NDA 215152
NDA 215153

NDA APPROVAL

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

Dear Dr. Knipfer:

Please refer to your new drug applications (NDAs) dated and received September 3, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

- NDA 215152: Voquezna Triple Pak (vonoprazan tablets; amoxicillin capsules; clarithromycin tablets) 20 mg, 500 mg, 500 mg, co-packaged

- NDA 215153: Voquezna Dual Pak (vonoprazan tablets; amoxicillin capsules) 20 mg, 500 mg, co-packaged

These NDAs provide for the use of Voquezna Triple Pak and Voquezna Dual Pak for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of the Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information) as well as annual reportable changes not included in the

enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit the labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate these submissions as "**Final Printed Carton and Container Labeling for approved NDA 215152"** and "**Final Printed Carton and Container Labeling for approved NDA 215153"**. Approval of these submissions by FDA are not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Voquezna Triple Pak and Voquezna Dual Pak shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F). Brief excursion permitted to 15° C to 30° C (59° F to 86°F). [See USP Controlled Room Temperature.]

ADVISORY COMMITTEE

Your applications for Voquezna Triple Pak and Voquezna Dual Pak were not referred to an FDA advisory committee because the applications did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for these applications because necessary studies are impossible or highly impracticable as the prevalence of *H. pylori* infection that requires treatment is low in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes and also to evaluate the long-term safety of vonoprazan-containing products in lactating women, including assessing risks of adverse effects on the developing neonate. We have also determined that the extent of various cytochrome P450 (CYP) enzymes' contributions to the metabolism of vonoprazan has not been adequately characterized to assess the risk of increased vonoprazan exposure and toxicity in patients with reduced CYP activity (e.g., poor metabolizers). In addition, the drug-drug interaction (DDI) potential of vonoprazan metabolite M-I-G has not been adequately characterized to assess overall DDI related risks with Voquezna Triple Pak and Voquezna Dual Pak

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4270-1: Conduct a prospective, registry based, observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to vonoprazan-containing products during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on April 26, 2022, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/ 2022
Final protocol submission:	07/ 2023
Interim report:	07/ 2024
	07/ 2025
	07/ 2026
	07/ 2027

	07/ 2028
	07/ 2029
	07/ 2030
	07/ 2031
	07/ 2032
	07/ 2033
	07/ 2034
	07/ 2035
Study completion date:	07/ 2035
Final report submission date:	04/ 2036

4270-2: An additional pregnancy study that uses a different design from the Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to vonoprazan-containing products during pregnancy compared to an unexposed control population.

The timetable you submitted on April 26, 2022, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/ 2022
Final protocol submission:	07/ 2023
Interim report:	07/ 2024
	07/ 2025
	07/ 2026
	07/ 2027
	07/ 2028
	07/ 2029
	07/ 2030
Study completion date:	07/ 2030
Final report submission date:	04/ 2031

4270-3: Conduct a lactation study (milk only) in lactating women who have received vonoprazan-containing products to assess concentrations of vonoprazan in breast milk using a validated assay. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

The timetable you submitted on April 26, 2022, states that you will conduct this study according to the following schedule:

Draft protocol submission:	11/ 2022
Final protocol submission:	06/ 2023
Study completion date:	08/ 2024

Final report submission date: 05/ 2025

4270-4: Conduct a post-marketing in vitro reaction phenotyping study with selective chemical inhibitors to determine the role of cytochrome P450 (CYP) enzymes (e.g., CYP3A4/5, CYP2B6, CYP2C19, CYP2C9, and CYP2D6) in vonoprazan metabolism at clinically relevant concentrations under the linear condition. This study should be designed and conducted in accordance with the FDA Guidance for Industry entitled "In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions". Depending on the results of this in vitro study, additional studies may be needed.

The timetable you submitted on April 26, 2022, states that you will conduct this study according to the following schedule:

Draft protocol submission:	07/ 2022
Final protocol submission:	09/ 2022
Study completion date:	12/ 2022
Final report submission date:	03/ 2023

4270-5: Conduct post-marketing in vitro DDI studies to evaluate the inhibition potential of vonoprazan metabolite M-I-G on CYP enzymes (except CYP3A) and transporters.

The timetable you submitted on April 29, 2022, states that you will conduct this study according to the following schedule:

Draft protocol submission:	01/ 2023
Final protocol submission:	03/ 2023
Study completion date:	07/ 2023
Final report submission date:	12/ 2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocol(s) to your IND 143190 (vonoprazan, amoxicillin, clarithromycin) and IND 144399 (vonoprazan, amoxicillin) with a cross-reference letter to these NDAs. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDAs. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your INDs is for the purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for your approved NDAs (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could

benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Eva Zuffova, PhD, Regulatory Project Manager, at (301) 796-0697.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Carton and Container Labeling

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/

JOHN J FARLEY
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