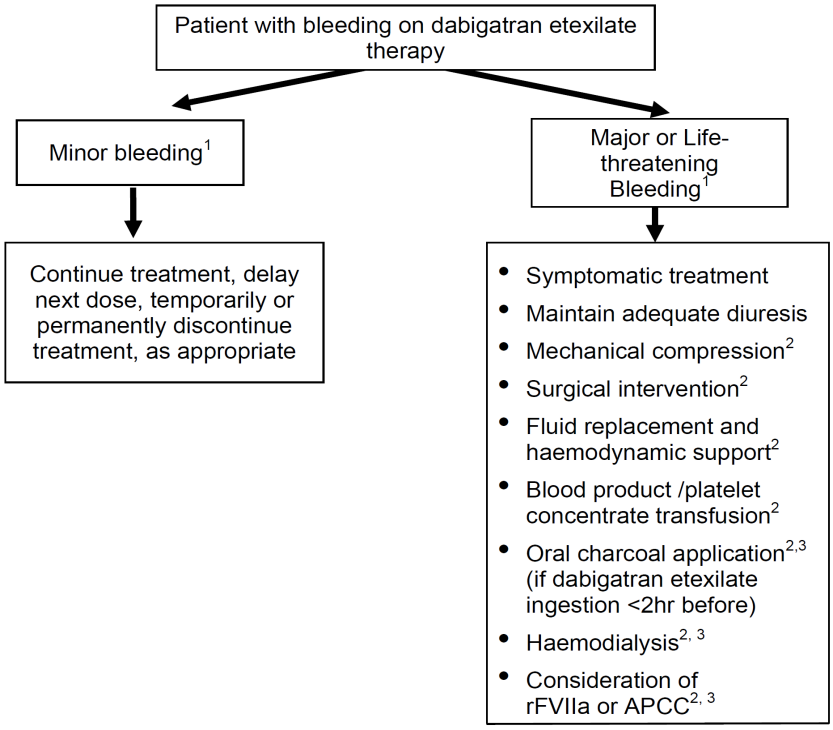
There is currently no specific reversal agent commercially available to counteract the antithrombotic activity of dabigatran in children, however such is in development (P15-06362). If a clinical study with specific reversal agent in paediatric patients is approved by the local health authority and ethic committees during the course of this study, instructions on how to use the specific reversal agent in appropriate cases or conditions and the requirements of participation in the respective clinical studies may be provided to the investigators. In such cases cross reporting of lab results might be applied in order to limit the blood volume required for analysis.

Since dabigatran is excreted predominantly by the renal route adequate diuresis must be maintained. Appropriate standard treatment, e.g. surgical haemostasis as indicated and volume replacement should be undertaken as appropriate. In addition, consideration may be given to the use of fresh frozen plasma (P10-03790). As protein binding is low, dabigatran is

dialyzable, however there is limited clinical experience in this setting. The amount of drug cleared by dialysis is proportional to the blood flow rate.

There is some experimental evidence to support the role of agents such as activated prothrombin complex concentrates (APCC, e.g. FEIBA), recombinant Factor VIIa and three or four factor concentrates (Factors II, IX and X with or without Factor VII) in reversing the anticoagulant activity of dabigatran. The usefulness in clinical settings has not yet been systematically demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. All symptomatic treatment has to be given according to the physician's judgment.

A summary of how to manage bleedings on dabigatran etexilate is outlined in Figure 4.2.1: 1.



[1] for bleeding definitions see Section 5.2.1
[2] when appropriate
[3] recommendations based on limited clinical or non-clinical data only, limited or no experience in volunteers or patients

Figure 4.2.1: 1 Management of bleeding on dabigatran therapy (P10-03790)

Dabigatran etexilate must be stopped if a major bleeding event is observed. Initiation of any other alternative therapy for secondary VTE prevention after complete haemostasis has been achieved is at the Investigator discretion.

Clinically relevant non-major bleeds or minor bleeds:

If a patient experiences a clinically relevant non-major bleed or minor bleed, dabigatran etexilate may be continued, temporarily interrupted or permanently discontinued, at the discretion of the Investigator. It is not a requirement, however, that study drug be stopped in these cases.

Management of dabigatran etexilate prior to and after planned surgery:

Dabigatran etexilate Treatment Discontinuation for Elective Surgical Interventions

Patients on dabigatran etexilate who undergo surgery or invasive procedures are at an increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate.

Preoperative Phase: Due to an increased risk of bleeding dabigatran etexilate may be stopped temporarily, in advance of invasive or surgical procedures (U11-1642-01). If possible, dabigatran etexilate should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required, stopping dabigatran etexilate 2-4 days before surgery should be considered. A TT/dTT should be performed 6-12 hours before elective surgery and a normal result as defined by the local lab should be obtained before a patient undergoes surgery.

In patients, who develop renal insufficiency before the surgery, the recommendations summarized in the table below should be considered (Table 4.2.1:1). The decision to re-start treatment with dabigatran etexilate after the surgery is at the Investigator's discretion and can be started any time as soon as haemostasis has been achieved.

Table 4.2.1:1 Recommendations on cessation of study drug in relation to the timing of surgery – under special consideration of the pharmacokinetics of dabigatran

Renal function (eGFR, mL/min)	**Estimated half-life in hours (for dabigatran)**	**Stop study drug before surgery**	
		High risk of bleeding[1]	**Standard risk**
>80	~13	2 days before	24 h before (2 doses)
≥50-80	~15 (12-18)	2-3 days before	1-2 days before
≥30 to <50	~18 (18-24)	4 days	at least 2 days (> 48 hours)
<30	~27 (>24)	> 5 days	2-5 days

[1] In addition to renal function, high risk determinants of bleeding risk include type of surgery, comorbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy. The type of surgery associated with a high risk of bleeding includes but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function.

The decision to use bridging therapy by UFH/LMWH during the peri-procedural period is left to the investigator's discretion and would depend on the bleeding and thrombotic risk in each patient.

Dabigatran etexilate Treatment discontinuation for Acute Surgical Interventions

If urgent surgery / acute intervention is required dabigatran etexilate should be temporarily discontinued. The surgery / intervention should be delayed at least 12 hours if possible after the last dabigatran etexilate dose. If surgery cannot be delayed there may be an increased risk of bleeding. The risk of bleeding should be weighed together with the urgency of the intervention. Local haemostasis and supportive care should be used during and after surgical intervention.

An elevated TT or dTT should lead the clinician to consider delaying surgery. If the TT/dTT test is not available, an aPTT, though less precise than the TT, can be used. A persistently prolonged thrombin time (TT or dTT) in the absence of heparin, fibrin / fibrinogen degradation products (e.g. with disseminated coagulation activation, sepsis, severe inflammation, and other conditions) or high concentrations of serum proteins (e.g. myeloma) suggests persistently elevated levels of dabigatran in the blood.

If a dabigatran specific reversal agent becomes available in a framework of clinical investigation during the conduct of this study and the patient fulfils the criteria for inclusion, it could be proposed to patients who require urgent reversal of dabigatran effects.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following treatments should not be taken prior to dabigatran etexilate administration:

- Fibrinolytic agents - within 48 hours (Please note the following exception: the use of tissue plasminogen activator (t-PA) e.g. alteplase, or any other thrombolytic agents to re-establish patency of obstructed central venous line are allowed as long as the used dose is devoid of relevant systemic effects)
- P-glycoprotein inducers including but not limited to: Rifampicin, St. John´s Wort, Carbamazepine, Phenytoin - within one week
- Asparaginase - within one week (or within 2 weeks in case of PEG-Asparaginase)

The following treatments should not be taken together with dabigatran etexilate:

- Any VKAs
- Therapeutic unfractionated heparin or LMWH (heparin flushes of indwelling catheters are allowed)
- Fibrinolytic agents (with the following exception: use of tissue plasminogen activators (t-PA) e.g. alteplase, or any other thrombolytic agents to re-establish patency of obstructed central venous line are allowed as long as the used dose is devoid of relevant systemic effects)
- P-glycoprotein inhibitors including but not limited to: Amiodarone, Cyclosporine, Dronedarone, Itraconazole, Ketoconazole, Nelfinavir, Quinidine, Ritonavir, Saquinavir, Tacrolimus, Verapamil
- P-glycoprotein inducers including but not limited to: Rifampicin, St. John´s Wort, Carbamazepine, Phenytoin
- Asparaginase
- Any other investigational drug (with the exception of a specific reversal agent to counteract the antithrombotic activity of dabigatran etexilate where the patient is eligible to participate in a specific trial in a framework of clinical investigation)

Note: Intended extended use of anti-inflammatory agents or agents containing ASA should be avoided. Corticosteroids in general should be avoided but may be administered if they are part of a chemotherapy regimen given in cycles, or if the benefits of corticosteroid therapy clearly outweigh risks.

4.2.2.2 Restrictions on diet and life style

Dabigatran etexilate may be taken with or without food. Dabigatran etexilate hard capsules should preferably be taken with a glass of water, if feasible to facilitate delivery to the stomach. If gastrointestinal symptoms develop it is recommended to take dabigatran etexilate with a meal and/or a proton pump inhibitor such as pantoprazole.

4.3 TREATMENT COMPLIANCE

Subjects or, if applicable, parents or legal guardians, will be asked to carefully complete a daily medication intake log for dabigatran. Subjects or, if applicable, parents or legal guardians, are requested to bring this completed log and all remaining trial medication to every clinic visit which they will attend. Empty dabigatran etexilate capsule containers, pellets boxes or solution vials must also be returned to the investigator's site for compliance calculation and disposal. Compliance will be calculated using the below equation preferably based on the returned medication (completed logs may also be used):

Compliance (in %) = (Actual number of dabigatran etexilate doses taken since last count / Planned number of dabigatran etexilate doses which should have been taken in the same period) X 100

If an interruption of dabigatran etexilate was medically required this would be considered by reducing the number of expected doses that "should have been taken" accordingly in the compliance calculation.

Unreliable subjects should not be entered in the study at the discretion of the investigator. Compliance during the treatment period should be between 80% and 120%. In cases where compliance is not achieved based on the above definition, the parent or legal guardian and when applicable the patient should be interviewed and re-informed about the purpose and the conduct of the trial and the importance to maintain good compliance. If non-compliance persists despite all possible efforts, patients should be removed from the treatment and alternative therapy should be proposed in such cases.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY

5.1.1 Endpoints of efficacy

All criteria in this study will be considered as safety endpoints.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Primary endpoints:

- Recurrence of venous thromboembolism (VTE) at 6 and 12 months
- Major and minor (including clinically relevant non-major (CRNM)) bleeding events at 6 and 12 months
- Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months

All elements of the primary endpoints will be assessed by qualified clinicians using an appropriate objective method and will be centrally adjudicated by an independent committee.

Secondary endpoints:

- Occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months

  An appropriate instrument (e.g. the Manco-Johnson Instrument or Villalta scale or a similar instrument; the chosen instrument will be available in the ISF)
- Pharmacodynamic assessments (central measurement of dTT (Anti-Factor IIa activity), aPTT and ECT) at Visit 3 (after at least six consecutive dabigatran etexilate doses) and after at least 3 days following any dabigatran etexilate dose adjustment
- Number of dabigatran etexilate dose adjustments during treatment period (i.e. Number of patients with dabigatran dose adjustments during treatment period)

Venous thromboembolism assessment

In case of suspected recurrent VTE, the event should be evaluated using appropriate imaging modalities per local guidelines or as required per investigator judgment. Example of appropriate evaluations methods are listed below.

- Suspected DVT: Venous compression ultrasonography (CUS) or venography
- Suspected PE: Ventilation-perfusion (V-Q) lung scan, pulmonary angiography or spiral (helical) CT
- Suspected paradoxical embolism (PDE): CT/MR angiography or other appropriate evaluation

Bleeding assessment

Patients will be carefully assessed for signs and symptoms of bleeding

The following definitions for bleeding are based on recommendations made by the Perinatal and Paediatric Haemostasis Subcommittee during the 56th-58th Scientific and Standardization Committee (SSC) Meetings of the ISTH (R11-4225).

Major bleeding:

- 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 is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system
- Bleeding that requires surgical intervention in an operating suite

Clinically relevant non-major (CRNM) bleeding:

- Overt bleeding for which a blood product is administered and which is not directly attributable to the patient's underlying medical condition
- Bleeding that requires medical or surgical intervention to restore haemostasis, other than in an operating suite.

Minor bleeding:

- Minor bleeds are any overt or macroscopic evidence of bleeding that does not fulfil the criteria for either major bleeding or clinically relevant, non-major bleeding.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is / are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

Protocol-specified Adverse Events of Special Interest (AESI)

The following are considered as Protocol-specified AESI:

- Hepatic injury defined by the following alterations of liver parameters: An elevation of AST and / or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample.
  Patients showing these lab abnormalities need to be followed up according to Appendix 10.2 of this clinical trial protocol and the "DILI checklist" provided in ISF/RDC.
- Creatinine value shows a ≥2 fold increase from baseline and is above the upper limit of normal.

Protocol-specified AESI are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria – for details please see Section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent until end of follow-up period) will be collected, documented and reported to the Sponsor by the investigator on the appropriate CRF(s)/ eCRFs/SAE reporting forms. The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol required residual effect period (REP) and / or follow-up), it should be reported by the investigator to the Sponsor if considered relevant by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

The residual effect period (REP) for dabigatran is 3 days after last drug administration. Therefore all AEs reported within 3 days of the last trial medication will be considered on treatment. All AEs, including those persisting after trial completion must be followed up until they have resolved or have been sufficiently characterized.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

The investigator must report the following events using paper process SAE form via telephone / fax immediately (within 24 hours) to the Sponsor: SAEs, AESIs and non-serious AEs relevant to the SAE and / or AESI.

BI has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these “always serious adverse events”, if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item “serious” needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified AESI becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the Sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours) to the defined unique entry point for SAE forms of the respective BI operative unit (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

A central laboratory will be used for the analysis of all laboratory measurements with the exception of serum or urine pregnancy test, INR, serum creatinine, HCT, Hb, Platelet count, ALT and AST measurement at screening (if applicable) which may be done locally to facilitate the eligibility assessment. If needed and when feasible a local laboratory may alternatively be used for dTT testing to evaluate dabigatran concentration. Local lab assessments are also acceptable in emergency situations (e.g. bleeding event or emergency surgery), see Appendix 10.1.

Refer to the Flow Chart and Section 5.7.2 for additional information.

For patients who have completed the treatment period of study 1160.106, the lab results from Visit 8 will be taken as Visit 1 or Visit 2 results of this trial, depending on the day Visit 1 and Visit 2 take place in correlation to Visit 8 of study 1160.106 (see Flow Chart, Footnotes 1 and 2).

A centralized serum pregnancy test for females who have reached menarche will be done as noted in the Flow Chart.

5.2.4 Electrocardiogram

An ECG will be done at screening and all other time points as noted in the Flow Chart. Documentation of, and findings from ECGs, must be part of the source documents available at the site.

Printed paper tracings from 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected and stored at the site. In the event of any cardiac symptoms or ECG abnormalities (i.e. heart rhythm disorders, PR prolongation, QRS enlargement, QT prolongation, etc.), additional ECGs will be recorded at investigator discretion. All ECGs will be evaluated (signed, dated and commented upon) by the treating physician / investigator and stored locally. Any clinically relevant changes (according to investigators judgment) in the ECG will be reported as AEs and followed up and / or treated locally until a normal or stable condition if feasible is achieved.

All ECGs performed at any time during the conduct of the trial (whether clinically relevant or routine) will be stored in the subject source notes.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Blood pressure (BP) and heart rate (HR) will be performed at the time points noted in the Flow Chart. For each patient, all BP recordings shall be made using preferably the same type of instrument on the same arm during the entire course of the study.

5.2.5.2 Weight assessment

Weight measurements should preferably be done on the same age-appropriate scale. In order to get comparable body weight values, weight measurements should be performed in the following way:

- shoes and coats / jackets should be taken off (when applicable)
- pockets should be emptied of heavy objects (i.e. keys, coins etc.) when applicable

5.3.2 Other assessments

- Incidence of adverse events, protocol-specified AESI and serious adverse events
-

5.4 APPROPRIATENESS OF MEASUREMENTS

All safety and clinical assessments are determined using standard methods and procedures.

5.6 BIOMARKER(S)

Please refer to Section 5.7.

5.7 PHARMACODYNAMICS

5.7.1 Pharmacodynamic endpoints

Determination of the exploratory pharmacodynamic parameters dTT (Anti-Factor IIa activity), aPTT and ECT will be performed in this trial. Diluted thrombin time (dTT) or alternative registered method / assay (where available and after consultation of the Sponsor) will be employed for the quantitative measurement of dabigatran concentrations for dose adjustment. The analysis of dTT will be done by a central laboratory. Diluted TT may also be analysed by a local laboratory, if feasible. The dabigatran etexilate dose administered to patients may be adjusted upon dabigatran plasma level measurement from Visit 3 or other future visits as needed to achieve the target plasma range, based on the assessment of dabigatran plasma levels. Further, alternative coagulation assays for dabigatran, e.g. ecarin based tests, may be explored.

5.7.2 Methods of sample collection

About 22.8 mL of blood (approximately 2.4 mL per sampling time point) in total per patient assigned to dabigatran etexilate is planned for collection for the PD samples.

The collection time point for aPTT, ECT and dTT (Anti-Factor IIa activity) (or alternative method) are indicated in the Flow Chart. The date and exact clock time of when these PD samples are taken is to be recorded in the eCRF. Further, the date and the exact clock time of dabigatran etexilate administration on the three days before the PD samples are taken is to be recorded in the eCRF. The PD samples should be taken immediately after the PK samples have been obtained. To ensure correct identification and tracking of the PD samples, all sample tubes will be labelled with trial number, patient number and day and exact time of sample collection.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of three periods, a screening period, an open-label dabigatran etexilate treatment period and a follow-up period.

The schedule for trial visits is summarised in the study Flow Chart including time windows for study visits. All visit dates are calculated from the date of treatment assignment (Visit 2). In the event that visits are missed or out of sequence, subsequent visits will be planned according to the date of Visit 2.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

No study procedures may be initiated prior to the patient's parents (or legal guardian) signing the informed consent and the patient providing assent (if applicable) in compliance with ICH-GCP and local legislation.

6.2.1 Screening period

For the schedule of assessments and procedures to be done during screening refer to the Flow Chart. In addition:

- Document consenting procedure (and assenting if applicable) in the patient's source file.
- Record enrolment (date of patient consent) on the enrolment log (located in the Investigator Site File).

For patients participating in study 1160.106 the Screening Visit may be conducted together with Visit 8 of 1160.106 trial.

6.2.2 Treatment period

Before giving the first dose of study medication, eligibility must be confirmed.

For the schedule of assessments and procedures during the treatment period refer to the Flow Chart. For information on dose selection and drug assignment and administration refer to Section 4.1.3 and Section 4.1.4. For details PD sample collection and analyses refer to and Section 5.7.

Visit 3 is not applicable for patients who have previously completed the treatment period of the 1160.106 study being on dabigatran etexilate and continue taking the same dose in this trial. For all other patients, during Visit 3 the trough dabigatran concentration will be determined

ensure maintenance within a 50 to < 250 ng/mL window. If target exposure of 50 to < 250 ng/mL is not achieved an Unscheduled Visit must be performed in order to adjust the dabigatran etexilate dose (refer to

Appendix 10.4.2). A Titration Visit must be scheduled preferably after 3 days have elapsed (or 6 new doses have been taken) after a dose adjustment to reassess if the new trough dabigatran concentration is within the target range. Patients must not be dosed at home prior to attending a Titration Visit; dosing will be done after a trough plasma sample is collected. If patients cannot reach trough plasma concentrations between 50 and < 250 ng/mL after one dose adjustment, they must discontinue the study medication.

Unscheduled Visits are to be conducted in all cases of suspected recurrent VTE, paradoxical embolism (PDE), occurrence of post-thrombotic syndrome (PTS), major or clinically-relevant bleeding events (MBEs/CRBEs) or other suspected AESI or SAE. The Unscheduled Visit should be performed as soon as possible, preferably within 24 hours after the site first becomes aware of a suspected event.

6.2.3 End of trial and follow-up period

Follow-up Visit should be planned for 28 days after last drug intake. For the assessments and procedures to be done during the Follow-up Visit refer to the Flow Chart.

All patients who prematurely discontinue treatment will be invited to perform an eEOT Visit. Subsequently they will be followed up according to the remaining visit schedule until the end of the study. At these visits collection of AEs, outcome events (e.g. occurrence of PTS, VTE, bleeding events, etc.) and use of concomitant medication will be made.

Patients that are not actively taking study drug and their parent/legal guardian may be less motivated to adhere to the study visit schedule. Investigator and site staff should work to detect early signs of losing interest and readily present such patients (not actively taking study drug) and their parent/legal guardian with the following opportunities to encourage continued participation:

- continue to attend regularly scheduled study visits until the trial ends
- conduct only the final visit in person. All other visits would be done over the phone.
- conduct all remaining study visits over the phone
- discontinue participation in remaining trial activities but permit collection of vital status and outcome events at the end of the trial.
- discontinue participation in remaining trial activities but permit collection of vital status at the end of the trial.

The patient / parent / legal guardian will be asked to choose the most rigorous follow-up they are willing to comply with.

For patients who completely withdraw consent no more data on their medical information will be requested.

The site must make periodic documented attempts (approximately every three months) to locate patients who are lost to follow up (LTFU).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial has a single treatment group with no control group. Overall assessment of safety will be based on descriptive statistics.

7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no hypothesis testing for this trial.

7.3 PLANNED ANALYSES

The primary analysis will include patients who were dispensed study medication and have received at least one dose of study medication (Treated set).

The analysis of the /PD parameters will be performed on Pharmacokinetic set (PKS). PKS will include all treated patients with at least one /PD measurement and having no protocol violations relevant to the evaluation of PD endpoints.

7.3.1 Primary analyses

The primary analyses will be based on the primary safety endpoints. The recurrence of VTE, major bleeding events, minor (including clinically relevant non-major (CRNM)) bleeding events, overall mortality and mortality related to thromboembolic events will be analysed as time-to-event and will be summarized by Kaplan-Meier estimates. The rate of occurrence of events at 6 and 12 months will also be provided by K-M estimation. Patients who do not have any of the events or drop out early will be considered as censored for this analysis. Additionally, descriptive rate with number of patients with event divided by total treated patients will also be provided. Early drop out and lost-to-follow-up will be considered as non-event. The components of the composite event will be summarized as below:

- Recurrence of venous thromboembolism will be summarized by Kaplan-Meier estimate of time to first recurrence of VTE. The rate of recurrence at 6 and 12 months will also be provided by K-M estimation. Patients, who do not experience recurrent VTE by the time of analyses, drop out from the study, or die from non-VTE related cause will be considered as censored. The descriptive rate of number of patients with event divided by total treated patients will also be provided. Early drop out and lost-to-follow-up will be considered as non-event when calculating the descriptive rate.

- Major bleeding and minor (including clinically relevant non-major (CRNM)) bleeding will be analysed by K-M estimate of time to first occurrence as competing events. The K-M rate estimate at 6 and 12 month will be provided. The descriptive rate will also be calculated by dividing number of patients with major / minor bleeding by the number of total treated patients. Early drop out, lost-to-follow-up and non-bleeding related death will be considered as non-event and censored.

- Mortality overall and related to thrombotic or thromboembolic event will be summarized separately by K-M estimate of time to death. The K-M rate and descriptive rate at 6 and 12 month will be calculated. Early drop out and lost-to-follow-up will be considered as non-event. Non-thrombotic or non-thromboembolic related death will be considered as censored case for mortality due to thrombotic or thromboembolic events.

7.3.2 Secondary analyses

Secondary analyses are planned for occurrence of post-thrombotic syndrome (PTS), number of dabigatran etexilate dose adjustments (i.e. Number of patients with dabigatran dose adjustments) and pharmacodynamic assessments at Visit 3 (after at least six consecutive dabigatran etexilate doses) and after at least 3 days following any dabigatran etexilate dose adjustment.

- Occurrence of PTS will be summarized by K-M estimate of time to first occurrence. The K-M rate and descriptive rate at 6 and 12 month will be calculated. Early drop out, lost-to-follow-up and death will be considered as non-event and censored.

- Frequency of dabigatran etexilate dose adjustments will be summarized descriptively. This refers to the number of patients with dabigatran etexilate dose adjustment during treatment period because each patient is allowed to have only one dose adjustment.

- pharmacodynamic analyses details can be found in Section 7.3.5 and 7.3.6.

7.3.3 Safety analyses

The safety analyses will be descriptive in nature and will be based on BI standards. Parameters to be evaluated for safety are described in Section 5.2.

AEs will be coded using the MedDRA dictionary. All AEs will be classified according to the following trial periods: screening, treatment, safety follow-up. All AEs with an onset date / time after administration of trial medication up to 3 days after the last intake of study medication will be assigned to the treatment period for evaluation. In addition, AEs with onset date before start of the trial treatment but with worsening in intensity during the treatment will also be assigned to the on-treatment period. Other AEs will be assigned to the screening or post-treatment period, respectively. All AEs (including bleeding) in the treatment period will be tabulated in total and according to seriousness, severity and possible relationship to trial medication. AEs in the screening or follow-up period will be listed.

7.3.6 Pharmacodynamic analyses

The following descriptive statistics will be calculated for the pharmacodynamic parameters aPTT, ECT and any additional PD assay: these include, but are not limited to N, arithmetic mean, standard deviation, minimum, median, and maximum. Further, ratios to baseline (i.e. Visit 2) for these parameters will be calculated and assessed by descriptive statistics.

Dabigatran concentrations derived from dTT or alternative methods, e.g. ecarin based tests, will be compared to dabigatran concentrations determined by HPLC-MS/MS. This comparison will be reported separately.

7.4 HANDLING OF MISSING DATA

Missing data will not be imputed in general. All patients will be followed to collect necessary efficacy and safety information, even if patients discontinue study medication prematurely.

7.5 RANDOMISATION

Randomisation is in general not applicable to this study. Only patients assigned to OLF will be randomized based on 1:1 ratio to receive flavoured or unflavoured solvent for reconstitution.

7.6 DETERMINATION OF SAMPLE SIZE

The design of this study (including the definition of endpoints and sample size) has been agreed with the European Medicines Agency's Paediatric Committee. A minimum of 100 patients will be entered in this trial, including patients rolling over from study 1160.106, who require secondary VTE prevention and new patients who should have completed treatment for an acute VTE episode. The Data Monitoring Committee (DMC) or Sponsor may decide to keep recruitment open after 100 patients have been recruited, in case additional safety data needs to be generated.

Under the assumption of 5% of event rate for the composite of recurrent VTE, major bleeds and mortality related to thromboembolic event at 12 months, 100 patients will provide more than 99% of probability observing at least 1 event, it will provide higher than 63% of probability if the event rate is 1%. The expected 95% Wilson confidence interval for event rates under the assumption of 100 patients are provided in Table 7.6: 1.

Table 7.6:1 Expected 95% Wilson confidence interval based on 100 available patients

Observed rate (%)	95% Wilson CI
1	(0.18 – 5.45)
2	(0.55 – 7.00)
3	(1.03 – 8.45)
4	(1.57 – 9.89)
5	(2.15 – 11.2)
10	(5.52 – 17.4)
20	(13.3 – 28.9)

The sample size is considered adequate to capture any safety signal for the primary safety endpoints defined in the study.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator should inform the Sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol / ICH GCP.

The rights of the investigator and of the Sponsor with regard to publication of the results of this trial are described in the investigator contract.

Depending upon local requirements:

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from parents or the legal guardian according to ICH GCP and to the regulatory and legal requirements of the participating country. In addition and if applicable an informed assent must be obtained from the patients. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent, assent and any additional patient information must be given to each patient or to the parents or the legal guardian. Should patients reach legal age during the trial they must personally sign and date the informed consent form as soon as possible and, at the latest, at the next visit.

Parents or the legal guardian and the patient (as appropriate) must be informed that personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient / parent / legal guardian.

Parents or the legal guardian and the patient (as appropriate) must be informed that medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

The trial will be conducted according to the principles of Good Clinical Practice (GCP) and the company standard operating procedures (SOPs).

The following measures will be taken to ensure accurate, consistent, complete and reliable data:

All required trial documents will be distributed to every trial site and kept in the Investigator Site File (ISF). An investigator meeting will be held (may be held by webcast or similar means) before the trial to assure a high quality and standardization across sites.

Trial teams at the sites will be trained on protocol requirements, trial procedures, adverse event reporting, and remote data capture during the investigator meeting and / or by Clinical Research Associates (CRAs) during the respective monitoring visits.

On-site monitoring: Data captured in the eCRF will be verified against source data and vice versa by CRAs. The identity and informed consent of all patients as well as SAE reporting will be checked. For the remaining parts of the eCRF source data verification will be performed as described in the Monitoring Manual.

Auditing (internal and, if required by any regulatory authorities, external) will be performed as necessary.

Coding (e.g., according to MedDRA for adverse events) will be performed according to the company's SOPs as described in the trial data management and analysis plan (TDMAP). The data management procedures to ensure the quality of the data are described in detail in the (TDMAP) available in the CTMF.

A quality assurance audit / inspection of this trial may be conducted by the Sponsor or Sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the Sponsor, either on paper or via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need

to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

Copies of source documents necessary for adjudication will be provided to the adjudication committee. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient´s name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients´ source documents.

8.3.2 Direct access to source data and documents

The investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For dabigatran etexilate this is the current version of the Investigator's Brochure (U98-3208).The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial

need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.6 COMPLETION OF TRIAL

For trials performed in EU member states: The EC / competent authority in each participating EU member state needs to be notified about the end of the trial (last patient / patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P04-10723 Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic Complications of Anticoagulant Treatment. Chest 2004;126(3 suppl):287S–310S.

P06-06652 Israels SJ, Michelson AD. Antiplatelet therapy in children. Thromb Res 2006;118(1):75-83.

P06-07928 Chan AK, Deveber G, Monagle P, Brooker LA, Massicotte PM. Venous thrombosis in children. J Thromb Haemost 2003. 1:1443-1455.

P08-05411 Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 2008;47(5):285-295.

P08-08706 Ryn J van, Ruehl D, Priepke H, Hauel N, Wienen W. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran, by recombinant factor VIIa or activated prothrombin complex concentrate. 13th Cong of the European Hematology Association, Copenhagen, 12 - 15 Jun 2008 Haematologica 2008;93(Suppl 1):148 Abstr 0370.

P08-09073 Mitchell LG, Dietrich K, Bajzar L, Bauman M, Massicotte P, Stang L, et al. A direct thrombin inhibitor (dabigatran) in pediatric patients: an in vitro study determining optimum dose and monitoring tests in plasma from healthy children. Pathophysiol Haemost Thromb 2008;36(Suppl 1):A41 Abstr P065.

P09-03357 Price VE, Chan AKC. Venous thrombosis in children. Expert Rev Cardiovasc Ther 2008. 6(3):411-418.

P09-11669 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-1151.

P10-03790 van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wiennen W, Feuring M, Clemens A. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 106 (6), 116-117. 2010.

P10-09826 Payne JH. Aspects of anticoagulation in children. Br J Haematol 2010. 150(3):259-277.

P11-13187 Chalmers E, Ganesen V, Liesner R, Maroo S, Nokes T, Saunders D, Williams M. Guideline on the investigation, management and prevention of venous thrombosis in children. Br J Haematol 2011. 154(2):196-207.

P12-03887 Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Goettl U, Vesely SK Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 141 (2) (Suppl), e737S - e801S (2012)

P13-05131 Schiele F, Ryn J van, Canada K, Newsome C, Sepulveda E, Park J, et. al. A specific antidote for dabigatran: functional and structural characterization. Blood. 2013. 121(18): 3554-3562.

P15-06362 Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI Idarucizumab for dabigatran reversal. N Engl J Med 373 (6), 511 - 520 (2015)

P94-81556 Andrew M, David M, Adams M, Ali K, Anderson R, Barnad D, Bernstein M, Brisson L, Cairney B, DeSai D, Grant R, Israels S, Jardine L, Luke B, Massicotte P, Silva M. Venous thromboembolic complications (VTE) in children: First analyses of the Canadian registry of VTE. Blood 1994. 83(5):1251-1257.

P98-11480 Michelson AD, Bovill E, Monagle P, Andrew M. Antithrombotic therapy in children. Chest 1998;114(5):748S-769S.

R04-1182 Guidance for the industry: general considerations for pediatric pharmacokinetic studies for drugs and biological products. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). 1998.

R06-2150 Mitchell LG, Andrew M, Hanna K, Abshire T, Halton J, Anderson R, et al. A prospective cohort study determining the prevalence of thrombotic events in children with acute lymphoblastic leukemia and a central venous line who are treated with L-asparaginase: results of the Prophylactic Antithrombin Replacement in Kids with Acute Lymphoblastic Leukemia Treated with Asparaginase (PARKAA) Study. Cancer 2003;97(2):508-516.

R06-2299 Hayton WL. Maturation and growth of renal function: dosing renally cleared drugs in children. AAPS PharmSci 2002;2(1):3.

R06-2301 van Ommen CH, Heijboer H, Buller HR, Hirasing RA, Heijmans HS, Peters M. Venous thromboembolism in childhood: a prospective two-year registry in The Netherlands. J Pediatr 2001;139(5):676-81.

R06-2304 REVIVE Study Group, Massicotte P, Julian JA, Gent M, Shields K, Marzinotto V, Szechtman B, Andrew M. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and oumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. Thromb Res 2003;109:85-92.

R06-2305 Male C, Chait P, Andrew M, Hanna K, Julian J, Mitchell L; et al. Central venous line-related thrombosis in children: association with central venous line location and insertion technique. Blood 2003;101(11):4273-4278.

R07-2936 Nowak-Goettl U, Junker R, Kreuz W, Eckardstein A von, Kosch A, Nohe N, Schobess R, Ehrenforth S, Childhood Thrombophilia Study Group. Risk of recurrent venous thrombosis in children with combined prothrombotic risk factors. Blood 2001. 97(4):858-862.

R07-2937 Revel-Vilk S, Sharathkumar A, Massicotte P, Marzinotto V, Daneman A, Dix D, Chan A. Natural history of arterial and venous thrombosis in children treated with low molecular weight heparin: a longitudinal study by ultrasound. J Thromb Haemost 2004;2:42-46.

R07-2938 Kuhle S, Eulmesekian P, Kavanagh B, Massicotte P, Vegh P, Mitchell LG. A clinically significant incidence of bleeding in critically ill children receiving therapeutic doses of unfractionated heparin: a prospective cohort study. Haematologica 2007;92(2):244-247.

R07-2939 Bonduel MM. Oral anticoagulation therapy in children. Thromb Res 2006;118(1):85-94.

R07-2940 Young G. Current and future antithrombotic agents in children. Expert Rev Cardiovasc Ther 2004;2(4):523-534.

R07-2954 Kahn SR. The post-thrombotic syndrome: the forgotten morbidity of deep venous thrombosis. J Thromb Thrombolysis 2006;21(1):41-48.

R07-2956 Balasa VV. New anticoagulants: a pediatric perspective. Pediatr Blood Cancer 2005;45(6):741-752.

R07-2959 Goldenberg NA. Long-term outcomes of venous thrombosis in children. Curr Opin Hemato 2005;12(5):370-376.

R07-2962 Barnes C, Newall F, Monagle P. Post-thrombotic syndrome. Arch Dis Child 2002;86(3):212-214.

R07-2964 Kenet G, Nowak-Gottl U. Bleeding and thrombosis issues in pediatric patients: current approach to diagnosis and treatment. Acta Haematol 2006;115(3-4):137-140.

R08-4306 Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 48, 303 - 332 (2008)

R08-4386 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873-890.

R09-1299 Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 1985;41:55-68.

R10-5669 ICH Harmonised Tripartite Guideline: Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorisation for Pharmaceuticals: M3(R2) (current step 4 version, 11 June 2009)

R11-4225 Mitchell L, Goldenberg N, Male C, Kenet G, Monagle P, Nowak-Gottl U. Definition of clinical efficacy and safety outcomes for clinical trials in deep vein thrombosis and pulmonary embolism in children. J Thromb Haemost 2011;9:1856-1858.

R12-0738 Jones S, Newall F, Manias E, Monagle P. Assessing outcome measures of oral anticoagulation management in children. Thromb Res 2011. 127:75-80.

R12-5109 Settty BA, O'Brien SH, Kerlin BA. Pediatric venous thromboembolism in the United States: a tertiary care complication of chronic diseases. Pediatr Blood Cancer 2012. 59:258-264.

R13-4251 Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. Pediatrics 124 (4), 1001 - 1008 (2009)

R13-4257 Young G, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. Circulation 2008. 118(13):1373-1382.

R14-1031 Dix D, Andrew M, Marzinotto V, Charpentier K, Bridge S, Monagle P, DeVeber G, Leaker M, Chan AKC, Massicotte MP. The use of low molecular weight heparin in pediatric patients: a prospective cohort study. J Pediatr 2000. 136(4):439-445.

R14-1032 Schobess R, Duering C, Bidlingmaier C, Heinecke A, Merkel N, Nowak-Goettl U. Long-term safety and efficacy data on childhood venous thrombosis treated with a low molecular weight heparin: an open-label pilot study of once-daily versus twice-daily enoxaparin administration. Haematologica 2006. 91(12):1701-1704.

R15-2999 Wardlaw JM, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013. 12, 822 - 838.

9.2 UNPUBLISHED REFERENCES

U00-1856 . Safety, pharmacodynamics and pharmacokinetics after multiple oral doses of 50, 100, 200 and 400 mg BIBR 1048 MS solution administered t.i.d. for 7 days to healthy volunteer subjects. An open study, placebo-controlled, randomized, double blind at each dose level. 1160.2. 22 August 2000.

U03-1878 . Pharmacokinetics of BIBR 953 ZW after 150 mg of BIBR 1048 (oral pro-drug of BIBR 953) administered as capsule twice daily over seven days with our without Pantoprazole co-treatment to healthy male and femaile elderly subjects. 1160.10. 08 December 2003.

U06-1614-01 Safety, pharmacodynamics and pharmacokinetics after single oral administration of 600 mg, 750 mg and 900 mg dabigatran etexilate as capsule in healthy subjects. A randomised, placebo-controlled study, double blind at each dose level. 1160.60. 25 August 2006.

U09-1399-02 . Combined population analysis of dabigatran etexilate. 30 October 2009.

U09-1400-01 . A Phase III, randomised, double blind, parallel-group study of the efficacy and safety of oral dabigatran etexilate (150 mg b.i.d.) compared to warfarin (INR 2.0-3.0) for 6 month treatment of acute symptomatic venous thromboembolism. 1160.53. 21 October 2009.

U09-1839-01 Relative bioavailability of dabigatran after administration of different application forms of a single oral dose of 150 mg dabigatran etexilate (capsule, powder for reconstitution into solution, pellets on food) in healthy male and female volunteers (an open-label, randomised, three-way crossover, clinical Phase I study). 1160.87. 20 October 2009.

U09-2262-01 2.7 Clinical Summary Dabigatran etexilate 75 mg, 110 mg and 150 mg hard capsules. 11 November 2009.

U09-3249-02 . Randomized Evaluation of Long term anticoagulant therapy (RE-LY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvularatrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® STUDY). 1160.26. 16 October 2009.

U10-2533-01 . A Phase III, randomised, multicenter, double-blind, parallel-group, active controlled study to evaluate the efficacy and safety of oral dabigatran etexilate (150 mg b.i.d.) compared to warfarin (INR 2.0 to 3.0) for the secondary prevention of venous thromboembolism. RE-MEDY. 1160.47. 12 July 2011.

U11-1642-01 . Amendment to Pradaxa ® CCDS after approval of dabigatran etexilate for SPAF in US and EU. Amendment to Pradaxa ® CCDS concerning the use of fibrinolytic agents for acute ischemic stroke and the simultaneous use of ticagrelor (plus ASA), selective serotonin re-uptake inhibitors or dronedarone (Multaq®). 21 September 2011.

U11-2267-02 Twice-daily oral direct thrombin inhibitor dabigatran etexilate in the long-term prevention of recurrent symptomatic venous thromboembolism in patients with symptomatic deep-vein thrombosis or pulmonary embolism. RE-SONATE. 1160.63 29 May 2012.

U11-2298-01 . A Phase III randomised, double blind, parallel-group study of the efficacy and safety of oral dabigatran etexilate (150 mg b.i.d.) compared to warfarin (INR 2.0-3.0) for 6 month treatment of acute symptomatic venous thromboembolism, following initial treatment for at least 5 days with a parenteral anticoagulant approved for this indication. RE-COVER II. 1160.46. 22 Sep 2011.

U12-3378-01 . Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years. 1160.88. 05 July 2012

U98-3208 . Dabigatran investigator's brochure (current version – see ISF).

c02248557 . Relative bioavailability of dabigatran after administration of different dosage forms of multiple doses of 150 mg dabigatran etexilate (hard capsule, granules resolved in reconstitution solution, pellets on food) in healthy male volunteers (an openlabel, randomised, multiple-dose, three-way crossover study). 1160.194. 26 September 2014.

c09069268 Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years. 1160.89. Clinical Trial Report. 27 July 2016.

c09085437 Open-label, single dose, tolerability, pharmacokinetic/pharmaco-dynamics and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old. 1160.105. Clinical Trial Report. 14 July 2016.

c09149467 Analysis of the PK-PD relationship of dabigatran etexilate in paediatric patients based on combined data from multiple studies.

10. APPENDICES

10.1 SAFETY AND OTHER CLINICAL LABORATORY EVALUATIONS

Standard Safety Lab Panels will include:

Comprehensive Metabolic Panel (central lab):	**Haematology Panel (central lab):**
Glucose (fasting or non-fasting)	White Blood Cell Count
Calcium	Red Blood Cell Count
Albumin	Haemoglobin
Total Protein	Haematocrit
Sodium	Red Blood Cell Indices
Potassium	Differential
Chloride	Platelet Count
BUN	
Creatinine	
Alkaline Phosphatase	
ALT (alanine aminotransaminase, SGPT)	
AST (aspartate aminotransaminase, SGOT)	
Bilirubin - total or conjugated (direct) / unconjugated (indirect)	
Other centralized labs tests:	
Serum pregnancy test performed on all female patients who have reached menarche	
Activated Partial Thromboplastin Time (aPTT)	
Ecarin Clotting Time (ECT)	
Diluted Thrombin Time / Anti-Factor IIa activity (dTT)	
Diluted Thrombin Time (dTT) to evaluate dabigatran concentration (or an alternative method for the quantitative determination of dabigatran plasma concentration)	
Other potential locally evaluated labs tests / exploratory biomarkers:	
Serum or urine pregnancy test, INR (International Normalized Ratio), serum creatinine, HCT, Hb, Platelet count, ALT and AST at screening - to facilitate the eligibility assessment	
Safety Lab Panel – in case of emergency (e.g. bleeding event or emergency surgery)	

Estimated Glomerular Filtration Rate (eGFR) for children using Schwartz formula. This employs serum creatinine (mg/dL), the child's height (cm) and a constant to estimate the glomerular filtration rate:

- eGFR (Schwartz) = (0.413 x Height in cm) / Serum Creatinine in mg/dL

Conversion from conventional unit to SI unit:

Conventional unit	Conversion Factor	SI Unit
mg/mL	88.4	µmol/L

10.1.1 Blood volume charts

The blood volumes to be collected during the course of the trial are age adjusted. Patients are generally divided in three age groups: 6 to 18 years, 2 to 6 years and 0 to 2 years of age. For patients assigned to the dabigatran etexilate arm, approximate blood volumes (in ml) to be collected for planned central safety laboratory assessments, /PD and exploratory markers are outlined in the age specific charts below:

- 6 to <18 years

Table 10.1.1: 1 Blood volume chart 6-<18 years

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Chemistry	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5	3,5
Haematology	2	2	2	2	2	2	2	2	2	2	2	2
PD (aPTT and ECT)		1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	
dTT			1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	
Total	5,5	6,7	9,1	9,1	9,1	9,1	9,1	9,1	9,1	9,1	9,1	5,5
4 weeks interval	30,4				9,1	9,1	9,1	9,1	9,1	9,1	9,1	5,5
Total (for trial - 13 months)	99,6											

- 2 to< 6 years

Table 10.1.1: 2 Blood volume chart 2-<6 years

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Chemistry	2,6	2,6	2,6	2,6	2,6	2,6	2,6	2,6	2,6	2,6	2,6	2,6
Haematology	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2
PD (aPTT and ECT)		1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	
dTT			1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	
Total	3,8	5	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	3,8
4 weeks interval	23,6				7,4	7,4	7,4	7,4	7,4	7,4	7,4	3,8
Total (for trial - 13 months)	79,2											

- 0 to ≤2 years

Table 10.1.1: 3 Blood volume chart 0-<2 years

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Chemistry	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2	2,2
Haematology	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5	0,5
PD (aPTT and ECT)		1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	
dTT			1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	1,2	
Total (per visit)	2,7	3,9	6,1	6,1	6,1	6,1	6,1	6,1	6,1	6,1	6,1	2,7
4 weeks interval	18,8				6,1	6,1	6,1	6,1	6,1	6,1	6,1	2,7
Total (for trial - 13 months)	64,2											

In case of infants and when medically required per Investigator judgment and/or per local guidelines, reduced blood collection will be implemented after consultation with the Sponsor (e.g. omission of exploratory coagulation markers, reduced frequency of safety labs during the treatment period, etc.). The decision for the reduced blood collection will be documented in the ISF.

10.2 CLINICAL EVALUATION OF LIVER INJURY

10.2.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (refer to Protocol-Specified AESI), are to be further evaluated using the following procedures:

10.2.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by local laboratory and results are made available to the investigator and to BI as soon as possible. If in such a case ALT and / or AST ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

Clinical chemistry

alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology

Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-

mitochondrial antibody. The need for hepatitis serology to be assessed by the investigator based on patient age and clinical presentation.

Hormones, tumormarker

TSH

Haematology

Thrombocytes, eosinophils

In addition,

- Obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the "DILI checklist" provided in the ISF
- Obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the "DILI checklist" provided in the ISF;
- Obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the "DILI checklist" provided in the ISF;
- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intra-hepatic pathology, e.g. bile de duct stones or neoplasm.
- Initiate close observation of patients by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgment and Good Clinical Practices (GCP).

and report these via the CRF.

10.3 TRANSITION TO NON-STUDY ANTITHROMBOTIC TREATMENT WITH EARLY STUDY DRUG DISCONTINUATION OR AT THE END OF THE TRIAL

Patients actively taking study drug at their final treatment visit and patients who stop study medication early may need to switch to a non-study antithrombotic treatment at the Investigator`s discretion. The following recommendations are provided for guidance only:

- If the non-study treatment is a Vitamin K antagonist, the starting time of the VKA should be adjusted according to the patient´s eGFR as follows:
    - eGFR ≥ 50 mL/min: start VKA 3 days before discontinuing study drug
    - eGFR ≥ 30-< 50 mL/min: start VKA 2 days before discontinuing study drug
- If the non-study treatment will be a LMWH, it is recommended to wait 12 hours after the last dose of dabigatran etexilate (study medication) before switching to a parenteral anticoagulant (e.g. UFH, LMWH).
- If the non-study treatment will be an antiplatelet agent, this medication can be initiated at any time-point after last intake of study medication.

10.4 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 pellets.

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 pellets provided that OLF supplies are available to the site.

Dabigatran etexilate is taken twice daily (BID).

Estimated age and weight adjusted doses are outlined in the following nomograms, which refer to the total amount of dabigatran etexilate to be taken at a single time-point.

10.4.1 Dosing nomogram (starting doses)

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

Initial Dose — **Single Dose [mg]**

Age [completed years]	Age [completed months]	Weight [kg] 9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31	31 to <41	41 to <51	51 to <61	61 to <71	71 to <81	81 to <91	≥ 91
8	96		100	100	125	150	150	185	220	260	300	300		
9	108			100	125	150	150	185	220	260	300	300		
10	120			100	125	150	150	185	220	260	300	300	330	330
11	132				125	150	150	185	220	260	300	300	330	330
12	144				125	150	150	185	220	260	300	300	330	330
13	156				125	150	150	185	220	260	300	300	330	330
14	168					150	150	185	220	260	300	300	330	330
15	180					150	150	185	220	260	300	300	330	330
16	192						150	185	220	260	300	300	330	330
17	204						150	185	220	260	300	300	330	330

Doses > 330 mg BID capped to 330 mg BID

100 2x50mg capsules
125 50mg + 75mg capsules
150 150mg or 2x75mg capsules
185 75mg + 110mg capsules
220 2x110mg capsules
260 110+150mg or 110+2x75mg capsules
300 2x150mg or 4x75mg capsules
330 3x110mg capsules

Figure 10.4.1: 1 Age and weight adjusted starting doses using capsules

- dabigatran etexilate pellets

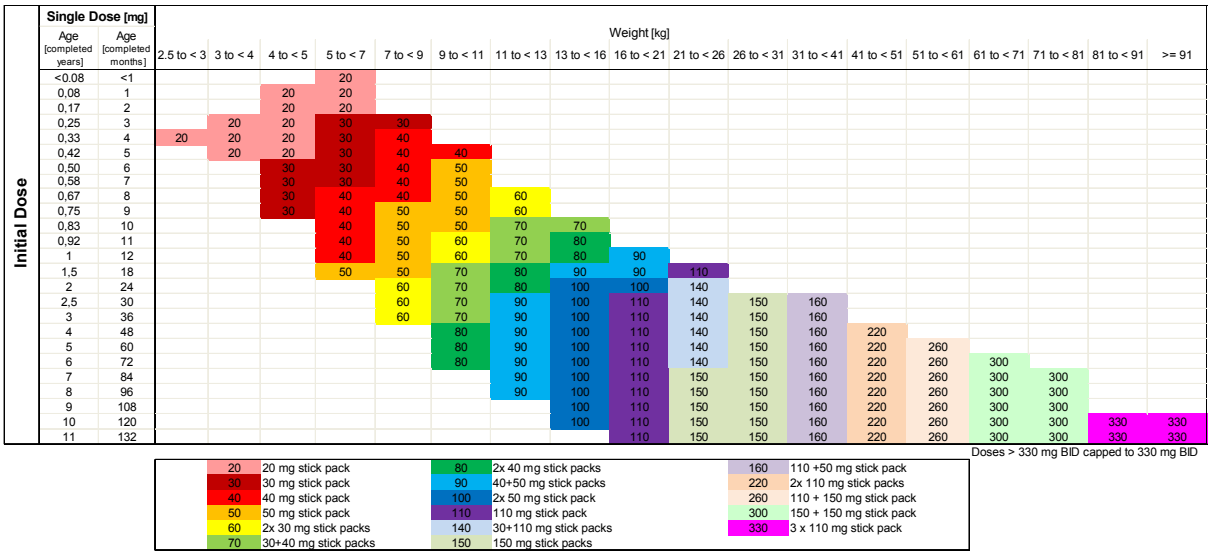


Figure 10.4.1: 2 Age and weight adjusted starting doses using pellets

- dabigatran etexilate OLF - 6.25 mg per mL

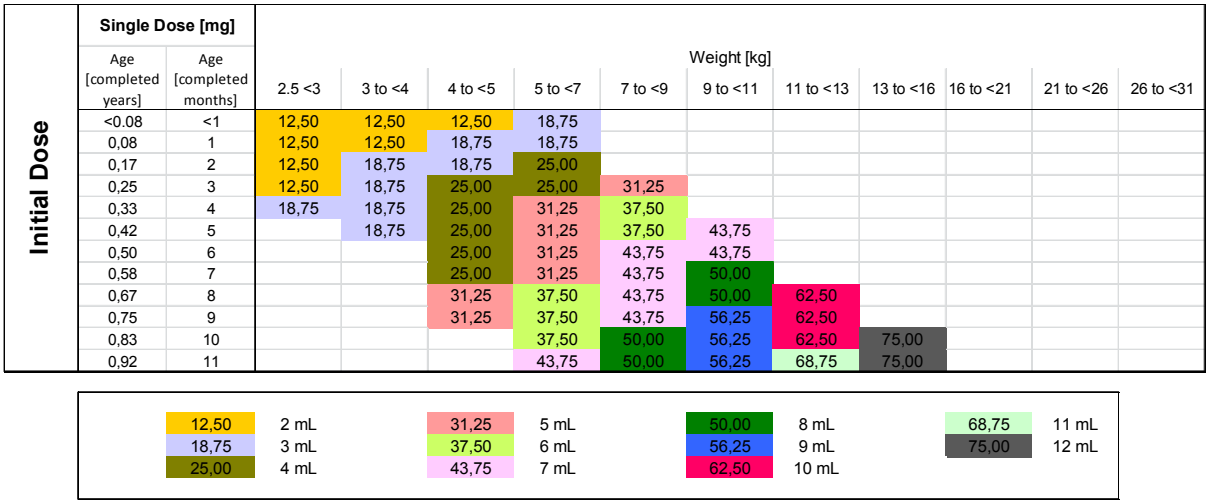


Figure 10.4.1: 3 Age and weight adjusted starting doses using OLF

10.4.2 Dose Adjustment nomogram

10.4.2.1 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 following nomograms:

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

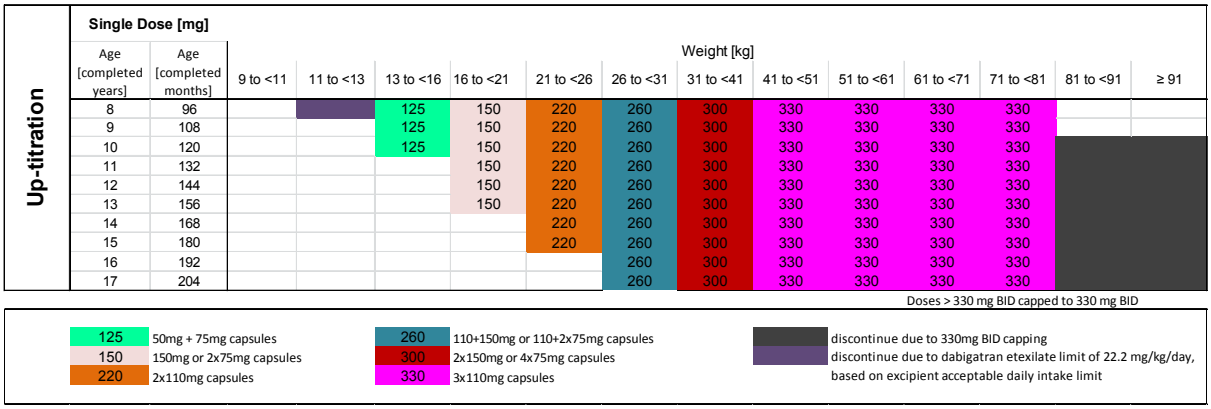


Figure 10.4.2.1: 1 Up-titration doses using capsules

- dabigatran etexilate pellets

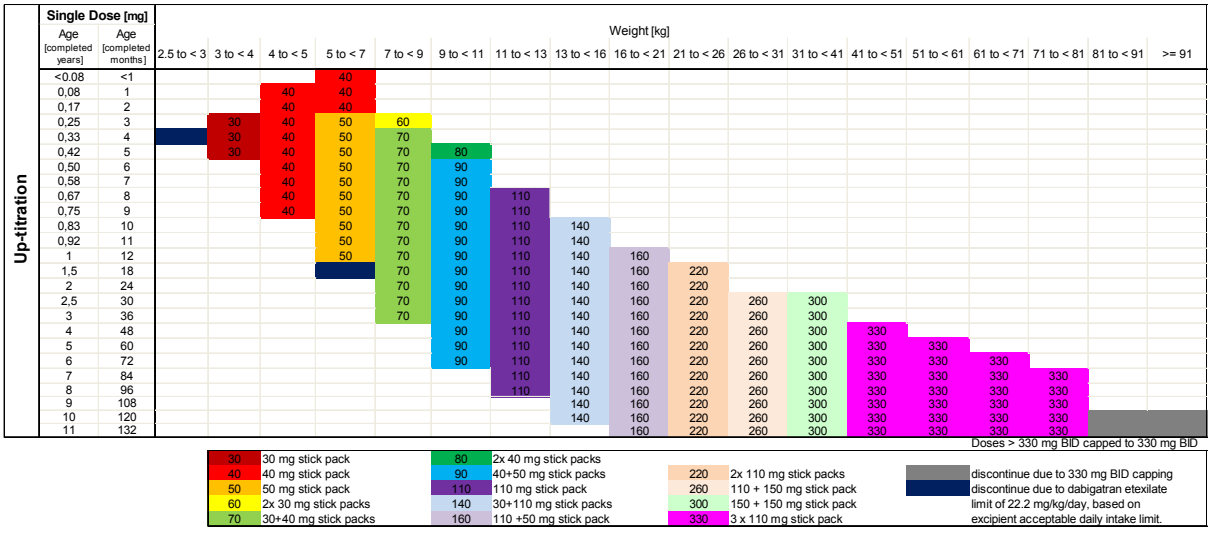


Figure 10.4.2.1: 2 Up-titration doses using pellets

- dabigatran etexilate OLF - 6.25 mg per mL

Up-titration

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	25,00	25,00	25,00	37,50							
0,08	1	25,00	25,00	37,50	37,50							
0,17	2	25,00	31,25	37,50	50,00							
0,25	3	25,00	31,25	43,75	50,00	62,50						
0,33	4	25,00	31,25	43,75	50,00	75,00						
0,42	5		31,25	43,75	50,00	75,00	87,50					
0,50	6			43,75	50,00	75,00	87,50					
0,58	7			43,75	50,00	75,00	93,75					
0,67	8			43,75	50,00	75,00	93,75	118,75				
0,75	9			43,75	50,00	75,00	93,75	118,75				
0,83	10				50,00	75,00	93,75	118,75	143,75			
0,92	11				50,00	75,00	93,75	118,75	143,75			

25,00	4 mL	43,75	7 mL	75,00	12 mL	118,75	19 mL
31,25	5 mL	50,00	8 mL	87,50	14 mL	143,75	23 mL
37,50	6 mL	62,50	10 mL	93,75	15 mL		

Figure 10.4.2.1: 3 Up-titration doses using OLF

10.4.2.2 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 following nomograms:

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

Down-titration

Single Dose [mg]		Weight [kg]												
Age [completed years]	Age [completed months]	9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31	31 to <41	41 to <51	51 to <61	61 to <71	71 to <81	81 to <91	≥ 91
8	96		50	50	75	75	75	110	110	150	150	150		
9	108			50	75	75	75	110	110	150	150	150		
10	120			50	75	75	75	110	110	150	150	150	185	185
11	132				75	75	75	110	110	150	150	150	185	185
12	144				75	75	75	110	110	150	150	150	185	185
13	156				75	75	75	110	110	150	150	150	185	185
14	168					75	75	110	110	150	150	150	185	185
15	180					75	75	110	110	150	150	150	185	185
16	192						75	110	110	150	150	150	185	185
17	204						75	110	110	150	150	150	185	185

Doses > 330 mg BID capped to 330 mg BID

50	50mg capsules	110	110mg capsules	185	75mg + 110mg capsules
75	75mg capsules	150	150mg or 2x75mg capsules		

Figure 10.4.2.2: 1 Down-titration doses using capsules

- dabigatran etexilate pellets

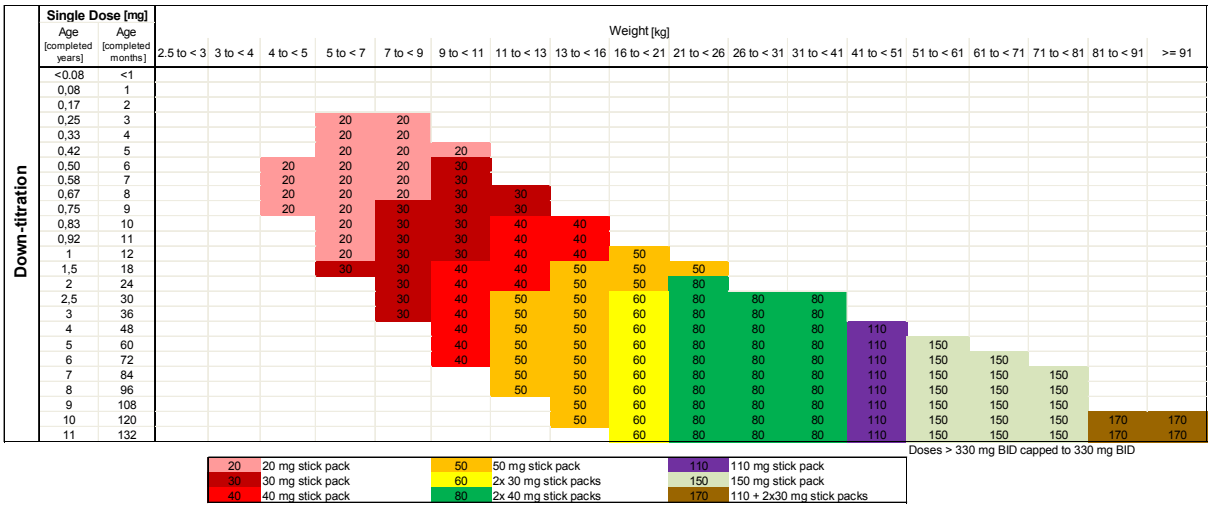


Figure 10.4.2.2: 2 Down-titration doses using pellets

- dabigatran etexilate OLF - 6.25 mg per mL

Down-titration	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	6,25	6,25	6,25	12,50							
	0,08	1	6,25	6,25	12,50	12,50							
	0,17	2	6,25	12,50	12,50	12,50							
	0,25	3	6,25	12,50	12,50	12,50	18,75						
	0,33	4	12,50	12,50	12,50	18,75	18,75						
	0,42	5		12,50	12,50	18,75	18,75	25,00					
	0,50	6			12,50	18,75	25,00	25,00					
	0,58	7			12,50	18,75	25,00	25,00					
	0,67	8			18,75	18,75	25,00	25,00	31,25				
	0,75	9			18,75	18,75	25,00	31,25	31,25				
	0,83	10				18,75	25,00	31,25	31,25	37,50			
	0,92	11				25,00	25,00	31,25	37,50	37,50			

6,25 1 mL
12,50 2 mL
18,75 3 mL
25,00 4 mL
31,25 5 mL
37,50 6 mL

Figure 10.4.2.2: 3 Down-titration doses using OLF

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		01
Date of CTP revision		*02 Oct 2014*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product(s)		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
To be implemented only after approval of the IRB/IEC/Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB/IEC/Competent Authority to be notified of change with request for approval		☒
Can be implemented without IRB/IEC/Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		*Detailed information about the dosing regimen was provided, as well as the current status of 1160.106 study.* *Decision to temporarily suspend the recruitment of patients with a body weight greater than 40kg.* *Announcement of the upcoming TID dosing regimen.*
Rationale for change		*To provide background for the decision to temporarily suspend the recruitment of patients with a body weight greater than 40kg until TID dosing regimen is implemented*

Section to be changed		3.3.2 Inclusion criteria
Description of change		*Inclusion criterion 1 was modified as follows:* Male or female subjects 0 to less than 18 years of age at the time of informed consent / assent **and body weight ≤ 40kg**
Rationale for change		*To temporarily suspend the recruitment of patients with a body weight greater than 40kg until TID dosing regimen is implemented*

Number of global amendment		02
Date of CTP revision		*28 Jan 2015*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product(s)		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB/IEC/Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/Competent Authority approval as changes involve logistical or administrative aspects only		☐

Section to be changed		2.3 BENEFIT - RISK ASSESSMENT and 4.1.3 Selection of doses in the trial
Description of change		*Rationale for dosing regimen has been provided*
Rationale for change		*Justification of dose regimen*

Section to be changed		All relevant sections of the CTP have been updated to implement BID regimen using actual calculated dosages (according to Hayton) rather than capped dosages
Description of change		*The maximal single dose was defined to be 330 mg. It was clarified that the maximal daily dose level will neither exceed a daily dose level of 22.2 mg/kg nor a single dose of 330 mg. In the higher*

		age / body weight group this results in a maximal daily dose of 660 mg. *Only one up-titration will be acceptable. The dose may be increased by 15-100% depending on the age and weight of the patient.* *Patients who cannot reach the target trough plasma concentrations after one dose adjustment must discontinue dabigatran treatment and be treated at the investigator's discretion on SOC.* *The extent of up-titration has been modified from initially 85-100% to now **15**-100% in order to not exceed maximum daily dosages based on acceptable toxicology limits.* *Dosing and dose adjustment nomograms were incorporated as Appendix 10.4*
Rationale for change		*The bleeding risk in the paediatric patient population is considered to be lower than that in adult populations (e.g. in the adult SPAF and VTE indications). Based on an overall benefit-risk assessment including the fact that the risk of thrombotic events is highest in the first 30 days, the predicted exposure in an uncapped BID regimen (up to a dose of 330 mg BID) is considered favourable*

Section to be changed		All relevant sections of the CTP
Description of change		*The dabigatran etexilate formulations assignment was clarified as follows:* Patients aged ≥ 8 years: Age and weight adjusted dabigatran etexilate capsules using 50 mg, 75 mg and 110 mg doses. Patients aged 6 months to < 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 pellets. Patients aged 0 to < 6 months or for patients who cannot take pellets at an age of 6 to 12 months: Age and weight adjusted dabigatran etexilate oral liquid formulation
Rationale for change		*Clarification on the use of age-appropriate formulations*

Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		*More detailed and current information about the status of the phase IIa studies 1160.89 and 11.60.145 has been provided*
Rationale for change		*To update the status of the phase IIa studies as they are prerequisite for opening the second age group (2 to <12 years)*

Section to be changed		3.1.1.1 Data Monitoring Committee
Description of change		*The following text was added:* *The DMC may implement a partial release of the youngest age group (0 to <2 years of age) depending on the availability of PK/PD data from respective age groups studied in the phase IIa studies.*
Rationale for change		*To allow partial release of the youngest age group (0 to <2 years of age) depending on completion of phase IIa studies and DMC decision*

Section to be changed		3.3.2 Inclusion criteria
Description of change		*Inclusion criterion 1 was modified as follows:* Male or female subjects 0 to less than 18 years of age at the time of informed consent / assent ~~**and body weight ≤ 40kg**~~
Rationale for change		*To terminate the temporarily suspension of recruitment of patients with a body weight greater than 40kg*

Section to be changed		3.3.2 Inclusion criteria
Description of change		*The following was added to Inclusion criterion 2:* In case of the initial VKA treatment the intended INR should be between 2 and 3. Patients, who during the treatment phase of 1160.106 trial were switched from dabigatran etexilate to SOC arm for any reason, are not eligible for this study.
Rationale for change		*Clarification*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*Additional exclusion criterion was introduced:* *7) Patients in age group 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)*
Rationale for change		*To exclude very vulnerable population*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*Exclusion criterion 5.b. was modified as follows:* *Persistent alanine aminotransferase (ALT) or aspartate transaminase (AST) or alkaline phosphatase (AP) > **3** × upper limit of normal (ULN) within 3 months of screening*
Rationale for change		*Less restrictive exclusion criterion was considered based on vast post-marketing experience with no signs of hepatotoxicity so far and in order to make criterion consistent across dabigatran etexilate paediatric trials*

Section to be changed		5.7.2 Methods of sample collection (PD)
Description of change		*It was specified that the date and the exact clock time of dabigatran administration on the three days before the /PD samples are taken is to be recorded in the eCRF*
Rationale for change		*To ensure precise assessment of the -pharmacodynamic relationship*

Section to be changed		Flow Chart footnote 10 and Appendix 10.1.1 Blood volume charts
Description of change		*The blood volume table was removed from the Flow Chart and more detailed, age specific charts were provided in Appendix 10.1.1*

Rationale for change		*To provide detailed and age specific description of the blood sample volumes collected during the trial*

Section to be changed		Flow Chart footnote 3, 3.3.4 Removal of patients from therapy or assessments and
Description of change		*HPLC-MS/MS assay could be used to assess the need of dabigatran etexilate dose adjustment*
Rationale for change		*To provide alternative to dTT (if needed)*

Section to be changed		All relevant sections of the CTP
Description of change		*The target dabigatran steady state trough concentration was precisely defined to be ≥50 to <250 ng/mL*
Rationale for change		*Clarification*

Section to be changed		4.2.2 Restrictions
Description of change		*The following exception was clarified: use of a specific reversal agent to counteract the antithrombotic activity of dabigatran etexilate is allowed if available in a framework of clinical investigation*
Rationale for change		*To allow use of a specific reversal agent in case available in a framework of clinical investigation*

Number of global amendment		03
Date of CTP revision		*27 Nov 2015*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product(s)		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
To be implemented only after approval of the IRB/IEC/Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB/IEC/Competent Authority to be notified of change with request for approval		☒
Can be implemented without IRB/IEC/Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		10.4.2 Dose Adjustment nomogram 10.4.2.1 Up-titration
Description of change		*Up-titration dosing nomograms for capsules and pellets have been updated*
Rationale for change		*To correct calculation errors identified to ensure the acceptable daily intake of tartaric acid for patients with body weight up to 31kg who would need up-titration would not be exceeded*

Section to be changed		10.4.1 Dosing nomogram (starting doses) 10.4.2 Dose Adjustment nomogram
Description of change		*Dosing nomograms for dabigatran etexilate OLF have been temporarily removed from the protocol*

Rationale for change		*The dosing nomograms for dabigatran etexilate OLF need to be revised in light of the errors identified for the capsule and pellet nomograms. These will be updated to reflect the acceptable daily intake of tartaric acid and will be re-introduced into the protocol, by a subsequent protocol amendment, in advance of opening the youngest age group (0 to <2 years.)*

Number of global amendment		04
Date of CTP revision		*16 Mar 2016*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product(s)		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB/IEC/Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/Competent Authority approval as changes involve logistical or administrative aspects only		☐

Section to be changed		All relevant sections of the CTP
Description of change		*Flavoured and unflavoured solvent will be used for reconstitution of OLF* *Patients assigned to OLF will be randomized based on 1:1 ratio to receive flavoured or unflavoured solvent for reconstitution* *Assessment of acceptability of all age-appropriate formulations, including OLF reconstituted with flavoured or unflavoured solvent, at days 4(V3) (for patients starting DE for the first time), 22(V4), 85(V6), 183(V8) and 365 (V11)(or eEOT, whichever comes first) was introduced as other safety assessment*

Rationale for change		*To assess acceptability of all age-appropriate formulations (capsules, pellets, OLF). To evaluate the acceptability of flavoured and unflavoured solvent types in a comparable number of patients.*

Section to be changed		1.2 DRUG PROFILE
Description of change		*Summary of phase I bioavailability study 1160.194 was provided*
Rationale for change		*To provide background for considering dabigatran etexilate formulations to be used interchangeable (no need for conversion factor).*

Section to be changed		2.3 BENEFIT - RISK ASSESSMENT
Description of change		*More detailed and current information about the status of the phase IIa study 1160.89 has been provided*
Rationale for change		*To update the status of the phase IIa study*

Section to be changed		All relevant sections of the CTP
Description of change		*It was clarified that a specific reversal agent for dabigatran is not yet available in children*
Rationale for change		*The specific reversal agent for dabigatran was recently approved for adults but is not approved for children.*

Section to be changed		3.3.2 Inclusion criteria
Description of change		*A temporary interruption of the anticoagulant therapy for the index VTE event will be acceptable*
Rationale for change		*To allow including of patients who had medically justifiable interruptions of the anticoagulant therapy for the index VTE event or after treatment of index VTE and prior to inclusion into this trial if certain pre-requisites are fulfilled and documented.*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*Insertion of a central venous line is not considered a major surgery provided haemostasis is achieved after the procedure*
Rationale for change		*Clarification that central venous line insertion is not considered a major surgery*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*It was clarified that patients with history of asymptomatic petechial or microbleeds are eligible for the study. Definition of microbleeds was provided in a footnote.*
Rationale for change		*Asymptomatic petechial or microbleeds are incidental findings that are not considered to increase the risk of bleeding. Therefore, they do not constitute an exclusion criterion. It was clarified in the footnote how microbleeds are defined in order to distinguish them from macrobleeds, which represent an exclusion criterion for this trial.*

Section to be changed		3.3.3 Exclusion criteria 3.3.4 Removal of patients from therapy or assessments
Description of change		*eGFR retesting during the screening period was allowed* *Patients will have to discontinue dabigatran treatment anytime during the course of the study if eGFR drops < 50 mL/min/1.73m^2 using the Schwartz formula and this is confirmed by one retesting within the next 14 calendar days*
Rationale for change		*This safeguard regarding renal function during the trial is considered overly conservative. It led to an unnecessary stop of dabigatran etexilate treatment in of some initial patients in this trial, where eGFR was measured to be just below 80 mL/min/1.73m$^{2.}$ Beyond renal function, this trial will use PK measurements of dabigatran and a target plasma level range as safeguard. In*

		addition, only patients with good renal function (eGFR of >80 mL/min/1.73m^2 are allowed to enter this trial. Thus, it is considered safe to lower the removal criterion of eGFR during the trial to 50 mL/min/1.73m^2.

Section to be changed		3.3.3 Exclusion criteria 4.2.2 Restrictions
Description of change		*P-glycoprotein inhibitors intake up until first dose of study medication will not be restricted or considered as exclusion criterion*
Rationale for change		*The interaction of P-gp inhibitors and dabigatran occurs on the gut level during the absorption of dabigatran. Peak plasma levels of dabigatran are reached within a few hours after intake of dabigatran. Therefore, the initially proposed washout period of one week is considered not necessary for P-gp inhibitors. As an additional safeguard, plasma level measurements of dabigatran will be performed*

Section to be changed		4.1 Treatments to be administered 10.4 Dosing of Dabigatran etexilate
Description of change		*150 mg capsule was introduced*
Rationale for change		*150 mg dabigatran etexilate capsule was introduced to the trial in order to reduce the number of capsules taken by patient at a single time point*

Section to be changed		4.1.3 Selection of doses in the trial
Description of change		*Table 4.1.3: 1 Target dabigatran etexilate doses (in mg) based on Hayton calculations for paediatric patients was updated*
Rationale for change		*To display the derived dabigatran etexilate target doses based on Hayton calculations for newborns aged < 1 month and with body weight < 3 kg*

Section to be changed		4.1.3 Selection of doses in the trial
Description of change		*Dose adjustment step ranges for up- and down-titration were corrected to reflect the respective dosing nomograms*
Rationale for change		*Correction*

Section to be changed		4.1.4 Drug assignment and administration of doses for each patient 4.2.2.2 Restrictions on diet and life style
Description of change		*If gastrointestinal symptoms develop it is recommended to take dabigatran etexilate with a meal and/or a proton pump inhibitor such as pantoprazole.*
Rationale for change		*To provide guidance to the Investigator in analogy to recommendations for adults.*

Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment
Description of change		*Cross reporting of lab results might be applied in case a patient receives specific reversal agent of dabigatran in frame of clinical study*
Rationale for change		*To limit the blood volume required for analysis and to make most effective use of blood drawn*

Section to be changed		4.2.1 Rescue medication, emergency procedures, and additional treatment
Description of change		*Treatment with dabigatran etexilate after the surgery can be re-started any time as soon as haemostasis has been achieved*
Rationale for change		*To provide guidance to the Investigator in analogy to recommendations for adults.*

Section to be changed		5.2.3 Assessment of safety laboratory parameters 10.1 Safety and other clinical laboratory evaluations
Description of change		*Local safety lab assessment will be acceptable in emergency cases only (e.g. bleeding event or emergency surgery)*
Rationale for change		*To ensure timely safety lab assessment in emergency cases*

Section to be changed		10.1 Safety and other clinical laboratory evaluations
Description of change		*eGFR Schwarz formula has been precisely defined*
Rationale for change		*Clarification*

Section to be changed		10.4.1 Dosing nomogram (starting doses) 10.4.2 Dose Adjustment nomogram
Description of change		*Dosing nomograms for dabigatran etexilate OLF have been restored into the protocol*
Rationale for change		*Calculation errors have been corrected to ensure the acceptable daily intake of tartaric acid for patients with body weight up to 31kg who would need up-titration would not be exceeded*

Section to be changed		10.4.1 Dosing nomogram (starting doses) 10.4.2 Dose Adjustment nomogram
Description of change		*Dosing nomograms for dabigatran etexilate capsules and pellets have been re-formatted*
Rationale for change		*To clearly display the age and weight ranges. There are no changes to the doses. This change is for clarification only.*

Number of global amendment		05
Date of CTP revision		*30 Nov 2016*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product(s)		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB/IEC/Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/Competent Authority approval as changes involve logistical or administrative aspects only		☐

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS 7.6 DETERMINATION OF SAMPLE SIZE
Description of change		*It was clarified that Sponsor may decide to keep recruitment open after 100 patients have been recruited, in case additional safety data needs to be generated.*
Rationale for change		*To allow inclusion of additional patients in case further scientific data is required*

Section to be changed		1.2 DRUG PROFILE 2.3 BENEFIT - RISK ASSESSMENT
Description of change		*Summary of phase IIa studies 1160.89 and 1160.105 was provided.*

Rationale for change		*To provide the final results of the completed phase IIa PK/PD studies relevant for the patients to be included in second age group (2 to<12 years) and in youngest age group (0 to <2 years)*

Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		*It was clarified that patients in in age group 2 yrs. to <12 yrs. will be included and treated in accordance to the availability of the age appropriate dabigatran etexilate formulations*
Rationale for change		*To reflect the sequential introduction of dabigatran age appropriate formulations and OLF in particular*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*eGFR level for exclusion criterion 2) relative to patients aged 12 to < 18 years was set at < 60 mL/min/1.73m^2.* *For patients aged 0 to < 12 years the eGFR level for exclusion remains < 80 mL/min/1.73m^2*
Rationale for change		*An interim analysis of 27 patients treated with dabigatran etexilate in the 1160.106 and 1160.108 has shown a good safety and tolerability profile in adolescent patients aged 12 to <18 years. Also, the currently used dosing algorithm with uncapped starting dose resulted into approximately 95% of PK trough plasma concentrations within the dabigatran target plasma range (50 to <250 ng/ml). After one dose adjustment more than 98% or measurement were within the target range. No measurement was above the target range. The previous exclusion criterion of eGFR <80 mL/min/1.73m^2 seems to be too restrictive in patients 12 to <18 years; therefore, a cut-off of 60 mL/min/1.73m^2 is considered acceptable for this age group and will allow inclusion of more patients who could benefit from the participation of the study.*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*Exclusion criterion 4) was modified to clarify that patients with be excluded if they have heart valve prosthesis requiring anticoagulation treatment.*
Rationale for change		*To comply with dabigatran etexilate IB, allowing patients with heart valve prosthesis not requiring anticoagulation treatment to be included in the study if they would benefit from their participation.*

Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		*The recommendation to use "a proton pump inhibitor such as pantoprazole" in case of development of gastrointestinal symptoms was replaced by recommendation to use a proton pump inhibitor according to "the local standard of care in accordance with local labelling recommendations".*
Rationale for change		*The locally approved labelling information, e.g. the Prescribing Information or Product Information of different proton pump inhibitors (PPIs) may vary between products and countries. Importantly, certain PPIs may only be approved for certain age groups according to local labelling information.* *The wording has been adapted accordingly.*

Section to be changed		7.3.2 Secondary analyses
Description of change		*It was clarified that all cases of death will be considered as non-event for occurrence of PTS and therefore censored*
Rationale for change		*Clarification. PTS itself could not be a direct cause of death*

Section to be changed		10.4 Dosing of Dabigatran Etexilate
Description of change		*Dosing nomograms for Dabigatran Etexilate pellets have been updated to remove 60 mg and 70 mg strengths*
Rationale for change		*Dabigatran Etexilate pellets 60 mg and 70 mg strengths will not be used in this trial*

Number of global amendment		06
Date of CTP revision		*19 Jan 2018*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
To be implemented only after approval of the IRB/IEC/Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☒
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		3.3.3 Exclusion criteria
Description of change		*Exclusion criterion 1 a) was modified adding: Active meningitis, encephalitis, or intracranial abscess at Visit 2.*
Rationale for change		*On 13 January 2018, the DMC recommended to exclude patients with active meningitis, encephalitis, or intracranial abscess from the study because of an increased risk of intracranial bleeding with these conditions.*

Section to be changed		3.3.4 Removal of patients from therapy or assessments 3.3.4.1 Removal of individual patients
Description of change		*Additional criterion to discontinue a patient from the trial was added: If a patient develops an active meningitis, encephalitis, or intracranial abscess.*

Rationale for change		*On 13 January 2018, the DMC recommended to exclude patients with active meningitis, encephalitis, or intracranial abscess from the study because of an increased risk of intracranial bleeding with these conditions.* *Also, patients who develop any of these conditions during the trial are to be discontinued from trial treatment due to the increased risk of bleeding.*

Number of global amendment		07
Date of CTP revision		*10 Sep 2018*
EudraCT number		*2014-000583-18*
BI Trial number		*1160.108*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
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Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		CTP Synopsis Section 4.1.3 Selection of the doses in the trial Section 4.1.4 Drug assignment and administration of the doses for each patient Section 10.4 Dosing of Dabigatran etexilate Section 10.4.1 Dosing nomogram (starting doses) Section 10.4.2 Dose Adjustment nomogram
Description of change		*The option to administer pellets was expanded to patients < 6 months of age. A preference for usage of OLF over pellets in patients <12 months of age was implemented, provided that OLF supplies are available to the site.*
Rationale for change		*To allow pellet treatment of patients < 6 months of age. To facilitate both, recruitment of patients below 6 months of age and collection of information on OLF treatment respectively.*

Section to be changed		Flow Chart
Description of change		*The time window from visit 1 (screening) to visit 2 (start of study medication) was expanded to 14 days.*
Rationale for change		*To facilitate screening procedures.*

Section to be changed		Flow Chart Section 3.3.4.1 Removal of individual patients
Description of change		*The preferred way of follow-up of patients who have discontinued study medication prematurely (eEOT, Follow-up Visit 12 after 28 days, further follow-up according remaining visit schedule) was implemented consistently throughout the protocol.*
Rationale for change		*To clarify the preferred way of follow-up of patients who have discontinued study medication prematurely.*

Section to be changed		Flow Chart, Footnotes 9 and 10 Section 3.1.1.3 Central laboratory Section 5.2.3 Assessment of safety laboratory parameters
Description of change		*The exceptions from the generally central laboratory assessments were implemented consistently throughout the protocol.*
Rationale for change		*To align the wording related to exceptions from central laboratory assessments between relevant protocol sections.*

Section to be changed		Section 3.3.4.1 Removal of individual patients
Description of change		*A Patient is to be discontinued from study medication if he experiences a drug-related significant or serious AE. This was changed to "a drug-related significant or drug- related serious AE".*
Rationale for change		*To clarify that the discontinuation from study medication is required in case of drug-related serious AEs, but not required in case of serious AEs that are not drug-related.*

Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		*It was added that the steady state of the currently assigned dabigatran etexilate formulation (i.e. at least 6 consecutive dabigatran etexilate doses have been taken) has to be achieved before a formulation switch could be considered.* *It was added that dabigatran etexilate up- or down-titration is not possible in some instances (limit of 22.2 mg/kg/day based on excipient acceptable daily intake, maximal single dose of 330 mg, unavailability of dosages) and affected patients have to be discontinued from dabigatran etexilate prematurely.*
Rationale for change		*To clarify the prerequisites for a potential dabigatran etexilate formulation switch.* *To clarify how to handle patients in case that up- or down-titration is not possible due to certain circumstances.*

Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		*Banana mush, strawberry jam and apple juice were added to the list of foods that are allowed to be mixed with dabigatran etexilate pellets.* *It was added that if a dabigatran etexilate dose has only been taken partially, there should be no attempt to administer a second dose at that time-point, and the next dose should be taken as scheduled approximately 12 hours later.*
Rationale for change		*To reflect the latest list of foods that are allowed to be mixed with dabigatran etexilate pellets.* *To give guidance how to proceed in case a dabigatran etexilate dose has been taken only partially.*

Section to be changed		Section 4.2.1 Rescue medication, emergency procedures, and additional treatment(s)
Description of change		*The option to re-start dabigatran etexilate after a major bleeding event has occurred was deleted.*

Rationale for change		*To align with Section 3.3.4.1 Removal of individual patients which states that patients have to be discontinued from study medication prematurely if they experience a drug-related serious AE.*

Section to be changed		Section 4.3 Treatment Compliance
Description of change		*It was added that subjects or, if applicable, parents or legal guardians, will be asked to carefully complete a daily medication intake log for dabigatran and are requested to bring this completed log to every clinic visit.* *It was added that the compliance calculation should **preferably** be based on the returned medication however completed logs may also be used.* *It was added that if an interruption of dabigatran etexilate was medically required this would be considered in the compliance calculation by reducing the number of expected doses that "should have been taken" accordingly.*
Rationale for change		*To reflect the process related to the medication intake log implemented in the trial.* *To clarify how to calculate the compliance in case of dabigatran etexliate interruptions.*

Section to be changed		CTP Synopsis Section 5.2.1 Endpoint(s) of safety Section 5.7.1 Pharmacodynamic endpoints Section 5.7.2 Methods of sample collection Section 7.3.2 Secondary analyses Appendix 10.1 Safety and other Clinical Laboratory Evaluations
Description of change		*The term dTT was supplemented with its synonym Anti-Factor IIa activity in connection with the secondary endpoint of "Pharmacodynamic assessments".* *For the secondary endpoint "Pharmacodynamic assessments" evaluations at Visit 3 (after at least six consecutive dabigatran etexilate doses) and after at least 3 days following any dabigatran etexilate dose adjustment will be considered. The reference to Visit 4 was deleted.*

Rationale for change		*To clarify and distinguish between dTT (Anti-Factor IIa activity) and dTT utilized for the evaluation of dabigatran etexilate plasma concentrations.* *To correct the secondary endpoint "Pharmacodynamic assessments".*

Section to be changed		Section 5.7.2 Methods of sample collection
Description of change		*It was added that if Aliquot 1 is not required for dabigatran concentration measurements guiding dose adjustment, Aliquot 1 may be sent to the central laboratory , Germany for analysis of pharmacodynamics and pharmacokinetics based on dTT (Anti-Factor IIa activity), aPTT and/or ECT.*
Rationale for change		*To clarify the handling of the pharmacodynamic sample Aliquot 1 in case it is not required for dabigatran concentration measurements guiding dose adjustment.*

Section to be changed		CTP Synopsis Section 5.2.1 Endpoint(s) of safety Section 7.3.2 Secondary analyses
Description of change		*The secondary endpoint of "Number of dabigatran etexilate dose adjustments during treatment period" was supplemented with the explanation "i.e. Number of patients with dabigatran dose adjustments during treatment period".*
Rationale for change		*To clarify the meaning of the secondary endpoint of "Number of dabigatran etexilate dose adjustments during treatment period".*

Section to be changed		Section 7.3 Planned Analyses
Description of change		*The wording that the primary analysis will be conducted after all patients completed the 12-months evaluation or otherwise dropped out from the study was deleted.*
Rationale for change		*To introduce flexibility in order to adapt for different regulatory requirements.*

Section to be changed		Section 8. Informed Consent, Data Protection, Trial records
Description of change		*The requirement not to publish any trial data prior finalisation of the Clinical Trial Report was deleted.*
Rationale for change		*To clarify the current publishing process.*

Section to be changed		Flow Chart, Footnote 6 Section 8.1 Study approval, Patient Information, and Informed Consent
Description of change		*It was added that in case patients reach legal age during the trial they must personally sign and date the informed consent form as soon as possible and, at the latest, at the next visit.*
Rationale for change		*To clarify the consenting process in patients reaching legal age in the course of the trial.*

Section to be changed		Section 8.3.1 Source documents
Description of change		*It was added that copies of source documents necessary for adjudication will be provided to the adjudication committee. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient´s name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients´ source documents.*

Rationale for change		*To clarify source data handling in the course of the adjudication process.*

Section to be changed		Section 10.4 Dosing of Dabigatran Etexliate
Description of change		*The reference to the dosing nomogram and titration guide document located the ISF for nomogram clarifications and dose calculation examples was deleted.*
Rationale for change		*To clarify that the process of dose calculation by the investigator is not applicable any longer. Required dabigatran etexilate dose is calculated by the IRT System only.*

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Date of CTP revision		*07 Feb 2019*
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BI Trial number		*1160.108*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years
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Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		*The eGFR level for exclusion criterion no. 2 was lowered to < 50 mL/min/1.73m^2 for all patients, irrespective of their age.*
Rationale for change		*The previous exclusion criteria regarding eGFR were set up when limited data of patients exposed to dabigatran were available. As currently, the available data show a favorable benefit/risk relationship for dabigatran and no excess of dabigatran plasma levels (≥ 250ng/ml) in patients below 12 years of age, these criteria seem to be too restrictive as they do not take into account the physiological maturation of renal function with age. A cut-off of 50 mL/min/1.73m^2 takes into account the physiologically lower eGFR at younger age, and would allow for the inclusion of*

Number of global amendment		08
		patients who may benefit from participation in the study. As an additional safeguard, the protocol eGFR criterion for stopping dabigatran treatment, i.e. if eGFR drops below 50 mL/min/1.73m^2 would remain unchanged.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		08 Feb 2019 09:11 CET
Author-Trial Clinical Pharmacokineticist		08 Feb 2019 10:28 CET
Author-Clinical Trial Leader		08 Feb 2019 11:11 CET
Author-Trial Statistician		08 Feb 2019 23:13 CET
Approval-Therapeutic Area		09 Feb 2019 21:27 CET
Verification-Paper Signature Completion		13 Feb 2019 10:40 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed