# CLINICAL AND STATISTICAL REVIEW

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| Application Type | Efficacy Supplement |
| Application Number(s) | sNDA 022512, S-0041; (b) (4) NDA 214358 |
| Priority or Standard | Priority |
| Submit Date(s) | 9/21/2020 |
| Received Date(s) | 9/21/2020 |
| PDUFA Goal Date | 3/21/2021 |
| Division/Office | Division of Non-malignant Hematology (DNH) |
| Reviewer Name(s) | Fadi Nossair |
| CDTL Name | Virginia Kwitkowski |
| Statistical Reviewer | Sarabdeep Singh |
| Statistical Team Leader | Yeh-Fong Chen |
| Review Completion Date | 2/23/2021 |
| Established/Proper Name | Pradaxa® |
| (Proposed) Trade Name | Dabigatran etexilate |
| Applicant | Boehringer Ingelheim Pharmaceuticals, Inc. |
| Dosage Form(s) | Capsule, oral pellets, (b) (4) |
| Applicant Proposed Dosing Regimen(s) | Twice-daily oral administration of actual weight-based and age-based dosing |
| Applicant Proposed Indication(s)/Population(s) | <u>For sNDA 022512, S-0041</u>:<br>- For the treatment of venous thromboembolism in pediatric patients 8 years of age and older who have been treated with parenteral anticoagulants for at least 5 days<br>- To reduce the risk of recurrence of venous thromboembolism in pediatric patients 8 years of age and older who have been previously treated<br>(b) (4)<br><br><u>For NDA 214358</u>:<br>- For the treatment of venous thromboembolism in pediatric patients (b) (4) 12 years of age who have been treated with parenteral anticoagulants for at least 5 days<br>- To reduce the risk of recurrence of venous thromboembolism in pediatric patients (b) (4) 12 years of age who have been previously treated |

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| Recommendation on Regulatory Action | Traditional Approval for sNDA 022512, S-004 and NDA 214358 (b) (4) |
| Recommended Indication(s)/Population(s) (if applicable) | For sNDA 022512, S-0041:<br>- For the treatment of venous thromboembolism in adult and pediatric patients 8 years of age and older who have been treated with parenteral anticoagulants for at least 5-10 days<br>- To reduce the risk of recurrence of venous thromboembolism in adult and pediatric patients 8 years of age and older who have been previously treated<br>NDA 214358 (for Pradaxa oral pellets):<br>- For the treatment of venous thromboembolism in pediatric patients (b) (4) to less than 12 years of age who have been treated with parenteral anticoagulants for at least 5 days.<br>- To reduce the risk of recurrence of venous thromboembolism in pediatric patients (b) (4) to less than 12 years of age who have been previously treated. |

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## Glossary

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| AC | advisory committee |
| ACT | Activated Clotting Time |
| ADaM | Analysis Data Model |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Aminotransferase |
| APS | Antiphospholipid antibody Syndrome |
| aPTT | Activated Partial Thromboplastin Time |
| AR | adverse reaction |
| ASA | Acetylsalicylic Acid |
| ASD | Atrial Septal Defect |
| AST | Aspartate Aminotransferase |
| BIMO | Bioresearch Monitoring |
| BPCA | Best Pharmaceuticals for Children Act |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CHD | Congenital Heart Disease |
| CHF | Congestive Heart Failure |
| CM | Concomitant Medication |
| CMC | chemistry, manufacturing, and controls |
| CRNM | Clinically Relevant Non-Major |
| CSR | Clinical Study Report |
| CSVT | Cerebral Sinovenous Thrombosis |
| CVC | Central Venous Catheter |
| DMC | Data Monitoring Committee |
| DNH | Division of Non-malignant Hematology |
| DOAC | Direct Oral Anticoagulant |
| dTT | Dilute Thrombin Time |
| DVT | Deep Venous Thrombosis |
| ECG | Electrocardiogram |
| ECT | Ecarin Clotting Time |
| eCTD | electronic common technical document |
| eGFR | Estimated Glomerular Filtration Rate |
| eEOT | Early End of Treatment |
| FDA | Food and Drug Administration |
| FDQ | Financial Disclosure Questionnaire |
| FPI | Full Prescribing Information |
| GCP | Good Clinical Practice |

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| HITT | Heparin-induced Thrombocytopenia Thrombosis |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IEC | Independent Ethics Committee |
| INR | International Normalized Ratio |
| IRB | Institutional Review Boards |
| ITT | Intent to Treat |
| LMWH | Low Molecular Weight Heparin |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MH | Medical History |
| NDA | New Drug Application |
| OSI | Office of Scientific Investigation |
| PA | Pulmonary Artery |
| PD | Pharmacodynamics |
| PDA | Patent Ductus Arteriosus |
| PE | Pulmonary Embolism |
| USPI | U.S. prescribing information or package insert |
| PICU | Pediatric Intensive Care Unit |
| PK | Pharmacokinetics |
| PMR | Postmarketing requirement |
| PPI | Proton Pump Inhibitor |
| PPSR | Proposed Pediatric Study Request |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PT | Preferred Term |
| PTS | Post-Thrombotic Syndrome |
| REMS | risk evaluation and mitigation strategy |
| TT | Thrombin Time |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SDTM | Study Data Tabulation Model |
| SOC | System Organ Class |
| SoC | Standard of Care |
| SVP | Single Ventricle Physiology |
| TEAE | treatment emergent adverse event |
| UFH | Unfractionated Heparin |
| ULN | Upper Limit of Normal |
| VKA | Vitamin K Antagonists |
| VSD | Ventricular Septal Defect |
| VTE | Venous Thromboembolic Events |
| WR | Written Request |

# 1. Executive Summary

## 1.1. Product Introduction

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| Proprietary Name | PRADAXA® |
| Established Name | dabigatran etexilate |
| Dosage Forms | - Capsules: 75 mg, 110 mg and 150 mg<br>- Oral pellets: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg<br>(b) (4) |
| Chemical Class | Small molecule pro-drug |
| Pharmacologic Class | Thrombin inhibitor |
| Mechanism of Action | Competitive direct reversible thrombin inhibition resulting in reduction of thrombin-mediated conversion of fibrinogen to fibrin and thrombin-induced platelet activation, thereby limiting arterial and venous thrombosis. |

PRADAXA® (dabigatran etexilate) received initial U.S. approval on 10/19/2010. The current approved indications are:

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days.
- To reduce the risk of recurrence of DVT and PE in patients who have been previously treated.
- For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.

The Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., submitted the following applications in support of the pediatric efficacy of Pradaxa, each application with their respective dosage formulations and proposed indications:

- Efficacy Supplement 041 to NDA 022512:
  - Marketed dosage formulation: Capsules (75 mg, 110 mg and 150 mg)
  - Proposed dosing regimen: Twice-daily oral administration of actual weight-based and age-based dosing, as summarized by Figure 1 in section 6.1.1 of this review. There was no titration method proposed by Applicant. (b) (4)
  - Proposed indication:
    - For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 years of age and older who have been treated with a parenteral anticoagulant for at least 5 days.
    - To reduce the risk of recurrence of VTE in pediatric patients 8 years of age and older who have been previously treated.
- NDA 214358:
  - New dosage formulation: Oral pellets (20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg)

- Dosing regimen: Twice-daily oral administration of actual weight-based and age-based dosing, as summarized by Figure 2 in section 6.1.1 of this review. There was no titration method proposed by Applicant. (b) (4).
- Proposed indication:
  - For the treatment of venous thromboembolic events (VTE) in pediatric patients (b) (4) 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days.
  - To reduce the risk of recurrence of VTE in pediatric patients (b) (4) 12 years of age who have been previously treated

(b) (4)

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness of Pradaxa for the following indications:

- The treatment of VTE in pediatric patients from (b) (4) to less than 18 years of age, who have been treated with parenteral anticoagulants for at least 5 days.
- The secondary prevention of VTE in pediatric patients from (b) (4) to less than 18 year of age, who have been previously treated with anticoagulants and who are at increased risk of VTE recurrence due to persistent VTE risk factors.

The first indication is based on the final results of a pre-specified non-inferiority analysis of a composite efficacy endpoint that evaluated the proportion of patients who achieved all of the following criteria: complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related mortality. The pivotal trial was a multi-center, open-label, randomized, active-controlled trial comparing Pradaxa to standard of care (SoC) anticoagulation in pediatric patients, from birth to less than 18 years of age, who were diagnosed with VTE, initially treated with parenteral anticoagulation therapy for at least 5 days, and needed at least 3 month of anticoagulation therapy. In this trial, 45.8% of patients on Pradaxa (81 of 177 patients), compared to 42.2% of patients on SoC (38 of 90 patients), met the criteria for the composite primary endpoint, with a rate difference of -0.038 (95% CI: -0.161,0.086), thus demonstrating the target non-inferiority margin of 20%.

The results of all sub-group analyses and pre-specified sensitivity analyses were consistent with the result of the primary endpoint, which was further supported by consistent results when all individual components of the primary efficacy endpoint were examined separately. Furthermore, the proportion of patients confirmed to be free from thrombus progression at the end of the intention to treat period was 83.6% in the Pradaxa arm and 81.1% in the SoC arm, further supporting the non-inferiority of Pradaxa to

SoC. It is important to note that the trial had sufficient representation of patients across the age spectrum and a variety of underlying VTE risk factors that is generally reflective of the epidemiology of VTE in pediatric patients, thus supportive of the generalizability of its results.

Given the mechanism of action of Pradaxa and the common pathophysiology between acute VTE and VTE recurrence, efficacy results from trial 1160.106 was used to support the second indication, related to the effectiveness of Pradaxa for the secondary prevention of VTE in pediatric patients. Furthermore, this indication was supported by the final results of a pre-specified analysis of the rate of recurrence of VTE over a 12-month treatment period of Pradaxa for the secondary prevention of VTE in pediatric patients. The trial was a multi-center, open-label, single arm prospective cohort Phase III trial evaluating the safety of Pradaxa in pediatric patients, from birth to less than 18 years of age, who have a previous history of a treated VTE and have a persistent risk factor for VTE. In this trial, using the full follow-up period, 5.1% of patients on Pradaxa developed a VTE recurrence within the 12-month treatment period, which is comparable to observed rates of pediatric VTE recurrence with SoC therapies (7-21%). The overall probability of being free from recurrence of VTE was 0.990 (95% CI 0.963, 0.998) at 3 months, 0.971 (95% CI 0.936, 0.987) at 6 months, and 0.938 (95% CI 0.890, 0.966) at 12 months. The trial had sufficient representation of patients across the age spectrum and a variety of underlying VTE risk factors that is generally reflective of the epidemiology of VTE in pediatric patients, thus supportive of the generalizability of its results.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Integrated Assessment

Venous thromboembolism (VTE) is an uncommon but serious life-threatening medical condition with significant morbidity and mortality in pediatric patients. Even though there are numerous VTE risk factors, the most significant risk factors are the presence of a central venous catheter, admission to an intensive care unit and conditions that lead to a hypercoagulable state, such as certain congenital heart disease, malignancy and thrombophilia. Standard of care (SoC) treatment options for pediatric patients with VTE, most of which are used in an off-label fashion, include heparin products, vitamin K antagonists, fondaparinux and parenteral thrombin inhibitors. Dalteparin, a low molecular weight heparin product, is the only FDA-approved product for the treatment and secondary prevention of VTE in pediatric patients 1 month and older. Direct oral anticoagulants (DOACs), such as dabigatran etexilate, rivaroxaban, apixaban and edoxaban, are approved for the treatment and secondary prevention of VTE in adults. The main advantages of DOACs over SoC therapies are the fixed dose administration without the need for monitoring, the oral formulation availability and the presence of a specific targeted antidote. It is important to note that DOACs have been less effective in the treatment of patients with prosthetic heart valves and in patients with antiphospholipid antibody syndrome. The main common adverse reaction among all anticoagulants is the risk of bleeding, which can result in life-threatening major bleeding in ~2-3% of patients.

This application is primarily supported by the results of a pre-specified non-inferiority analysis of trial 1160.106, a multi-center, open-label, randomized, active-controlled trial in 267 pediatric patients, from birth to less than 18 years of age, with image-proven VTE, initially treated with parenteral anticoagulation therapy for at least 5 days and in need for at least 3 month of anticoagulation therapy. This trial demonstrated the non-inferiority of Pradaxa, compared to SoC anticoagulation, as evident by a rate difference of -0.038 (95% CI: -0.161,0.086) in the composite primary endpoint of complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related mortality. This was further supported by consistent results when all individual components of the primary efficacy endpoint were examined separately, and when the proportion of patients confirmed to be free from thrombus progression at the end of therapy was examined. This trial is considered adequate and well-controlled, with primary and key secondary endpoints agreed to by the FDA, conducted in response to a written request under the Best Pharmaceuticals for Children Act.

The Applicant's proposed indications are also supported by the results of a pre-specified analysis of trial 1160.108, a multi-center, open-label, single arm prospective cohort Phase III trial in 213 pediatric patients, from birth to less than 18 years of age, who have a previous history of a treated VTE and have a persistent risk factor for VTE that increases the risk of VTE recurrence. These patients were treated with Pradaxa over a 12-month period for the secondary prevention of VTE. This trial demonstrated a comparable rate of VTE recurrence of 5.1%, when compared to the observed rates of pediatric VTE recurrence with SoC therapies (7-21%). The overall probability of being free from recurrence of VTE was 0.990 (95% CI 0.963, 0.998) at 3 months, 0.971 (95% CI 0.936, 0.987) at 6 months, and 0.938 (95% CI 0.890, 0.966) at 12 months.

The safety profile of Pradaxa in pediatric patients is similar to the observed safety profile in adult patients. The most common non-bleeding adverse reactions (ARs), defined as ARs that occur in at least 5% of patients on Pradaxa, were: headache (10%), abdominal pain (9%), gastritis (8.5%) and nasopharyngitis (8%), with the majority being mild to moderate in severity. The main category of non-bleeding AR that showed a significant difference, when compared to the SoC

arm, were GI disturbances, occurring in 35% of patients on Pradaxa (vs. 11% of patients on SoC), which included abdominal pain, gastritis, nausea, vomiting and diarrhea. With the exception of GI bleeding (9% in the Pradaxa arm vs. 1% in the SoC arm), the overall rate of all other types of bleeding, including all severity sub-groups, was comparable between the two treatment arms. This similarity includes major bleeding (3% in the Pradaxa arm vs. 2% in the SoC arm) and clinically relevant non-major bleeding (1.5% in the Pradaxa arm vs. 1% in the SoC arm). GI bleed ARs in the Pradaxa arm were recurrent and occurred at a relatively higher rate in younger pediatric patients. Similar results were observed in trial 1160.108, evaluating the long-term use of Pradaxa in pediatric patients. The only trial medication-related death in trial 1160.106 occurred in a patient on the SoC arm, secondary to a major retroperitoneal bleeding event, resulting in hemorrhagic shock and cardiac arrest. The only trial medication-related death in trial 1160.108 occurred secondary to a treatment failure of Pradaxa, resulting in the recurrence of a fatal PE in a patient with underlying antiphospholipid antibody syndrome. Overall, the safety monitoring and size of the safety database was adequate to identify important safety concerns in pediatric patients.

For each of the three formulations, specific Pradaxa dosing nomograms were utilized in both trials and drug monitoring was implemented to achieve target trough dabigatran concentration of 50-<250 ng/ml, while allowing a single dose adjustment using specific titration nomograms. Due to inability to achieve within-target levels after one dose adjustment, there was a Pradaxa discontinuation rate of 7-12%, with 19-27% of patients needing a dose adjustment due to low trough concentrations, occurring with a significantly higher frequency in younger age groups. In addition, patients who received capsules had trough dabigatran concentrations twice the levels observed in adult trials. Even though an associated higher rate of bleeding events was not observed, the observed levels may result in an increased risk of adverse reactions, without additional efficacy-related benefit, in the adolescent population. Given the recommended dose modifications for patients receiving capsules and the observed high rate of concentration-based discontinuation in younger patients, drug monitoring with dTT (refer to section 8.3.3 for details) is necessary for all pediatric age groups to ensure patients on Pradaxa achieve target trough concentration, thus ensuring the safe and effective use of Pradaxa in all pediatric patients.

In the opinion of the medical reviewer, the submitted evidence meets the statutory evidentiary standard for regular approval of the proposed pediatric indications for sNDA 022512 – S041 (for the Pradaxa capsules) and NDA 214358 (for Pradaxa oral pellets). (b) (4) my regulatory recommendation is to grant Pradaxa regular approval for the following applications, with their respective indications:

- sNDA 022512 – S041 (for the Pradaxa capsules):
  - For the treatment of VTE in adult and pediatric patients 8 years of age and older who have been treated with parenteral anticoagulants for at least 5-10 days.
  - To reduce the risk of recurrence of VTE in adult and pediatric patients 8 years of age and older who have been previously treated.
- NDA 214358 (for Pradaxa oral pellets):

- For the treatment of VTE in pediatric patients [redacted] (b) (4) 12 years of age who have been treated with parenteral anticoagulants for at least 5-10 days.
- To reduce the risk of recurrence of VTE in pediatric patients [redacted] (b) (4) 12 years of age who have been previously treated.

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | ▪ The annual incidence of VTE in children is reported as 0.07 - 0.14 per 10,000 children[1], with higher rates in neonates and adolescents[3].<br>▪ The rate of VTE in hospitalized children has increased by 70% over the past 10-20 years[2].<br>▪ The most significant VTE risk factors are the presence of a central venous catheter, admission to an intensive care unit and conditions that lead to a hypercoagulable state[5-7].<br>▪ VTE is serious life-threatening medical condition with significant morbidity and mortality in pediatric patients, such as pulmonary embolism[25], post-thrombotic syndrome[27] and an untreated VTE-related mortality rate of ~3%. | VTE is an uncommon but serious disease in children.<br><br>If untreated, VTE can lead to serious and life-threatening outcome, with significant morbidity and mortality. |
| Current Treatment Options | ▪ Standard of care (SoC) treatment options, most of which are used in an off-label fashion, include heparin products, vitamin K antagonists, fondaparinux and parenteral thrombin inhibitors.<br>▪ Dalteparin is the only FDA-approved product for the treatment and secondary prevention of VTE in pediatric patients 1 month and older.<br>▪ Direct oral anticoagulants (DOACs), such as dabigatran etexilate, are approved for the treatment and secondary prevention of VTE in adults.<br>▪ The main advantages of DOACs over SoC therapies are the fixed dose administration without the need for monitoring, the oral formulation availability and the presence of a specific targeted antidote. | There is a need for new therapies for pediatric patients with VTE and for those at risk for VTE recurrence due to persistent VTE risk factors.<br><br>Specifically, there is a need for oral anticoagulant therapies in pediatric patients that require minimal to no monitoring and have a dependable reversal agent.<br><br>DOACs offer a potentially significant new therapy for VTE in pediatric patients. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | ▪ In trial 1160.106, 45.8% of patients on Pradaxa (81 of 177 patients), compared to 42.2% of patients on SoC (38 of 90 patients), met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related mortality), with a rate difference of -0.038 (95% CI: -0.161,0.086), thus demonstrating the target non-inferiority margin of 20%.<br>▪ All individual components of the primary efficacy endpoint of trial 1160.106 were consistent with the results of the primary endpoint.<br>▪ The proportion of patients confirmed to be free from thrombus progression at the end of the intention to treat period in trial 1160.106 was 83.6% in the Pradaxa arm and 81.1% in the SoC arm<br>▪ Trial 1160.108 demonstrated a comparable rate of VTE recurrence of 5.1%, when compared to the observed rate of pediatric VTE recurrence with SoC therapies of 7-21%.<br>▪ The overall probability of being free from recurrence of VTE in trial 1160.108 was 0.990 (95% CI 0.963, 0.998) at 3 months, 0.971 (95% CI 0.936, 0.987) at 6 months, and 0.938 (95% CI 0.890, 0.966) at 12 months.<br>▪ Both trials had sufficient representation of patients across the age spectrum and a variety of underlying VTE risk factors, supportive of the generalizability of its results. | There is substantial evidence of effectiveness for Pradaxa in the treatment of VTE in pediatric patients, based on non-inferior rates of complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related mortality, when compared to SoC therapies.<br><br>There is substantial evidence of effectiveness for Pradaxa in the secondary prevention of VTE in pediatric patients, based on the comparable rate of VTE recurrence, when compared to the observed rates of pediatric VTE recurrence with SoC therapies in the literature. |
| Risk and Risk Management | ▪ The most common non-bleeding adverse reactions (ARs), defined as ARs that occur in at least 5% of patients on Pradaxa, were: headache (10%), abdominal pain (9%), gastritis (8.5%) and nasopharyngitis (8%).<br>▪ The main non-bleeding AR with significant difference, when compared to the SoC arm, were GI disturbances (35% in Pradaxa arm vs. 11% in SoC arm).<br>▪ With the exception of GI bleeding ARs (9% in the Pradaxa arm vs. 1% in the SoC arm), the overall rate of all other types of bleeding ARs, including all severity sub-groups, was comparable between the two treatment arms, including rates of major bleeding and clinically relevant non-major bleeding. | The safety profile of Pradaxa in pediatric patients is similar to the safety profile in adult patients.<br><br>Treatment of pediatric patients with Pradaxa did not reveal any new safety signal, with the majority of ARs being mild-moderate in severity. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | ▪ Severe ARs, SAEs and deaths were uncommon in the two pivotal trials.<br>▪ Pradaxa is less effective in the treatment of patients with prosthetic heart valves and antiphospholipid antibody syndrome, thus should be avoided in these patients.<br>▪ Both pivotal trials included drug monitoring with one allowed dose adjustment to achieve target trough dabigatran concentration of 50-<250 ng/ml. The resulting rate of discontinuation of Pradaxa due to inability to achieve within-target trough concentration after one dose adjustment was 7-12%, with 19-27% of patient needing any dose adjustment due to low trough concentrations, which occurred with significantly higher frequency in younger age groups.<br>▪ The dosing nomograms utilized in both trials resulted in trough dabigatran concentrations, in patients who received capsules, that were twice the levels observed in adult trials. Even though a higher rate of bleeding events was not observed, the observed levels may result in an increased risk of adverse reactions, without additional efficacy-related benefit, in the adolescent population.<br>(b) (4) | If patients experience GI disturbances and GI bleeds with Pradaxa, the Agency recommends administration with food.<br><br>Given the recommended dose modifications for patients receiving capsules and the observed high rate of concentration-based discontinuation in younger patients, drug Monitoring with dTT (refer to section 8.3.3 for details) is necessary for all pediatric age groups to ensure patients on Pradaxa achieve target trough concentration of 50-<250 ng/ml, thus ensuring the safe and effective use of Pradaxa in all pediatric patients. This approach is the same approach used in the two pivotal trials.<br>(b) (4)<br>(b) (4) |

## 1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

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| □ | The patient experience data that was submitted as part of the application include: | Section where discussed, if applicable |
| | □ Clinical outcome assessment (COA) data, such as | [e.g., Sec 6.1 Study endpoints] |
| | □ Patient reported outcome (PRO) | |
| | □ Observer reported outcome (ObsRO) | |
| | □ Clinician reported outcome (ClinRO) | |
| | □ Performance outcome (PerfO) | |
| | □ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Sec 2.1 Analysis of Condition] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Natural history studies | |
| | □ Patient preference studies (e.g., submitted studies or scientific publications) | |
| | □ Other: (Please specify) | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | |
| | □ Input informed from participation in meetings with patient stakeholders | |
| | □ Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | □ Observational survey studies designed to capture patient experience data | |
| | □ Other: (Please specify) | |
| X | Patient experience data was not submitted as part of this application. | |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Venous thromboembolism (VTE) includes DVT, PE, cerebral sinovenous thrombosis (CSVT) and central VTE (i.e. intra-cardiac thrombosis and thrombosis located in other large veins such as inferior vena cava, superior vena cava, innominate veins, hepatic veins, portal vein, splenic veins, renal veins and umbilical vein). The annual incidence of VTE in children is reported as 0.07 - 0.14 per 10,000 children[1]. The rate of VTE in hospitalized children has increased by 70% from 2001 to 2007 across all pediatric age groups to an annual incidence of 34 – 58/10,000 admissions[2]. Pediatric VTE occurs with highest frequency in the neonates and adolescents[3], with neonates forming an especially unique and challenging population due to the presence of developmental hemostasis and other congenital pathologies unique to this group[4]. The increasing incidence of VTE and the overall improvements in the care of tertiary care pediatric patients with complex medical conditions with expected long-term survival of these patients, emphasize the need for effective and safe treatment of VTE in the pediatrics population.

There are many known inherited and acquired clinical risk factors for the development of VTE in children, including venous stasis, endothelial injury, inflammation and thrombophilia[5-7]. More than 90% of pediatric patients who develop VTE have > 1 VTE risk factor, where the presence of a central venous catheter (CVC)[8] and admission to a pediatric intensive care unit (PICU)[9] considered as two of the strongest risk factors for the development of VTE in children. Other risk factors for VTE in children include: chronic inflammatory conditions such as inflammatory bowel disease[10] and cystic fibrosis[11], sickle cell disease[12], acute inflammatory conditions such as systemic infections and sepsis, obesity, acute trauma[13], major surgery especially orthopedic procedures or interventions leading to prolonged immobilization, malignancies[14], nephrotic syndrome[15], congenital heart disease (CHD) and other acquired cardiac diseases with and without congestive heart failure (CHF)[16,17], inherited thrombophilias[18], antiphospholipid antibody syndrome (APS)[19], and contraceptive use[20,21] and other drug-associated risk factors such as asparaginase, corticosteroids and heparin-containing products, with the latter resulting in heparin-induced thrombocytopenia thrombosis (HITT)[22].

There are recognized differences in the etiology and pathophysiology of VTE between the adult and pediatric population. In pediatrics, VTE are more likely to be related to the presence of multiple underlying transient or persistent risk factors (i.e. provoked VTE), while spontaneous VTE is more common in the adult population (i.e. unprovoked VTE). Similar to adults, VTE can result in significant morbidity and mortality in children, both related to the disease and to the treatment adverse events. Complications of VTE in children include: 1) VTE progression resulting in symptomatic pathology in the affected region such as post-CSVT chronic headache[23] and superior vena cava syndrome[24], 2) PE[25], 3) post-thrombotic syndrome (PTS)[26], with a rate of moderate-severe PTS of 11-23%[27], 4) persistent bacteremia and systemic infection, and 5) loss of catheter function in the case of catheter related VTE, 6) VTE recurrence, with a rate of 7-21%[3], 7) Death, with an untreated VTE-related mortality of ~3%. These short and long term VTE-related complications should be considered when weighing the benefits and risks of treatment, as pediatric VTE is a serious and life-threatening condition.

The treatment of children with VTE is similar to the treatment of adults with VTE since the majority of cases will not resolve without treatment. Once a child has developed an image-proven[28,29] symptomatic VTE, treatment with anticoagulant therapy is recommended to allow the gradual intrinsic thrombolysis of the thrombus while preventing its acute progression. Furthermore, since one of the strongest risk factors for VTE in children is the presence of past history of VTE, the persistence of significant VTE risk factors after completion of the acute treatment course may indicate the continuation of anticoagulant therapy to prevent the recurrence of VTE [30,31]. In certain situation, thrombolytic therapy maybe indicated in children with more severe VTE[32,33]. Overall, there is a need for effective and safe treatment of VTE in the pediatrics population. However, given the known VTE-related complications and the established treatment-associated risk of bleeding, there must be a comprehensive benefit and risk assessment of the treatment of VTE in children.

## 2.2. Analysis of Current Treatment Options

The treatment of pediatric thromboembolism has been historically based upon adult experience and indications[34]. Pediatric patients with symptomatic VTE are typically treated in tertiary care centers with pediatric hematology involvement and the majority of patients are treated with anticoagulants on an off-label basis[35]. In general, randomized clinical trials or large single arm trials to inform dosing for anticoagulants in children are lacking, thus dosing guidelines are based on smaller, single arm studies and expert opinion [36,37]. Unique considerations with regards to the treatment of children with VTE include the dynamics of the coagulation system in the developing child, pharmacokinetics (PK) and pharmacodynamic (PD) differences in younger pediatric patients requiring higher doses of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in younger patients, and potential distress caused by frequent therapeutic and/or diagnostic interventions involving needles.

Currently, Fragmin (dalteparin) is the only FDA approved anticoagulant in children, approved on 5/6/2019 for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. Fragmin is a LMWH that was approved based on efficacy data from a single-arm, open-label, multi-center trial in 34 patients with symptomatic VTE, of which 26 patients had an active malignancy. Therapeutic anti-Xa levels of 0.5 to 1 IU/ml were achieved within a mean of 2.6 days (range 1 – 7 days) and patients < 2 years needed ~ twice the median dose level when compared to those ≥ 2 years. At study completion, 62% (21 patients) showed full resolution, 21% (7 patients) showed partial resolution, 6% (2 patients) showed stable thrombus and 3% (1 patient) experienced a new VTE while on treatment[38]. This conclusion was supported by results from another multicenter study published by O'Brien et al[39]. Additionally, even though UFH is not formally indicated for pediatric patients, it may be considered to have an implied indication because the Dosage and Administration (2.4) section of labeling provides specific pediatric dosing for the indication of prophylaxis and treatment of venous thrombosis and PE.

The three main classic classes of anticoagulants used as the SoC off-label treatment in children are UFH, LMWH and vitamin K antagonists (VKA)[40,41]. Of note, higher doses of LMWH are required in neonates and children compared to adults to achieve therapeutic anti-Xa levels, which is thought to be at least partially due to increased clearance and decrease antithrombin levels in infants and young children. Other, less commonly used but more novel classes of anticoagulants include factor Xa inhibitors and factor IIa (i.e. thrombin) inhibitors. Table 1 lists the different anticoagulant classes, their mechanism of actions and lists

the drug products that are under each class. Table 2 lists the specific drug product and relevant dosing, efficacy and safety information for their recommended off-label use in children.

Table 1: Anticoagulant Drug Classes and Their Mechanism of Action

| Drug Class | Drug Products | Mechanism of Action and PK/PD information |
|---|---|---|
| UFH | Heparin | ▪ Potentiates the inhibitory effects of antithrombin on IIa and Xa<br>▪ Biological product, derived from animal sources<br>▪ Has a short $t_{1/2}$ (~30 minutes) |
| LMWH | Dalteparin<br>Enoxaparin<br>Tinzaparin* | ▪ Potentiates the inhibitory effect of antithrombin on Xa >>> IIa<br>▪ Derived from UFH, thus have the same animal sources<br>▪ Stable dose-effect with minimal interactions and longer $t_{1/2}$ (~6 hours) |
| VKA | Warfarin | ▪ Inhibits synthesis of vitamin K-dependent clotting factors (II, VII, IX and X) and natural anticoagulants (protein C and protein S)<br>▪ Good oral bioavailability with longer $t_{1/2}$ (~24 hours)<br>▪ Narrow therapeutic index & Multiple drug and food interactions |
| Xa Inhibitor | Fondaparinux<br>Rivaroxaban<br>Apixaban | ▪ Inhibits factor Xa indirectly (through potentiating of the inhibitory effect of antithrombin on Xa, as with Fondaparinux) or directly (as with the direct oral anticoagulants – DOACs, such as Rivaroxaban and Apixaban) |
| IIa Inhibitor | Bivalirudin<br>Argatroban<br>Dabigatran | ▪ Direct Inhibition of factor IIa<br>▪ Different routes of administration: oral (as with dabigatran) and IV (as with bivalirudin and argatroban)<br>▪ Different $t_{1/2}$ contribute to different administration strategies: IV drugs have short $t_{1/2}$ (bivalirudin $t_{1/2}$ ~ 25 minutes, argatroban $t_{1/2}$ ~ 40 min)<br>▪ Different methods of elimination: bivalirudin has predominate renal elimination vs. argatroban has predominate hepatic elimination |

* Tinzaparin has very limited pediatric data, with the following once-daily dosing recommendation by age (adjusted according to intermittent LMWH-specific anti-Xa measurement with goal level 0.5 – 1.0 IU/L): 0-2 months – 275 u/kg/dose, 2-12 months – 250 u/kg/dose , 1-5 years – 240 u/kg/dose , 5-10 years – 200 u/kg/dose and 10-16 years – 175 u/kg/dose[42]. Since Tinzaparin is uncommonly used as an anticoagulant in children with VTE in the U.S., it will not be discussed further.

Table 2: Summary of Anticoagulant Treatment of VTE in Pediatric Patients

| Drug Product / Drug Class | Dosing (initial) | Efficacy Information | Safety Information |
|---|---|---|---|
| Products with Pediatric Indication and/or Pediatric Dosing Information | | | |
| Heparin / UFH | ▪ Continuous IV infusion<br>▪ Loading Dose: 75 units/kg IV over 10 minutes<br>▪ Maintenance dose:<br>o 28 units/kg/hour for infants < 1 year<br>o 20 units/kg/hour for children > 1 year | ▪ Ideal in PICU setting due to short half-life & continuous IV infusion<br>▪ Anti-thrombin dependent<br>▪ Require continuous laboratory monitoring (aPPT, Heparin-specific anti-Xa, ACT):<br>o Titration to achieve target anti-Xa level 0.5 – 1 IU/ml<br>o Limitation in correlation between anti-coagulant effect and laboratory value. | ▪ Ideal in high bleeding risk situation due to short half-life<br>▪ Antidote – Protamine (full reversal)<br>▪ Risk of HITT<br>▪ Risk of contamination due to animal-source of product |
| Dalteparin / LMWH | ▪ Q12 hours SC<br>▪ Age-dependent dose: | ▪ Ideal for outpatient setting<br>▪ Anti-thrombin dependent | ▪ Antidote – Protamine (partial reversal) |

| | | | |
|---|---|---|---|
| | o 150 IU/kg for 1 month to <2 years<br>o 125 IU/kg for 2 years to <8 years<br>o 100 IU/kg for 8 years to <17 years | ▪ Require intermittent laboratory monitoring with LMWH-specific anti-Xa measurement 4-6 hours after dose (prior to 4th dose)<br>▪ Titration to achieve target anti-Xa level 0.5 – 1 IU/ml | ▪ Risk of HITT but lower than risk with UFH<br>▪ Risk of contamination due to animal-source of product<br>▪ Frequent SC injection<br>▪ Osteoporosis risk with long-term therapy |
| Products Used Off-Label in Pediatric Patients | | | |
| Enoxaparin / LMWH | ▪ Q12 hours SC<br>▪ Age-dependent dose:<br>o 1.5 mg/kg/dose for ≤2 months<br>o 1 mg/kg/dose for >2 months | ▪ Ideal for outpatient setting<br>▪ Anti-thrombin dependent<br>▪ Require intermittent laboratory monitoring with LMWH-specific anti-Xa measurement 4-6 hours after dose (prior to 4th dose),<br>▪ Titration to achieve target anti-Xa level 0.5 – 1 IU/ml | ▪ Antidote – Protamine (partial reversal)<br>▪ Risk of HITT but lower than risk with UFH<br>▪ Risk of contamination due to animal-source of product<br>▪ Frequent SC injection<br>▪ Osteoporosis risk with long-term therapy |
| Warfarin / VKA | ▪ Once daily Oral<br>▪ Loading dose 0.2 mg/kg with maximum dose of 10 mg | ▪ Ideal for outpatient setting<br>▪ Needs compounding into liquid formulation, which may not be consistent<br>▪ Require continuous laboratory monitoring with INR<br>▪ Titration to achieve INR 2-3 in most cases | ▪ Antidote – Vitamin K and Prothrombin Complex Concentrates<br>▪ Narrow therapeutic index<br>▪ Multiple drug and food interactions<br>▪ Require overlap with therapeutic anticoagulation during initial period to prevent tissue necrosis |
| Fondaparinux/ Xa inhibitor[43-45] | ▪ Once daily SC<br>▪ 0.1 mg/kg with weight-tier dosing for children ≥ 1 years[46]:<br>o 10 – 20 kg – exact dose to nearest 0.1 mg<br>o 20 – 40 kg – 2.5 mg<br>o 40 – 60 kg – 5 mg<br>o > 60 kg – 7.5 kg | ▪ Ideal SC drug for children, given the once daily dosing (due to longer $t_{1/2}$ (~17 hours)<br>▪ Anti-thrombin dependent<br>▪ Require intermittent laboratory monitoring with fondaparinux-specific anti-Xa measurement 3 hours after dose (prior to 4th dose),<br>▪ Titration to achieve target anti-Xa level 0.5 – 1 mg/L | ▪ No specific antidote<br>▪ Safety has not been evaluated in children < 1 years |
| Bivalirudin[47,48] | ▪ Continuous IV infusion<br>▪ Loading Dose: 0.125 mg/kg IV bolus<br>▪ Maintenance dose: 0.125 mg/kg/hour | ▪ Used in patients with HITTS<br>▪ Preferred in patients with evidence of hepatic impairment<br>▪ Require continuous laboratory monitoring with aPPT but limitation in correlation between anti-coagulant effect | ▪ No specific antidote<br>▪ Limited published data relating to VTE in pediatric patients |

| | | | |
|---|---|---|---|
| | | and laboratory value. Goal aPTT is 1.5-2.5 baselines aPTT. | |
| Argatroban[49,50] | ▪ Continuous IV infusion<br>▪ Maintenance dose: 0.1 mcg/kg/min (no loading dose indicated) | ▪ Used in patients with HITTS<br>▪ Preferred in patients with evidence of renal impairment<br>▪ Require continuous laboratory monitoring with aPPT. Goal aPTT is 1.5-2.5 baselines aPTT | ▪ No specific antidote<br>▪ Limited published data relating to VTE in pediatric patients |

The recommended duration of treatment for VTE in children is 3 months, which is extended to 6 months in the setting of a pulmonary embolism. Currently, there are on-going trials evaluating the optimal treatment duration of VTE in children[51,52]. Continuation of anticoagulant therapy after completion of the acute therapy is generally dependent on several factors: 1) If the VTE was provoked (i.e. secondary to acquired transient risk factors) or unprovoked (i.e. secondary to inherited persistent risk factors or unexplained), 2) If the VTE risk factors are persistent, 3) The severity of the initial VTE event, and 4) The presence of VTE-associated complications, such as PTS.

Overall, efficacy of anticoagulants in children is comparable among the different SoC treatment options, if compliance is established and appropriate monitoring is used ensuring therapeutic drug levels. In addition, bleeding event rates, which are the most common and significant adverse events (AE) associated with the use of anticoagulants, are comparable to adult rates for major bleeding at 2.5 – 3% but continue to be variable in the literature, depending on the patient population and clinical setting[53].

Based on recently published registry-based data[54], direct oral anticoagulants (DOAC) are being used in an off-label fashion, which was mainly prescribed in patients older than 13 years, based on extrapolation from adult-based data. Currently, there are approved DOACs for the treatment and secondary prevention of VTE in adults. Overall, DOACs have the three unique advantages when compared to the classic anticoagulants used in children: 1) Fixed dose administration without the need for apparent monitoring, 2) Oral formulation availability, when compared to LMWH, the most commonly used drug in children, and 3) Presence of a specific targeted antidotes that result in complete and rapid reversal of anticoagulant effects. Review of the current progress of development of DOACs in children and insight on the future potential role of DOACs in the treatment of VTE in children has been published by several groups[55-57].

Over the past 5 years, under direct guidance from organizations and experts in the development of anticoagulants[58], and regulatory organizations[59], the following DOACs have been under development for potential pediatric indications for the treatment and secondary prevention of VTE in children: rivaroxaban[60-66], apixaban (ongoing trial – NCT02464969), edoxaban (ongoing trial – NCT02798471)[67] and dabigatran etexilate[68-72], the latter being the subject of this review. In relation to anticoagulant reversal agents for DOACs, Andexxa (andexanet alfa)[73-75] is the FDA-approved drug for the reversal of rivaroxaban and apixaban, and Praxbind (idarucizumab) is the FDA-approved drug for the reversal of Pradaxa in adults[76-79]. At this time, idarucizumab is also being studied as a reversal agent for Pradaxa in children in an on-going phase 3 trial (NCT02815670)[80].

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Dabigatran etexilate (75 mg and 150 mg as oral capsules), under the proprietary name Pradaxa®, was approved for use in the U.S. on October 19th, 2010, to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The application was approved with a REMS to evaluate patients' understanding of the serious risks of Pradaxa. The REMS was removed on 04/05/2011. At the time of initial approval, the pediatric study requirement under the Pediatric Research Equity Act (PREA) was waived because the necessary studies were "impossible because the disease is rare in children".

Two new indications were added for Pradaxa on April 4th, 2014 for the treatment of DVT and PE in patients who have been treated with a parenteral anticoagulant for 5-10 days and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. These indications were subject to the Pediatric Research Equity Act (PREA) and the following post-marketing requirements (PMR) were issued under PREA:

- PMR 2139-1:
  - Conduct an open-label, single dose, single arm, tolerability, PK/PD and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old.
  - Final report submission planned for 06/30/2017.
  - PMR satisfied by the completion of study 1160.105 titled "Open-label, single dose, tolerability, pharmacokinetic / pharmacodynamics and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old"

- PMR 2139-2:
  - Conduct an open-label, randomized, parallel-group, active-controlled, multicenter, non-inferiority efficacy study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age. Include PK/PD (sparse sampling) in all patients. The anticipated enrollment is 240 evaluable patients for the efficacy analysis. Enroll adequate numbers of patients in 3 age groups, from 12 to <18 years of age, from 2 to <12 years of age and from birth to <2 years of age. Submit the clinical study report with datasets. Patients from birth to <2 years of age may be enrolled only after data from a planned interim analysis have shown efficacy and safety of dabigatran in the older pediatric age groups.
  - Final report submission planned for 6/30/2019.
  - This PMR is the subject of the review of this application

- PMR 2139-3:
  - Conduct an open label, single arm trial to evaluate safety of dabigatran etexilate for secondary prevention of venous thromboembolism in children aged 0 to less than 18 years. The anticipated enrollment is 100 patients. Submit the clinical study report with datasets.
  - Final report submission planned for 12/31/2019.

- This PMR is the subject of the review of this application

Pradaxa was approved on November 20th, 2015 for the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

To satisfy PMR 2139-2 and 2139-3, the Applicant submitted an initial proposed pediatric study request (PPSR) on 3/30/2017, describing studies 1160.106 and 1160.108. In addition, the Applicant submitted a development summary for their development of (b) (4) pediatric formulation; oral pellets to mix with food (b) (4). In their proposal, the Applicant modified the planned final report submission date to 12/31/2019 for both studies and a goal sNDA submission date of 9/28/2020. The Agency responded to the Applicant's request with a letter of non-agreement on 07/28/2017, outlining some limitations in their proposal in relation to proposed sample size, lack of inclusion of patients < 6 months and lack of accounting for higher bioavailability of the proposed age-appropriate formulations.

(b) (4)

The Applicant resubmitted their PPSR on 2/23/2018, incorporating the Agency's recommendation. However, the Agency responded with a letter of non-agreement on 5/17/2018 requesting additional PK/PK data collection for patients < 6 months, expansion of the inclusion criteria for the study population and modification of the primary efficacy endpoint. Secondary to the occurrence of an intracranial bleed in an infant who received Pradaxa in the context of meningitis and CSVT, the data monitoring committee (DMC) recommended exclusion of patients with meningitis, encephalitis or intracranial abscess, which was implemented in amendment 7 of the protocol for trial 1160.106 and amendment 6 of the protocol for trial 1160.108.

The Applicant resubmitted their PPSR on 9/20/2018, incorporating the Agency' recommendation. On 1/25/2019, FDA issued a pediatric written request (WR) to Boehringer Ingelheim Pharmaceuticals for pediatric trials to investigate the potential use of Pradaxa in the treatment and prophylaxis of VTE in pediatric patients. The WR contained studies 1160.106 and 1160.108, with the future determination of granting pediatric exclusivity. The WR specified the following aspects of each of the requested trials:

- General trial design, trial objectives and trial population defining criteria.
- Minimum expected number of enrolled patients in each specified age group and request to ensure appropriate representation of ethnic and racial minorities.
- Specific primary and efficacy endpoints, including PK/PD-related endpoints, with general statistical information to guide the analysis.
- The presence of an independent adjudication committee that will confirm or refute outcome events.
- The presence of a single independent DMC, whose activities are described in a DMC charter.
- The development of age-appropriate formulation with sufficient bioavailability and PK/PD data to guide pediatric dosing recommendations.

- Provided a submission deadline of all reports on or before 9/28/2020.

The Applicant submitted a request to amend the initial WR on 3/15/2019, proposing to modify the minimum expected number of enrolled patients for the age group of birth to < 2 years and for patients < 6 months for both requested trials. Upon review of the request, the Agency agreed to issue an amended WR on 6/22/2019.

A pre-NDA meeting was requested by the Applicant on 10/18/2019 to discuss the proposed content of the sNDA and the two original NDA, which are subject of this review. Sufficient responses were provided by the Agency to appropriately address the Applicant's questions on 12/18/2019.

The Applicant submitted sNDA 022512 – S-041, NDA 214358 (b) (4) on 9/21/2020. The filing review for documents relevant to the clinical review was completed on 10/28/2020 that resulted in a request for the Applicant to provide further detailed information in relation to the financial disclosure, which was satisfactorily provided by the Applicant. The Application was filed as a priority review in accordance with MaPP 6020.3 which states that "applications submitted in response to a written request under the Best Pharmaceuticals for Children Act (BPCA) will automatically receive a priority review designation".

## 3.3. Foreign Regulatory Actions and Marketing History

Per the Applicant, Pradaxa is approved in more than 100 countries worldwide for a variety of antithrombotic indications in adults. (b) (4)

# 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

Using the FDA CDER Clinical Investigator Site Selection Tool (v.2.8.03) and the Applicant-provided BIMO dataset for trial 1160.106, we suggested the following four sites for inspection to the FDA Office of Scientific Investigations (OSI): site 70001 (Russia), site 10001 (Canada), site 20010 (US) and site 20003 (US). Our selection was based on many factors, with the following factors having stronger contribution to the site ranking: 1) Total number of patients per site, 2) Treatment efficacy results and site-specific treatment effect, 3) Serious adverse event (SAE) ratio and 4) Principal Investigator and site regulatory history. However, given the limitation of travel and access to sites outside of the US due to the COVID-19 pandemic, we limited our request to the two US-based sites listed above. The inspection of site 20010 and site 20003 were unremarkable, resulting in a No Action Indicated letter. In addition, DNH reviewed data generated at each clinical site and noted no anomalies in enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, or patterns of SAE reporting. Sensitivity analyses were performed when appropriate, with no significant differences to report.

Summary from OSI Review
Clinical data from a single study, Study 1160.106, was submitted to the Agency in support of a New Drug Application (NDA 022512 S-041) for dabigatran etexilate mesylate (Pradaxa®), proposed for treatment and prophylaxis of venous thromboembolism in pediatric patients. Two clinical investigator sites (Anjali Sharathkumar, M.D. and Judy Felgenhauer, M.D.) were inspected for Study 1160.106, in support of NDA 022512 S-041.

Based on these inspections, the conduct of the above Study 1160.106 appears to be adequate, and the study data derived from Dr. Sharathkumar's and Dr. Felgenhauer's clinical investigator sites are considered reliable. The study data submitted to the Agency appear acceptable in support of this NDA and the proposed pediatric indication.

## 4.2. Product Quality

NDA 22512, S41: The Quality review was conducted by primary reviewer Wei-Hua Emily Wu and her CMC Lead Ramesh Raghavachari. Below is an executive summary of the Quality review for Pradaxa capsules. This Quality review, archived on 2/11/2021, recommends approval.

This supplement provides for the following CMC changes to the controls for the drug substance and the drug product:

- *Changes to the drug substance specification and relevant eCTD sections*: There are no changes to the drug substance manufacturing processes, hence, there are no new potential or actual impurities. (b) (4) the applicant has proposed changes to the drug substance specification, including (b) (4) the control for the degradation product, (b) (4), from ≤ (b) (4)% to ≤ (b) (4)%; removal the controls for the (b) (4) impurities (b) (4);

[redacted] the control for the [redacted] impurity [redacted] from ≤ [redacted] ppm to ≤ [redacted] ppm; removal of the heavy metal test. As a result of the proposed changes to the drug substance specification, the eCTD sections such as justification of specification and analytical procedures for the drug substance have been updated or revised. After a round of Agency's IR dated 12/7/2020 and the applicant's response dated 12/18/2020, the applicant provided adequate information and data to support the proposed changes.

- ***Changes to the drug substance retest period***: The applicant re-evaluated the long-term and accelerated stability study results based on the proposed drug substance specification, the applicant restricted the storage condition from currently [redacted] to [redacted] " and [redacted] the retest period to [redacted] months.

- ***Changes to the drug product section 3.2.P.3 manufacture***:
  - Elemental Impurities (EI) Risk Assessment: Per ICH Q3D option 2B, the applicant conducted the EI risk assessment by evaluating potential sources of elemental impurities from container closure system, drug substance, [redacted], manufacturing process and equipment, and excipients. The applicant concluded that the potential total daily intake of [redacted] is consistently far below the 30% control threshold of the oral PDEs
  - Drug Product Manufacture: There are no changes to the drug product composition or the drug product manufacturing process. The applicant added non-critical process parameters, currently used but not reported in the previous versions of the registered document; updated excipients names to align with USP; and added further descriptions to describe the manufacturing process more precisely. [redacted]
  - Control of Drug Product: [redacted] Overall, the applicant provided adequate information and data to support the proposed changes. The toxicology reviewer does not have any concerns with the removal of the controls for [redacted]

- ***Changes to the Control of Excipients***: Based on the results of the elemental impurities risk assessment, the applicant has revised the specification for the [redacted] capsules (sizes 0, 1, and 2) by removing the [redacted]. Additionally, the applicant has removed the tests for characters [redacted] and for purity [redacted] because these tests are required by the Japanese Pharmacopeia not relevant to the products for the U.S. market.



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(b) (4)

(b) (4)

NDA 214358: The Quality review was conducted by primary reviewers Ben Zhang and Dhanalakshmi Kasi and their Quality Leads Suong Tran and David Claffey. Below is an executive summary of the Quality review for Pradaxa oral pellets (20mg, 30mg, 40mg, 50mg, 110mg, 150mg), administered immediately or within 30 minutes after mixing with rice cereal prepared with water, apple sauce, carrot mush, banana mush, or apple juice for 30 minutes at room temperature. The integrated quality review, archived on 02/18/2021, recommends approval.

*Drug Substance*

Dabigatran etexilate mesylate is a yellow-white or yellow crystalline powder with no chiral centers. It is practically insoluble in water, and the solubility increases with acidic pH. Most of the drug substance information is referenced to the approved information in NDA 022512. The difference between NDA 214358 and the previously approved NDA 022512 is with respect to polymorphism, degradant (b) (4), and an ICH M7 re-evaluation. The applicant identified two polymorphs, (b) (4), by x-ray diffraction measurement. (b) (4) is the desired form and it is controlled (b) (4). The impurity limit for degradant (b) (4) is (b) (4)% and Pharmacology Toxicology reviewer found this limit acceptable for the pediatric indication. The acceptance criterion for (b) (4) is based on ICH M7. The test limit for (b) (4) is re-evaluated as per ICH M7 for potential immunogenicity for pediatric dosing of up to 660 mg. The limit of < (b) (4) ppm on (b) (4) in the drug substance specification would ensure the limit of < (b) (4) ppm in the drug product specification. The batch release data are adequate to support the use of drug substance in the manufacture of drug product pellets. Re-test period is (b) (4) months when stored (b) (4). The storage condition for the drug substance is (b) (4) and the proposed shelf life is (b) (4) months. The drug substance reviewer is recommending approval.

*Drug Product*

The drug product pellets are manufactured by (b) (4) ll facilities appear adequate both in the experience in operations performed and in GMP compliance history.

The maximum intake of all excipients has been evaluated from a toxicological perspective. The drug product is tested for appearance, identification, assay, impurities, (b) (4), uniformity of dosage units, dissolution and microbiological quality. Impurities (b) (4) and (b) (4) are in vivo (b) (4) and are therefore considered qualified per ICH Q3A and Q3B. The

dabigatran etexilate (b) (4) pellets contained in packets are packaged additionally in an aluminum bag containing desiccant to guarantee an adequate drug product quality over the intended shelf life of 36 months at room temperature.

The proposed dissolution method is same as the method approved for capsule formulation (NDA 022512). The proposed dissolution acceptance criterion (NLT (b) (4)%(Q) in 15 min) is based on clinical trial and primary stability batches and it is (b) (4) than approved capsule formulation. The compatibility study demonstrated that the recommended fluid/soft-food is not likely to have any effect on the in vitro dissolution performance of the product.

## 4.3. Nonclinical Pharmacology/Toxicology

NDA 22512 – S041, (b) (4) and NDA 214358: The primary non-clinical review was conducted by Victor Long and Team Leader Xuan Chi. Below is an executive summary of the non-clinical review for Pradaxa capsules, oral pellets (b) (4) This non-clinical review, archived on 01/26/2021, recommends approval.

*Executive Summary*
In support of a pediatric indication, the sponsor submitted two nonclinical juvenile toxicity studies under NDA 022512 (dabigatran etexilate mesylate capsules). In both the preliminary and definitive juvenile toxicity studies, bleeding-related mortality was observed. The bleeding is an extension of the pharmacodynamic effect of dabigatran (BIBR 953 ZW). In the case of the definitive study, bleeding-related mortality occurred at the lowest dose, and therefore a NOAEL could not be determined from the study.

All impurities from NDA 022512 were considered qualified. For NDAs (b) (4) 214358, the only impurities exceeding the threshold set forth in ICH Q3A/Q3B were (b) (4), and (b) (4) (b) (4) is a degradation impurity in (b) (4) dabigatran etexitate mesylate pellets. (b) (4) has no anti-thrombin activity and the structure of (b) (4) is similar to (b) (4) The proposed limits of this impurity are NMT (b) (4)% in the drug substance for both dosage forms, and (b) (4) for the drug product (b) (4) These limits exceed the thresholds in drug substance and drug product set forth in ICH Q3A/Q3B.

Due to the youngest age of the intended population (< 1 year old) for the (b) (4) pellets, the juvenile tox study is appropriate for calculating a margin of safety. However, a NOAEL could not be determined from this toxicology study as the lowest dose in the study (15 mg/kg/day) resulted in bleeding-related mortality. Conservatively, applying 10x uncertainty factor to this LOAEL and performing a margin of safety calculation, resulted in a number < 1 for both NDAs.

As an alternative approach to qualify the impurity, we asked Fadi Nossair (Medical reviewer) if he could look at the adverse events from the Phase 3 trial to determine if the younger population was more sensitive to bleeding than adolescents. Using a contingency table, with a p-value computed by Fisher's exact test, there was no statistically significant difference in bleeding events from AE STDM, (b) (4)

Given (b) (4) is not genotoxic, has no anti-thrombin activity, (b) (4) and there is no significant difference between frequencies of bleeding between the younger and older pediatric population in the clinical studies, we conclude that, for the purpose of impurity qualification for (b) (4), we can use the adult rat NOAEL for our margin of safety calculation. This resulted in an adequate margin of safety (>1) for (b) (4) NDA 214358. As a result, all excipients and impurities for (b) (4) dosage forms are considered qualified and acceptable for use.

Moreover, NDAs 022512 (b) (4) and 0214358 are approvable from a nonclinical perspective for the proposed indications since most of the toxicities identified in the juvenile toxicity are attributable to the pharmacodynamic effect of dabigatran (BIBR 953 ZW). No additional labeling is required under Nonclinical Toxicology (Section 13). No nonclinical labeling update is needed for Section 8 since no new animal data submitted.

## 4.4. Clinical Pharmacology

NDA 22512 – S041 (b) (4) and NDA 214358: The primary clinical pharmacology reviewer was Peng Zou and team leader was Sudharshan Hariharan. The pharmacometric primary reviewer was Jihye Ahn and team leader was Justin Earp. Below is an executive summary of the clinical pharmacology review for Pradaxa capsules, oral pellets (b) (4) Approval is recommended, provided the Agency and the applicant reach an agreement on the dosing regimen.

*Executive Summary*

The key review issues with specific recommendations/comments are summarized below:

- Dose adjustment for capsules: The applicant's proposed dosing regimen is similar to that used in Studies 106 and 108 with minor adjustments. In the two trials, the geometric mean of pre-titration steady-state trough concentration (Ctrough,ss) in pediatric patients receiving PRADAXA capsules was 68% higher than that observed in adult patients of RE-COVER trial. Approximately 15 – 25% of patients receiving PRADAXA capsules had pre-titration Ctrough,ss higher than the 90th percentile of adult Ctrough,ss (146 ng/mL) observed in RE-COVER. Given the known exposure-response relationship for major bleeding events in the adult trial (RE-COVER), the review team is concerned with the higher dabigatran exposure (when compared to adults) expected with the applicant's dosing regimen. The review team proposed up to 32% of reduction in the starting dosing targeting the simulated Ctrough,ss range (10th - 90th percentiles) in pediatric patients that lay within the 90th percentile of adult exposure range while maintaining most of the patients above the trial titration Ctrough,ss bound of 50 ng/mL. The review team's recommended dosing regimen was communicated with the applicant and is agreed upon.

- Dose adjustment for (b) (4) granules: There was discrepancy in the relative bioavailability (BA) of (b) (4) granules when compared to capsules between the relative BA study (Study 194) in healthy adults and the population PK analysis performed based on pediatric data. In healthy adults, dabigatran etexilate granules resulted in 37% higher relative BA compared to dabigatran etexilate capsules. In contrast, the applicant's population PK analysis estimated that the relative BA of dabigatran (b) (4) granules was 38% lower than that for capsules in pediatric population.

  A direct BA comparison of between the (b) (4) granules and capsules in the pediatric population

was not feasible because the capsule and (b) (4) granules were used in different age groups (8 to <18 years, and 0 to <12 years, respectively) with limited PK data available from the age group (8 to <12 years) who could receive either formulation. The observed Ctrough,ss following administration of (b) (4) granules (mean Ctrough,ss = 78.1 ng/mL, N = 6) and capsules (mean Ctrough,ss = 87.2 ng/mL, N = 19) in patients aged 8 to <12 years showed that the relative BA is closer to 1.00.

Given the knowledge gaps and the limitation of data confounding age with formulations, the review team noted a greater uncertainty in the projected exposures based on the population PK analysis which uses a model derived relative BA estimate of 0.62 in pediatric patients. The team could not rule out the scenario that pediatric patients have similar relative BA (137%) for (b) (4) granules vs capsules as observed in healthy adults. Therefore, in a worst-case scenario, (b) (4) granules could potentially lead to higher exposures than the capsule formulation for the same dose. The review team's analyses identified the body weight groups (>31 kg) where the greatest uncertainty is expected due to the sparse nature of the data and proposed 13-40% of reduction of starting dosing for (b) (4) granules in patients with body weight > 31 kg. The modified dosing proposal for (b) (4) granules will be shared with the applicant.

- (b) (4)

- Dosing in patient subgroups: Following recommendations are provided for special populations.
  - Avoid use of dabigatran etexilate in pediatric patients with eGFR < 50 mL/min/1.73 m2.
  - Avoid concomitant use of P-gp inhibitors and PRADAXA capsules in pediatric patients.
  - Avoid concomitant use of P-gp inducers and dabigatran etexilate in pediatric patients.

## 4.5. Consumer Study Reviews

(b) (4)



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# 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

Table 3: Early Phase Clinical Pharmacology Trials evaluating PK/PD and Safety of Pradaxa in Pediatric Population

| Trial identifier / NCT no. | Trial Design | Regimen / schedule / route | Trial endpoints | Treatment duration | Total No. Patients Enrolled | Trial population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| 1160.88 / 00844415<br><br>Completed | Single arm, uncontrolled open-label<br><br>DMC to assess all bleeding events and AEs, and continuation of the study | Pradaxa orally twice daily after completion of SoC for primary VTE.<br><br>Only Capsules were used in this study.<br><br>Starting dose at 1.71 mg/kg/dose (80% of adult dose) with lab-based up-titration after first dose to goal of 2.14 mg/kg (100% of adult dose) with maximum dosing of 150 mg BID. | Primary:<br>- PK parameters of dabigatran and its metabolites<br>- PD parameters: TT measurement<br>- All minor and major bleeds<br>- All AE<br><br>Secondary:<br>- PD parameters: aPTT and ECT<br>- Population PK model for prediction of dabigatran concentration<br>- Changes in laboratory, clinical, ECG and physical examination<br>- Occurrence of VTE-related clinical outcomes | 3 days | 9 | Patients 12 to < 18 years who successfully completed of primary VTE with planned SoC treatment | 4 sites, 1 country (Canada) |
| 1160.89 / 01083732<br><br>Completed | Single arm, uncontrolled open-label<br><br>DMC to assess all bleeding events and AEs, and continuation of the study | Pradaxa orally twice daily after completion of SoC for primary VTE.<br><br>Only oral solution was used in this study.<br><br>Target dose = 64.6% of adult dose, determined by a bioavailability study in adults of all three formulations (Trial 1160.87) and adjusted for difference in eGFR, which is dependent on age (in months) and weight (in kg). This resulted in a Nomogram, used in | Primary:<br>- PK parameters of dabigatran and its metabolites<br>- PD parameters: TT measurement only (pre-amendment) vs. aPTT, ECT and TT (post-amendment)<br>- All minor and major bleeds<br>- All AE<br><br>Secondary:<br>- PD parameters: aPTT (pre-amendment) vs. made a primary endpoint post-amendment<br>- Population PK model for prediction of | 3 days<br><br>Duration modified by Global Amendment 5 to 1 day with a single dose design | 20 enrolled (2 screen failures) – 18 treated<br><br>3 in group 1 pre-amendment<br><br>9 in group 1 post-amendment<br><br>6 in group 2 post-amendment | Patients 1 to < 12 years who successfully completed of primary VTE with planned SoC treatment<br><br>Patients enrolled in successive groups of 2 to < 12 years (group 1) then 1 to < 2 years (group 2) | 8 sites, 6 countries |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | the study post-amendment.<br><br>Pre-amendment starting dose at 0.69 mg/kg/dose (50% of target dose) with lab-based 1st up-titration after day 1 to 1.11 mg/kg (80% of target dose) and 2nd up-titration after day 2 to 1.38 mg/kg (100% of target dose) with maximum dosing of 97 mg BID.<br><br>Post-amendment starting dose at 100% of target dose, adjusted based on nomogram, to be equivalent to adult dose of 150 mg | dabigatran concentration<br>- Changes in laboratory, clinical, ECG and physical examination<br>- Occurrence of VTE-related clinical outcomes | | | | |
| 1160.105 / 02223260<br><br>Completed | Single arm, uncontrolled open-label<br><br>DMC to assess all bleeding events and AEs, and continuation of the study | Pradaxa orally twice daily after completion of SoC for primary VTE.<br><br>Only oral solution was used in this study.<br><br>Target dose = 64.6% of adult dose, determined by 2 bioavailability study in adults of all three formulations (Trial 1160.87 & 1160.194) and adjusted for difference in eGFR, which is dependent on age (in months) and weight (in kg). This resulted in a Nomogram, used in the study post-amendment.<br><br>Starting dose at 100% of target dose, adjusted based on nomogram, to be equivalent to adult dose of 150 mg. | Primary:<br>- PK parameters of dabigatran and its metabolites<br>- PD parameters: aPTT, ECT and dTT<br><br>Secondary:<br>- PD-PK relationship<br>- All minor and major bleeds<br>- All AE<br>- Formulation acceptability and tolerability<br>- Changes in laboratory, clinical, ECG and physical examination<br>- Occurrence of VTE-related clinical outcomes | 1 day with a single dose design | 10 enrolled (2 screen failures) – 8 treated | Patients < 1 year (gestational age ≥ 37 weeks) who successfully completed of primary VTE with planned SoC treatment | 4 sites, 3 countries |

Table 4: Pivotal Clinical Trials Evaluating Efficacy and Safety of Pradaxa in Pediatric Population

| Trial identifier / NCT no. | Trial Design | Regimen / schedule / route | Trial endpoints | Treatment duration | Total No. Patients Enrolled | Trial population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| 1160.106 / 01895777 (DIVERSITY study)<br><br>Completed | Phase 2b/3, Open-label, randomized (2:1), parallel-group, active-controlled, non-inferiority trial<br><br>DMC to adjudicate all bleeding and VTE-related events, and decide on enrollment in successive strata depending on all data collected. | Pradaxa orally twice daily vs. SoC treatment for pediatric VTE (LMWH, VKA or fondaparinux)<br><br>Capsules (for patients ≥ 8 years able to swallow capsules), oral pellets (for patients 1 to <8 years) and oral solution (for patients < 12 months) were used in this study.<br><br>Starting dose determined by dosing algorithm / nomogram developed for each formulation from data collected in early phase trials, based on relative bioavailability compared to adult PK and adjustment for difference in eGFR, depending on weight and age.<br><br>A single lab-based up-titration was allowed if drug concentration was not within target trough of 50-<250 ng/ml, with up-titration amount of 10-100% and maximum dose of 22.2 mg/kg/dose (330 mg/dose). | Primary:<br>- Composite endpoint of the proportion of patient with all three of the following: complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related mortality.<br>- Incidence of major, CRNM and minor bleeds<br><br>Secondary:<br>- Freedom from major bleeds<br>- PK/PD assessment at visit 3<br>- Frequency of dose adjustments<br>- Assessment of acceptability of formulations<br>- Incidence of AE, protocol-specific AESIs, SAE and treatment discontinuation due to AE | 3 months | 328 enrolled (50 screen failure, 11 withdrawn prior to being randomized) – 267 patients randomized, 266 patients treated | Patients from birth (gestational age ≥ 37 weeks) to < 18 years with confirmed acute VTE needing at least 3 months of treatment with anticoagulants and completed a minimum of 5-7 days (≤ 21 days) of parenteral treatment (UFH or LMWH)<br><br>Patients enrolled in successive age stratums:<br>- Stratum 1: 12 to < 18 years<br>- Stratum 2: 2 to < 12 years<br>- Stratum 3: birth to < 2 years | 62 sites, 26 countries |
| 1160.108 / 02197416<br><br>Completed | Phase 2b/3, Open-label, single-arm, prospective cohort study<br><br>DMC to adjudicate all bleeding | Pradaxa orally twice daily<br><br>Capsules (for patients ≥ 8 years able to swallow capsules), oral pellets (for patients 1 to 8 years) and | Primary:<br>- Recurrence of VTE at 6 and 12 months<br>- Incidence of major, CRNM and minor bleeds at 6 and 12 months | Up to a maximum of 12 month or until the clinical VTE risk factor has resolved, | 231 enrolled (13 screen failure, 4 withdrawn prior to start of treatment) – 214 patients treated | Patients from birth (gestational age ≥ 37 weeks) to < 18 years with history of confirmed VTE who completed at least 3 | 62 sites, 22 countries |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | and VTE-related events, and decide on enrollment in successive strata depending on all data collected. | oral solution (for patients < 12 months) were used in this study.<br><br>Starting dose determined by dosing algorithm / Nomogram developed for each formulation from data collected in early phase trials, based on relative bioavailability compared to adult PK and adjustment for difference in eGFR, depending on weight and age.<br><br>A single lab-based up-titration was allowed if drug concentration was not within target trough of 50-<250 ng/ml with up-titration amount of 10-100% and maximum dose of 22.2 mg/kg/dose (330 mg/dose). | - Overall mortality and VTE-related mortality at 5 and 12 months<br><br>Secondary:<br>- Occurrence of PTS at 6 and 12 months<br>- PK/PD assessment at visit 3<br>- Frequency of dose adjustments<br>- Assessment of acceptability of formulations<br>- Incidence of AE, protocol-specific AESIs, SAE and treatment discontinuation due to AE | whichever occurs earlier | | months of treatment with anticoagulants and required continued anticoagulation for secondary prevention of VTE due to presence of clinical VTE risk factor.<br><br>Patients who were discontinued from Pradaxa in 1160.106 were not eligible.<br><br>Patients enrolled in successive age stratums:<br>- Stratum 1: 12 to < 18 years<br>- Stratum 2: 2 to < 12 years<br>- Stratum 3: birth to < 2 years | |

## 5.2. Review Strategy

The primary clinical review was conducted by Fadi Nossair. The primary statistical review was conducted by Sarabdeep Singh.

Table 3 lists the early phase clinical pharmacology trials evaluating PK/PD and safety of Pradaxa in the pediatric population. Trial 1160.88, trial 1160.89 and trial 1160.105 provided uncontrolled data partially informing the safety profile of Pradaxa in pediatric patients but did not provide data supporting efficacy, given their uncontrolled design and limited dosing in patients who completed initial VTE treatment.

Table 4 lists the pivotal clinical trials evaluating the efficacy and safety of Pradaxa in the pediatric population. Trial 1160.106 was an adequate and well-controlled trial that provided sufficient data for the proper evaluation of both the efficacy and the safety of Pradaxa in the pediatric population. Trial 1160.108 was designed as a single-arm extension trial to evaluate the safety of long-term use (up to a maximum of 12 months) of Pradaxa in pediatric patients. In addition, it provided data that was adequate to evaluate the secondary prevention of VTE in pediatric patients, when compared to established pediatric VTE recurrence rates in the literature. Given the significant difference in trial design, data from the two pivotal trials were not pooled, when evaluating the safety profile of Pradaxa in pediatric patients; instead safety

was evaluated separately. As a result, we did not conduct an integrated review of effectiveness. Analysis of the two pivotal trials formed the core of the FDA clinical assessment of the application.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on VTE in the pediatric population, epidemiology and treatment along with the Applicant's background materials.
- Review of trial 1160.88, trial 1160.89, trial 1160.105, trial 1160.106 and trial 1160.108, including the clinical study report (CSR), protocol, protocol amendments, case reports forms and narratives, statistical analysis plan (SAP) and SAP amendments.
- Review of datasets submitted as SAS transport files.
- Review of submitted Bioresearch Monitoring (BIMO) datasets and reviewer's guides.
- Review and evaluation of proposed labeling.

The electronic submission including protocols and protocol amendments, SAP, CSRs, patient listings, supporting literature, and SAS transport datasets in legacy, SDTM, and ADaM format, with reviewer's guides, for the sNDA submission are located in Global Submit Review as an original submission in NDA 022512 SDN 2336 (eCTD 0452).

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication. The primary analysis was generally reproducible, with minor differences secondary to differing definitions of relevant terms. Overall, the reviewers were able to confirm the Applicant's analyses of the primary and secondary endpoints.

# 6. Review of Relevant Individual Trials Used to Support Efficacy

## 6.1. Trial 1160.106

### 6.1.1. Study Design

#### Title

Open-label, randomized, parallel-group, active-controlled, multi-center, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study

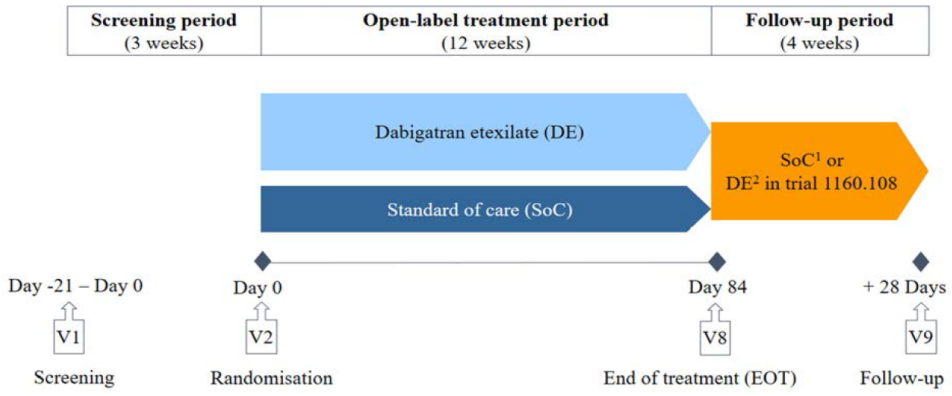
#### Overview and Objective

Trial 1160.106 was a multi-center, multinational, open-label, randomized, parallel-group, active-controlled, non-inferiority trial of Pradaxa versus SoC in children from birth to < 18 years of age. Recruitment was first initiated in stratum 1 (12 to <18 years of age) and was consecutively opened to stratum 2 (2 to <12 years of age) and stratum 3 (0 to <2 years of age).

The main objectives of this Phase IIb/III pediatric trial were to assess the efficacy and safety of Pradaxa relative to SoC and to document the appropriateness of the proposed Pradaxa dosing algorithm for use in patients from birth to < 18 years of age.

#### Trial Design

The trial consisted of 3 periods: a screening period, an open-label treatment period, and a follow-up period. Trial design is provided in Figure 1. After consent (and assent, if applicable), the patients entered a screening period while they were completing their initial phase of VTE treatment. After a maximum duration of 21 days of initial VTE treatment, patients were randomized in a 2:1 ratio to Pradaxa or SoC. The intended SoC (LMWH, VKA, or fondaparinux) was required to be specified at randomization. Once eligibility had been confirmed, patients received either daily Pradaxa or SoC, for up to 3 months after randomization. All patients were followed up until 28 days after termination of trial medication. Baseline (i.e. prior to enrollment) and final (i.e. at early End of Treatment [eEOT] visit) assessment of the VTE should be performed using an appropriate imaging method, depending on location of the VTE. The imaging method of assessment must be the same for both timepoints.




[1] Patients requiring further VTE treatment after the end of the 12-week treatment period were to be treated with SoC
[2] Patients requiring further VTE secondary prevention after the end of the 12-week treatment period were offered to be enrolled into trial 1160.108
V8: For patients who prematurely discontinued treatment before V8, an early End-of-treatment visit (eEOT) was to be performed as soon as possible. In this case, V9 was to be scheduled 28 days after the eEOT visit.
V9: For patients who enrolled into trial 1160.108, the follow-up visit was not required.

Figure 1: Trial Design for Trial 1160.106
Source: 1160-0106--1-15--study-report-body.pdf page 34.

Starting dose Nomogram for Pradaxa capsules (Figure 2), oral pellets (Figure 3) and oral solution (Figure 4) for both trial 1160.106 and trial 1160.108 are provided below. PK/PD parameters for Pradaxa were measured as a trough concentration every visit to ensure drug concentration is within the target goal of 50-<250 ng/ml. Specific dose adjustment nomograms for each formulation was provided for both up-titration (by 15-100% of starting dose) and down-titration (by 40-50% of starting dose). Repeat drug concentration was measured after steady state of new dose was achieved (i.e. after at least 6 consecutive doses were administered). Only one dose adjustment was allowed on-protocol. If target goal concentration was not achieved, Pradaxa was discontinued and SoC treatment was initiated, if appropriate. However, these patients were followed on trial as scheduled. This dose adjustment protocol was applied to both trial 1160.106 and trial 1160.108. The following are important per-protocol medication intake guidelines applied to both trial 1160.106 and trial 1160.108:

- If patients on Pradaxa experience GI disturbances, it was recommended to take Pradaxa with a meal or prescribe patients a proton pump inhibitor (PPI).
- Oral pellets were to be mixed with food (baby rice cereal, carrot mush, banana mush, strawberry jam, or apple sauce) or apple juice. As a result, even though oral solution was preferred for patients < 12 months of age, patients at birth could receive oral pellets using apply juice if supplies are available and if cleared by trial investigator.
- Patients receiving oral solution were also randomized (1:1) to received flavored or unflavored solution for reconstitution.
- Switching between different Pradaxa formulation was not recommended but was considered on a case-by-case basis.
- The specified dosing interval instructions were different, among the different formulation, in the protocol. Specifically, instruction for capsules did not specify an interval but stated to “be taken in the morning and in the evening, at approximately the same time every day”. In contrast, instruction for oral pellets and oral solution specifically stated that doses “should be as close to 12 hours as possible”.

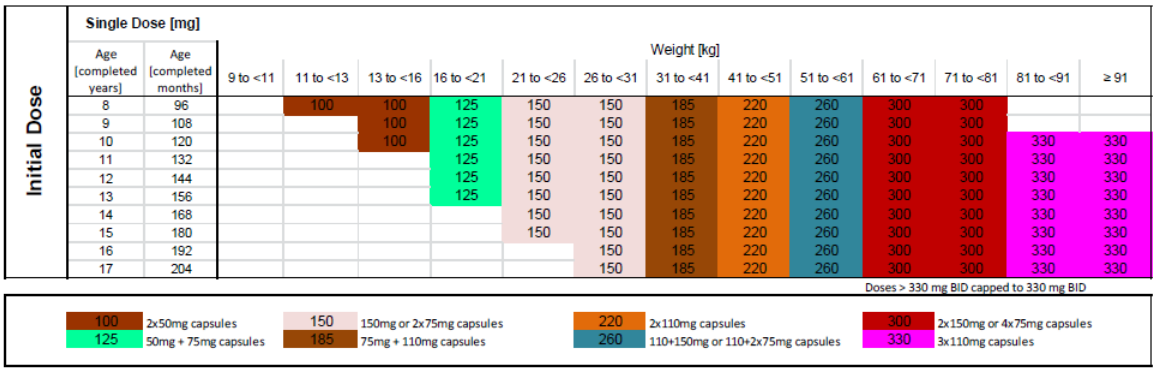



Figure 2: Dosing Nomogram for Starting Dose of Pradaxa Capsules in Trials 1160.106 and Trial 1160.108

Source: 1160-0106--16101--protocol-or-amendment.pdf page 177.

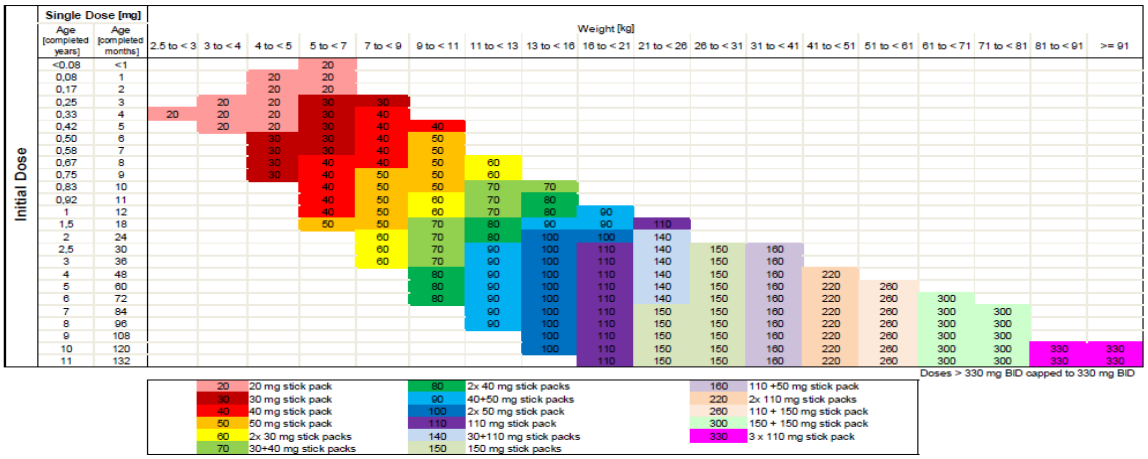



Figure 3: Dosing Nomogram for Starting Dose of Pradaxa Oral Pellets in Trials 1160.106 and Trial 1160.108

Source: 1160-0106--16101--protocol-or-amendment.pdf page 177.

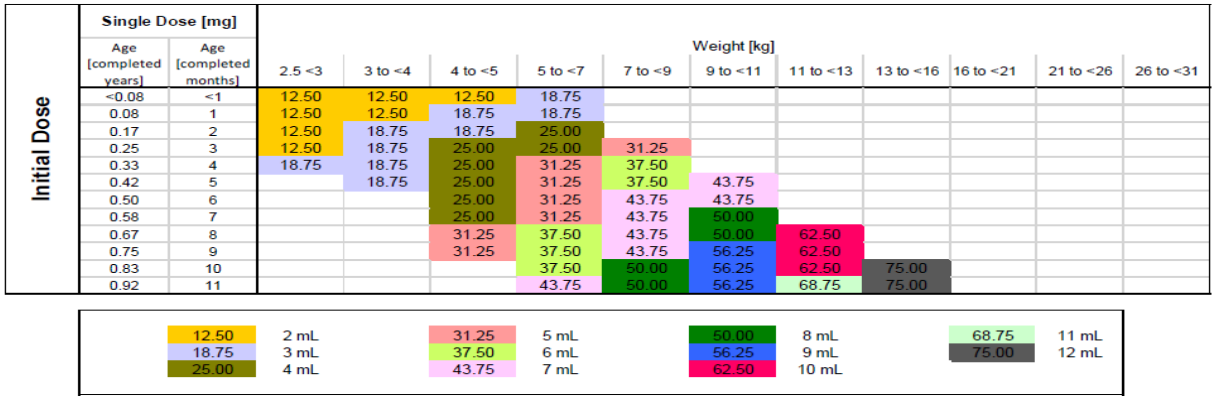



Figure 4: Dosing Nomogram for Starting Dose of Pradaxa Oral Solution in Trials 1160.106 and Trial 1160.108

Source: 1160-0106--16101--protocol-or-amendment.pdf page 178.

## Key eligibility criteria

*Key inclusion criteria* were:

- Male or female patients from birth to <18 years of age at the time of informed consent/assent.
- Documented diagnosis of clinically stable VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis) per investigator judgement, initially treated (minimum of 5 to 7 days, but not longer than 21 days) with parenteral anticoagulation therapy, such as UFH or LMWH. Short-term pre-treatment with VKAs was permitted if the INR had not yet reached a therapeutic level (i.e. the INR was still <2.0).
- Anticipated treatment duration with anticoagulants for the VTE episode (under inclusion criterion 2) for at least 3 months, inclusive of the initial parenteral therapy.

*Key exclusion criteria were:*

- Conditions associated with an increased risk of bleeding.
- Anemia (hemoglobin < 8 g/dL) or thrombocytopenia (platelet count < $80x10^9$/L) at screening.
- Renal dysfunction (eGFR <50 mL/min/1.73m2 using the Schwartz formula) or requirement for dialysis.
- Hepatic disease, with active liver disease or Persistent ALT or AST or Alkaline Phosphatase >3x ULN within 3 months of screening.
- Active infective endocarditis.
- Patients with a heart valve prosthesis requiring anticoagulation.
- Pregnant or breast-feeding female patients.
- Patients in stratum 3 (0 to <2 years) with gestational age at birth <37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards).

## Study Endpoints

Primary Endpoint:

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

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

The events outlined in the above combined primary endpoint were assessed by radiologists or other such qualified clinicians using an appropriate method such as ultrasound, echocardiography, venography, or computed tomography (CT) scan, based on the location of the thrombus and the test used to perform the baseline assessment. All components of the primary efficacy endpoint as well as all bleeding and all fatal events were centrally adjudicated by an independent blinded committee.

*Secondary Endpoints:*

- Freedom from major bleeding events, defined as either fatal bleeding; clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L in a 24-hour period; bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system; or bleeding that requires intervention in an operating suite
- PK and PD assessments at Visit 3 (after at least 6 consecutive DE doses) and after at least 3 days following any DE dose adjustment

- Frequency of dose adjustments (i.e. number of patients with dose adjustment), temporary and permanent discontinuation from therapy, and number of patients with laboratory monitoring requirements for dose adjustment during the treatment phase
- Frequency of switch of type of anti-coagulation therapy (including DE to SoC), i.e. frequency of patients switching the type of anti-coagulation therapy including DE to SoC and switching from an intended SoC treatment to another
- Freedom from thrombus progression at end of therapy (Day 84 after randomization (Visit 8) or eEOT whichever came first), compared with baseline
- Assessment of the acceptability of an age-appropriate formulation at end of therapy
- All bleeding events
- All-cause mortality
- All individual components of the primary efficacy endpoints

Other Endpoints:

- Proportion of patients with thrombus progression, unchanged thrombus, thrombus with partial regression and complete resolution, per treatment group at Day 84 after randomization (Visit 8) or at eEOT (whichever came first)
- Proportion of patients with freedom from recurrent VTE and freedom from mortality related to VTE
- Proportion of patients with either complete or partial thrombus resolution, freedom from recurrent VTE, and freedom from mortality related to VTE
- Assessment of acceptability of capsules, oral pellets, and oral solution reconstituted with flavored or unflavored solvent at Days 3 (Visit 3), 21 (Visit 5) and 84 (Visit 8 or eEOT) after randomization

## Statistical Analysis Plan

*Sample Size Determination:*

Using data from the 11 trials, a Bayesian meta-analysis approach concluded stable mean complete thrombus resolution rate of 72% regarding SoC. In the absence of solid evidence of spontaneous thrombus resolution, a precise effect size was difficult to be determined. As an alternative, a wide range of plausible complete thrombus resolution rates without treatment (5% to 20%) were considered, and it was demonstrated that the proposed 20% non-inferiority margin can preserve at least 62% and up to 70% of the effect size under SoC treatment (see Table 5).

Table 5: Effect Size for 20% Non-inferiority Margin for Trial 1160.106

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

Source: 1160-0106--16101--protocol-or-amendment.pdf page 159.

The study planned to enroll a total of 141 patients and a 2:1 randomization to Pradaxa or SoC with

approximately 94 patients randomized to Pradaxa and 47 patients to SoC. A simulation had been performed to consider the variability in the estimate of the complete thrombus resolution rate. Assuming the number of complete thrombus resolution follows binomial distribution with unknown probability of success, the estimates of the complete thrombus resolution rate are subject to the variability of this distribution. One hundred thousand binomial samples were generated for the Pradaxa and SoC arms. The lower bound of the 90% confidence interval was calculated for each simulation. Under the assumption that the true unknown complete thrombus resolution rate is 72% for both Pradaxa and SoC, the proposed sample size of 141 was considered sufficient to demonstrate non-inferiority with adequate power (82%).

*Randomization:*
Interactive response technology was used to randomize patients to treatment groups. The randomization was performed in blocks and stratified by age groups, and the allocation ratio was 2:1 for Pradaxa to SoC.

*Futility Interim Analysis:*
One futility interim analysis was planned and conducted when 66% of patients completed visit 8. The futility boundaries were calculated based on a 10% conditional power at the interim analysis. The futility boundary was combined with other clinical evidence when making decisions to stop the trial for futility.

*Missing Data:*
Missing data were not imputed. For complete thrombus resolution assessment, if the assessment at visit 8 (84 days) was missing, then the last observation at visit 3 (21 days) was carried forward (LOCF), providing there were no VTE-related event that occurred between the two visits.

*Primary Efficacy Analysis:*
The trial was designed to assess the efficacy and safety of Pradaxa, using the proposed dosing algorithm, compared to SoC, for treatment of pediatric VTE in patients from birth to less than 18 years of age. This trial was a prospective, multicenter, international, open-label, randomized, parallel-group, non-inferiority trial comparing Pradaxa (D) to SoC (C). The non-inferiority hypothesis for the primary endpoint (proportion of patients with complete thrombus resolution, with no recurrent VTE and no VTE-related death) was:

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

Upon showing significance of non-inferiority for the primary endpoint (using a 95% confidence interval), a test of superiority was performed subsequently (with a one-sided significance level of 0.025), in the following order:

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

The primary analysis of the primary efficacy endpoint used the randomized set, following the intention-to-treat principle. Mantel-Haenszel type weighted average approach was used to analyze the primary endpoint with age as a stratification factor.

The primary efficacy endpoint contained 3 components (freedom from mortality related to VTE, freedom from recurrent VTE, and complete thrombus resolution). Each component was evaluated separately, and only if the criteria for all 3 components were satisfied, the primary endpoint was considered achieved and

patient as responder.

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

Another sensitivity analysis was conducted to assess the period from randomization until the end of trial (complete observation period), covering the longest possible observation time for patients recruited in this trial. This included all available follow-up data.

Additional sensitivity analyses, such as the summary of all investigator-reported events, were performed based on the same patient population and the same primary analysis.

Final sensitivity analysis was conducted to study differences between Last Observation Carried Forward (LOCF) data and the worst-case imputation.

*Sub-group Analyses:*
Sub-group analyses were conducted for the primary endpoint with the subgroups identified as: age, sex, region, type of control treatment (LMWH; VKA; fondaparinux), presence of central venous line, presence of congenital heart disease, and presence of malignant disease. Differences in the proportion of patients achieving the primary endpoint was reported by Mantel-Haenszel estimate with the subgroup of interest as the stratification factor (e.g. stratification factor region for the subgroup analysis by region).

*Secondary Efficacy Analyses:*
Major bleeding events were analyzed using Kaplan-Meier method. The proportion of patients free from MBEs at the end of treatment period (84 days (Visit 8) or eEOT) was provided by Kaplan-Meier estimates for the 2 treatment arms, pooling all age groups. Due to the low event rate of MBEs, age group stratification was not considered. Patients who discontinued from the trial prematurely without having MBEs were censored.

All bleeding events and all-cause mortality were analyzed using a stratified Cox proportional hazard model, with treatment as a covariate in the model and age group as the stratification factor. A pooling of age groups was considered if no events were observed in a certain age group. Patients that did not experience any bleeding events were included as censored observations at the date of the last visit or the date of death not related to bleeding, whichever came first.

## Protocol Amendments

There were nine global amendments to the original protocol, which was dated June 4th, 2013. The majority of amendments contained a large number of changes, with differing importance. It is important to note that throughout the protocol life-cycle, the Applicant provided updates in relation to dose justification, non-clinical study results and early phase trial results. In general, we will only include the amendments of most importance in our review:

- Global amendment 1 (October 2nd, 2014) implemented suspension of recruitment of patients > 40 kg until suggested TID dosing is implemented.

- Global amendment 2 (January 28th, 2015):
  - Modify stratum 2 age range from "1 to < 12 years" to "2 to < 12 years) and modify stratum 3 age range from "birth to < 1 year" to "birth to < 2 years", to facilitate recruitment by allowing earlier opening of stratum 2.
  - Modify minimum recruitment goals to: total of 240 evaluable patients, 80 patients in stratum 1, 75 patients in stratum 2, 25 patients in stratum 3, with at least 20 patients < 1 year of age.
  - Dosing regimen details added to the protocol, including implementation of BID dosing, rather than the previously suggested TID dosing.
  - The maximal single dose was defined as 330 mg/dose and 22.2 mg/kg/dose. This was modified because the risk of thrombosis in the first 30 days is high in pediatric patients while the risk of bleeding is lower than adults. As a result, this higher cap will allow for decrease in potential medication failures.
  - Only one up-titration will be acceptable, with an up-titration dose range of 15-100%, modified from the initial 85-100%, depending on age and weight of the patients. This was changed to avoid exceeding the maximum daily dosage, defined above. Dose adjustment nomogram were incorporated.
  - Patients who cannot reach the target trough plasma concentrations after one dose adjustment must discontinue dabigatran treatment and be treated at the investigator's discretion on SoC.
  - Age-specific assignments were given to the different formulations, as follows: patients aged ≥ 8 years received capsules, patients aged 6 months to < 8 years or patients ≥ 8 - < 12 years who cannot take capsules received oral pellets, and patients birth to < 6 months or patients 6-12 months who cannot take oral pellets received oral solution.
  - Removal of weight limitation of 40 kg implemented to inclusion criteria in amendment 1.
  - Addition of exclusion criteria to exclude patients with gestational age at birth < 37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards).
  - Exclusion criterion 1c was changed to clarify the exclusion of patients who will have "any major planned procedure that might put the patient at an increased risk of a bleed per investigator judgment within 5 days prior to (not of) taking study medication".
  - To clarify that all patients who continue treatment for VTE, regardless of whether this is a switch from dabigatran etexilate to SoC or from one SoC to another, are not considered early discontinued. These patients remain in the treatment period and should follow the remaining visit schedule until the end of the study.
  - To clarify that HPLC-MS/MS assay could be used to assess the need of dabigatran etexilate dose adjustment, as an alternative to dTT, if needed.
  - The target dabigatran steady state trough concentration was precisely defined to be ≥50 to <250 ng/mL.
  - Added the use of a reversal agent, in the context of a clinical investigation, as an exception to the restriction of investigational medication use.
  - The need to assess ability to swallow capsules with test placebo capsules was removed from the protocol, as this is not necessary or used in clinical practice.

- Global amendment 3 (November 26th, 2015):
  - Up-titration nomogram for capsules and oral pellets modified to comply with specific intake limits.
  - Dosing nomogram for oral solution temporarily removed to allow for modification to comply with specific intake limits.

- Global amendment 4 (March 16th, 2016):
  - The assessment of thrombus extension at visit 5 was removed to better reflect the clinical routine for follow-up of patients with VTE, to eliminate potential unwarranted radiation exposure and to reduce trial complexity. On a case-by-case basis, if suspicion for recurrence is present, an additional assessment will be done during an unscheduled visit.
  - ECG requirement at visit 5 was removed, as this is not necessary in the context of treatment with Pradaxa.
  - To evaluate the acceptability of oral solution, flavored vs. unflavored solution will be assigned in a randomized fashion (1:1 ratio) to patients taking oral solution.
  - Clarification that patients requiring VTE therapy beyond 3 months have to be switched at Visit 8 (day 84) to SoC treatment (if randomized to dabigatran etexilate) or continue SoC treatment (if randomized to the SoC arm) and could be maintained on SoC during the follow-up period. Patients requiring further anticoagulation for secondary VTE prevention due to unresolved clinical risk factor may be enrolled in Trial 1160.108.
  - The following clarification relating to the inclusion/exclusion criteria were added:
    - The need for parenteral anticoagulation therapy until randomization to trial medication.
    - The need for an anticipated requirement of antithrombotic treatment of at least 3 months.
    - The duration of initial parenteral treatment was defined to be up to a maximum of 21 days.
    - Insertion of a central venous line is not considered a major surgery provided hemostasis is achieved after the procedure.
    - It was clarified that patients with asymptomatic petechial or microbleeds are eligible for the study. Definition of microbleeds was provided in a footnote.
    - eGFR retesting during the screening period was allowed (once). Patients will have to discontinue dabigatran treatment anytime during the course of the study if eGFR drops < 50 mL/min/1.73m$^2$, decreased from < 80 mL/min/1.73m$^2$, using the Schwartz formula and this is confirmed by one retesting within the next 14 calendar days. The earlier cut-off led to unnecessary discontinuation of study drug in some initial patients.
    - P-glycoprotein inhibitors intake up until first dose of study medication will not be considered as exclusion criterion
  - Modification to initial dosing recommendation for newborn < 1 month and < 3 kg were done. Corrected dosing nomogram for oral solution restored into protocol.
  - If gastrointestinal symptoms develop it is recommended to take dabigatran etexilate with a meal and/or a PPI such as pantoprazole. In amendment 5, the recommendation for PPI was changed to include "according to the local standard of care in accordance with local labelling recommendations " . The recommendation was analogous to recommendations used in adults.

- Modification of the earliest time-point for conducting the interim analyses to provide data to inform the DMC's decision:
  - For age strata 1 and 2, changed to after the 18th patient randomized to dabigatran etexilate in respective age stratum has reached the time point where 2 consecutive PK samples are available. Data from unique patients recruited into trials 1160.106 and 1160.108 will be considered.
  - For age stratum 3, changed to after the 7th patient on dabigatran etexilate in this age group has reached the time point where 2 consecutive PK samples are available. Data from unique patients recruited into trials 1160.106 and 1160.108 will be considered.

- Global amendment 5 (November 29th, 2016):
  - Reduction of minimum recruitment goals to improve feasibility: total 180 evaluable patients, 60 patients in stratum 1 and 50 patients in stratum 2. Secondary to these reductions, the number of futility interim analyses has been decreased to one, and this futility interim analysis will be conducted when 66% patients have completed Visit 8.
  - The duration of the follow-up period was reduced from currently nine months to one month after the end of study medication (i.e. after Visit 8, which is at 3 months, or eEOT, whatever comes first) since long-term exposure data will be captured by trial 1160.108. As a result, long-term secondary efficacy endpoints assessing VTE recurrence and PTS at 6, 9 and 12 months were removed.
  - Clarification that freedom from thrombus progression at the end of therapy will be assessed in comparison to baseline.
  - Clarification that all patients who received at least one dose of study medication will be considered evaluable.
  - Inclusion criteria specified that patients should be clinically stable and should have been treated with a parenteral anticoagulant for a minimum of 5 days before being randomized, thus reflecting the adult VTE treatment program.
  - Exclusion criteria changed to modify the eGFR level for exclusion for patients aged 12 to < 18 years to < 60 mL/min/1.73m$^2$, while keeping the eGFR level for patients < 12 years at < 80 mL/min/1.73m$^2$. This was supported by an interim analysis in adolescent patients, in relation to both PK/PD and safety data.
  - Exclusion criteria clarified that patients will be excluded if they have heart valve prosthesis requiring anticoagulation treatment.
  - Justification of non-inferiority margin for primary efficacy endpoint has been updated, as per Agency's recommendation. Further calculation of the effect size preserved with the proposed sample size based on a meta-analysis from published trials, also taking the variability in the complete resolution rate without treatment into consideration, has been added to this section.

- Global amendment 6 (October 30th, 2017):
  - Reduction of minimum recruitment goals to improve feasibility: total 141 evaluable patients, 18 patients in stratum 2, 15 patients in stratum 3, with at least 8 patients < 1 year of age. The recruitment of patients will be continued after achieving the minimum total number of patients and the minimum number of patients per age strata, if required by Regulatory Authorities.

  - With agreement from the Agency, freedom from major bleeding events has been changed from the co-primary safety endpoint to a secondary endpoint.
  - Fondaparinux has been added as standard of care treatment.
  - Clarification that patients having switched from dabigatran etexilate to SoC are considered as having early discontinued of dabigatran etexilate treatment, which is the opposite of the clarification presented in amendment 2. However, such patients will still remain in the trial and be followed as per the visit schedule till the end of the study.

- Global amendment 7 (January 16th, 2018):
  - Addition of the exclusion of patients with meningitis, encephalitis or intracranial abscess, based on the recommendation of the DMC secondary to the occurrence of an intracranial bleed in an infant on Pradaxa in the context of meningitis and CSVT.

- Global amendment 8 (September 11th, 2018):
  - The option to administer oral pellets was expanded to patients < 6 months of age. A preference for the usage of oral solution over oral pellets in patients < 12 months of age was implemented.
  - Clarification that the steady state of the currently assigned dabigatran etexilate formulation (i.e. at least 6 consecutive dabigatran etexilate doses have been taken) has to be achieved before a formulation switch could be considered.
  - Clarification that dabigatran etexilate up- or down-titration is not possible in some instances (limit of 22.2 mg/kg/day based on excipient acceptable daily intake, maximal single dose of 330 mg, unavailability of dosages) and affected patients have to be discontinued from study medication prematurely.
  - Clarification that, if deemed necessary, the type of SoC may be changed in SoC patients during the treatment period and will not be considered as having discontinued study medication early but will remain to be on study medication and will be followed per the visit schedule until the end of the study.
  - Patients assigned to take dabigatran and who have been treated with parenteral anticoagulants should start the study medication 0-2 hours prior to the time that the next dose of the alternate therapy (e.g. LMWH) would be due, or at the time of discontinuation in case of continuous treatment (e.g. UFH). In case pre-treatment with VKAs has been initiated during the screening period, a local INR measurement should be performed at Visit 2 to confirm eligibility (INR < 2.0).
  - Banana mush, strawberry jam and apple juice were added to the list of foods that are allowed to be mixed with dabigatran etexilate oral pellets.
  - If a dabigatran etexilate dose has only been taken partially, there should be no attempt to administer a second dose at that timepoint, and the next dose should be taken as scheduled approximately 12 hours later.
  - Fibrinolytic agents should not be taken within 48 hours prior to dabigatran administration and P-glycoprotein inducers should not be taken within one week to prior dabigatran administration. Generally excluded corticosteroids may be included if the benefits of corticosteroid therapy clearly outweigh risks.
  - Several statements were added to the secondary endpoints to clarify their exact meaning.
  - Clarification that copies of de-identified source documents necessary for adjudication will be

provided to the adjudication committee.

- Global amendment 9 (February 6th, 2019):
  - Exclusion criteria changed to modify the eGFR level to < 50 mL/min/1.73m$^2$ for all patients, irrespective of age. This was supported by an interim analysis that show a favorable benefit/risk relationship and no excess levels ≥ 250 ng/ml in patients < 12 years. However, the protocol eGFR criterion for stopping dabigatran treatment (i.e. if eGFR drops below 50 mL/min/1.73m$^2$) remained unchanged.

### 6.1.2. Study Results

#### Compliance with Good Clinical Practices

The applicant stated that the clinical trial protocol, informed consent form (ICF), and printed patient information materials were reviewed and approved by the independent ethics committee (IEC) and/or institutional review boards (IRB) for each site before any study procedures were performed. Any subsequent informed consent revisions were approved by the IRB or IEC before any changes were initiated.

According to the applicant, the study was conducted according to International Conferences on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines concerning Good Clinical Practice (GCP), the European Union Clinical Trials Directive (2001/20/EC), Title 21 of the US Code of Federal Regulations (21 CFR) and the practices and regulations of each participating nation. Written informed consent to participate in the study was obtained from each patient (or patient's guardian) before any study-specific procedures were performed.

#### Financial Disclosure

Trials 1160.106 was a covered trial included in the submission for sNDA 022512 – s041. In accordance with 21 CFR 54, the Applicant submitted financial disclosure certification documents for these trials. In addition, the Applicant stated that there were no Investigators/Sub-investigators participating in either trials that were a part-time or full-time employee of Boehringer Ingelheim

For trial 1160.106, 393 Investigators/Sub-investigators reported no financial arrangements or interests to disclose but 44 Investigators/Sub-investigators were lacking financial disclosure questionnaire (FDQ). Of those lacking a completed FDQ, 31 individuals were working in a site that did not initiate and 12 individuals did not participate as Investigators/Sub-investigators. The one remaining individual is no longer at the site and that site closed prematurely due to lack of enrollment.

For trial 1160.106, only one Sub-investigator from (b) (6) (site code (b) (6)), (b) (6), reported a significant payment made by the Applicant to support activities that had a monetary value of more than $25,000, exclusive of the costs of conducting the clinical trial, during the time (b) (6) was involved in carrying out the trial. The total amount of the payment was equivalent to ~ $95,920 and it was paid to the cardiovascular diseases and cardiology department to support the department and the research project (b) (6)". The Applicant concluded that since the payment was not given to the Sub-investigator

directly and was directed to the department for resources support, no further intervention is needed to minimize the potential for bias.

The following measures were also in place to minimize bias: use of multiple clinical sites, clinical site monitoring and audits, independent/centralized review of efficacy and response data, and limitation of enrollment to no more than 20% of the total trial enrollment at each site where an Investigator/ Sub-investigator had disclosable financial interests.

Form 3454 was certified by Thomas Seck 07/22/2020.

*Medical reviewer comment: During the filing review of the application, an information request was sent to the Applicant to submit a list of investigators who were part-time or full-time employees, and to discuss the due diligence taken to attempt to obtain the FDQ for Investigators/Sub-investigators for which FDQ was not submitted. The Applicant's response was complete and resolved the majority of the missing information. Given the current completeness of the provided financial disclosure information and our agreement that the single disclosure per trial will not have significant impact on the integrity of the trials or the validity of the results, we do not have any concerns.*

## Patient Disposition

In trial 1160.06, 328 patients were enrolled but 61 patients were not randomized after signing informed consent, resulting in a total of 267 patient being randomized. Table 6 summarizes the initial disposition data for the two trials.

Table 6: Disposition Data for Enrolled Patients on Trial 1160.106

| | Trial 1160.106 |
|---|---|
| Number of patients screened / obtained informed consent | 328 |
| Number of patients who were screen failure[1] | 50 |
| Number of patients withdrawn not due to AE prior to entering trial | 8 |
| Number of patients consented but unable to be enter trial | 3 |
| Number of patients successfully screened & entered trial | 267 |
| Number of patients assigned to Pradaxa | 177 |
| Number of patients assigned to SoC | 90 |
| Number of patients entered trial but not treated | 1[2] |

Source: MEDICAL reviewer's analyses. [1] Most common reason for failure to meet inclusion/exclusion criteria leading to screen failure were eGFR < 80 mL/min/1.73m$^2$, aspartate aminotransferase (AST) / alanine aminotransferase (ALT) above upper limit of normal (ULN) and risk of bleeding due to a recent surgery, [2] One patient in Pradaxa arm randomized but not treated in 1160.106 trial.

Of the 266 patients who received trial medication, 253 patients (95.1%) completed the planned observation period (i.e. attended follow-up visit – visit 9), regardless of timing of discontinuation of trial medication, with 13 patients (4.9%) prematurely discontinuing the trial (8 patients – 4.5% in Pradaxa arm vs. 5 patients – 5.6% in SoC arm) due to: 1) Loss to follow-up (2 patients in Pradaxa arm vs. none in SoC arm), 2) Non-compliance (2 patients in Pradaxa arm vs. 1 patient in SoC arm), 3) Discontinued due to parental or treating physician recommendation (1 patients in Pradaxa arm vs. 1 patient in SoC arm), and 4) Occurrence of AE (1 patients in Pradaxa arm vs. 2 patient in SoC arm).

Of those who completed the planned observation period, 215 patients (80.8%) completed trial medication

without premature discontinuation, with 38 patients prematurely discontinuing trial medication but completed the planned observation period (33 patients – 18.8% in Pradaxa arm vs. 5 patients – 5.6% in SoC arm), due to: 1) Occurrence of AE (13 patients in Pradaxa arm vs. 1 patient in SoC arm), with bleeding and renal abnormalities being the most common AEs, 2) Recurrence of VTE (1 patients in Pradaxa arm vs. 1 patient in SoC arm), 3) Non-compliance (3 patients in Pradaxa arm vs. 0 patient in SoC arm), 4) Use of prohibited concomitant medication (2 patients in Pradaxa arm vs. none in SoC arm), and 5) Inability to meet target concentration after 1 titration (12 patients in Pradaxa arm vs. none in SoC arm).

*Medical reviewer comment:*
*For trial 1160.106, there was a significant difference among patients who prematurely discontinued Pradaxa while continuing on the trial, as compared to those who discontinued SoC therapy while continuing on the trial. There are two main drivers of this difference:*

1) *Higher rate of AE leading to discontinuation:*
   - *Detailed discussion of AEs leading to medication discontinuation is presented in section 8.4.3.*
   - *Evaluation of AEs leading to medication discontinuation revealed that the main source of imbalance is due to renal-based AEs, which depended on a changing definition throughout the protocol life cycle. As a result, if the final definition was used initially, these patients would not be classified as having a renal-based AE.*
   - *In addition, there was an imbalance of AE unrelated to trial medication in the Pradaxa arm, which contributed to higher overall rates of AE leading to discontinuation in that arm.*
2) *Higher rate of discontinuation due to inability to reach target trough concentrations after one titration per protocol:*
   - *Detailed discussion of trough concentration-related medication discontinuation is present in section 8.2.1.*
   - *Sensitivity analyses assessing the primary endpoints, if patients who discontinued Pradaxa due to inability to attain trough concentration were removed, showed no difference in trial results.*

## Protocol Violations/Deviations

A total of 61 patients (22.8%) had at least 1 important protocol deviation, with the following reasons and frequencies:

- Deviation related to inclusion/exclusion criteria occurred in 24 patients (13.6%) in the Pradaxa arm vs. in 8 patients (8.9%) in the SoC arm. The specific criteria of concern are:
  - No documented diagnosis of clinically stable VTE (n=5) or not initially treated with parenteral anticoagulation within pre-specified duration (n=17) or anticipated treatment duration < 3 months (n=1): 16 patients (9%) in the Pradaxa arm vs. in 7 patients (7.8%) in the SoC arm.
  - Baseline abnormal laboratory results indicating organ dysfunction (i.e. hepatic disease, renal dysfunction, anemia or thrombocytopenia): 6 patients (3.4%) in the Pradaxa arm vs. in 1 patient (1.1%) in the SoC arm.
  - Prohibited or restricted medication (including an investigational drug) prior to first dose: 2 patients (1.1%) in the Pradaxa arm vs. none in the SoC arm.
  - Other exclusion criteria: 1 patient whose gestational age at birth was < 37 weeks or body weight < 3$^{rd}$ percentile (in Pradaxa arm) vs. 1 patient who had a condition associated with an increased risk of bleeding (in SoC arm).
- Deviation related to the use of prohibited concomitant medication occurred in 7 patients (4%) in

the Pradaxa arm vs. none in the SoC arm, due to the presence of additional restrictions related to the use of concomitant medication present with Pradaxa but not with SoC therapies.

- Deviation related to non-compliance occurred in 9 patients (5.1%) in the Pradaxa arm vs. in 1 patient (1.1%) in the SoC arm.
- Deviation related to medication error (e.g. wrong dose, wrong formulation, incorrect titration) occurred in 15 patients (8.5%) in the Pradaxa arm vs. in none in the SoC arm. Because SoC therapy was not provided by the Applicant and per-protocol titration was not applicable to SoC therapy, all events occurred in the Pradaxa arm.

There were two patients who had per-protocol indications for stopping Pradaxa, but study drug was not stopped: one patient did not achieve trough target after 1 dose adjustment and one patient had evidence of new VTE event or clear progression of baseline VTE.

*Medical reviewer comment:*
*For trial 1160.106, deviations related to important inclusion criteria are equally present in both treatment arms, while deviations related to exclusion criteria are infrequent. As a result, we do not anticipate that either types of deviations would impact the final results of the trial. In relation to deviations related to prohibited concomitant medication use and medication error in trial 1160.106, given that there was no difference observed in the occurrence of AEs between the two arms and the specific relatedness of these deviation to the study drug, these deviations cannot be assessed as being significant. Deviations due to non-compliance were significant. For trial 1160.106, even though the difference in compliance between the two arms is significant, the overall number of patients is small and there was no observed impact on efficacy endpoints that favored the SoC arm, thus this does not affect the outcome of the trial. As a result, we conclude that these findings are reasonable and do not anticipate any impact on the final results of the trial.*

## Table of Demographic Characteristics

Table 7 summarizes the demographics in the randomized/intention-to-treat (ITT) dataset (N=267). The mean age was 11.1 years old; 49.8% were male, and 91.8% were white. Patients were recruited from 62 sites in 26 countries, with 9 sites located in the US that contributed 11% (30 patients) of patients in the ITT dataset.

Table 7: Demographic Characteristics of Trial 1160.106

| Demographic Parameters | Pradaxa – n (%) (N = 177) | SoC – n (%) (N = 90) | Total – n (%) (N = 267) |
|---|---|---|---|
| Sex | | | |
| Female | 96 (54.2) | 38 (42.2) | 134 (50.2) |
| Male | 81 (45.8) | 52 (57.8) | 133 (49.8) |
| Age | | | |
| Mean (SD) | 11.2 (6) | 11.1 (6) | 11.1 (6) |
| Median (Min-Max) | 14 (0-17) | 14 (0.1-17) | 14 (0-17) |
| Age Group | | | |
| Stratum 3 (0 - < 2 years) | 22 (12.4) | 13 (14.4) | 35 (13.1) |
| Stratum 2 (2 - < 12 years) | 43 (24.3) | 21 (23.3) | 64 (24.0) |
| Stratum 1 (12 - < 18 years) | 112 (63.3) | 56 (62.2) | 168 (62.9) |

| | | | |
|---|---|---|---|
| Race | | | |
| White | 163 (92.1) | 82 (91.1) | 245 (91.8) |
| Black or African American | 1 (0.6) | 3 (3.3) | 4 (1.5) |
| Asian | 10 (5.6) | 3 (3.3) | 13 (4.9) |
| Other | 2 (1.1) | 0 (0.0) | 2 (0.7) |
| Missing | 1 (0.6) | 2 (2.2) | 3 (1.1) |
| Ethnicity | | | |
| Not Hispanic or Latino | 169 (95.5) | 86 (95.6) | 255 (95.5) |
| Hispanic or Latino | 8 (4.5) | 3 (3.3) | 11 (4.1) |
| Missing | 0 (0.0) | 1 (1.1) | 1 (0.4) |
| Region | | | |
| North America[1] | 39 (22.0) | 17 (18.9) | 56 (21.0) |
| Western Europe[2] | 35 (19.8) | 20 (22.2) | 55 (20.6) |
| Eastern Europe[3] | 93 (52.5) | 51 (56.7) | 144 (53.9) |
| South/Central America[4] | 4 (2.3) | 2 (2.2) | 6 (2.2) |
| Asia[5] | 6 (3.4) | 0 (0.0) | 6 (2.2) |

Source: MEDICAL reviewer's analyses. [1] North America includes USA and Canada, [2] Western Europe includes Austria, Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, Greece, Hungary, Italy, Norway and Sweden, [3] Eastern Europe includes Czech Republic, Russia, Ukraine, Lithuania and Turkey, [4] South/Central America includes Brazil, Argentina and Mexico, [5] Asia includes Taiwan, Israel and Thailand.

*Medical reviewer comment: Demographic characteristics are equal between the two trial arms. However, three imbalances were noted in the trial population:*

- *The number of patients from outside the US is significantly larger, with significant majority coming from Eastern European countries.*
- *The proportion of White and non-White patients is not reflective of the U.S. general population.*
- *The age distribution among the pre-defined stratum is not reflective of the epidemiology of VTE in pediatric patients.*

*An information request was sent to the Applicant to describe their efforts in relation to recruitment of a patient population with demographic characteristics representative of a U.S. population. Their response outlined several strategies: 1) Diverse international sites were selected on the basis of potential contribution to the diversity of the trial population, 2) Competitive enrolment and intensification of recruitment efforts, 3) Extension of enrolment period, resulting in a total trial duration of ~ 5 years for trial 1160.106 and ~4 years for trial 1160.108, and 4) Opening sites in states with higher rates of minorities (e.g. California, Nevada, Virginia and North Carolina).*

*In relation to the differential contribution of Ex-US patients to the trial population, this finding was a result of the predominate contribution of Eastern European countries to the trial population. This imbalance occurred despite the Applicant sufficient efforts and, after thorough evaluation of the integrity of the trial data, it is unlikely to impact the results of the trials. The lack of racial and ethnic representation reflective of the proportions seen in the U.S. population is directly related to the above-mentioned differential contribution of Ex-US patients and has occurred despite the Applicant's best efforts. Given the lack of contribution of race and ethnicity to the epidemiology of pediatric VTE, this finding is unlikely to impact the results of the trials.*

*Finally, the lack of representation of the younger age group in the trials was anticipated given the inherent difficulty in the recruitment of this age group in clinical trials, despite their strong contribution to the prevalence of pediatric VTE. To overcome this limitation, the Applicant has implemented several strategies and committed to minimum numbers of enrollment, as outlined in the WR. Appropriate recruitment goals were achieved to ensure appropriate PK/PD and safety data were collected for analysis, which will be discussed in detail in section 8. While efficacy can be extrapolated from older age groups with minimal supportive data in the younger age group, we conducted sensitivity analyses looking at the efficacy endpoint in the two arms of trial 1160.106 among the three age-group stratums (Table 8). There was no significant difference in efficacy among the younger age groups (i.e. stratum 2 and 3). In contrast, there seems to be a trend favoring the higher efficacy of Pradaxa for adolescents (i.e. stratum 1). However, given the post-hoc nature of the analysis, these conclusions should be used with caution and may be re-evaluated in future studies.*

Table 8: Sensitivity Analysis of Efficacy Endpoint Among the 3 Age-group Stratums in Trial 1160.106 Using the ITT Dataset

| Baseline Characteristics | Stratum 3 (n=35) | | Stratum 2 (n=64) | | Stratum 1 (n=168) | |
|---|---|---|---|---|---|---|
| | Pradaxa (n=22) | SoC (n=13) | Pradaxa (n=43) | SoC (n=21) | Pradaxa (n=112) | SoC (n=56) |
| Efficacy Composite – n (%) | 13 (59) | 7 (54) | 21 (49) | 12 (57) | 47 (42) | 19 (34) |
| Complete Resolution – n (%) | 13 (59) | 7 (54) | 21 (49) | 12 (57) | 47 (42) | 19 (34) |
| VTE Recurrence – n (%) | 0 (0) | 0 (0) | 1 (2) | 1 (5) | 6 (5) | 6 (11) |
| VTE-related Death – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) |

Source: MEDICAL reviewer's analyses.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Using the concomitant medication (CM) SDTM for the on-treatment dataset (N=267), we obtained data relating to the presence of relevant concomitant medications in the patient population. From the CM SDTM, the three relevant CMs were contraceptive use prior to initiation of trial medication, medications associated with a bleeding risk that were used during the treatment period, and red blood cell transfusion need during the treatment period. The specific list of CM used are present in Appendix 13.3. The medical reviewer confirmed the accuracy of entry categorization for each variable manually and using other related variables in the dataset. As an example, the age of all patients who received contraception was checked to ensure absence of outliers and this analysis resulted in a mean age (SD) of 15.6 (1.3) years in the Pradaxa arm vs. 16.6 (0.9) years in the SoC arm (p-value 0.075). Secondary to the need for bridging with a parenteral anticoagulant, as per protocol, we evaluated the lag from index VTE diagnosis and start of trial medication in both trial arms, to assess if there was a significant difference that may impact the results of the trial, with the results shown in Table 9. There was no statistically significant difference between the two arms (p-value = 0.6309).

Table 9: Lag from Index VTE Diagnosis and Start of trial medication in trial 1160.106

| Lag from Index VTE diagnosis to start of trial medication | Dabigatran (n=177) | SOC (n=90) | Total (n=267) |
|---|---|---|---|
| Mean in days (SD, 95%CI)1 | 15 (7, 14-16) | 16 (6, 15-17) | 16 (6, 15-16) |
| Lag ≤ 7 days – n (%) | 21 (12) | 11 (12) | 32 (12) |
| Lag 8 - ≤ 14 days – n (%) | 49 (28) | 22 (24) | 71 (27) |
| Lag > 14 days – n (%) | 90 (51) | 54 (60) | 144 (54) |

Source: MEDICAL reviewer's analyses. [1] 17 patients missing data in dabigatran arm (10%) and 3 missing in SOC arm (3%).

Using the medical history (MH) SDTM for the on-treatment dataset (N=267), we also obtained data relating to the index VTE being treated (Table 10). In relation to the index VTE event, we were not able to differentiate between deep and superficial limb VTE, as the specific veins involved were not regularly documented in the dataset. Overall, we noted a dichotomy of age, when the location of VTE was evaluated, with younger patients experiencing higher proportions of central VTE, CSVT and neck vein thrombosis, while older patients are experiencing higher proportions of limb VTE and PE, as illustrated in Figure 5.

Table 10: Index VTE by Location and CVC-relatedness for Patients Treated in Trial 1160.106

| Index VTE Characteristics | Dabigatran (n=177) | SoC (n=90) | Total (n=267) |
|---|---|---|---|
| Lower extremities – n (%) | 65 (37) | 42 (47) | 107 (40) |
| Upper extremities – n (%) | 20 (11) | 6 (7) | 26 (10) |
| Pulmonary Embolism – n (%) | 20 (11) | 4 (4) | 24 (9) |
| Neck – n (%) | 20 (11) | 21 (23) | 41 (15) |
| Cerebral Sinovenous Thrombosis – n (%) | 22 (12) | 6 (7) | 28 (11) |
| Central Thrombosis[1] – n (%) | 11 (6) | 2 (2) | 13 (5) |
| Unknown location[2] – n (%) | 19 (11) | 9 (10) | 28 (11) |
| | | | |
| CVC-related Thrombosis[3] – n (%) of eligible patients | 28 (21) | 20 (25) | 48 (22) |

Source: MEDICAL reviewer's analyses. [1] Central VTE includes intra-cardiac thrombosis and thrombosis located in other large veins such as inferior vena cava, superior vena cava, innominate veins, hepatic veins, portal vein, splenic veins, renal veins and umbilical vein, [2] Unknown indicates VTE with an unknown location per the MH SDTM dataset, [3] Analysis excluded patients with PE and CSVT since these VTE subtypes cannot be CVC-related, thus proportions of eligible patients used n=215 (i.e. 81% of the study population) for total patients, with 135 patients for Pradaxa arm and 80 patients for SoC arm.

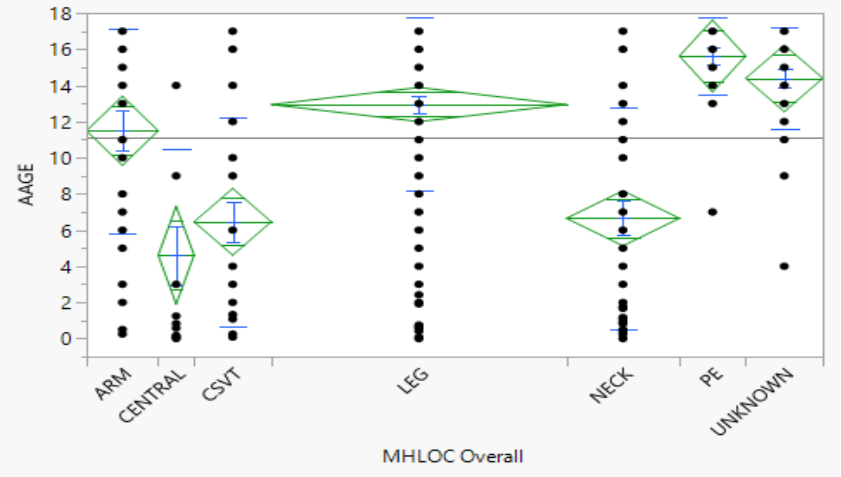



Figure 5: Spread of Index VTE Location by Age for Patients Treated in Trial 1160.106
Source: MEDICAL reviewer's analyses. VTE – Venous Thromboembolism, CSVT – Cerebrosinus Venous Thrombosis

Using the medical history (MH) SDTM for the on-treatment dataset (N=267), we obtained data relating to the presence of relevant VTE risk factors in the patient population, which are summarized in Table 11. The specific list of MH-related risk factor categorization (i.e. single ventricle physiology [SVP] CHD, non-single

ventricle physiology [non-SVP] cyanotic CHD, other CHD, arrythmia, malignancy, thrombophilia, vascular VTE risk factors, stroke, serious infection, protein-losing pathology, immobility and autoimmune disease) used are present in Appendix 13.3. We noted the following risk factors were over-represented in the Pradaxa arm: exposure to contraception prior to VTE, history of malignancy and history of iron-deficiency anemia. In contrast, the following risk factors were noted to be over-represented in the SoC arm: previous history of VTE, history of CHF, history of CHD and specifically SVP-CHD.

Table 11: Baseline Characteristics relating to CM use and MH of patients in Trial 1160.106

| Baseline Characteristics | Dabigatran (n=177) | SOC (n=90) | Total (n=267) |
|---|---|---|---|
| Concomitant Medication Use | | | |
| Exposure to contraception prior to VTE – n (%) | 21 (12) | 5 (6) | 26 (10) |
| Bleeding-related concomitant medication – n (%) | 42 (24) | 18 (20) | 60 (23) |
| Transfusion during treatment period – n (%) | 9 (5) | 1 (1) | 10 (4) |
| VTE-specific Risk Factors | | | |
| Previous history of VTE – n (%) | 14 (8) | 14 (16) | 28 (10) |
| History of CVC prior to index VTE – n (%) | 41 (23) | 24 (27) | 65 (24) |
| Presence of Vascular Risk Factors – n (%) | 15 (9) | 9 (10) | 24 (9) |
| Presence of Thrombophilia[1] – n (%) of eligible patients | 36 (27) | 20 (27) | 56 (27) |
| History of Stroke – n (%) | 4 (2) | 4 (4) | 8 (3) |
| History of PTS at baseline – n (%) | 2 (1) | 3 (3) | 5 (1.5) |
| Cardiac-related VTE Risk Factors | | | |
| History of CHF – n (%) | 9 (5) | 21 (23) | 30 (11) |
| History of Arrythmia – n (%) | 6 (3) | 2 (2) | 8 (3) |
| History of CHD – n (%) | 22 (12) | 26 (29) | 48 (18) |
| SVP CHD – n (%) | 5 (3) | 8 (9) | 13 (5) |
| Non-SVP Cyanotic Lesions – n (%) | 10 (6) | 5 (6) | 15 (6) |
| Non-obstructive Lesions – n (%) | 7 (4) | 13 (14) | 20 (8) |
| History of Hypertension – n (%) | 2 (1) | 1 (1) | 3 (1) |
| Common VTE Risk Factors | | | |
| History of serious infections – n (%) | 30 (17) | 14 (16) | 44 (17) |
| History of Malignancy – n (%) | 19 (11) | 3 (3) | 22 (8) |
| History of Immobility – n (%) | 26 (15) | 13 (14) | 39 (15) |
| History of Orthopedic Trauma – n (%) | 16 (9) | 11 (12) | 27 (10) |
| History of Iron-deficiency Anemia – n (%) | 15 (9) | 1 (1) | 16 (6) |
| Uncommon VTE Risk Factors | | | |
| History of Diabetes – n (%) | 5 (3) | 1 (1) | 8 (3) |
| History of Obesity – n (%) | 4 (2) | 2 (2) | 6 (2) |
| History of Dyslipidemia – n (%) | 1 (0.5) | 2 (2) | 3 (1) |
| History of Sickle Cell Anemia – n (%) | 2 (1) | 1 (1) | 3 (2) |
| History of Autoimmune Disease – n (%) | 1 (0.5) | 2 (2) | 3 (1) |
| History of Protein Losing State – n (%) | 2 (1) | 0 (0) | 2 (1) |
| History of Burns – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |
| History of Pancreatitis – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |

Source: MEDICAL reviewer's analyses. [1] Eligible patients are those who were tested for thrombophilia, thus proportions of eligible patients used is n=207 (i.e. 78% of the study population) for total patients, with 133 patients for the Pradaxa arm and 74 patients for the SoC arm.

*Medical reviewer comment:*

*There were several detected baseline imbalances noted between the two trial arms, as summarized in the section above:*

- *In relation to VTE location, the higher prevalence of more serious VTE subtypes (i.e. PE, CSVT and central thrombosis) in the Pradaxa arm did not negatively affect the results, as the trial drug proved to be non-inferior, despite this apparent disadvantage.*
- *The dichotomy of age in terms of VTE location is most likely explained by the epidemiology of VTE and associated VTE risk factor in pediatric patients. For example, CSVT is most associated with mastoiditis from ear infection, which most commonly occur in younger patients. It is important to note that even though this dichotomy results in younger patients having more serious VTE subtypes, there was no difference in efficacy endpoint between younger and older patients.*
- *To ensure that the observed over-representation of certain VTE risk factors among the two trial arms, sensitivity analyses were conducted to examine at the efficacy endpoint in the two trial arms among the following specific sub-populations with persistent VTE risk factors: patients with history of malignancy, patients with previous history of VTE, patients with CHF and patients with CHD (Table 12). In relation to efficacy endpoints, there was a trend favoring Pradaxa in all evaluated sub-populations, with variable magnitude of differential efficacy. In relation to safety endpoints, there was also a trend towards patients on Pradaxa having more bleeding AEs that are mostly mild in severity, with the exception of patients with history of VTE, who experienced slightly more bleeding events in the SoC arm. However, given the post-hoc nature of the analysis and the resultant small sample size of the sub-populations, these conclusions should be made with caution and may be re-evaluated in future studies.*

Table 12: Sensitivity Analysis of Imbalanced VTE Risk Factor-Specific Sub-Populations in Trial 1160.106

| Baseline Characteristics | Hx of VTE (n=28) | | Hx of CHF (n=30) | | Hx of CHD (n=48) | | Hx of Cancer (n=22) | |
|---|---|---|---|---|---|---|---|---|
| | Pradaxa (n=14) | SoC (n=14) | Pradaxa (n=9) | SoC (n=21) | Pradaxa (n=22) | SoC (n=26) | Pradaxa (n=19) | SoC (n=3) |
| Efficacy Composite – n (%) | 4 (29) | 2 (14) | 7 (78) | 15 (71) | 16 (73) | 16 (62) | 8 (42) | 0 (0) |
| Complete Resolution – n (%) | 4 (29) | 2 (14) | 7 (78) | 15 (71) | 16 (73) | 16 (62) | 8 (42) | 0 (0) |
| VTE Recurrence – n (%) | 1 (7) | 2 (14) | 0 (0) | 1 (5) | 0 (0) | 2 (8) | 2 (11) | 0 (0) |
| VTE-related Death – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Major Bleed – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (11) | 0 (0) |
| CRNM Bleed – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Minor Bleed – n (%) | 3 (21) | 5 (36) | 1 (11) | 0 (0) | 4 (18) | 1 (4) | 5 (26) | 0 (0) |
| Any Bleed – n (%) | 3 (21) | 5 (36) | 1 (11) | 0 (0) | 4 (18) | 1 (4) | 6 (32) | 0 (0) |

Source: MEDICAL reviewer's analyses.

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:

In the Pradaxa arm, 171 patients (97.2%) had an average compliance within the range of 80 to 120%. Four patients (2.3%) had a compliance <80%, and 1 patient had a missing eCRF entry (because treatment was discontinued early). None of the patients had a documented compliance >120%.

In the SoC arm, 89 patients (98.9%) had an average compliance within the range of 80 to 120%. One

patient had a missing eCRF entry (because treatment was discontinued early). As a result, none of the patients had a documented compliance <80% or >120%.

Concomitant medications:
Concomitant medications included all medications taken prior to informed consent and continued during the trial as well as all medications started after informed consent. Overall, 213 patients (79.8%) took concomitant medications with similar frequencies in both treatment groups (DE: 79.1%; SoC: 81.1%). The main concomitant medications were paracetamol (24.3%), spironolactone (11.2%), and ibuprofen (7.5%).

Rescue medication use:
Rescue medication use was defined depending on the medication-associated negative outcome it will be treating:

- *For major bleeding events*: There were no patients needing anticoagulation reversal in the SoC arm in trial 1160.106. All trial sites were offered to participate in the on-going trial evaluating the use of idarucizumab, as a reversal agent for Pradaxa, in pediatric patients. There were no patients needing anticoagulation reversal and/or receiving idarucizumab in the Pradaxa arm in trial 1160.106.
- *For VTE recurrence*: Seven patients in the SoC arm experienced VTE recurrence in trial 1160.106. Because the protocol did not specify collection of data relating to the specific anticoagulant that was used to rescue these treatment failures, no data is available on rescue medication use in this group. The SoC therapies that were used for patients that experienced a VTE recurrence were VKA (4/7) and LMWH (3/7). Seven patients in the Pradaxa arm experienced VTE recurrence in trial 1160.106. All patients were switched to SoC therapies to treat their VTE recurrence, but specific rescue medication use data is not available.

*Medical reviewer comment: Analysis of exposure data demonstrates that overall compliance was. Concomitant medication observed are typical for a pediatric population. The proportion of patients using medication with associated bleeding risk was equivalent between the two treatment arms of trial 1160.106, thus unlikely to contribute unequally to the bleeding event rate among arms. There was no potentially confounding role for the use of rescue medication on the results of the trial.*

## Efficacy Results – Primary Endpoint

*Trial 1160.106:*
Primary Analysis:
The primary efficacy endpoint for trial 1160.106 was defined as proportion of patients that met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The non-inferiority hypothesis for the primary endpoint was planned with non-inferiority margin of 20%. Given significance of non-inferiority, a test of superiority was planned with a one-sided significance level of 0.025.

Of the 267 randomized patients, 81 patients (45.8%) in the Pradaxa group and 38 patients (42.2%) in the SoC group met the criteria for the composite primary endpoint. The corresponding rate difference and 95% CI was -0.038 (-0.161,0.086), thus demonstrated non-inferiority margin of 20% (see Table 13).

Superiority of DE vs SoC could not be established.

Table 13: Composite primary endpoint results for Trial 1160.106

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

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

Source: 1160-0106--1-15--study-report-body.pdf page 104.

Sub-group Analyses:

Consistent results were observed across different sub-groups. No numeric differences in the treatment effect for the sub-groups by age, sex, region, and presence of certain risk factors (e.g. CVC, CHD, malignant disease) were observed. However, small sample size for these sub-group analyses resulted in very wide confidence intervals (see Figure 6).

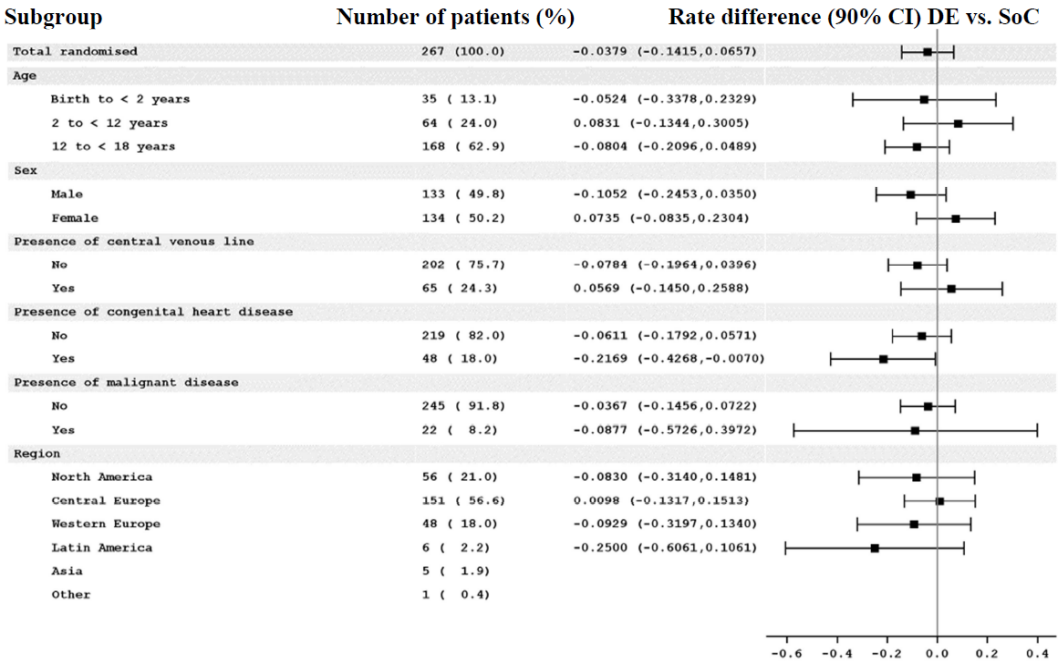



Figure 6: Subgroup Analysis Results for Trial 1160.106

Source: 1160-0106--1-15--study-report-body.pdf page 106.

Sensitivity Analysis:

The results of the sensitivity analyses were consistent with the result of the primary endpoint. Independent of the data source (adjudication-confirmed vs. investigator-reported), analysis period (on-treatment vs. intention-to-treat vs. full follow-up), and missing data imputation (LOCF vs. worst case), the upper bounds of the 90% CIs were consistently lower than the predefined non-inferiority margin of 20% (see Figure 7).

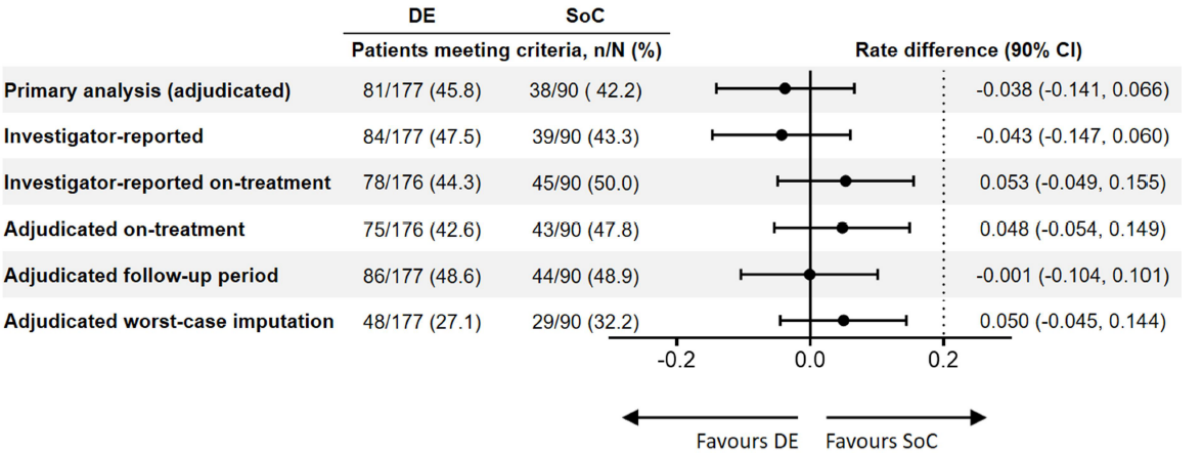



Figure 7: Sensitivity Analysis Results for Trial 1160.108
Source: 1160-0106--1-15--study-report-body.pdf page 105.

*Medical reviewer comment: Results from trial 1160.106 demonstrated non-inferiority of Pradaxa, compared to SoC therapy, in the acute treatment of VTE in pediatric patients, with no observed confounding impact during sub-group and sensitivity analysis.*

## Data Quality and Integrity

Materials reviewed include the protocol, statistical analysis plan, and study report for this study. Data of this submission, provided with SDTM and ADaM formats, are acceptable. The Applicant also provided clear definition file for datasets and, reviewer guide and detailed analysis SAS programs for assisting review.

*Statistical reviewer comment: Appropriate material were provided to replicate the Applicant trial results for both trial 1160.106.*

## Efficacy Results – Secondary and other relevant endpoints

<u>All bleeding events:</u>

Adjudication-confirmed major bleed was reported for 4 patients (2.3%) in the Pradaxa arm and 2 patients (2.2%) in the SoC arm, with the difference not being statistically significant. In total 38 patients (21.6%) in the Pradaxa arm and 22 patients (24.4%) in the SoC arm had an adjudication-confirmed bleeding event, most of them were categorized as minor bleeding. The rate difference for the probability of freedom from any bleeding event and the hazard ratio of events showed that there was no difference in risk of any bleeding events between the 2 treatment arms (see Table 14). Additional details concerning bleeding events are present in section 8.4.5.

Table 14: Summary of All Adjudicated Bleeding Events in Trial 1160.106

| | DE | | SoC | |
|---|---|---|---|---|
| Number of patients treated, N (%) | 176 | (100.0) | 90 | (100.0) |
| Major bleeding | 4 | (2.3) | 2 | (2.2) |
| Fatal bleeding | 0 | | 1 | (1.1) |
| CRNM bleeding | 2 | (1.1) | 1 | (1.1) |
| Minor bleeding | 33 | (18.8) | 21 | (23.3) |
| Major and CRNM bleeding | 6 | (3.4) | 3 | (3.3) |
| Any bleeding | 38 | (21.6) | 22 | (24.4) |
| Kaplan-Meier estimate for the probability of freedom from any bleeding at Day 84 (90% CI)[1] | 0.776 (0.718, 0.824) | | 0.748 (0.662, 0.816) | |
| Kaplan-Meier estimate of the difference in rate (90% CI) | −0.028 (−0.120, 0.065) | | | |
| Hazard ratio SoC vs. DE, any bleeding (90% CI)[2] | 1.145 (0.736, 1.780) | | | |

Source: 1160-0106--1-15--study-report-body.pdf page 108.

All-cause mortality:
One patient (in the SoC group; stratum 12 to <18 years) died on-treatment of an adjudication confirmed major bleed. Additional details concerning all-cause mortality are present in section 8.4.5.

All individual components of the primary efficacy endpoints:
Individual components of the primary endpoint occurred in comparable frequencies across treatment groups, except for recurrent VTE, which was less frequent with Pradaxa (4.0%) than with SoC (7.8%) (see Table 15).

Table 15: Summary of Adjudicated Individual Components of The Primary Endpoint in Trial 1160.106

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

Source: 1160-0106--1-15--study-report-body.pdf page 111.

The proportion of patients with individual components of the primary endpoint occurred in comparable frequencies across age strata. For the youngest age stratum, 7 of the 13 patients with complete response in the Pradaxa arm and 1 of the 7 patients in the SoC arm were <6 months (see Table 16).

Table 16: Summary of Adjudicated Individual Components of The Primary Endpoint by Age Strata in Trial 1160.106

| | DE | | | SoC | | |
|---|---|---|---|---|---|---|
| Age stratum | Birth to <2 years | 2 to <12 years | 12 to <18 years | Birth to <2 years | 2 to <12 years | 12 to <18 years |
| Number of patients randomised, N (%) | 22 (100.0) | 43 (100.0) | 112 (100.0) | 13 (100.0) | 21 (100.0) | 56 (100.0) |
| Complete thrombus resolution by Day 84 | 13 (59.1) | 21 (48.8) | 47 (42.0) | 7 (53.8) | 12 (57.1) | 19 (33.9) |
| Recurrent VTE by Day 84 | 0 | 1 (2.3) | 6 (5.4) | 0 | 1 (4.8) | 6 (10.7) |
| VTE-related death by Day 84 | 0 | 0 | 0 | 0 | 0 | 1 (1.8) |

Source: 1160-0106--1-15--study-report-body.pdf page 111.

Freedom from thrombus progression at end of therapy:
A total of 35 patients (13.1%) had missing a VTE assessment at the end of the trial (23 patient in the Pradaxa arm vs. 12 patients in the SoC arm), which was equally distributed between the two trial arms (13.0% vs. 13.3%). Image-based VTE response categorization during the intention-to-treat period, per treatment arm, is as follows: 1) Complete response was 45.8% (81 patients) in Pradaxa arm vs. 42.2% (38 patients) in SoC arm, 2) Partial response was 32.2% (57 patients) in Pradaxa arm vs. 27.8% (25 patients) in SoC arm, 3) Stable disease was 6.2% (11 patients) in Pradaxa arm vs. 11.1% (10 patients) in SoC arm, and 4) Progressive disease was 2.8% (5 patients) in Pradaxa arm vs. 4.4% (4 patients) in SoC arm. There was no significant difference between the rate of VTE response categorization in relation to differing lag time from VTE diagnosis to start of trial treatment, within 3 examined lag periods of ≤ 7 days, 8 - ≤ 14 days and > 14 days. The proportion of patients confirmed to be free from thrombus progression at the end of the intention to treat period, using an appropriate imaging modality identical to the modality used at baseline VTE diagnosis, was 83.6% (148 patients) in the Pradaxa arm and 81.1% (73 patients) in the SoC arm.

*Medical reviewer comment: Analysis of the secondary endpoints for trial 1160.106 demonstrated no clinically or statistically significant difference in efficacy outcome between treatment arms when the individual components of the composite primary efficacy endpoint were examined and when rates of the different image-based VTE response categorizations were examined. In addition, from a safety perspective, the rate of bleeding events was comparable between treatment arm, with no Pradaxa-related deaths observed in the Pradaxa arm. There was no observed confounding impact during sub-group and sensitivity analysis. This further supports the non-inferiority status of Pradaxa, compared to SoC therapies, in the acute treatment of VTE in pediatric patients.*

*Evaluation of dose adjustment in trial 1160.106 showed a high rate of Pradaxa treatment discontinuation secondary to sub-target trough concentration. This is further discussed in detail in the patient disposition sub-section of section 6.2.1 and section 8.2.1.*

## Dose/Dose Response

The relationship of drug dose or drug concentration to response was not assessed for Trial 1160.106.

## Durability of Response

*Trial 1160.106*

The applicant submitted study 1160.106 to demonstrate the effect of Pradaxa for the treatment of venous thromboembolism in children from birth to less than 18 years of age. The primary endpoint was defined as proportion of patients who met the criteria for the composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE, and freedom from mortality-related VTE). The composite primary endpoint demonstrated non-inferiority (20% margin) of DE to SoC (95% CI was -0.038 (-0.161,0.086)).

*Medical and Statistical reviewer comment:*
*For trial 1160.106, the non-inferiority of Pradaxa to SoC was demonstrated. There were no major statistical issues identified from this review.*

### Persistence of Effect

*Trial 1160.106*

Based on the statistical evidence provided from the trial, it is concluded that the submitted data in this NDA demonstrated the non-inferiority treatment effect of Pradaxa compared to SoC for the treatment of VTE in children (b) (4) to less than 18 years of age.

### Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted for Trial 1160.106.

## 6.2. Trial 1160.108

### 6.2.1. Study Design

#### Title

Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years

#### Overview and Objective

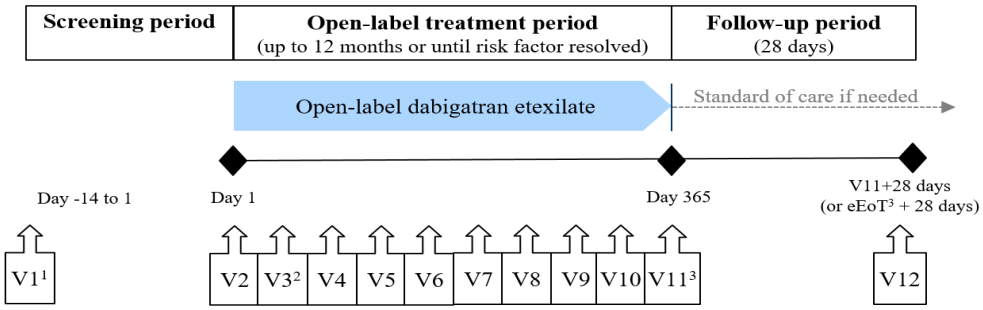
Trial 1160.108 was a multi-center, multinational, open-label, single arm prospective cohort Phase III trial of Pradaxa to evaluate safety in the secondary prevention of VTE in children from birth to <18 years. Recruitment was first initiated in stratum 1 (12 to <18 years of age) and was consecutively opened to stratum 2 (2 to <12 years of age) and stratum 3 (0 to <2 years of age).

The main objective of this pediatric prospective cohort trial is to assess the safety of Pradaxa for secondary prevention of VTE in children from 0 to less than 18 years of age.

#### Trial Design

Three trial periods were defined: a screening period, an open-label Pradaxa treatment period and a follow-up period. Trial design is provided in Figure 8. If all eligibility criteria were met, treatment with Pradaxa was initiated or continued (if patients had already been treated in trial 1160.106). Per trial design, patients received Pradaxa until the clinical risk factor requiring secondary VTE prevention had resolved,

or up to a maximum of 12 months. The clinical risk factor was to be specified at screening and evaluated at every visit. After 12 months of treatment, patients needed to discontinue Pradaxa and, if there was continued need for anticoagulant treatment, switch to SoC. Patients who stopped treatment with Pradaxa earlier than the 12 months were asked to perform an eEOT Visit. All patients treated with Pradaxa were followed up until 28 days after termination of Pradaxa. All adverse events (AEs), serious and nonserious, occurring from informed consent until the end of the follow-up period were reported by the investigator. Patient participation was concluded when the Follow-up Visit was completed. The end of the trial was defined as last visit completed by the last patient. The initial dose nomograms and the dose adjustment protocol used in trial 1160.106, including the important per-protocol medication intake guidelines, applies trial 1160.108.




1 Screening Visit and Visit 8 of trial 1160.106 may have been combined for patients who had completed the treatment period of the 1160.106 trial (tests were done only once). V1 and V2 could occur on the same day provided that results from the local laboratory were available to confirm eligibility.
2 Visit 3 was not applicable for patients from trial 1160.106 who continued taking the same dose of DE in this trial. For all other patients, trough dabigatran concentration was determined at Visit 3.
3 An eEOT Visit before Visit 11 was required for all patients who had taken a dose of DE but the trial medication was discontinued early for any reason (e.g. the clinical risk factor has resolved) before Visit 11.

Figure 8: Trial Design for Trial 1160.108
Source: 1160-0108--1-15--study-report-body.pdf page 34.

## Key eligibility criteria

*Key inclusion criteria* were:

- Male or female patients from birth to <18 years of age at the time of informed consent/assent.
- Previously documented objective diagnosis of VTE (e.g. DVT, PE, central line thrombosis, sinus vein thrombosis), followed by completed course of initial VTE treatment for at least 3 months (in case of VKA - intended INR between 2 and 3) or completed trial treatment (i.e. reached Visit 8) in the 1160.106 trial. Patients who during the treatment phase of 1160.106 trial were switched from DE to the SoC arm for any reason, were not eligible for this trial.
- Presence of an unresolved clinical risk factor requiring further anticoagulation for secondary VTE prevention (e.g. central venous line, underlying disease, thrombophilia, etc.)

*Key exclusion criteria were:*

- Conditions associated with an increased risk of bleeding.
- Anemia (hemoglobin < 8 g/dL) or thrombocytopenia (platelet count < $80x10^9$/L) at screening.
- Renal dysfunction (eGFR <50 mL/min/1.73m2 using the Schwartz formula) or requirement for dialysis.

- Hepatic disease, with active liver disease or Persistent ALT or AST or Alkaline Phosphatase >3x ULN within 3 months of screening.
- Active infective endocarditis.
- Patients with a heart valve prosthesis requiring anticoagulation.
- Pregnant or breast-feeding female patients.
- Patients 0 to <2 years with gestational age at birth <37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards).

## Study Endpoints

Primary Endpoint:

- Recurrence of VTE at 6 and 12 months
- Major and minor (including clinically relevant non-major [CRNM]) bleeding events at 6 and 12 months
- All-cause mortality and mortality related to thrombotic or thromboembolic events at 6 and 12 months

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

*Secondary Endpoints:*

- Occurrence of PTS (newly developed and worsening) at 6 and 12 months. An appropriate instrument (e.g. the Manco-Johnson Instrument or Villalta scale or a similar instrument; the chosen instrument will be available in the ISF)
- Pharmacodynamic assessments (central measurement of dTT, aPTT and ECT) at Visit 3 (after at least six consecutive Pradaxa doses) and after at least 3 days following any Pradaxa dose adjustment
- Number of Pradaxa dose adjustments during treatment period (i.e. Number of patients with Pradaxa dose adjustments during treatment period)

## Statistical Analysis Plan

*Sample Size Determination:*

A minimum of 100 patients were planned to be enrolled, including new patients who had completed treatment for acute VTE episodes and patients rolling over from trial 1160.106 who required secondary VTE prevention. Under the assumption of 5% of event rate for the composite of recurrent VTE, major bleeds and mortality related to thromboembolic event at 12 months, 100 patients provide more than 99% of probability observing at least 1 event, and higher than 63% of probability if the event rate is 1%.
Trial 1160.108 has a single treatment group with no control group. Overall assessment of safety was based on descriptive statistics. No null hypothesis was pre-specified for this trial.

*Futility Interim Analysis:*

Multiple PK/PD and safety interim analyses were conducted for the DMC to evaluate the PK, PD, and safety data of the respective age group. Data from patients rolled over from trial 1160.106 were considered. Since no statistical analysis was planned for this study, adjusting for type I error was not required.

*Missing Data:*
In general, missing data were not imputed. All patients were followed to collect necessary efficacy and safety information, even if patients discontinued trial medication prematurely. Missing or incomplete AE dates were imputed according to Applicant standards. Missing data and outliers of PK data and repeated safety laboratory measurements were handled according to Applicant standards.

*Primary Analysis:*
Frequency and percentage of patients with recurrence of VTE, major and minor (including CRNM) bleeding, and mortality overall and mortality related to thrombotic or thromboembolic events at 3, 6 and 12 months were summarized descriptively for each age group and the overall population. The survival/event-free probability of primary safety endpoints were provided by Kaplan-Meier estimation with its 95% confidence intervals (CIs) at 3, 6 and 12 months.

*Sensitivity Analysis:*
A sensitivity analysis for the primary and secondary safety endpoints considered the full follow-up period and all entered patients.

*Sub-group Analyses:*
In general, the summaries and analyses are provided by age stratum and the overall population. Patients were allocated to a certain age group according to their age at screening.

In addition to the 3 different age strata, analyses for the following sub-groups were performed for the primary endpoints and selected secondary endpoints:

- Source of enrolled patients (rollover patients treated with Pradaxa in 1160.106, rollover patients treated with SoC in 1160.106, not from 1160.106 [i.e. new patients])
- Sex (female, male)
- Region (Eastern Europe, Western Europe, North America, South/Central America, Asia)
- Type of most recent VTE (e.g. DVT, CVC-related thrombosis, PE, CSVT)

The stratification factor of age groups was provided for each subgroup. Differences in descriptive statistics and Kaplan-Meier estimators were summarized.

*Secondary Efficacy Analyses:*
Descriptive frequency and percentage of patients with PTS at 3, 6 and 12 months were presented. Patients who did not experience PTS, dropped out from the trial early, were lost to follow-up, or had died were considered as non-events and censored. The PTS event-free probability was estimated by Kaplan-Meier curve with its 95% CIs at the predefined time points. The analysis was performed with the on-treatment set during the on-treatment period. Sensitivity analyses were done with the entered set for the full follow-up period.

The number and frequency of Pradaxa dose adjustments during the on-treatment period were summarized descriptively. The number of dose adjustments is equivalent to the number of patients with Pradaxa dose adjustment since each patient was allowed to have only one Pradaxa dose adjustment during the trial.

## Protocol Amendments

*Trial 1160.108:*

There were eight global amendments to the original protocol, which was dated April 8th, 2014. The majority of amendments contained a large number of changes, with differing importance. It is important to note that throughout the protocol life-cycle, the Applicant provided updates in relation to dose justification, non-clinical study results and early phase trial results. The majority of global amendments also applied to the protocol for trial 1160.106. In general, we will only include the amendments of most importance in our review:

- Global amendment 1 (October 2nd, 2014) implemented suspension of recruitment of patients > 40 kg until suggested TID dosing is implemented.

- Global amendment 2 (January 28th, 2015):
  - Dosing regimen details added to the protocol, including implementation of BID dosing, rather than the previously suggested TID dosing.
  - The maximal single dose was defined as 330 mg/dose and 22.2 mg/kg/dose. This was modified because the risk of thrombosis in the first 30 days is high in pediatric patients while the risk of bleeding is lower than adults. As a result, this higher cap will allow for decrease in potential medication failures.
  - Only one up-titration will be acceptable, with an up-titration dose range of 15-100%, modified from the initial 85-100%, depending on age and weight of the patients. This was changed to avoid exceeding the maximum daily dosage, defined above. Dose adjustment nomogram were incorporated.
  - Patients who cannot reach the target trough plasma concentrations after one dose adjustment must discontinue dabigatran treatment and be treated at the investigator's discretion on SoC.
  - Age-specific assignments were given to the different formulations, as follows: patients aged ≥ 8 years received capsules, patients aged 6 months to < 8 years or patients ≥ 8 - < 12 years who cannot take capsules received oral pellets, and patients birth to < 6 months or patients 6-12 months who cannot take oral pellets received oral solution.
  - Removal of weight limitation of 40 kg implemented to inclusion criteria in amendment 1.
  - Clarification that any patients, who during the treatment phase of 1160.106 trial were switched from dabigatran etexilate to SoC arm for any reason, are not eligible for this study.
  - Addition of exclusion criteria to exclude patients with gestational age at birth < 37 weeks or with body weight lower than the 3rd percentile (according to the WHO Child growth standards).
  - Modified exclusion criteria to include Persistent alanine aminotransferase or aspartate transaminase or alkaline phosphatase > 3 × upper limit of normal within 3 months of screening.
  - To clarify that HPLC-MS/MS assay could be used to assess the need of dabigatran etexilate dose adjustment, as an alternative to dTT, if needed.
  - The target dabigatran steady state trough concentration was precisely defined to be ≥50 to <250 ng/mL.
  - Added the use of a reversal agent, in the context of a clinical investigation, as an exception to the restriction of investigational medication use.

- Global amendment 3 (November 27th, 2015):
  - Up-titration nomogram for capsules and oral pellets modified to comply with specific intake limits.
  - Dosing nomogram for oral solution temporarily removed to allow for modification to comply with specific intake limits.

- Global amendment 4 (March 16th, 2016):
  - To evaluate the acceptability of oral solution, flavored vs. unflavored solution will be assigned in a randomized fashion (1:1 ratio) to patients taking oral solution.
  - A temporary interruption of the anticoagulant therapy for the index VTE event will be acceptable, to allow inclusion of patients who had medically justifiable interruptions of the anticoagulant therapy during or after treatment of index VTE and prior to inclusion into this trial, if certain pre-requisites are fulfilled and documented.
  - The following clarification relating to the inclusion/exclusion criteria were added:
    - Insertion of a central venous line is not considered a major surgery provided hemostasis is achieved after the procedure.
    - It was clarified that patients with asymptomatic petechial or microbleeds are eligible for the study. Definition of microbleeds was provided in a footnote.
    - eGFR retesting during the screening period was allowed (once). Patients will have to discontinue dabigatran treatment anytime during the course of the study if eGFR drops < 50 mL/min/1.73m$^2$, decreased from < 80 mL/min/1.73m$^2$, using the Schwartz formula and this is confirmed by one retesting within the next 14 calendar days. The earlier cut-off led to unnecessary discontinuation of study drug in some initial patients.
    - P-glycoprotein inhibitors intake up until first dose of study medication will not be considered as exclusion criterion
  - Modification to initial dosing recommendation for newborn < 1 month and < 3 kg were done. Corrected dosing nomogram for oral solution restored into protocol.
  - If gastrointestinal symptoms develop it is recommended to take dabigatran etexilate with a meal and/or a PPI such as pantoprazole. In amendment 5, the recommendation for PPI was changed to include "according to the local standard of care in accordance with local labelling recommendations " . The recommendation was analogous to recommendations used in adults.
  - Treatment with dabigatran etexilate after the surgery can be re-started any time as soon as hemostasis has been achieved, which is analogous to recommendations for adults.

- Global amendment 5 (November 30th, 2016):
  - Clarification that Applicant may decide to keep recruitment open after 100 patients have been recruited, in case additional safety data needs to be generated.
  - Exclusion criteria changed to modify the eGFR level for exclusion for patients aged 12 to < 18 years to < 60 mL/min/1.73m$^2$, while keeping the eGFR level for patients < 12 years at < 80 mL/min/1.73m$^2$. This was supported by an interim analysis in adolescent patients, in relation to both PK/PD and safety data.
  - Exclusion criteria clarified that patients will be excluded if they have heart valve prosthesis requiring anticoagulation treatment.
  - Clarification that all cases of death will be considered as non-event for occurrence of PTS and

therefore censored.

- Global amendment 6 (January 19th, 2018):
  - Addition of the exclusion of patients with meningitis, encephalitis or intracranial abscess, based on the recommendation of the DMC secondary to the occurrence of an intracranial bleed in an infant on Pradaxa in the context of meningitis and CSVT.

- Global amendment 7 (September 10th, 2018):
  - The option to administer oral pellets was expanded to patients < 6 months of age. A preference for the usage of oral solution over oral pellets in patients < 12 months of age was implemented.
  - Clarification that the steady state of the currently assigned dabigatran etexilate formulation (i.e. at least 6 consecutive dabigatran etexilate doses have been taken) has to be achieved before a formulation switch could be considered.
  - Clarification that dabigatran etexilate up- or down-titration is not possible in some instances (limit of 22.2 mg/kg/day based on excipient acceptable daily intake, maximal single dose of 330 mg, unavailability of dosages) and affected patients have to be discontinued from study medication prematurely.
  - Banana mush, strawberry jam and apple juice were added to the list of foods that are allowed to be mixed with dabigatran etexilate oral pellets.
  - If a dabigatran etexilate dose has only been taken partially, there should be no attempt to administer a second dose at that timepoint, and the next dose should be taken as scheduled approximately 12 hours later.
  - The option to re-start dabigatran etexilate after a major bleeding event has occurred was deleted, as this criterion is a subject-stopping criterion.
  - Subjects or, if applicable, parents or legal guardians, will be asked to carefully complete a daily medication intake log for dabigatran and are requested to bring this completed log to every clinic visit. Compliance calculation should preferably be based on the returned medication, however completed logs may also be used.
  - Several statements were added to the secondary endpoints to clarify their exact meaning.
  - Clarification that copies of de-identified source documents necessary for adjudication will be provided to the adjudication committee.

- Global amendment 8 (February 7th, 2019):
  - Exclusion criteria changed to modify the eGFR level to < 50 mL/min/1.73m$^2$ for all patients, irrespective of age. This was supported by an interim analysis that show a favorable benefit/risk relationship and no excess levels ≥ 250 ng/ml in patients < 12 years. However, the protocol eGFR criterion for stopping dabigatran treatment (i.e. if eGFR drops below 50 mL/min/1.73m$^2$) remained unchanged.

For both trial 1160.106 and 1160.108, there were several local amendments to the protocol that were specific to Russia. These amendments ensured that sequential enrollment in age-specific groups will be determined by Russian regulatory authority after review of the data and reports from the Applicant. As a result, the inclusion criteria and protocol were modified sequentially in future amendments, as data/reports from older age groups became available and were reviewed by the Russian regulatory

authority.

There were two local amendments only to the protocol for trial 1160.108 that were specific to France:

- Exclusion of patients in stratum 3 that have a hemoglobin level < 10 g/dL.
- Do not allow the concomitant treatment of acetylsalicylic acid (ASA), ibuprofen or agents containing ASA or ibuprofen for patients on Pradaxa.

### 6.2.2. Study Results

#### Compliance with Good Clinical Practices

The applicant stated that the clinical trial protocol, informed consent form (ICF), and printed patient information materials were reviewed and approved by the independent ethics committee (IEC) and/or institutional review boards (IRB) for each site before any study procedures were performed. Any subsequent informed consent revisions were approved by the IRB or IEC before any changes were initiated.

According to the applicant, the study was conducted according to International Conferences on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines concerning Good Clinical Practice (GCP), the European Union Clinical Trials Directive (2001/20/EC), Title 21 of the US Code of Federal Regulations (21 CFR) and the practices and regulations of each participating nation. Written informed consent to participate in the study was obtained from each patient (or patient's guardian) before any study-specific procedures were performed.

#### Financial Disclosure

Trial 1160.108 were covered trials included in the submission for sNDA 022512 – s041. In accordance with 21 CFR 54, the Applicant submitted financial disclosure certification documents for these trials. In addition, the Applicant stated that there were no Investigators/Sub-investigators participating in either trials that were a part-time or full-time employee of Boehringer Ingelheim

For trial 1160.108, 347 Investigators/Sub-investigators reported no financial arrangements or interests to disclose but 47 Investigators/Sub-investigators were lacking financial disclosure information. Of those lacking a completed FDQ, 33 individuals were working in a site that did not initiate and 13 individuals did not participate as Investigators/Sub-investigators. The one remaining individual had an incomplete FDQ for trial 1160.108 but had a fully completed FDQ for trial 1160.106, with no disclosures.

For trial 1160.108, only one Sub-investigator from (b) (6) (site code (b) (6)), (b) (6), reported a significant payment made by the Applicant to support activities that had a monetary value of more than $25,000, exclusive of the costs of conducting the clinical trial, during the time (b) (6) was involved in carrying out the trial. The total amount of the payment was equivalent to ~ $95,920 and it was paid to the cardiovascular diseases and cardiology department to support the department and the research project (b) (6) The Applicant concluded that since the payment was not given to the Sub-investigator directly and was directed to the department for resources support, no further intervention is needed to minimize the potential for bias.

The following measures were also in place to minimize bias: use of multiple clinical sites, clinical site monitoring and audits, independent/centralized review of efficacy and response data, and limitation of enrollment to no more than 20% of the total trial enrollment at each site where an Investigator/ Sub-investigator had disclosable financial interests.

Form 3454 was certified by Thomas Seck 07/22/2020.

*Medical reviewer comment: During the filling review of the application, an information request was sent to the Applicant to submit a list of investigators who were part-time or full-time employees, and to discuss the due diligence taken to attempt to obtain the FDQ for Investigators/Sub-investigators for which FDQ was not submitted. The Applicant's response was complete and resolved the majority of the missing information. Given the current completeness of the provided financial disclosure information and our agreement that the single disclosure per trial will not have significant impact on the integrity of the trials or the validity of the results, we do not have any concerns.*

## Patient Disposition

In trial 1160.108, 231 patients were enrolled but 17 patients withdrew, resulting in 214 patients entered into the trial, with one patient withdrawing later prior to taking the first medication dose, due to inability to swallow capsules. Table 17 summarizes the initial disposition data for the two trials.

Table 17: Disposition Data for Enrolled Patients on Trial 1160.108

| | Trial 1160.108 |
|---|---|
| Number of patients screened / obtained informed consent | 231 |
| Number of patients who were screen failure[1] | 11 |
| Number of patients withdrawn not due to AE prior to entering trial | 2 |
| Number of patients consented but unable to be enter trial | 4 |
| Number of patients successfully screened & entered trial | 214 |
| Number of patients assigned to Pradaxa | 213 |
| Number of patients assigned to SoC | N/A |
| Number of patients entered trial but not treated | 1[2] |

Source: MEDICAL reviewer's analyses. [1] Most common reason for failure to meet inclusion/exclusion criteria leading to screen failure were eGFR < 80 mL/min/1.73m$^2$, aspartate aminotransferase (AST) / alanine aminotransferase (ALT) above upper limit of normal (ULN) and risk of bleeding due to a recent surgery, [2] One patient could not swallow capsules and withdrew from trial after being entered as a trial patient.

The breakdown, by age group, of patients recruited to trial 1160.108 from trial 1160.106 vs. those who were newly recruited is summarized in Table 18. Of the 213 patients who received trial medication, 200 patients (93.9%) completed the planned observation period (i.e. attended follow-up visit – visit 12), regardless of timing of discontinuation of trial medication, with 13 patients (6.1%) prematurely discontinuing the trial, most commonly due to withdrawal of consent without reason provided (in 3 patients) and non-compliance (in 2 patients), with no patients being lost to follow-up.

Of those who completed the planned observation period, 132 patients (62%) completed trial medication without premature discontinuation, where 96 patients (45.1%) completed the 12-months trial period and 36 patients (16.9%) discontinued due to resolution of VTE risk factors. In contrast, 81 patients (38%) prematurely discontinued Pradaxa due to: 1) Failure to reach target trough concentrations after one titration per protocol in 26 patients (12.2%), 2) Recurrence of VTE in 5 patients (2.3%), 3) Secondary to

other AE in 5 patients (2.3%), 4) Non-compliance in 4 patients, 5) Worsening of pre-existing disease in 2 patients (0.9%), and 6) Secondary to pregnancy in 1 patient (0.4%). It is important to note that the majority of the remaining patients were categorized as having a premature discontinuation due to the completion of the global trial. As a result, the more accurate rate of premature discontinuation is ~30%.

Table 18: Source of patients recruited for trial 1160.108

| | Stratum 3 (0 - <2) – n (%) | Stratum 2 (2 - <12) – n (%) | Stratum 1 (12 - < 18) – n (%) | Total – n (%) |
|---|---|---|---|---|
| Treated in trial 1160.108 | 9 (4) | 43 (20) | 161 (76) | 213 (100) |
| Newly recruited | 8 (3.5) | 27 (12) | 87 (41) | 122 (57) |
| Recruited from trial 1160.108 | 1 (0.5) | 16 (8) | 74 (35) | 91 (43) |
| Pradaxa arm | 1 (0.5) | 12 (6) | 48 (23) | 61 (29) |
| SoC arm | 0 | 4 (2) | 26 (12) | 30 (14) |

Source: MEDICAL reviewer's analyses.

*Medical reviewer comment:*
*For trial 1160.108, there was a significant rate of premature discontinuation of ~30%, with the most common reason for the premature stoppage of Pradaxa being failure to reach target trough concentrations after one titration, similar to what was observed in trial 1160.106. Otherwise, the rate of AEs and VTE recurrence is comparable to historical controls with SoC anticoagulation therapy. Sensitivity analyses assessing the primary endpoints, if patients who discontinued Pradaxa due to inability to attain trough concentration were removed, showed no difference in trial results.*

## Protocol Violations/Deviations

A total of 47 patients (22%) had at least 1 important protocol deviation, with the following reasons and frequencies:

- Deviation related to inclusion/exclusion criteria occurred in 13 patients (6.1%). The specific criteria of concern are:
  - Not meeting inclusion criteria due to age > 17 years (n=1) and not receiving initial VTE treatment for at least 3 months (n=4): 5 patients (2.3%)
  - Baseline abnormal laboratory results indicating organ dysfunction (i.e. hepatic disease, renal dysfunction, anemia or thrombocytopenia): 8 patients (3.7%)
  - Other exclusion criteria: 1 patient (0.5%) who had a condition associated with an increased risk of bleeding and 1 patient who had active meningitis, encephalitis or intracranial abscess.
- Deviation related to the use of prohibited concomitant medication: 9 patients (4.2%)
- Deviation related to non-compliance: 23 patients (10.7%), with 18 patients in stratum 1 (11.1% of stratum), 3 patients in stratum 2 (7% of stratum) and 2 patients in stratum 3 (22.2% of stratum).
- Deviation related to medication error (e.g. wrong dose) occurred in 2 patients (0.9%), all of which were in stratum 1.

There were six patients who had per-protocol indications for stopping Pradaxa, but study drug was not stopped: three patients did not achieve trough target after 1 dose adjustment, one patient had evidence of recurrent VTE, and 2 patients had drug-related significant or serious AE.

*Medical reviewer comment:*
*For trial 1160.108, with the exception of deviations related to non-compliance, the number of patients for*

*each of the remaining deviations is small and we do not anticipate any impact on the final results of the trial. Deviations due to non-compliance were significant. For trial 1160.108, the rate of non-compliance is significant but is lower than rates of non-compliance of long-term anticoagulants in the literature (~25-30%)[81]. In addition, this finding did not seem to impact the rate of recurrent VTE and PTS occurrence, both of which are comparable to historical rates in the literature. As a result, we conclude that these findings are reasonable and do not anticipate any impact on the final results of the trial.*

## Table of Demographic Characteristics

Table 19 summarizes the demographics in the treatment dataset (N=213) of patients who received at least one dose of the trial drug. The mean age was 12.8 years old; 55% were male, and 91% were white. Patients were recruited from 62 sites in 22 countries, with 9 sites located in the US that contributed 13% (28 patients) of patients in the treatment dataset.

Table 19: Demographic Characteristics of Trial 1160.108

| Demographic Parameters | Pradaxa (N = 213) |
|---|---|
| Sex, n (%) | |
| Male | 117 (55) |
| Female | 96 (45) |
| Age, years | |
| Mean (SD) | 12.8 (4.6) |
| Median (Min-Max) | 14 (0-18) |
| Age Group, n (%) | |
| Stratum 3 (Birth to < 2 years) | 9 (4) |
| Stratum 2 (2 to < 12 years) | 43 (20) |
| Stratum 1 (12 to < 18 years) | 161 (76) |
| Race, n (%) | |
| White | 194 (91) |
| Black or African American | 8 (4) |
| Asian | 7 (3) |
| Other | 3 (1.5) |
| Missing | 1 (0.5) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 11 (5) |
| Not Hispanic or Latino | 201 (94.5) |
| Missing | 1 (0.5) |
| Region, n (%) | |
| North America[1] | 44 (21) |
| Western Europe[2] | 56 (26) |
| Eastern Europe[3] | 100 (47) |
| South/Central America[4] | 7 (3) |
| Asia[5] | 6 (3) |

Source: MEDICAL reviewer's analyses. [1] North America includes USA and Canada, [2] Western Europe includes Austria, Belgium, Switzerland, Germany, Denmark, France, Italy, Norway, Hungary and Sweden, [3] Eastern Europe includes Czech Republic, Russia, Ukraine, Lithuania and Turkey, [4] South/Central America includes Brazil and Mexico, [5] Asia includes Taiwan, Israel and Thailand.

## Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Overall, 171 patients (80%) had at least 1 identified persistent VTE risk factor. Table 20 summarizes key index VTE characteristics (i.e. location of index VTE, if index VTE was related to a CVC, if index VTE was without any risk factor despite an extensive workup – thus truly idiopathic, and the duration from diagnosis of index VTE to start of trial medication). In addition, the prevalence of the most clinically important, persistent VTE risk factor resulting in the need for secondary VTE prophylaxis are summarized.

Table 20: Index VTE Characteristics and Persistent Risk Factors in Patients Treated on Trial 1160.108

| | Stratum 3 N = 9 | Stratum 2 N = 43 | Stratum 1 N = 161 | Total N = 213 |
|---|---|---|---|---|
| Index VTE Characteristics | | | | |
| DVT – n (%) | 6 (67) | 25 (58) | 133 (83) | 164 (77) |
| PE – n (%) | 0 (0) | 1 (2) | 19 (12) | 20 (9) |
| CSVT – n (%) | 1 (11) | 14 (33) | 9 (6) | 24 (11) |
| CVC-related VTE – n (%) | 2 (22) | 3 (7) | 2 (1) | 7 (3) |
| Idiopathic VTE (i.e. unprovoked without risk factor identified after workup) – n (%) | 1 (11) | 8 (19) | 21 (13) | 30 (14) |
| Duration from Diagnosis of Index VTE to Start of Trial Medication | | | | |
| Mean (SD) – days | 158 (58) | 256 (406) | 262 (451) | 256 (432) |
| Median (range) – days | 148 (99-290) | 115 (24-2273) | 109 (40-3798) | 110 (24-2798) |
| VTE Risk Factors | | | | |
| Previous history of VTE – n (%) | 2 (22) | 6 (14) | 31 (19) | 39 (18) |
| Persistent need for CVC – n (%) | 4 (44) | 5 (12) | 6 (4) | 15 (7) |
| History of PTS at baseline – n (%) | 1 (11) | 5 (12) | 30 (19) | 36 (17) |
| Presence of Vascular Risk Factors – n (%) | 0 (0) | 6 (14) | 23 (14) | 29 (14) |
| History of Thrombophilia – n (%) | 1 (11) | 12 (28) | 84 (52) | 97 (46) |
| History of APS – n (%) | 1 (11) | 1 (2) | 19 (12) | 21 (10) |
| History of CHF – n (%) | 3 (33) | 1 (2) | 1 (0.5) | 5 (2) |
| History of CHD – n (%) | 4 (44) | 5 (12) | 8 (5) | 17 (8) |
| History of Malignancy – n (%) | 1 (11) | 9 (21) | 6 (4) | 16 (8) |
| History of Immobility – n (%) | 0 (0) | 0 (0) | 8 (5) | 8 (4) |

Source: MEDICAL reviewer's analyses.

*Medical reviewer comment:*
*For trial 1160.108, the prevalence of index VTE subtypes and VTE risk factors is comparable to those documented in the literature and are consistent with known clinical features of pediatric patients needing anticoagulation for secondary prevention of VTE.*

## Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
Overall, 209 patients (98.1%) had an average compliance within the range of 80 to 120%. Three patients (1.4%) had an average compliance <80%. Reasons for non-compliance were: difficulty swallowing the Pradaxa pellets, occurrence of AEs (i.e. headache and dyspepsia), and forgetting medication intake despite

being re-informed about its importance. None of the patients had a documented compliance >120%.

Concomitant medications:
Overall, 167 patients (78.4%) took concomitant medications. The main concomitant medications, taken by more than 15% of patients based on the ATC3 code, were other analgesics and antipyretics (74 patients, 34.7%), decongestants and other nasal preparations for topical use (42 patients, 19.7%), topical products for joint and muscular pain (38 patients, 17.8%), stomatological preparations (35 patients, 16.4%), throat preparations (35 patients, 16.4%), and anti-inflammatory and antirheumatic products - non-steroids (35 patients, 16.4%).

Rescue medication use:
Rescue medication use was defined depending on the medication-associated negative outcome it will be treating:

- *For major bleeding events*: One patient experienced a major bleeding event leading to the use idarucizumab for acute emergent reversal of the anticoagulant effects of Pradaxa. The patient was a 17-year old female with MH of right leg venous malformation, who developed a major spontaneous external bleed from a malformation-related varicose vein, which was successfully controlled by active reversal with on-trial idarucizumab and surgical local control, with complete resolution after 4 days.
- *For VTE recurrence*: Eleven patients on Pradaxa arm experienced VTE recurrence in trial 1160.108. All patients were switched to SoC therapies to treat their VTE recurrence, but specific rescue medication use data is not available.

*Medical reviewer comment: Analysis of exposure data demonstrates that overall compliance was high. Concomitant medication observed are typical for a pediatric population. There was no potentially confounding role for the use of rescue medication on the results of the trial.*

## Efficacy Results – Primary Endpoint

Primary Analysis:
In relation to recurrence of VTE, three patients (1.4% of the treated patients) had a recurrent VTE within the first 12 months after treatment start. All 3 patients were in the oldest age group. The overall probability of being free from recurrence of VTE during the on-treatment period was 0.990 (95% CI 0.960, 0.997) at 3 months, 0.984 (95% CI 0.950, 0.995) at 6 months, and 0.984 (95% CI 0.950, 0.995) at 12 months.

Given that bleeding events, all-cause mortality, and VTE-related mortality at 6 and 12 months were primary safety endpoints, they are discussed in detail in section 8.4.5.

Sub-group Analysis:
In relation to recurrence of VTE, the small number of patients with VTE events resulted in non-informative sub-group analyses. Significant sub-group analysis results relating to bleeding events, all-cause mortality, and VTE-related mortality at 6 and 12 months were discussed in detail in section 8.4.5 because they were primary safety endpoints.

Sensitivity Analysis:

Sensitivity analysis based on full follow-up period for recurrent VTE was reported for 11 patients (5.1%) within the first 12 months (9 patients in the oldest age group and 2 patients in the age group 2 to <12 years). The overall probability of being free from recurrence of VTE was 0.990 (95% CI 0.963, 0.998) at 3 months, 0.971 (95% CI 0.936, 0.987) at 6 months, and 0.938 (95% CI 0.890, 0.966) at 12 months. Significant sensitivity analysis results relating to bleeding events, all-cause mortality, and VTE-related mortality at 6 and 12 months were discussed in detail in section 8.4.5 because they were primary safety endpoints.

*Medical reviewer comment: Results from trial 1160.108 demonstrated comparable rates of VTE recurrence, compared to those observed in the literature with SoC therapies, supporting the use of Pradaxa for secondary prevention of VTE in pediatric patients, with no observed confounding impact during sub-group and sensitivity analysis.*

## Data Quality and Integrity

Materials reviewed include the protocol, statistical analysis plan, and study report for this study. Data of this submission, provided with SDTM and ADaM formats, are acceptable. The Applicant also provided clear definition file for datasets and, reviewer guide and detailed analysis SAS programs for assisting review.

*Statistical reviewer comment: Appropriate material were provided to replicate the Applicant trial results for trial 1160.108.*

## Efficacy Results – Secondary and other relevant endpoints

Secondary Analysis

*Occurrence of post-thrombotic syndrome at 6 and 12 months:*

In total, 3 patients (1.4% of the treated patients) developed PTS or had worsening of PTS within the first 12 months; all 3 patients were in the oldest age group. The overall probability of being free from the event during the on-treatment period was 0.989 (95% CI 0.958, 0.997) at 3 months, 0.983 (95% CI 0.948, 0.994) at 6 months, and 0.983 (95% CI 0.948, 0.994) at 12 months.

Sub-group Analysis:

Considering the small number of patients with newly developed or worsened PTS within the first 12 months (3 out of 213 treated patients), the subgroup analyses are not conclusive.

Sensitivity Analysis:

When considering the full follow-up period and the entered set, occurrence of PTS (newly developed as well as worsening) was reported for 4 patients (1.9%) within the first 12 months (3 patients in the oldest age group and 1 patient in the age group 2 to < 12 years). The probability of being free from PTS was 0.990 (95% CI 0.962, 0.998) at 3 months, 0.980 (95% CI 0.949, 0.993) at 6 months, and 0.980 (95% CI 0.949, 0.993) at 12 months.

*Number of DE dose adjustments during on-treatment period:*

The number of patients with DE dose adjustments during the on-treatment period was analyzed. Since only one dose adjustment was allowed, this is equivalent to the number of DE dose adjustments. Overall, the DE dose was adjusted in 57 patients (26.8%) during the on-treatment period. In most of these patients,

the DE dose was increased. DE dose adjustments were more frequent in the younger age groups than in the oldest age group. The percentage of patients requiring dose adjustment was lower in the group of patients rolled over from trial 1160.106 and treated with DE (14.8%) than in the group of patients rolled over from trial 1160.106 and treated with SoC (40.0%) or in the group of newly recruited patients (29.5%). There was no relevant difference between male (29.1%) and female patients (24.0%). Up-titration was more frequent in Eastern Europe (29.0%) than in North America (11.4%) and Western Europe (16.3%). In Asia and Latin America, only a few patients were recruited (3 and 7 patients, respectively) and thus results in these regions are not conclusive.

*Medical reviewer comment:*
*For trial 1160.108, even though the evaluation of the occurrence of PTS in pediatric patients on Pradaxa for secondary VTE prevention showed relatively low rates, conclusion concerning the effectiveness of Pradaxa on preventing PTS cannot be reached due to the uncontrolled trial design, relatively small sample size given the relative rarity of the condition and the limited standardization of PTS evaluation that was implemented in the trial by the Applicant. As a result, this finding can only be considered as hypothesis-producing and need further evaluation in future trials.*

*Evaluation of dose adjustment in trial 1160.108 showed a high rate of Pradaxa treatment discontinuation secondary to sub-target trough concentration. This is further discussed in detail in the patient disposition sub-section of section 6.2.1 and section 8.2.1.*

## Dose/Dose Response

The relationship of drug dose or drug concentration to response was not assessed for Trial 1160.108.

## Durability of Response

The Applicant submitted study 1160.108 to demonstrate the safety of Pradaxa for the treatment of venous thromboembolism in children from birth to less than 18 years of age. Recurrence of VTE, bleeding events (major, CRNM, and minor events), all-cause mortality and mortality related to thrombotic and thromboembolic events were defined as the primary endpoints. Recurrence of adjudication-confirmed VTE in patients treated with Pradaxa was rare (3 patients 1.4% at 12 months during the on-treatment period). Three patients (1.4%) had an adjudication confirmed major bleeding event within the first 12 months. Three patients (1.4%) had an adjudication-confirmed CRNM bleeding within the first 12 months. Overall, adjudication-confirmed bleeding events (major, CRNM, and minor) during the on-treatment period were reported for 48 patients (22.5%) within the first 12 months. No on-treatment deaths occurred but one VTE-related death occurred. Overall, these results clearly show the safety of Pradaxa by reducing the risk of recurrence of VTE, while having minimized the occurrence of major blood events and VTE-related death, at rates comparable to those present in the literature for SoC therapies for VTE in pediatric patients.

*Medical and Statistical reviewer comment:*
*The results for trial 1160.108 demonstrate the safety of Pradaxa by reducing the risk of VTE recurrence in pediatric patients, while having minimized the occurrence of major blood events and VTE-related death. The observed rates are comparable to those present in the literature for SoC therapies pediatric patients with VTE. There are no major statistical issues identified from this review. There were no major statistical issues identified from this review.*

### Persistence of Effect

Based on the descriptive evidence provided from the trial, it is concluded that the submitted data in this NDA demonstrated the safety of Pradaxa for the secondary prevention of VTE in children from birth to less than 18 years of age.

### Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted for Trial 1160.108.

### Pediatric Exclusivity determination

The Applicant submitted a request for evaluation of pediatric exclusivity pursuant to the provisions of 21 CFR 314.108. We conducted a pediatric exclusivity review to evaluate if the Applicant has fully satisfied all the different aspects detailed in the amended final WR. In addition to satisfying the minimum number of patients per age group agreed upon with the Agency and developing appropriate pediatric formulations to allow the reliable administration of Pradaxa to the entire pediatric age spectrum, each of the submitted trials has satisfied all the aspects of the WR outlined in section 3.2. As a result, the pediatric exclusivity board has granted pediatric exclusivity to the Applicant, effective February 12th, 2021, under section 505A of the Federal Food, Drug and Cosmetic Act (21 U.S.C 355a).

## 7. Integrated Review of Effectiveness

Given the uncontrolled design and limited dosing in patients who already completed initial VTE treatment, trials 1160.88, 1160.89 and 1160.105 did not provide adequate data to support effectiveness. In contrast, trial 1160.106 was an adequate and well-controlled trial that provided sufficient data for the proper evaluation of the effectiveness of Pradaxa in the treatment of acute VTE in pediatric patients. In addition, trial 1160.108 was a single-arm extension long-term trial that provided some data for proper evaluation of the effectiveness of Pradaxa in the secondary prevention of VTE in pediatric patients, when compared to established pediatric VTE recurrence rates in the literature.

However, given the significant difference in trial design and trial endpoints between trial 1160.106 and 1160.108, data from the two pivotal trials were not pooled, when evaluating the effectiveness of Pradaxa in pediatric patients. As a result, an integrated review of effectiveness based on pooled data is not applicable to this review.

## 8. Review of Safety

### 8.1. Safety Review Approach

The safety of Pradaxa in adults has been evaluated in more than 45 individual Phase I studies, 7 Phase II studies and several Phase III studies (e.g. RE-LY, RE-NOVATE, RE-NOVATE-2, RE-COVER, RESPECT ESUS), with more than 35,000 adult patients treated with Pradaxa in clinical trials, most of these trials having an active control of warfarin. Clinically significant AEs described in the warnings and precautions section of the existing U.S. prescribing information (USPI) include:

- Increased risk of thrombotic events after premature discontinuation, in the absence of adequate alternative anticoagulation.
- Spinal/Epidural anesthesia or puncture may result in a spinal hematoma that can result in long-term or permanent paralysis if the procedure is done while patients are on Pradaxa.
- Thromboembolic events (including valve thrombosis) and bleeding events (predominantly post-operative pericardial effusions) in patients with prosthetic heart valves. As a result, Pradaxa is contraindicated in all patients with mechanical prosthetic valves, including pediatric patients.
- Increase risk of recurrent thrombosis in patients with APS, especially those with triple-positive APS. As a result, Pradaxa is not recommended for use in these patients.

The most common adverse reaction (AR) associated with Pradaxa is bleeding. Risk of bleeding is increased when Pradaxa is used concomitantly with other drugs that increase the risk of bleeding (e.g. anti-platelet agents, non-steroidal anti-inflammatory drugs [NSAIDs], fibrinolytic therapy and other anticoagulants). In addition to defining bleeding using anatomical location, the severity of bleeding is categorized as follows:

- *Major bleeding*: Fatal bleeding, clinically overt bleeding associated with a decrease in hemoglobin of at least 2 g/dL in a 24-hour period, bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system, or bleeding that required surgical intervention in an operating suite.
- *Clinically relevant non-major (CRNM) bleeding*: Overt bleeding for which a blood product was administered, and which was not directly attributable to the patient's underlying medical condition, or bleeding that required medical or surgical intervention to restore hemostasis, other than in an operating suite.
- *Minor bleeding*: Any overt or macroscopic evidence of bleeding that did not fulfil the criteria for either major bleeding or CRNM bleeding.

In adults treated with Pradaxa to reduce the risk of stroke and systemic embolism in non-valvular atrial fibrillation, the rate of major bleeding was comparable with warfarin (3.47%/year vs. 3.58%/year), with a lower rate of intracranial bleeds (0.22%/year vs. 0.77%/year) but a higher rate of gastrointestinal (GI) bleeds (1.59%/year vs. 1.05%/year). In adults treated with Pradaxa to treat and reduce the risk of recurrence of VTE, the rate of major bleeding (0.9-1.4% vs. 1.8-2.0%), CRNM bleeding (4.0-5.0% vs. 6.7-8.8%) and all bleeding (16.1-19.4% vs. 22.7-26.2%) was lower than warfarin, with significant differences among bleeding sites of major bleeding. Of note, the rate of any GI bleeds was higher in Pradaxa compared to warfarin (3.1% vs. 2.4%).

Another common ARs associated with Pradaxa are gastrointestinal events (i.e. dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea), which occurred at a higher rate, compared to warfarin (24.7-35% vs. 22.7-24%). In addition, the following are post-marketing AR reported in the USPI: angioedema, thrombocytopenia, esophageal ulcer, alopecia, neutropenia and agranulocytosis. The events of alopecia reported in adults were mostly non-serious with a rate of 0.4 cases per 10,000 patient years, with the rate of alopecia in adult trial comparable between Pradaxa and warfarin (0.6% vs. 0.4%).

The safety review focused on evaluating the safety profile of Pradaxa in pediatric patients and comparing it with the safety profile in adults to defect new safety signals that were unique to pediatric patients. The safety evaluation was mainly based on analysis of the final data from the two completed pivotal trials, trial 1160.106 and trial 1160.108. We also analyzed the safety data from early phase completed trials,

such as trial 1160.88, trial 1160.89 and trial 1160.105, which will be described briefly in section 8.4. We did not pool the data from any of the evaluated trials due to the presence of significant difference in their trial design.

To assess the reliability and quality of the data, the clinical reviewer compared the coding of verbatim reported adverse event terms to the Medical Dictionary for Regulatory Activities (MedDRA) lower level terms for 808 on-treatment adverse events (AETERM) submitted in the safety dataset for trial 1160.106 and 863 on-treatment AETERM submitted in the safety dataset for trial 1160.108, to the MedDRA lowest coded level (AELLT). The coding was consistently performed between the two terms. In addition, detailed evaluation of the MedDRA preferred terms (PTs) and system organ classes (SOCs) to ensure appropriate splitting and grouping was conducted to allow for meaningful and consistent evaluation of adverse reactions. This was consistently performed across all patients and is described in detail in Appendix 13.3.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

*Trial 1160.106:*
Of the 328 patients that were enrolled on the trial, 267 patients were randomized but 266 patients received trial medication as assigned because one patient in the Pradaxa arm withdrew consent after randomization. Of the 266 patients that form the on-treatment safety dataset, 176 patients were on Pradaxa and 90 patients were on SoC. In relation to the dosage forms given to patients on Pradaxa, 121 patients (69%) received capsules, 41 patients (23%) received oral pellets and 14 patients (8%) received oral solution. Only 2 patients needed a dosage form change during the trial. The median (IQR, range) duration of therapy for patients in the Pradaxa arm was 81 days (36-87, 1-106) and the median (IQR, range) amount per dose was 260 mg (150-310, 2-330). There were 26 patients (14.8%) that had 34 documented dose interruptions due to: 1) scheduled procedures (in 14 patients), 2) bleeding AR (in 5 patients) with 1 event leading to permanent discontinuation, 3) esophagitis (in 1 patient), 4) non-specific SAE (in 2 patients), 5) non-specific AE (in 3 patients) with 1 event leading to discontinuation, and 6) thrombocytopenia (in 1 patient).

Dose titration was applied per protocol to achieve target drug trough concentration 50 - <250 ng/mL in 65 patients (36.9%), of which 57 patients (32.4%) needed up-titration and 8 patients (4.5%) needed down-titration. The need for up-titration was more prevalent in younger patients, with a significant difference (p-value 0.002) observed between the mean age of those who required up-titration, 7.6 years (SD=6), and those who did not require up-titration, 10 years (SD=6). These results were consistent across analysis of both the EX SDTM dataset and the SWITCH ADAM dataset. In addition, we analyzed dTT values obtained at a scheduled or unscheduled visit 3 to evaluate the occurrence of initial sub-target Pradaxa concentration. There were 34 patients (19.3%) who had sub-target drug concentrations with the nomogram-guided starting dose. Twenty-two patients (12.5%) had drug concentration within the target range after one dose adjustment but the median duration between sub-target and first within-target measurement was significantly long at 18 days (range 8-42).

Patients that did not achieve trough concentration within target after one dose adjustment were either switched to the SoC arm per protocol (n=9) or discontinued from Pradaxa since were very close to the 12-

week treatment duration with Pradaxa exposure at 82, 85 and 87 days (n=3). As a result, 12 patients (6.8%) were discontinued from Pradaxa due to this reason. In addition, there 3 patients who did not achieve trough concentration within target at their initial dose and could not have one dose adjustment because they were already at the maximal dose for age, thus were discontinued prematurely from Pradaxa without one dose adjustment.

Detailed dose exposures from the SoC treatment arm was not possible because 65% of dose entries were missing. However, data on the drug used, number of dose changes and duration of therapy was available and is summarized in table 21. Dose interruption due to AE occurred in 12 patients (6.8%) on Pradaxa and 6 patients (6.7%) on SoC, with no significant difference in age between the two groups.

Table 21: Details of Exposure to Different Anticoagulants Used in The SoC Arm in Trial 1160.106

| SoC Anticoagulant Used | Number of Subjects[1] (%) – n = 90 | Number of Dose Changes – Median (IQR) | Age Median (IQR) | Duration of therapy Mean (SD) |
|---|---|---|---|---|
| VKA[2] | 51 (57) | 3 (2-7) | 14 (5-16) | 92 (22) |
| Enoxaparin | 30 (33) | 1 (1-2) | 14 (5-17) | 86 (60) |
| Dalteparin | 6 (7) | 2 (1-3) | 13 (2-17) | 88 (12) |
| Tinzaparin | 4 (4) | 2 (1-3) | 16 (14-17) | 49 (10) |
| Nadroparin | 1 (1) | 4 | 17 | 41 |
| Heparin | 1 (1) | 1 | 0.2 | 21 |
| Fondaparinux | 1 (1) | 1 | 16 | 2 |

Source: MEDICAL reviewer's analyses. [1] 8 patients were exposed to two SOC drugs but only SOC present for majority of duration was included, [2] VKA include Acenocoumarol (1 subject), Coumadin (3 subjects), Marevan (1 subject), Orfarin (1 subject), Phenprocoumon (3 subjects) and Warfarin (42 subjects).

*Trial 1160.108:*

The safety population dataset is composed of 213 patients, who received at least one dose of the trial medication. The median (range) duration of therapy was 41.9 weeks (0.3 – 56), with ~50% of patients (104 patients) treated for > 42 weeks. There was a decreasing trend in duration of treatment by age, as follows: 44.3 weeks (1 – 56) in stratum 1, 32.4 weeks (0.3 – 55) in stratum 2 and 16.3 weeks (2 – 51) in stratum 3. The median (range) amount per dose was 260 mg (30 – 330). There were 179 patients (84%) who received capsules, 161 patients from stratum 1 and 18 patients from stratum 2. The remaining patients from stratum 2 (25 patients) and all patients from stratum 3 (9 patients) received oral pellets. No patient received more than one formulation or received the oral solution formulation.

Dose adjustment due to inability to achieve target drug trough concentration 50 - <250 ng/mL occurred in 57 patients (27%), with 40 patients receiving capsules (22% of all patients who received capsules) and 17 patients receiving oral pellets (50% of all patients who received oral pellets). Of the 57 patients who needed dose adjustment, 26 patients (12% of the on-treatment population and 46% of patients who required a dose adjustment) discontinued trial medication prematurely secondary to not achieving the target trough concentration after one dose adjustment, as per protocol.

*Medical reviewer comment: When looking at results from both trials, 19.3-27% of patients did not achieve the target trough concentration mandated by the trial protocols. The rate of not achieving the target concentration among younger patients taking oral pellets or oral solutions was 47-50%, while the rate of*

*not achieving the target concentration among older patients taking capsules was 7-22%. Among those needing titration, failure to achieve target concentration with one titration leading to premature discontinuation was 35-46%, with an overall rate of discontinuation of 7-12%, occurring more commonly in younger patients.*

*Excluding patients who were discontinued prematurely due to low trough levels from trial 1160.106, we conducted sensitivity analyses of efficacy and safety among the 3 age-group stratum and compared the results with results from the complete dataset, as summarized in table 12 and table 22. There was no significant difference in safety results between the two analyses populations. However, there was a decrease in the primary efficacy of Pradaxa across all age groups, leading to a trend favoring the SoC arm in one of the two younger age groups. Given the post-hoc nature of the analysis, these conclusions should be used with caution but highlight the added uncertainty that resulted from the significantly high rate of early discontinuation of patients in the Pradaxa arm.*

Table 22: Sensitivity Analysis of Efficacy Endpoint Among the 3 Age-group Stratums in Trial 1160.106 Using the ITT Dataset Excluding Patients with Premature Discontinuation due to Trough Levels

| Baseline Characteristics | Stratum 3 (n=31) | | Stratum 2 (n=56) | | Stratum 1 (n=165) | |
|---|---|---|---|---|---|---|
| | Pradaxa (n=18) | SoC (n=13) | Pradaxa (n=35) | SoC (n=21) | Pradaxa (n=109) | SoC (n=56) |
| Efficacy Composite – n (%) | 10 (56) | 7 (54) | 17 (49) | 12 (57) | 45 (42) | 19 (34) |
| Complete Resolution – n (%) | 10 (56) | 7 (54) | 17 (49) | 12 (57) | 45 (42) | 19 (34) |
| VTE Recurrence – n (%) | 0 (0) | 0 (0) | 1 (2) | 1 (5) | 6 (5) | 6 (11) |
| VTE-related Death – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) |
| Major Bleed – n (%) | 1 (6) | 0 (0) | 1 (3) | 0 (0) | 2 (2) | 2 (4) |
| CRNM Bleed – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (2) | 1 (2) |
| Minor Bleed – n (%) | 4 (22) | 0 (0) | 5 (14) | 2 (10) | 19 (17) | 19 (34) |
| Any Bleed – n (%) | 5 (28) | 0 (0) | 6 (17) | 2 (10) | 22 (20) | 20 (36) |

Source: MEDICAL reviewer's analyses.

*Given the results of our sensitivity analyses and the over-representation of these findings in the younger age-groups, who are already under-represented in the trial populations, we cannot rule-out the significance of these findings. As a result of these findings, and to ensure that our recommendations align with the procedures followed in the protocol, we propose two strategies to resolve the problem of subtherapeutic dosing in younger patients taking the oral pellets and the oral solution:*

- *Increase all proposed starting doses for both formulations, based on population PK modeling. After thorough consideration, we decided that this strategy is not optimal for the following reasons:*
  - *Developmental hemostasis results in increased sensitivity to anticoagulant therapy and as increased risk of bleeding with any universal increase in dosing.*
  - *The prevalence of complex medical conditions in the majority of younger pediatric patients with VTE predisposes them to having other risk factors for bleeding complications, such as surgeries and devices.*
  - *There is uncertainty of the effect of a universal dose increase on the rate of bleeding AEs, given the expected higher exposure in patients who had an initial within target concentration.*
- *Drug monitoring and dose titration to achieve a trough concentration target of 50 - <250 ng/mL, as was implemented in the trial protocols but without any limitation on the number of dose*

*adjustments allowed. Once drug concentration is within target range, no further monitoring is required unless does modification occurs secondary to weight changes. This strategy is the one recommended by the Agency* (b) (4)

### 8.2.2. Relevant characteristics of the safety population:

Only patients who were enrolled in the trials and received at least one dose of the trial drug were included in the safety analysis dataset. Given that only one patient was randomized but not treated, the safety and efficacy population are essentially the same, with a total of 266 patients in trial 1160.106 and 213 patients in trial 1160.108. As a result, refer to the following two sub-sections of section 6.2.1 for a detailed description of relevant characteristics of the safety population and their associated reviewer comments: Table of Demographic Characteristics and Other Baseline Characteristics.

Given that the most common safety signal associated with anticoagulants, such as Pradaxa, is bleeding, we determined the proportions of patient who had the following bleeding-associated risk factors in trial 1160.106, which have potential confounding effects on the safety analysis results:

- *On-treatment traumatic injury*: The rate and severity of these events was obtained from analysis of the AE STDM dataset. The specific list of AE-related traumatic injuries used are present in Appendix 13.3. Overall, there was a higher rate of traumatic injuries report in the SoC arm (11 patients – 12%) compared to the Pradaxa arm (12 patients – 7%). However, when the severity of injury was considered, the higher rate observed was mainly present in mild events, with 9 patients (10%) from the SoC arm and 5 patients (3%) from the Pradaxa Arm. As a result, it is unlikely that this difference contributed significantly to the observed safety results.
- *History of bleeding symptoms prior to start of trial treatment:* The rate and severity of these events was obtained from analysis of the AE STDM dataset. The rate and severity of these events were equivalent between the two arms, with 7 patients in the Pradaxa arm (4%) and 4 patients (4%) in the SoC arm.
- *Concomitant use of bleeding-associated medication*: The rate of use of these medications was obtained from analysis of the CM STDM dataset. The specific list of CM used are present in Appendix 13.3. The rate of concomitant use of these medications was comparable between the two arms, with 42 patients in the Pradaxa arm (24%) and 18 patients (20%) in the SoC arm. As a result, it is unlikely that this difference contributed significantly to the observed safety results.

### 8.2.3. Adequacy of the safety database:

The size of the safety database is adequate to provide a reasonable estimate of adverse events that may be observed with Pradaxa in the pediatric population. With some exceptions outlined in sections 6.2.1 and section 8.2.2, the characteristics of the safety population are consistent with the epidemiologic data available for pediatric VTE. In general, these exceptions were the result of two main reasons:

- Recruitment limitation, inherent to conducting clinical research in pediatric patients, resulting in imbalances in age and race/ethnicity. The Applicant has demonstrated true diligence in addressing these imbalances throughout the developmental life cycle.
- High number of potential confounding factors, represented in the numerous risk factors contributing to VTE risk in pediatric patients, in combination with the relatively limited sample

size, resulted in imbalances in the trial population, despite randomization. This resulted in imbalances in specific sub-populations summarized in section 6.2.1.

*Medical reviewer comment: After thorough evaluation, we do not believe that these exceptions have impacted the adequacy of the safety database or the validity of the safety results.*

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission contained all required components of the eCTD. The review did not identify any major issues involving data integrity or submission quality.

### 8.3.2. Categorization of Adverse Events

For all trials contributing to the safety data, the following safety terms and definitions apply:

- An AE is any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product, regardless of having a causal relationship with this treatment.
- An AE was considered serious if it was fatal, immediately life threatening, resulted in persistent or significant disability or incapacity, constitutes a birth defect or congenital anomaly, requires or prolongs inpatient hospitalization, or is considered otherwise medically since may require medical or surgical intervention to prevent one of the outcomes listed in the definition.
- The severity of bleeding ARs were defined using the ISTH definitions, listed in section 8.1, as major bleeding, CRNM bleeding and minor bleeding.
- The severity of all AEs and Ars were graded using the following definitions:
  - Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated.
  - Moderate: Enough discomfort to cause interference with usual activity.
  - Severe: Incapacitating or causing inability to work or to perform usual activities.

AEs were reported by verbatim term and coded and categorized using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. The Applicant considered the following two AE as Protocol-specified Adverse Events of Special Interest (AESI):

- Hepatic injury: Elevation of AST and/or ALT > 3x ULN combined with an elevation of total bilirubin >2x ULN measured in the same blood draw sample.
- Renal dysfunction: Creatinine increased ≥ 2x from baseline and is above the ULN.

*Trial 1160.106:*

Adverse events were collected from signing the ICF through the end of follow-up visit (visit 9), which occurred 28 days after the last dose of trial medication. In addition, if patients ended treatment prior to visit 8 (i.e. week 12), an eEOT will take place as close as possible to the date of premature discontinuation of trial medication. Treatment emergent adverse events (TEAEs) were defined as AEs occurring or worsening during the on-treatment period, defined as the period from the day of first trial medication administration until the end of the residual effect period (REP), defined as 6 days after the last trial medication administration. SAEs were collected from ICF signing to the end of follow-up visit (visit 9).

*Trial 1160.108:*
Adverse events were collected from signing the ICF through the end of follow-up visit (visit 12), which occurred 28 days after the last dose of trial medication. In addition, if patients ended treatment prior to visit 11, an eEOT will take place as close as possible to the date of premature discontinuation of trial medication. Treatment emergent adverse events (TEAEs) were defined as AEs occurring or worsening during the on-treatment period, defined as the period from the day of first trial medication administration until the end of the residual effect period (REP), defined as 3 days after the last trial medication administration. SAEs were collected from signing the ICF through the end of follow-up visit (visit 12).

### 8.3.3. Routine Clinical Tests

*Trial 1160.106:*
All trial visits were in-person clinic visits, approximately every 3 weeks. Full physical examinations, height assessment, ECG, assessment of thrombus extension using an appropriate imaging modality per protocol, and pregnancy testing for female patients of child-bearing potential were performed at screening (i.e. visit 1), visit 8 and eEOT. In addition, a full physical examination was performed during follow-up (i.e. visit 9). Vital signs, weight assessment, evaluation of thrombosis-related symptoms, AEs, concomitant medication and medication compliance was performed during every visit. Complete blood count (CBC) and comprehensive metabolic panel (CMP), including ALT/AST and Bili T/D, were performed during every visit. For patients on Pradaxa, the following coagulation tests were performed during every visit and after reaching steady state post-dose adjustment, as a pre-dose trough level (i.e. ~10-16 hours after the last dose): aPTT, Ecarin Clotting Time (ECT) and diluted Thrombin Time (dTT) / Hemoclot assay. An optional post-dose sampling, ~2 hours after the Pradaxa dose, was also collected during every visit. In addition, PK sampling for Pradaxa was performed during every visit as a pre-dose trough level (i.e. ~10-16 hours after the last dose). For patients on SoC therapy, appropriate drug monitoring was performed every visit and after reaching steady state post-dose adjustment, depending on the type of SoC therapy, by measuring PT/INR or anti-Xa activity.

*Trial 1160.108:*
All trial visits were in-person clinic visits, approximately every 3-8 weeks. Assessment of thrombus using an appropriate imaging modality per protocol were performed at screening. Full physical examinations, height assessment, ECG, and pregnancy testing for female patients of child-bearing potential were performed at screening (i.e. visit 1), visit 8 (i.e. 6 months), visit 11 (i.e. 12 months) and eEOT. In addition, a full physical examination was performed during follow-up (i.e. visit 12). Vital signs, weight assessment, evaluation of thrombosis-related symptoms, AEs, concomitant medication and medication compliance was performed during every visit. Evaluation for PTS was performed on visit 8 and visit 11. Complete blood count (CBC) and comprehensive metabolic panel (CMP), including ALT/AST and Bili T/D, were performed during every visit. The following coagulation tests were performed during every visit and after reaching steady state post-dose adjustment, as a pre-dose trough level (i.e. ~10-16 hours after the last dose): aPTT, ECT and dTT / Hemoclot assay. In addition, PK sampling for Pradaxa was performed during every visit as a pre-dose trough level (i.e. ~10-16 hours after the last dose).

*Medical reviewer comment: Overall, the safety assessment methods and schedule described in the protocol for both trials were reasonable and adequate for the safety evaluation of the trial populations.*

*The target trough concentration for Pradaxa used in both trials was 50 - < 250 ng/ml. Dabigatran concentrations were obtained using two methods:*

- *An analytical method for PK measurement (i.e. HPLC-MS/MS method)*
- *A functional clot-based assay method for PD measurement, which used extrapolation of dabigatran concentration using a calibration curve based on a clotting time. There are two main functional assays used:*
  - *ECT: a clotting assay that uses a venom as a specific activator of prothrombin, resulting in an intermediate of thrombin (i.e. meizothrombin) that has proteolytic activity on fibrinogen but is only inhibited by direct thrombin inhibitors, such as Pradaxa.*
  - *dTT: a modification to the classical thrombin time (TT) that involve diluting the patient's citrated plasma with pooled normal plasma, prior to adding the activator, bovine thrombin. Even though this assay maybe sensitive to the effect of many anticoagulants, the modification allows for the assay to be sensitive to changes in direct thrombin inhibitor concentrations.*

*It is important to note that there is sufficient evidence supporting the strong linear correlation between the two functional methods and the actual PK measurement of Pradaxa. Even though ECT is not available as a clinical coagulation test, dTT is commonly available in many clinical laboratories, thus is relatively convenient to use[82]. In addition to strong supporting data from population PK modeling obtained from the Pradaxa adult and pediatric development program, there is a large body of literature supporting the clinical use of dTT as an adequate and reliable method to evaluate dabigatran concentration in core laboratories with coagulation testing capabilities[83,84]. This strong correlation has been shown even in very low dabigatran concentration, to a minimum of 30 ng/ml, using both commercial (i.e. Hemoclot) [85,86] and similar in-house assays[87]. Given the findings described in section 8.2.1 and the preferred strategy described to address the observed deficit in the data, dTT is recommended as a reliable and available assay that can be used drug monitoring and dose titration, to achieve the protocol-based trough concentration target of 50 - <250 ng/ml.*

## 8.4. Safety Results

### 8.4.1. Deaths

*Trial 1160.106:*

There were 4 patient deaths (1.5%) reported in the safety population dataset (2 patients in Pradaxa arm [1.1%] vs. 2 patients in SoC arm [2.2%]), with relevant details summarized in Table 23. After thorough review of the provided narratives, we agree with the following conclusions provided by the Applicant:

- One of the four deaths (patient # (b) (6)) occurred during the on-treatment period, which was in the SoC arm (i.e. consistent with the Applicant's definition of all-cause mortality).
- One of the four deaths (patient # (b) (6)) was considered VTE-related (i.e. occurring within ITT period of days 1-84 of treatment and adjudicated as VTE-related), which was in the SoC arm, thus counting towards the primary efficacy endpoint.
- One of the four deaths (patient # (b) (6)) was considered directly related a major bleeding event since occurred during the on-treatment period and adjudicated as a fatal bleed, which was in the SoC arm.

The Applicant did not consider any of the deaths attributable to trial medication. In addition, the Applicant

did not consider the bleeding events for patient # (b) (6) and patient # (b) (6) not attributable to trial medication.

*Trial 1160.108:*
The Applicant reported that there were no patient deaths during the on-treatment period of trial 1160.108. However, a 16-year old male with MH of hyperhomocysteinemia, APS and PE, was treated with Pradaxa for 325 days, when he experienced a major bleeding event of hemoptysis, resulting in discontinuation of trial medication and start of another SoC therapy. Six days after the bleed event, he was admitted to the PICU for PE and acute respiratory failure, resulting in his death on the same day. The Applicant considered this a VTE-related death but did not attribute the death to a failure of trial medication.

*Medical reviewer comment: Overall, we agree with the conclusions provided by the Applicant for trial 1160.106. All the relevant deaths highlighted in the conclusions occurred in the SoC arm. However, we disagree with several of their attribution decisions. We believe that the death of patient # (b) (6) is directly attributable to trial medication. In addition, we believe that the bleeding events experienced by # (b) (6) and patient # (b) (6) are also directly attributable to the trial medication. For trial 1160.108, we disagree with the Applicant conclusion. The single reported death is both VTE-related and due to failure of Pradaxa in the secondary prevention of VTE. Given the patient's underlying condition of APS and recently added warning in the USPI concerning the increase risk of recurrent thrombosis in patients with APS, this case further supports the inclusion of the same warning for pediatric patients with VTE.*

*Overall, with the exception of use in pediatric patient with APS, the death-related safety data is favorable towards the use of Pradaxa, over SoC therapy, in the treatment and secondary prevention of pediatric patients with VTE.*

Table 23: Summary of Relevant Details of Patient Deaths in Trial 1160.106

| Patient Number | Age (year) / Gender | Trial Arm/ Dose / Country | Baseline MH and VTE Risk Factors | Acute MH Relating to Death | Trial Day of Death | Cause of Death | On Trial Drug at Death / Trial Day of Last Dose | Attribution / Agreement |
|---|---|---|---|---|---|---|---|---|
| (b) (6) | 17 / M | Pradaxa / 330 mg BID / Canada | Osteo-sarcoma, recent surgery | Respiratory failure due to cancer progression | 380 | Cancer progress | No / 11 | Not attributed to trial drug / Yes |
| (b) (6) | 14 / M | Pradaxa / 300 mg BID / Thailand | Adreno-carcinoma of the lung | Respiratory distress / failure, hematuria (D7), non-contiguous DVT (D10), hepatic encephalo-pathy | 29 | Multi-organ failure including renal failure | No / 7 | Not attributed to trial drug / Yes |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (b) (6) | 15 / F | SoC / LMWH / Turkey | Sickle cell disease, on ASA | SC pain crisis, Peritoneal bleed of retro-peritoneal origin | 25 | Shock & cardiac arrest due to major bleed | No / 24 | Not attributed to trial drug / No |
| (b) (6) | 16 / M | SoC / LMWH / Turkey | Ulcerative Colitis | Worsening CSVT with hemorrhagic infarction (off anti-coagulation due to Hemato-chezia 3 days prior) | 26 | Hemorr-hagic infarctio n and Cardiac arrest | No / 15 | Not attributed to trial drug / Yes |

Source: MEDICAL reviewer's analyses.

### 8.4.2. Serious Adverse Events

*Trial 1160.106:*

In the safety population dataset of trial 1160.106, 94 on-treatment SAEs (12%) occurred in 49 patients (18%), with 30 patients (17%) in Pradaxa arm vs. 19 patients (21%) in SoC arm. Overall, 25 SAEs (3%) were deemed related to trial medication by the reviewer, with 21 SAEs (2.6%) related to bleeding. Table 24 summarizes the occurrence of SAEs by AEs of special interest and SOC-based breakdown. The specific list of MedDRA PT for SOC terms used for SAEs are present in Appendix 13.3. Overall, the proportion of patients who experienced a bleeding-related SAE is higher in the Pradaxa arm (7 patients [4%]) compared to the SoC arm (2 patients [2%]). When bleed-related SAE is considered according to age-group stratum, the proportion of patients with bleed-related SAE is the same (2%), resulting in a higher occurrence of bleed-related SAE in the younger age groups (2 patients, 1 in each younger stratum [total of 2%], when compared to the SoC arm, who had no bleed-related SAE in the younger age groups.

Table 24: Summary of SAEs in Trial 1160.108

| | Pradaxa (n=625) | SOC (n=183) | Total (n=808) |
|---|---|---|---|
| Any SAE during on-treatment period – n (%) | 61 (9.8) | 33 (18) | 94 (11.6) |
| Bleeding-related SAE – n (%) | 10 (1.6) | 3 (1.5) | 13 (1.65) |
| GI Bleed – n (%) | 6 (1) | 1 (0.5) | 7 (0.9) |
| Major Cutaneous Bleed – n (%) | 2 (0.3) | 0 (0) | 2 (0.25) |
| Cranial Bleed – n (%) | 1 (0.15) | 1 (0.5) | 2 (0.25) |
| Other Bleeds – n (%) | 1 (0.15)[1] | 1 (0.5)[2] | 2 (0.25) |
| Anemia – n (%) | 4 (0.6) | 0 (0) | 4 (0.5) |
| Thrombosis-related SAE SOC – n (%) | 7 (1.1) | 8 (4.4) | 15 (1.9) |
| Infections and Infestations SOC – n (%) | 8 (1.3) | 7 (3.8) | 15 (1.9) |
| Gastrointestinal disorders SOC – n (%) | 6 (1) | 0 (0) | 6 (0.7) |
| Blood and lymphatic system disorders SOC – n (%) | 5 (0.8) | 1 (0.5) | 6 (0.7) |
| Metabolic and nutrition disorders SOC – n (%) | 6 (1) | 0 (0) | 6 (0.7) |

| | | | |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders SOC – n (%) | 3 (0.5) | 3 (1.5) | 6 (0.7) |
| Nervous system disorders SOC – n (%) | 2 (0.3) | 3 (1.5) | 5 (0.6) |
| Cardiac and Vascular disorders SOC – n (%) | 2 (0.3) | 4 (2.2) | 6 (0.7) |

Source: MEDICAL reviewer's analyses. [1] Other bleeds for the Dabigatran arm consists of a case of uterine hemorrhage, [2] Other bleeds for the SOC arm consists of a case of peritoneal hemorrhage.

*Trial 1160.108:*

In the safety population dataset of trial 1160.108, 48 on-treatment SAEs (5.6%) occurred in 29 patients (13.6%), of which 8 (0.9%) were deemed related to Pradaxa by the reviewer and 5 (0.6%) were related to bleeding. SAEs that occurred in > 1 patient are: pneumonia, tonsillitis and deep vein thrombosis (2 patients each). Immediately life threatening SAEs occurred in two patients, one of which lead to the patient's death, described in section 8.4.1. The other patient was a 17-year old female with MH of right leg venous malformation, who developed a major spontaneous external bleed from a malformation-related varicose vein that was controlled interruption of Pradaxa, active reversal with on-trial idarucizumab and surgical local control, resulting in complete resolution after 4 days. Pradaxa was restarted 7 days after the onset of the SAE, without recurrence of bleeding.

*Medical reviewer comment: Overall, the rate of treatment-related SAE with Pradaxa is low (~1-2%), which is comparable to the rate experienced by patients in the SoC arm. Not surprisingly, the majority of the treatment-related SAEs were related to bleeding, with a significant minority related to GI disturbances. We observed a trend towards a higher rate of bleed-related SAE in younger patients on Pradaxa, when compared to those on SoC but these results need to be interpreted with caution, given the small number of events. It is important to note that idarucizumab was successfully used for drug reversal in one adolescent patient with a life-threatening major bleed.*

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

*Trial 1160.106:*

For details relating to dropouts, discontinuation not related to AEs and drug interruptions, please refer to patient disposition in section 6.1.2 and overall exposure in section 8.2.1. Drug withdrawal secondary to AE occurred in 17 patients (6.2%), 14 patients (8%) in the Pradaxa arm vs. 3 patients (3.3%) in the SoC, with a total of 24 TEAEs (3%) considered TEAEs leading to trial medication discontinuation. Specifically, TEAE-related drug interruptions were categorized as follows:

- Bleeding-related AEs in 8 patients (3%), 6 patients (3.4%) in the Pradaxa arm vs. 2 patients (2.2%) in the SoC arm. Bleeding AEs leading to discontinuation of Pradaxa were intracranial bleed, hematuria, stoma bleed, GI bleed and epistaxis. Bleeding AEs leading to discontinuation of SoC were peritoneal bleed and GI bleed. In addition, two other patients required dose reduction due to bleeding, one from each arm, and both continued on their assigned trial treatment without further interruptions or future discontinuation.
- Thrombosis-related AE occurred in 1 patient (0.6%) in the Pradaxa arm.
- Renal-related AEs occurred in 4 patients, all receiving Pradaxa enrolled at the same site in the Czech Republic. Three of the four patients were discontinued per protocol due to the designated cut-off in eGFR without any other clinically significant abnormalities. Given that the lower limit of tolerated eGFR evolved throughout the protocol life-cycle and that these patients would not have been discontinued if the final cut-off was applied to them, their discontinuation is not significant. However, one patient with normal baseline renal function developed significant renal impairment

on D23, leading to drug discontinuation and resolution of all renal deficits within 1 week of discontinuation. After review, we believe that this event was drug-related and significant.
- Other AEs include an allergic reaction (1 patient in the SoC arm), accidents (2 patients in the Pradaxa arm) and infection (1 patient in the Pradaxa arm).

*Trial 1160.108:*
For details relating to dropouts and discontinuation not related to AEs, please refer to patient disposition in section 6.1.2 and overall exposure in section 8.2.1. Drug withdrawal secondary to AE occurred in 13 patients (6.1%), with a total of 13 TEAEs (1.5%) considered TEAEs leading to trial medication discontinuation. Specifically, TEAE-related drug interruptions were categorized as follows:
- Thrombosis-related AE occurred in 5 patients (2.3%)
- Renal-related AEs occurred in 2 patients (0.9%), both discontinued per protocol due to the designated cut-off in eGFR without any other clinically significant abnormalities. Given that the lower limit of tolerated eGFR evolved throughout the protocol life-cycle and that these patients would not have been discontinued if the final cut-off was applied to them, their discontinuation is not significant.
- Pregnancy occurred in 1 patient (0.5%), which was detected early in the first trimester with an approximate maximum exposure duration of 4 weeks. The patient delivered a healthy normal male newborn at 38 weeks gestation, with no reported complications.
- Other AEs include immune-related worsening thrombocytopenia (1 patient with APS), infection (varicella with secondary cellulitis in 1 patient), headache (1 patient), dyspepsia (1 patient) and relapse acute lymphoblastic leukemia (1 patient)

*Medical reviewer comment: Overall, if cases related to protocol-determined low eGFR and other AEs unrelated to trial medication were excluded, the rate of TEAE-related discontinuation with Pradaxa is low (4.5%), which is comparable to the rate experienced by patients in the SoC arm (3.3%). In addition, the rate of bleeding-related AEs leading to discontinuation is also comparable between the two arms. The VTE recurrence rate in patients on Pradaxa for secondary prevention is comparable to the known historical VTE recurrence rates in pediatric patients.*

### 8.4.4. Significant Adverse Events

According to the ICH E3 guidance, other potentially important abnormalities include severe AEs, which do not meet the definition of a serious AE. Using safety population dataset, we conducted specific analyses to evaluate the general and AE-specific distribution of severity grades among the two treatment arms of trial 1160.106 and among the three age-group strata of trial 1160.108. The results of our analysis are documented in section 8.4.5.

### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The safety experience from the three early phase clinical pharmacology trials are as follows:
- For trial 1160.88, conducted in 9 patients (age 12 to < 18 years) receiving twice daily Pradaxa for 3 days, there were 3 TEAEs in 2 patients, all of which were gastrointestinal (i.e. reflux, and abdominal discomfort) and mild in severity. None of these events led to discontinuation of trial medication. There were no bleeding events. There were no related SAE and no deaths.

- For trial 1160.89, conducted in 18 patients (age 1 to < 12 years) mostly receiving single dose Pradaxa, there was 1 patient who experienced TEAEs of leukopenia and dizziness of mild intensity. There were no bleeding events. There were no related SAE and no deaths. In relation to the global assessment of tolerability of the oral liquid, 9 patients (6 in group 1 and 3 in group 2) had a good or satisfactory experience vs. 8 patients (6 in group 1 and 2 in group 2) had a bad or not satisfactory experience, resulting in an overall 50% acceptability assessment.
- For trial 1160.105, conducted in 8 patients (age <1 year) receiving single dose Pradaxa, there were no TEAE, no related SAE and no deaths. There were no bleeding events. In relation to the global assessment of tolerability of the oral liquid, 7 patients had a good or satisfactory experience vs. 1 patient had a bad experience.

*Trial 1160.106:*

In the safety population dataset, there was a total number of 808 TEAEs, of which 609 (75%) were mild, 147 (18%) were moderate and 52 (7%) were severe, with 71-79% of each severity category occurring in a patient on the Pradaxa arm. However, a similar number of patients in each arm reported having ≥ 1 severe TEAE, with 19 patients (11%) in the Pradaxa arm vs. 8 patients (9%) in the SoC arm. A total of 201 patients (76%) experience at least one TEAE of any grade, with 140 patients (80%) in the Pradaxa arm vs. 61 patients (68%) in the SoC arm. There were 111 ARs (13.7%) that were determined to be related to trial medication by the investigator, with 79 ARs (12.6%) related to Pradaxa vs. 32 ARs (17.5%) related to SoC.

ARs that occurred in ≥ 5% of patients on Pradaxa were considered significant for our safety analysis, with alopecia being the only exception. The specific list of MedDRA PT for AE evaluation in safety population are present in Appendix 13.3. Table 25 summarizes the significant non-bleeding ARs, with respective severity data for each AR. It is important to note that a significantly higher number of patients reported GI ARs in the Pradaxa arm (61 patients [35%]), as compared to the SoC arm (10 patients [ 11%]), with some patients reporting recurrence of the same GI AR and a variety of GI ARs. It is important to note the of the 60 patients who experienced any bleeding AR, 26 patients (43%) had > 1 bleeding AR, with 1 patient having 8 bleeding ARs, 3 patients having 4 bleeding ARs, 7 patients having 3 bleeding ARs and 15 patients having 2 bleeding ARs.

Table 25: Non-Bleed ARs by Severity in Trial 1160.106 (Safety Analysis Set)

| Non-bleeding Adverse Reactions (AR) | Dabigatran (n=176) | SOC (n=90) | Total (n=266) |
|---|---|---|---|
| Headache – n (%) | 18 (10) | 8 (9) | 26 (10) |
| *Moderate – n (%)* | *4 (2)* | *1 (1)* | *5 (2)* |
| *Mild – n (%)* | *14 (8)* | *7 (8)* | *21 (8)* |
| *Gastrointestinal disorders* | | | |
| Abdominal pain – n (%) | 16 (9) | 2 (2) | 18 (7) |
| *Severe – n (%)* | *1 (0.5)* | *0 (0)* | *1 (0.5)* |
| *Moderate – n (%)* | *3 (1.5)* | *0 (0)* | *3 (1)* |
| *Mild – n (%)* | *12 (7)* | *2 (2)* | *14 (5.5)* |
| Diarrhea – n (%)[1] | *10 (6)* | *1 (1)* | *11 (4)* |
| GERD/Gastritis – n (%) | 15 (8.5) | 1 (1) | 16 (6) |
| *Moderate – n (%)* | *4 (2)* | *0 (0)* | *4 (1.5)* |
| *Mild – n (%)* | *11 (6.5)* | *1 (1)* | *12 (4.5)* |
| Vomiting – n (%)[2] | 16 (9) | 1 (1) | 17 (6) |

| | | | |
|---|---|---|---|
| Nausea (only mild) – n (%) | 10 (6) | 4 (4) | 14 (5) |
| *Infections and infestations* | | | |
| Nasopharyngitis – n (%)[3] | 14 (8) | 8 (9) | 22 (8) |
| URTI (only mild) – n (%) | 9 (5) | 1 (1) | 10 (4) |
| Rhinitis – n (%) | 8 (5) | 2 (2) | 10 (4) |
| *Respiratory, thoracic and mediastinal disorders* | | | |
| Cough – n (%)[4] | 9 (5) | 3 (3) | 12 (5) |
| Oropharyngeal pain (only mild) – n (%) | 8 (5) | 4 (4) | 12 (5) |
| Pyrexia – n (%) | 13 (7) | 5 (6) | 18 (7) |
| Pain in extremity – n (%)[5] | 11 (6) | 5 (6) | 16 (6) |
| Rash (only mild) – n (%)[8] | 10 (6) | 1 (1) | 11 (4) |
| Alopecia – n (%) | 6 (3) | 0 (0) | 6 (2) |

Source: MEDICAL reviewer's analyses. URTI – Upper Respiratory Tract Infection, [1] Most diarrhea AR (>90%) were mild in severity, [2] Most vomiting AR (>90%) were mild in severity, [3] Most nasopharyngitis AR (>90%) were mild in severity, [4] Most cough AR (>90%) were mild in severity, [5] Most pain in extremity (>80%) are mild in severity.

Table 26 summarizes the bleeding ARs, with respective severity data for each AR. Table 27 summarizes the bleeding ARs, according to the 3 different age-group strata.

Table 26: Bleeding ARs by Severity in Trial 1160.106 (Safety Analysis Set)

| Bleeding Adverse Reactions (AR) | Dabigatran (n=176) | SOC (n=90) | Total (n=266) |
|---|---|---|---|
| Any bleeding event | 39 (22) | 21 (23) | 60 (23) |
| Severe – n (%) | 6 (3.5) | 2 (2) | 8 (3) |
| Moderate – n (%) | 7 (4) | 3 (3) | 10 (4) |
| Mild – (%) | 26 (15) | 16 (18) | 42 (16) |
| *Mucosal Bleed [1] – n (%)* | 10 (6) | 8 (9) | 18 (7) |
| Epistaxis[2] – n (%) | 8 (4.5) | 6 (7) | 14 (5) |
| Moderate – n (%) | 0 (0) | 1 (1) | 1 (0.5) |
| Mild – n (%) | 8 (4.5) | 5 (6) | 13 (4.5) |
| Minor cutaneous bleed[3] – *n (%)* | 10 (5.5) | 7 (8) | 17 (6) |
| Moderate – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |
| Mild – n (%) | 9 (5) | 7 (8) | 16 (5.5) |
| *GI Bleed [4] – n (%)* | 9 (5) | 1 (1) | 10 (4) |
| Severe – n (%) | 3 (1.5) | 1 (1) | 4 (1.5) |
| Mild – n (%) | 6 (3.5) | 0 (0) | 6 (2.5) |
| *GU bleed [5] – n (%)* | 6 (3.5) | 4 (4) | 10 (4) |
| Severe – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |
| Moderate – n (%) | 4 (2.5) | 2 (2) | 6 (2.5) |
| Mild – n (%) | 1 (0.5) | 2 (2) | 3 (1) |
| *Major cutaneous bleed [6] – n (%)* | 4 (2.5) | 3 (3) | 7 (3) |
| Severe – n (%) | 2 (1.5) | 0 (0) | 2 (1) |
| Moderate – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |
| Mild – n (%) | 1 (0.5) | 3 (3) | 4 (1.5) |
| Hematuria (only Moderate) – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |
| Cranial bleed (only severe) – n (%) | 1 (0.5) | 1 (1) | 2 (1) |
| Peritoneal bleed (only severe) – n (%) | 0 (0) | 1 (1) | 1 (0.5) |
| *Non-specific bleed [7] – n (%)* | 6 (3.5) | 3 (3) | 9 (3.5) |
| Severe – n (%) | 1 (0.5) | 0 (0) | 1 (0.5) |

| | | | |
|---|---|---|---|
| Mild – n (%) | 5 (3) | 3 (3) | 8 (3) |
| Adjudicated Major bleeding – n (%) | 5 (3) | 2 (2) | 7 (3) |
| Adjudicated CRNM bleeding – n (%) | 3 (1.5) | 1 (1) | 4 (1.5) |
| Adjudicated Minor bleeding – n (%) | 34 (19) | 21 (23) | 55 (21) |

Source: MEDICAL reviewer's analyses. [2] Epistaxis is the only bleeding adverse reaction that occurred at > or = 5% in treatment arm

Table 27: Bleeding ARs by Age Strata in Trial 1160.106 (Safety Analysis Set)

| Bleeding Adverse Reactions (AR) | Dabigatran (n=176) | SOC (n=90) | Total (n=266) |
|---|---|---|---|
| Any bleeds – n (%) | 39 (22) | 21 (23) | 60 (23) |
| Stratum 1 – n (%) | 27 (15) | 19 (21) | 46 (18) |
| Stratum 2 – n (%) | 7 (4) | 2 (2) | 9 (3) |
| Stratum 3 – n (%) | 5 (3) | 0 (0) | 5 (2) |
| *Mucosal Bleeds – n (%)* | 10 (5.5) | 8 (9) | 18 (7) |
| Stratum 1 – n (%) | 7 (3.5) | 8 (9) | 15 (6) |
| Stratum 2 – n (%) | 3 (2) | 0 (0) | 3 (1) |
| Stratum 3 – n (%) | 0 (0) | 0 (0) | 0 (0) |
| Cutaneous Bleeds – *n (%)* | 14 (8) | 10 (11) | 24 (9) |
| Stratum 1 – n (%) | 11 (6) | 8 (9) | 19 (7) |
| Stratum 2 – n (%) | 2 (1) | 2 (2) | 4 (2) |
| Stratum 3 – n (%) | 1 (1) | 0 (0) | 1 (0) |
| *GI Bleeds – n (%)* | 9 (5) | 1 (1) | 10 (4) |
| Stratum 1 – n (%) | 5 (3) | 1 (1) | 6 (2) |
| Stratum 2 – n (%) | 2 (1) | 0 (0) | 2 (1) |
| Stratum 3 – n (%) | 2 (1) | 0 (0) | 2 (1) |
| Other Bleeds[1] | 8 (5) | 5 (6) | 13 (5) |
| Stratum 1 – n (%) | 6 (4) | 5 (6) | 11 (4) |
| Stratum 2 – n (%) | 0 (0) | 0 (0) | 0 (0) |
| Stratum 3 – n (%) | 2 (1) | 0 (0) | 2 (1) |

Source: MEDICAL reviewer's analyses. [1] Other bleeds include non-specific bleeding, cranial bleeding, urinary bleeding and deep bleeding

Table 28 summarizes the bleeding AR in patients on the Pradaxa arm, categorized according to age-group stratum and formulation received, which also includes adjudicated data relating to major bleeding, CRNM bleeding and minor bleeding. This table allows for a side-by-side comparison of the rate of both non-adjudicated and adjudicated bleeding ARs, as a function of the patient's age-group and the formulation used.

Table 28: Bleeding ARs in Pradaxa Arm by Age Strata and Formulation in Trial 1160.106 (Safety Analysis Set)

| Bleeding AR in Pradaxa arm | Stratum 3 (n=22) | Oral Solution (n=14) | Stratum 2 (n=43) | Oral Pellet (n=41) | Stratum 1 (n=111) | Capsules (n=121) |
|---|---|---|---|---|---|---|
| Any bleeds – n (%) | 5 (23) | 4 (29) | 7 (16) | 6 (15) | 27 (24) | 29 (24) |
| *Mucosal Bleeds – n (%)* | 0 (0) | 0 (0) | 3 (7) | 3 (7) | 7 (6) | 8 (7) |
| Cutaneous Bleeds – *n (%)* | 1 (5) | 1 (7) | 2 (5) | 1 (2) | 11 (9) | 11 (9) |
| *GI Bleeds – n (%)* | 2 (9) | 1 (7) | 2 (5) | 2 (5) | 5 (5) | 6 (5) |
| Other Bleeds[1] | 2 (9) | 2 (14) | 0 (0) | 0 (0) | 6 (6) | 6 (5) |
| Serious bleeding AEs | 2 (9) | 2 (14) | 1 (2) | 0 (0) | 4 (4) | 5 (4) |
| Major bleeding – n (%) | 1 (5) | 1 (7) | 1 (2) | 0 (0) | 2 (2) | 3 (3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| CRNM bleeding – n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (2) | 2 (2) |
| Minor bleeding – n (%) | 5 (23) | 4 (29) | 7 (2) | 6 (15) | 21 (19) | 23 (19) |

Source: MEDICAL reviewer's analyses. [1] Other bleeds include non-specific bleeding, cranial bleeding, urinary bleeding and deep bleeding

*Trial 1160.108:*

In the safety population dataset, there was a total number of 863 TEAEs, of which 687 (80%) were mild, 153 (17%) were moderate and 23 (3%) were severe. A total of 165 patients (78%) experienced at least one TEAE, with 129 patients (80%) in stratum 1, 28 patients (65%) in stratum 2 and 8 patients (90%) in stratum 3. A total of 14 patients (7%) experienced ≥ 1 severe TEAE. There were 46 patients (22%) with at least 1 ARs that were determined to be related to trial medication by the investigator, with the most frequent ARs being dyspepsia/gastritis (14 patients [7%]), epistaxis (7 patients [3.5%]) and abdominal pain (7 patients [3.5%]).

AEs that occurred in ≥ 5% of patients on Pradaxa were considered significant for our safety analysis, with bleeding ARs being the only exception. Table 29 summarizes the significant non-bleeding and bleeding AEs from the safety population dataset. Overall, similar rates were observed, when compared to AE rates of patients in the Pradaxa arm in trial 1160.106. The Applicant determined that the probability of being free from any bleeding events over the entire 12-month treatment period was lower for stratum 1 (0.691, 95%CI 0.603-0.763) than for stratum 2 (0.831 95%CI 0.592-0.936) and stratum 3 (0.889 95%CI 0.433-0984), with a gradual decrease in probability over the treatment period.

Sensitivity analysis, considering the full follow-up period and the entered set, showed similar number of events and probability results. In addition, demographic sub-group analyses of bleeding showed that the percentage of patients with minor bleeding during the on-treatment period was greater in female than in male patients within the first 12 months (26.0% vs. 16.2%), which was mainly due to urogenital/vaginal/menstrual bleeding. Overall, since trial 1160.108 was uncontrolled and given the small sample size of the younger age strata, we cannot determine the significance of these findings.

Table 29: Non-Bleed and Bleed AEs in Trial 1160.108 (Safety Analysis Set)

| On-Treatment AEs | Pradaxa (n=213) |
|---|---|
| Non-bleeding AEs | |
| Headache – n (%) | 35 (16.5) |
| *Gastrointestinal disorders* | |
| Abdominal pain – n (%) | 23 (11) |
| Diarrhea – n (%) | 15 (7) |
| Dyspepsia – n (%) | 15 (7) |
| Nausea – n (%) | 15 (7) |
| Vomiting – n (%) | 15 (7) |
| *Infections and infestations* | |
| Nasopharyngitis – n (%) | 34 (16) |
| URTI – n (%) | 14 (6.6) |
| *Respiratory, thoracic and mediastinal disorders* | |
| Cough – n (%) | 14 (6.5) |
| Oropharyngeal pain – n (%) | 10 (5) |
| Pyrexia – n (%) | 15 (7) |
| Pain in extremity – n (%) | 24 (11.5) |

| | |
|---|---|
| Alopecia – n (%) | 11 (5.5) |
| Bleeding AEs | |
| Any bleeding event – n (%) | 48 (23) |
| Epistaxis – n (%) | 14 (6.5) |
| Cutaneous – n (%) | 19 (8.5) |
| GI bleed – n (%) | 4 (2) |
| GU bleed – n (%) | 7 (3.5) |
| Adjudicated Major bleeding within 12 months – n (%)[1] | 3 (1.5) |
| Adjudicated CRNM bleeding within 12 months – n (%)[2] | 3 (1.5) |
| Adjudicated Minor bleeding within 12 months – n (%) | 44 (21) |

Source: MEDICAL reviewer's analyses. URTI – Upper Respiratory Tract Infection, [1] Major bleeding included post-operative bleed, hemoptysis due to lung infarction and vascular malformation-associated external bleed, [2] CRNM bleeding included skin laceration bleed, Hematochezia and rectal bleed.

The evaluation of VTE recurrence, occurrence of PTS, VTE-related deaths and all-cause mortality at 6 and 12 months was considered as a safety analysis since these endpoints were defined as primary safety endpoints for trial 1160.108. VTE-related deaths and all-cause mortality were discussed in section 8.4.1. VTE recurrence occurred in 11 patients (5.1%), 9 patients (5.6%) in stratum 1 and 2 patients (4.7%) in stratum 2, with a 12-months probability of being free from VTE recurrence of 0.938 (95%CI 0.890-0.966). Newly diagnosed PTS or worsening of existing PTS occurred in 4 patients (2%), 3 patients (1.5%) in stratum 1 and 1 patient (0.5%) in stratum 2, all presenting by the 6-month timepoint, with a 6-month probability of being free from PTS of 0.980 (95%CI 0.949-0.993).

*Medical reviewer comment:*
*Our safety evaluation was mainly based on safety data from trial 1160.106, which was supported by safety data from 1160.108, which found similar results of both non-bleeding and bleeding events, when compared to the rates obtained from the Pradaxa arm. The VTE recurrence rate and PTS rate obtained from trial 1160.108 was also comparable to the historical pediatric rate quoted in the literature.*

*Overall, we observed a higher proportion of TEAE in the Pradaxa arm, with ~75% of the 199 moderate-severe TEAE occurring in the Pradaxa arm. However, the proportion of patients with at least 1 severe TEAE is similar between the two arms, indicating the patients on Pradaxa who experience at least one TEAE are at higher likelihood to have > 1 TEAE, compared to patients on the SoC arm. Even though the investigator-reported relatedness of the AE to the drug signals a higher prevalence of AR in the SoC arm, our detailed review of the AETERMs and their clinical relevance indicates a drastic underestimation of investigator-reported relatedness. As a result, we determined relatedness to drug therapy independently and used this determination in our safety analysis.*

*In addition, the reported rates for AR and their severities were comparable between treatment arms and were similar to rates obtained from adult trials with Pradaxa. However, there were three ARs that were important to note:*

- *<u>GI-related ARs:</u> There is a higher proportion of patients who experienced GI-related ARs in the Pradaxa arm compared to the SoC arm, with consistently higher rates of abdominal pain, diarrhea, GERD/Gastritis symptoms and vomiting. Specifically, the rate of these ARs are 3-9x higher compared to rates in the SoC arm, with all patients with moderate-severe GI-related ARs present in the Pradaxa arm. It is important to note that GI-related ARs have resulted in cases of dose*

*interruption and drug discontinuation in patients on Pradaxa.*

- *GI Bleed ARs: There is a higher rate of GI bleed ARs in the Pradaxa arm, which tends to be recurrent (1 patient having 3 GI bleed events and 4 patients having 2 GI bleeds events, with the majority not leading to discontinuation but frequent interruptions) and has a higher rate in younger pediatric patients.*
- *Alopecia: there was 6 patients who experienced alopecia on the Pradaxa arm vs. no patients on the SoC arm. Alopecia was reported as a significant post-marketing safety signal in adults and has been added to the USPI. When reviewing the narrative for patients who experienced alopecia on the trial, we could not find any alternative explanation for the alopecia. The majority of patients were female (F:M = 5:1) and adolescents (one patient was 1.25 year, with the rest being > 12 years old). All patients reported mild symptoms, compliance was not affected by the alopecia and 2 patients reported recovery vs. 2 patients reported no recovery, after stopping Pradaxa. Given the mild nature of the alopecia and since it was previously reported in the post-marketing experience, no further mitigation is necessary.*

*The overall rate of all other types of bleeding ARs, including all severity groups, major bleeding and CRNM bleeding, was comparable between the two treatment arms. To ensure lack of confounders, the rate of Bleeding-related concomitant medication and traumatic injury during on-treatment period was analyzed between the two treatment arms and no significant difference was observed.*

*In relation to Pradaxa-related bleeding rate and age strata, there is a trend towards higher rates of serious and major bleeding in younger patients, with higher rates also observed in patients receiving oral solution. This trend may be explained by multiple factors unique to this age group such as developmental hemostasis and the higher prevalence of complex medical conditions that predisposes to other risk factors for bleeding complications. Conclusions concerning this trend cannot be reached and must be evaluated in future studies.*

*To avoid out-of-target drug concentrations that can result in unnecessary AE risk, the Agency has recommended population PK-guided starting dose modification and drug monitoring dose titration to be implemented to the final approved USPI. In addition, to ameliorate the risk of GI-related ARs and GI bleed ARs, the Agency has also recommended administration with food if such ARs occur, as this will not impact absorption of Pradaxa.*

### 8.4.6. Laboratory Findings

*Trial 1160.106:*
There were no significant changes in the mean values of hematological parameters from baseline to end of treatment. The proportion of patients who had hemoglobin (8.1% in the Pradaxa arm vs. 8.6% in the SoC arm) and white blood cell count (6.7% in the Pradaxa arm vs. 7.0% in the SoC arm) below lower limit of normal at any point during the trial was comparable between the two arms.

There were no significant changes in the mean values of biochemistry parameters (including electrolytes, glucose, liver function testing and renal function testing) from baseline to end of treatment. The proportion of patients who had ALT (5.9% in the Pradaxa arm vs. 6.1% in the SoC arm) and AST (3.0% in the Pradaxa arm vs. 6.1% in the SoC arm) above ULN at any point during the trial was comparable between

the two arms. No patients satisfied the protocol-specified AESI definition for hepatic injury. Two patients satisfied the protocol-specified AESI definition for renal dysfunction; one patient (0.5%) in the Pradaxa arm and one patient (1%) in the SoC arm, both resolving after 2 weeks without intervention or discontinuation of trial medication. For discussion of eGFR measurement and impact on trial-related activity, please refer to section 8.4.3.

*Trial 1160.108:*
There were minor non-significant changes in the mean values of hematological parameters from baseline to end of treatment. The proportion of patients who had hemoglobin and white blood cell count below lower limit of normal at any point during the trial were 7% and 6.3%, respectively.

There were minor non-significant changes in the mean values of biochemistry parameters (including electrolytes, glucose, liver function testing and renal function testing) from baseline to end of treatment. The proportion of patients who had ALT, AST and total bilirubin above ULN at any point during the trial were 2.5%, 4.8% and 2.6%, respectively. The majority of these patients has an alternative explanation for the mild elevation in liver function testing. Only one patient (0.5%) satisfied the protocol-specified AESI definition for hepatic injury secondary to receiving concomitant methotrexate and mercaptopurine for the maintenance chemotherapeutic treatment of acute lymphoblastic leukemia. The abnormal liver function tests resolved after 1 week without intervention or discontinuation of trial medication No patients satisfied the protocol-specified AESI definition for renal dysfunction. For discussion of eGFR measurement and impact on trial-related activity, please refer to section 8.4.3.

### 8.4.7. Vital Signs

Analysis of vital signs collected from baseline to end of study did not identify any clinically significant mean changes in any parameter, including systolic blood pressure, pulse, respiration, and temperature from baseline to scheduled assessments.

### 8.4.8. Electrocardiograms (ECGs)

There is sufficient adult data demonstrating that Pradaxa does not have a risk of QT prolongation. However, ECG evaluation was conducted at screening, visit 8 and eEOT during trial 1160.106, and at screening, visit 8, visit 11 and eEOT during trial 1160.108. There were no reported significant findings in trial 1160.106. Significant findings were found in two patients in trial 1160.108 (atrial flutter and ventricular pre-excitation) but these findings were unrelated to trial medication and did not impact any of the trial-related activities.

## 8.5. Analysis of Submission-Specific Safety Issues

There were no specific safety issues unique to this application.

## 8.6. Safety Analyses by Demographic Subgroups

Analysis of the TEAEs by gender or race/ethnicity did not show any meaningful differences in overall frequency of TEAE, SAEs or severe events. However, analysis by age group did show a trend for higher

rates of GI disturbances and GI bleeds for younger age groups in the Pradaxa arm, compared to the SoC arm, in trial 1160.106. Please refer to section 8.4.2 and 8.4.5 for detailed discussion of this observation.

## 8.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies submitted as part of this application.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

Assessment of the human carcinogenic effect of Pradaxa was not specifically evaluated in the submitted trials. However, there is no known biological mechanism supporting any concern for the potential human carcinogenic effect of Pradaxa in children. Given that malignancy is a strong risk factor for VTE in pediatric patients, 22 patients with history of malignancy (19 in the Pradaxa arm vs. 3 in the SoC arm) were enrolled in trial 1160.106 and 16 patients were enrolled in trial 1160.108. However, there were no observed treatment-related events of tumor development or progression in the submitted trials. Once approved, routine post-market surveillance will be sufficient to detect any potential impact on tumor development, if present.

### 8.8.2. Human Reproduction and Pregnancy

Pregnancy occurred in 1 patient (0.5%), which was detected early in the first trimester with an approximate maximum exposure duration of 4 weeks. The patient delivered a healthy normal male newborn at 38 weeks gestation, with no reported complications. Otherwise, there are limited available data on the use of Pradaxa in pregnant women, thus insufficient to determine drug-associated risks for adverse developmental outcomes.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

Assessment of effect of Pradaxa on growth was not specifically evaluated in the submitted trials. However, there is no known biological mechanism supporting any concern for the potential impact of Pradaxa on growth in children. In addition, there were no observed impact of Pradaxa on growth in the submitted trials. Once approved, routine post-market surveillance will be sufficient to detect any potential impact on growth, if present.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was one case of accidental overdose of Pradaxa in a patient enrolled in trial 1160.108 (0.5%). It was determined to be mild, non-serious without any associated adverse events. As a result, overdose may occur due to medication error, but it is very infrequent. In addition, accidental overdose is also possible if the patient lives in a household with younger children. To help address the potential life-threatening events associated with an overdose of Pradaxa in children, idarucizumab is being studied as a reversal agent for Pradaxa in children in an on-going phase 3 trial and has been used in emergency situations, as per the published literature.

### 8.9. Safety in the Post-market Setting

#### 8.9.1. Safety Concerns Identified Through Post-Market Experience

At this time, Pradaxa is not approved for use in pediatric patients in any part of the world. As a result, there were no identified safety concerns through post-market experience at this time. However, there were two safety concerns that arose from the adult experience in the post-market setting:

- Increase risk of recurrent thrombosis in patients with APS. As a result, Pradaxa is not recommended for use in these patients. It is important to note the only patient with a recurrent VTE that lead to a VTE-related death in the trial 1160.108 had APS. This warning will also apply to pediatric patients.
- Alopecia was added as a post-marketing AE secondary to detection in adults at a rate of 0.6%. However, it has been reported at a much higher rate of 3-5.5% in pediatric trials. However, given its mild severity and potential reversibility after stopping medication, we recommend continual post-marketing surveillance to detect any changes that will affects the benefit-risk ratio.

## 9. Advisory Committee Meeting and Other External Consultations

An advisory committee was not convened for this application because the Division has experience with the drug under review, other drugs in the class, and selected endpoints used in the trials. In addition, the application did not raise significant public health questions on the role of Pradaxa in the diagnosis, cure, mitigation, treatment, or prevention of a disease. Overall, the review of the application was consistent with the results obtained from clinical trials involving the use of Pradaxa in adults, without any significant concerns affecting the approvability of Pradaxa for the acute treatment and secondary prevention of VTE in the pediatric population.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

The Applicant submitted (b) (4) different USPIs; one for capsules, one for oral pellets (b) (4) During the review, the review team requested that the Applicant combine all of the labeling into one document, since much of the information in the various sections are consistent, and to streamline future revisions by avoiding editing of multiple documents. The Applicant declined to do this. Therefore, the Division proceeded with work on separate documents for each dosage form. This review will focus upon the capsules labeling as it pertains to NDA 22512 S041.

High level summary of Agency edits to each labeling section:

| *Summary of Significant Labeling Changes (High level changes and not direct quotations)* | |
|---|---|
| Section | Proposed Labeling Changes |
| Throughout the USPI | The Applicant proposed no new proprietary name for the new dosage forms, so that Pradaxa is now associated with all three dosage forms. Therefore, using the name "Pradaxa" alone is not appropriate if the information is only specific to one dosage form. Throughout the labeling, the term "capsule" has been added where necessary.<br><br>The terms "Deep Venous Thrombosis and Pulmonary Embolism" were revised to "Venous Thromboembolism" in all sections of labeling for simplicity. |
| Highlights | Revised for brevity, clarity, and to be consistent with changes made to the full prescribing information (FPI).<br><br>The Applicant proposed in Adverse Reactions, to state that (b) (4) We deleted that text and simply removed "adults" from the existing sentence, since the events were similar.<br><br>To the Dosage and Administration subsection, we added "Pradaxa capsules are not substitutable on a milligram-to-milligram basis with other dabigatran etexilate products" because there are PK differences between the capsules and other formulations.<br><br>Updated 'Recent Major Changes' to include Indications and Usage and Dosage and Administration. No significant changes to the sections relevant to RMCs were made. |
| Indications and Usage (1) | We added age groups to the indication statements per the 'Indications and Usage Section of Labeling Guidance'.<br><br>Since the adult indications for VTE treatment and reduction in risk of recurrence are nearly identical for adult and pediatric patients, we determined that the adult and pediatric indications should be combined. Therefore, 1.5 and 1.6 were deleted and 1.2 and 1.3 were specified as "adult and pediatric patients 8 years of age and older". |

| | |
|---|---|
| | The pediatric indications had noted "who have been treated with a parenteral anticoagulant for at least 5 days" while the adult indications stated "at least 5-10 days". The resulting indication leaves "at least 5-10 days", which covers both adult and pediatric patients. |
| Dosage and Administration (3) | We added section 2.1 "Important Dosage Information" to call attention to the availability of different dosage forms. A similar approach has been used for other products with available pediatric dosage forms (e.g., Afinitor and Afinitor Disperz).<br><br>Section 2.3 was added to describe the dosage for Pediatrics. We added an Administration subsection.<br><br>We added that actual weight was to be used for the weight-based dosing.<br><br>The labeling describes dosing as "twice daily". In clinical practice, "twice daily" has been defined as either 10a & 6p, or every 12 hours. We checked the protocol for the adult trials and no clarity was provided regarding when the doses were received. Therefore, we opted not to define the "twice daily" for adults. In the pediatric trials, the capsules were recommended to be taken as "one dose in the morning and one dose in the evening, at approximately the same time every day", so we recommend these instructions for dosing.<br><br>We limited the age range for the capsules to 8 years and older because this is the approximate age when children should be able to swallow capsules.<br><br>We removed the age cohorts from Table 1 as the dosing only changes with body weight.<br><br>We added language to describe avoidance of use in patients with impaired renal function.<br><br>We added text recommending that in pediatric patients, dTT is measured as a trough level prior to the 7th dose of any new dose amount to determine dabigatran concentration at steady state, and to titrate the dose to reach target dabigatran trough levels between 50 and 250 ng/ml, per the table below (table is being drafted by Clinical Pharmacology at this time).<br><br>We added a recommendation to administer with food if stomach upset occurs. |
| Contraindications (4) | We replaced "Pradaxa" with "dabigatran" because this section should list the active ingredient. |
| Adverse Reactions (6) | We added a "Pediatric Trials" subsection in which we described the safety database per the Adverse Reactions Section of Labeling Guidance. |
| Use in Specific Populations, Pediatric Use (8.4) | We revised this to be consistent with the Pediatric labeling guidance. We defined the populations for which Pradaxa was approved and described the basis of approval in pediatric patients. We added a statement that Pradaxa was not approved for the treatment of pediatric patients with non-valvular atrial fibrillation or those after hip replacement surgery. |
| Clinical Studies (14) | We revised subsection 14.4 to be consistent with our current approach. We removed text such as "primary endpoint" and instead described what efficacy was based upon. |

## 11. Risk Evaluation and Mitigation Strategies (REMS)

After completion of our safety review, we have not identified any potential safety issues that necessitate the application of REMS to the pediatric population that will be affected by the new indications. Even though our review has concluded the need for monitoring to guide titration of Pradaxa in pediatric patients, we believe that information included in the USPI is sufficient to guide the clinicians in the appropriate dosing of Pradaxa to avoid potential treatment failure and/or drug-related AEs such as bleeding and gastrointestinal disturbance.

## 12. Postmarketing Requirements and Commitments

PMR 2139-2 was fulfilled by submission of the study report for study 1160.106 titled "Open-label, randomized, parallel-group, active-controlled, multi-center, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study"

PMR 2139-3 was fulfilled by submission of the study report for study 1160.108 titled "Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years".

There were no new safety signals that would indicate the need for any new post-marketing requirements or post-marketing commitments.

# 13. Appendices

## 13.1. References

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## 13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Trial 1160.106

| | | |
|---|---|---|
| Was a list of clinical investigators provided? | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 393 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements? | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided? | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason? | Yes ☐ | No ☒ (since N/A) |

Covered Clinical Study (Name and/or Number): Trial 1160.108

| | | |
|---|---|---|
| Was a list of clinical investigators provided? | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 347 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in Sponsor of covered study: 0 | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements? | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided? | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason? | Yes ☐ | No ☒ (since N/A) |

## 13.3 Description of Splitting/Grouping using MedDRA Preferred Terms

*Specific list of medications used during the analysis for relevant CM for trial 1160.106*

- Contraceptives = Azalia, Diecyclen, Dienelle, Ebelya, Gravistat, Jangee, Katya, Linessa, Lo loestrin, Luisea, Marvelon, Maxim, Mononessa, Norethindrone, Norethisteron, Ocella, Ortho tri-cyclen, Proluton, Sprintec, Sunya, Synphasic and Yaz
- Medications associated with a bleeding risk = Nurofen / Brufen, Acetylsalicylic acid / Aspirin, Advil, Antithrombin III, Deksketoprofen, Detralex, Diclofenac, Etamsylate, Ibalgin, Ibuprofen / Ibuprofenum / Ibuprophenum, Ipren, Ketorolac, Migralgin, Numesulide, Nimulid, Pentasa, Pentoxifylline, Pepto-bismol, Stacyl and Trental

*Specific list of medical history terms used during the analysis for relevant MH for trial 1160.106*

- SVP CHD = Aortic hypoplasia, Aortic stenosis, Aortic aplasia, Bicuspid aortic valve, Balloon valvoplasty, Condition after Glenn & other complex procedures, Double outlet right ventricle and Double inlet left ventricle.
- Non-SVP cyanotic CHD = Aortic arch plasty, Aortic coarctation, Aortic insufficiency, Atrial septal defect (ASD) with total anomalous pulmonary venous return, ASD with right atrial dilation and pulmonary stenosis, Pulmonary artery (PA) banding, Interrupted arch/subvalvular aortic stenosis/ventricular septal defect (VSD), Transposition of the great vessels, Atrioventricular canal defect, PA atresia, PA stenosis and Tetralogy of Fallot.
- Other CHD = ASD/VSD/patent ductus arteriosus (PDA), ASD, ASD with right heart failure, ASD/PDA and mitral insufficiency, ASD/VSD/PDA/extra SVC, CHD, Dilation of right atrium/right. ventricle/aorta/left atrium/left ventricle, Mitral disease and Tricuspid disease.
- Arrythmia = Atrioventricular heart block and cardiac pacemaker.
- Malignancy:
  - Leukemia = Acute lymphoblastic leukemia (ALL), Acute myeloblastic leukemia (AML) and Hematologic malignancy.
  - Lymphoma = Burkitt lymphoma, Diffuse large B-cell lymphoma, Hodgkin lymphoma and Non-Hodgkin T-cell lymphoma.
  - Solid tumors = Wilms tumor, Adenocarcinoma of the lung, Astrocytoma, Osteosarcoma, Desmoid-type fibromatosis, Inguinal tumor, Nephroblastoma, Oothecoma, Osteochrondromatosis, Embryonal rhabdomyosarcoma, Glioma and Teratoma.
- Thrombophilia = Anti-thrombin 3 deficiency, Low protein C, Protein S deficiency, Factor V lieden, Pro-thrombin mutation, Homocysteinemia, APS and positive Lupus anticoagulant.
- Vascular VTE risk factors = Absence of right distal inferior vena cava, arteriovenous malformation, Klippel-Tranaunay-Weber syndrome, Hemihypertrophy, May Thurner syndrome, Paget Shroetter syndrome and venous malformation.
- Serious infection = Abdominal tuberculosis, Abscess, Acute bronchitis, Acute orbito-cellulitis, Adenomyosis, Bronchopneumonia, Cellulitis, Chronic sinusitis, Congenital, pneumonia, Endocarditis, Epidural abscess, Erysipelas, Fungal infection, Fusobacterium, CVC-associated infection,

Pyelonephritis, Osteomyelitis, Mastoiditis, Bacteremia, Myositis, Omphalitis, Sepsis, Toxic shock syndrome and Viral encephalitis.

- Stroke = Acute cerebrovascular accident, Cerebral ischemia, Hypoxic-ischemic encephalopathy, Hypoxemic syndrome and Ischemic spinal stroke.
- Protein-losing pathology = Chylothorax, Moderate protein-calorie malnutrition and Nephrotic syndrome.
- Immobility = Bilateral lower paraplegia, Cerebral palsy and Muscular hypotonia.
- Autoimmune disease = Autoinflammatory disease, Juvenile idiopathic arthritis, Systemic lupus erythromatosis and Ulcerative colitis.

*MedDRA PT splitting and grouping for AE evaluation in safety population for trial 1160.106*

- GI bleed = Rectal hemorrhage, Intestinal hemorrhage, Gastrointestinal hemorrhage, Anal fissure hemorrhage, Hematochezia and Proctitis hemorrhagic.
- Minor cutaneous bleed = Contusion, Petechiae, Ecchymosis, Vessel puncture site bruise and Injection site bruising.
- Major cutaneous bleed = Injection site hemorrhage, Vessel puncture site hematoma, Application site hematoma, Procedural hemorrhage, Subcutaneous hematoma and Stoma site hemorrhage.
- Mucosal bleed = Mouth hemorrhage, Bleeding traumatic lesions inner legion of cheeks - Mouth injury, Gingival bleeding, Ear hemorrhage and Epistaxis.
- GU bleed = Menorrhagia and Uterine hemorrhage.
- Cranial bleed = Hemorrhage intracranial and Hemorrhagic infarction.
- Non-specific bleed = Traumatic hemorrhage, Hemorrhage, Coagulopathy and Hematoma.
- Renal Abnormality = Glomerular filtration rate decreased, Blood creatinine increased, Blood urea increased, Hyperuricemia, Blood uric acid increased, Oliguria, Renal impairment and Renal failure
- Liver Abnormality = Aspartate aminotransferase increased, Alanine aminotransferase increased, Hepatocellular injury, Hepatic encephalopathy, Blood bilirubin unconjugated increased, Transaminases increased, and Blood bilirubin increased.
- Traumatic Injury = Nasal injury, Skin Injury, Skin laceration, Skin abrasion, Head injury, Joint injury, Ligament sprain, Foot fracture, Fall, Road traffic accident, Lower limb fracture, Multiple injuries, Meniscus injury, Ligament rupture, Craniocerebral injury, Limb injury and Joint dislocation.
- Allergic Rash = Dermatitis allergic, Urticaria, and Allergic skin reaction - medication / drug hypersensitivity.
- Rash = Rash, erythema, Catheter site erythema and Injection site rash.
- Respiratory tract infection viral = Rhinitis, Respiratory tract infection viral, Nasopharyngitis, Influenza, Influenza like illness, Upper respiratory tract infection, Nasal congestion, Rhinorrhea, Rhinovirus infection, Pneumonia viral, Viral rhinitis, Viral upper respiratory tract infection.
- CardioResp Failure = Cardiopulmonary failure, Acute respiratory distress syndrome, Acute respiratory failure, Cardiac arrest, Cardiac failure and Respiratory failure
- Chest pain = Chest discomfort
- Pharyngeal erythema = Erythematous throat / Erythema
- Abdominal Pain = Abdominal discomfort, Abdominal pain lower and Abdominal pain upper.

- GERD/Gastritis = Gastroesophageal reflux disease, Chronic gastritis, Dyspepsia, Gastric pH decreased and Esophagitis.
- Decreased appetite = Appetite disorder and Hypophagia.
- Headache = Headache and tension headache
- Anemia = Hemoglobin decreased, hematocrit decreased, Blood loss anemia, iron deficiency, iron deficiency anemia and Red blood cell count decreased.
- Thrombosis = Pulmonary embolism, Deep vein thrombosis, Embolism venous, Thrombosis, Pelvic venous thrombosis, Renal vein thrombosis and Venous thrombosis.
- Non-specific Thrombosis = Device occlusion, Hypercoagulation, Implant site necrosis, Thrombophlebitis and Thrombophlebitis superficial.

*MedDRA PT for SOC terms used for SAEs in safety population for trial 1160.106*

- Infections and Infestations SOC term: Erysipelas, Gastroenteritis, Gastroenteritis rotavirus, Mastoiditis, Meningitis herpes, Osteomyelitis, Periodontitis, Pharyngitis streptococcal, Respiratory tract infection, Sepsis, Septic shock, Staphylococcal sepsis and Wound sepsis.
- Gastrointestinal disorders SOC term: Pancreatitis chronic, Abdominal pain and Hemorrhoids.
- Blood and lymphatic system disorders SOC term: Febrile neutropenia, Pancytopenia, Sickle cell anemia with crises and Thrombocytopenia.
- Metabolic and nutrition disorders SOC term: Diabetic ketoacidosis, Dehydration, Hyperglycemia, Hypoalbuminemia and Hypoproteinemia.
- Respiratory, thoracic and mediastinal disorders SOC term: Respiratory failure, Acute respiratory failure, Acute respiratory distress syndrome, Asthmatic crisis, Dyspnea and Tachypnea.
- Nervous system disorders SOC term: Headache, Hydrocephalus and Hepatic encephalopathy.
- Cardiac and Vascular disorders SOC terms: Cardiac arrest, Cardiopulmonary failure, Cardiac failure, Tachycardia, Shock and Takayasu's arteritis.

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