NDA 202155

WRITTEN REQUEST – AMENDMENT 3

Bristol-Myers Squibb Company
Attention: Dipika Shringarpure
US Regulatory Strategist, Global Regulatory Strategy and Policy
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dipika Shringarpure:

Please refer to your correspondence dated December 23, 2022, requesting changes to FDA's March 24, 2017, Written Request for pediatric studies for Eliquis (apixaban).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on March 24, 2017, and as amended on January 25, 2018, and September 23, 2020, remain the same. Refer to the attached document which shows the changes from the previous Written Request.

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 March 24, 2017, as amended by this letter and by previous amendments dated January 25, 2018, and September 23, 2020, must be submitted to the Agency on or before October 18, 2024, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these 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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);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.[1]

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 Carleveva Thompson, Regulatory Project Manager, at 301-796-1403.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Complete Copy of the Written Request as Amended, with Changed Marked
- Complete Copy of Written Request as Amended

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

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BACKGROUND:

Approved treatment and prophylaxis of pediatric thromboembolism (TE) is an important yet unmet public health need. TE occurs in children of all age groups, including neonates. An increase in the rate of TE in children has been observed ~~over the last 6 to 8 years,~~ most likely due to better survival of acutely ill patients and increased use of central venous access devices (CVAD). The observed increase in the annual rate of venous TE (VTE) was most commonly associated with pediatric malignancy (overall incidence of 58/100,000 hospitalized patients). Additional significant risk factors for TE/VTE include mechanical ventilation, infection, any type of surgery, and inflammatory disease. Certain medications also increase thrombosis risk such as corticosteroids and L-asparaginase. A VTE incidence of ~20% is observed in children with acute lymphoblastic leukemia (ALL), CVAD, and L-asparaginase treatment.

Currently there ~~is one anticoagulant~~ are two Direct Oral Anticoagulants (DOACs) approved for use in children for treatment or prophylaxis of TEs in the United States (US) or European Union (EU), and there remain~~s~~ limited clinical trial data in pediatric patients. Other anticoagulants ~~Anticoagulants~~ (namely, vitamin K antagonists [VKAs] and heparins) are still currently used off-label in children.

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.

To obtain needed pediatric information on apixaban, 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 non-clinical 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 CV185118 is a single-dose study to evaluate the PK, PD, safety, and

tolerability of apixaban in pediatric subjects at risk for a venous or arterial thrombotic disorder.

Study 2:

CV185155 is a phase 3, randomized, open-label, multi-center safety and efficacy study of apixaban for VTE prevention versus no systemic anticoagulant prophylaxis in children with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) treated with asparaginase. Enrollment for children ages 1 to <2 years old will commence following dose selection by the Sponsor based on data from this age group in the single-dose PK study.

Study 3:

Study CV185325 is an open-label, active-controlled safety and descriptive efficacy study comparing apixaban to SOC for anticoagulation in pediatric subjects with image-confirmed VTE that requires anticoagulation. A~~n initial~~ cohort of 5 completed apixaban-treated neonatal ~~neonate~~ (birth to ≤27 days) subjects with complete data will be assessed for PK in this trial ~~("PK Cohort").~~
~~Enrollment for the balance of the neonates in this study will commence following dose selection by the Sponsor based on the analysis of the PK cohort.~~ Dose selection for all age cohorts must be submitted to and agreed upon by the Agency.

~~*Pediatric Formulation*~~

~~An apixaban formulation for pediatric patients has been successfully developed. An~~ (b) (4) ~~oral solution of apixaban (0.4 mg/mL) has been developed for use in children. The apixaban oral liquid solution will be administered either via swallowing by mouth or via an enteral tube (nasogastric or gastrostomy tube). Alternate age-appropriate oral formulation(s) will be assessed.~~

~~Study 1 utilizes the oral solution~~ and other age-appropriate formulations(s). ~~In studies 2 and 3, apixaban tablets and other age-appropriate formulation(s) will be provided to those who meet the age and weight requirements and have the ability and desire to swallow tablets. For all other subjects in the apixaban arms, the oral solution and other age-appropriate formulation(s) will be provided.~~

- *Objectives of each study:*

  Study 1:

  The primary objective is to assess the PK of a single dose of apixaban in pediatric subjects. The secondary objectives of the study are:

  - To assess the single-dose safety and tolerability of apixaban in pediatric subjects

- To assess the single-dose anti-Factor Xa activity (AXA) in pediatric subjects

Study 2:

The primary objectives of the study are:

- To compare the effect of prophylactic oral or enteral apixaban versus no systemic anticoagulant during ~~~28 days of~~ induction chemotherapy including asparaginase, on the composite endpoint of adjudicated non-fatal deep vein thromboses (DVT; including symptomatic and asymptomatic), pulmonary embolism (PE), and cerebral sinovenous thrombosis (CSVT); and VTE-related death.

- To assess the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~~~28 days of~~ induction chemotherapy, including asparaginase on adjudicated major bleeding events.

Timing of initiation of treatment during induction and timing of measurement of the primary endpoints must be agreed upon with the Agency in the protocol.

Secondary Objectives are:

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during ~~~28 days of~~ induction chemotherapy including asparaginase, on single adjudicated endpoints of non-fatal DVT (including symptomatic and asymptomatic), PE, and CSVT; and VTE-related death.

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during ~~~28 days of~~ induction chemotherapy, including asparaginase on the composite endpoint of adjudicated major and clinically relevant non-major (CRNM) bleeding events.

Timing of initiation of treatment during induction and timing of measurement of the secondary endpoints must be agreed upon with the Agency in the protocol.

Study 3:

The primary objective of the study is to assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE.

The secondary objective is to evaluate apixaban PK and AXA in pediatric subjects requiring anticoagulation for the treatment of a VTE. ~~Measurement of PK and AXA must be agreed upon with the Agency in the protocol.~~

~~In neonatal subjects, AXA testing is dependent on the clinical status of the subject and concerns over blood volume to be collected (e.g., dried blood spot (DBS) or sampling via an indwelling line). As the DBS sampling method does not allow for AXA testing, it will not be performed in patients for whom this sampling method is performed.~~

- *Patients to be Studied:*
  - *Age group in which study(ies) will be performed:*

    Study 1:

    The following age groups will be studied:

    - Infants: ≥28 days to <9 months
    - Infants: ≥9 months to <2 years
    - Young children: ≥2 to <6 years
    - Children: ≥6 to <12 years
    - Adolescents: ≥12 to <18 years

    All PK and single-dose tolerability data from the neonate (n=1) enrolled in Study 1 (CV185118) will ~~also~~ be reported in the Study 1 CSR and also included in the Study 3 (CV185325) PK/PD analysis and reporting.

    Study 2:

    Recruitment of pediatric subjects (both male and female) 1 to <18 years old is planned.

    Study 3:

    The following age groups will be studied:

    - Neonates (cohort 4): defined as:
      - Full-term infants born at ≥38 weeks gestational age but not more than 27 days of life; or
      - For infants born between 34 and <38 weeks gestational age
        - A subject may be enrolled from date of birth but no more than 27 days of life, or
        - The Investigator may choose to wait until 37 weeks post-conceptual age and enroll the subject no more than 27 days thereafter

- For any infants born between 32 and <34 weeks gestational age: the Investigator would be required to wait until the infant was 37 weeks post-conceptual age and the subject would be allowed to enroll within 27 days of that date.

  - 28 days to <2 years (cohort 3)
  - 2 years to <12 years (cohort 2)
  - 12 years to <18 years (cohort 1)

- *Number of patients to be studied:*

  Study 1:

  The study will include ~~in~~ a minimum of 36 subjects, with 8 subjects in each age group (≥ 2 years); ~~(~~a minimum of 4 subjects for ≥9 months to 2 years and a minimum of 4 subjects for age ≥ 28 days to < 9 months~~)~~; and 1 subject for neonate age.

  Study 2:

  The study will randomize a minimum of 500 subjects to apixaban or placebo at a ratio of 1 to 1.

  Study 3:

  The study will randomize ~~approximately~~ a minimum of 150 subjects to apixaban or SOC at a ratio of 2 to 1. A target of at least 30 subjects ~~in each of the 4 age groups will be randomized. Specifically, within the neonate age group, PK data will be collected from at least 5 subjects on apixaban and the remaining patients in this group will be randomized.~~ in each of the cohorts 1-3 (children ≥ 28 days) will be randomized. At least 5 subjects in Cohort 4 (neonates) will be treated with apixaban. ~~At least 2 subjects in Cohort 4 will have AXA testing performed.~~

- *Study endpoints:*

  ☐ Pharmacokinetic/Pharmacodynamic Endpoints:

  Study 1:

Pharmacokinetics

Apixaban PK will be characterized using a population PK (PPK) model of plasma concentration versus time data. The mean and individual PK parameters of the PPK model will be estimated using a nonlinear mixed-effects population estimation algorithm and summarized by age group.

Pharmacodynamics

The PD of apixaban will be characterized using a population PK-PD (PPK-PD) model developed using both the plasma concentration and the measured AXA vs. time data. The mean and individual PD parameters of the PPK-PD model will be estimated using a nonlinear mixed-effects population estimation algorithm. If variability in PK-AXA data is sufficient to be estimated in the PPK-PD model, the linear slope (SLP) of the relationship between plasma concentration and AXA will be summarized by age group.

The individual estimated PK and PD parameters will be used to derive apixaban PD parameters that represent the individual subjects' AXA. The maximum estimated AXA (AXAmax) will be summarized by dose and age group. In addition, standard clotting tests such as PT, aPTT, and INR will be performed as safety laboratory tests.

Study 2:

PK and AXA assessments will only be performed for patients randomized to the apixaban arm. Sparse sampling for apixaban concentrations and AXA will be collected at selected study visits and used to develop a PPK model to estimate Cmax, Cmin, and AUC(TAU) in each subject and a PPK-AXA model to estimate maximum and minimum AXA in each subject.

Study 3:

Secondary endpoints include assessments of apixaban concentration and of AXA. ~~Measurement of PK and AXA must be agreed upon with the Agency in the protocol.~~

~~In neonatal subjects, AXA testing is dependent on the clinical status of the subject and concerns over blood volume to be collected (e.g., using DBS or sampling via an indwelling line). As the DBS sampling method does not allow for AXA testing, it will not be performed in patients for whom this sampling method is performed.~~

☐ *Efficacy Endpoints:*

Study 2:

The primary efficacy endpoint is a composite of non-fatal DVT (including asymptomatic and symptomatic), PE, CSVT, and VTE-related death. Adjudication ~~All components~~ of the primary efficacy endpoint will be performed in accordance with ~~adjudicated by a blinded, independent adjudication committee~~ the protocol.

Secondary efficacy endpoints will include:

- Non-fatal asymptomatic DVT
- Non-fatal symptomatic DVT
- Non-fatal PE
- Non-fatal CVST
- VTE-related death

Study 3:

The primary efficacy endpoint is a composite of:

- All ~~all~~ image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression (defined as unequivocal increase [>50%] of the total volume/mass of the thrombus compared to the index event) or non-contiguous new thrombus and including DVT, PE, and paradoxical embolism (when a thrombus from the systemic venous circulation crosses to the systemic circulation via an intracardiac communication such as an atrial or ventricular septal defect)
- VTE-related mortality

Secondary efficacy endpoints include assessments of:

- all cause death
- index VTE status (e.g., unchanged, regression, resolution)
- stroke
- new symptomatic and asymptomatic DVT
- new symptomatic PE

Children 2 years to <18 years: New radiologic images of the index VTE site will be obtained in accordance with the protocol at the midpoint of the study

(Day 42 ± 14 days) and at the end of treatment (Day 84 ± 7 days). Radiologic images that require sedation or radiation may be omitted if not medically necessary. At the midpoint and end of treatment visits, the investigator will reassess the index event and all areas around the index event that were scanned initially based on the clinical assessment, to account for the presence of any new asymptomatic clots. All assessments obtained in the evaluation of symptomatic or asymptomatic recurrent VTEs will be adjudicated in accordance with the protocol.

Patients less than 2 years of age: Imaging to be conducted at the end-of-treatment. Additional imaging assessments, if indicated, can be performed at the discretion of the Investigator.

☐ Safety Endpoints:

Study 1:

Safety assessments will be based on review of adverse event (AE) reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

Study 2:

The primary safety endpoint will be adjudicated major bleeding, which includes the following defined events:

- Fatal bleeding
- Clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (i.e., 2 g/dL) in a 24-hour period
- Bleeding that is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system
- Bleeding that requires surgical intervention in an operating suite, including interventional radiology

The major secondary safety endpoint will be the composite of major and CRNM bleeding.

Adjudication of the ~~All~~ bleeding events will be ~~adjudicated by a blinded, independent adjudication committee as major bleeding, CRNM bleeding, or minor bleeding using International Society on Thrombosis and Hemostasis (ISTH) criteria for pediatric clinical trials in VTE~~ performed in accordance with the protocol.

Study 3:

The primary safety endpoint is the composite of major and CRNM bleeding. For safety, at least 100 subjects (age ≥ 2 years) treated with apixaban for 12 weeks are required. Additionally, a minimum of 20 subjects (age <2 years) (4-6 subjects age birth to ≤27 days and 14-16 subjects age 28 days to <2 years) treated with apixaban for 6-12 weeks are required.

- *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.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1:

  The study must enroll a sufficient number of patients to adequately characterize the PK of Apixaban. ~~A sample size of approximately 44 total subjects is expected to provide sufficient confidence in the PK model parameter estimates such that there would be at least 95% probability that the model-predicted mean AUC(INF) is within 60% to 140% of the true mean AUC(INF) for pediatric subjects of any age.~~ Summary statistics will be provided for the study endpoints.

  Study 2:

  Sample Size Calculation

  With a minimum ~~total~~ of 500 subjects allocated with 1:1 ratio to the systemic thromboprophylaxis with apixaban or no systemic anticoagulant prophylaxis (control) group, there is more than 80% power to demonstrate superiority at a 1-sided 0.025 level, assuming the true event rates are 17% and 8.5% in the control and the apixaban groups, respectively. Sample size can be calculated based on Pearson's chi-square test but the anticipated dropouts may need to be considered to prevent significant power loss given that the number of dropouts should be kept minimal.

  Statistical Assessments

The analyses for efficacy will be based on the intent-to-treat (ITT) principle. The safety analysis will be based on the safety population. For primary efficacy endpoint and primary safety endpoint, single event rate, 95% CI for single event rate, relative risk, 95% CI for relative risk, and *P* value will be provided. For other endpoints, descriptive statistics including single event rate, 95% CI for single event rate, relative risk and 95% CI for relative risk will be provided.

To construct *P* values, the Cochran-Mantel-Haenszel (CMH) test stratified by age group (<10 years old, and ≥10 years old) will be used at the 1-sided $\alpha = 0.025$ level. To construct descriptive statistics, the 95% CI for the relative risk will be computed based on CMH method stratified by age group. Construction of CIs for single event rates will be based on the Agresti-Coull method.

Frequency and summary statistics for key demographic and baseline variables will be presented by treatment group and for all subjects combined.

~~Several sensitivity analyses should be conducted to examine the impact of missing data and dropouts.~~ Sensitivity analyses as agreed upon with the Agency in the SAP will be conducted to examine the impact of missing data and dropouts.

A final statistical analysis plan (SAP) must be submitted to and agreed upon by the Agency before data lock and unblinding.

Study 3:

~~Sample Size Determination~~

~~It is expected that the sample size of approximately 150 subjects will provide a reasonable safety and pharmacokinetic database along with limited descriptive efficacy data in pediatric subjects. This sample size is meaningful based on exposure matching and efficacy assessments proposed for the study, which are consistent with ISTH recommendations for pediatric clinical trials in venous thromboembolism. Acknowledging that these data are limited due to low event rates, they nonetheless will be useful when evaluated in the context of the full data set of the adult VTEt study and benefit risk assessment.~~

Statistical Assessments

Appropriate summary statistics, including point estimates and their 95% confidence intervals should be presented for all efficacy and safety endpoints. ~~No inferential analyses need to be planned.~~ Inferential analyses are not required.

Model-derived population and individual PK parameters (e.g., CL/F, Vc/F, KA) will be used to estimate Cmax, Cmin, and AUC in each subject. Model-derived population and individual PD parameters (e.g., slope of AXA vs. apixaban concentration relationship) will be used to estimate maximum and minimum AXA in

~~each~~ subjects for whom AXA testing is performed.

The following information pertains to all clinical studies in the Written Request.

- *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:*

  Pediatric Formulation

  An apixaban formulation for pediatric patients has been successfully developed. An (b) (4) oral solution of apixaban (0.4 mg/mL) has been developed for use in children. The apixaban oral liquid solution will be administered either via swallowing by mouth or via an enteral tube (nasogastric or gastrostomy tube). Alternate age-appropriate oral formulation(s) will be assessed.

  Study 1 utilizes the oral solution and other age-appropriate formulations(s). In studies 2 and 3, apixaban tablets and other age-appropriate formulation(s) will be provided to those who meet the age and weight requirements and have the ability and desire to swallow tablets. For all other subjects in the apixaban arms, the oral solution and other age-appropriate formulation(s) will be provided.

  - *dosage form: oral solution, tablets, or alternate age-appropriate formulation(s)*
  - *route of administration: oral, enteral (PO, NG, or G-tube)*
  - *regimen: per agreed protocols*

  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.

- *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 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 ~~April 30, 2024~~ ~~2025~~ October 18, 2024. 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.

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BACKGROUND:

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Currently there are two Direct Oral Anticoagulants (DOACs) approved for use in children for treatment or prophylaxis of TEs in the United States (US) or European Union (EU), and there remain limited clinical trial data in pediatric patients. Other anticoagulants (namely, vitamin K antagonists [VKAs] and heparins) are still currently used off-label in children.

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.

To obtain needed pediatric information on apixaban, 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 non-clinical 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 CV185118 is a single-dose study to evaluate the PK, PD, safety, and tolerability of apixaban in pediatric subjects at risk for a venous or arterial thrombotic disorder.

Study 2:

CV185155 is a phase 3, randomized, open-label, multi-center safety and efficacy study of apixaban for VTE prevention versus no systemic anticoagulant prophylaxis in children with newly diagnosed ALL or lymphoblastic lymphoma (T or B cell) treated with asparaginase. Enrollment for children ages 1 to <2 years old will commence following dose selection by the Sponsor based on data from this age group in the single-dose PK study.

Study 3:

Study CV185325 is an open-label, active-controlled safety and descriptive efficacy study comparing apixaban to SOC for anticoagulation in pediatric subjects with image-confirmed VTE that requires anticoagulation. A cohort of 5 completed apixaban-treated neonatal (birth to ≤27 days) subjects with complete data will be assessed for PK in this trial. Dose selection for all age cohorts must be submitted to and agreed upon by the Agency.

- *Objectives of each study:*

  Study 1:

  The primary objective is to assess the PK of a single dose of apixaban in pediatric subjects. The secondary objectives of the study are:

  - To assess the single-dose safety and tolerability of apixaban in pediatric subjects
  - To assess the single-dose anti-Factor Xa activity (AXA) in pediatric subjects

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  The primary objectives of the study are:

  - To compare the effect of prophylactic oral or enteral apixaban versus no systemic anticoagulant during induction chemotherapy including asparaginase, on the composite endpoint of adjudicated non-fatal deep vein thromboses (DVT; including symptomatic and asymptomatic), pulmonary embolism (PE), and cerebral sinovenous thrombosis (CSVT); and VTE-related death.
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  Timing of initiation of treatment during induction and timing of measurement of the

primary endpoints must be agreed upon with the Agency in the protocol.

Secondary Objectives are:

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during induction chemotherapy including asparaginase, on single adjudicated endpoints of non-fatal DVT (including symptomatic and asymptomatic), PE, and CSVT; and VTE-related death.

- To assess the effect of prophylactic apixaban versus no systemic anticoagulant during induction chemotherapy, including asparaginase on the composite endpoint of adjudicated major and clinically relevant non-major (CRNM) bleeding events.

Timing of initiation of treatment during induction and timing of measurement of the secondary endpoints must be agreed upon with the Agency in the protocol.

Study 3:

The primary objective of the study is to assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE.

The secondary objective is to evaluate apixaban PK and AXA in pediatric subjects requiring anticoagulation for the treatment of a VTE.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed:*

    Study 1:

    The following age groups will be studied:

    - Infants: ≥28 days to <9 months
    - Infants: ≥9 months to <2 years
    - Young children: ≥2 to <6 years
    - Children: ≥6 to <12 years
    - Adolescents: ≥12 to <18 years

    All PK and single-dose tolerability data from the neonate (n=1) enrolled in Study 1 (CV185118) will be reported in the Study 1 CSR and also included in the Study 3 (CV185325) PK/PD analysis and reporting.

    Study 2:

Recruitment of pediatric subjects (both male and female) 1 to <18 years old is planned.

Study 3:

The following age groups will be studied:

- Neonates (cohort 4): defined as:
  - Full-term infants born at ≥38 weeks gestational age but not more than 27 days of life; or
  - For infants born between 34 and <38 weeks gestational age
    - A subject may be enrolled from date of birth but no more than 27 days of life, or
    - The Investigator may choose to wait until 37 weeks post-conceptual age and enroll the subject no more than 27 days thereafter
  - For any infants born between 32 and <34 weeks gestational age: the Investigator would be required to wait until the infant was 37 weeks post-conceptual age and the subject would be allowed to enroll within 27 days of that date.
    - 28 days to <2 years (cohort 3)
    - 2 years to <12 years (cohort 2)
    - 12 years to <18 years (cohort 1)

- *Number of patients to be studied:*

  Study 1:

  The study will include a minimum of 36 subjects, with 8 subjects in each age group (≥ 2 years); a minimum of 4 subjects for ≥9 months to 2 years and a minimum of 4 subjects for age ≥ 28 days to < 9 months; and 1 subject for neonate age.

  Study 2:

  The study will randomize a minimum of 500 subjects to apixaban or placebo at a ratio of 1 to 1.

Study 3:

The study will randomize a minimum of 150 subjects to apixaban or SOC at a ratio of 2 to 1. A target of at least 30 subjects in each of the cohorts 1-3 (children ≥ 28 days) will be randomized. At least 5 subjects in Cohort 4 (neonates) will be treated with apixaban.

- *Study endpoints:*

  ☐ Pharmacokinetic/Pharmacodynamic Endpoints:

  Study 1:

  Pharmacokinetics

  Apixaban PK will be characterized using a population PK (PPK) model of plasma concentration versus time data. The mean and individual PK parameters of the PPK model will be estimated using a nonlinear mixed-effects population estimation algorithm and summarized by age group.

  Pharmacodynamics

  The PD of apixaban will be characterized using a population PK-PD (PPK-PD) model developed using both the plasma concentration and the measured AXA vs. time data. The mean and individual PD parameters of the PPK-PD model will be estimated using a nonlinear mixed-effects population estimation algorithm. If variability in PK-AXA data is sufficient to be estimated in the PPK-PD model, the linear slope (SLP) of the relationship between plasma concentration and AXA will be summarized by age group.

  The individual estimated PK and PD parameters will be used to derive apixaban PD parameters that represent the individual subjects' AXA. The maximum estimated AXA (AXAmax) will be summarized by dose and age group. In addition, standard clotting tests such as PT, aPTT, and INR will be performed as safety laboratory tests.

  Study 2:

  PK and AXA assessments will only be performed for patients randomized to the apixaban arm. Sparse sampling for apixaban concentrations and AXA will be collected at selected study visits and used to develop a PPK model to estimate Cmax, Cmin, and AUC(TAU) in each subject and a PPK-AXA model to estimate maximum and minimum AXA in each subject.

  Study 3:

Secondary endpoints include assessments of apixaban concentration and of AXA.

☐ *Efficacy Endpoints:*

Study 2:

The primary efficacy endpoint is a composite of non-fatal DVT (including asymptomatic and symptomatic), PE, CSVT, and VTE-related death. Adjudication of the primary efficacy endpoint will be performed in accordance with the protocol.

Secondary efficacy endpoints will include:

- Non-fatal asymptomatic DVT
- Non-fatal symptomatic DVT
- Non-fatal PE
- Non-fatal CVST
- VTE-related death

Study 3:

The primary efficacy endpoint is a composite of:

- All image-confirmed and adjudicated symptomatic and asymptomatic recurrent VTE defined as either contiguous progression (defined as unequivocal increase [>50%] of the total volume/mass of the thrombus compared to the index event) or non-contiguous new thrombus and including DVT, PE, and paradoxical embolism (when a thrombus from the systemic venous circulation crosses to the systemic circulation via an intracardiac communication such as an atrial or ventricular septal defect)
- VTE-related mortality

Secondary efficacy endpoints include assessments of:

- all cause death
- index VTE status (e.g., unchanged, regression, resolution)

- stroke
- new symptomatic and asymptomatic DVT
- new symptomatic PE

Children 2 years to <18 years: New radiologic images of the index VTE site will be obtained in accordance with the protocol at the midpoint of the study (Day 42 ± 14 days) and at the end of treatment (Day 84 ± 7 days). Radiologic images that require sedation or radiation may be omitted if not medically necessary. At the midpoint and end of treatment visits, the investigator will reassess the index event and all areas around the index event that were scanned initially based on the clinical assessment, to account for the presence of any new asymptomatic clots. All assessments obtained in the evaluation of symptomatic or asymptomatic recurrent VTEs will be adjudicated in accordance with the protocol.
Patients less than 2 years of age: Imaging to be conducted at the end-of-treatment. Additional imaging assessments, if indicated, can be performed at the discretion of the Investigator.

☐ Safety Endpoints:

Study 1:

Safety assessments will be based on review of adverse event (AE) reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. The incidence of AEs will be tabulated and reviewed for potential significance and clinical importance.

Study 2:

The primary safety endpoint will be adjudicated major bleeding, which includes the following defined events:

- Fatal bleeding
- Clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (i.e., 2 g/dL) in a 24-hour period
- Bleeding that is retroperitoneal, pulmonary, intracranial or otherwise involves the central nervous system
- Bleeding that requires surgical intervention in an operating suite, including interventional radiology

The major secondary safety endpoint will be the composite of major and

CRNM bleeding.

Adjudication of the bleeding events will be performed in accordance with the protocol.

Study 3:

The primary safety endpoint is the composite of major and CRNM bleeding. For safety, at least 100 subjects (age ≥ 2 years) treated with apixaban for 12 weeks are required. Additionally, a minimum of 20 subjects (age <2 years) (4-6 subjects age birth to ≤27 days and 14-16 subjects age 28 days to <2 years) treated with apixaban for 6-12 weeks are required.

- *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.

- *Statistical information, including power of study(ies) and statistical assessments:*

  Study 1:

  The study must enroll a sufficient number of patients to adequately characterize the PK of Apixaban. Summary statistics will be provided for the study endpoints.

  Study 2:

  Sample Size Calculation

  With a minimum of 500 subjects allocated with 1:1 ratio to the systemic thromboprophylaxis with apixaban or no systemic anticoagulant prophylaxis (control) group, there is more than 80% power to demonstrate superiority at a 1-sided 0.025 level, assuming the true event rates are 17% and 8.5% in the control and the apixaban groups, respectively. Sample size can be calculated based on Pearson's chi-square test but the anticipated dropouts may need to be considered to prevent significant power loss given that the number of dropouts should be kept minimal.

  Statistical Assessments

  The analyses for efficacy will be based on the intent-to-treat (ITT) principle. The safety analysis will be based on the safety population. For primary efficacy

endpoint and primary safety endpoint, single event rate, 95% CI for single event rate, relative risk, 95% CI for relative risk, and *P* value will be provided. For other endpoints, descriptive statistics including single event rate, 95% CI for single event rate, relative risk and 95% CI for relative risk will be provided.

To construct *P* values, the Cochran-Mantel-Haenszel (CMH) test stratified by age group (<10 years old, and ≥10 years old) will be used at the 1-sided $\alpha = 0.025$ level. To construct descriptive statistics, the 95% CI for the relative risk will be computed based on CMH method stratified by age group. Construction of CIs for single event rates will be based on the Agresti-Coull method.

Frequency and summary statistics for key demographic and baseline variables will be presented by treatment group and for all subjects combined.

Sensitivity analyses as agreed upon with the Agency in the SAP will be conducted to examine the impact of missing data and dropouts.

A final statistical analysis plan (SAP) must be submitted to and agreed upon by the Agency before data lock and unblinding.

Study 3:

Statistical Assessments

Appropriate summary statistics, including point estimates and their 95% confidence intervals should be presented for all efficacy and safety endpoints. Inferential analyses are not required.

Model-derived population and individual PK parameters (e.g., CL/F, Vc/F, KA) will be used to estimate Cmax, Cmin, and AUC in each subject. Model-derived population and individual PD parameters (e.g., slope of AXA vs. apixaban concentration relationship) will be used to estimate maximum and minimum AXA in subjects for whom AXA testing is performed.

The following information pertains to all clinical studies in the Written Request.

- *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:*

Pediatric Formulation

An apixaban formulation for pediatric patients has been successfully developed. An (b) (4) oral solution of apixaban (0.4 mg/mL) has been developed for use in children. The apixaban oral liquid solution will be administered either via swallowing by mouth or via an enteral tube (nasogastric or gastrostomy tube). Alternate age-appropriate oral formulation(s) will be assessed.

Study 1 utilizes the oral solution and other age-appropriate formulations(s). In studies 2 and 3, apixaban tablets and other age-appropriate formulation(s) will be provided to those who meet the age and weight requirements and have the ability and desire to swallow tablets. For all other subjects in the apixaban arms, the oral solution and other age-appropriate formulation(s) will be provided.

- *dosage form: oral solution, tablets, or alternate age-appropriate formulation(s)*
- *route of administration: oral, enteral (PO, NG, or G-tube)*
- *regimen: per agreed protocols*

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.

- *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 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 October 18, 2024. 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.

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/

HYLTON V JOFFE
11/17/2023 03:51:09 PM