CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215151Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 079212

MEETING PRELIMINARY COMMENTS

Phathom Pharmaceuticals
Attention: Nancianne Knipfer, Ph.D., RAC
Senior Director, Regulatory Affairs
2150 East Lake Cook Road, Suite 800
Buffalo Grove, IL 60089

Dear Dr. Knipfer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TAK-438 (vonoprazan).

We also refer to your September 24, 2021, correspondence, received September 24, 2021, requesting a meeting to discuss the proposed submission strategy for a New Drug Application (NDA).

Our preliminary responses to your teleconference questions are enclosed.

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

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-0845.

Sincerely,

{See appended electronic signature page}

Maureen Dewey, M.P.H., RAC
Senior Regulatory Project Manager
Division of Gastroenterology
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 18, 2021

Application Number: 079212
Product Name: TAK-438 (vonoprazan)
Indication: Healing of all grades of erosive esophagitis and relief of heartburn and maintenance of healing of all grades of erosive esophagitis and relief of heartburn.
Sponsor Name: Phathom Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

FDA ATTENDEES

Office of Immunology and Inflammation

Julie Beitz, M.D., Director

Division of Gastroenterology Office of Immunology and Inflammation

Jessica J. Lee, M.D., M.M.Sc., Director
Joyce Korvick, M.D., M.P.H., Deputy Director for Safety
Juli Tomaino, M.D., M.S., Deputy Director
Joette Meyer, Pharm.D., Associate Director for Labeling
Matthew Kowalik, M.D., Clinical Team Leader
Laura Finkelstein, M.D., Medical Officer
Sushanta Chakder, R.Ph., Ph.D., Supervisory Pharmacologist
Jackye Peretz, Ph.D., Lead Pharmacologist
Dinesh Gautam, Ph.D., Pharmacologist

Division of Inflammation and Immune Pharmacology (DIIP)

Insook Kim, Ph.D., Clinical Pharmacology Team Leader
Sojeong Yi, Ph.D., Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality

Donna Christner, Ph.D., New Drug API Branch Chief, Office of Product Quality (OPQ)
Jeffery Medwid, Ph.D., Product Quality Reviewer, OPQ
Hong Cai, Ph.D., Branch Chief, OPQ
Nina Ni, Ph.D., Product Reviewer, OPQ

Yubing Tang, Ph.D., Facility and Manufacturing Team Leader
Mesfin Abdi, Ph.D., Facility and Manufacturing Reviewer
Vaikunth Prabhu, Ph.D., Facility and Manufacturing Reviewer

Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations

Renmet Grewal, Pharm.D., RAC, Deputy Director, ORO
Richard Whitehead, M.S., Supervisory Consumer Safety Officer
Maureen Dewey, MPH, RAC, Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Esha Desai, MS, RAC, Director, Regulatory Affairs
Thomas Harris, BSc., Pharm, Head of Regulatory Affairs, CMC, R&D Quality/Biostatistics
Barb Hunt, MS, Senior Director, Biostatistics
Nancianne Knipfer, PhD, RAC, Senior Director, Regulatory Affairs
Eckhard Leifke, MD, Chief Medical Officer
Azmi Nabulsi, MD, Chief Operating Officer and Head of Research and Development
Neila Smith, MD, Vice President Clinical and Patient Safety
Jennifer Stanek, BA Senior Director, CMC and Clinical Supplies

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for November 18, 2021 between Phathom and the Division of Gastroenterology. 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. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (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

Phathom is developing TAK-438 (vonoprazan) for the healing of all grades of erosive esophagitis (EE) and relief of heartburn, and maintenance of healing of all grades of EE and relief of heartburn.

The Sponsor states that vonoprazan is an orally active potassium competitive acid blocker (PCAB) originally developed by Takeda for a variety of acid related gastrointestinal disorders. TAK-438 (TAKECAB) has received regulatory approval in Japan and other countries in Asia and Latin America for indications of EE healing and maintenance, gastric ulcer/duodenal ulcer healing and prevention of recurrence of ulcers during NSAID or aspirin administration.

A pre-IND meeting was held on July 10, 2019, with the Division of Gastroenterology and Inborn Errors Products (DGIEP) to discuss the proposed phase 3 study design to assess the effect of vonoprazan on the healing and maintenance of healing in patients with EE. FDA granted a type C meeting on March 3, 2020, and issued final written responses regarding planned *in-vitro* and *in-vivo* drug-drug interaction studies.

A second pre-IND meeting was held on July 9, 2019, in collaboration with the Division of Anti-Infective Products to discuss the concurrent development program for vonoprazan in use with amoxicillin and clarithromycin (i.e., triple therapy) or vonoprazan in use with amoxicillin (i.e., dual therapy) for treatment of *Helicobacter pylori* (*H pylori*).

IND 79212 became active on September 8, 2019, for the indications of healing of all grades of EE and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, (b) (4)

On September 24, 2020, FDA issued an agreed initial Pediatric Study Plan for the healing of all grades of EE and relief of heartburn, and maintenance of healing of all grades of EE and relief of heartburn.

An end-of-phase 2 meeting discussing aspects related to chemistry, manufacturing and controls was canceled by the Sponsor on April 14, 2020, upon receipt of Preliminary Comments.

A pre-NDA meeting was granted by the Division of Anti-Infective Products and held on November 10, 2020, to discuss the adequacy of the non-clinical and clinical pharmacology development program to support a New Drug Application (NDA) filing.

On July 1, 2021, FDA issued final written responses (WRO) regarding Phathom's proposed strategy for the Integrated Summary of Effectiveness (ISE) and the Integrated Summary of Safety (ISS) and related data requirements for a NDA for vonoprazan for the healing and maintenance of healing of all grades of EE and relief of heartburn.

The goal of this pre-NDA meeting request submitted on September 24, 2021, is to discuss Phathom's submission strategy of the clinical and chemistry, manufacturing, and controls sections in support of a NDA (NDA 215151).

According to the background package received on October 18, 2021, Phathom submitted NDA 215152 (b) (4) Triple Pak and NDA 215153 (b) (4) Dual Pak on September 2, 2021, to the Division of Anti-Infectives.

2.0 DISCUSSION

2.1. CLINICAL/REGULATORY

Question 1:
Does the Agency agree with Phathom's proposed plan to include the *H* pylori indication in the labeling for NDA 215151 or have an alternative recommendation to the inclusion of this information as part of the NDA?

FDA Response to Question 1:
Your plan to include the proposed *H pylori* indication statement(s) in the labeling that will be submitted with NDA 215151 (i.e., the NDA for the erosive esophagitis indications) is reasonable. We acknowledge that NDAs 215152 and 215153 are currently under review in the Division of Anti-Infectives (DAI) for the *H pylori* indication(s) and that you will provide updated labeling to NDA 215151 consistent with the final labeling for those NDAs, if they are approved during the review cycle for NDA 215151. We remind you that the proposed *H pylori* indication would need to be included with the initial submission of NDA 215151 and although that indication could be modified, new indications should not be introduced during the review of the application. The labeling language for NDA 215151 will be determined during review of the NDA submission. For example, if the applications (NDAs 215152 and 215153) are subsequently not approved prior to the PDUFA goal date of NDA 215151, the *H pylori* portion of the label would not be included in the labeling for NDA 215151.

You may also wait to submit the *H pylori* indication as a supplement to NDA 215151 (once the review has been completed and if the application is approved).

Question 2a:
Does the Agency agree with the cross-referencing strategy to NDA 215152?

FDA Response to Question 2a:
Your plan to cross reference NDA 215152 for portions of the NDA 215151 submission, as outlined below, is generally acceptable:

- **Module 1: Transfer of Obligation, Financial Certification and Disclosure for Helicobacter pylori Studies (e.g., HP-301, TAK-438/CCT-401), Pediatric Information for H pylori indications, and the Biopharmaceutics Classification (b) (4) designation request.**

- **Module 2: Nonclinical Overview, Written and Tabulated Summaries, H pylori clinical documents.**

- **Module 3: CMC documents related to the drug substance and 20 mg strength tablet, development pharmaceutics and analytical methods applicable to both 10 mg and 20 mg tablets.**

- **Module 4: all non-clinical study reports and literature references.**

- **Module 5: Reports and data from H pylori studies (i.e., HP-301 and TAK-438/CCT-401) and thorough QTc study TAK-438_111 (including analysis programs and ECG waveforms).**

Question 2b:
Does the Agency agree with the proposed filing strategy for NDA 215151?

FDA Response to Question 2b:
Your proposed filing strategy to submit the following documents to NDA 215151, excluding those planned for cross-reference is generally acceptable:

- **Module 1: Administrative Documents (e.g., Certifications of Debarment, Financial Certification and Disclosure, Patents and Exclusivity, References, Correspondence, Pediatric Information, Labeling and Global IB, Risk Management Plan, and Proprietary Name Review Request).**

  - **We note your plan to include a Section 1.4.2 Statement of Right of Reference to NDA 215152.**

- **Module 2: Quality Overall Summary, Clinical Overview, Summary of Biopharmaceutic Studies and Summary of Clinical Pharmacology to include data from study VONO-103, Summary of Clinical Efficacy for EE indications, Summary of Clinical Safety, References, Individual Study Synopses.**

- **Module 3: Drug product information applicable to the 10 mg strength and non-copackaged 20 mg strength tablets.**

- **We note that your filing strategy for Module 3 omitted the submission of section 3.2.S.2.1 under NDA 215151. Your submission should include a complete listing of the manufacturing facilities for commercial production on Form FDA 356h and in 3.2.S.2.1 and 3.2.P.3.2. For submission of the manufacturing facilities related to an NDA, refer to FDA Guidance on Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers.[1] The need for facility evaluation will be determined upon receipt of NDA 215151 and will be independent of NDA 215152.**

- **Module 5: All CSRs (except those for cross-reference, above), Integrated Summary of Safety (ISS) and Integrated Summary of Safety (ISE), Datasets for EE-301, TAK-438/CCT-002, TAK-438/CCT-003, TAK-438_303, TAK-438_305 and the ISS, Literature Reference, Periodic Benefit Risk Evaluation Report with data lock of June 21, 2021.**

Question 3:
Does the Agency agree with this approach proposed by Phathom to provide the literature references for Module 2.5 Clinical Overview and any other literature references will be available upon request?

FDA Response to Question 3:
We cannot agree with your plan to provide literature references only for Module 2.5 Clinical Overview. The submitted application is intended to be self-contained and all literature references should be included in the submission. Each literature reference introduced in the application should ordinarily be submitted as individual files to the relevant section of the eCTD. If a list of references is included at the end of a document, there should be hypertext links to the appropriate publication. We refer you to the Guidance for Industry, M2 eCTD: Electronic Common Technical Document Specification.[2]

[1] Current guidance may be retrieved at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] Current Guidance may be retrieved here: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m2-ectd-electronic-common-technical-document-specification.We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Question 4:
Does the Agency agree with Phathom's proposal (b) (4)

FDA Response to Question 4:
Yes, your plan appears reasonable to exclude complete study reports for Studies (b) (4) and (b) (4) (b) (4) is not relevant to the proposed product, (b) (4). However, you should provide case report forms for any deaths, serious adverse events (AEs), treatment emergent AEs leading to discontinuation, and AEs of special interest from these two studies.

2.2. CMC

Question 5
Does the Agency agree with the proposed Executed Batch Records (EBR) to be included in the NDA?

FDA Response to Question 5
Yes, your proposal appears to be reasonable. The proposed Executed Batch Records (EBRs) appear to be representative of the manufacturing processes in both facilities. The adequacy of the cross-referenced data in NDA 215152 to support the approval of this NDA 215151 will be determined upon review of the submission.

Question 6
Does the Agency agree that the existing nonclinical development, clinical pharmacology and CMC program are complete and adequate to support review of the planned NDAs?
Error! Reference source not found.

FDA Response to Question 6
The existing nonclinical development, clinical pharmacology, and CMC program appear adequate to support the review of the planned NDA submission. Ultimately, the final determination of whether the information provided in the NDA is complete will be determined during the filing review upon receipt of the NDA submission.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 8, 2021 communication granting this meeting, if, at the time of

submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[3]

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

[3] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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 draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[4] 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.[5]

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 Information[6] and Pregnancy and Lactation Labeling Final Rule[7] 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

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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,* 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*.[10]

[10] https://www.fda.gov/media/85061/download

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/

MAUREEN D DEWEY
11/15/2021 12:48:31 PM