CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220073Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 066106

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb Company
Attention: Dipika Tuteja Shringarpure, PhD, RAC
Senior Manager, Global Regulatory Strategy & Safety Science
P.O. Box 5326
Princeton, NJ 08643

Dear Dr. Shringapure:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for apixaban.

We also refer to your correspondence, dated and received May 23, 2024, requesting a meeting to discuss fulfillment of PMR 3103-2, adequacy of the proposed submission to support pediatric exclusivity determination, and the proposed format and content of the supplemental NDA (sNDA) filing.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at 301-796-1403 or Carleveva.Thompson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Carleveva Thompson, MS
Senior Regulatory Project Manager
Nonmalignant Hematology
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Preliminary Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-sNDA

Meeting Date and Time: July 22, 2024, 3:00 PM – 4:00 PM (EDT)
Meeting Location: Videoconference

Application Number: IND 066106
Product Name: apixaban
Indication: treatment of venous thromboembolism
Sponsor Name: Bristol-Myers Squibb Company (BMS)
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for July 22, 2024, 3:00 PM – 4:00 PM (EDT), via videoconference between Bristol-Myers Squibb Company and the Division of Nonmalignant Hematology. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Apixaban is approved for the following adult indications in the United States: reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation (NVAF), prophylaxis of deep vein thrombosis (DVT) following hip or knee replacement surgery, treatment of DVT, treatment of pulmonary embolism (PE), and reduction in the risk of recurrence of DVT and PE.

Under the Pediatric Research Equity Act (PREA), there are three pediatric clinical studies that were conducted to fulfill the issued postmarketing requirements (PMRs), PMR 3103-1 and 3103-2 (CV185079, CV185118 and CV185325). A final clinical study report (CSR) of study CV185118 for PMR-3103-1 was submitted on December 10, 2020. A final report of study CV185079 was submitted on April 8, 2013.

In relation to the Best Pharmaceuticals for Children Act (BPCA), the terms of the current Written Request (WR), (Amendment 3, dated November 17, 2023), include conducting three pediatric clinical studies (CV185118, CV185155, CV185325), pharmacokinetic analyses to establish pediatric dosing recommendations, and the development of age-appropriate formulations for administration to the pediatric population(s) studied.

The studies included in the meeting package are:

- Study CV185325, an open-label, active-control, safety, and efficacy study comparing apixaban to standard of care (SOC) in pediatric subjects with image-confirmed VTE that required anticoagulation. It is the pivotal study in the proposed sNDA submission package. The study randomized 229 subjects in four age groups to open-label, fixed-dose, bodyweight-tiered regimen of apixaban or SOC for at least 12 weeks. Subjects <2 years of age received apixaban for 6 to 12 weeks. Under Protocol Amendment 8, neonates were no longer randomized to either treatment arm and were only randomized to receive apixaban. The agreed upon number of completed apixaban-treated neonates (birth to ≤27 days) with the Agency was a cohort of five neonates with complete data (include anti-Factor Xa data or AXA). PK data will be available for five other neonates.

  Preliminary results show that the largest age group was 12 to <18 years (137 subjects; 59%) were randomized. A total of 16 subjects were enrolled in the Birth to ≤27 days age group (Apixaban: 12 (7.7%) and SOC: 4 (5.4%)). Four subjects in the apixaban group (2.6%; 95% CI: 0.8,6.7) and 2 subjects in the SOC group (2.7%; 95% CI: 0.2,9.9) had at least 1 adjudicated symptomatic or asymptomatic recurrent VTE event. No subjects in either treatment groups had an adjudicated major bleeding event. There were three deaths reported in the apixaban group and one death in the SOC group.

- Study CV185118, an open-label, single dose study to evaluate PK, PD, safety, and tolerability of apixaban in pediatric subjects at risk for a venous or arterial thrombotic disorder. The study enrolled 49 subjects across the six age groups. All PK and single-dose tolerability data was submitted to the final Clinical Study Report (CSR) as of December 31, 2021. This includes data from one neonate. The Sponsor states that PK data will be pooled with data from Study CV185325 PPK analysis and simulations. The anti-Factor Xa (AXA) data will not be pooled for Study CV185325 PK/PD analysis.

- Study CV185155, a Phase 3, randomized, open-label, multicenter, safety and efficacy study of apixaban versus no systemic anticoagulation to evaluate prophylaxis for VTE in children with newly diagnosed ALL or lymphoblastic lymphoma (T cell or B cell) treated with asparaginase. The study randomized a total of 512 subjects in a 1:1 ratio 1 to <18 years of age to systemic thromboprophylaxis with apixaban or no systemic anticoagulant prophylaxis groups.

- Study CV185362, a prospective, randomized, open-label, multicenter study of safety and PK of apixaban versus vitamin K antagonist or LMWH in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboembolism prevention. A total of 192 subjects were randomized in this study.

- Study CV185079, a multiple dose study to evaluate PK, PD, safety, and tolerability of apixaban in pediatric subjects with an indwelling central venous catheter. total of 13 subjects were enrolled, 8 subjects were treated, and 6 subjects completed the study. The study was terminated early due to recruitment difficulties. The final CSR was submitted on April 8, 2013.

The purpose of this Type B meeting is to align with FDA on the adequacy of the data package from pediatric Study CV185325, additional supportive clinical studies (CV185118, CV185155, and CV185362), and modeling & simulation analyses extrapolating adult exposures to those in pediatric patients to support an sNDA for a pediatric indication for the treatment of venous thromboembolism (VTE) and reduction of the risk of recurrent VTE in pediatric patients from birth to <18 years of age.

BMS would also like to obtain the Agency's feedback and agreement on:

- Fulfillment of PMR 3103-2 with the data from pediatric subjects treated in Study CV185325.
- Proposed format and content of the sNDA filing, and review of the submission dossier to support the proposed pediatric indication/label update.
- Adequacy of the proposed submission to support FDA's review of the request for pediatric exclusivity determination and fulfillment of the Written Request requirement.

2.0 DISCUSSION

Question 1: Does the FDA agree with the Sponsor's proposal that the data from the completed study CV185325 fulfills PMR 3103-2?

FDA Response to Question 1: It is premature to comment on the adequacy of data from the completed Study CV185325 to fulfill PMR 3103-2. This will be determined after review of the final Clinical Study Report (CSR), once submitted to the NDA.

Question 2: Does the FDA have comments on the Sponsor's proposal that the data from the completed pediatric studies (CV185325, CV185118, CV185155) will fulfill the agreed PWR requirements and support the request for Eliquis pediatric exclusivity determination?

FDA Response to Question 2: Fulfillment of the WR and a decision regarding pediatric exclusivity will be a separate review, pending submission of the final clinical study reports. We remind you that 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.

Question 3: Does the FDA agree that the pediatric clinical study data and the M&S analyses extrapolating the favorable efficacy and safety profile of apixaban from adult to pediatric patients are adequate to support the review of the sNDA and proposed indication?

FDA Response to Question 3: Your proposal to include in the sNDA the CSR with data from pediatric subjects for Study CV185325 and CSRs for 4 additional supportive studies described above appears adequate to support a review in the proposed indication. However, the pediatric extrapolation for efficacy and safety of apixaban to support approval of your indication will be a review issue.

For the extrapolation framework, comparison of apixaban exposure-PD relationship between adults and pediatric patients will be supportive. Plan to include a comparison of exposure-PD relationship in the sNDA submission.

Question 4: Does the FDA agree with the Sponsor's approach to submit the data from the pivotal and supportive clinical studies separately in a Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) in the planned sNDA?

FDA Response to Question 4: You intend to submit a Summary of Clinical Efficacy (SCE), which will include Studies CV185325, CV185118, CV185155, and CV185362. The SCE will present and discuss the efficacy results of these studies separately rather than pooled due to differences in study design, populations, dosing, treatment duration. An integrated discussion of efficacy findings will be included in the clinical overview.

The Summary of Clinical Safety (SCS) will present safety data from Studies CV185325, CV185118, CV185155 and CV185362. The safety data from these four studies will not be pooled for the similar reasons provided above.

We find your approach for both the SCE and SCS acceptable.

Question 5: Does the FDA agree with the proposed format and content of the clinical pharmacology package, including PPK and PK/PD M&S analyses from studies CV185325, CV185118, CV185155, and CV185362, to support the review of the sNDA?

FDA Response to Question 5: We agree with your proposed format and content of the clinical pharmacology package.

Question 6: Considering that all pediatric studies are complete and no new safety data are expected during the sNDA review, does the FDA agree with the proposal not to submit a safety update report?

FDA Response to Question 6: No, you must provide a 120-day safety update. The update should contain any new safety information about apixaban that may reasonably affect the information in the draft drug labeling submitted with the sNDA. This would include safety data from clinical trials obtained after the data cutoffs used for the data sets submitted with the sNDA and any other sources.

Question 7: The Sponsor will provide safety narratives for subjects in study CV185325 who were treated with apixaban but not those with SOC as per the Safety Narrative Plan, does the FDA agree with this proposal?

FDA Response to Question 7: We agree with your proposal to provide safety narratives for patients in study CV185525 who received apixaban. We reserve the right, however, to request additional narratives from any participant(s) during the review process if we consider them relevant to our review.

Question 8: Does the FDA agree with the provision of BIMO data for pivotal study CV185325 only and not for supportive studies CV185118, CV185155 and CV185362?

FDA Response to Question 8: We agree with the provision of the BIMO data for CV185325 only and not of the supportive studies.

Additional Comments:

1. **For the major efficacy and safety studies, in addition to the study data, we also have the following requests:**

    a. **Provide executable SAS programs with adequate document(s) to allow FDA to derive the analysis datasets from the raw datasets you submitted.**

    b. **Provide the SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.**

c. **Include all study protocols, amendments, and all minutes as well as related materials for discussion during IND meetings.**

2. **With respect to financial information, we consider study CV185325 a covered trial.**

3.0 IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

[1] https://www.fda.gov/media/86340/download
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and*

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[6] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

SPLIT REAL TIME APPLICATION REVIEW (STAR) PILOT PROGRAM

The FDA is conducting a pilot program, the Split Real Time Application Review (STAR). STAR is a pilot review process allowing earlier patient access to therapies that address an unmet medical need via interactive engagement with the application so that review and analysis of data may commence prior to full supplemental new drug application (sNDA)/supplemental biologics license application (sBLA) submission. An applicant can communicate interest in participating in this pilot program to the FDA review division by submitting a STAR Entry Request if the applicant believes a proposed efficacy supplement fulfills the conditions outlined in the eligibility criteria. Those applicants who do not wish to participate in the pilot program will follow the usual submission process with no impact on review timelines. More information on this pilot program, including

[5] https://www.fda.gov/media/85061/download
[6] https://www.fda.gov/media/124795/download

eligibility criteria and timelines, can be found at the FDA website for STAR.[7]

[7] https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star

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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/

CARLEVEVA J THOMPSON
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