21 February 2013
EMA/CHMP/653299/2013
Committee for Medicinal Products for Human Use (CHMP)

Pradaxa

(dabigatran etexilate)

Procedure No. EMA/H/C/000829/A46/0033.1

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Administrative information

Invented name of the medicinal product:	Pradaxa
INN (or common name) of the active substance:	Dabigatran etexilate
MAH:	Boehringer Ingelheim International GmbH
Currently approved Indication	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: • previous stroke, transient ischemic attack, or systemic embolism; • left ventricular ejection fraction < 40%; • symptomatic heart failure ≥ New York Heart Association (NYHA) class 2; • age ≥ 75 years; • age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension.
Pharmaco-therapeutic group (ATC Code):	B01AE07
Pharmaceutical form and strengths:	Hard capsule, 50 mg. Hard capsule, 75 mg.
Rapporteur:	Jens Heisterberg

Introduction

On August 8, the MAH submitted a completed paediatric study for Pradaxa, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Pradaxa and that no consequential regulatory action is required.

Scientific discussion

Information on the development program

The MAH stated that "Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years" (study code 1160.88) is a standalone study.

The MAH stated that "Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years" (study code 1160.88) is part of a clinical development program. A line listing of all the concerned studies is annexed.

Information on the pharmaceutical formulation used in the study

In the study capsules of 50 mg and 75 mg dabigatran etexilate strengths were administered. These capsules represent clinical trial formulations, formulated based on the initial Marketing Authorization from 18 Mar 2008 (EU/1/08/442/001-008). The MAH is currently investigating, which capsule dose strengths and sizes could be used in children. Dabigatran etexilate is marketed as capsules of 75 mg, 110 mg and 150 mg strengths for the adult patient population.

In the recently completed RE-COVER Trials the adult dose of 150 mg twice daily has been identified as a potential effective dose for treatment of acute venous thromboembolism. An estimated pediatric weight-adjusted dose of dabigatran etexilate is 2.15 mg/kg twice daily (or 4.3mg/kg daily), which is equivalent to an adult dose of 150 mg twice daily for an adult weight of 70 kg.

Clinical aspects

1. Introduction

The MAH submitted a final report for:

- Study 1160.88. Titled "Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years"

Background

Dabigatran etexilate is a prodrug. After oral administration, it is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. In adults there is a close correlation of dabigatran plasma concentrations and pharmacodynamic effect (e.g. changes in ecarin clotting time (ECT), thrombin time (TT), and activated partial thromboplastin time (aPTT). Based on in-vitro paediatric data it was found that both the TT and ECT are linearly and sensitively correlated with dabigatran plasma concentrations.

Currently dabigatran etexilate is under investigation in the following indications: Acute venous thromboembolism treatment; and secondary prevention of venous thromboembolism. Since there is no relevant use of dabigatran etexilate in the pediatric population in the two approved indications, ("Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery and "Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors" previous stroke, transient ischemic attack, or systemic embolism; left ventricular ejection fraction < 40%; symptomatic heart failure ≥ New York Heart Association (NYHA) class 2; age ≥ 75 years; age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension) EMA has adopted a Paediatric Investigational Plan for dabigatran etexilate to explore the indication "treatment of thromboembolic events in pediatric patients (secondary venous thrombotic event prevention)".

In contrast to adults, venous thromboembolism in children is a rare event. The incidence rate of symptomatic venous thromboembolism differs for neonates, children and adolescents, thus the overall annual incidence is approximately 0.07-0.14 events per 10,000 children. The distribution of venous thromboembolism events in pediatric patients is bimodal with the majority of events occurring in neonates and infants and in adolescents. Teenage girls have twice the rate of venous thromboembolism as do teenage boys due to the use of oral contraceptives and pregnancy. As survival for major childhood illnesses such as CHD and cancer improves, the incidence of venous thromboembolism has increased during the last decades.

Pediatric venous thromboembolism differs from adult venous thromboembolism in different aspect such as primary underlying disorder, distribution of affected vessels, interaction of anticoagulant with the haemostatic system, and risk of complications due to underlying disease and or to treatment. It is estimated that more than 90% of children with venous thromboembolism have a serious underlying disorder (e.g. cancer, congenital heart disease, nephritic syndrome, etc), or a precipitation factor (central venous line), or a hereditary pro-thrombotic condition. Idiopathic thrombosis occurs in less than 10% of pediatric patients compared to 40% of adult patients.

The current treatment of venous thromboembolism in children is unfractionated heparin (UFH) or low molecular weight heparin (LMWH) administered for 5-7 days followed by three months of LMWH or oral anticoagulation. Pediatric patients with uncomplicated venous thrombosis are usually treated for 3 to 6 months.

2. Clinical study

Study number: 1160.88

Title: "Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years"

Description

The study is an exploratory, open-label, multi-centre, non-randomized, multiple dose safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years. It was initiated on 28 Aug 2009 and had last patient out on 16 Feb 2012 and was carried out in Canada.

Methods

- Objective(s)

The study objectives were to:

- investigate tolerability and safety of dabigatran etexilate capsules in adolescents
- explore preliminary pharmacokinetic and pharmacodynamic parameters in adolescent patients.

- Study design

At the end of standard anticoagulant therapy the patients entered a three day dabigatran etexilate treatment period and took a total of six doses of dabigatran etexilate at 12 hour intervals. The first dose of study medication was given at 80% of the adult dose (1.71 mg/kg) adjusted for the patient's weight. Thereafter, unless further dose adjustment was required, the patient took the full adult dose (2.14 mg/kg; Dose 2) of dabigatran etexilate adjusted for the patient's weight. To determine if a dose adjustment would be required, peak dabigatran concentrations were derived daily at the site using a calibrated direct thrombin inhibitors assay (Hemoclot®). Trough dabigatran concentrations were measured just prior to the fifth dose of study medication and 12 hours after the last dose of study medication. Plasma samples for central analysis of pharmacokinetics and pharmacodynamics were taken at peak on day1, at trough and peak on day 3 and at trough 12 hours after the last dose of study medication. At the end of the three day treatment period, the patient entered a 30 (±7) day follow-up period.

Table 9.1: 1 Table of procedures

DAY	EXPECTED TIME (HR)		PROCEDURE
DAY 1	0:00	Dose 1	– First dose of dabigatran etexilate administered at 80% of adult dose adjusted for patient weight (1.71 mg/kg)[1].
	2:00 (+1 hr)	Peak: PD & PK	– TT, aPTT, ECT, and PK samples collected and processed[2]. – Local TT (Hemoclot®)[3], aPTT, and ECT analysed[4].
	12:00 & 24:00	Dose 2 & Dose 3	– If the peak dabigatran plasma concentration were < 500ng/mL & there were no other safety concerns, the dose was increased to 100% of adult dose adjusted for patient's weight (2.14 mg/kg)[1]. – Dabigatran etexilate was dispensed.
DAY 2	26:00 (+1 hr)	Peak: PD	– TT, aPTT, ECT, and PK samples collected and processed[2]. – Local TT (Hemoclot®)[3], aPTT, and ECT analysed[4]
	36:00	Dose 4	– If required, based upon peak TT measure taken after Dose 3, the dose of dabigatran etexilate was adjusted[5]. – Dabigatran etexilate was dispensed.
	38:00 (+1 hr)[6]	Peak: PD	– TT, aPTT, ECT, and PK samples collected and processed[2]. – Local TT (Hemoclot®)[3], aPTT, and ECT analysed[4]
DAY 3	~47:30	Trough: PD & PK	– TT, aPTT, ECT, and PK samples collected and processed[2]. – Local TT (Hemoclot®)[3], aPTT, and ECT analysed[4]
	48:00	Dose 5	– Dabigatran etexilate given at same dose as Dose 4[5].
	50:00 (+1 hr)	Peak: PD & PK	– TT, aPTT, ECT, and PK samples collected and processed[2]. – Local TT (Hemoclot®)[3], aPTT, and ECT analysed[4]
	60:00	Dose 6	– If required, based upon based upon trough and peak TT measures taken on Day 3, the dose of dabigatran etexilate was adjusted[5]. – Dabigatran etexilate was dispensed.
DAY 4	~72:00	Trough: PD & PK	– TT, aPTT, ECT, and PK samples collected and processed[2]. – Local TT (Hemoclot®)[3], aPTT, and ECT analysed[4] – Standard safety labs collected. – 12-lead ECG taken.

The choice of study length indicates that the time of steady state for dabigatran in children is the same as for adults (3 days). This lead to the potential risk of a too short data collection PK/PD-period. Thus the applicant should justify the length of study especially with regard to future phase II studies.

- Study population

In total nine subjects were enrolled, 8 subjects completed the trial; one subject was discontinued for administrative reasons after first dosing.

Criteria for inclusion: Adolescent (12 to <18years) patients who successfully completed planned treatment with either low molecular weight heparins or oral anticoagulation for primary venous thromboembolisme

Exclusion criteria: Weight less than 32 kg; conditions associated with an increased risk of bleeding: Any hemorrhagic stroke, major surgery in the previous month, planned surgery or invasive procedure in the next 30 days, history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding, Gastrointestinal haemorrhage within the past year unless the cause had been permanently eliminated (e.g., by surgery), any history of gastroduodenal ulcer disease, hemorrhagic disorder or bleeding diathesis, required concurrent treatment with another LMWH, UFH, oral anticoagulant or antiplatelet agent, fibrinolytic agents within 48 hours of study entry, uncontrolled hypertension on antihypertensive medication (twice the upper limit of normal for age sustained for over 24 h); severe renal dysfunction (serum creatinine ≥200 µM) or requirement for dialysis; active infective endocarditis; hepatic disease: INR >2.5 (>3.0 if on OAC) or an activated partial thromboplastin time (aPTT) >100 s and / or active liver disease, including known hepatitis A, B or C and / or persistent ALT, AST, Alk. Phos >2 x ULN; females with a positive serum β-hCG pregnancy test or not using a medically accepted contraceptive method. Anaemia (haemoglobin <100g/L) or thrombocytopenia (platelet count <100 x 109/L); patients who had taken any prohibited / restricted medication / treatment within one week of first dose of study medication; patients who received an investigational drug in the past 30 days; patients considered unreliable by the investigator.

- Sample size

The MAH planned to include a total of eight patients in the study. The planned sample size was not based on a power calculation. But the MAH considered it as sufficient for the exploratory evaluation of multiple dose safety, tolerability and pharmacokinetics.

- Treatments

Dabigatran etexilate was administered twice daily for three consecutive days (total 6 doses) in eight stable adolescents (12 to <18 years) who had completed planned treatment with a low molecular weight heparin or an oral anticoagulant for primary venous thromboembolisme.

All patients received an initial oral dose of 1.71 (± 10%) mg/kg of dabigatran etexilate (80% of the adult dose of 150 mg/70 kg adjusted for the patient's weight).After the first dose, the dose was adjusted to the target dose of 2.14 (± 10%) mg/kg of dabigatran etexilate (100% of the adult dose adjusted for the patient's weight) after clinical assessment and also assessment of dabigatran concentrations. If the plasma dabigatran concentration had exceeded 500 ng/mL at any time, the dose would have been reduced by 50%.

For Dose 1 (80%), the mean dose given was 1.6 mg/kg; the minimum Dose 1 adjusted for body weight was 1.4 mg/kg and the maximum dose was 1.9 mg/kg. The mean dose given for Doses 2 through 6 (100%) adjusted for body weight was 2.1 mg/kg; the minimum dose was 1.8 mg/kg and the maximum dose was 2.3 mg/kg.

Table 9.4.1.4: 1 Dosing nomogram

80% of adult dose (based on 150 bid for 70 kg adult: 1.71 mg/kg) (±10%)		
Weight (kg)	**Single Dose (capsules)**	**Total Dose**
32 to <40	50	50
40 to <53	75	75
53 to <66	50x2	100
≥66	75+50	125
Adult dose (based on 150 bid for 70 kg adult: 2.14 mg/kg) (±10%)		
Weight (kg)	**Single Dose (capsules)**	**Total Dose**
32 to <43	75	75
43 to <53	50x2	100
53 to <66	75+50	125
≥66	75x2	150

Note: Lower 5th percentile for 12 year old girls is about 32 kg.

- Outcomes/endpoints

Safety:

Primary:

- Incidence of all major and minor bleeding events
- Incidence of all adverse events.

Secondary:

- Changes in laboratory and clinical parameters such as liver enzymes, ECG, and physical examination
- Occurrences of clinical outcomes including recurrent thrombosis, post thrombotic syndrome, pulmonary emboli, and total and venous thrombolic event related mortality.

Clinical pharmacology:

Primary:

- Pharmacokinetic parameters: plasma concentrations of free(BIBR 953 ZW) and total (SUM BIBR 953 ZW) dabigatran, unchanged and intermediate metabolites (BIBR 1048 BS, BIBR 951BS, and BIBR 1087 SE)
- Pharmacodynamic parameters: central and local measurement of TT(standardized commercial direct thrombin inhibitor kit Hemoclot® Thrombin Inhibitor clotting assay)

Secondary:

- Pharmacodynamic parameters: central and local measurement of aPTT and ECT.

Further:

- Population pharmacokinetic (PopPK) model based on adult population for the prediction of dabigatran plasma concentrations

- Statistical Methods

Descriptive statistics were performed for safety and the blood coagulation parameters aPTT, ECT and Hemoclot® TT.

The measured dabigatran concentrations were summarized descriptively and dose-normalized or grouped by dose to allow comparison.

A population pharmacokinetic (PopPK) model developed on adult data was used for the prediction of dabigatran plasma concentrations in this pediatric population.

Results

- Recruitment/ Number analysed

In total nine subjects were enrolled, 8 subjects completed the trial; one subject was withdrawn after the first dose of study medication when it was discovered that his foster parents were not his legal guardians and therefore, could not legally provide informed consent . The eight patients who completed treatment were from a single site. The 3 other sites in the study did not enroll any patients.

- Baseline data

Six patients were female and 3 patients were male. All patients were white. The mean age was 15.7 years. The youngest patient was 13 years of age and the oldest, 17. The mean weight was 58.91 kg, range 47 kg to 84 kg. All patients had underlying conditions that could pre-dispose the patient to developing a thrombus. Four of the nine patients had gene variations in the coagulation cascade. Two patients had malignancy (T-Cell ALL, Hodgkin's disease) and the remaining three patients had osteomyelitis, Crohn's disease and cystic fibrosis. Three of the nine patients had their anticoagulant therapy (two enoxaparin, one warfarin) stopped within one week of signing informed consent.

Three patients received 75 mg dabigatran etexilate (first dose) followed by 100 mg BID. Three patients took dabigatran etexilate 100 mg (first dose) followed by 125 mg BID. Two patients received a dose of 125 mg dabigatran etexilate followed by 150 mg BID. The subject that was withdrawn received a single dose of dabigatran etexilate (75 mg).

Table 10.1: 1 Dabigatran etexilate doses administered to adolescent patients

Patient	Dose 1 [mg]	Dose 2 [mg]	Dose 3 [mg]	Dose 4 [mg]	Dose 5 [mg]	Dose 6 [mg]	Resulting dose regimen
10	125	150	150	150	150	150	125 mg then 150 mg BID
11	125	150	150	150	150	150	125 mg then 150 mg BID
12	100	125	125	125	125	125	100 mg then 125 mg BID
13	75	100	100	100	100	100	75 mg then 100 mg BID
14	75	100	100	100	100	100	75 mg then 100 mg BID
15	100	125	125	125	125	125	100 mg then 125 mg BID
16	100	125	125	125	125	125	100 mg then 125 mg BID
17	75	100	100	100	100	100	75 mg then 100 mg BID
20	75	---	---	---	---	---	75 mg

The induvidualized treatment plans for the included adolescents.

All nine patients had underlying conditions that could pre-dispose to development of a thrombus. Thus, the included patients adequately reflect the adolescent population where idiopathic thrombosis is a rare event and treatment of a thrombus must be initiated in addition to concomitant primary therapies.

- Efficacy results

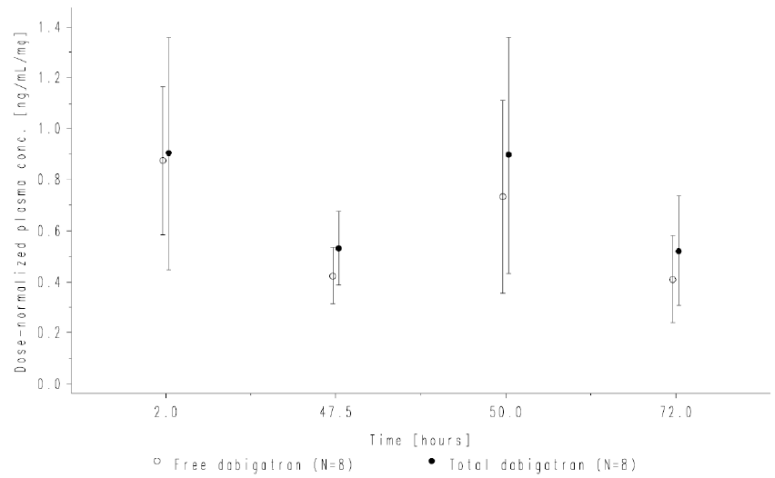
No efficacy measurements were performed.

Pharmacokinetic results

Central measurements

Dose-normalized geometric trough means (gMean) were for total dabigatran concentration at 47.5 hrs of 0.517 ng/mL/mg (range 0.375-0.806 ng/mL/mg) and at 72 hrs of 0.493 ng/mL/mg (range 0.339-1.04 ng/mL/mg). The peak dose-normalized geometric means were at 2 hrs 0.587 ng/mL/mg (range 0.0156-1.35 ng/mL/mg) and at 50 hrs 0.493 ng/mL/mg (range 0.339-1.04 ng/mL/mg)

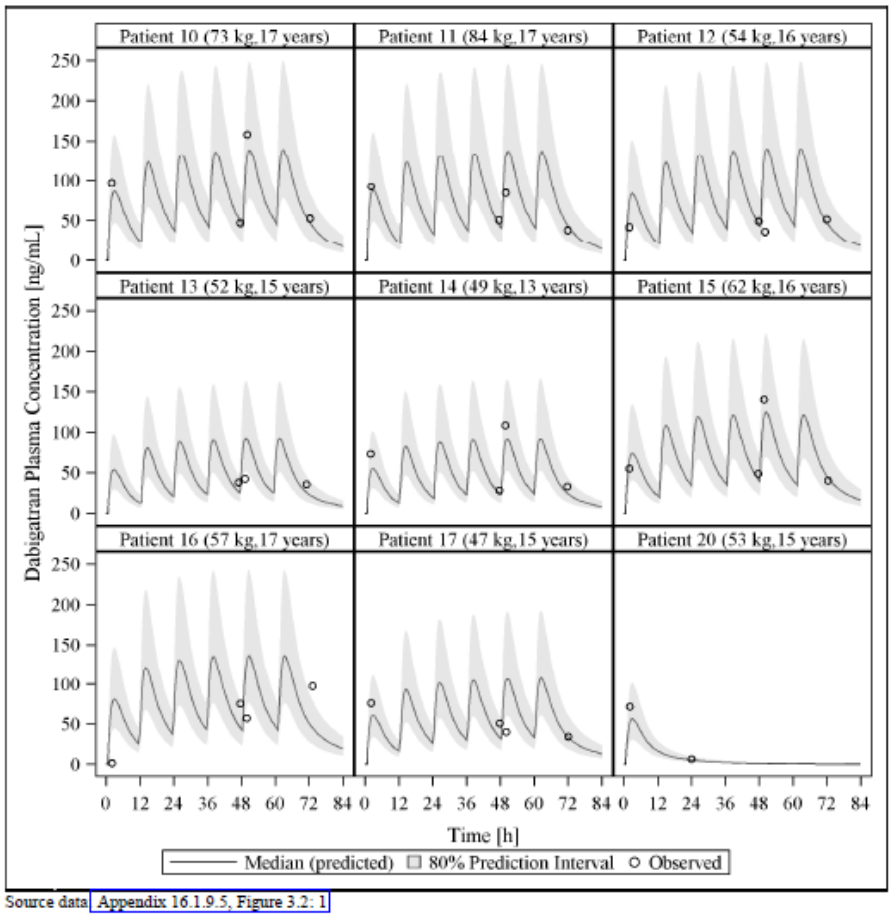
Dabigatran plasma concentrations observed at 72 hrs (presumed dabigatran trough level at steady state or close to steady state conditions) were slightly lower (gMean dose normalized total dabigatran plasma concentration of 0.493 ng/mL/mg) when compared to previous reports with adult data. The gMean dose-normalized pre-dose total dabigatran concentrationat steady state, Cpre,ss, norm, was 0.795 ng/mL/mg in RE-LY (Trial 1160.26) and 0.530 ng/mL/mg in RE-COVER (Trial 1160.53). The lower levels in these adolescent patients can be explained by the good renal function indicated by creatinine clearance values of greater than 90 mL/min at baseline



Source data: Figure 15.6.5.3: 2

Figure 11.5.2: 1 Arithmetic mean (with standard deviation, bars) dose-normalized plasma concentration-time data of free (open circles) and total (closed circles) dabigatran after multiple oral administration of dabigatran etexilate (various doses, BID) to adolescent patients

The predictions of dabigatran PK in adolescent patients is based on the RE-LY model. that takes into account the actual administration, sampling times, age, sex, race, creatinine clearance (calculated by Cockcroft-Gault), proton pump inhibitors as co medication during dabigatran treatment, body weight, and haemoglobin levels at the PK visit. The 16 of 17 trough concentrations (94%) obtained in the study were within the 80% prediction interval. For patient 16 lower dabigatran concentrations were predicted for trough at around 72 hrs.



Source data: Appendix 16.1.9.5, Figure 3.2: 1

Figure 11.5.2: 2 Predicted plasma concentration-time profiles (grey line and shaded area = 80% prediction interval) versus observed concentrations (open circles)

One of the two male patients had a lower dabigatran concentration at sampling time point 72 hrs compared to female subjects. Age was not reported to influence different dabigatran plasma concentrations; and creatinine clearance at baseline (all > 90 mL/min) did not reveal a trend when plotted against dabigatran concentrations in the investigated patients.

However, in some of the patients (12, 13, 16, and 17) the absorption rate of dose number 5 given at day 3 is slower than expected. The applicant is asked to address the lack of peak value measurements in 4 of 8 patients in day 3 with respect to optimizing the PopPK-model for this population.

Locale measurements

Dabigatran concentrations determined by the Hemoclot® TT locally assay were compared to concentrations determined by HPLC-MS/MS. The highest dabigatran concentrations measured were 156 ng/mL (Hemoclot® TT) and 158 ng/mL (HPLC-MS/MS) for the 50 hrs (peak) sample obtained from Patient 10. The greatest difference between dabigatran concentrations by Hemoclot® TT and by 158 HPLC-MS/MS were seen for the 2 hrs (peak) sample in Patient 20 (107 ng/mL vs. 71.5 ng/mL, respectively). Not any of the locally determined dabigatran concentrations did not exceed 500 ng/mL.

The applicant is asked to make and comment correlation plots between all biomarkers analyzed both central and locally. Furthermore the applicant is asked to supply information concerning the reference intervals for all the evaluated biomarkers in adolescents and the expected prolongation of these by

dabigatran.

Pharmacodynamic results

Central measurements

Baseline pharmacodynamic measurements (aPTT, ECT, Hemoclot® TT (Anti-FIIa)) were taken at the screening visit and 2 hrs, 26 hrs, 47.5hrs, 50 hrs, and 72 hrs after first dosing. At sampling time points where dabigatran peak concentrations were expected the pharmacodynamic changes from baseline were for some patients greater compared to the other time points. The maximum aPTT prolongation was 1.98 time baseline, ECT 2.27 times baseline and Anti-FIIa times baseline 1.64. Two in 8 patients experience the maximum prolongation of aPTT 2 hrs after the initial administration of dabigatran etexilate. (80% of full dose).

Local measurements

When aPTT was determined locally values were lower compared to the results from central aPTT measurements. However, local baseline aPTT values were also lower and a change from baseline was observed. ECT prolongation was determined locally only for Patient 20. When compared to the central measurements, the two locally determined ECT values from this patient were lower.

The applicant is asked to provide ratios for aPTT and Anti-FIIa analyzed locally.

Pharmacokinetic – pharmacodynamic results

Linear regression models were used to explore the relationship between the plasma concentrations of total dabigatran and the coagulation parameters aPTT, ECT, and Hemoclot® TT (Anti-FIIa) ratios as determined centrally. For the correlation dabigatran concentrations vs. aPTT levels an R^2 of 0.432 was determined indicating a non-linear relationship. The R^2 for the correlation dabigatran concentrations vs. ECT levels was 0.806 and for dabigatran concentrations vs. Hemoclot® TT (Anti-FIIa), the R^2 was 0.901.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. However, the correlation dabigatran concentrations vs. aPTT levels indicating a non-linear relationship. For earlier dabigatran studies it's known that the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran.

- Safety results

Safety evaluation was based on physical examination, vital signs (BT and pulse), 12-lead ECG, laboratory tests and incidence of adverse events as well as assessment of tolerability by the investigator.

All nine patients who entered the study took at least one dose of study medication. All nine are included in the safety analysis.

In general blood pressure, pulse, and laboratory were not affected by the treatment. However, the mean QTC interval (Bazett) was prolonged 9.56 ms from baseline during treatment.

Two (patients 10 and 12) of the nine patients had minor gastro intestinal adverse events during the treatment period. One patient (patient 20) experienced a serious adverse event (VTE) post treatment.

The two patients experienced three treatment emergent gastrointestinal adverse events. One patient reported mild gastro-esophageal reflux three hours after the first dose of study medication and mild abdominal pain that started on the second day of treatment. The other patient reported mild abdominal discomfort on the second day of treatment that lasted for one hour. These events were considered to be related to dabigatran etexilate. None of these events led to a patient discontinuing study medication.

Patient 20, a 16 year old white male patient, completed standard enoxaparin therapy 60 mg BID sc for the primary venous thrombolic event (VTE) on 12 Sep 2010 at 07:00 hrs. The patient took one dose of study medication on 13 Sep 2010 at 09:17. The study stopped for administrative reasons. Due to presence of the implanted vascular access device (IVAD), as prophylaxis, enoxaparin 60 mg BID sc was started on 14 Sep 2010 at 19:00 hrs. On 20 Sep 2010, the patient presented to the clinic with persistent left leg pain starting over the weekend (18 Sep 2010 at 19:00 hrs; five days after the single dose of study medication). An ultrasound of the left lower limb on 20 Sep 2010 confirmed the presence of thrombus in the left external iliac and left common femoral vein, with extension into the left greater saphenous vein. Enoxaparin was taken by the patient until 19 Sep 2010 at 07:00 hrs but was held the evening of 19 Sep 2010 in anticipation of starting study medication again the following morning. Enoxaparin was restarted at the same dose on 20 Sep 2010 at 11:00 hrs due to the presence of new thrombus. This was reported as a serious adverse event. The investigator did not consider the SAE to be related to study medication.

Patient 20 had past and concomitant diseases relevant to the event included: T cell acute lymphoblastic leukemia (ALL) diagnosed 02 Feb 2010, thrombus (a nonocclusive right subclavian vein, right internal jugular vein and pulmonary emboli diagnosed 05 Mar 2010), pseudotumor cerebri diagnosed 01Apr2010 and a new pulmonary emboli diagnosed 25 May 2010. The patient had an implanted vascular access device in the left iliac vein.

Patient 20 had past and concomitant therapies relevant to the event included enoxaparin for the treatment of the primary VTE from 14 Mar 2010 to 12 Sep 2010, Colace and Senokot for constipation starting in Mar 2010, Septra as chemotherapy support starting in Mar 2010, acetazolamide for the pseudotumor cerebri starting on 17 Mar 2010, Ondansetron for nausea starting on 01 Mar 2010, codeine for pain starting on 14 Mar 2010, Concerta and risperidone for ADHD and FASD since 2004, and for the treatment of the ALL, the chemotherapy agents, cytarabine from 25 Aug 2010 to 02 Sep 2010, methotrexate (intrathecal) 30 Aug 2010, vincristine from 06 to 13 Sep 2010, and Erwinia asparaginase from 06 to 17 Sep 2010. The patient also had radiation therapy from 13 to 23 Sep 2010. Labs completed to assess for any predisposing reasons for the thrombus showed low protein S and low antithrombin III. The investigator felt that both of these could be explained as consumption of factors for the active clot or could represent an inherited prothrombotic condition.

The investigator did consider that the event could be causally related to treatment with Erwinia asparaginase. However, addressing that the event could also due to the presence of an *implanted vascular access device* and to holding of the enoxaparin doses.

In general, children with serious underlying disorder and/or a precipitation factors like an implanted vascular access device are at high risk of venous thromboembolism. The serious adverse event reported in the one patient is believed not to be directly related to dabigatran etexilate but more to the implanted vascular access device and the underlying disorder (T-ALL) and the concomitant use of chemotherapy.

The gastrointestinal adverse events reported in adolescents appear to be mild. Gastrointestinal adverse events are also a known adverse event in the adult population.

The applicant is requested to follow up the QTC prolongation in the future PIP studies.

1. Discussion on clinical aspects

The study is the first completed investigation in the pediatric population in the frame of a PIP for dabigatran etexilate in the indication “Treatment of venous thromboembolic events in paediatric patients. The study design is exploratory. It was conducted open-labeled, non-randomized, at one location. Six weight adjusted doses of dabigatran etexilate was given for 3 days at the end of standard anticoagulant therapy in eight children aged 12 years to less than 18 years. All eight patients had underlying conditions that could pre-dispose to development of a thrombus. Thus, the included patients adequately reflect the adolescent population where idiopathic thrombosis is a rare event and treatment of a thrombus must be initiate in addition concomitant primary therapies.

The eight adolescents tolerated well dabigatran etexilate taken twice daily for three days. No patient required a reduction in dose due to high dabigatran plasma concentrations. Two of the eight patients who took all six doses of study medication had treatment emergent gastrointestinal adverse events that were mild and transient in nature and did not cause the patients to discontinue study medication. The only serious adverse event occurred five days after the dose of study medication. This event is not considered be related to study medication.

The most critical safety issue observed in the study is the prolongation of the mean QTC interval (Bazett) by 9.56 ms from baseline during treatment. It might be a coincidence but nevertheless it must be addressed in the future PIP studies.

The applicant investigated the pharmacokinetic of dabigatran etexilate and metabolites. All dabigatran plasma concentrations observed were in the predefined acceptable safe area (500 ng/mL). The metabolites were almost non-detectable.

Using the population pharmacokinetic (PopPK) model all but one dabigatran concentration were within the prediction interval. However, the study indicated a slower absorption phase of dabigatran in four of the children than expected giving incorrect the Cmax measurements in these patients. This is a weakness of the study.

The correlations between central and local measurements are difficult to interpret given the different units in presented data.

There is a lack of information concerning the reference intervals for all the evaluated biomarkers in adolescents and a priori expected prolongation of these by dabigatran.

Benefits and risks conclusions

CHMP’s overall conclusion and recommendation

Benefits

The current treatment of venous thromboembolism in children is heparins for 5-7 days followed by three months of heparin or oral anticoagulation. Pediatric patients with uncomplicated venous thrombosis are usually treated for 3 to 6 months. Due to the fact that heparins have to be given parenteral the treatment can be challenging. Thus, pediatric studies in oral anticoagulation therapies for acute venous thromboembolisme is encouraged.

In general dabigatran etexilate taken twice daily for three days was tolerated well. No patient required a reduction in dose due to high dabigatran plasma concentrations. Only mild gastrointestinal adverse events were reported.

Risks

The short study duration and small study population.

One serious adverse event occurred five days after the dose of study medication. However the event was not considered to be related to study medication.

The most critical safety issue observed in the study is the prolongation of the mean QTC interval (Bazett) by 9.56 ms from baseline during treatment.

The study indicated a slower absorption phase of dabigatran in four of the children than expected giving incorrect the C_{max} measurements in these patients. This is a weakness of the study and PopPK model.

Overall conclusion

Dabigatran etexilate was tolerated in the study cohort. However, the study was entirely explorative and no final conclusions can be made regarding safety or PK/PD.

From data presented it is currently not justified to apply the adapted RE-LY population pharmacokinetic model to simulate total dabigatran plasma concentration-time profiles in pediatric populations.

The observed QTC prolongation must be addressed in future studies.

The applicability of biomarkers measured locally and PopPk is to be included in future studies.

Recommendation

Not fulfilled:
Based on the data submitted, the MAH should provide answers to the list of questions as part of this procedure.

Additional clarifications requested

The timetable as proposed by the CHMP is as follows:

a 30 day response timetable with clock stop will apply.

List of Question:

1. The choice of study length indicates that the time of steady state for dabigatran in children is the same as for adults (3 days). This lead to the potential risk of a too short data collection PK/PD-period. Thus the applicant should justify the length of study especially with regard to future phase II studies.
2. In some of the patients the absorption rate of dose number 5 given at day 3 is slower than expected. The applicant is asked to address the lack of peak value measurements in 4 of 8 patients in day 3 with respect to optimizing the PopPK-model for this population.
3. The applicant is asked to provide rations for aPTT and Anti-FIIa analyzed locally.
4. The applicant is asked to make and comment correlation plots between all biomarkers analyzed both centrally and locally.
5. The applicant is asked to supply information concerning the reference intervals for all the evaluated biomarkers in adolescents and the expected prolongation of these by dabigatran.

Assessment of the LoQ

1. *The choice of study length indicates that the time of steady state for dabigatran in children is the same as for adults (3 days). This leads to the potential risk of a too short data collection PK/PD-period. Thus the applicant should justify the length of study especially with regards to future phase II studies.*

MAH response:

The study 1160.88 is part of the PDCO agreed Paediatric Investigation Plan (PIP) for Pradaxa® (dabigatran etexilate) EMEA-000081-PIP01-07 (initial EMEA decision P/76/2008, 15 Sep 2008) according to Regulation (EC) No 1901/2006 as amended. In the meantime the PIP was modified several times and the current version was adopted with the Agency´s decision (P/0228/2012) of 01 Oct 2012.

With the initial PIP decision the duration of study 1160.88 was agreed to be "3 days at the end of standard treatment". Hence, in the Day 30 Compliance Report of the currently ongoing partial compliance check on study 1160.88 the PDCO considered the study compliant with the latest Agency's Decision (P/0228/2012) of 01 Oct 2012.

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 h in young (U06-1614, U00-1856) and 12 to 13 h in elderly healthy adult volunteers (U03-1878), respectively. In adults, steady state is attained by the third day of treatment with dabigatran administered b.i.d. Dabigatran has linear PK and is predominantly renally excreted by passive glomerular filtration and not tubular secretion or reabsorption and as such renal function is the major determinate of dabigatran elimination. In general, the glomerular filtration rate reaches adult levels 8 to 12 months after birth [R07-4220]. Similarly, tubular secretion is immature at birth and reaches adult capacity during the first year of life [R07-4221].

In study 1160.88, dabigatran concentrations were measured at 47.5 h and 72 h (presumed trough levels). For these two time points, the gMean dose-normalized concentrations were similar (Table 1.1) and no trend could be identified in either direction, hence no formal statistical analysis of the attainment of steady state was performed. This may indicate that steady state could have been reached even before the third day of treatment. Further, the adult PopPK model was able to predict total dabigatran concentrations with high precision (80% prediction interval). Here, trough concentrations were well predicted by the model as 16 of 17 trough concentrations (94%) were within the 80% prediction interval. This is in agreement with the expectations, concluding that the model is predictive for trough concentrations.
In the phase IIb/III study 1160.106 further PK/PD data will be collected. This trial will include all paediatric age-groups (i.e. also adolescents). The duration of this trial is three months and weekly PK/PD sampling is planned for at least the first three weeks of treatment.

Table 1.1 Descriptive statistics of dose-normalized individual trough plasma concentrations of total dabigatran after oral administration of dabigatran etexilate (various doses, BID)

	Total dabigatran plasma concentrations [ng/mL/mg]	
	Planned times [h]	
	47.5 h	72 h
N	8	8
gMean	0.517	0.493
gCV [%]	25.5	33.6
Mean	0.532	0.521
CV [%]	26.8	41.4
SD	0.143	0.215
Min	0.375	0.339
Median	0.509	0.459
Max	0.806	1.04

Source Data: 1212-3378, Table 11.5.2: 2

Assessment:

According to the MAH the terminal half-life in young is 11 to 17 h and 12 to 13 h in elderly healthy adult volunteers.

Steady-state is expected to be reached for the present study-cohort within approximately 65 h (range 55 to 85 h). The study duration was only 72 h and the initial safety doses, 65% to 89% of the 2.14 mg/kg. Thus, the study design does not support investigation of PK/PD of dabigatran etexilate under steady-state conditions in adolescents.

In the study, dabigatran concentrations were measured at 47.5 h and 72. According to the MAH the gMean dose-normalized concentrations were similar and no trend could be identified in either direction. However, this observation is based on only eight individuals and must not be over interpreted.

According to the MAH the adult PopPK model was able to predict total dabigatran concentrations with high precision. (See the assessment part in question 2)

The MAH has planned a phase IIb/III study for further PK/PD data collection. This trial is designed to include all paediatric age groups. The duration of the trial is set to three months and with weekly PK/PD sampling for at least the first three weeks of treatment.

Conclusion:

The present study design does not ensure and support standard PK/PD steady-state investigation of dabigatran etexilate in adolescents.

However, the main objective of the study was to investigate the tolerability and safety of dabigatran etexilate capsules and to explore preliminary pharmacokinetics and pharmacodynamics (PK/PD) in adolescents. Consequently, the MAH has planned to address the pharmacokinetics and pharmacodynamics of dabigatran etexilate in a long term study including all paediatric age-groups.

2. *In some of the patients the absorption rate of dose number 5 given on day 3 is slower than expected. The applicant is asked to address the lack of peak value measurements in 4 of 8 patients in day 3 with respect to optimizing the PopPK-model for this population.*

MAH response:

As per protocol, PK sampling was scheduled for 2 h, 47.5 h, 50 h, and 72 h. This sampling scheme included two peak samples at 2 h and 50 h (both 2 h post dose) as dabigatran's maximum plasma concentrations are reported with approximately 2 hours after oral administration. In healthy volunteers, the median time to maximum plasma concentrations increased under food intake from 2 hrs to 4 hrs (BI Trial 1160.40, U04-1459). In 1160.88, none of the peak samples were drawn outside the allowed time window (Table 15.6.1.1: 1, U12-3378). Therefore, due to the sparse sampling approach it is possible that the maximum plasma concentrations were missed. Patients 16 and 17 had not been fasting during the treatment period (Appendix 16.2.8.1.5) and the effect of food intake and the time of food intake (both parameters are no covariates in the PK model) may have contributed to the low dabigatran concentrations at the 50 h timepoint. For patients 12 and 13, no information on food intake was available. In the report, a potential influence of comedication (omeprazole, ranitidine) was discussed.

Of note, study 1160.88 was not used to further refine or optimize the adult PopPK model. The model was only used to predict dabigatran concentration in the adolescent population. The conclusion of this trial was that the model is predictive for trough concentrations as 16 or 17 (93%) of the measured trough values were within the 80% prediction interval. Further, the ongoing phase IIa study 1160.89 and 1160.145 in children with age from 1 to < 12 years may allow a better characterization of dabigatran peak concentrations. In fact, in contrast to the 1160.88, those two studies were designed as a single dose study with more frequent sampling (PK sample collection are 1, 2, 4, 6 and 10 h post dose). By design those two studies may be preferred to better characterize dabigatran concentration time-profiles.

Assessment:

In adults, food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours. Thus, due to the sparse sampling in the present study it is possible that the maximum plasma concentrations were missed by the MAH.

According to the MAH the adult PopPK model was able to predict total dabigatran concentrations with high precision. Illustrated by trough concentrations were well predicted by the model as 16 of 17 trough concentrations (93%) were within the 80% prediction interval. However, in three of eight patients the real trough concentrations were seen later than expected.

Conclusion:

In agreement with the MAH the future PK studies have to be designed with more frequent sampling. We endorse, if possible, an even more frequent PK sample than the one suggested by the MAH to ensure the most reliable measurements of Cmax and trough in the pediatric population and the best platform for a pediatric PopPK model.

3. *The applicant is asked to provide ratios for aPTT and Anti-FIIa analyzed locally.*

MAH response:

Ratios for aPTT and TT (Anti-FIIa) are shown in Table 3.1 and 3.2, respectively.

Table 3.1 Individual effect–time data of aPTT ratio in plasma after multiple oral administration of dabigatran etexilate (various doses, BID) to adolescent patients (with baseline value = 1, local measurement)

		APTT ratio plasma effect–time data				
		Planned times [h]				
Dose	Patient	2	26	47.5	50	72
75 mg then 100 mg BID	13	0.966	1.05	1.13	1.17	1.13
	14	1.42	1.34	1.19	1.50	1.21
	17	1.22	1.31	1.01	0.993	1.02
100 mg then 125 mg BID	12	1.19	1.15	1.21	1.16	1.24
	15	1.36	1.59	1.26	1.68	1.17
	16	1.00	1.58	1.40	1.34	1.48
125 mg then 150 mg BID	10	1.38	1.46	1.18	1.50	1.23
	11	1.51	1.51	1.28	1.57	1.31
75 mg	20	4.44	NC	NC	NC	0.800

NC not calculated
Source Data: 1160.88, Tables 16.1.9.6.1: 11, 16.1.9.6.1: 13, 16.1.9.6.1: 15, 16.1.9.6.1: 17

Table 3.2 Individual effect–time data of TT ratio in plasma after multiple oral administration of dabigatran etexilate (various doses, BID) to adolescent patients (with baseline value = 1, local measurement)

		TT ratio plasma effect–time data				
		Planned times [h]				
Dose	Patient	2	26	47.5	50	72
75 mg then 100 mg BID	13	1.02	1.07	1.12	1.15	1.08
	14	1.22	1.20	1.10	1.43	1.09
	17	1.29	1.52	1.18	1.15	1.15
100 mg then 125 mg BID	12	1.12	1.16	1.17	1.15	1.13
	15	1.22	1.50	1.21	1.52	1.13
	16	0.991	1.51	1.28	1.18	1.35
125 mg then 150 mg BID	10	1.18	1.27	1.12	1.38	1.10
	11	1.17	1.28	1.11	1.18	1.05
75 mg	20	1.62	NC	NC	NC	1.08

NC not calculated
Source Data: 1160.88, Tables 16.1.9.6.1: 12, 16.1.9.6.1: 14, 16.1.9.6.1: 16, 16.1.9.6.1: 18

Assessment:

The APTT ratio increases compared to baseline for most of the patients within the study period. There is a huge inter-individual difference at C_{max} (2h) (range: 0.966-4.44), at C_{max}(26h) (range: 1.05-1.59) and at Cmax(50h) (range: 0.993-1.68). The intra-individual difference in ratio at C_{max} ranges from 0.03 to 0.58. At trough the intra-individual difference in aPTT ratio differs less (range 0.00 to 0.09). The inter-individual difference at trough at 47.5 h ranges from 1.01 to 1.40, and at 72h from 1.02 to 1.48.

Also the TT ratio increases compared to baseline for most of the patients within the study period. There is an inter-individual difference at C_{max} (2h) (range: 0.991-1.62), at C_{max} (26h) (range: 1.07-1.52) and at C_{max}(50h) (range: 1.15-1.52). The intra-individual difference in ratio at C_{max} ranges from 0.010 to 0.52. At trough intra-individual difference in TT ration differs less (range 0.01 to 0.08). The inter-individual difference at trough at 47.5 h ranges from 1.10 to 1.28, and at 72h from 1.05 to 1.35.

Conclusion:

There are some intra and inter-individual differences in both aPTT and TT rations at C_{max} and thus the results must be interpreted with caution. However, at trough intra-individual differences in both aPTT and TT are small.

4. *The applicant is asked to make and comment correlation plots between all biomarkers analyzed both centrally and locally.*

MAH response:

Using Hemoclot® TT assay kits calibrated for known concentrations of dabigatran and back-calculation from the established calibration curves, local dabigatran concentrations were used to determined if dabigatran concentrations did not exceed 500 ng/mL (a criterion for dose reduction). Therefore, these local concentration measurements were primarily used for safety reasons but not to evaluate the PK/PD relationship. Consequently, for the requested correlation plots only centrally determined concentrations were considered as these were determined by the reference method: HPLC-MS/MS.

The relationship between the plasma concentrations of total dabigatran and the coagulation parameters aPTT, ECT, and Hemoclot® TT (Anti-FIIa) ratios as determined centrally, is shown in Figures 4.1, 4.3, and 4.5, respectively (based on the treated set). For the correlation dabigatran concentrations vs. aPTT expressed as ratio an R2 of 0.432 was determined when applying the linear model (aPTT ratio = a + b*conc.). When applying the linear model for the correlation dabigatran concentrations vs. aPTT levels (raw values) the R2 was 0.391 (Figure 4.2). Linear regression models were also used for the parameters ECT and Hemoclot TT (Anti-FIIa). Here, the R2 for the correlation dabigatran concentrations vs. ECT ratio was 0.806 (Figure 4.3) and 0.767 for the respective ECT raw values (Figure 4.4). For dabigatran concentrations vs. Hemoclot® TT (Anti-FIIa) ratio to baseline, the R2 was 0.901 (Figure 4.5). When the raw values were used, the R2 was 0.499 (Figure 4.6). These differences in R2 values between Anti-FIIa ratio and Anti-FIIa raw values may be explained by a reduced variability in the dataset when calculating individual ratios to baseline.

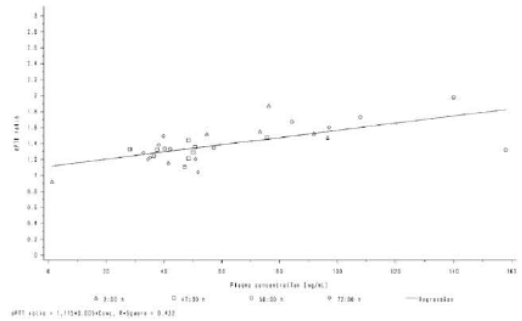


Figure 4.1 Relationship between plasma concentration of total dabigatran and coagulation parameter aPTT ratio (central measurements)

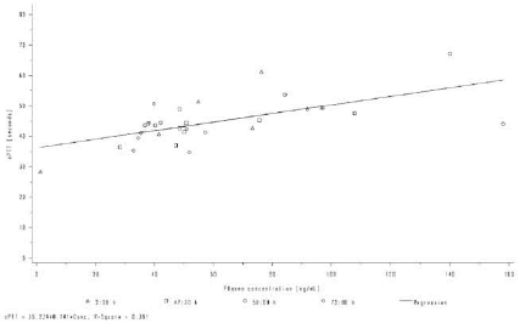


Figure 4.2 Relationship between plasma concentration of total dabigatran and coagulation parameter aPTT (central measurements)

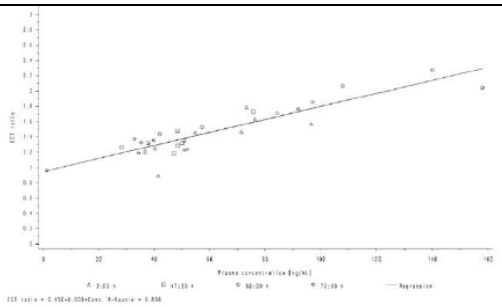


Figure 4.3 Relationship between plasma concentration of total dabigatran and coagulation parameter ECT ratio (central measurements)

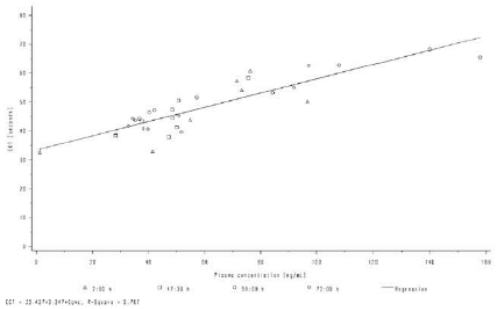


Figure 4.4 Relationship between plasma concentration of total dabigatran and coagulation parameter ECT (central measurements)

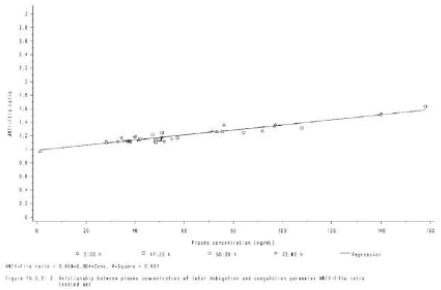


Figure 4.5 Relationship between plasma concentration of total dabigatran and coagulation parameter ANTI-FIIa ratio (central measurements)

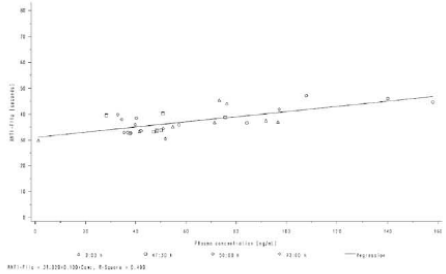


Figure 4.6 Relationship between plasma concentration of total dabigatran and coagulation parameter ANTI-FIIa (central measurements)

The relationship between the plasma concentrations of total dabigatran and the coagulation parameters aPTT ratio and TT ratio as determined locally, is shown in Figures 4.8 and 4.10 respectively (based on the treated set). No PK/PD relationship was assessed with ECT measured locally as ECT prolongation was determined locally only for Patient 20 (two local measurements). ECT was not done for the other eight patients as the site did not have the ECT assay readily available.

For the correlation dabigatran concentrations vs. locally determined aPTT ratio an R2 of 0.697 was determined when applying the linear model (Figure 4.8). When aPTT levels were used the R2 was 0.508 (Figure 4.7). These R2 values indicate a better correlation compared to the central aPTT measurements. However, from adult data the relationship was shown to be non-linear (e.g. RE-COVER, U09-1400, RE-LY U09-3249). Therefore applying a linear model to the correlations between aPTT and dabigatran concentrations may not be considered as appropriate. In contrast, the R2 for the correlation dabigatran concentrations vs. TT ratio (local) was worse when compared to the central measurements (0.754 vs. 0.901). When the raw TT values were used, the R2 values were in a similar range (0.542 vs. 0.499). The local measurements are depicted in Figures 4.9 and 4.10.

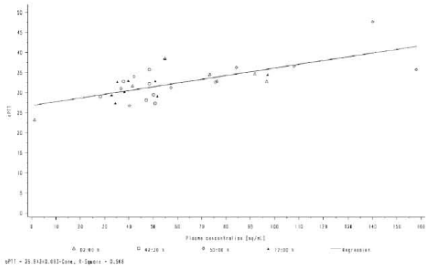


Figure 4.7 Relationship between plasma concentration of total dabigatran (determined from HPLC-MS/MS) and coagulation parameter aPTT (determined locally)

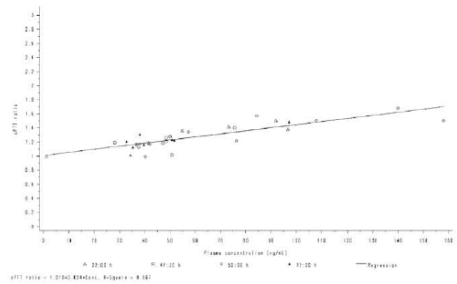


Figure 4.8 Relationship between plasma concentration of total dabigatran (determined from HPLC-MS/MS) and coagulation parameter aPTT ratio (determined locally)

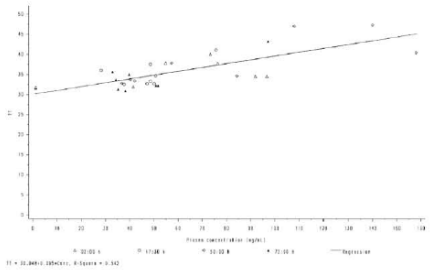


Figure 4.9 Relationship between plasma concentration of total dabigatran (determined from HPLC-MS/MS) and coagulation parameter TT (determined locally)

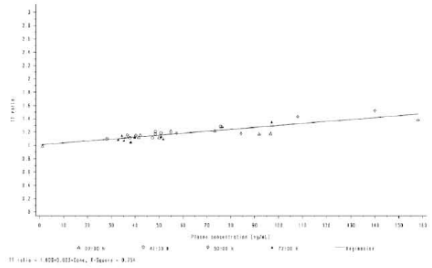


Figure 4.10 Relationship between plasma concentration of total dabigatran (determined from HPLC-MS/MS) and coagulation parameter TT ratio (determined locally)

In summary: when applying a linear model to the relationship between dabigatran concentrations and local laboratory biomarkers, correlation coefficients were either similar or worse than central measurements for TT ratio and TT levels but were better for aPTT ratio and aPTT levels. This curious finding may be interpreted by the fact that a linear correlation between TT ratio and dabigatran concentrations is expected whereas the relationship between aPTT and dabigatran concentrations was shown to be curvilinear and a linear model may inadequately fit this correlation. Further, in this study 8 of 9 patients were recruited in one center and, most of the local laboratory measurements were performed in a single local laboratory. Consequently, any deduction regarding the utility of local laboratory values to predict dabigatran concentrations could not be generalized to studies where multiple local laboratories will be involved.

Assessment:

As requested the relationship between the plasma concentrations of total dabigatran and the coagulation parameters aPTT and TT including ratios were determined both local and central. For ECT only central measurements were possible.

As stated by the MAH applying a linear model to the correlations between aPTT and dabigatran concentrations is not considered appropriate.

The R2 for the correlation dabigatran concentrations vs. TT ratio (local) was worse when compared to the central measurements (0.754 vs. 0.901).

Conclusion:

The applicant has submitted correlation plots between all biomarkers analyzed both centrally and locally.

The best correlation is found between the centrally measured Hemoclot® TT and dabigatran where the proportion of the total variation in the ratio that can be explained by the regression is 81%. For the locally measured Hemoclot® TT the proportion of the total variation in the ratio that can be explained by the regression is only 57%.

5. *The applicant is asked to supply information concerning the reference intervals for all the evaluated biomarkers in adolescents and the expected prolongation of these by dabigatran.*

MAH response:

No reference intervals were determined from the results of 1160.88. However, the PK/PD relationship in this population does not indicate differences to adults. In the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study, the median (10th to 90th percentile) trough aPTT in patients receiving the 150 mg dose was 52 (40 to 76) seconds. Due to a curvilinear relationship of aPTT with dabigatran plasma concentrations and the lack of standardization of aPTT assay across laboratories, aPTT appears not to be useful for the quantitative determination of dabigatran. However, an aPTT result >2.5 times the control is suggestive of excess anticoagulation.

The Hemoclot® assay is a standardized and calibrated assay for the quantitative determination of dabigatran in plasma samples with adequate assay accuracy and precision. The manufacturer claims a range of 50 ng/mL to 500 ng/ml.

In the RE-LY trial, the median (10th to 90th percentile) trough ECT in patients receiving the 150 mg dose was 63 (44 to 103) seconds. However, due to the lack of standardisation of ECT assays between laboratories and lot-to-lot variability of ecarin, calibration of the ECT assay with dabigatran standards and quality control samples would be required.

Assessment:

According to MAH the study does not indicate that the PK/PD relationship for dabigatran etexilate in adolescents is different from what is known for adults. Thus, estimates of aPTT, ECT and the Hemoclot® assay (dTT) appear to be within the known intervals for adults.

The MAH states that, an aPTT result >2.5 times the control is suggestive of excess anticoagulation. However, in adults the coagulation test thresholds at trough that may be associated with an increased risk of bleeding is for aPTT [x-fold upper limit of normal] > 1.3 (SmPC).

Conclusion:

At the moment there is very sparse knowledge of the PK/PD relationship for dabigatran etexilate in adolescents. Furthermore, it is likely that the PK/PD relationship is different in some of the pediatric age groups. We endorse and welcome the planned and ongoing pediatric PK/PD studies.

Comments to the cover letter

In the cover letter the applicant has address the four conclusions in the Assessment Report.

1) Dabigatran etexilate was tolerated in the study cohort. However, the study was entirely explorative and no final conclusions can be made regarding safety or PK/PD.

MAH response:

The approved dabigatran Paediatric Investigation Plan (PIP) comprises:

a) Phase IIa studies conducted in the 3 age groups: in patients with age from 12 to < 18 years (PIP study 3, 1160.88), in patients with age from 1 to < 12 years (PIP study 4, two sister studies 1160.89 (global study excluding USA) and 1160.145 (USA only)) and a study in patients with age from 0 to < 1 year (PIP study 5, 1160.105) The objectives of the phase IIa studies are to provide exploratory safety and tolerability information and to evaluate PK and PK/PD relationship in the respective age groups.
b) A randomized, double-blind, active-controlled, phase IIb/III study. This study comprises two periods: an exploratory period and a confirmatory period. The study is stratified by age groups.
c) A single arm, extended, secondary prevention of venous thromboembolism study in children aged from 0 to < 18 years

The objectives of the IIb/III studies are to confirm the dosing algorithm in reaching plasma trough concentrations in the predetermined target range, to confirm efficacy and safety of dabigatran etexilate comparatively to the standard of care and to provide extended efficacy and safety data in VTE secondary prevention setting.

PK data collected in the Phase IIa studies are important pre-requisites for the phase IIb/III program since they establish the basis for dosing initial estimation in the phase IIb/III. However, it is important to keep in mind that further PK and PD assessments will take place in the phase IIb/III particulaiiy in the exploratory period where dose adjustments aiming to reach target exposure are planned.

The PIP study 3 (1160.88) was the first phase IIa study to be completed. As it is indicated in the clinical trial report, dabigatran etexilate capsules were well tolerated with only three mild and transient gastrointestinal adverse events reported by two patients. Exposure in this adolescent population was slightly lower compared to the exposure seen in adults. Dabigatran doses were not adjusted to renal function in this study which could explain the slightly lower exposure to dabigatran in this population. Consequently, all other Phase IIa and IIb/III studies in the program will take renal function into account for dose determination.

The PK/PD relationship in this population was similar to the relationship seen in adults. This is particularly important to identify target exposure for paediatric patients based on the dabigatran proven efficacy and safety in adults and similar PK/PD relationship. BI believes that this study has fulfilled its objectives in term of providing exploratory safety information, PK and PD data allowing initial dose determination for this population in the phase IIb/III. In the Day 30 Compliance Report of the currently ongoing partial compliance check on study 1160.88 the PDCO considered the study compliant with the latest Agency's Decision (P/0228/2012) of 01 Oct 2012. However, it should be acknowledged that only phase IIb/III program could confirm the dosing algorithm and provide final conclusion regarding efficacy and safety of dabigatran compared to the standard of care.

Comment:

The study 1160.88 has fulfilled its objectives in term of providing exploratory safety information, PK and PD data allowing initial dose determination for adolescence in the phase IIb/III.
It is supported that only phase IIb/III program could confirm the dosing algorithm and provide final conclusion regarding efficacy and safety of dabigatran compared to the standard of care

2) From data presented it is currently not justified to apply the adapted RELY population pharmacokinetic model to simulate total dabigatran plasma concentration-time profiles in pediatric populations.

MAH response:

As it is explained in the answer to question 1 in the assessment report dt. 15 Nov 2012, the adult PopPK model could accurately predict dabigatran plasma trough concentrations in this adolescent population. The sparse sampling approach in the study 1160.88 might have not captured the peak concentrations in some cases. However, due a tight correlation between dabigatran plasma peak and trough concentrations, it is anticipated that the adult PopPK model would be able to accurately predict dabigatran plasma-time concentration-time profile in standardised conditions (fasting conditions, frequent sampling, ect…).

Of note the ongoing phase IIa studies 1160.89 and 1160.145 in children with age from 1 to < 12 years may allow a better characterization of dabigatran peak concentrations. In fact, in contrast to the 1160.88, those two studies were designed as single-dose studies with more frequent sampling (PK sample collection are 1,2, 4, 6 and 10 hours post dose). By design those two studies may be preferred to better characterize dabigatran concentration time-profiles.

Dabigatran trough concentration was a powerful predictor for both efficacy and safety endpoints in adult studies (UlO-3483, U09-3741). In the phase IIb/III program, the initial dabigatran dosing estimation was determined to achieve dabigatran plasma trough concentrations within a predefined therapeutic range. Subsequently, trough concentrations will be frequently evaluated and dabigatran dose will be adjusted as appropriate to reach and maintain patients within the predefined therapeutic range for dabigatran trough concentrations.

Since dabigatran trough concentrations will be used for initial dosing estimation and dose adjustment in paediatric phase IIb/III program and taking into considerations the well-established accuracy of adult PopPK model to predict dabigatran plasma concentrations at trough, BI is of the opinion that using this model is still justified for future studies to predict dabigatran exposure particularly at trough.

Comment:

BI is of the opinion that using the adult model is justified for future studies in the pediatric population to predict dabigatran exposure particularly at trough

This is not supported. Thus, in study 1160.88 the real trough concentrations were seen later than expected in three of eight patients. A pediatric PopPK model must developed and constantly be adjusted to ensure the optimal initial dosing selection in the future pediatric studies. However we acknowledge that the adult PopPK model is a relevant point of reference.

3) The observed QTc prolongation must be addressed in future studies.

MAH response:

The potential impact of dabigatran etexilate on QT-interval was evaluated in the study 1160.54 (U06-1609, *see Module 5.3.3.1, Vol. 50, Feb 2007 CTD).* Therapeutic (150 mg) and supratherapeutic (600 mg) doses of dabigatran etexilate were compared to placebo and moxifloxacin in a single dose, randomised, double-blind, 4-way crossover study. In this study, the gMean of Cmax attained with 600 mg dose was 383 ng/mL, which is several folds higher than the concentrations attained in the study 1160.88. The upper limit of the 95% CI for the mean time-matched QTcI change from baseline and between 1.5 and 3 hours post dosing was 1.5 ms, and thus below the predefined MID of 10 ms. The validity of the results was confirmed by a placebo subtracted mean change from baseline in QTcI of

14.2 ms with moxifloxacin between 1.5 and 3 hours. All secondary parameters were close to zero and other analyses including outlier analyses did not reveal any QT prolongation potential with dabigatran.

The extensive clinical development program in adults did not reveal any association between dabigatran etexilate and QTc prolongation potential.

The study 1160.88 included local ECG assessments. ECGs were performed 12 hours after last dosing (at trough). In this study a mean change from baseline in QTc Bazett of 9.56 ms was reported. In BI view this QTc change is not to be considered as relevant for the following reasons:
- Lack of appropriate methodology and standardisation for the ECG review such as central laboratory, trained readers, appropriate quality control, etc...

- High variability between individuals (high SD)

- Changes in QTc Bazett occurred at trough.

- Dabigatran trough concentrations were low in this study compared to adult studies and far below concentrations attained in the study1160.54.

Based on above, BI believes that these data are not appropriate to suggest any QTc prolongation potential with dabigatran etexilate in paediatric patients. Nonetheless, ECG will be performed as part of the safety evaluation in the phase IIa and phase IIb/III studies. Central ECG is not considered as justified, therefore not planned for future studies.

Comment:

It is acknowledged that the clinical development program in adults did not reveal any association between dabigatran etexilate and QTc prolongation potential.

It is possible that the observed QTc prolongation at trough with low dabigatran concentration is of no relevance. However, we welcome that ECG will be performed as part of the safety evaluation in the phase IIa and phase IIb/III studies. Furthermore we endorse standardization for the ECG review to ensure appropriate trained readers.

Presently it is supported that a thorough QT (TQT) study is not needed in children.

4) The applicability of biomarkers measured locally and FopPk is to be included in future studies.

MAH response:

Due the lack of standardization, high variability and difference in reference ranges with local laboratories; all biomarkers will be centrally measured in future pediatric studies with dabigatran etexilate. The centralization of biomarkers measurements is particularly important in ongoing and future studies since, in contrast to the 1160.88 study, where most patients were recruited in one institute, the ongoing phase IIa study "1160.89" in children with age from 1 to < 12 years involves 13 countries and 23 sites. The phase IIb/III program will involve hundreds of sites worldwide making the collection of local laboratory data extremely unpractical. If adverse events occur, sites may evaluate coagulation parameters; in this case BI intends to gather all relevant information related to the adverse events including locally performed coagulation tests. However BI does not believe that

collecting all local laboratory results would have any added value for the subsequent studies in the program.

PopPK will be implemented and constantly evaluated for the optimization of initial dosing selection in the future studies. Moreover PK data generated from completed pediatric studies will be used to further refine the dabigatran PopPK model and enhance prediction.

Comment:

Both the centralization of biomarkers measurements and a non static pediatric PopPK model are endorsed.

CHMP's final conclusion and recommendations

The study 1160.88 has fulfilled its objectives in term of providing exploratory safety information, PK and PD data allowing initial dose determination for adolescence in the phase IIb/III.

The applicant has addressed all of the questions adequately and thus there are no unresolved issues.

Recommendations for the future pediatric studies:

Development of a non static pediatric PopPK model.

A thorough QT (TQT) study is not needed in children at the moment.

Centralization of biomarkers measurements are endorsed.

Annex.
Line listing of all the studies included in the development program

Clinical studies

Study title	Study number	Date of completion	Date of submission of final study report
Relative bioavailability study of the paediatric and adult formulations.	1160.87	04 May 2009	n.a.*
Open-label trial to evaluate pharmacokinetics and safety of dabigatran etexilate in children aged 12 years to less than 18 years	1160.88	16 Feb 2012	8 Aug 2012
Open-label trial to evaluate pharmacokinetics, pharmacodynamics, safety and tolerability of dabigatran etexilate in children aged 1 year to less than 12 years	1160.89	Plan Dec 2012 (currently ongoing)	
Open-label, randomized, active-controlled study to evaluate pharmacokinetics, pharmacodynamics and safety of dabigatran etexilate versus enoxaparin in children aged 12 years to less than 18 years, 2 years to less than 12 years, and 1 year to less than 2 years.	1160.104	Plan Mar 2014	
Open-label, randomized, active-controlled study to valuate pharmacokinetics, pharmacodynamics and safety of dabigatran etexilate versus enoxaparin in children aged less than 1 year.	1160.105	Plan Mar 2014	
Open-label, randomised, active-controlled, multi-centre, noninferiority study to evaluate efficacy and safety ofdabigatran etexilate versus enoxaparin in children from birth to less than 18 years.	1160.106	Plan Jun 2017	
Open-label, single-arm, longterm study to evaluate the safety of dabigatran etexilate in children from birth to less than 18 years.	1160.108	Plan Jun 2017	

* The study 1160.87 was a bioavailability study in healthy adult volunteers and therefore did not qualify for submission under Art. 46 of Regulation (EC) No 1901/2006. The study report was submitted in the frame of the extension application EMEA/H/C/X/0013/G for the SPAF indication, which was approved on 01 Aug 2011. Furthermore, a change of the pVTEp EU SmPC resulting from study 1160.87 was submitted with EMEA/H/C/000829/II/0014, which was approved with Commission Decision on 01 Jul 2010.