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Human Medicines Evaluation Division

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

Pradaxa

dabigatran etexilate

Procedure no: EMEA/H/C/000829/P46/046

Note

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

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1. Introduction

On 3 August 2016, the MAH submitted the completed paediatric study 1160.89 as part of the clinical development program, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure Paediatric Investigation Plan (PIP study 4).

A short critical expert overview has also been provided.

The MAH states that the study does not alter the benefit and risk evaluations for dabigatran etexilate in adult or paediatric patients and supports pursuing development of dabigatran etexilate in paediatric patients, taken into consideration that additional safeguards will be implemented for patients at an age of < 2 months.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that **study 1160.89**: "Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years" is part of a clinical development program. The extension application is expected to be submitted by Sep/2019.

2.2. Information on the pharmaceutical formulation used in the study<ies>

N/A

2.3. Non-clinical aspects

Both the EMA and the MAH were in agreement that juvenile animal toxicity studies in relation to this PIP were not considered necessary because of the well tolerated profile of dabigatran etexilate in non-clinical species. The US FDA, however, was of the opinion that a juvenile toxicity study with particular emphasis on neurobehavioral, learning, and memory endpoints was required for patients of < 10 years of age for chronic treatment. After agreeing with the FDA on the study design, the MAH has therefore conducted a study in juvenile rats (n00251085) preceded by a dose-range finding study (n00249900).

2.3.1. Results from juvenile toxicity studies

Preliminary dose-range finding study (n00249900-01)

In a preliminary dose-range juvenile toxicity study, dabigatran was administered daily by oral gavage to juvenile Han Wistar rats from Postnatal Day 7 (PND 7) to PND 28 at dosages of 20, 30, 45, 70, 100 and 200 mg/kg. Each group consisted of eight male and female animals each with additional animals for toxicokinetics.

Dosages of 100 and 200 mg/kg were not tolerated and resulted in premature deaths or euthanasia before end of study, mainly due to test-article related haemorrhages. At 70 and 45 mg/kg clinical signs indicative of haemorrhage were limited to few or one animal, respectively. Dosage levels of 20 mg/kg/day and 30 mg/kg/day did not result in any adverse effects.

Histopathological evaluation revealed a mild increase in haemorrhagic events at 70, 100 and 200 mg/kg/day, which are considered to be related to the pharmacodynamic activity of dabigatran etexilate. The toxicokinetic evaluation revealed considerably (up to 5-fold) higher exposures on PND 7 compared to PND 28. The exposure increased less than proportionally to dose in 7 days old rats, but roughly dose-proportionally on PND 28.

Pivotal juvenile toxicity study (n00251085)

In the pivotal juvenile toxicity study, dabigatran etexilate (15, 32.5 or 70 mg/kg/day) or vehicle was administered daily by oral gavage for eight weeks to immature Han Wistar rats from PND 7 to PND 62, inclusive. The maximum dose was derived from the preliminary juvenile study described above.

No effect on neurobehavioral, learning and memory endpoints, bone formation and bone resorption, on developmental landmarks, body weight development, growth or sexual maturation was observed. The No Observed Effect Level (NOEL) for treatment-related macroscopic or microscopic changes in the full range of tissues examined in surviving animals after 8 weeks of treatment was concluded to be equal to or above 70 mg/kg/day.

In four prematurely died animals at 32.5 or 70 mg/kg/day each, pharmacologically induced ocular lesions secondary to haemorrhages were observed. Several other premature deaths also occurred in these dosage groups, however, due to the nature and timing of these deaths (prior to weaning with many cannibalised by the dam) it was not possible to establish a cause of death. One female given 15 mg/kg/day was prematurely killed prior to weaning and due to the macroscopic observation of blood in the abdomen a relationship to treatment was considered possible. It was therefore concluded that the No Observed Adverse Effect Level (NOAEL) for survival and ocular lesions was below 15 mg/kg/day. However, clinical signs indicative of bleeding or mortality started in very young animals (prior to weaning) were probably due to the considerably higher exposure in neonatal rats. The toxicokinetic evaluation confirmed the considerably higher exposures on PND 7 in juvenile rats already seen in the dose-range finding study.

Discussion on results by the MAH in relation to clinical relevance

The pharmacokinetic evaluation of results from both the preliminary and the pivotal juvenile toxicity study showed a high level of comparability between studies. Thus, considerably (up to 5-fold) higher exposures in neonates (7-day old) than in child rats (28-day old), markedly different concentration-time profiles in neonate rats with Cmax around 8 hours after administration compared to child rats with Cmax around 2 hours, and non-linear kinetics in neonatal rats with notably less than dose-proportional increase of exposure was demonstrated in both studies.

The MAH proposes the following probable explanations for the observed differences in pharmacokinetics:

- Reduced activity of P-glycoprotein (P-gp) in neonate rats (increase in intestinal P-gp mRNA from day 7 to day 28) yielding higher exposure.
- Lower activity of carboxylesterase (CES) 2 in the intestines of neonate rats (as indicated by the high and long-lasting levels of the mono-prodrug BIBR 1087 in neonate rats) resulting in different concentration-time profiles with “delayed” tmax values in neonate rats.
- pH-dependent saturation of absorption due to high gastric pH (approximately 5.5) in 7 day-old rats in contrast to low gastric pH (approximately 1.5) in 28 day-old rats, resulting in non-linear pharmacokinetics in neonate rats.

Taking into account the existing labelling for adult patients of concomitant administration of P-gp inhibiting drugs due to the expected increase in exposure, the potentially immature P-gp expression in neonates could result in a likewise increase in exposure in very young patients (i.e. in the first few months after birth). The increase in P-gp mRNA expression from neonates to children is well documented for rats [R16-2422] and mice [R16-3376] and has also been described for the human blood-brain barrier [R16-1881], however for the human intestine the observed difference in P-gp mRNA expression between neonates and infants was small in a limited number of subjects [R16-3234].

2.3.2. Discussion on non-clinical aspects

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

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

2.4. Clinical aspects

2.4.1. Introduction

In parallel with the development of dabigatran adult indications, a paediatric development program was initiated in paediatric patients diagnosed with venous thromboembolism. The paediatric program components include: a) development of an age-approriate formulation; b) determination of bioavailability of paediatric formulation(s) compared with the adult formulation; c) performing phase II and III clinical trials using paediatric formulation to determine safety and efficacy of dabigatran etexilate. The following study is part of this paediatric development program.

The MAH submitted a final report for:

- Study 1160.89: “Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years”.

2.4.2. Clinical study

Clinical study number and title

Study number: 1160.89

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

Description

Methods

Objectives

- To provide paediatric PK/PD data
- To investigate tolerability and safety of dabigatran etexilate solution in children aged 1 to <12 years of age.

Study design

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

Study population /Sample size

Study population

The study included stable paediatric patients from age 1 to less than 2 years and 2 to less than 12 years who were objectively diagnosed with a VTE and who had completed standard anticoagulant treatment for this VTE.

Sample size

It was planned to include approximately 16 patients in this study (approximately 8 patients in each age group). The sample size was not based on a power calculation. Based on the Opinion of the Paediatric Committee (PDCO) of the European Medicines Agency dated 29 Jan 2016 followed by the European Medicines Agency Decision dated 18 Mar 2016, the sample size in the younger age group was reduced to 4 patients aged 1 to <2 years. The size of the study is generally considered sufficient for exploratory evaluations.

Treatments

Multiple doses of dabigatran etexilate were administered in the first three patients from 2 to <12 years (before introduction of single dose application by a protocol amendment); a single dose was administered in nine patients from 2 to <12 years and six patients from 1 to <2 years, at the end of standard anticoagulant therapy for VTE. All patients received the oral liquid formulation (OLF) of dabigatran etexilate. The determination of the total required adjusted nomogram, which was based on the estimated renal function.

In trial 1160.89, a dose conversion factor (bioavailability factor) of 0.646 was applied to the calculated capsule dose to correct for dosing with an oral liquid formulation in paediatric patients. This conversion factor was based on a first relative bioavailability study (trial 1160.87) conducted in healthy adult volunteers, which showed that, following single dose administration, the oral liquid formulation had a 55% higher exposure (AUC0-∞ compared with capsules [U09-1839-01]. However, it was later

recognised based on a larger relative bioavailability trial in a multiple dose setting, that the difference was much smaller and a conversion factor was not needed for defining starting doses in dose finding studies with the option to adjust doses. In the subsequent dosing nomograms, including those used for phase IIb/III, no conversion factor was applied.

All 6 patients in the single dose group aged 1 to <2 years were treated with the planned single dose of dabigatran etexilate which was adjusted based on age and weight of the individual patient.

In the single dose group aged 2 to <12 years, 7 patients received their planned single dose of dabigatran etexilate and 2 patients received less than the planned dose but more than the minimum required dose. All 3 patients in the multiple dose group were to receive 80% of the target dose on Dose 1, followed by 100% for all subsequent 5 doses. Of these 3 patients, 2 patients received the planned dose with very mi nor deviations in volume and 1 patient received a higher volume for all 6 doses (Dose 1: 4.96 mL instead of 4.4 mL; Doses 2 to 6: 6.24 mL instead of 5.4 mL).

Outcomes/endpoints

Pharmacokinetics

The primary PK endpoints were the plasma concentration of total dabigatran (SUM BIBR 953 ZW), free dabigatran (BIBR 953 ZW), unchanged dabigatran etexilate (BIBR 1048 BS), and intermediate metabolites BIBR 951 BS and BIBR 1087 SE, which were determined by a validated high performance liquid chromatography tandem mass spectrometry (HPLCMS/ MS) method. The plasma concentration was measured at 1, 2, 4, 6, and 10 h after single administration of dabigatran etexilate and at 2, 50, and 72 h after multiple dose administration of dabigatran etexilate. In addition Cmax, tmax, and AUCt1-t2 were calculated.

Pharmacodynamics

The primary PD endpoints were the central measurements of aPTT, dTT, and ECT at predose (-2 h) and 2 and 10 h after single intake of study medication. For patients in the multiple dose group, the planned measurements for aPTT and dTT were at screening and 2 h, 26 h, 50 h, and 72 h after the first dose of dabigatran etexilate.

Statistical Methods

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

Descriptive statistics were used for the clinical endpoints, safety, and for PK and PD endpoints including aPTT, ECT, and dTT. Using the centrally measured PD values (aPTT, ECT, dTT) the relationship between total plasma dabigatran concentration and PD endpoints was assessed and compared with the PK/PD relationship observed in older children and adults.

For analysis of the PK/PD relationship a linear regression model and a non-linear Emax model were used.

Results

Recruitment/ Number analysed

A total of 20 patients were screened / enrolled in Canada, Italy, Russia, Lithuania, Thailand, and Switzerland. Of these, 2 patients were screening failures. All 18 patients who were entered into the

study were treated with dabigatran etexilate. All 6 patients aged 1 to <2 years who entered the study were treated with a single dose of dabigatran etexilate. In the age group of 2 to <12 years, 9 entered patients received a single dose of dabigatran etexilate and 3 entered patients were treated with multiple doses of dabigatran etexilate (3 days, twice daily). None of the 18 treated patients prematurely discontinued the trial medication or the trial.

PK / PD

Pharmacokinetics

Single dose group aged 1 to <2 years

After a single dose of dabigatran etexilate (age- and weight-adjusted) in patients aged 1 to <2 years, the gMean AUC0-tz, Cmax, and C10 (concentration at 10h) were 715 ng/mL· h, 129 ng/mL, and 34.8 ng/mL, respectively, with gCVs of 22.5%, 9.84%, and 41.4%. The median tmax was 1.99 h. The concentration values of free dabigatran were a little lower than those observed for total dabigatran.

Single dose group aged 2 to <12 years

After a single dose of dabigatran etexilate (age- and weight-adjusted) in patients aged 2 to <12 year old, the gMean AUC0-tz, Cmax, and C10 were 658 ng/mL· h, 116 ng/mL, and 28.2 ng/mL, respectively, with gCVs of 32.5%, 38.6%, and 37%.

Multiple dose group aged 2 to <12 years

The dosing in the multiple dose group was adjusted for age and weight. In addition, the first dose on Day 1 corresponded to 80% of the target dose. After multiple doses of dabigatran etexilate in patients aged 2 to <12 years, the plasma concentration values of total dabigatran etexilate increased from the planned time points 2 h (peak) after dosing to 50h (peak) and decreased thereafter until the planned time 72 h (trough). The plasma concentration ranged from 13.3 to 39.0 ng/mL at 2 h (peak), from 30.3 to 69.9 ng/mL at 50 h (peak), and from 8.52 to 19.9 ng/mL at 72 h (trough). The concentration values of free dabigatran were a little lower than those observed for total dabigatran.

No apparent pattern or trend was observed of the relationships between AUC0-tz and body weight, age, and eGFR (normalised to adult body surface area).

A sensitivity analysis were performed excluding the 2 patients in the single dose group aged 2 to <12 years who received less dabigatran etexilate than planned (patient nos. 342 and 343) and excluding patient no. 303 in the single dose group aged 1 to <2 years. The latter patient was excluded because the investigator confirmed that the patient spat out the complete medication after the first attempt of administration of medication. When excluding or including the 2 patients in the dose group 2 to <12 years, the difference in gMean AUC0-tz values was less than 15% compared with the original analysis including their values. For the patient in the dose group aged 1 to <2 years, the difference in gMean AUC0-tz values was less than 5%. Thus, the impact of this incorrect dosing was considered irrelevant and therefore all data were included in the final PK analysis.

Pharmacodynamics

The primary PD endpoints were blood coagulation parameters aPTT, ECT and dTT which were analysed using validated methods. All concentrations were listed based on the treated set. The centrally measured concentrations were summarized descriptively. For assessment of aPTT and ECT in the multiple dose group, evaluable data was only available for the time point 72 h after dosing. For dTT, only 2 of 3 patients provided coagulation data within the pre-specified time window.

aPTT in patients receiving a single dose of dabigatran etexilate

For patients aged 1 to <2 years (single dose of dabigatran etexilate), the mean aPTT coagulation times were 32.3 s (baseline), 47.5 s (2 h post dosing) and 40.3 s (10 h post dosing). The mean aPTT ratios were 1.51 (2 h post dosing) and 1.27 (10 h post dosing). The variability was low with CVs of less than 30%.

For patients aged 2 to <12 years receiving a single dose of dabigatran etexilate, the mean aPTT coagulation times were 34.9 s (baseline), 77 s (2 h post dosing), and 58.4 s (10 h post dosing). The mean aPTT ratios were 2.48 (2 h post dosing) and 2.1 (10 h post dosing). The variability was moderate to high with CVs of 24.5 to 59.4%.

dTT in patients receiving a single dose of dabigatran etexilate

For patients aged 1 to <2 years (single dose of dabigatran etexilate), the mean dTT coagulation times were 31.9 s (baseline), 46.6 s (2 h post dosing) and 35.5 s (10 h post dosing). The mean dTT ratios were 1.46 (2 h post dosing) and 1.11 (10 h post dosing). The variability was low with CVs of less than 7%.

For patients aged 2 to <12 years receiving a single dose of dabigatran etexilate, the mean dTT coagulation times were 35.6 s (baseline), 53.6 s (2 h post dosing), and 39.7 s (10 h post dosing). The mean dTT ratios were 1.51 (2 h post dosing) and 1.12 (10 h post dosing). The variability was low to moderate with CVs of less than 19%.

ECT

For patients aged 1 to <2 years (single dose of dabigatran etexilate), the mean ECT coagulation times were 36.9 s (baseline), 79.8 s (2 h post dosing) and 49.7 s (10 h post dosing). The mean ECT ratios were 2.17 (2 h post dosing) and 1.33 (10 h post dosing). The variability was low with CVs of less than 8%.

For patients aged 2 to <12 years receiving a single dose of dabigatran etexilate, the mean ECT coagulation times were 36.8 s (baseline), 73.6 s (2 h post dosing), and 52.2 s (10 h post dosing). The mean ECT ratios were 2.04 (2 h post dosing) and 1.44 (10 h post dosing). The variability was low to moderate with the majority of CVs below 22%.

Multiple dose group

Due to very limited amount of evaluable data, PD data from the multiple dose group were not included in the evaluation of PD parameters.

PK/PD

PK/PD relationship

Using the centrally measured PD values (aPTT, dTT, and ECT), the relationship between total dabigatran plasma concentration and PD endpoints was assessed. Only patients with single doses of dabigatran etexilate were evaluated because of the different times schemes of measurement for single and multiple dose patients.

A linear PK/PD relationship was observed for ECT (ECT ratio) and dTT (dTT ratio). For aPTT (aPTT ratio) a non-linear relationship was observed. The observed PK/PD relationships were similar to those observed in adult (all parameters) and adolescent patients (for dTT and ECT) with VTE.

Impact of age on the PK/PD relationship in patients receiving a single dose of dabigatran etexilate

In addition, the PK/PD relationship was investigated by linear regression with age (in months) as covariate. Since all patients had a different age ranging from 13 to 102 months, this analysis investigated differences between the patients. Because intercepts and slope varied between the patients, in addition individual regression parameters were estimated for aPTT, ECT and dTT. For all investigated PD parameters, age did not seem to influence the PK/PD relationship.

Although dTT values at baseline were higher in older patients compared with younger patients, the slopes of the PK/PD relationship were comparable between all patients. For ECT, the PK/PD relationship was similar for all patients. For aPTT, age did not seem to influence the PK/PD relationship.

In conclusion, following a single dose of dabigatran etexilate (age- and weight-adjusted dose) in patients aged 2 to <12 years, the gMean AUC0-tz, Cmax, and C10 of total dabigatran were 658 ng/mL · h (gCV: 32.5%), 116 ng/mL (gCV: 38.6%) and 28.2 ng/mL (gCV: 37%), respectively. For the single dose group aged 1 to <2 years, the gMean total dabigatran AUC0- tz, Cmax, and C10 were 715 ng/mL · h (gCV: 22.5%), 129 ng/mL (gCV: 9.84%) and 34.8 ng/mL (gCV: 41.4%), respectively.

In patients receiving a single dose of dabigatran etexilate, a linear PK/PD relationship was observed for ECT (ECT ratio) and dTT (dTT ratio). For aPTT (aPTT ratio), the non-linear model described the relationship between dabigatran concentration and prolongation of clotting time appropriately.

The observed PK/PD relationships were similar to those observed in VTE studies in adults and adolescents.

Baseline data

This study included more male (11 patients, 61.1%) than female patients (7 patients, 38.9%). The majority of patients in this trial were White (14 patients, 77.8%). A total of 4 patients (22.2%) in the single dose groups were Asian. All 3 patients in the multiple-dose group were White. In the single dose group aged 1 to <2 years, the mean (SD) age was 17.33 (4.03) months. In the age group 2 to <12 years, patients receiving a multiple dose were about 3 years older than those receiving a single dose (mean [SD] age in single dose group: 5.2 [2.6] years, multiple dose group: 8.3 [2.5] years).

Consistent with the increase in mean age in the 3 treatment groups, the mean (SD) height and weight increased from 80.0 (6.8) cm and 10.68 (2.27) kg in the single dose group aged 1 to <2 years to 110.9 (17.3) cm and 22.56 (11.00) kg in the single dose group aged 2 to <12 years to 132.3 (7.2) cm and 25.67 (1.15) kg in the multiple dose group aged 2 to <12 years. The mean BMI was similar in the single dose groups (1 to <2 years: 16.55 kg/m2, 2 to<12 years: 17.27 kg/m2) and lower in the multiple dose group (14.73 kg/m2).

The mean overall baseline eGFR was 124.75 mL/min/1.73m^2 and was similar in all 3 groups.

As per inclusion criteria, all 18 treated patients had an objective diagnosis of VTE at screening. The most frequent relevant medical histories/baseline conditions were vascular disorders (8 patients, 44.4%), infections and infestations (7 patients, 38.9%), nervous system disorders (6 patients, 33.3%), benign, malignant, and unspecified neoplasms (5 patients, 27.8%), and congenital, familial and genetic disorders (4 patients, 22.2%). Within vascular disorders, jugular vein thrombosis was the most frequent baseline condition (3 patients, 16.7%). Within infections and infestations, the most frequent was mastoiditis (3 patients, 16.7%). Within nervous system disorders, 3 patients each (16.7%) reported cerebral venous thrombosis or intracranial venous sinus thrombosis.

Laboratory analyses (haematology and clinical chemistry) did not reveal any clinically significant findings compared to baseline. Regarding transitions relative to the reference range, no clinically

relevant or unexpected findings were observed for any of the measured parameters. Regarding vital signs, there were no clinically meaningful findings or changes from baseline to each measured time point in blood pressure or pulse rate values.

Efficacy results

Not applicable.

Safety results

Safety analyses in trial 1160.89 were descriptive in nature for all patients who were screened/enrolled, and were based on physical examination, vital signs, 12-lead ECG, laboratory tests and incidence of adverse events as well as assessment of tolerability by the investigator.

Adverse events

A total of 3 patients (16.7%) in this study had AEs during screening (respiratory tract infection, nasopharyngitis, ear pain, and back pain) and 1 patient (5.6%) had AEs during the on-treatment period (leukopenia and dizziness). All AEs were of mild intensity, non-serious and considered to be not related to study drug intake in the opinion of the investigator; all patients recovered. None of the patients had a recurrent VTE during this study.

There were no AEs during the post-treatment or post-study periods. There were no SAEs, no deaths, no AEs leading to discontinuation of trial drug, no drug related AEs (in the opinion of the investigator), no AESIs, and no other significant AEs according to ICH E3 at any time of the trial.

Bleeding events

During the entire study, no bleeding events were reported for the 20 screened patients.

Global assessment of tolerability of the study medication and taste assessment

Most patients had a ‘good’ or ‘not satisfactory’ tolerability. Few patients had ‘satisfactory’ or ‘bad’ tolerability. Within the single dose groups, the younger population seemed to tolerate the medication better than the older population.

The taste assessment was only provided when the patient was old enough to evaluate, i.e. 7 of 9 patients in the single dose group aged 2 to <12 years and 3 patients in the multiple dose group evaluated the taste. Five patients (27.78%) rated the medication as bitter (single dose: 4 patients [44.44%], multiple dose: 1 patient [33.33%]) and 4 patients (22.22%) described the taste as sour (single dose: 2 patients [22.22%], multiple dose: 2 patients [66.67%]).

One patient (11.11%) in the single dose group described the taste as neither bitter, sweet, salty nor sour. Five patients (27.8%) assessed the taste as satisfactory (single dose: 4 patients [44.44%], multiple dose: 1 patient [33.33%]), 3 patients (33.33%) in the single dose group rated the taste as very bad and 2 patients (66.67%) in the multiple dose group described the taste as bad. Of the 5 patients who described the medication as bitter, 4 patients rated the taste as satisfactory and one as very bad. Of the 4 patients who judged the taste as sour, 2 patients described the taste as bad, and 1 patient each as satisfactory or very bad.

2.4.3. Discussion on clinical aspects

This post-authorisation study was part of the Paediatric Investigation Plan. The main objective was to provide paediatric PK and PD data and to assess tolerability and safety of dabigatran etexilate in

successive groups of patients aged 2 to <12 years followed by patients aged 1 to <2 years using an oral liquid formulation of dabigatran etexilate. Further, investigation of safety and tolerability of the dabigatran etexilate solution was an objective.

The study population was small (18 patients). Of these, 6 patients belonged to the group 1-<2 years of age and 12 patients belonged to the group 2-<12 years of age. Originally, sample size was intended to be 8 patients in each group. However, the PDCO subsequently decided to reduce the sample size requirements of the younger age group to 4. Thus, The predetermined goal was met.

Three patients belonging to the older age group were treated with multiple doses of dabigatran etexilate. However, following a protocol amendment, all subsequently included patients were treated with a single dose. Dabigatran etexilate oral liquid formulation was well tolerated and no related AEs occurred during the study period. The two AEs occurring during the on-treatment study period were mild, non-serious, and not considered related to study drug intake. This is considered reasonable. Further, no bleeding events or VTEs occurred and no SAEs or deaths were reported.

The projected steady-state dabigatran trough concentrations of the present study were largely comparable to those observed in adult patients with VTE (see Table 2).

Table 2 Comparison of plasma trough total dabigatran concentrations of patients aged 1 to <2 years and patients aged 2 to <12 years (trial 1160.89) with those of RE-COVER (1160.53) in adults.

	1160.89				RE-COVER[a]
	Total dabigatran concentration 10 hr post-dosing (ng/mL)		Projected steady-state total dabigatran trough concentration (ng/mL)		Total dabigatran trough concentration (ng/mL)
	1 to < 2yrs	2 to < 12 yrs	1 to < 2yrs	2 to < 12 yrs	
N	6	9	6	9	850
gMean	34.8[a]	28.2[b]	53.1–87.6[c]	40.8–67.3[d]	59.7
gCV (%)	41.4	37.0	-	-	81.6
Median	30.2	28.8	-	-	58.7
CV (%)	41.7	35.4	-	-	79.7
Q1	-	-	-	-	38.6
Q3	-	-	-	-	94.5
P10					26.3
P90					146

[a] Taken from Visit 4 data in RE-COVER [U09-1400-01, Table 15.6.1.1:1]
Projected steady-state trough (c) or (d) = (C_{10} [a] or [b]) /BA factor x AR x 2 h decay rate. BA = dose conversion factor (0.646); AR = accumulation ratio = $1/(1- e^{-k*tau})$, where $k = 0.693/t_{1/2}$, tau =12h, $t_{1/2}$ = 5 - 10 h. 2 h decay rate = e^{-kt}; where $k = t_{1/2}/0.693$, t=2h, $t_{1/2}$ = 5 -10 h

Pharmacodynamic results generally showed low to moderate variability albeit aPTT ratios in the age group 2-<12 years had CVs of 24.5-59.4% (ie. high variability).

The PK/PD relationship for dTT and ECT was linear, whereas the PK/PD relationship was non-linear for aPTT. These findings were similar to those observed in adults and adolescents with VTE.

APTT, ECT and dTT values obtained at baseline and through the follow-up period (single-dose) are presented below:

	Baseline Mean (seconds)	**2 h post dosing** Mean (seconds)	**10 h post dosing** Mean (seconds)
Age: 1-<2			
APTT	32.3	47.5	40.3
ECT	36.9	79.8	49.7
dTT	31.9	46.6	35.5
Age 2-<12			
aPTT	34.9	77	58.4
ECT	36.8	73.6	52.2
dTT	35.6	53.6	39.7

No reference ranges are listed in the clinical overview or in the clinical summary of safety. However, while the study participants belonging to the older age group appear to maintain the anticoagulant effect of one dose of dabigatran both 2 hours and 10 hours post dosing, the effect in the study participants belonging to the younger age group is questionable. While they appear to be sufficiently anticoagulated after 2 hours, the anticoagulant effect of one single dose of dabigatran has decreased markedly after 10 hours for all three parameters. The Applicant is requested to discuss whether this restoration of seemingly normal coagulation after 10 hours represents a problem – i.e. in the event that a BID regimen based on the nomogram investigated in children will be implemented, are children belonging to the age group of 1-<2 years at risk of experiencing periods of insufficient anticoagulation prior to the next dose of dabigatran? Further, references ranges used for all PD parameters should be included.

Combined PK/PD analyses based on three paediatric studies (1160.88, 1160.89 and 1160.105) indicate that very young children aged <2 months who have higher baseline aPTT and ECT values may show an increased sensitivity to dabigatran exposure. The ongoing studies 1160.106 and 1160.108 include several safeguard measures to reduce the potential risk for paediatric study participants. However, in light of the above-mentioned results, additional safeguard measures are suggested for implementation in the ongoing phase IIb/III program (PIP study 7) and will be introduced as amendments to the global protocol. They will allow for rapid assessment of potential over-exposure as indicated by aPTT exceeding 2-fold of ULN. This is considered appropriate.

Overall, the present study has not contributed new safety signals regarding dabigatran etexilate.

The results support the future use of a dosing algorithm based on an age- and weight-adjusted dosing nomogram taking into account estimated renal function.

The MAH has not submitted an updated SmPC reflecting the results obtained in the current study. The MAH suggests a SmPC update in September 2019 when the full PIP package is submitted. However,

this postponement by 3 years of updating the SmPC is not acceptable as the SmPC must reflect current knowledge.

3. Rapporteur's overall conclusion and recommendation

Overall, no new safety signals regarding dabigatran etexilate have emerged following the completion of the present study. However, an outstanding question regarding PD parameters (as indicative of effect) in the age group 1-<2 remains to be addressed.

The MAH has not submitted an updates SmPC reflecting the data generated in children aged 1-<12 years of age but suggests postponing this until September 2019 when the full PIP package is submitted. This is not acceptable as the SmPC must reflect current knowledge. Consequently, the MAH is requested to update the SmPc.

☐ **Fulfilled:**

X Not fulfilled:

Based on the data submitted, the MAH should provide an updated SmPC reflecting the data generated in the present study regarding the use of dabigatran etexilate in children aged 1-<12 years of age (see section "Additional clarification requested").

4. Additional clarification requested

Based on the data submitted, the MAH should address the following question as part of this procedure:

1. No reference ranges are listed. However, while the study participants belonging to the older age group appear to maintain the anticoagulant effect of one dose of dabigatran both 2 hours and 10 hours post dosing, the effect in the study participants belonging to the younger age group is questionable. While they appear to be sufficiently anticoagulated after 2 hours, the anticoagulant effect of one single dose of dabigatran has decreased markedly after 10 hours for all three parameters. The Applicant is requested to discuss whether this restoration of seemingly normal coagulation after 10 hours represents a problem – i.e. in the event that a BID regimen based on the nomogram investigated in children will be implemented, are children belonging to the age group of 1-<2 years at risk of experiencing periods of insufficient anticoagulation prior to the next dose of dabigatran? Further, references ranges used for all PD parameters should be included.
2. The MAH is requested to provide an updated version of the SmPC reflecting the data generated in the present study regarding the use of dabigatran etexilate in children aged 1-<12 years of age in section 5.2. This update may be submitted in conjunction with an update of the SmPC involving the results of study 1160.105 (PIP study 6).

MAH responses to Request for supplementary information

1. No reference ranges are listed. However, while the study participants belonging to the older age group appear to maintain the anticoagulant effect of one dose of dabigatran both 2 hours and 10 hours post dosing, the effect in the study participants belonging to the younger age group is questionable. While they appear to be sufficiently anticoagulated after 2 hours, the anticoagulant effect of one single dose of dabigatran has decreased markedly after 10 hours for all three parameters. The Applicant is requested to discuss whether this restoration of seemingly normal coagulation after 10 hours represents a problem – i.e. in the event that a BID regimen based on the nomogram investigated in children will be implemented, are children belonging to the age group of 1-<2 years at risk of experiencing periods of insufficient anticoagulation prior to the next dose of dabigatran? Further, references ranges used for all PD parameters should be included.

MAH response

BI acknowledges that in the 1160.89 study (c09069268-01), the participants aged 2 to <12 years showed slightly higher aPTT, dTT, and ECT values at 10 hours post dabigatran etexilate dosing in comparison with the participants aged 1 to <2 years (table 1/1).

Table 1/1 aPTT, dTT, and ECT at baseline, 2 h, and 10 h after a single dose of dabigatran etexilate

	aPTT			dTT			ECT		
	N	Mean	CV [%]	N	Mean	CV [%]	N	Mean	CV [%]
Single dose, 1 to <2 y									
E_{base} [s]	6	32.3	24.6	6	31.9	4.67	6	36.9	7.49
E_2 [s]	6	47.5	24.7	6	46.6	6.02	6	79.8	5.15
E_{10} [s]	5	40.3	19.6	6	35.5	6.02	5	49.7	5.36
Single dose, 2 to <12 y									
E_{base} [s]	7	34.9	24.5	9	35.6	10.1	6	36.8	10.5
E_2 [s]	9	77	54.6	9	53.6	18.4	7	73.6	22.1
E_{10} [s]	8	58.4	40.6	9	39.7	9.76	7	52.2	10.3

However the following needs to be considered:

- The aim of the 1160.89 study was to establish some preliminary PK-PD guidance for development of a therapeutic starting dose in the phase IIb/III studies. Whether or not the starting dose in phase IIb/III can be maintained or needs adjustment is subject of several plasma level measurements in phase IIb/III studies (still ongoing).
- The age group of patients 2 to <12 years could represent a more heterogeneous group than the group of patients aged 1 to <2 years. This notion is supported by the generally higher variability (CV%) in the former group.
- The sample size of the study was small with only 6 patients aged 1 to <2 years and 12 patients aged 2 to <12 years. The majority of patients (15/18) received a single dose of oral liquid formulation (OLF) of dabigatran etexilate and only 3 patients aged 2 to <12 years received 6 doses of an OLF of dabigatran etexilate.

- Taken together, the above two points on patient composition and sample size make comparisons between the two groups difficult to interpret.
- The pharmacodynamic effect observed in the study after a single dose administration of dabigatran etexilate needs to be interpreted with caution as this effect would be expected to increase when achieving the steady state (i.e. after 3 days of dabigatran etexilate BID administration) in patients who would receive repeated administration of dabigatran etexilate.
- In the 1160.89 study, the dose of dabigatran etexilate was calculated according to a dose conversion factor of 0.646 which was applied to the calculated capsule dose to correct for bioavailability of an OLF versus capsules based on a first bioavailability study (BI trial 1160.87, U09-1839). However, it was later recognized via a more robust study (BI trial 1160.194, c02248557) that this conversion factor was not needed. If no conversion factor had been applied in the 1160.89 trial, the geometric mean value of total dabigatran plasma concentrations at 10 hours (C10) for both age groups 2 to <12 years and 1 to <2 years old would have been higher as it can be projected as "observed C10 value/BA factor of 0.646" (table 1/2). The resulting impact on expected plasma levels under steady state conditions has also been projected in Table 1/2 below. Based on the above mentioned more robust bioavailability study (BI trial 1160.194), in subsequent dosing nomograms, including those used for the phase IIb/III studies, no conversion factor will be applied and consecutively the applied starting doses in the phase IIb/III studies are actually higher as compared to the single dose applied in trial 1160.89.

Table 1/2 **Comparison of plasma trough total dabigatran plasma concentrations of patients aged 1 to <2 years and patients aged 2 to <12 years (trial 1160.89) with those of RE-COVER (1160.53) in adults**

	1160.89				RE-COVER*
	Total dabigatran concentration 10 hr post-dosing (ng/mL)		Projected steady-state total dabigatran trough concentration (ng/mL)		Total dabigatran trough concentration (ng/mL)
	1 to < 2yrs	2 to < 12 yrs	1 to < 2yrs	2 to < 12 yrs	
N	6	9	6	9	850
gMean	34.8[a]	28.2[b]	53.1–87.6[c]	40.8–67.3[d]	59.7
gCV (%)	41.4	37.0	-	-	81.6
Median	30.2	28.8	-	-	58.7
CV (%)	41.7	35.4	-	-	79.7
Q1	-	-	-	-	38.6
Q3	-	-	-	-	94.5
P10					26.3
P90					146

*Taken from Visit 4 data in RE-COVER (U09-1400-01)

Projected steady-state trough (c) or (d) = (C_{10} [a] or [b]) /BA factor x AR x 2 h decay rate. BA = dose conversion factor (0.646); AR = accumulation ratio = $1/(1- e^{-k*tau})$, where k = $0.693/t_{1/2}$, tau =12h, $t_{1/2}$ = 5 -10 h. 2 h decay rate = e^{-kt}; where k = $t_{1/2}/0.693$, t=2h, $t_{1/2}$ = 5 -10 h

- Based on the pharmacokinetic parameters after single dose administration, the steady state projected dabigatran trough plasma concentrations were calculated. These calculations show that dabigatran plasma concentrations are largely comparable to those observed in adult patients with VTE (U09-1400-01) (see table 1/2). Therefore, the projected pharmacokinetic trough plasma concentrations indicate that an adequate anticoagulation effect seems to be achievable if reaching steady state.
- The PK-PD relationship between dabigatran plasma concentrations and the coagulation parameters was linear for dTT and ECT and a non-linear for aPTT. This PK-PD relationship was similar for patients aged 1 to <2 years and patients aged 2 to <12 years. Moreover, the observed PK/PD relationships in study 1160.89 were similar to those observed in adult (U09-1400-01) and adolescent patients (U12-3378-01, P16- 07842) with VTE.
- In the 1160.89 study, aPTT, dTT and ECT were pharmacodynamic endpoints and not safety endpoints; therefore, reference values were not defined, as it was expected that these parameters would be prolonged beyond the upper limit of normal (ULN) under dabigatran treatment.

- Additionally, no age specific values were available for the study. However, the normal ranges for adults used by the Central Laboratory that analysed the samples of the study (Menal GmbH Emmendingen, Germany) can be used as a reference. These reference values are the following:

    - aPTT: baseline 31.4 seconds, ULN: 39.8 seconds.
    - dTT: baseline 32.1 seconds, ULN: 35.5 seconds.
    - ECT: baseline: 36.0 seconds, ULN: 41.3 seconds.

  It has to be taken into account that although the analytical methods are kept as constant as possible, differences between adult and paediatric baseline values may arise from different reagent lots (e.g. thrombin, which varies in activity) and from subject intrinsic factors.

- The aPTT, dTT, and ECT values after 10 hours of dabigatran etexilate administration were above the ULN values mentioned above for the two age groups analysed in the study, except for the dTT values in patients aged 1 to <2 years, which were below the above mentioned (i.e. not age-adjusted) ULN. Therefore, in the patients included in the study, an anticoagulant effect is still present at the 10 hour time point after dabigatran etexilate administration. As mentioned above, this effect is expected to increase further when steady state is reached and with a higher starting dose used in phase IIb/III trials compared to trial 1160.89 (due to the omission of the conversion factor in the ongoing phase IIb/III trials).

- The pharmacodynamic effect is evaluated in the ongoing phase IIb/III efficacy and safety study 1160.106 and in the phase IIb/III safety study 1160.108. These studies will provide data on the effect of dabigatran on the coagulation parameters (aPTT, dTT, ECT) after repeated administrations in patients aged from 0 to <18 years old, and without conversion factor for OLF. Therefore, the effect on aPTT, dTT, and ECT in patients <2 years will be available from these studies.

- The twice daily (BID) dosing nomogram used in studies 1160.106 and 1160.108 was developed to achieve the steady state trough concentrations (C12) of dabigatran between 50 and <250 ng/ml (target range) which has a reasonable likelihood to be effective, safe and thus have a positive benefit/risk ratio in children of all ages. Plasma concentrations is these patients are measured repeatedly and the dose of dabigatran is adjusted, if the concentration is outside the target range

In summary, the 1160.89 study was a preliminary PK-PD study including patients aged 1 to <12 years. The majority of patients received only a single dose of an OLF of dabigatran etexilate. OLF doses were lower compared to those currently used in phase IIb/III studies based on the conversion factor of 0.646 applied in 1160.89. The steady state projected dabigatran trough plasma concentrations show results largely comparable to those observed in adult patients for patients aged 1 to <2 years and patients aged 2 to <12 years. An adequate anticoagulation effect seems to be achievable with trough plasma concentrations at steadystate. The effect of dabigatran on coagulation parameters after repeated administration in patients aged 0 to <18 years is evaluated in the ongoing phase IIb/III studies.

Assessment

The Applicant has provided reference ranges for aPTT, dTT and ECT. However, the Applicant emphasizes that these are general reference ranges for adults and that extrapolation to the population under study may only be done with caution. This is acknowledged.

The MAH recognizes that the aPTT, dTT and ECT values after 10 hours of dabigatran etexilate administration were not above the ULN reference values for adults. However, the MAH maintains that an anticoagulant effect is still present since the reference values have not been age adjusted.

The PD effects of dabigatran etexilate will be further evaluated throughout Phase IIb/III studies of the PIP package and results from these studies will provide data on the effect of dabigatran etexilate on aPTT, dTT and ECT after multiple administrations in patients aged 0-<18 years of age, and without conversion factor for oral liquid formulation. Thus, also data regarding aPTT, dTT and ECT in patients <2 years of age will be generated. This is considered acceptable.

Conclusion

Issue resolved.

2. The MAH is requested to provide an updated version of the SmPC reflecting the data generated in the present study regarding the use of dabigatran etexilate in children aged 1-<12 years of age in section 5.2. This update may be submitted in conjunction with an update of the SmPC involving the results of study 1160.105 (PIP study 6).

MAH response

BI acknowledges the question provided, however, considers an update of the SmPC at this stage of development not warranted based on the justification provided below.

The current SmPC Guideline (September 2009, Revision 2) accounts for a regular update of section “5 PHARMACOLOGICAL PROPERTIES” once new information becomes available, especially in relation to the paediatric population. Noteworthy, the SmPC

Guideline, for specific sections, foresees inclusion of scientific data only in case clinical relevance is given, e.g. section “5.1 Pharmacodynamic properties”.

BI considers the results obtained from clinical studies 1160.89 and 1160.105 comprising no new information and being of clinically non-relevant nature for the following two reasons:

- The PK, PD, and safety data from both studies confirm the previously obtained results in adolescents and are similar to that retrieved from adults and are already being presented in the current approved PRADAXA SmPC.
- No safety issues specific to the paediatric population have been observed in above studies, which are not yet described per adult SmPC.

As stated in a comment received by a Member State, the presented studies are only the first steps in the agreed PIP, with an aim to establish some preliminary PK/PD guidance for development of a therapeutic dosing scheme in the phase IIb/III studies. Both studies are single dose, tolerability,

pharmacokinetic/ pharmacodynamics and safety studies only and included a small number of patients only. For the multiple dose group (n=3 patients only), very limited PK/PD data are available that does not allow for a robust conclusion.

Moreover, the dosing scheme that had been used in both above studies differs from the dosing schedule currently being used in the phase IIb/III paediatric studies, which is based on a specifically developed age and weight-based nomogram and potential dose correction based on dabigatran plasma level measurements. Age determines the renal function of a child and is essential for dosing of dabigatran etexilate. Therefore the dosing in children differs from adult dosing. Whereas changes in renal function are physiological across the years of childhood, maturation or renal function is completed after adolescence allowing for simplified fixed dosing in healthy adults. Dosing based on the Hayton Formula accounts for the maturation of renal function across childhood, which results into a more individualized dosing algorithm in children.

Importantly, the OLF used in the two trials is not commercially available (and not formally bioequivalent to capsules) and final dosing instructions can only be defined after phase IIb/III trials are completed. Presenting such preliminary paediatric PK/PD data may stimulate offlabel use by paediatricians based on an outdated dosing scheme which should not be used for therapeutic dosing.

Given the rationale above, BI proposes to refrain from including preliminary and potentially misleading PK/PD information from studies 1160.89 and 1160.105 in section 5.2 of the SmPC and suggests updating the SmPC with the paediatric PK/PD data obtained at time of submission of the paediatric VTE treatment indication, when more robust paediatric PK/PD information is available from two larger-sized phase IIb/III studies (1160.106 & 1160.108).

Assessment

The MAH emphasizes that current data are preliminary and based on a very limited number of patients making them less robust. Further, the oral liquid formulation used in the two paediatric studies is not commercially available and formally no bioequivalence has been established. This is endorsed.

The MAH proposes to await robust data from Phase IIb/III trials and completion of the full PIP package before updating the SmPC. The full PIP package will be completed by September 2019. This strategy is considered acceptable.

Conclusion

Issue resolved.

5. Rapporteur's overall conclusion and recommendation

Overall, no new safety signals regarding dabigatran etexilate have emerged following the completion of the present study. The Benefit-risk balance remains positive. The MAH proposes to await robust data from Phase IIb/III trials and completion of the full PIP package before updating the SmPC. The full PIP package will be completed by September 2019. This is considered acceptable.

☒ **Fulfilled:**

☐ **Not fulfilled:**