Clinical Trial Protocol

Doc. No.: c02102933-16

EudraCT No.:	2013-002114-12
BI Trial No.:	1160.106
BI Investigational Product:	Dabigatran etexilate, BIBR 1048 MS
Title:	Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of *d*ab*i*gatran etexilate *ver*sus *s*tandard of care for venous thromboembolism treatment in ch*i*ldren from birth *t*o less than 18 *y*ears of age: The DIVERSITY study
Clinical Phase:	IIb/III
Trial Clinical Monitor:	**Telephone:** **Fax:**
Co-ordinating Investigators:	Phone: Fax: Phone: Fax:
Status:	**Final Protocol (Revised protocol (based on Global Amendment 9))**
Version and Date:	**Version: 10.0** **Date: 06 Feb 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: Dabigatran etexilate, BIBR 1048 MS			
Protocol date: 05 June 2013	**Trial number:** 1160.106		**Revision date:** **06 Feb 2019**
Title of trial:	Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study		
Co-ordinating Investigator:	Phone: Fax: Phone: Fax:		
Trial sites:	Multi-centre trial		
Clinical phase:	IIb/III		
Objectives:	Main objectives: • To assess the efficacy and safety of dabigatran etexilate relative to standard of care. • To document the appropriateness of the proposed dabigatran etexilate dosing algorithm.		
Methodology:	An active-controlled, open-label, randomized, parallel-group study designed to confirm a proposed dabigatran etexilate dosing algorithm and to assess the safety and effectiveness of dabigatran etexilate compared to standard of care (SOC) for treatment of paediatric venous thromboembolism.		
No. of patients:			

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total entered:	A minimum of 141 evaluable patients for the primary efficacy endpoint including a target of: 60 patients in age stratum 1 (from 12 to < 18 years of age), 18 patients in age stratum 2 (from 2 to < 12 years of age) and 15 patients in age stratum 3 (from birth to < 2 years of age). 8 patients in stratum 3 are targeted to be below one year of age. The recruitment of patients could continue after achieving the minimum total number of patients and the minimum number of patients per age strata if required by Regulatory Authorities. Recruitment will be initiated in stratum 1 and consecutively opened to age stratum 2 and then 3 based on Data Monitoring Committee (DMC) recommendations that take into account information from the current stratum (from this trial and the secondary VTE prevention trial 1160.108); data analyses of PK, PD, dose adjustments from current stratum, exposure-response model updated with relevant paediatric and adult data as well as the appropriateness of dosing algorithm for consecutive stratum.
each treatment:	A 2:1 randomization scheme is planned (dabigatran etexilate : standard of care comprised of low molecular weight heparins (LMWH) or vitamin K antagonists (VKA) or fondaparinux). Therefore approximately 94 evaluable patients on dabigatran etexilate and 47 evaluable patients on SOC are expected. The intended SOC treatment must be specified at randomization.
Diagnosis:	Confirmed acute venous thromboembolism with an anticipated requirement for at least 3 months of treatment with anticoagulants, including an initial parenteral treatment of a minimum of 5 to 7 days (but not longer than 21 days) with an unfractionated heparin (UFH) or a low molecular weight heparin (LMWH).
Main criteria for inclusion:	Clinically stable patients diagnosed with acute venous thromboembolism (VTE) who have completed an initial parenteral treatment with an unfractionated or a low molecular weight heparin for a minimum of 5 to 7 days (but not longer than 21 days) and who have an anticipated need for continued anticoagulation therapy for at least 3 months (including the initial parenteral therapy).
Test product:	Dabigatran etexilate
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 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 oral liquid formulation or any other alternative age-appropriate formulation.
mode of admin.:	Oral
Comparator products:	A comparator product is not provided for this study

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dose:	This is not applicable per above		
mode of admin.:	This is not applicable per above		
Duration of treatment:	Patients assigned to take dabigatran etexilate or standard of care will be treated for a planned duration of 3 months which includes the initial parenteral therapy.		
Criteria for pharmacokinetics: and pharmacodynamics:	• Pharmacokinetic parameters: Plasma concentrations of total dabigatran • Pharmacodynamic parameters: Central measurement of aPTT, ECT and dTT		

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Criteria for efficacy:

Primary endpoint:

Efficacy combined endpoint. Proportion of patients with:

- Complete thrombus resolution and;
- Freedom from recurrent venous thromboembolic event (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism, thrombus progression) and;
- Freedom from mortality related to venous thromboembolic event.

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

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

Secondary endpoints:

- Freedom from major bleeding events (MBEs), defined as either fatal bleeding, clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L in a 24-hour period, bleeding that is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system, or bleeding that requires intervention in an operating suite.
- Pharmacokinetic 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
- Frequency of dose adjustments (i.e. Number of subjects with dose adjustment), temporary and permanent discontinuation from therapy and number of subjects with laboratory monitoring requirements for dose adjustment during the treatment phase
- Frequency of switch of type of anti-coaguation therapy (including from dabigatran etexilate to standard of care) (Frequency of subjects switching the type of anti-coagulation therapy including dabigatran etexilate to standard of care and switching from an intended standard of care treatment to another)
- Freedom from thrombus progression at end of therapy (day 84 after randomisation or eEOT, whichever comes first) compared to baseline
- Assessment of the acceptability of an age-appropriate formulations at end of therapy
- All bleeding events
- All-cause mortality
- All components of the primary efficacy endpoints

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Criteria for safety:	• Incidence of bleeding events including: o Major bleeding events, clinically relevant non-major (CRNM) bleeding events, minor bleeding events and any bleeding events o Combined endpoint of major and CRNM bleeding events • Incidence of adverse events, protocol-specified AESIs and serious adverse events • Treatment discontinuation due to an adverse event • Change from baseline in safety laboratory values, vital signs and physical examination • Global assessment of tolerability (measured as treatment discontinuation and adherence) to study medication		
Statistical methods:	The primary efficacy endpoint will be tested for non-inferiority using non-inferiority margin of 20% at one-sided level of 0.05. Upon showing non-inferiority for the primary endpoint, superiority test for the primary endpoint will be performed subsequently at one-sided level of 0.05 without multiplicity correction. Mantel-Haenszel type weighted average of proportion difference, Kaplan-Meier method, Cox proportional hazard model, Logistic regression and descriptive statistics will be used in the planned analyses.		

FLOW CHART

Trial Period	**Screening**	**Treatment Period (open-label) with Dabigatran Etexilate *(Dabi)* or Standard Of Care *(SOC)***											**Follow-up [A]**
Visit (V) #:	**1 [X]**	**2**	**3 [B]**	**4**	**5 [Y]**	**6**	**7**	**8 [C]**	***Dabi* Titration Visit if needed [B]**	**INR/anti-Xa Visit if needed [B]**	**Unscheduled Visit if needed [D]**	**eEOT [E]**	**9**
Study week	**-2**	**1**	**1**	**2**	**3**	**6**	**9**	**12**				**Only for early discontinued patients (before V8)**	**V8 or eEOT + 28 days**
Days from Visit 2 ***preferred visit window***	**-21** ***-1***	**0**	**3** ***+2***	**7** *-1 to +7*	**21** *±7*	**42** *±7*	**63** *±7*	**84** *±7*					***+14***
In-person clinic visits	X	X	X	X	X	X	X	X	X	X	X	X	X
Informed consent / assent [F]	X												
Inclusion / exclusion criteria [G]	X	X											
Medical history / demographics	X												
Physical examination [H]	X							X				X	X
Baseline assessment of VTE	X												
Vital signs (BP and HR)	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X							X				X	
Weight	X	X	X	X	X	X	X	X				X	
12-lead resting-ECG (5 min supine) [I]	X							X				X	
Evaluate thrombosis or symptoms [J]		X	X	X	X	X	X	X	X	X	X	X	X
Assessment of thrombus extension [J]	X							X				X	
Pregnancy test [K]	X							X				X	
Laboratory tests (blood) [L]	X [Z]	X	X	X	X	X	X	X	X	X	X	X	X
aPTT and ECT *(only for Dabi)*		X	X	X	X [T]	X	X	X	X		X	X	
Diluted thrombin time *(only for Dabi)*			X	X	X [T]	X	X	X	X			X	
INR or Anti-Factor Xa (*only for SOC)* [M]		X		X	X	X	X	X		X		X	
PK sample *(only for Dabi)* [O]			X [Z]	X	X [T]	X	X	X	X		X	X	
Select *Dabi* dose per age and weight [P]		X											
Medication intake evaluation [Q]		X				X							
Dispense *Dabi* or prescribe *SOC* [W]		X	X	X	X	X	X				X		
Possible titration of *Dabi* dose			X	X	X	X	X				X		
Possible titration of *SOC* dose		X	X	X	X	X	X			X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy [R]	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication compliance [U]			X	X	X	X	X	X	X		X	X	
Patient treatment assessment [V]			X		X			X				X	
Investigator treatment evaluation			X		X			X				X	
Termination of trial medication								X				X	
Conclusion of patient participation													X [S]

A. Visits 9 should occur at least 28 days after Visit 8 or the early End Of Treatment (eEOT) visit which is planned for early discontinued patients.

B. Patients are randomised at visit 2 to dabigatran etexilate or standard therapy (LMWH or VKA or fondaparinux) in a 2 to 1 ratio. Visit 3 will only be required for patients assigned to dabigatran etexilate. During this visit the trough dabigatran concentration will be determined by high performance liquid chromatography – tandem mass spectrometry (HPLC-MS/MS) assay at the central lab or assessed by central lab measurement of diluted thrombin time (dTT) (or alternatively by local lab if needed and when feasible) to ensure maintenance within a 50 to < 250 ng/mL window. In case the use of the HPLC-MS/MS or dTT assays is not feasible, an alternative method may be used. The first concentration assessment will be done at Visit 3 (after at least 6 consecutive dabigatran etexilate doses are taken), a dose adjustment must occur if a target dose exposure of 50 to < 250 ng/mL is not achieved (refer to Appendix 10.3.2). A titration visit must be scheduled preferably after 3 days have elapsed (or 6 new doses have been taken) since 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. Also, additional INR/anti-Xa visits (prothrombin time (PT) / INR: international normalized ratio and/or anti-factor Xa activity) to adjust standard of care therapy may be scheduled at any time point during the treatment phase outside of scheduled titration measurements as outlined in the Flow Chart. Refer to footnote M for additional information related to SOC. Refer to footnote Z for patients less than 2 months of age.

C. Eligible patients requiring secondary VTE prevention due to unresolved clinical risk factor may roll over into 1160.108 trial. For such patients, the 1160.106 trial follow-up visit is no longer required as they will be followed in the secondary VTE prevention study.

D. Unscheduled clinic visits are to be conducted in all cases of suspected symptomatic and asymptomatic VTE, progression/recurrence of VTE, paradoxical embolism (PDE), occurrence of post-thrombotic syndrome (PTS), major or clinically relevant bleeding events (MBEs / CRBEs) or other suspected significant AE 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. This visit should include all appropriate diagnostic procedures. If VTE progression/recurrence, PDE, PTS, MBEs, CRBEs are confirmed, the patient taking dabigatran etexilate is to be discontinued from the dabigatran etexilate treatment arm (eEOT visit to be performed as soon as possible), and an appropriate standard of care VTE treatment should be initiated per the investigator's discretion and/or local guidelines and the patient should be followed for the remainder of the study. If it is decided that a patient is to be discontinued from treatment due to an event, an eEOT visit should be conducted.
An unscheduled Visit is also to be performed in case a dabigatran etexilate dose adjustment is needed.

E. The early End Of Treatment (eEOT) visit will be required for all patients who have taken a dose of dabigatran etexilate but failed to complete the full planned treatment observation period (completion of Visit 8). If feasible, this visit is also required for patients randomized to SOC should they decide to discontinue the trial or permanently stop SOC treatment for any reason. eEOT visit is not required if the SOC treatment is changed during the course of the trial.

F. 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

G. Prior to start of therapy, all study inclusion and exclusion criteria must be checked to confirm patient eligibility.

H. A complete physical examination is required at Visit 1, Visit 8, eEOT Visit and Visit 9. 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 eCRFs.

I. The required ECGs 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.

J. Based on physical examination and in case of suspected 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 PTS: 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)

- Suspected PDE: CT / MR angiography or other appropriate evaluation

The final assessment (at end of therapy) of the resolution status of the thrombus must be done using the same method as the baseline evaluation when appropriate. Note: If clinical evaluations warrant imaging (e.g. suspected thrombus extension), then per investigator judgment, appropriate imaging may be performed. During the screening period, when feasible, a baseline radiological assessment (e.g. CT) may be supplemented with an acceptable non-radiological assessment (e.g. MRI) at baseline which could then be repeated at study day 84 (Visit 8) or at eEOT visit (whichever comes first) hence alleviating any potential unwarranted radiation exposure.

Patients who have worsening of their VTE any time during the study must be discontinued from dabigatran etexilate and should be treated with SOC per the investigator's judgment. If feasible, such early discontinued patients should continue the trial period on SOC. Early discontinued patients will be followed using the intent-to-treat principle and should preferably complete the remaining visit schedule until the end of the study (at minimum complete follow-up Visit 9 and scheduled Visit 8).

K. A pregnancy test will be done in female adolescents of child bearing potential (subjects who have reached menarche). More frequent testing can be done if required by the local regulation and/or authority or per investigator judgment.

L. Laboratory tests will be performed according to protocol Section 5.2.3.

For patients assigned to the dabigatran etexilate arm, approximate blood volumes (in ml) to be collected for planned central safety laboratory assessments, PK/PD are outlined in Appendix 10.1.1. 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.

M. Patients on standard of care treated with LMWH or VKA or fondaparinux, may be monitored respectively with anti-factor Xa activity (anti-Xa) or prothrombin time (PT) / INR (international normalized ratio) when applicable. Related analyses will be performed at the central lab. Alternatively local lab testing for anti-factor Xa activity, prothrombin time (PT) / INR (international normalized ratio) or aPTT (activated partial thromboplastin time) is also acceptable, see Section 5.2.3

O. Collection of pre-dose trough PK samples will be done as indicated in the Flow Chart for patients assigned to dabigatran etexilate. Pre-dose trough PK samples should be taken at approximately 10 to 16 hours after the last dose. Dabigatran etexilate doses must not be delayed to accommodate a preferred pre-dose collection time point.

P. The appropriate dabigatran etexilate starting dose must be based on the latest age and weight-based nomogram provided in Appendix 10.3.1. More frequent 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.

Q. If the patient aged 8 to < 12 years is randomized to the dabigatran etexilate arm, the investigator may assign capsules or pellets formulation depending on the patient's ability to swallow capsules. The decision will be done in the clinic at Visit 2 prior to dispensing dabigatran etexilate. The choice of the formulation to be used as treatment will be recorded in the eCRF. The patient and parent / legal guardian should be reminded about the proper procedures for administration of dabigatran etexilate (dabigatran etexilate capsules for patients aged ≥ 8 years, dabigatran etexilate pellets for patients aged < 8 years or for patients who cannot take capsules even if older than 8 (but below 12 years of age) and dabigatran etexilate oral liquid formulation (OLF) for patients less than 12 months of age). More frequent training can take place as needed. Similarly, the procedures to take standard of care (LWMH or VKA or fondaparinux) will also be explained to patients and parents / legal guardians based on local requirements.

R. Concomitant therapies, which were stopped within 14 days prior to informed consent, are to be recorded on specific eCRF pages.

S. For patients completing study medication per protocol at Visit 8, the Follow-up Visit 9, which corresponds to approximately 4 months after start of trial drug, represents the end of trial.

T. Pre-dose and post-dose sampling will be performed for PK, dTT, and aPTT/ECT only for patients on the dabigatran etexilate arm. Pre-dose sampling should occur immediately before intake of dabigatran etexilate, post-dose sampling should be performed at 2 hours post-dabigatran etexilate dose (this time point corresponds to the approximately peak dabigatran plasma concentration). Pre-dose sampling is mandatory for all dabigatran etexilate assigned patients. The post-dose sample is optional for dabigatran etexilate patients.

U. Compliance for dabigatran etexilate and SOC will be calculated by the investigator or designee preferably based on actual medication count (or alternatively based on daily medication intake logs which will be completed by the patient or if appropriate by the parent/legal guardian). Counting the returned medication is the preferred calculation method to assess compliance.

V. 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).

W. Dabigatran etexilate or SOC (not supplied in the study) may be re-dispensed as needed in appropriate cases (e.g. dabigatran etexilate at Visit 3 and Visit 4).

X. Screening procedures may begin as soon as informed consent is obtained and after the patient is diagnosed with a VTE requiring at least 3 months of treatment with anticoagulants including an initial parenteral treatment course of at minimum 5 to 7 days (but not longer than 21 days). Screening procedures may take place at different time points during the screening window. Screening laboratory tests are to be collected early enough during the screening window to ensure that results are received and reviewed by Visit 2 and that there is enough time for retesting, if needed.
In case pre-treatment with VKAs has been initiated during the screening period, a local INR measurement should be performed at Visit 2 to confirm eligibility (INR < 2.0)

Y. Visit 5 should be performed at least 3 days (6 consecutive dabigatran etexilate doses are taken) after Visit 4.

Z. Patients below 2 months must have a baseline aPTT measurement available (before any anticoagulant treatment is started). For these patients who are randomized to dabigatran etexilate, the first trough dabigatran concentration assessment (at Visit 3) must be supplemented by a local aPTT measurement. If the aPTT level at Visit 3 is ≥ 2-fold over aPTT at baseline or exceeds 100 seconds, the dabigatran etexilate dose must be down-titrated. In order to ensure maintenance of trough dabigatran concentration within a 50 to < 250 ng/mL window, all further assessments for these patients will be based on HPLC-MS/MS assay or dTT assay performed at the central lab. See Section 5.2.3.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine-Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate-Aminotransferase
AUC	Area Under the Curve
aPTT	Activated partial thromboplastin time
aVTEt	Acute Venous thromboembolism treatment
BI	Boehringer Ingelheim
BIBR 1048 MS	Indicates the mesylate salt. Unless otherwise specified BIBR 1048 MS has been used interchangeably with BIBR 1048
BID, b.i.d.	Twice daily
BUN	Blood Urea Nitrogen
C	Centigrade/Celsius
CA	Competent Authority
Cmax	Maximum Measured Concentration
CML	Local Clinical Monitor
CPMP	Committee for Proprietary Medicinal Products
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CRNM	Clinically relevant non-major (bleeding)
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
EU SPC	European Union Summary of Product Characteristics
EOT	End of Treatment
eEOT	Early End of Treatment
F	Fahrenheit
FIIA	Factor IIA (synonym for thrombin)
FAS	Full Analysis Set
FDA	Food and Drug Administration

FEIBA	Factor Eight Inhibitor Bypassing Activity
FRAC	Fraction of Adult Dose
GCP	Good Clinical Practice
h	Hour
HPLC	High Pressure Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISF	Investigator Site File
ISTH	International Society on Thrombosis and Haemostasis
IRB	Institutional Review Board
IUD	Intra-Uterine Device
IVRS / IWRS	Interactive Voice Response System / Interactive Web Response System
LMWH	Low Molecular Weight Heparin
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
mg	Milligram
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
Na	Sodium
ng	Nanogram
No.	Number
OAC	Oral anticoagulant
OLF	Oral Liquid Formulation
OPU	Operative Unit (of BI)
PE	Pulmonary embolism
PD	Pharmacodynamic
PDCO	Paediatric Committee (of the European Medicines Agency)
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PPI	Proton Pump Inhibitor
PT	Prothrombin Time
PTS	Post Thrombotic Syndrome
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
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 dilemma 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 (VKA) (R07-2939).

There are frequent challenges with the use of UFH and 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 slow patient accrual, 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).

1.2 DRUG PROFILE

Dabigatran inhibits free thrombin, fibrin-bound thrombin, clot-bound thrombin and thrombin-induced platelet aggregation. Dabigatran is not absorbed via the oral route. However, dabigatran etexilate, a small molecule prodrug which does not exhibit any anticoagulant activity, is orally bioavailable.

Overall, the efficacy and safety of dabigatran etexilate (also referred to in this document as dabigatran) have been evaluated in Phase III trials that involved over 38,000 adult patients. 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 study program with RE-COVER (1160.53, U09-1400-01) and RE-COVER II (1160.46, U11-2298-01) and the two secondary prevention studies (RE-MEDY: 1160.47, U10-2533-01) and RE-SONATE: 1160.63, U11-2267-01) have been recently completed.

The clinical program investigating the efficacy and safety of dabigatran etexilate for treatment of acute VTE consists of two studies: 1160.53 (RE-COVER) and 1160.46 (RE-COVER II). RE-COVER I and RE-COVER II were almost identical in design. Both of these studies were randomized, double-blind, active-controlled trials comparing dabigatran etexilate 150 mg b.i.d. to warfarin in a 1 to 1 ratio, with all patients starting VTE treatment with an initial period of at least 5 days of a parenteral anticoagulant. The primary endpoint was recurrent symptomatic VTE and deaths related to VTE. The secondary endpoint was DVT, PE, all deaths. The primary safety endpoint was major bleeding.

The RE-COVER study, conducted in 2,539 patients diagnosed with acute VTE, demonstrated that the rate of recurrent symptomatic VTE and VTE related death was similar in the dabigatran etexilate and warfarin treatment group and the pre-specified criteria for declaring non-inferiority was met. At 6 months, the primary endpoint occurred in 30 out of 1274 patients (2.4%) randomized to dabigatran etexilate group vs. 27 out of 1265 patients (2.1%) randomized to warfarin (risk difference 0.4; 95% CI. -0.8 to 1.5; $p<0.001$ for the prespecified noninferiority margin). The rate of major bleeding events was also similar between the two treatment groups. Major bleeding occurred in 20 out of 1274 patients (1.6%) randomized to dabigatran and 24 out of 1265 patients (1.9%) randomized to warfarin (hazard ratio 0.82; 95% CI, 0.45 to 1.48). The rates of clinically relevant bleeding events and of any bleeding events were significantly lower in the group treated with dabigatran vs. warfarin (1160.53, U09-1400-01).

The RE-COVER II study, conducted in 2,559 patients diagnosed with acute VTE, demonstrated that dabigatran etexilate was non-inferior to warfarin for the primary efficacy endpoint and the pre-specified criteria for declaring non-inferiority was met. At 6 months, the primary endpoint occurred in 30 out of 1270 patients (2.4%) randomized to the dabigatran etexilate group vs. 28 out of 1289 patients (2.2%) randomized to warfarin (risk difference

0.2; 95% CI. -1.0 to 1.3; p<0.0001 for the prespecified noninferiority margin). Major bleeding occurred in 15 out of 1270 patients (1.2%) randomized to dabigatran and 22 out of 1289 patients (1.7%) randomized to warfarin (hazard ratio 0.69; 95% CI, 0.36 to 1.32); (1160.46, U11-2298-01).

RE-COVER and RE-COVER II's pooled results showed similar outcomes for the components of the primary efficacy endpoint (hazard ratio DE/W 1.09; 95% CI. 0.77-1.53), and lower incidence of major bleeding events (hazard ratio DE/W 0.48; 95% CI 0.29 to 0.78).

The RE-MEDY study assessed the safety and efficacy of oral dabigatran etexilate (150 mg b.i.d.) compared to warfarin in the secondary prevention of VTE in patients with a prior history of DVT or PE. This trial demonstrated that dabigatran etexilate was non-inferior to very well controlled warfarin for the primary endpoint (the composite of recurrent symptomatic VTE and VTE-related death). In the active-control study, recurrent venous thromboembolism occurred in 26 out of the 1430 patients (1.8%) in the dabigatran group and 18 out of 1426 patients (1.3%) in the warfarin group (hazard ratio with dabigatran, 1.44; 95% 95% CI, 0.78 to 2.64; p=0.01 for non-inferiority). The frequency of major bleedings was numerically lower but not statistically significant for the dabigatran etexilate group. Major bleeding occurred in 13 out of 1430 patients (0.9%) in the dabigatran group and 25 out of 1426 patients (1.8%) in the warfarin group (hazard ratio, 0.52; 95% CI, 0.27 to 1.02). The incidence of patients with any bleeding events was, statistically, significantly lower in the dabigatran etexilate group than in the warfarin group. Fewer patients in the dabigatran etexilate group than in the warfarin group reported multiple bleeding events.

The long term secondary VTE prevention RE-SONATE trial established that dabigatran etexilate was superior to placebo with at least a 75% reduction in the occurrence of VTE. The frequency of patients with major bleeding was low (0.3%); however, the incidence of patients with any bleeding events was greater in the dabigatran etexilate group (95/684 treated patients) than in the placebo group (50/684 treated patients).

The efficacy and safety of dabigatran etexilate for stroke prevention in patients with atrial fibrillation was evaluated in the "Randomized Evaluation of Long term anticoagulation therapy (RE-LY) study" (U09-3249-02). In total, 18,113 patients with non-valvular atrial fibrillation and, at least, one additional risk factor for stroke were randomized to dabigatran etexilate 110 mg b.i.d., dabigatran etexilate 150 mg b.i.d. or warfarin, titrated to a target INR of 2 to 3. The RE-LY study results demonstrate that 150 mg dabigatran etexilate is superior to warfarin for the prevention of stroke/SEE and similar to warfarin with respect to the rate of major bleeding. The 110 mg dose of dabigatran etexilate was non-inferior to warfarin in the prevention of stroke/SEE and superior with respect to the rate of major bleeding. In addition, for both doses of dabigatran etexilate, there is a reduced risk of intracranial haemorrhage and total bleeding compared to warfarin. The risk of myocardial infarction was low for all treatment groups but numerically higher in the dabigatran groups. In conclusion, in atrial fibrillation patients with moderate to high risk of stroke, dabigatran etexilate has similar or superior efficacy compared to standard treatment with clinically meaningful reductions in the bleeding risks associated with standard anticoagulation regimen.

Two investigational phase II trials examined dabigatran etexilate and warfarin in patients with recent mechanical heart valve surgery (i.e. within the current hospital stay) and in patients who received a mechanical heart valve replacement more than three months prior to screening in these studies. In these two phase II studies, 252 patients were entered and dabigatran etexilate doses between 150 mg b.i.d. and 300 mg b.i.d. were tested. During the conduct of these studies, an imbalance in thromboembolic events (primarily stroke) in disfavour of dabigatran in comparison to warfarin was observed. Furthermore, the frequency of total bleeding events was higher in patients treated with dabigatran etexilate in comparison with warfarin. This imbalance in total bleeding events was mainly driven by a higher number of minor bleeding events with dabigatran etexilate. In the early post-operative patients, major bleeding manifested predominantly as post-operative haemorrhagic pericardial effusion, specifically in patients starting dabigatran etexilate early after surgery (i.e. on day 3). Based on the above data, dabigatran etexilate treatment was stopped and all patients were switched to warfarin. Dabigatran etexilate is contraindicated in patients with prosthetic heart valve replacement.

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 41 individual Phase I studies and the collection of pharmacokinetic and pharmacodynamic data from seven Phase II studies and three Phase III studies (RE-LY, RE-NOVATE 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 close correlation between dabigatran plasma concentrations and its pharmacodynamic effects (e.g. changes in ecarin clotting time (ECT), thrombin time (TT), 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. aPTT prolongation) 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. 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 10th percentile "26 ng/mL" of the trough concentrations observed in RE-COVER. Based on the anticipated similarity of the physiopathology of thrombotic events in the two populations, 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 AUC0-∞ and Cmax, respectively. The corresponding 90% confidence intervals for the ratios of AUC0-∞ 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 AUC0-∞ and Cmax, respectively. The corresponding 90% confidence intervals for the ratios of AUC0-∞ 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. 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.

However, it is worth mentioning that the goals of the dosing algorithm for initial dabigatran etexilate dosing and for dose-titrations are to reach the pre-defined target exposure for dabigatran. This target will be amended based on further data from phase I and IIa studies as well as data from this study population.

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.

Combined PK-PD analysis of studies 1160.88, 1160.89, and 1160.105):

A combined PK-PD analysis conducted on data from three paediatric studies (1160.88, 1160.89 and 1160.105) covering the full age spectrum of paediatric patients has shown that the concentration-coagulation time relationships observed in paediatric patients of all age groups, including the age range 0 to <2 years, were similar to those observed in adult populations when considering ratios over baseline (c09149467). When considering absolute clotting times, the relationships are similar across age groups for dTT. For ECT and aPTT, PK-PD relationships are similar for all age groups, except for the ages <2 months. PK-PD relationships for aPTT and ECT in infants <2 months old are shifted upward by on average 10-15% (ECT) and 10-20% (aPTT) relative to the most sensitive predicted PK-PD profiles in the adult volunteer population. These results indicate that very young children at an age of < 2 months who have higher baseline aPTT and ECT values may show an increased sensitivity to dabigatran exposure.

Pharmacokinetic evaluation in juvenile rats:

The pharmacokinetic evaluation of juvenile toxicity studies in rats has shown higher dabigatran exposures (up to 5-fold) in neonate rats (7 days of age) than in child rats (28 days of age) or adolescent rats (8 weeks of age) (n00249900, n00251085) . The exposures, profiles and linear kinetics found in child rats (28 days of age) and adolescent rats (8 weeks of age) were completely in line with the respective observations in adult rats. The most probable explanation for the pharmacokinetic differences in neonate rats in comparison to child rats and adolescent rats may be a reduced activity of P-glycoprotein, a lower activity of carboxyl esterase 2 in the intestines, and a pH-dependent saturation of absorption due to higher gastric pH in neonate rats (c01632884).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

VTE treatment 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 regards as the preferred agent for paediatric VTE treatment. 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 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 may provide such an option.

The present study is a non-inferiority trial of dabigatran etexilate versus standard of care in children from birth to less than 18 years of age. This study is an agreed upon design based on the recommendations of the European Medicines Agency's Paediatric Committee. This study is part of the paediatric dabigatran clinical development program for VTE treatment and has the potential to provide critical information regarding the safety and efficacy of dabigatran etexilate for VTE treatment 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 objectives of this large phase IIb/III paediatric study are to assess the efficacy and safety of dabigatran etexilate relative to standard of care and to document the appropriateness of the proposed dabigatran etexilate dosing algorithm for use in patients from birth to less than 18 years of age.

2.3 BENEFIT - RISK ASSESSMENT

Individuals participating in this trial will benefit from the close medical care which will be provided within the framework of this study. Patients assigned to dabigatran etexilate treatment may also benefit from receiving an extensively evaluated drug which was shown to be safe and effective in adult patients with VTE. In fact, 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. Moreover this study may help to bring a new and innovative therapy to paediatric patients with VTE, therefore providing a general benefit to society and to the entire paediatric patient population with VTE.

The tolerability and PK/PD profile of dabigatran has also been evaluated in paediatric patients. Data obtained from 8 adolescent patients in trial 1160.88 (U12-3378-01) demonstrated that dabigatran capsules were apparently safe and well tolerated in this small study. 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.

The PK findings of the juvenile toxicity studies (n00249900, n00251085) as well as the results from the combined PK-PD analysis of studies 1160.88, 1160.89, and 1160.105 (c09149467), could be potentially relevant for dabigatran exposure in patients aged from birth to less than 2 months old.

Dabigatran plasma concentrations will be evaluated at all treatment study visits and the dabigatran dose will be up or down titrated to maintain dabigatran plasma concentrations within the proposed therapeutic range. This is expected to enhance efficacy and also minimize the risk of bleeding.

In addition, the potential risk of bleeding in patients below 2 months randomized to dabigatran etexilate will be assessed in an expedited manner after at least six doses of study medication (at steady state, Visit 3), based on aPTT ratio over baseline and the absolute aPTT value measured locally. Down-titration of the dose will occur if the aPTT level at Visit 3 is ≥ 2-fold over aPTT at baseline or exceeds 100 seconds. In order to ensure maintenance of trough dabigatran concentration within a 50 to < 250 ng/mL window, all further assessments for these patients will be based on HPLC-MS/MS assay or dTT assay performed at the central lab.

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 1160.106, 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 (250ng/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) rather than 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 or as early as possible after Visit 3 in case of patients < 2 months based on aPTT ratio over baseline and the absolute aPTT value obtained locally.

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 > 250ng/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.

To further minimize risk, individual patient risk will be carefully monitored by close observation during the treatment and follow-up periods. A Data Monitoring Committee (DMC) will also be utilized during the study to further insure the participants' safety. A separate charter specifies their roles and responsibilities. The planned tiered-approach of only evaluating younger age groups (stratum-2 and then 3) after a DMC-evaluation of a relevant number of older patients will provide added safety. This approach ensures that the younger age groups will only be evaluated after the dosing algorithm is confirmed and preliminary efficacy and safety data are obtained from older age group(s), and preliminary PK, PD and safety data are available from other phase IIa studies. These measures are expected to provide adequate safety protection for all study participants.

A specific reversal agent for dabigatran in children is not available yet, however, a development program in children is ongoing (P15-06362).

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 ensure patient safety.

Overall, dabigatran etexilate, as an oral treatment, may offer an alternative to LMWHs, without any need for daily injections for VTE treatment. It may also reduce the need for frequent blood samples for therapeutic drug monitoring as is the case with currently available VKAs. This study has the potential to offer to the participating subjects close medical care and an alternative therapy which was shown to be safe and effective in adults, hence potentially providing a real therapeutic benefit to individual subjects as well as benefit the entire paediatric patient population with VTE by developing an alternative therapeutic option for this disease.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, open-label, randomized, parallel-group, active-controlled, non-inferiority study of dabigatran etexilate versus standard of care (SOC) in children from birth to less than 18 years of age. This study will be conducted at approximately 100 sites located in approximately 30 countries.

After a signed consent form (and assent, if applicable) has been obtained, the patients will enter a screening period while they are completing their initial phase of their VTE treatment by parenteral therapy. A 2:1 randomization scheme is planned (dabigatran to standard of care). The intended SOC (LMWH or VKA or fondaparinux) must be specified at randomization. Once eligibility has been confirmed, patients will receive either daily dabigatran etexilate or SOC for up to 3 months (inclusive of the initial parenteral therapy). Guidance on how to switch from parenteral therapy to dabigatran etexilate is provided in Section 4.1.4. Refer to Section 4.1.3 for information on dose selection. Patient experiencing an event requiring discontinuation of dabigatran per protocol will be switched to an appropriate SOC therapy and will be followed until the end of the study based on an intent-to-treat principle. Patients requiring VTE therapy beyond 3 months have to be switched at Visit 8 (day 84) to SOC treatment (if randomized to dabigatran etexilate) or continue SOC treatment (if randomized to the SOC arm) and could be maintained on SOC during the follow-up period. Patients requiring further anticoagulation for secondary VTE prevention due to an unresolved clinical risk factor may be enrolled in an open-label secondary prevention trial and their follow-up visits will be performed within this separate study

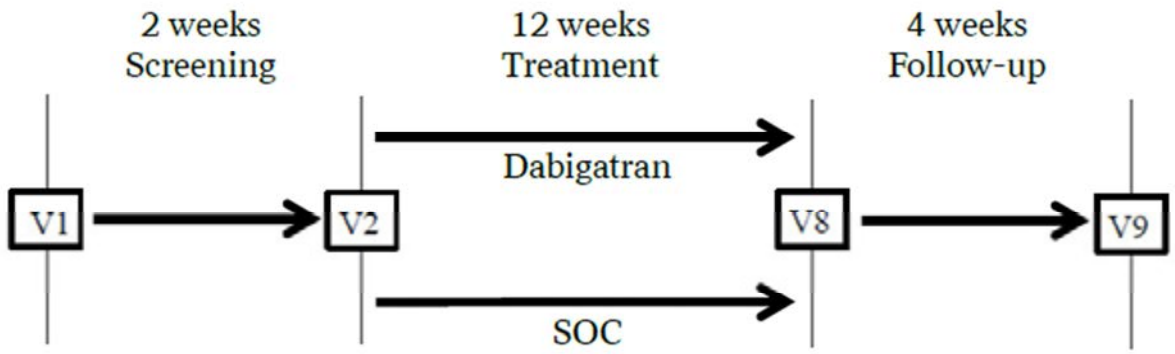

Figure 3.1: 1 Diagram representing the major study periods

Study visits and procedures will be performed as outlined in the Flow Chart. Collection and processing of PK samples is described in Section 5.5.2 and for the PD samples, in Section 5.7.2.

All patients who have taken dabigatran or SOC will have a follow-up visit at least 28 days after Visit 8 (end of planned treatment) or after early EOT. Study participation of a subject, who did not prematurely discontinue study medication, is concluded when the last planned

study visit (Visit 9) has been completed. For information about study procedures for patients who prematurely discontinued from study medication see Section 3.3.4. Patients who will require secondary VTE prevention due to unresolved clinical risk factor may continue in a long-term secondary VTE prevention study and their follow-up visit will be performed within this separate study.

The residual effect period for which AEs will still be considered on-treatment following the last intake of trial medication (dabigatran and SOC) is ≤ 6 days. In case of an ongoing AE at the end of the planned follow-up period, the patient will be evaluated until resolution of the AE or until the investigator and sponsor agree that no further follow-up is necessary. If a patient develops a VTE or a MBE, they should be followed until the resolution of the event.

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.

Boehringer Ingelheim (BI) will appoint 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, a Trial Programmer and a Trial Statistician will be 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 organisation of the trial will be done by the respective local BI organisation (Operating Unit (OPU)) or a 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 will be 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.

Documents on the participating principal investigators 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 an independent Data Monitoring Committee (DMC). A detailed DMC charter will govern the activities of this committee. The recommendations of the DMC will be maintained in the clinical trial master file.

The members of the DMC will be external experts in the fields of VTE treatment and anticoagulation; members with statistical expertise will also be included in the committee as outlined in the DMC charter. The committee will review efficacy and 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 relevant dabigatran adult and paediatric study results as well as monitor the overall paediatric program to ensure patient safety. The DMC will also have access to information collected in ongoing and previously completed paediatric phase IIa trials. The DMC may open the trial to age stratum 2 and then 3 based on available safety and efficacy data 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 stratum. The DMC may implement a partial release of stratum 3 depending on the availability of PK/PD data from respective age groups studied in the phase IIa studies.

Specifically, the DMC will have the ability to recommend to the sponsor modifications with respect to the target dabigatran plasma concentration range based on available data. The dose regimen will be reviewed on an ongoing basis by the committee and can be further revised as data on dabigatran levels and safety and efficacy data become available during the course of the 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.

3.1.1.2 Central Independent Blinded Adjudication Committee

All components of the primary efficacy endpoint as well as all bleeding and all fatal events will be centrally adjudicated by an independent adjudication committee that will be blinded to all treatment assignments and will confirm or refute outcome events.

3.1.1.3 Central laboratory

All planned safety samples will be analysed at a central laboratory. If approved by the sponsor, a local laboratory may be used in certain circumstances where centralized assessments are not feasible. Pharmacokinetic and 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 or more Coordinating Investigators (CIs) and other representatives. The sponsor will be represented on this committee.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

This is an open-label, randomized, parallel-group, active-controlled, multi-centre non-inferiority study of dabigatran etexilate versus standard of care for the treatment of VTE in paediatric patients. Children from birth to less than 18 years of age will be eligible to participate and will be stratified based on three age groups; refer to Section 3.3 for details.

The design of this study (including the definition of endpoints and SOC comparators) is based upon the European Medicines Agency's Paediatric Committee's recommendations. This committee has previously reviewed and approved the principal design elements and endpoints of this trial. For details on the primary efficacy endpoint, refer to Section 5.1.1. The components of the primary efficacy endpoint as well as all bleeding and all fatal events will be centrally adjudicated in a blinded fashion.

3.3 SELECTION OF TRIAL POPULATION

Subjects will be stratified in 3 separate age groups: Age stratum 1 (from 12 to < 18 years of age), age stratum 2 (from 2 to < 12 years of age) and age stratum 3 (from birth to < 2 years of age). A minimum of 141 randomized evaluable patients will be needed to evaluate the primary endpoint including a target of 60 patients in age stratum 1, 18 patients in age stratum 2 and 15 patients in age stratum 3. 8 patients in stratum 3 are targeted to be below one year of age. The recruitment of patients could continue after achieving the minimum total number of patients and the targeted number of patients per age strata if required by Regulatory Authorities. All patients who received at least one dose of study medication will be considered evaluable. Recruitment will be initiated in stratum 1 and may be opened to age stratum 2 and then 3 based on Data Monitoring Committee (DMC) recommendations. Patients in stratum 3 will be included and treated in accordance to the availability of the age appropriate dabigatran etexilate formulations

Patient eligibility will be assessed based upon a complete medical history including a physical examination and laboratory testing. A log of all patients screened and included in the study (i.e. having given informed consent) 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 between 0 to less than 18 years of age with a confirmed acute venous thromboembolism diagnosis and an anticipated requirement for at least 3 months of anti-thrombotic treatment; patient screening may start as soon as the patient has been diagnosed with a VTE. It is expected that parenteral therapy would be administered for a minimum of 5

to 7 days using an unfractionated heparin (UFH) or a low molecular weight heparin (LMWH) in all study participants, although for some patients a longer period of initial therapy may be given (but not exceeding 21 days).

3.3.2 Inclusion criteria

1) Male or female subjects 0 to less than 18 years of age at the time of informed consent / assent**.**
2) Documented diagnosis of clinically stable VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis) per investigator judgment, initially treated (minimum of 5 to 7 days, but not longer than 21 days) with parenteral anticoagulation therapy, such as unfractionated heparin (UFH) or a low molecular weight heparin (LMWH)[2].
3) Anticipated treatment duration with anticoagulants for the VTE episode (under inclusion 2) for at least 3 month period, inclusive of the initial parenteral therapy.
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.

3.3.3 Exclusion criteria

1) Conditions associated with an increased risk of bleeding:
    a) Any prior intracranial haemorrhage, classified as a macrobleed[1]. Any intracranial anatomical abnormality or intracranial aneurysm. Active meningitis, encephalitis, or intracranial abscess at randomisation.
    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, in major surgery, a mesenchymal barrier is opened (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.

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[1] Patients with 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.
[2] Short-term pre-treatment with VKAs is permitted if the INR has not yet reached a therapeutic level (i.e. the INR is still < 2.0). The duration of the initial parenteral therapy inclusive VKA treatment if applicable must not exceed 21 days.

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) Fibrinolytic agents within 48 hours of dabigatran administration (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).

i) Uncontrolled hypertension on antihypertensive medication (systolic and/or diastolic blood pressure (BP) 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) > 3x 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 a medically accepted contraceptive method per local guidelines. 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 stratum 3 (0 to < 2 years) with gestational age at birth < 37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards - will be provided in the ISF).

8) Anaemia (haemoglobin < 80g/L) or thrombocytopenia (platelet count < $80x10^9$/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 prohibited or restricted medication within one week of the first dose of study medication other than medication for prior VTE treatment and P-glycoprotein inhibitors. 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.

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.

13) Patients or parents/legal guardians who are unwilling or unable to undergo or permit repeat of the baseline imaging tests required to confirm thrombus resolution at study day 84 (or at eEOT, whichever comes first) or in whom repeating such imaging tests at these pre-specified time points may not be medically in the patient's best interest. Examples may include unwarranted radiation exposure as a result of a repeat CT scan at study day 84 (or eEOT, whichever comes first) for a patient with an isolated case of pulmonary embolism evaluated at baseline solely by a CT scan. In such cases, the baseline radiological assessment (e.g. CT) may be supplemented with an acceptable non-radiological assessment at baseline (e.g. MRI) which could then be repeated at day 84 (or eEOT, whichever comes first) hence alleviating any potential unwarranted radiation exposure.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

The parent(s) / legal guardian(s) and/or their child may decide to be removed from the study as follows:

- The patient/parent/legal guardian may decide to discontinue from treatment and wish to switch to another treatment prior to end of trial and be willing to be followed up within the clinical trial until the time at which study completion would have occurred.

- The patient/parent/legal guardian may decide to discontinue study treatment or not participate in any further trial related activities, but be willing to be contacted once at a time point at which the patient would have completed the study to determine the patient's vital status.

- In very rare cases, the patient/parent/legal guardian may withdraw consent/assent to continue in the study for any reason; in doing so they refuse to participate in any further trial related activities and decline any contact or data to be collected for trial purposes. If this occurs, this decision must be clearly documented.

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

- If the patient is no longer able to participate for other medical reasons (e.g. surgery, AEs, other diseases or concomitant therapies).

- In the event that a new thromboembolic event or a clear clinical progression of the baseline VTE (e.g. based on ISTH guidelines) are observed as assessed by the Investigator and using appropriate imaging modalities or if the patient experiences a drug-related significant or drug-related serious AE or if drug toxicity is observed, then the patient is to be removed from the dabigatran treatment arm and be put on standard of care per investigator judgment and be followed until the end of the study. Subjects in the SOC arm may also require changes in their therapy.

- Patients who do not reach a total dabigatran plasma trough concentration within the pre-specified therapeutic range after one dose adjustment.

- In the opinion of the Investigator, continuation in the trial is not in the patient's best interest. If treatment non-compliance persists despite all possible efforts, patients should be removed from the allocated treatment and alternative therapy should be proposed in such cases.

- If a patient becomes pregnant or a pregnancy is suspected during the trial the investigational drug (dabigatran) will be stopped, the patient will be discontinued from the dabigatran treatment arm and will be put on an appropriate SOC 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 a 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 14 calendar days), treatment with dabigatran must be stopped and the patient must be switched to an appropriate SOC regimen.
  If a patient develops eGFR < 50 mL/min/1.73m^2 using the Schwartz formula for

second time during the course of the study, treatment with dabigatran etexilate (when applicable) must be stopped without further retesting and the patient must be switched to an appropriate SOC regimen.

- The patient does not require treatment with anticoagulants any longer due to a complete thrombus resolution as confirmed by appropriate imaging modalities prior to 12 weeks 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.

A patient can be discontinued from treatment after discussion between patient/parent/legal guardian, sponsor and Investigator if eligibility criteria are being violated, or if the patient and/or parent/legal guardian fail to comply with the protocol (e.g. non-attendance at trial assessments, improper drug intake, etc.). In such cases and when feasible, the patient is to be followed until the end of study preferably according to the remaining visit schedule.

In addition, in order to protect patient safety, measurements of dabigatran trough plasma levels will be performed in a central laboratory using HPLC-MS/MS or dTT assay or an alternative assay from blood samples taken at steady state (initially after a minimum of three to five days on study treatment, i.e. at minimum after six consecutive dabigatran doses are taken). If a patient has a dabigatran plasma level of < 50ng/mL or ≥ 250ng/mL confirmed despite a dose adjustment, they will stop taking dabigatran and will be switched to SOC for the remainder of the study.

Dabigatran is predominantly excreted by the kidney; special attention should be given to the kidney function of these patients when needed. As stated above, patients with an eGFR < 50 mL/min/1.73m^2 using the Schwartz formula at the screening visit (Visit 1) or any patient with confirmed eGFR < 50 mL/min/1.73m^2 at any time during the treatment period will be excluded from the dabigatran arm and will be switched to SOC for the remainder of the study. Any suspected worsening of renal function during the study should be investigated by eGFR evaluation.

Patients who drop out during screening (i.e. prior to randomisation at Visit 2) 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 is required.

Patients who discontinue study drug or withdraw from the trial after randomisation (Visit 2) will be considered as “early discontinuations” and the reason for premature discontinuation must be recorded in the eCRF. The data will be included in the trial database and will be reported.

All patients that prematurely discontinue dabigatran for various reasons as outlined above and who do not withdraw consent/assent will be switched to SOC after a dabigatran eEOT visit and then followed for the remainder of the study preferably according to the remaining visit schedule. In cases where the patient/parent/legal guardian does not allow for a follow-up according to the remaining schedule and where consent/assent is not withdrawn, the patient/parent/legal guardian will be contacted by the Investigator to perform a dabigatran

eEOT visit (i.e. before 12 weeks of treatment) and subsequently be contacted at 4 months in order to gather information for study endpoints (e.g. bleeding events, survival, occurrence of VTE, etc.). If an outcome event is reported to the site (e.g. bleeding events, occurrence of VTE, etc.) then, to ensure patient safety, the patient/parent/legal guardian will be asked to come to clinic for an unplanned visit as soon as possible.

Procedures to be followed for patients prematurely terminating the trial are detailed in Section 6.2.3.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the entire trial, or terminate the conduct of the trial at all sites within a particular country or at any individual site.

The following reasons are examples that may lead to discontinuation of some or all of the trial sites:

- 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

4.1.1 Identity of BI investigational product and comparator products

The investigational product dabigatran etexilate will be supplied by Boehringer Ingelheim. The composition of planned formulations is detailed below.

Dabigatran etexilate capsules:

- Substance: Dabigatran etexilate
- Pharmaceutical formulation: Capsule
- Source: Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
- Unit strength: 50 mg, 75 mg, 110 mg and 150 mg
- Total Daily dose: The administered dose (BID) is based on an age and weight adjusted nomogram included in Appendix 10.3.1. 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 10.3.1). Detailed preparation and administration instructions will be included in the ISF.
- Total Daily dose: The administered dose (BID) is based on an age and weight adjusted nomogram included in Appendix 10.3.1. 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 (BID) based on an age and weight adjusted nomogram included in Appendix 10.3.1. 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

The active comparator (e.g. LMWHs or VKAs or fondaparinux used as SOC) will not be supplied as part of the investigational medicinal product.

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.

Eligible patients who meet all inclusion and exclusion criteria will be randomly assigned to receive either dabigatran or standard of care (LMWH or VKA or fondaparinux) in an open-label fashion based on a 2:1 ratio (dabigatran:SOC). In addition, patients assigned to dabigatran etexilate OLF will be randomized based on 1:1 ratio to receive flavoured or unflavoured solvent for reconstitution. The intended SOC treatment must be specified at randomization. Patient assignment to the treatment groups will be managed by IRT. Access to the randomisation code will be controlled and documented. 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 randomization, to track medication assignments, to monitor the appropriate age stratification according to strata 1, 2 and 3 and the minimum number of patients required in each age group. The IRT will also be used to control aspects of the medication supply chain.

Randomization will be initiated in stratum 1 and progressively open to stratum 2 and then 3 once the DMC authorizes the start of recruitment in strata 2 and 3 following the review of ongoing data in stratum 1 (considering patients from this trial and from the secondary VTE

prevention trial 1160.108), data from previously completed phase IIa studies and any other relevant information as described in the DMC charter.

4.1.3 Selection of doses in the trial

Estimated doses for paediatric patients assigned to take dabigatran will be based on age and weight according to a nomogram (please refer to Appendix 10.3). Provided that a dabigatran assignment is confirmed, patients aged ≥ 8 years who are able to swallow capsules 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, however, 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 SOC (including LMWH or VKA or fondaparinux) will be monitored regularly and dose adjusted throughout the treatment period as needed based on investigator recommendations and local guidelines. In case of VKA use, the patient will be adjusted to ensure the INR for the patient is maintained at a level appropriate for the individual thromboembolic risk factors as recommended by local guidelines and investigator. In case of LMWH use, monitoring may be done (although it is not required) using anti-factor Xa activity and the LMWH dose may be adjusted when needed according to local guidelines and investigator recommendations to ensure maintenance within an acceptable therapeutic range.

The dose of dabigatran etexilate may 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 most extensive data set comes from over 12,000 patients exposed to dabigatran for a median of 2 years in the completed atrial fibrillation program. Dabigatran etexilate 150 mg BID was shown to be more effective at preventing strokes than well-controlled warfarin (median time in therapeutic range of the INR between 2.0 and 3.0 was 67%) with comparable or less bleeding. A large dataset is also available from adult VTE patients treated with 150 mg bid (1160.53, U09-1400-01) where dabigatran had about half the bleeding of well controlled warfarin while being non-inferior for VTE prevention, albeit with a hazard ratio slightly greater than 1.0. 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 developed.

In the RE-LY study, 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 clearly associated with 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 10th percentile "26 ng/mL" of the trough concentrations observed in RE-COVER. Based on the anticipated similarity of the physiopathology of thrombotic events in the two populations, a trough concentration ≥ 50 ng/mL is expected to provide a satisfactory benefit risk ratio for paediatric patients. Furthermore, based on a low risk of major bleeding events with rising total dabigatran trough concentrations even beyond 250 ng/mL, it is considered that trough concentrations between 50 and < 250 ng/mL have the potential to have a positive benefit/risk ratio in children of all ages.

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 RE-COVER (mean age 55.0), the general paediatric population is characterised 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 10.3.1. Dosing of patients should only occur according to the adjusted nomogram provided in Appendix 10.3.1.

Table 4.1.3: 1 Target dabigatran etexilate doses (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 may be increased by 10 to 100%. 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 safe. 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

may 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 10.3.2.

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%

For patients below 2 months at Visit 3 the dabigatran etexilate dose will be down-titrated if the locally measured aPTT level is > 2-fold over aPTT at baseline or exceeds 100 seconds.

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 will be repeated at about 3 days after dose adjustment (after at least 6 adjusted consecutive dabigatran doses have been taken) to confirm the new dose. After dose adjustment, the total dabigatran trough concentration should be ≥ 50 ng/mL and < 250 ng/mL.

If patients cannot reach trough plasma concentrations between 50 and < 250 ng/mL after one dose adjustment, they must discontinue dabigatran treatment and be treated at the investigator's discretion on SOC but will remain in the study according to the visit schedule until the end of the trial.

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 10.3.2. 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 could 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

Treatment will be randomly assigned in this trial and then dispensed in an open-label fashion. Patients will either take dabigatran (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) or they will be assigned to take SOC (LMWH or VKA or fondaparinux). The intended SOC treatment must be specified prior to randomization. If deemed necessary the type of SOC may be changed during the treatment period. Concerned patients will not be considered as having discontinued study medication early, will remain to be on study medication and will be followed per the visit schedule until the end of the study (see Flow Chart and Section 6.2.3).

Eligible patients, who meet all inclusion and exclusion criteria at visit 2, will be randomised to receive either dabigatran or SOC (LMWH or VKA or fondaparinux) in a ratio of 2:1 (dabigatran:SOC). Patients assigned to take SOC are to follow the investigator's recommendation for adequate dosing and administration based on the product's locally approved label and in consideration of local treatment guidelines. Patients assigned to take dabigatran and 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). In case pre-treatment with VKAs has been initiated during the screening period, a local INR measurement should be performed at Visit 2 to confirm eligibility (INR < 2.0) (see Flow Chart).

The estimated dosages for paediatric patients assigned to take dabigatran as capsules, pellets to be sprinkled on food or the oral liquid formulation will be based on age and weight according to a nomogram provided in Appendix 10.3.1. Provided that a dabigatran assignment is confirmed, patients aged ≥ 8 years who are able to swallow capsules (per investigator judgment) will be assigned to take capsules. In case a patient aged ≥ 8 years but below 12 years of age is unable to take capsules, 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 up to < 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 capsules 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 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 dose (or the recommended SOC dose) is properly taken.

The interval between dabigatran 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.

In the event that a patient has to be switched from dabigatran therapy to SOC, the investigator should plan for each subject's transition to SOC taking into consideration the patient's risk profile and previous experience with a VKA or a LMWH or fondaparinux. 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. Close monitoring of the patient's coagulation profile during the transition period must be implemented to optimize safety. In general, dabigatran therapy should not be overlapped with LMWH, VKA or fondaparinux therapy.

Investigators should recognise that the presence of dabigatran could elevate the INR. Once dabigatran has been stopped for >2 days, the INR will better reflect the effect of VKA therapy alone. Investigators should also be mindful that the use of LMWH needs to be monitored closely in patients with an extreme weight for their age and height or in patients with potential renal dysfunction due to the renal-based clearance of LMWHs. Anti-factor Xa activity may be useful for monitoring anticoagulation with LMWH therapy.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label study. Due to the safety obligation in this paediatric setting, the trial will be conducted in an unblinded fashion to ensure a rigorous supervision of the study. Investigators, patients, and trial members will be unblinded. The only party blinded to treatment assignment are members of the adjudication committee.

4.1.5.2 Procedures for emergency unblinding

Not applicable as this is an open-label study.

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

Patients/parents/legal guardians should be reminded to store and use LMWHs or VKAs or fondaparinux according to investigator instructions in consideration of local product labels.

Dabigatran should be kept out of the reach of children and be stored protected from moisture and direct sunlight. Dabigatran capsules should be kept in their supplied container and the bottle lid must be kept closed. Dabigatran capsules must not be transferred to other types of containers. The medication stick packs containing the dabigatran etexilate granules should be kept sealed until just prior to reconstitution. The medication stick packs containing the dabigatran etexilate pellets should be kept sealed until just prior to intake.

Patients/parents/legal guardians should be instructed to keep medication containers tightly closed and not to remove capsules from the original packaging material until immediately prior to the time of intake. Dabigatran may only be dispensed to trial patients 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.

For storage conditions refer to the locally approved medication label and the STORM (Storage conditions for Trial Medications) document in the ISF.

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

If the storage conditions are found to be outside the specified range, the local Clinical Monitor (CML) for the study should be contacted immediately and the medication should be quarantined in the IRT until further notice.

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. A temperature log

must be maintained to make certain that the drug supplies are stored at the correct temperature.

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 randomisation until the patient completes follow up. In addition, at the randomisation visit, information regarding specific drugs (e.g. antithrombotic medication, medications with a potential drug-drug interaction with dabigatran etexilate (P-glycoprotein inhibitors and inducers)), administered in the 14 days prior to informed consent until time of randomisation and any medication given to directly treat an adverse event during the screening period will be recorded.

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

At the screening visit, the site must document details of the initial parenteral anticoagulant therapy given for the treatment of the VTE.

4.2.1 Rescue medication, emergency procedures, and additional treatment

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).

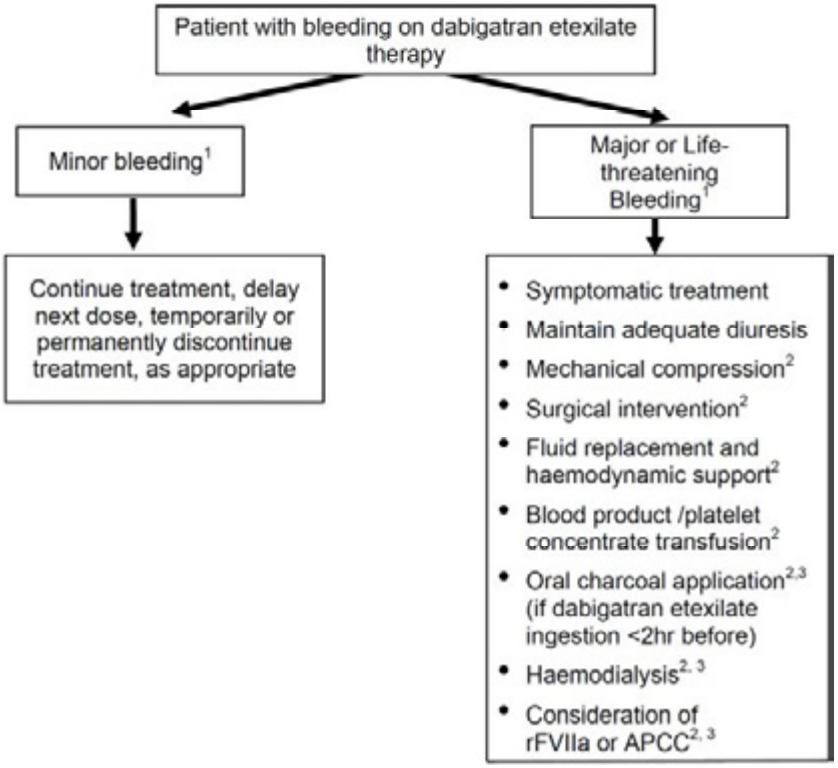
Major bleeds for patients on dabigatran:

If a patient experiences a major bleed, dabigatran 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, 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 there is one 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. 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. 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 5.1.2.3
[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 must be stopped if a major bleeding event is observed. The patient must be treated and stabilized. Thereafter, the patient should be given SOC per investigator judgment and followed until the end of the trial based on the Flow Chart visit schedule.

Major bleeds for patients on SOC:

The local product label and local treatment guidelines should be followed in case a major bleed is observed with a LMWH or a VKA or fondaparinux. For major bleeding under LMWH therapy, protamine sulphate will reverse about 75% of the effects of LMWH. With VKA, treatment should be temporarily stopped and the anticoagulant effect reversed with vitamin K, prothrombin complex concentrates and/or fresh frozen plasma. Readministration of SOC, after the bleeding has been resolved and haemostasis has been achieved, is at the discretion of the investigator.

Clinically relevant non-major bleeds or minor bleeds:

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

Management of dabigatran and SOC prior to and after planned surgery:

Dabigatran Treatment Discontinuation for Elective Surgical Interventions

For minor surgery or interventions with a low risk for bleeding per investigator judgment, elective procedures could take place 36 hours after the last dabigatran intake (two missed doses). Treatment can restart at investigator's discretion but not earlier than 2 days after minor surgical interventions.

For major surgery with high risk for bleeding per investigator judgment, interventions could take place at least 72 hours after the last dabigatran intake (5 missed doses). The decision to re-start treatment with dabigatran is at the investigator's discretion but should not occur prior to 7 days after major surgery. Patients should not re-start treatment with dabigatran after major surgery if there is a persistent increased risk of bleeding. The choice of alternative treatment is at the investigator's discretion. For minor procedures involving a critical organ such as lumbar or epidural punctures, interventions could only take place at least 72 hours after the last dabigatran intake (5 missed doses). The decision to re-start treatment with dabigatran is at the investigator's discretion but should not occur prior to 3 days after intervention.

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 risk and the thrombotic risk in each patient.

Dabigatran 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 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. 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.

SOC Treatment discontinuation for Elective and Acute Surgical Interventions

Local treatment guidelines should be followed for discontinuation and reintroduction of SOC in cases of planned or emergency surgery.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following treatments should not be taken with dabigatran:

- All VKAs
- Therapeutic unfractionated heparin or LMWH (heparin flushes of indwelling catheters is allowed) or fondaparinux
- Fibrinolytic agents (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)
  Note: Additionally fibrinolytic agents should not be taken within 48 hours prior to dabigatran administration.
- 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
  Note: Additionally P-glycoprotein inducers should not be taken within one week prior to dabigatran administration.
- Asparaginase - one week wash-out period to be considered (two weeks in case of PEG- Asparaginase)
- Any other investigational drug (with the exception of the 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 excluded but may be included 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. For more details please refer to Section 4.1.4.

SOC restrictions should be followed based on locally approved product labels.

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 or SOC. Subjects / parents / legal guardians will be asked to bring this completed log to every clinic visit which they will attend. Empty dabigatran capsule containers or solution vials or any unused drug should also be returned to the investigator's site for disposal and compliance calculation. Compliance should be calculated using the below equation preferably based on the returned medication (completed logs may also be used):

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

If an interruption of SOC or 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 allocated treatment and alternative therapy should be proposed in such cases.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

Primary endpoint:

Efficacy combined endpoint Proportion of patients with:

- Complete thrombus resolution and;
- Freedom from recurrent VTE (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism, thrombus progression) and;
- Freedom from mortality related to VTE.

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

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

Secondary endpoints:

- Freedom from major bleeding events (MBEs), defined as either fatal bleeding; clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L in a 24-hour period; bleeding that is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system; or bleeding that requires intervention in an operating suite.
- Pharmacokinetic and pharmacodynamic assessments at visit 3 (after at least six consecutive dabigatran doses) and after at least 3 days following any dabigatran dose adjustment
- Frequency of dose adjustments (i.e. Number of subjects with dose adjustment), temporary and permanent discontinuation from therapy and number of subjects with laboratory monitoring requirements for dose adjustment during the treatment phase
- Frequency of switch of type of anti-coagulation therapy (including dabigatran to SOC) (Frequency of subjects switching the type of anti-coagulation therapy including dabigatran etexilate to standard of care and switching from an intended standard of care treatment to another)
- Freedom from thrombus progression at end of therapy (day 84 after randomisation (Visit 8) or eEOT whichever comes first) compared to baseline
- Assessment of the acceptability of an age-appropriate formulation at end of therapy
- All bleeding events

- All-cause mortality
- All components of the primary efficacy endpoints

5.1.2 Assessment of efficacy

5.1.2.1 Physical examination

A complete physical examination will be completed for all patients at the time points noted in the Flow Chart. All abnormal findings at the screening visit will be recorded on the Medical History/Baseline Conditions eCRF page. New abnormal findings or worsening of baseline conditions detected at follow-up physical examinations will be recorded as AEs on the appropriate eCRF page, if judged clinically relevant by the investigator. A complete physical examination should be done when a patient discontinues the trial prematurely. In the event that clinically relevant findings are observed during the physical examination at the end of the study (or at early withdrawal from the trial), the patient should be followed by the investigator until resolution of the event, or an agreement has been made with the sponsor that follow-up is sufficient on that patient.

5.1.2.2 Venous thromboembolism assessment

In case of suspected 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 PTS: 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)
- Suspected paradoxical embolism (PDE): CT / MR angiography or other appropriate evaluation

The final assessment (at end of therapy) of the resolution status of the thrombus must be done using the same method as the baseline evaluation when appropriate.

Note: If clinical evaluations warrant imaging (e.g. suspected thrombus extension), then per investigator judgment, appropriate imaging may be performed. When feasible, a baseline radiological assessment (e.g. CT) may be supplemented with an acceptable non-radiological assessment (e.g. MRI) at baseline which could then be repeated at the end of therapy (study day 84 (visit 8) or eEOT, whichever comes first) hence alleviating any potential unwarranted radiation exposure.

5.1.2.3 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 SAFETY

5.2.1 Endpoints of safety

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

Other safety endpoints:

- Incidence of bleeding events including:
    - Major bleeding events; clinically relevant non-major bleeding events (CRNM), minor bleeding events and any bleeding events
    - Combined endpoint of major and CRNM bleeding events
- Incidence of adverse events, protocol-specified AESI and serious adverse events
- Treatment discontinuation due to an adverse event
- Change from baseline in safety laboratory values, vital signs and physical examination
- Global assessment of tolerability (measured as treatment discontinuation and adherence) to study medication

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 in a clinical investigation 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.

- 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 chapter 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 onwards through the follow-up period) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific

definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

The end of residual effect period (REP) for dabigatran etexilate and SOC is set at 6 days after last drug administration. Therefore all events reported within 6 days of the last trial medication will be considered on treatment. All adverse events will be reported up until the end of the follow-up period, which is approximately 16 weeks after randomization.

Post Study:
The investigator may report SAEs which occurred in a subject after the end of the follow-up period, if the investigator becomes aware of them.

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 or the next business day whichever is shorter) 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 RDC.

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 of awareness) to the defined unique entry point for SAE forms of the respective BI OPU (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 lab will be used for the analysis of the standard safety laboratory panel, see Appendix 10.1. If needed and when feasible a local laboratory may alternatively be used for dTT testing to evaluate dabigatran concentration. Local safety lab assessment is acceptable in emergency cases (e.g. bleeding event or emergency surgery). Furthermore local lab assessment of PT (prothrombin time)/ INR (international normalized ratio), aPTT (activated partial thromboplastin time) or Anti-Factor Xa activity for coagulation monitoring in SOC patients is an acceptable alternative to central lab testing. Refer to the Flow Chart and Section 5.7.2 for additional information.
If a patient has already begun treatment with VKA, a local lab will be used for INR measurement at Visit 2 to confirm eligibility.

An aPTT assessment at Visit 3 (taken locally) will be performed for all patients < 2 months of age. Patients < 2 months must have a locally performed baseline (i.e. before start of any anticoagulant therapy) aPTT measurement available.

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 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. 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)
- if applicable, pockets should be emptied of heavy objects (i.e. keys, coins, etc.)

5.3.2 Other assessments

5.3.2.1 Acceptability and tolerability of age appropriate formulations

Acceptability is defined as the overall ability and willingness of the patient and/or parent (legal guardian) to use the medicinal product as intended.

The global clinical assessment of acceptability will be performed by the patient (if old enough per investigator judgment) or by the parent / legal guardian.

In between study visits, the parent /legal guardian will be asked to document any failed or missed intake of medication (e.g. the patient did not swallow the medication, or doses missed, etc.) and provide this documentation to the investigator at the next study visit. The parent / legal guardian will be instructed to inform the investigator immediately if two or more consecutive doses of study medication are missed or not taken correctly.

In addition, for patients taking OLF, the acceptability will be described by the parent / legal guardian's ability to administer the medicine as intended (under consideration of total volume to be administered and swallowed by the patient). It is determined by the caregiver based on his assessment of medication intake by the patient, and may depend on palatability of the study medication.

5.4 APPROPRIATENESS OF MEASUREMENTS

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.5.1 Pharmacokinetic endpoints

Exposure of dabigatran as assessed by measurement of the following plasma concentrations for total (after alkaline cleavage of glucuronide conjugates) dabigatran.

- $C_{pre,ss}$ (pre-dose concentration of the analyte in plasma at steady state immediately before administration of the next dose) taken at 10 to 16 hours after the last dose (trough)

- $C_{2,ss}$ (concentration of the analyte in plasma at steady state at 2 hours after administration of the last dose) taken at 1 to 3 hours after the last dose (peak)

The dabigatran dose administered to patients may be adjusted based on the determined pre-dose dabigatran plasma concentration ($C_{pre,ss}$) at Visit 3 or at other future visits as needed.

5.5.2 Methods of sample collection

Approximately 28.8 mL blood will be taken per subject during the whole course of the study for pharmacokinetic/pharmacodynamic purposes.

5.5.2.1 Plasma sampling for pharmacokinetic analysis

The visits where the pharmacokinetic (PK) samples are taken are noted in the Flow Chart. The date and exact clock time a PK sample is 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 PK sample collection should be recorded in the eCRF. About 8.4 mL of blood (approximately 1.2 mL per sampling time point) in total per patient is planned for collection for the PK samples.

5.5.3 Analytical determinations

Analytical determination of total dabigatran will be performed by a validated high performance liquid chromatography – tandem mass spectrometry (HPLC-MS/MS) assay at a central laboratory. The procedure and specification of the analytical method are available at the analytical laboratory.

5.6 BIOMARKERS

Refer to section 5.7

5.6.1 Endpoints based on biomarkers

Refer to section 5.7

5.6.2 Methods of sample collection

Refer to section 5.7

5.6.3 Analytical determinations

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) will be employed for the quantitative measurement of dabigatran concentrations. The analysis of dTT will be done by a central laboratory. If centralized dTT testing is not possible, dTT may also be analysed by a local laboratory. In case the use of the dTT assay is not feasible, an alternative method may be used. The dabigatran dose administered to patients may be adjusted at Visit 3 or other future visits as needed, based on the assessment of dabigatran plasma levels.

5.7.2 Methods of sample collection

The collection time point for aPTT + ECT + dTT (Anti-Factor IIa activity) (for dabigatran-assigned patients) and potentially other exploratory coagulation markers (for all patients) 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 are 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 treatment period and a follow-up period.

During the treatment period, patients will receive open-label dabigatran etexilate or SOC. Dabigatran dose selection and titration instructions are described in Section 4.1.3; detailed instructions are also located in the ISF.

All required assessments and procedures are listed in the Flow Chart and are further described in Section 5.

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).

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).

6.2.2 Treatment period

Before giving the first dose of study medication, eligibility must be confirmed. Throughout the treatment period, unscheduled visits and titration visits can be scheduled at any time to optimize dabigatran or SOC VTE treatment.

For the schedule of assessments and procedures during the treatment period refer to the Flow Chart. For information on dose selection refer to Section 4.1.3. For details on PK and PD sample collection and analyses refer to Section 5.5 and Section 5.7.

6.2.3 End of trial and follow-up period

Patients who complete the treatment period and are not enrolled into the secondary VTE prevention study (BI trial 1160.108) are to be followed at Visit 9. For the schedule of assessments and procedures to be done at the follow-up visit refer to the Flow Chart.

All patients who prematurely discontinue study medication will be invited to perform an eEOT Visit and the follow-up Visit 9, taking place 28 days thereafter. Subsequently they will be followed-up preferably 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 done.

Patients having switched from dabigatran etexilate to SOC are considered as having early discontinuation of dabigatran etexilate treatment. However, such patients will still remain in the trial and will be followed as per the visit schedule till the end of the study. Patients having switched from one SOC to another during the treatment period, are not considered as having early discontinuation of treatment and should remain in the treatment period and be followed as per the visit schedule till the end of the study.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The study is designed to assess the efficacy and safety of dabigatran etexilate using a dosing algorithm to SOC for treatment and/or secondary prevention of paediatric VTE in patients from birth to less than 18 years of age. This trial is a prospective, multicentre, international, open-label, randomized, parallel-group, non-inferiority study comparing dabigatran etexilate to SOC.

7.2 NULL AND ALTERNATIVE HYPOTHESES

This trial is designed to provide evidence of efficacy and safety in paediatric patients by showing non-inferiority of dabigatran compared with SOC for paediatric VTE treatment. For the primary endpoint, proportion of patients with complete thrombus resolution, with no recurrent VTE and no VTE-related death, the non-inferiority hypothesis is:

H_{01}: $p_{1C} - p_{1D} \geq \delta_1$ vs. H_{11}: $p_{1C} - p_{1D} < \delta_1$ for the primary endpoint ($\delta_1 = 20\%$)

The selection of non-inferiority margin ($\delta_1 = 20\%$) is summarized in Section 7.6.

Upon showing significance of non-inferiority for the primary endpoint using 90% confidence interval, test of superiority will be performed subsequently at one-sided level of 0.05 in the following order without multiplicity correction.

H_{03}: $p_{1C} - p_{1D} \geq 0$ vs. H_{13}: $p_{1C} - p_{1D} < 0$ for the primary endpoint

The efficacy and safety of dabigatran for VTE treatment have been established in adult studies (U09-1400-01 and U11-2298-01). The objective of this paediatric trial is to confirm the dosing algorithm for paediatric patients and to provide evidence of efficacy and safety of dabigatran treatment in paediatric population. Therefore the one-side statistical significance level of 0.05 is considered adequate. The sample size and power calculations are detailed in Section 7.6.

7.3 PLANNED ANALYSES

The following analysis populations will be defined:

The randomized set (RS) will include all randomized patients in the treatment groups to which they are randomized. The intent-to-treat (ITT) principle will be applied to the randomized set including events from the time of randomization to the time point of interest (e.g. visit 8 for the primary efficacy endpoint). Patients who terminate the study medication prematurely will be followed and the events which occur after premature discontinuation of medication and before the time point of interest will be included in the analysis using the randomized set.

The treated set (TS) will include all patients who are dispensed study medication and are documented to have taken at least one dose of study medication in the treatment groups according to their initial treatment. The analyses using the treated set will include the efficacy and safety endpoint events which occur from the date of first drug administration to visit 8 or date of last drug administration + 6 days if discontinued prematurely.

The pharmacokinetic set (PKS) will include all treated patients with at least one PK/PD measurement and having no protocol violations relevant to the evaluation of PK or PD endpoints.

More details will be specified in the TSAP.

7.3.1 Primary analyses

The primary efficacy endpoint, proportion of patients with complete thrombus resolution and freedom from recurrent VTE or mortality related to VTE, will be analysed following the ITT principle on the randomized set. Age group will be used as stratification factor using a Mantel-Haenszel type weighted average of differences with weights as proposed by Greenland and Robins (R09-1299).

The primary analyses for primary endpoints will include only adjudicated events.

The planned analyses are summarized in Table 7.3.1: 1 for each population set. More details and additional analyses will be specified in TSAP if deemed necessary.

Table 7.3.1: 1 Summary of planned analyses

Population / analysis	Intent-to-treat analysis (from randomization to the time point of interest)	On-treatment analysis (from treatment start to drug stop date + 6 days)
Randomized set	1. Primary efficacy endpoint: primary and secondary analysis 2. Secondary efficacy endpoints 4. All cause mortality	
Treated set		1. Major bleeding events analysis 4. All cause mortality

7.3.2 Secondary analyses

Secondary analyses of primary endpoint

Secondary analysis of the proportion of patients with complete thrombus resolution, with no recurrent VTE and no VTE-related death will consider age group as covariate and the treatment and age group interaction in a logistic regression model using ITT as the primary analysis.

Analyses of secondary endpoints

Major bleeding events will be analysed as time-to-event endpoint using Kaplan-Meier method. The proportion of patients free from major bleeding events at the end of planned treatment period (84 days (Visit 8) or eEOT) will be provided by Kaplan-Meier estimates for the two treatment arms pooling all age groups. Due to the low event rate of major bleeding, age group stratification will not be considered in the primary model for this endpoint. The confidence interval of proportion difference will be calculated based on Kaplan-Meier estimates and its variances. This safety analysis will be based on the treated set which will include events that occur between the date of first dose of study medication to the date of last dose of medication plus six-days (on treatment analysis). Patients who do not have major bleeding events during the treatment period and patients who discontinue from the trial prematurely without having major bleeding events will be censored. For patients who have more than one event during the trial, the time to the first occurrence of the event will be considered for the analysis.

Pharmacokinetic and pharmacodynamic analyses will be summarized in Section 7.3.5 and Section 7.3.6.

Frequency of dose adjustments, temporary and permanent discontinuation from therapy, number of laboratory monitoring requirements for dose adjustment during the treatment phase and frequency of switch of type of anti-coagulation therapy (including dabigatran to SOC) will be summarized descriptively for each treatment arm.

Freedom from thrombus progression at baseline will be summarized descriptively and for each treatment arm. Frequency of patients free from thrombus progression at day 84 after randomization (or eEOT, whichever comes first) will be analysed descriptively.

The assessment of the acceptability of an age-appropriate formulation at the end of therapy will be provided descriptively.

All bleeding events and all-cause mortality will be analysed as time-to-event endpoint using stratified Cox proportional hazard model with treatment being a factor in the model and age group as stratification factor. A pooling of age groups might be necessary if no event is observed in certain age group.

The components of the primary efficacy endpoint will be analysed as proportions using the same model as the primary analysis.

7.3.3 Safety analyses

Major bleeding events will be analysed as a secondary endpoint. All bleeding events and combined endpoint of major and clinical-relevant bleeding events will be analysed by the Cox proportional hazards model with treatment being the factor and stratified by age group if appropriate. Pooling of age groups or non-stratified analysis might be performed if the event rate is low. All safety analyses as well as all bleeding events and all-cause mortality analysed as efficacy endpoints will be performed on the treated set.

The safety analysis set will include all randomized patients who take at least one dose of study medication. Patients in the safety population will be analysed according to the study treatment they have received. The safety analyses will be descriptive in nature and will be based on BI standards. The safety analyses will include the following parameters:

- All AEs
- protocol-specified AESI
- serious AEs
- AEs leading to treatment discontinuation

AEs will be coded using the MedDRA dictionary. All AEs will be classified according to the following trial periods: screening, on-treatment, post treatment. All AEs with an onset date/time after the 1st dose of trial medication up to 6 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.

Other lab data, vital signs, physical examinations data and ECG data will be reported descriptively.

7.3.5 Pharmacokinetic analyses

The analysis of the PK/PD parameters will be performed on PKS.

All concentrations will be listed and summarized descriptively. The concentrations will be compared descriptively with the exposure observed in adult patients or healthy subjects previously.

PK data from this study along with data from other trials in the dabigatran program will be used to further refine the adult population pharmacokinetic model, allowing it to be used for the generation of predictions optimized for paediatric populations. The results of this model refinement will be reported separately.

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.

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

Missing data will not be imputed in general. For complete thrombus resolution assessment, if the assessment at Visit 8 (84 days) is missing, then the last observation at eEOT visit will be carried forward providing there is no VTE related events occurred between the two visits. All patients will be followed to collect necessary efficacy and safety information, even if patients discontinue study medication prematurely.

7.5 RANDOMISATION

Interactive response technology (IRT) will be used to randomize patients to treatment groups. The randomization will be performed in blocks and stratified by age groups, and the allocation ratio will be 2:1 for dabigatran to SOC. The randomization list will be generated using a validated system, which involves a pseudo-random number generator to guarantee the reproducibility of the assignments. In addition, patients assigned to dabigatran OLF will be

randomized based on 1:1 ratio to receive flavoured or unflavoured solvent for reconstitution. This randomization list will be checked by an independent statistician and will be used by a third-party IRT to assign randomization numbers to eligible patients.

7.6 DETERMINATION OF SAMPLE SIZE

After an extensive literature search, 11 articles which were relevant to thrombus resolution in paediatric patients with VTE (R07-2937, P16-07690, P08-12132, P11-06995, P14-05231, R16-2873, R16-2876, R16-2877, R16-2878, R16-2879, P16-03657) were included in a meta-analysis of the complete thrombus resolution rate using SOC anticoagulants (predominantly low-molecular weight heparins or vitamin K antagonists) after a careful screening. Most of the studies are not randomized controlled clinical trials. However, a Bayesian meta-analysis concluded a stable mean complete thrombus resolution rate of 72% using data from the 11 studies. This rate was used as the assumption which both dabigatran etexilate and SOC would have achieved in this trial.

A complete thrombus resolution rate without treatment cannot be established from recent publications. It is uncommon to see patient completely without treatment, and the rate of complete thrombus resolution is believed to be low. This is specifically true for cases not involving a central line, such as DVT/PE, which will represent the majority of case in this trial. Central line thrombosis, which has a potentially better resolution rate due to catheter removal, is predominantly expected to occur in younger children (below the age of approximately 2 years). However, the number patients in stratum 3 is approximately 15 only, therefore, the number of central line thrombosis in this trial is expected to be low overall. Thus, the clot resolution rate under no treatment in this trial is predominantly resulting from the DVT/ PE cases included.

In the absence of solid evidence of spontaneous thrombus resolution, a precise effect size is difficult to be determined. As an alternative, a wide range of plausible complete thrombus resolution rate without treatment (5% to 20%) have been considered, and it has been demonstrated that the proposed 20% non-inferiority margin can preserve at least 62% and up to 70% of the effect size under SOC treatment.

Table 7.6: 1 Effect size preserved by 20% NI margin

Complete thrombus resolution rate of SOC (based on meta-analysis result)	72%			
Complete thrombus resolution rate without treatment (plausible assumptions)	5%	10%	15%	20%
Effect size preserved by 20% NI margin	70%	68%	65%	62%

With a total sample size of 141 patients and a 2:1 randomization to dabigatran and SOC, respectively, approximately 94 patients will be randomized to receive dabigatran and approximately 47 patients to receive SOC. The following simulation has been performed to consider the variability in the estimate of the complete thrombus resolution rate. Assuming the number of complete thrombus resolution follows binomial distribution with unknown probability of success, the estimates of the complete thrombus resolution rate are subject to the variability of this distribution. One hundred thousand binomial samples were generated

for dabigatran arm and SOC arm, with 94 and 47 patients respectively. The lower bound of the 90% confidence interval was calculated for each simulation using:

$$\hat{p}_{dabi} - \hat{p}_{soc} - 1.64 \times \sqrt{\frac{\hat{p}_{dabi}(1-\hat{p}_{dabi})}{94} + \frac{\hat{p}_{soc}(1-\hat{p}_{soc})}{47}}$$

where, $\hat{p}_{dabi}$ and $\hat{p}_{soc}$ are point estimates of the complete thrombus resolution rates of dabigatran arm and stand of care arm from each simulation. Samples are generated from binomial distribution assuming the true complete thrombus resolution rates are p_{dabi} and p_{soc}, respectively. The proportions of the lower bound above the non-inferiority margin among the 100,000 simulations are provided in the table below, under various assumptions of binomial distributions.

Table 7.6: 2 Summary of power estimates for primary efficacy endpoint with a sample size of 141

Assumptions used in generating simulated samples	Power of 90% CI lower bound above the non-inferiority margin -20%
Superior assumption: (p_{dabi}, p_{soc}) = (0.77, 0.72)	95%
Non-inferior assumption: (p_{dabi}, p_{soc}) = (0.72, 0.72)	82%
Suboptimal assumption: (p_{dabi}, p_{soc}) = (0.68, 0.72)	63%
Extremely conservative but non-inferior assumption: (p_{dabi}, p_{soc}) = (0.62, 0.72)	33%
Inferior assumption: (p_{dabi}, p_{soc}) = (0.52, 0.72)	5% (false positive)

Under the assumption that the true unknown complete thrombus resolution rate is 72% of both dabigatran and SOC, the proposed sample size of 141 is sufficient to demonstrate non-inferiority with adequate power (82%).

If the complete thrombus resolution rate in dabigatran is truly lower than the SOC, the chance of showing non-inferiority drops to 33% when the difference is 10% (complete thrombus resolution rate 62% vs 72% for dabigatran and SOC, respectively), and to below 5% when the non-inferiority margin of 20% is reached (complete thrombus resolution rate 52% vs 72% for dabigatran and SOC, respectively).

However, the most likely scenario for the paediatric population is to assume similar thrombus resolution rates with both dabigatran and SOC, based on the following considerations: primary efficacy results obtained from adult VTE RE-COVER-trials (P13-16985) demonstrated robust non-inferiority. In addition, it is the expectation that the gMean trough concentration in the paediatric trials will exceed the average trough exposure of RE-COVER due to the option of up-titration of the dose if initial exposure is < 50 ng/ml compared to fixed dosing in the adult trials. Therefore the Sponsor considers the sample size and 20% margin are reasonably sensitive to evaluate non-inferiority in the paediatric population. See Table 7.6: 3 for summary.

Table 7.6: 3 Summary of power estimates for the primary endpoint with a sample size of 141

One-sided confidence level	Primary endpoints (non-event rate)	True rate difference	Margin for rate difference	Power[#]
90%	72%	0.0%	20%	82%
95%	72%	0.0%	20%	71%

[#] Power for the non-inferiority approach is computed as the proportion of 100,000 simulations in which the observed upper bound of one-sided confidence intervals for $p_{1C} - p_{1D}$ and $p_{2C} - p_{2D}$ (assuming 94 and 47 evaluable patients in dabigatran arm and control arm, respectively) are below the specified equivalence margin. The confidence interval for the VTE endpoint is estimated by Newcombe-Wilson method (R08-4386).

A discontinuation rate of up to 15% before the completion of at least 3 months treatment with dabigatran has been estimated for both 1160.106 and 1160.108 trials. 94 patients will be randomized to receive dabigatran in 1160.106 trial. It is estimated that there will be 120 patients entering 1160.108 by end of recruitment. Assuming that 20% of 1160.106 dabigatran patients will be rolled over to 1160.108, this would result in roughly 101 of the 120 total patients receiving dabigatran treatment in 1160.108 trial to be unique patients. Across both trials, this would result in 94 + 101 = 195 unique patients treated with dabigatran. With a discontinuation rate of 15% (i.e. stop of treatment earlier than 3 months), a total of 166 unique patients are expected to complete at least 3 months of dabigatran treatment in both trials together.

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 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 each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. 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 and any additional patient information must be given to each patient or the patient's legally accepted representative. 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.

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 the dabigatran this is the current version of the Investigator's Brochure (c01632884). For Standard of Care this is the EU sPC. No AEs are classified as listed for 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.

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10. APPENDICES

10.1 SAFETY AND OTHER CLINICAL LABORATORY EVALUATIONS

Standard Safety Lab Panels may 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 lab tests:	
Serum pregnancy test performed on all female patients who have reached menarche	
Prothrombin Time (PT) / INR (International Normalized Ratio)	
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 only if performing dTT is not feasible)	
Anti-factor Xa activity	

Other potential locally evaluated lab tests / exploratory biomarkers:
Diluted Thrombin Time (dTT) to evaluate dabigatran concentration – *in case locally required and feasible*
Safety Lab Panel – only in case of emergency (e.g. bleeding event or emergency surgery)
INR at Visit 2 – to confirm eligibility in case VKA pre-treatment has been already initiated
aPTT at Visit 3 – for expedited bleeding risk assessment in patients < 2 months of age
PT/INR, aPTT or Anti-Factor Xa activity - for routine coagulation monitoring in SOC patients

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, PK/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
Chemistry	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
PK			1,2	1,2	2,4	1,2	1,2	1,2	
PD		1,2	1,2	1,2	2,4	1,2	1,2	1,2	
dTT			1,2	1,2	2,4	1,2	1,2	1,2	
Exploratory coagulation markers		1,2						1,2	
Total (per visit)	5,5	7,9	9,1	9,1	12,7	9,1	9,1	10,3	5,5
4 weeks interval	31,6				21,8		19,4		5,5
Total (for trial - 4 months)	78,3								

- 2 to <6 years

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

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Chemistry	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
PK			1,2	1,2	2,4	1,2	1,2	1,2	
PD		1,2	1,2	1,2	2,4	1,2	1,2	1,2	
dTT			1,2	1,2	2,4	1,2	1,2	1,2	
Exploratory coagulation markers		1,2						1,2	
Total (per visit)	3,8	6,2	7,4	7,4	11	7,4	7,4	8,6	3,8
4 weeks interval	24,8				18,4		16		3,8
Total (for trial - 4 months)	63								

- 0 to < 2 years

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

	V1	V2	V3	V4	V5	V6	V7	V8	V9
Chemistry	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
PK			1	1	2	1	1	1	
PD		1,2	1,2	1,2	2,4	1,2	1,2	1,2	
dTT			1,2	1,2	2,4	1,2	1,2	1,2	
Exploratory coagulation markers		1,2						1,2	
Total (per visit)	2,7	5,1	6,1	6,1	9,5	6,1	6,1	7,3	2,7
4 weeks interval	20				15,6		13,4		2,7
Total (for trial - 4 months)	51,7								

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 in Section 5.2.2.1), 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 an 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, ceruloplasmin, α-1 antitrypsin, transferrin, 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, Antimitochondrial antibody. The need for hepatitis serology to be assessed by the investigator based on patient age and clinical presentation.

Hormones, tumor marker

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 subjects 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 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.

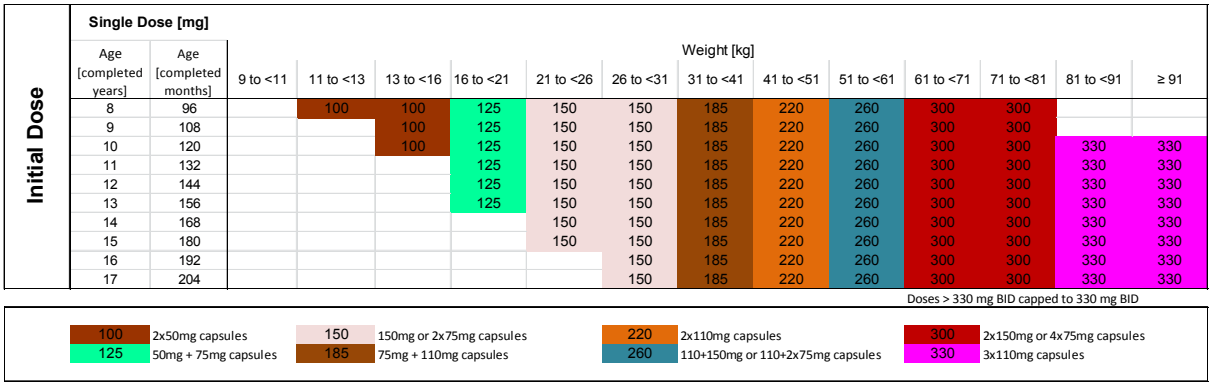
Patients aged < 12 months: Age and weight adjusted dabigatran etexilate OLF or any other alternative age-appropriate formulation. For patients < 12 months of age, OLF is preferred over pellets provided that OLF supplies are available to the site.

Dabigatran etexilate is taken twice daily (BID).

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

10.3.1 Dosing nomogram (starting doses)

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



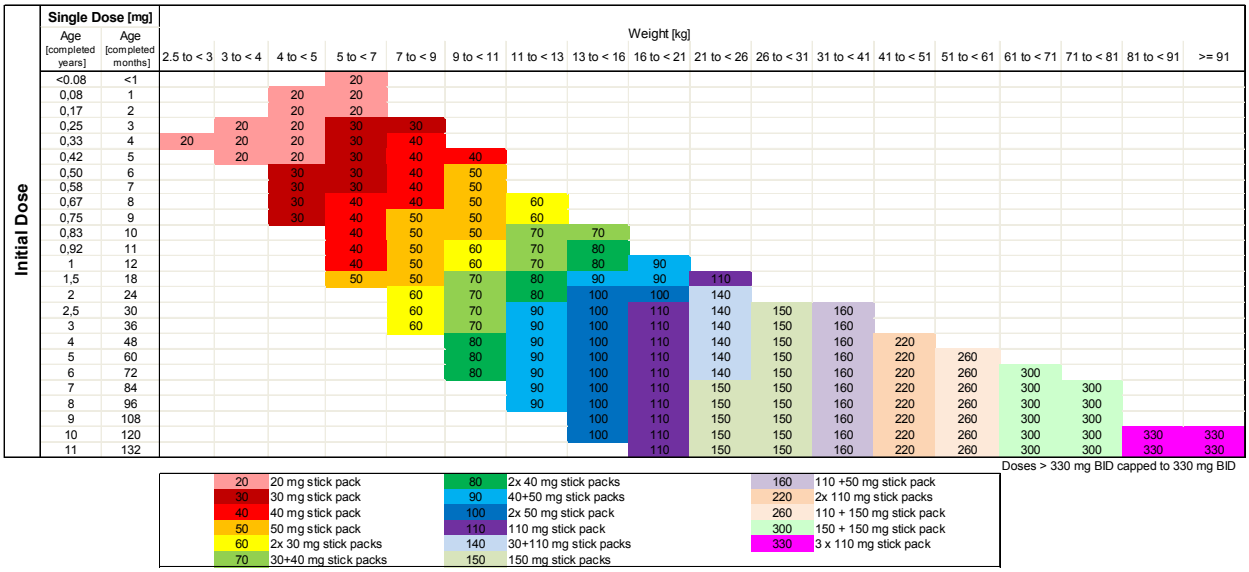
Initial Dose – Single Dose [mg]																
Age [completed years]	Age [completed months]	Weight [kg] 9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31	31 to <41	41 to <51	51 to <61	61 to <71	71 to <81	81 to <91	≥ 91
8	96		100	100	125	150	150	185	220	260	300	300		
9	108			100	125	150	150	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	150	150mg or 2x75mg capsules	220	2x110mg capsules	300	2x150mg or 4x75mg capsules
125	50mg + 75mg capsules	185	75mg + 110mg capsules	260	110+150mg or 110+2x75mg capsules	330	3x110mg capsules

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

- *dabigatran etexilate pellets*



Initial Dose – Single Dose [mg]																						
Age [completed years]	Age [completed months]	Weight [kg] 2.5 to < 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	31 to < 41	41 to < 51	51 to < 61	61 to < 71	71 to < 81	81 to < 91	>= 91
<0.08	<1				20														
0,08	1			20	20														
0,17	2			20	20														
0,25	3		20	20	30	30													
0,33	4	20	20	20	30	40													
0,42	5		20	20	30	40	40												
0,50	6			30	30	40	50												
0,58	7			30	30	40	50												
0,67	8			30	40	40	50	60											
0,75	9			30	40	50	50	60											
0,83	10				40	50	50	70	70										
0,92	11				40	50	60	70	80										
1	12				40	50	60	70	80	90									
1,5	18				50	50	70	80	90	90	110								
2	24					60	70	80	100	100	140								
2,5	30					60	70	90	100	110	140	150	160						
3	36					60	70	90	100	110	140	150	160						
4	48						80	90	100	110	140	150	160	220					
5	60						80	90	100	110	140	150	160	220	260				
6	72						80	90	100	110	140	150	160	220	260	300			
7	84							90	100	110	150	150	160	220	260	300	300		
8	96							90	100	110	150	150	160	220	260	300	300		
9	108								100	110	150	150	160	220	260	300	300		
10	120								100	110	150	150	160	220	260	300	300	330	330
11	132									110	150	150	160	220	260	300	300	330	330

Doses > 330 mg BID capped to 330 mg BID

20	20 mg stick pack	80	2x 40 mg stick packs	160	110 +50 mg stick pack
30	30 mg stick pack	90	40+50 mg stick packs	220	2x 110 mg stick packs
40	40 mg stick pack	100	2x 50 mg stick pack	260	110 + 150 mg stick pack
50	50 mg stick pack	110	110 mg stick pack	300	150 + 150 mg stick pack
60	2x 30 mg stick packs	140	30+110 mg stick packs	330	3 x 110 mg stick pack
70	30+40 mg stick packs	150	150 mg stick packs		

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

- dabigatran etexilate OLF - 6.25 mg per mL

Initial Dose

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

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

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

10.3.2 Dose Adjustment nomogram

10.3.2.1 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

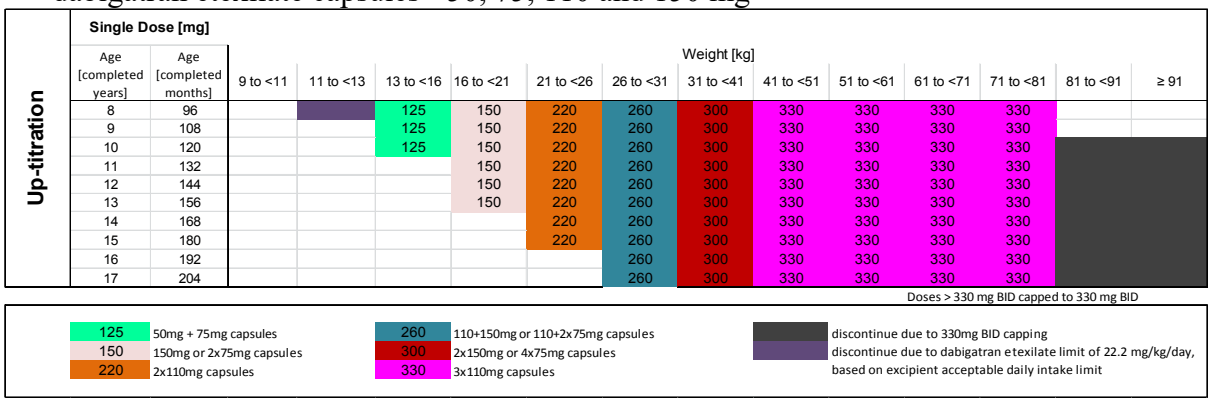


Figure 10.3.2.1: 1 Up-titration doses using capsules

- *dabigatran etexilate pellets*

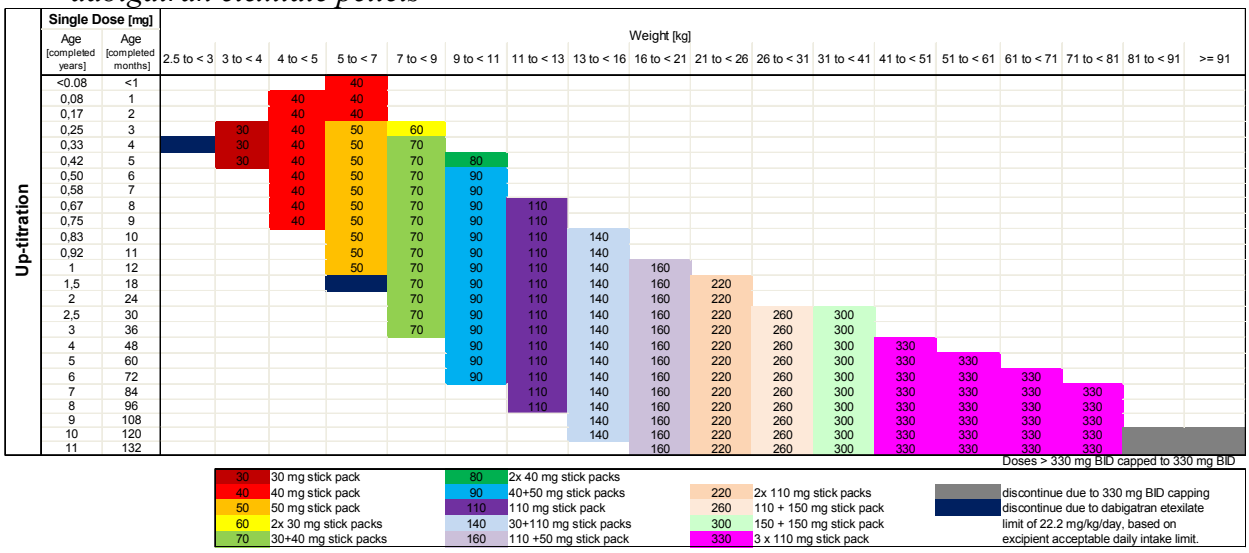


Figure 10.3.2.1: 2 Up-titration doses using pellets

- 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 10.3.2.1: 3 Up-titration doses using OLF

10.3.2.2 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]

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

Figure 10.3.2.2: 1 Down-titration doses using capsules

- dabigatran etexilate pellets

Down-titration

Single Dose [mg]

Age [completed years]	Age [completed months]	Weight [kg] 2.5 to < 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	31 to < 41	41 to < 51	51 to < 61	61 to < 71	71 to < 81	81 to < 91	>= 91
<0.08	<1																		
0,08	1																		
0,17	2																		
0,25	3				20	20													
0,33	4				20	20													
0,42	5				20	20	20												
0,50	6			20	20	20	30												
0,58	7			20	20	20	30												
0,67	8			20	20	20	30	30											
0,75	9			20	20	30	30	30											
0,83	10				20	30	30	40	40										
0,92	11				20	30	30	40	40										
1	12				20	30	30	40	40	50									
1,5	18				30	30	40	40	50	50	50								
2	24					30	40	40	50	50	80								
2,5	30					30	40	50	50	60	80	80	80						
3	36					30	40	50	50	60	80	80	80						
4	48						40	50	50	60	80	80	80	110					
5	60						40	50	50	60	80	80	80	110	150				
6	72						40	50	50	60	80	80	80	110	150	150			
7	84							50	50	60	80	80	80	110	150	150	150		
8	96							50	50	60	80	80	80	110	150	150	150		
9	108								50	60	80	80	80	110	150	150	150		
10	120								50	60	80	80	80	110	150	150	150	170	170
11	132									60	80	80	80	110	150	150	150	170	170

Doses > 330 mg BID capped to 330 mg BID

20 20 mg stick pack
30 30 mg stick pack
40 40 mg stick pack
50 50 mg stick pack
60 2x 30 mg stick packs
80 2x 40 mg stick packs
110 110 mg stick pack
150 150 mg stick pack
170 110 + 2x30 mg stick packs

Figure 10.3.2.2: 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	18.75	3 mL
12.50	2 mL	25.00	4 mL
31.25	5 mL		
37.50	6 mL		

Figure 10.3.2.2: 3 Down-titration doses using OLF

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		01
Date of CTP revision		*02 Oct 2014*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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 trial status. 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*

Section to be changed		Title Page
Description of change		*Trial Clinical Monitor*
Rationale for change		*Personal change*

Number of global amendment		02
Date of CTP revision		*28 Jan 2015*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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 have been updated to reflect the change of age cut-offs of strata 2 and 3 ☐
Description of change		*Based on European Medicines Agency's Paediatric Committee (PDCO) final opinion and the European Medicines Agency's decision (dated 29 September 2014),the age cut-offs of strata 2 and 3 have been changed as follows:* • *Stratum 2 - from "from 1 to < 12 years of age" to "from 2 to < 12 years of age"* • *Stratum 3 - from "from birth to < 1 year of age" to " from birth to < 2 years of age"*
Rationale for change		*The change will facilitate the recruitment in this study by allowing for earlier opening of stratum 2 (based on availability of respective phase IIa PK*

		data) and support a more timely completion of the clinical phase IIb/III program.

Section to be changed		All relevant sections of the CTP have been updated to modify the minimum number of patients required for strata 2 and 3
Description of change		*A minimum of 240 evaluable patients for the efficacy component of the co-primary endpoint including a minimum of: 80 patients in age stratum 1 (from 12 to < 18 years of age),* ***75*** *patients in age stratum 2 (from 12 to < 12 years of age) and* ***25*** *patients in age stratum 3 (from birth to < 2 years of age).* ***At least 20 patients in stratum 3 must be below one year of age.***
Rationale for change		*To reflect the change of age cut-offs of strata 2 and 3 based on European Medicines Agency's Paediatric Committee (PDCO) opinion and the European Medicines Agency's decision (dated 29 September 2014)*

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 10.3*
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 stratum 2*

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 stratum 3 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 stratum 3 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		3.3.3 Exclusion criteria
Description of change		*Additional exclusion criterion was introduced:* *7) Patients in stratum 3 (0 to < 2 years) with gestational age at birth < 37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards)*
Rationale for change		*To exclude very vulnerable population*

Section to be changed		3.3.3 Exclusion criteria
Description of change		*Exclusion criterion 1c was changed to:* *Any major planned procedure that might put the patient at an increased risk of a bleed per investigator judgment within 5 days* ~~*of*~~ ***prior to*** *taking study medication*
		Exclusion criterion 6 was modified to list the acceptable methods of birth control
Rationale for change		*Clarification*

Section to be changed		All relevant sections of the CTP
Description of change		*It was clarified that all patients who continue treatment for VTE, regardless of whether this is a switch from dabigatran etexilate to SOC or from one SOC to another, are not considered early discontinued. These patients remain in the treatment period and should follow the remaining visit schedule until the end of the study*
Rationale for change		*Clarification*

Section to be changed		5.5.2 Methods of sample collection (PK) and 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 PK/PD samples are taken is to be recorded in the eCRF*
Rationale for change		*To ensure precise assessment of the pharmacokinetic-pharmacodynamic relationship*

Section to be changed		Flow Chart footnote L 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 B, 3.3.4 Removal of patients from therapy or assessments and 5.5.1 Pharmacokinetic endpoints
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		*Any other investigational drug was added to the restricted medications.* *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*

Section to be changed		All relevant sections of the CTP
Description of change		*The assessment of the patient's ability to swallow capsules with test placebo capsules was removed from the protocol*
Rationale for change		*In everyday paediatric practice, caregivers are usually aware about the ability of their child to swallow capsules of a size comparable to the dabigatran etexilate capsules. In case of any unexpected difficulties in acceptance of capsules, dabigatran etexilate pellets will be introduced to the child.*

Number of global amendment		03
Date of CTP revision		*26 Nov 2015*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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		10.3.2 Dose Adjustment nomogram 10.3.2.1 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		10.3.1 Dosing nomogram (starting doses) 10.3.2 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 age stratum 3*

Number of global amendment		04
Date of CTP revision		*16 Mar 2016*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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		*The assessment of thrombus extension at visit 5 was removed from the protocol. The related secondary were modified accordingly*

Rationale for change		*To better reflect the clinical routine for follow-up of patients with VTE. To eliminate potential unwarranted radiation exposure and to reduce trial complexity.* *In case needed (e.g. suspected recurrent VTE) thrombus assessment, using appropriate imaging modalities, will be performed during an unscheduled visit.*
Section to be changed		All relevant sections of the CTP
Description of change		*The assessment of 12-lead resting-ECG (5 min supine) at visit 5 was removed from the protocol*
Rationale for change		*To reduce trial complexity. This additional ECG does not follow clinical standard of care and is not considered necessary in the context of treatment with dabigatran.*

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 capsules, pellets and OLF reconstituted with flavoured or unflavoured solvent at days 3(V3), 21 (V5) and 84(V8) or eEOT after randomization was introduced as other endpoint*
Rationale for change		*To evaluate the acceptability of capsules, pellets and OLF reconstituted with flavoured or unflavoured solvent types in a comparable number of patients*

Section to be changed		FLOW CHART
Description of change		*The time window for Visit 4 was extended to +7 days* *Visit 5 should be performed at least 3 days after visit 4 (footnote Y)*

Rationale for change		*To allow the sites to receive first PK results before Visit 4 and to adjust the dose of dabigatran (if needed) as early as possible.*
Section to be changed		FLOW CHART footnote E
Description of change		*eEOT visit will not be required in case of switching between different types of SOC treatments*
Rationale for change		*To eliminate unnecessary patient procedures. A patient switching SOC treatment types is still considered to be on treatment and eEOT visit is not required.*

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 as it is a prerequisite for opening stratum 2*

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		3.1 Overall trial design and plan
Description of change		*It was clarified that patients requiring VTE therapy beyond 3 months have to be switched at Visit 8 (day 84) to SOC treatment (if randomized to dabigatran etexilate) or continue SOC treatment (if randomized to the SOC arm) and could be maintained on SOC during the follow-up period. Patients requiring further anticoagulation for secondary VTE prevention due to unresolved clinical risk factor may be enrolled in an open-label secondary prevention trial and their follow-*
		up visits will be performed within this separate study.
Rationale for change		*Clarification that patients intended for VTE treatment for more than 3 months will need to switch from dabigatran to SOC after the 12 week treatment duration in this study. Patients randomized to SOC may remain on this therapy beyond 3 months.*

Section to be changed		3.3.1 Main diagnosis for study entry 3.3.2 Inclusion criteria
Description of change		*Example of possible VTE diagnoses were given* *It was clarified that patients should be on parenteral anticoagulation therapy until randomization to trial medication* *It was clarified that patients should have anticipated requirement for **at least** 3 months of antithrombotic treatment*
Rationale for change		*Clarification and alignment with the European Pediatric Investigation Plan (PIP)*

Section to be changed		3.3.2 Inclusion criteria

Description of change		*The duration of initial parenteral treatment was more precisely defined to be up to 21 days at maximum*
Rationale for change		*To ensure enough time window for screening procedures and obtaining safety lab results from Visit 1*

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 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 (once)* *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
Description of change		*P-glycoprotein inhibitors intake up until first dose of study medication will not be 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 10.3 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 add 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 how to treat gastrointestinal symptoms such as dyspepsia 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		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 Schwartz formula has been precisely defined*
Rationale for change		*Clarification*

Section to be changed		10.3.1 Dosing nomogram (starting doses) 10.3.2 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		10.3.1 Dosing nomogram (starting doses) 10.3.2 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 dosages of dabigatran. This change is for clarification only.*

Number of global amendment		05
Date of CTP revision		*29 Nov 2016*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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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		All relevant sections of the CTP
Description of change		*The sample size was reduced from a minimum of 240 to a minimum of 180 evaluable patients for the efficacy component of the co-primary endpoint. The minimum required number of patients for age stratum 1(from 12 to < 18 years of age) was reduced from 80 to 60 and for age stratum 2 (from 2 to < 12 years of age) from 75 to 50.* *The minimum required number of 25 patients for age stratum 3 (from birth to < 2 years of age) remains unchanged. At least 20 patients in stratum 3 must be below one year of age.*

Rationale for change		*The sample size was reduced in order to improve the feasibility of study completion and results delivery and at the same time maintain its objectives and scientific validity* *The reduction is affecting strata 1 and 2 only and is considered in the statistical approach.* *The change has been agreed with Regulatory Authorities (EMA/PDCO, FDA).*

Section to be changed		All relevant sections of the CTP
Description of change		*The duration of the follow-up period was reduced from currently nine months to one month after the end of study medication (i.e. after Visit 8, which is at 3 months, or eEOT, whatever comes first)*
Rationale for change		*A follow-up period longer than 28 days will provide only limited additional information related to the study medication. The adverse event data that will be observed at Visits 10, 11 and 12 (i.e. at 6, 9 and 12 months) will be largely unrelated to the study medication.* *The reduction of the follow-up period from currently 9 months off study drug to one month will reduce the number of visits form currently 12 to 9. For patients who are continuing to receive dabigatran etexilate as participants in study 1160.108 (long-term secondary VTE prevention) the follow-up of 12 months will be maintained unchanged. The follow-up in the 1160.108 study is more likely to deliver dabigatran-related information, because patients have the opportunity to receive dabigatran treatment for up to 12 months.*

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS 5.1.1 Endpoints of efficacy

Description of change		*The following secondary endpoints were removed and will no longer be assessed:* • *Freedom from recurrence of venous thromboembolic events at 6, 9 and 12 months* • *Freedom from occurrence of post-thrombotic syndrome at 6, 9 and 12 months*
Rationale for change		*Current guideline recommendations are supporting the concept of three months treatment duration in 1160.106. Potential events of recurrence of venous thromboembolic at 6, 9 and 12 months (respectively 3, 6 and 9 months after the end of 3 months treatment phase) would be largely unrelated to the study medication.* *The development of post-thrombotic syndrome (PTS) is a long-term complication after VTE, which sometimes takes years to develop. Therefore the potential information loss regarding PTS is considered minimal.* *For patients who are continuing to receive dabigatran etexilate as participants in the long-term secondary VTE prevention study (1160.108), PTS assessment as well as recurrent VTE assessment will still occur at the 12 months follow-up time-point.*

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS 5.1.1 Endpoints of efficacy
Description of change		*It was clarified that freedom from thrombus progression at the end of therapy (day 84 after randomization or eEOT whichever comes first) will be assessed in comparison to baseline*
Rationale for change		*Clarification*

Section to be changed		Flow Chart

Description of change		*The time window for Visit 1 has been extended to -14 days* *The time window for Visit 9 has been changed from ±7 to +14 days*
Rationale for change		*To allow for an earlier start of screening procedures.* *To ensure at least one month of Follow-up*

Section to be changed		All relevant sections of the CTP
Description of change		*Pre-treatment with VKAs during the initial parenteral treatment is acceptable, provided that INR has not reached a therapeutic level (INR < 2.0) at the time of randomization.* *In such cases, a local INR measurement should be performed at Visit 2 to confirm eligibility*
Rationale for change		*To allow for the inclusion of patients treated with VKAs if the INR has not reached a therapeutic level (INR < 2.0) and who could benefit from participation in the study.*

Section to be changed		All relevant sections of the CTP
Description of change		*The first trough dabigatran concentration assessment (at Visit 3) should be supplemented by a local aPTT measurement for patients < 2 months.* *Baseline aPTT must be also available for these patients* *If the aPTT level at Visit 3 is ≥ 2-fold over aPTT at baseline or exceeds 100 seconds, the dabigatran etexilate dose must be down-titrated*
Rationale for change		*To facilitate an expedited evaluation of the risk of bleeding in patients below 2 months based on aPTT over baseline ratio and the absolute (locally available) aPTT value.*

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.* *Summary of preclinical toxicology study in juvenile rats 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 strata 2 and 3.* *To provide data on juvenile preclinical studies that may be relevant to paediatric population < 2 months of age.*

Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		*It was clarified that all patients who received at least one dose of study medication will be considered evaluable*
Rationale for change		*Clarification*

Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		*It was clarified that patients in stratum 3 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		3.3.2 Inclusion criteria
Description of change		*For inclusion criterion 2) it was clarified that the patient should be clinically stable and should have been treated with a parenteral anticoagulant for a minimum of 5 days before being randomized.*

Rationale for change		*The efficacy and safety of dabigatran etexilate in the first 5 days after VTE has not been established in adults. To be consistent with the adult VTE treatment program, where the earliest possible start of dabigatran etexilate was after 5 days of parenteral medication after index VTE.*

Section to be changed		3.3.3 Exclusion criteria 3.3.4.1 Removal of individual patients
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 <250ng/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 Planned analyses 7.3.5 Pharmacokinetic analyses
Description of change		*Analysis set for pharmacokinetic analyses has been defined and will be used for PK/PD analyses.*
Rationale for change		*Previously defined Full Analysis Set (FAS) is not appropriate for PK/PD analyses. The analysis set for PK/PD analyses needs to be modified.*

Section to be changed		7.6 Determination of sample size
Description of change		*Sample size has been decreased from 240 to 180 patients and the power values have been updated accordingly.*

Rationale for change		*The sample size was reduced in order to improve the feasibility of study completion and results delivery and at the same time maintain its objectives and scientific validity. The change has been agreed with Regulatory Authorities (EMA/PDCO, FDA).* *The reduction is affecting the minimum number of patients in age strata 1 and 2 only, and power for the primary endpoints is considered adequate with this reduced sample size.*

Section to be changed		7.6 Determination of sample size
Description of change		*Justification of non-inferiority margin for primary efficacy endpoint has been updated.* *Further calculation of the effect size preserved with the proposed sample size based on a meta-analysis from published trials, also taking the variability in the complete resolution rate without treatment into consideration, has been added to this section.*
Rationale for change		*Justification has been updated as per FDA recommendation.*

Section to be changed		10.3 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		*30Oct2017*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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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		Title Page
Description of change		*Trial Clinical ~~M~~onitor* ☐
Rationale for change		*Personal change*

Section to be changed		Clinical trial protocol synopsis 3.3 Selection of trial population 7.6 Determination of sample size
Description of change		*The sample size was reduced from a minimum of 180 to a minimum of 141 evaluable patients for the efficacy primary endpoint.* *The minimum required number of patients for age*

		stratum 2 (from 2 to < 12 years of age) was reduced from 50 to 18 and for age stratum 3 (from birth to < 2 years of age) from 25 to 15. The minimum required number of patients in stratum 3 who must be below one year of age was reduced from 20 to 8. The recruitment of patients could be continued after achieving the minimum total number of patients and the minimum number of patients per age strata if required by Regulatory Authorities.
Rationale for change		*The sample size was reduced in order to improve the feasibility of study completion and results delivery and at the same time maintain its objectives and scientific validity This change has been agreed with Regulatory Authorities (EMA/PDCO).*

Section to be changed		Clinical trial protocol synopsis 5.1.1 Endpoints of efficacy 7.2 Null and alternative hypotheses 7.3 Planned analyses
Description of change		*Freedom from major bleeding events (MBEs) has been changed from the co-primary safety endpoint to a secondary endpoint in the synopsis and in Section 5.1.1. Major bleeding events have been removed from the related null hypotheses from Section 7.2. The analyses of MBE have been moved from Section 7.3.1 to Section 7.3.2.*
Rationale for change		*The FDA has advised to analyse the major bleeding component of the primary endpoint as a secondary endpoint. According to the FDA comments, the proposed non-inferiority margin for major bleeding (9%) would not preserve the effect size of the bleeding rate based on the active control arm and would not permit the non-inferiority of dabigatran etexilate compared to LMWH/VKA to be claimed. As agreed with Regulatory Authorities (EMA/PDCO, FDA), major bleeding events will be analysed as a secondary endpoint in 1160.106.*

Section to be changed		Clinical trial protocol synopsis FLOW CHART footnotes 3.1 OVERALL TRIAL DESIGN AND PLAN 4.1 TREATMENTS TO BE ADMINISTERED 4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT
Description of change		*Fondaparinux has been added as standard of care treatment*
Rationale for change		*According to the Guidelines of Antithrombotic Therapy and Prevention of Thrombosis the use of fondaparinux is considered together with low molecular weight heparin and unfractionated heparin as a possible therapeutic option in the acute phase of DVT or PE, for both, adult and paediatric patients. The use of fondaparinux is considered a potential candidate to replace low molecular weight heparin in normal clinical practice; specifically in children with heparin-induced thrombocytopenia. Therefore, is considered appropriate to include fondaparinux as part of standard of care in the comparator arm in study 1160.106.* *This change has been agreed with Regulatory Authorities (EMA/PDCO).*

Section to be changed		FLOW CHART footnote A 3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		*Changed "approximate 28 days" to "at least 28 days" in flow chart footnote A.*
Rationale for change		*As the term "approximately 28 days" is ambiguous, PDCO proposed to change it to "at least 28 days".*

Section to be changed		FLOW CHART footnote T

Description of change		*The collection of post-dose sample for dabigatran etexilate patients in stratum 3 has been changed to optional in flow chart footnote T.* *The requirement of post-dose sample collection in 12 patients treated with dabigatran etexilate in*
		stratum 3 has been deleted.
Rationale for change		*The amount of blood volume to be obtained in patients in stratum 3 is limited and the post-dose sample requirements should be the same for all patients treated with dabigatran etexilate in all age strata.*

Section to be changed		6.2.3 End of trial and follow-up period
Description of change		*Clarification that patients having switched from dabigatran etexilate to SOC are considered as having early discontinued of dabigatran etexilate treatment. However, such patients will still remain in the trial and be followed as per the visit schedule till the end of the study.*
Rationale for change		*Patients that switch from dabigatran etexilate to SOC are considered as having an early discontinued of dabigatran etexilate treatment and remain in the trial to be followed as per the visit schedule till the end of the study. This was not made clear in the previous version of the protocol.*
Section to be changed		7.6 Determination of sample size
Description of change		*Change of the assumptions to estimate how the FDA requirement regarding 150 unique patients on dabigatran etexilate treatment for at least 3 months for 1160.106 and 1160.108 combined could be met.* *The number of patients in 1160.108 has been changed from 100 to 120. The percentage of 1160.108 patients who were rolled over from 1160.106 dabigatran etexilate group has been changed from 40% to 20%.*

Rationale for change		*The change in the assumptions on number of patients in 1160.108 is based on the current actual enrolment status, projection of recruitments and trial timeline for 1160.108. The change in the assumptions on the percentage of patients on dabigatran etexilate rolled over from 1160.106 to 1160.108 is based on the current actual figures.*

Number of global amendment		07
Date of CTP revision		*16 Jan 2018*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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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 randomisation.*
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		08
Date of CTP revision		*11 September 2018*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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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 Flow Chart, Footnote Q 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 10.3 Dosing of Dabigatran etexilate Section 10.3.1 Dosing nomogram (starting doses) Section 10.3.2 Dose Adjustment nomogram
Description of change		*The option to administer pellets was expanded to patients < 6 months of age. A preference for the 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, Flow Chart Footnote X
Description of change		*The time window from visit 1 (screening) to visit 2 (start of study medication) was expanded to 21 days. The recommendation to collect the screening laboratory tests best 10 days before Visit 2 was deleted from Footnote X.*
Rationale for change		*The maximal time period for initial parenteral anticoagulation treatment according inclusion criterion #2 is 21 days. Expanding the time window from visit 1 to visit 2 to 21 days facilitates the conduct of screening procedures.*

Section to be changed		Flow Chart, Footnotes D, J and S Section 3.1 Overall trial design and plan Section 3.3.4.1 Removal of individual patients Section 4.1.3 Selection of doses in the trial Section 6.2.3 End of trial and follow-up period
Description of change		*The preferred way of follow-up of patients who have discontinued study medication prematurely (eEOT, Follow-up Visit 9 after 28 days, further follow-up according remaining visit schedule) was implemented consistently throughout the protocol.* *It was added in Section 6.2.3 that for patients prematurely discontinued from study medication, who are within the follow-up period after Follow-up Visit 9, the following will be collected: AEs, outcome events (e.g. occurrence of PTS, VTE, bleeding events, etc.) and use of concomitant*
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, Footnote M Section 5.2.3 Assessment of safety laboratory parameters Appendix 10.1 Safety and other clinical laboratory evaluations

Description of change		*The exceptions from the generally central laboratory assessments were implemented consistently throughout the protocol.* *It was added that local lab assessment of PT (prothrombin time)/ INR (international normalized ratio), aPTT (activated partial thromboplastin time) or Anti-Factor Xa activity for coagulation monitoring in SOC patients is an acceptable alternative to central lab testing.*
Rationale for change		*To align the wording related to exceptions from central laboratory assessments between relevant protocol sections.* *To facilitate the coagulation monitoring in SOC patients.*

Section to be changed		Flow Chart, Footnotes D, H and W
Description of change		*It was added to Footnote D that an unscheduled Visit is also to be performed in case a dabigatran dose adjustment is needed.* *It was added to Footnote H that a complete physical examination is required at eEOT Visit and Visit 9, additionally to the physical examination at Visit 1 and Visit 8.* *Two examples for re-dispensation of study medication were added to Footnote W. Dabigatran etexilate may be re-dispensed at Visit 3 and at Visit 4.*
Rationale for change		*To clarify and to correct omissions.*

Section to be changed		CTP Synopsis Section 3.3 Selection of trial population
Description of change		*The required patient numbers in stratum 1, 2 and 3 were expressed as targets rather than as minimum numbers.*
Rationale for change		*To introduce flexibility in order to adapt for different regulatory requirements.*

Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		*Footnote 2 referring to inclusion criterion #2 was clarified.* ***Short-term*** *pre-treatment with VKAs is permitted if the INR has not yet reached a therapeutic level (i.e. the INR is still < 2.0). It was added that the duration of the initial parenteral therapy inclusive VKA treatment if applicable must not exceed 21 days.*

Rationale for change		*To provide clarification on pre-treatment with VKAs.*

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 study medication 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		*It was added that if deemed necessary the type of SOC may be changed in SOC patients during the treatment period. Concerned patients will not be considered as having discontinued study medication early, will remain to be on study medication and will be followed per the visit schedule until the end of the study.*
Rationale for change		*To clarify that switching of the type of SOC in SOC patients is not considered as premature study medication discontinuation.*

Section to be changed		Section 3.1 Overall trial design and plan Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		*It was added that patients assigned to take dabigatran and 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). In case pre-treatment with VKAs has been initiated during the screening period, a local INR measurement should be performed at Visit 2 to confirm eligibility (INR < 2.0).* *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 provide guidance on how to switch from the alternate therapy to the study medication dabigatran etexilate.* *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 4.1.7 Storage conditions
Description of change		*It was added that for information on storage conditions one should refer to the locally approved medication label and the STORM (Storage condition for Trial Medications) document in the ISF. Mentioned storage temperatures and the permitted excursion were deleted from the protocol.*
Rationale for change		*To cover all storage conditions applicable in the countries participating in the trial.*

Section to be changed		Section 4.2.2.1 Restrictions regarding concomitant treatment

Description of change		*It was added that fibrinolytic agents should not be taken within 48 hours prior to dabigatran administration and that P-glycoprotein inducers should not be taken within one week to prior dabigatran administration.* *It was added that generally excluded corticosteroids may be included if the benefits of corticosteroid therapy clearly outweigh risks.*
Rationale for change		*To give further guidance on treatment restrictions.*

Section to be changed		Section 4.3 Treatment Compliance
Description of change		*It was added that if an interruption of dabigatran etexilate or SOC 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 clarify how to calculate the compliance in case of dabigatran etexilate interruptions.*

Section to be changed		CTP Synopsis Section 5.1.1 Endpoints of efficacy

Description of change		*It was clarified that the secondary endpoint "Pharmacokinetic and pharmacodynamic assessments" is referring to assessments at visit 3 and to assessments after at least 3 days following any dabigatran dose adjustment.* *To the secondary endpoint "Frequency of dose adjustments" the explanation "(i.e. Number of subjects with dose adjustment)" was added.* *The secondary endpoint "Number of laboratory monitoring requirements for dose adjustment during the treatment phase" was changed to "Number of subjects with laboratory monitoring requirements for dose adjustment during the treatment phase".* *To the secondary endpoint "Frequency of switch of type of anti-coagulation therapy (including dabigatran to SOC)" the explanation "(Frequency of subjects switching the type of anti-coagulation therapy including dabigatran etexilate to standard of care)" was added.* *To the other endpoint "Assessment of acceptability of capsules, pellets and OLF", which is assessed at specified days, the respective visit numbers were added.*
Rationale for change		*To clarify the meaning of the respective endpoints.*

Section to be changed		CTP Synopsis
Description of change		*The explanation"(measured as treatment discontinuation and adherence)" was added to the safety criterion "Global assessment of tolerability".*
Rationale for change		*To correct an omission and align with Section 5.2.1 Endpoints of safety.*

Section to be changed		Flow Chart, Footnote J Section 5.1.2.2 Venous thromboembolism assessment
Description of change		*The wording "For day 7 (visit 4)" was deleted from the note, which now reads: If clinical evaluations warrant imaging (e.g. suspected thrombus extension), then per investigator judgment, appropriate imaging may be performed.*

Rationale for change		*To correct the meaning of the respective note. Imaging may be performed in case of need any time throughout the trial.*

Section to be changed		Section 5.7.1 Pharmacodynamics endpoints Section 5.7.2 Methods of sample collection 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.*
Rationale for change		*To clarify and distinguish between dTT (Anti-Factor IIa activity) and dTT utilized for the evaluation of dabigatran etexilate plasma concentrations.*

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 F 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 10.3 Dosing of Dabigatran etexilate
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. The required dabigatran etexilate dose is calculated by the IRT System only.*

Section to be changed		Abbreviations
Description of change		*PT - Prothrombin Time was added to the list of abbreviations.*
Rationale for change		*To correct for an omission regarding prothrombin time.*

Number of global amendment		09
Date of CTP revision		*06 February 2019*
EudraCT number		*2013-002114-12*
BI Trial number		*1160.106*
BI Investigational Product		*Dabigatran etexilate, BIBR 1048 MS*
Title of protocol		Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study
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		Section 3.3.3 Exclusion criteria Section 3.3.4.1 Removal of individual patients
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 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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Title: Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		07 Feb 2019 12:21 CET
Author-Clinical Trial Leader		07 Feb 2019 12:31 CET
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Approval-Therapeutic Area		07 Feb 2019 12:55 CET
Author-Trial Statistician		08 Feb 2019 04:45 CET
Verification-Paper Signature Completion		11 Feb 2019 14:42 CET

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Meaning of Signature	**Signed by**	**Date Signed**