IND 063267

WRITTEN REQUEST – AMENDMENT 1

Boehringer Ingelheim Pharmaceuticals Inc.
Attention: Charles R. Mazzarella
Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877-0368

Dear Mr. Mazzarella:[1]

Please refer to your correspondence dated March 15, 2019, from Boehringer Ingelheim (BI), requesting changes to FDA's January 25, 2019, Written Request for pediatric studies for PRADAXA® (dabigatran etexilate mesylate).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. These amendments are clarifying the requirements for the number of patients less than 2 year of age in the studies. All other terms stated in our Written Request issued on January 25, 2019 remain the same (Text added is underlined. Text deleted is strikethrough).

BACKGROUND:

These studies will investigate the potential use of dabigatran etexilate mesylate in the treatment and prophylaxis of venous thromboembolism in pediatric patients.

Venous thromboembolism (VTE) is now recognized in the pediatric population as a complication of improved treatment strategies for previously lethal childhood diseases. The overall annual incidence rate of VTE in children is approximately 0.07 to 0.14 events per 10,000 children. The most common etiologic factor for VTE in children is the presence of central venous lines; other etiologic factors include thrombophilia, surgery, trauma or malignancy. The current guidelines recommendations for pediatric VTE is largely based on case series, cohort studies or extrapolated from adult VTE treatment experience.

Approved treatment and prophylaxis of pediatric thromboembolism (TE) is an important yet unmet public health need. TE occurs in children of all groups, including neonates. An increase in the rate of TE in children has been observed over the last 6-8 years, most likely due to better survival of acutely ill patients and increased use of central venous access devices (CVAD). In contrast to adults, idiopathic TE in children is rare.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Notable risk factors for TE in children include malignancy, CVAD use, congenital heart disease, infection, surgery, and inflammatory disease.

As studies of anticoagulation in children that are fully powered for safety and efficacy have feasibility challenges and some aspects of VTE pathophysiology are comparable between adults and children, the Food and Drug Administration (FDA) supports partial extrapolation of efficacy data from adult patients treated with dabigatran. However, as the coagulation system in children matures with age, and the cause of VTE differ between adults and children, partial extrapolation must be supported by an adequate PK and PD bridge to determine the appropriate dose, as well as sufficient safety and efficacy data to screen for large discrepancies in these endpoints between adults and children that could be caused by differences in underlying coagulation system maturity or VTE pathophysiology. As children of all ages, including neonates, experience VTE, studies of anticoagulants used as treatment for pediatric TE should be conducted in children from birth through late adolescence.

To obtain needed pediatric information on dabigatran etexilate mesylate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

  - *Study 1 (Study Number 1160.106, DIVERSITY Study*):
    A phase IIb/III, active-controlled, open-label, randomized, parallel-group study of dabigatran versus standard of care (SOC) in pediatric patients with venous thromboembolism. The study will evaluate dabigatran in children from birth to less than 18 years of age. The study will enroll a minimum of 240 children diagnosed with acute venous thromboembolism who have completed an initial parenteral treatment with an unfractionated or a low-molecular weight heparin for a minimum of 5 to 7 days who require continued anticoagulation for at least 3 months. Patients are randomly assigned to either dabigatran etexilate or standard of care on a 2:1 ratio.

  - *Study 2 (Study Number 1160.108):*
    A phase IIb/III, open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of pediatric patients with venous thromboembolism from 0 to less than 18 years of age and will enroll a

minimum of 200 patients. Patients who were diagnosed with acute venous thromboembolism who have either completed an initial course of anticoagulation (for at least 3 months) or completed the 1160.106 study treatment and require anticoagulation for secondary prevention of venous thromboembolism due to the presence of a persistent (unresolved) clinical factor with be enrolled in the study. Duration of treatment will be until clinical risk factor is resolved and up to 12 months.

- *Objective of each study:*

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):*
    The primary objective is to assess the efficacy and safety of dabigatran etexilate relative to standard of care and to document the appropriateness of the proposed dabigatran etexilate dosing algorithm for use in patients from birth to less than 18 years of age. An additional objective is to evaluate the appropriateness of the dosing nomogram to achieve trough plasma concentrations in the range of 50-250 ng/ml.

  - *Study 2 (Study Number 1160.108):*
    The primary objective is to assess the safety of dabigatran etexilate used for secondary prevention of venous thromboembolism in children from 0 to less than 18 years of age. Determining the appropriate trough plasma concentration (50-250 ng/ml) is an additional objective in this study.

- *Patients to be Studied:*

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):*
    - *Age group in which study will be performed:* Patients with venous thromboembolism ages birth to <18 years of age. The following 3 age groups and number of patients will be studied:
      - 0 to < 2 years: See below ~~At least 15 patients must be enrolled; at least 6 patients aged < 6 months enrolled into this study~~
      - 2 to < 12 years: At least 40 patients must be enrolled
      - 12 to < 18 years: At least 120 patients will be enrolled in this stratum ~~The remaining patients will be enrolled in this stratum~~
    - *Total* ~~N~~*number of patients to be studied:* At least 240 patients ~~for a minimum of 3 months; there will be at least 6 patients aged < 6 months enrolled into this study~~

  - *Study 2 (Study Number 1160.108):*
    - *Age group in which study will be performed:* Patients with venous thromboembolism ages 0 to <18 years of age. The following 3 age groups and number of patients will be studied:
      - 0 to < 2 years: See below ~~At least 15 patients must be enrolled; at least 6 patients aged < 6 months enrolled into this study~~

- 2 to < 12 years: At least 25 patients must be enrolled
- 12 to < 18 years: At least 110 patients will be enrolled in this stratum. ~~The remaining will enroll in this stratum.~~

o *Total ~~N~~number of patients to be studied:* At least 200 patients. ~~for a minimum of 3 months; there will be at least 6 patients aged < 6 months enrolled into this study~~

- *Study 1 and 2 Combined:*
  - *0 to < 2 years: At least 15 unique patients must be enrolled. Of those at least 6 patients must be aged < 6 months*
  - *At least 200 unique pediatric patients of any age treated for at least 12 weeks*

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):*
    - *Primary Efficacy Endpoint:*
      The combined efficacy endpoints are the proportion of patients with:
      - Complete thrombus resolution and;
      - Freedom from recurrent venous thromboembolism event (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism, thrombus progression) and;
      - Freedom from mortality related to venous thromboembolism event

    - *Secondary endpoints:*
      - Freedom from major bleeding events (MBEs), 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 is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system, or bleeding that requires intervention in an operating suite.
      - Frequency of dose adjustments, temporary and permanent discontinuation from therapy and number of laboratory monitoring requirements for dose adjustment during the treatment phase
      - Frequency of switch of type of anti-coagulation therapy (to standard of care treatment) and a switch from an intended standard of care treatment to another

- Freedom from thrombus progression at the end of therapy (EOT) (day 84 after randomization or early EOT which is planned for early discontinued patients, whichever comes first) compared to baseline
- Assessment of the acceptability of an age-appropriate formulation at the end of therapy
- All bleeding events
- All-cause mortality

o *PK/PD Assessments:*
- PK/PD assessments three days after start of treatment (after at least six consecutive dabigatran etexilate doses) and after 3 days following any dabigatran etexilate dose adjustment.
- The PK/PD studies in pediatric patients included in stratum-1 (12 to < 18 years) and stratum-2 (2 to < 12 years) will be used to assess and/or improve the predictability of dosing algorithms and models for dabigatran in the pediatric population. The Sponsor will include a minimum of 15 unique patients in age Stratum 3 (0 to < 2 years) and of those, at least 6 unique patients below 6 months of age from both studies where they will extrapolate PK in the 0 to <2 year age group because PK-PD modeling analyses suggest that patients aged < 2 months show an increased sensitivity to dabigatran exposure based on higher baseline aPTT and ECT values.

- *Study 2 (Study Number 1160.108):*
  o *Primary Endpoints*
  All primary endpoints are considered as safety endpoints:
  - Recurrence of venous thromboembolism (VTE) at 6 and 12 months
  - Major and minor (including clinically relevant non-major (CRNM)) bleeding events at 6 and 12 months
  - Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months.

  o *Secondary Endpoints*:
  - Occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months
  - Pharmacodynamic assessments (central measurement of aPTT and ECT) at Visit 4
  - Frequency of dose adjustments (e.g. Number of subjects with dose adjustment) ~~Number of dabigatran etexilate dose adjustments during treatment period.~~

  o *PK/PD Assessments:*
  The same PK/PD assessments will be done on pediatric patients as in Study 1.

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

- *Known Drug Safety concerns and monitoring:* As anticipated for an anticoagulant, bleeding is a drug-specific safety concern. These studies will be conducted under the monitoring of a single independent DMC, whose activities are described in a DMC charter. The DMC will use their clinical and statistical judgment to recommend that the study proceed or be terminated early.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug Information:*

  - *Dosage form:* There will be three age-appropriate formulations developed.
  - *Route of Administration:* Study drug will be administered orally (PO) by age-appropriate formulation.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-

appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:* The details of the statistical analysis will need to be further addressed in the trial statistical analysis plan (TSAP) clearly listing what types of descriptive statistics will be used to analyze the primary endpoint. The detailed primary method and several sensitivity methods for dealing with missing data will need to be included. A final statistical analysis plans (SAP) for studies 1 and 2 must be submitted to and agreed upon by the Agency.

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):* It is expected that the sample size of approximately 240 patients will provide a reasonable safety and efficacy database. The sample size is based on a feasibility assessment and does not include a formal sample size calculation based on the study objectives. Demographics and baseline characteristics will be described with summary statistics. The primary efficacy endpoint, proportion of patients with complete thrombus resolution and freedom from recurrent VTE or mortality related to VTE, will be analyzed using descriptive statistics. Mantel-Haenszel type weighted average of differences with age as a stratification factor will also be provided. Appropriate summary statistics will be presented for all efficacy and safety endpoints.

  - *Study 2 (Study Number 1160.108):* It is expected that the sample size of a minimum of 200 patients in the study and will be treated with dabigatran etexilate until l clinical risk factor has resolve or up to a maximum of 12 months. Sample size is based on feasibility assessment and does not include a formal sample size calculation for study objectives. The primary safety endpoints: recurrence of VTE, major bleeding events, minor (including clinically relevant non-major (CRNM)) bleeding events, overall mortality and

mortality related to thromboembolic events will be analyzed as time-to-event and will be summarized by Kaplan-Meier estimates.

- ~~Both studies together (1160.106 and 1160.108) will deliver at least 200 unique patients for at least 3 months.~~

- The safety database will include data from patients included in the phase IIA studies which evaluated the PK, PD, safety and tolerability of dabigatran. ~~and included 9 patients aged 12-18 years (Study 1160.88), 18 patients aged 1 to < 12 years (Study 1160.89) and 8 patients aged 0 to 1 year (Study 1160.105).~~

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that dabigatran etexilate mesylate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[2] You are encouraged to contact the reviewing Division for further guidance.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[3] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before September 28, 2020. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated January 25, 2019, as amended by this letter must be submitted to the Agency on or before September 28, 2020, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these

[3] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[4]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Michael Gwathmey, Regulatory Project Manager, at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Gregory H. Reaman, MD
Associate Director Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Complete Copy of Written Request as Amended

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

IND 063267

WRITTEN REQUEST

Boehringer Ingelheim Pharmaceuticals Inc.
Attention: Charles R. Mazzarella
Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877-0368

Dear Mr. Mazzarella:

Reference is made to your September 20, 2018 Proposed Pediatric Study Request for PRADAXA® (dabigatran etexilate mesylate).

BACKGROUND:

These studies will investigate the potential use of dabigatran etexilate mesylate in the treatment and prophylaxis of venous thromboembolism in pediatric patients.

Venous thromboembolism (VTE) is now recognized in the pediatric population as a complication of improved treatment strategies for previously lethal childhood diseases. The overall annual incidence rate of VTE in children is approximately 0.07 to 0.14 events per 10,000 children. The most common etiologic factor for VTE in children is the presence of central venous lines; other etiologic factors include thrombophilia, surgery, trauma or malignancy. The current guidelines recommendations for pediatric VTE is largely based on case series, cohort studies or extrapolated from adult VTE treatment experience.

Approved treatment and prophylaxis of pediatric thromboembolism (TE) is an important yet unmet public health need. TE occurs in children of all groups, including neonates. An increase in the rate of TE in children has been observed over the last 6-8 years, most likely due to better survival of acutely ill patients and increased use of central venous access devices (CVAD). In contrast to adults, idiopathic TE in children is rare. Notable risk factors for TE in children include malignancy, CVAD use, congenital heart disease, infection, surgery, and inflammatory disease.

As studies of anticoagulation in children that are fully powered for safety and efficacy have feasibility challenges and some aspects of VTE pathophysiology are comparable between adults and children, the Food and Drug Administration (FDA) supports partial extrapolation of efficacy data from adult patients treated with dabigatran. However, as the coagulation system in children matures with age, and the cause of VTE differ between adults and children, partial extrapolation must be supported by an adequate PK and PD bridge to determine the appropriate dose, as well as sufficient safety and efficacy data to screen for large discrepancies in these endpoints between adults and

children that could be caused by differences in underlying coagulation system maturity or VTE pathophysiology. As children of all ages, including neonates, experience VTE, studies of anticoagulants used as treatment for pediatric TE should be conducted in children from birth through late adolescence.

To obtain needed pediatric information on dabigatran etexilate mesylate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

  - *Study 1 (Study Number 1160.106, DIVERSITY Study*):
    A phase IIb/III, active-controlled, open-label, randomized, parallel-group study of dabigatran versus standard of care (SOC) in pediatric patients with venous thromboembolism. The study will evaluate dabigatran in children from birth to less than 18 years of age. The study will enroll a minimum of 240 children diagnosed with acute venous thromboembolism who have completed an initial parenteral treatment with an unfractionated or a low-molecular weight heparin for a minimum of 5 to 7 days who require continued anticoagulation for at least 3 months. Patients are randomly assigned to either dabigatran etexilate or standard of care on a 2:1 ratio.

  - *Study 2 (Study Number 1160.108):*
    A phase IIb/III, open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of pediatric patients with venous thromboembolism from 0 to less than 18 years of age and will enroll a minimum of 200 patients. Patients who were diagnosed with acute venous thromboembolism who have either completed an initial course of anticoagulation (for at least 3 months) or completed the 1160.106 study treatment and require anticoagulation for secondary prevention of venous thromboembolism due to the presence of a persistent (unresolved) clinical factor with be enrolled in the study. Duration of treatment will be until clinical risk factor is resolved and up to 12 months.

- *Objective of each study:*

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):*

The primary objective is to assess the efficacy and safety of dabigatran etexilate relative to standard of care and to document the appropriateness of the proposed dabigatran etexilate dosing algorithm for use in patients from birth to less than 18 years of age. An additional objective is to evaluate the appropriateness of the dosing nomogram to achieve trough plasma concentrations in the range of 50-250 ng/ml.

- *Study 2 (Study Number 1160.108):*
  The primary objective is to assess the safety of dabigatran etexilate used for secondary prevention of venous thromboembolism in children from 0 to less than 18 years of age. Determining the appropriate trough plasma concentration (50-250 ng/ml) is an additional objective in this study.

- *Patients to be Studied:*

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):*
    - *Age group in which study will be performed:* Patients with venous thromboembolism ages birth to <18 years of age. The following 3 age groups and number of patients will be studied:
      - 0 to < 2 years: See below
      - 2 to < 12 years: At least 40 patients must be enrolled
      - 12 to < 18 years: At least 120 patients will be enrolled in this stratum
    - *Total number of patients to be studied:* At least 240 patients

  - *Study 2 (Study Number 1160.108):*
    - *Age group in which study will be performed:* Patients with venous thromboembolism ages 0 to <18 years of age. The following 3 age groups and number of patients will be studied:
      - 0 to < 2 years: See below
      - 2 to < 12 years: At least 25 patients must be enrolled
      - 12 to < 18 years: At least 110 patients will be enrolled in this stratum.
    - *Total number of patients to be studied:* At least 200 patients

  - *Study 1 and 2 Combined:*
    - *0 to < 2 years: At least 15 unique patients must be enrolled. Of those at least 6 patients must be aged < 6 months*
    - *At least 200 unique pediatric patients of any age treated for at least 12 weeks*

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate

number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):*
    - *Primary Efficacy Endpoint:*
      The combined efficacy endpoints are the proportion of patients with:
      - Complete thrombus resolution and;
      - Freedom from recurrent venous thromboembolism event (including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism, thrombus progression) and;
      - Freedom from mortality related to venous thromboembolism event

    - *Secondary endpoints:*
      - Freedom from major bleeding events (MBEs), 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 is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system, or bleeding that requires intervention in an operating suite.
      - Frequency of dose adjustments, temporary and permanent discontinuation from therapy and number of laboratory monitoring requirements for dose adjustment during the treatment phase
      - Frequency of switch of type of anti-coagulation therapy (to standard of care treatment) and a switch from an intended standard of care treatment to another
      - Freedom from thrombus progression at the end of therapy (EOT) (day 84 after randomization or early EOT which is planned for early discontinued patients, whichever comes first) compared to baseline
      - Assessment of the acceptability of an age-appropriate formulation at the end of therapy
      - All bleeding events
      - All-cause mortality

    - *PK/PD Assessments:*
      - PK/PD assessments three days after start of treatment (after at least six consecutive dabigatran etexilate doses) and after 3 days following any dabigatran etexilate dose adjustment.
      - The PK/PD studies in pediatric patients included in stratum-1 (12 to < 18 years) and stratum-2 (2 to < 12 years) will be used to assess and/or improve the predictability of dosing algorithms and models for dabigatran in the pediatric population. The Sponsor will include a minimum of 15 unique patients in age Stratum 3 (0 to < 2 years)

and of those, at least 6 unique patients below 6 months of age from both studies where they will extrapolate PK in the 0 to <2 year age group because PK-PD modeling analyses suggest that patients aged < 2 months show an increased sensitivity to dabigatran exposure based on higher baseline aPTT and ECT values.

- *Study 2 (Study Number 1160.108):*
  - *Primary Endpoints*
    All primary endpoints are considered as safety endpoints:
    - Recurrence of venous thromboembolism (VTE) at 6 and 12 months
    - Major and minor (including clinically relevant non-major (CRNM)) bleeding events at 6 and 12 months
    - Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months.

  - *Secondary Endpoints*:
    - Occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months
    - Pharmacodynamic assessments (central measurement of aPTT and ECT) at Visit 4
    - Frequency of dose adjustments (i.e. Number of subjects with dose adjustment)

  - *PK/PD Assessments:*
    The same PK/PD assessments will be done on pediatric patients as in Study 1.

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

- *Known Drug Safety concerns and monitoring:* As anticipated for an anticoagulant, bleeding is a drug-specific safety concern. These studies will be conducted under the monitoring of a single independent DMC, whose activities are described in a DMC charter. The DMC will use their clinical and statistical judgment to recommend that the study proceed or be terminated early.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

    - *Dosage form:* There will be three age-appropriate formulations developed.
    - *Route of Administration:* Study drug will be administered orally (PO) by age-appropriate formulation.

    Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

    In accordance with section 505A(e)(2), if

    (1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

    (2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

    (3) you have not marketed the formulation within one year after the Agency publishes such notice,

    the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

    If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:* The details of the statistical analysis will need to be further addressed in the trial statistical analysis plan (TSAP) clearly listing what types of descriptive statistics will be used to analyze the primary endpoint. The detailed primary method and several sensitivity methods for dealing with missing data will need to be included. A final statistical analysis plans (SAP) for studies 1 and 2 must be submitted to and agreed upon by the Agency.

  - *Study 1 (Study Number 1160.106: DIVERSITY Study):* It is expected that the sample size of approximately 240 patients will provide a reasonable safety and efficacy database. The sample size is based on a feasibility assessment and does not include a formal sample size calculation based on the study objectives. Demographics and baseline characteristics will be described with summary statistics. The primary efficacy endpoint, proportion of patients with complete thrombus resolution and freedom from recurrent VTE or mortality related to VTE, will be analyzed using descriptive statistics. Mantel-Haenszel type weighted average of differences with age as a stratification factor will also be provided. Appropriate summary statistics will be presented for all efficacy and safety endpoints.

  - *Study 2 (Study Number 1160.108):* It is expected that the sample size of a minimum of 200 patients in the study and will be treated with dabigatran etexilate until l clinical risk factor has resolve or up to a maximum of 12 months. Sample size is based on feasibility assessment and does not include a formal sample size calculation for study objectives. The primary safety endpoints: recurrence of VTE, major bleeding events, minor (including clinically relevant non-major (CRNM)) bleeding events, overall mortality and mortality related to thromboembolic events will be analyzed as time-to-event and will be summarized by Kaplan-Meier estimates.

  - The safety database will include data from patients included in the phase IIA studies which evaluated the PK, PD, safety and tolerability of dabigatran.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that dabigatran etexilate mesylate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the

public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before September 28, 2020. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

(1) the type of response to the Written Request (i.e. complete or partial response);

(2) the status of the application (i.e. withdrawn after the supplement has been filed or pending);

(3) the action taken (i.e. approval, complete response); or

(4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews FDA.gov.[3]

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.[4]

If you have any questions, call Michael Gwathmey, Regulatory Project Manager, at (301) 796-8498.

Sincerely,

{See appended electronic signature page}

Gregory H. Reaman, MD
Associate Director Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

[4] www.ClinicalTrials.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GREGORY H REAMAN
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