CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215151Orig1s000

INTEGRATED REVIEW

Clinical Reviewer/Cross-Discipline Team Leader/Division Signatory Summary Review for Regulatory Action

Date	(electronic stamp)
From	Laura Finkelstein, MD, Clinical Reviewer Joette Meyer, PharmD, Cross-Discipline Team Leader Juli Tomaino, MD, Deputy Division Director
Subject	Clinical Reviewer/Cross-Discipline Team Leader/Division Signatory Summary Review
Application Type	NDA Resubmission to Complete Response
Priority or Standard	Standard, Class 2 Resubmission
NDA/BLA # and Supplement #	NDA 215151
Applicant	Phathom Pharmaceuticals
Initial Date of Submission	March 11, 2022
Complete Response Action Date (Initial)	February 7, 2023
Date of Resubmission	May 13, 2023
Resubmission PDUFA Goal Date	November 17, 2023
Proprietary Name	Voquezna
Established or Proper Name	Vonoprazan
Dosage Form(s)	Oral tablets, 10 mg and 20 mg
Applicant Proposed Indication(s)/Population(s) in Initial Submission	• Healing of all grades of erosive esophagitis (EE) and relief of heartburn associated with EE • Maintenance of healed EE and relief of heartburn associated with EE • Treatment of *Helicobacter pylori* in combination with antibiotics
Action or Recommended Action:	Approval
Approved/Recommended Indication(s)/Population(s) (if applicable)	• for healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults. • to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults. • in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults. • in combination with amoxicillin for the treatment of *H. pylori* infection in adults.

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ADL=Associate Director for Labeling
DPV=Division of Pharmacovigilance
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs

1. Benefit-Risk Assessment

Phathom Pharmaceuticals submitted new drug application (NDA) 215151 for Voquezna (vonoprazan) 10 mg and 20 tablets under the 505(b)(1) pathway on March 11, 2022, seeking the following indications: healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *H. pylori* infection. Voquezna Triple Pak and Voquezna Dual Pak (NDA 215152, co-package of vonoprazan/amoxicillin/clarithromycin and NDA 215153, co-package of vonoprazan/amoxicillin) for the treatment of *H. pylori* infection were approved on May 5, 2022, by the Division of Anti-Infectives. A cross-reference letter to NDA 215152 supported the safety and efficacy information for the use of vonoprazan for treatment of *H. pylori* infection.

A single adequate, and well-controlled study (Study EE-301) was conducted to support the safety and effectiveness of Voquezna for the proposed indications related to EE. Two additional studies each of healing and maintenance of healed EE, conducted outside the United States, served as confirmatory studies of efficacy, and also provided supportive safety data.

Although there were no observed safety or efficacy concerns with the nonclinical or clinical data in the NDA, the Applicant identified the presence of (b) (4) (b) (4) impurity, (b) (4) during the review cycle. The presence (b) (4) resulted in an unfavorable benefit-risk assessment during the initial review cycle and the application was given a Complete Response (CR) action on February 7, 2023. Refer to the Integrated Review, dated February 7, 2023 (Reference ID: 5122433).

The following benefit-risk assessment is based upon review of the Applicant's NDA resubmission of May 13, 2023, in response to the CR action. As discussed below, the CMC deficiencies from the original review cycle have been addressed. No new deficiencies were identified and the application is recommended for approval by all disciplines for all indications:

- healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults.
- in combination with amoxicillin for the treatment of *H. pylori* infection in adults.

The benefit risk assessment framework focuses on the indications of (1) healing of all grades of EE and relief of heartburn associated with EE in adults; and (2) maintenance of healing of all grades of EE and relief of heartburn associated with EE in adults. Refer to the Integrated Review for NDAs 215152/215153 dated May 3, 2022, for the benefit-risk assessment of Voquezna with clarithromycin and/or amoxicillin for the treatment of *Helicobacter pylori* (Voquezna Triple Pak/Voquezna Dual Pak).

Designated Signatory Authority Comments

I concur with the recommendation of the review team to approve NDA 215151 for Voquezna (vonoprazan) 10 mg and 20 tablets under the 505(b)(1) pathway, for the following indications:

- healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- to maintain healing of all grades of erosive esophagitis and relief of heartburn associated with erosive esophagitis in adults.
- in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults.
- in combination with amoxicillin for the treatment of *H. pylori* infection in adults.

The CMC deficiencies from the original review cycle that resulted in the Complete Response action, February 7, 2023, have been addressed in this resubmission (see Section 2 of this review for a summary of the OPQ assessment). The clinical safety and efficacy data contained in the original NDA, submitted March 11, 2022, supported a favorable benefit-risk assessment (See the Integrated Review, dated February 7, 2023 [Reference ID: 5122433]). The resubmission did not contain new clinical studies, and the additional safety data from a long-term study, Vonoprazan-4003 (VISION), were consistent with the safety findings in the original review. The postmarketing requirements were negotiated and agreed during this review cycle and will be issued as outlined in Section 11 of this review. The overall benefit-risk assessment supports approval, and the labeling is adequate to communicate the known and potential risks to healthcare providers and patients.

Benefit-Risk Assessment Framework

Voquezna (vonoprazan) tablets (NDA 215151) demonstrated safety and effectiveness in adults for the healing of all grades of EE and relief of heartburn associated with EE in adults and to maintain healing of all grades of EE and relief of heartburn associated with EE in adults in the original NDA submission submitted March 11, 2022, which received a complete response on February 7, 2023, due to CMC deficiencies relating to a (b) (4) impurity, (b) (4). In the NDA, the Applicant proposes two dosage forms: 10 mg and 20 mg tablets. The proposed recommended dosage regimen is 20 mg once daily for 8 weeks for healing of EE and 10 mg once daily for up to 6 months for maintenance of healed EE. In the NDA resubmission, received May 19, 2023, the Applicant made changes in the manufacturing process (b) (4). Based on review of the six-month accelerated and long-term stability data it has been concluded that the level (b) (4) will not exceed the acceptance criterion for the drug product by the end of the proposed drug product expiration dating period of 24 months. There are no remaining CMC deficiencies, and the regulatory recommendation is for approval.

Erosive esophagitis is a complication of severe gastroesophageal reflux disease (GERD), defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms (e.g., heartburn). GERD, along with EE, represents a significant disease burden globally, with the U.S. population being highly affected. Persistent erosions can lead to morbidity associated with complications such as bleeding and strictures, and failure to control EE symptoms can have a significant impact on patients. Current treatment options include proton pump inhibitors (PPIs) which are effective for healing of EE and generally well-tolerated for short-term use, but adult patients frequently have recurrence of EE which may lead to use of higher doses, more frequent dosing, and long-term/chronic use which may be associated with safety risks related to long-term acid suppression. Additionally, some patients do not respond to individual PPIs. Availability of Voquezna, a potassium-competitive acid blocker and related to the PPI drug class, will provide patients with an alternative therapy option.

The effectiveness of Voquezna was established in the original NDA 215151 submission and is supported by the results of a single adequate and well-controlled study (Study EE-301) that demonstrated efficacy of vonoprazan 20 mg in healing of all grades of erosive esophagitis by Week 8 and vonoprazan 10 mg in maintenance of healed EE at week 24. In the healing phase, subjects were randomized to receive vonoprazan 20 mg or active comparator (lansoprazole 30 mg) once daily. Subjects who were healed were re-randomized to receive vonoprazan 10 mg or 20 mg or active comparator (lansoprazole 15 mg) once daily for the maintenance phase. The study met its primary endpoints of the proportion of subjects with complete healing of EE by Week 8 (non-inferior to comparator) and proportion of subjects with maintained healing at week 24 (non-inferior to comparator). The study also met secondary endpoints of non-inferiority for the percentage of 24-hour heartburn-free days in both the healing and maintenance phases. Data from four similarly designed ex-U.S. studies of EE provided confirmatory evidence of the efficacy observed in Study EE-301.

The safety of vonoprazan was supported by Study EE-301, by data from the four ex-U.S. EE studies, pooled safety data from studies in other indications, and foreign post-marketing data. The safety profile of vonoprazan was generally favorable and comparable to the safety drugs in the

related class of PPIs. In the healing phase, most common adverse reactions were gastrointestinal, including gastritis, diarrhea, abdominal distension, abdominal pain, and nausea. In the maintenance phase, the common reactions were similar, but also included dyspepsia, hypertension, urinary tract infection and headache. A case of acute interstitial nephritis was reported during Study EE-301 and evaluation of post-marketing data supported a potential association. The resubmission included additional safety data from a long-term study, Vonoprazan-4003 (VISION), conducted in Japan, which randomized adults with EE 2:1 to vonoprazan 20 mg or comparator (lansoprazole 30 mg) once daily for healing of EE. Subjects who healed by 8 weeks continued to receive vonoprazan 10 mg or lansoprazole 15 mg once daily for up to 5 years. Long-term safety data of vonoprazan from VISION were consistent with the safety findings in the original review. No new safety signals were identified.

The overall benefit-risk assessment supports the approval of Voquezna as an oral tablet for healing of EE and relief of heartburn associated with EE in adults and for the maintenance of healed EE and relief of heartburn associated with EE in adults. Labeling will communicate the potential risks related to vonoprazan, including those associated with long-term acid suppression. Routine pharmacovigilance is adequate to monitor for new safety signals. The Applicant will conduct five postmarketing studies required under the Pediatric Research Equity Act (PREA) for pediatric patients aged 1 month to < 18 years of age and develop an age-appropriate formulation for pediatric patients less than 6 months. The two existing pregnancy registry studies (a prospective study and an additional study that uses a different design) agreed to by the Applicant for NDAs 215152 and 215153 as FDAAA PMRs, will include patients exposed to vonoprazan as monotherapy.

1. Regulatory Background

NDA 215151 was originally submitted on March 11, 2022. During review of the original submission, the review team determined that the Applicant adequately demonstrated the safety and effectiveness of Voquezna for the indications sought. Although there were no reported adverse reactions or laboratory abnormalities observed in the NDA that precluded approval, the OPQ review identified deficiencies in the drug product due to the presence of a (b) (4) impurity, (b) (4) identified by the Applicant during the review cycle. The Applicant's proposed acceptance criteria for the (b) (4) impurity in the drug product specifications exceeded the acceptable intake limit resulting in a lack of chemistry manufacturing and controls (CMC) information to support a viable shelf life for both the 10 mg and 20 mg tablets. A complete response letter was issued for NDA 215151 on February 7, 2023, citing the following product quality issues:

(b) (4)

On February 9, 2023, the Applicant, submitted a meeting request and meeting background package to discuss the submission of a reformulation of vonoprazan tablets (b) (4) . Preliminary comments were sent on March 3, 2023, and the Type A meeting was held March 7, 2023. The Agency responded that the overall proposed plan to modify the drug product formulation (b) (4) was reasonable, including the proposed stability program and change in drug substance manufacturer and testing site facilities. The Agency agreed with the Applicant's proposed safety update strategy for the resubmission to include a safety summary of the completed and ongoing clinical trials, including new safety data from the completed 5-year comparative safety study in patients with healed EE (Vonoprazan-4003; VISION), and a worldwide postmarketing safety update.

In a post-meeting comment in the Meeting Minutes of March 24, 2023, the Agency clarified that (b) (4) , the Applicant may request a biowaiver based on scientific justification or conduct a relative bioavailability study.

In a follow-up request for clarification received on March 29, 2023, the Applicant requested confirmation on the elements to be included in the formal biowaiver request in the NDA resubmission. The Agency's response of March 31, 2023 was that the approach outlined in the meeting package, and further discussed at the Type A meeting and in the post-meeting comments, appeared reasonable.

On May 13, 2023, the NDA resubmission to the complete response action of February 7, 2023, was received.

2. Product Quality

The specific product quality deficiencies in the complete response letter of February 7, 2023, were:

1. Revise the acceptance criterion (b) (4) for the drug product release and stability specifications.
2. Perform a root cause investigation (b) (4)
3. Submit long term, intermediate (if applicable), and accelerated stability data for at least three batches for each strength (i.e., 10 mg and 20 mg tablets) representative of the to-be-marketed product demonstrating that the stability data meet the updated specifications, including acceptance criterion (b) (4) . Refer to the guidance for industry, *Q1A(R2) Stability Testing of New Drug Substances and Products (November 2003)*.

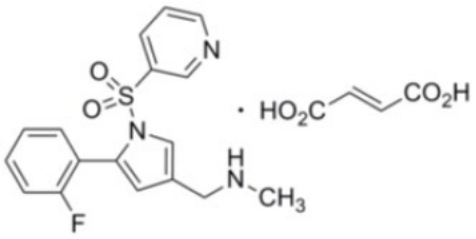
In the NDA resubmission, the Applicant made updates to the drug substance, reformulated the drug product (b) (4) , and provided supporting stability data to show that the (b) (4) impurity is well controlled throughout the proposed shelf-life and dissolutions data to support the proposed formulation change.

The drug product specification was also updated by the Applicant with the test and acceptance criteria (b) (4) .

Drug Substance

The pharmaceutical active ingredient, vonoprazan fumarate is the fumarate salt of the active moiety vonoprazan which belongs to a new class of acid-inhibitory agents called potassium competitive acid blockers (PCAB). Vonoprazan fumarate is white to nearly white crystals or crystalline powder with a melting point of 194.8°C. Vonoprazan fumarate is soluble in dimethyl sulfoxide; sparingly soluble in N,N–dimethylacetamide, slightly soluble in N,1-dimethylformamide, methanol and water; very slightly soluble in ethanol (99.5%); and practically insoluble in 2-propanol, acetone, 1-octanol, and acetonitrile.

Vonoprazan fumarate has the chemical name, 1-[5-(2-Fluorophenyl)-1-(pyridine-3-ylsulfonyl)-1Hpyrrol- 3-yl]-N-methymethanamine monofumarate, molecular formular, C17H16FN3O2S . C4H4O4, molecular weight, 461.46 g/mol, and the chemical structure below:



The original NDA included cross-references to NDA 215152 for the drug substance and for the 20 mg strength tablets, including development pharmaceutics and analytical methods applicable to both the 10 mg and 20 mg tablets. The NDA resubmission includes the previously cross-referenced information and data supporting the manufacture of vonoprazan fumarate drug substance at Evonik Operations GmbHk, previously approved as an alternate drug substance manufacturer under NDAs 215152/215153. The drug substance manufacturers included in the original NDA 215151 (b) (4) are withdrawn in the resubmission. The resubmission also includes data supporting the addition of (b) (4) as a testing site (b) (4) in the drug substance and drug product.

In the resubmission, the Applicant has reformulated the vonoprazan tablets (b) (4) and the drug product specification limits (b) (4) were revised to not more than (NMT) (b) (4) ppm for release and at NMT (b) (4) ppm for stability. Analytical analysis of several batches of the drug substance showed the level (b) (4) to be approximately (b) (4) ppm. A control of this (b) (4) impurity has been added to the drug substance specification with an acceptance limit of NMT (b) (4) ppm. A limit of (b) (4) ppm translates to a daily exposure of (b) (4) day. During the original NDA review cycle, FDA agreed to the Applicant's proposal to use (b) (4) as a read-across surrogate for the derivation of an acceptable intake (AI) for (b) (4) in the drug product. The corresponding acceptance criterion for (b) (4) in the drug product in based on the AI of (b) (4) /day and the maximum daily dose (MDD) of the product (40 mg/day), is (b) (4) ppm. Refer to the Integrated Review, dated February 7, 2023 (Reference ID: 5122433).

Therefore, the acceptance criteria of NMT (b) (4) ppm for release and NMT (b) (4) ppm for stability are acceptable.

In summary, OPQ determined that vonoprazan fumarate in the resubmission is manufactured at Evonik Operations GmbH in accordance with the current Good Manufacturing Practices (cGMP) requirement. It is tested and released against a specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of (b) (4) months. Based on the stability data, the applicant's proposal to test the drug substance for (b) (4) (b) (4) every (b) (4) months is acceptable.

Drug Product

Voquezna (vonoprazan) is supplied as 10 mg and 20 mg tablets for oral administration. The 10 mg tablets are pale yellow, oval, film-coated tablets debossed with "V10" on one side and plain on the other side. Each tablet contains 10 mg of vonoprazan (equivalent to 13.36 mg of vonoprazan fumarate) as the active ingredient. The 20 mg tablets are pale red, oval, film-coated tablets debossed with "V20" on one side and plain on the other side. Each tablet contains 20 mg of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate) as the active ingredient.

Voquezna tablets also contain the following inactive ingredients: ascorbic acid, croscarmellose sodium, ferric oxide red (only in 20 mg tablets), ferric oxide yellow (only in 10 mg tablets), fumaric acid, hydroxypropyl

cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide. The inactive ingredients used in the tablet composition are all compendial materials.

The drug product has been reformulated (b) (4) There were no changes to the container closure system. All excipients in the vonoprazan tablets are within the Inactive Ingredients Database limits of previously approved oral drug products and there are no novel excipients.

The manufacturing process for the drug product has not changed since the original NDA submission. The (b) (4) is used for manufacture of the 10 mg and 20 mg (b) (4) tablets. (b) (4) The container closure system has not changed. Voquezna tablets are packaged as 30 tablets in high density polyethylene (HDPE) bottles with (b) (4) closure.

As noted above, the drug product specification has been updated in the resubmission with the test and acceptance criteria for the (b) (4) impurity. In the revised drug product specifications, the acceptance limits (b) (4) to NMT (b) (4) ppm at release and NMT (b) (4) ppm during the shelf-life is acceptable for the drug product.

Based on the six-month accelerated and long-term stability data on three primary batches of vonoprazan tablets, 10 mg and 20 mg the OPQ review team has concluded the level of the (b) (4) impurity (b) (4) will not exceed the acceptance criterion by the end of the proposed drug product expiration dating period of 24 months and that a shelf-life of 24 months is granted when stored in the HDPE bottle with (b) (4) closure at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).

Manufacturing

The manufacturing site for drug product (unchanged from the previous submission) is Catalent Pharma Solutions, LLC, Kentucky. Voquezna tablets are manufactured at Catalent Pharma Solutions, LLC in accordance with the cGMP requirement and are tested and released against a specification that assures the identity, strength, purity and quality of the drug product at release and throughout its assigned expiration dating period of 24 months.

No inspections were conducted during the resubmission. The Office Pharmaceutical Manufacturing Assessment has made the overall recommendation for approval of facilities involved in this application based upon previous history (Catalent Pharma Solutions, LLC, Kentucky; (b) (4) and district recommendation (Evonik Operations GmbH).

Biopharmaceutics

In the original NDA submission, the dissolution method and acceptance criterion were acceptable. In the resubmission, the Applicant has requested a biowaiver for the reformulated drug product.

OPQ agrees that a biowaiver can be granted for the reformulated vonoprazan tablets, 10 mg and 20 mg, based on the following rationale:

- Vonoprazan fumarate is a highly soluble drug substance, and the drug product is very rapidly dissolving; therefore, the tablets have low biopharmaceutics risk.

- (b) (4)

- Two in vivo bioavailability studies conducted comparing a vonoprazan orally disintegrating tablet and (b) (4) sprinkle capsule to the 20 mg vonoprazan immediate-release tablets (b) (4) did not show an effect of excipient changes on the absorption of vonoprazan.
- Comparative dissolution testing results demonstrate that the dissolution profiles of the original tablets and reformulated tablets exhibit similar dissolution profiles in three different media and that both formulations display very rapid drug release.

Environmental Assessment

The Applicant's request for a categorical exclusion from the requirement to submit an Environmental Assessment per 21 CFR 25.31(b) is acceptable (also refer to the Integrated Quality Assessment for the original NDA submission, dated February 6, 2023).

Labeling

The CMC issues on labels/labeling were conducted and satisfactorily resolved during the first review cycle and no additional CMC labeling review was performed in this review cycle.

OPQ Recommendation

In the resubmission, the Applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, vonoprazan fumarate and the drug product, Voquezna (vonoprazan) tablets, 10mg and 20mg. All CMC deficiencies from the complete response letter of February 7, 2023, have been satisfactorily resolved.

OPQ recommends approval of this application with the expiration dating period of 24 months.

3. Nonclinical Pharmacology/Toxicology

The nonclinical safety profile of vonoprazan (TAK-438) and its metabolites have been studied extensively and reviewed under NDAs 215152 and 215153 for the treatment of *H. pylori* infection in adults and was summarized in the Integrated Review, dated February 7, 2023 (Reference ID: 5122433). The NDA resubmission included reports from pharmacokinetic studies conducted in juvenile rats: absorption (one study), metabolism (two studies) and juvenile toxicology (two three studies). The studies were previously reviewed under IND 079212. Similar to other acid-suppressive medications, bone effects (femur metaphysis/diaphysis and, in females only, lumbar vertebrae) were observed in the 6-week juvenile rat toxicity study with 8-week recovery period. However, the no observed adverse event level (NOAEL) of 10 mg/kg (based on body weight, bone mass and bone density) provides an assurance of safety for proposed future pediatric studies. Refer to the Nonclinical Review by Dinesh Gautam, dated July 20, 2023 (Reference ID: 5212357).

4. Clinical Pharmacology

No new clinical pharmacology data were included in the resubmission. Refer to the Integrated Review, dated February 7, 2023 (Reference ID: 5122433).

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

No new efficacy data were included in the resubmission. Evidence of effectiveness of vonoprazan for healing of EE and relief of heartburn and maintenance of healed EE and relief of heartburn was established during the original review cycle, based on a single adequate and well-controlled trial EE-301 with confirmatory evidence from four studies of similar design conducted outside the United States (i.e., Studies TAK-438/CCT-002, TAK-439_303, TAK-438/CCT-003 and TAK-438_305). Refer to the Integrated Review, dated February 7, 2023 (Reference ID: 5122433).

During the resubmission review, the statistical review team noted that a rounding error was made in the calculation of the rate of healed EE through Week 24 in a subgroup of the population in Study EE-301, which prompted a correction to the CLINICAL STUDIES section of the Voquezna prescribing information (PI). See the Labeling section of the review for additional details.

7. Safety

The safety of vonoprazan for the healing of EE and relief of heartburn and maintenance of healed EE and relief of heartburn was established during the original review cycle. Refer to the Integrated Review, dated February 7, 2023 (Reference ID: 5122433).

In the original review, the most common adverse reactions in Study EE-301 for the healing of EE (≥2%) with Voquezna 20 mg once daily were gastrointestinal in nature and consisted of gastritis, diarrhea, abdominal distension, abdominal pain, and nausea. The most common adverse reactions in Study EE-301 for the maintenance of healed EE (≥3%) with Voquezna 10 mg once daily were gastritis, abdominal pain, dyspepsia, hypertension, and urinary tract infection. Pooled adverse event data from four confirmatory studies in subjects with EE conducted outside the United States were consistent with the findings in Study EE-301.

The original safety assessment evaluated adverse events of special interest (AESIs) identified based on potential risks associated with vonoprazan (i.e., hepatotoxicity, cytopenia), related to long-term acid suppression (i.e., *Clostridiodes difficile*-Associated Diarrhea [CDAD], bone fracture, vitamin B12 deficiency, hypomagnesemia, fundic gland polyps), or associated with PPIs but not related to acid suppression (i.e., acute tubulointerstitial nephritis, severe cutaneous adverse reactions, systemic or cutaneous lupus erythematosis). The review team recommended including the following AESIs in the WARNINGS AND PRECAUTIONS section of the Voquezna PI.

- Acute Tubulointerstitial Nephritis
- *Clostridiodes difficile*-Associated Diarrhea
- Bone Fracture
- Severe Cutaneous Adverse Reactions

- Vitamin B12 (Cobalamin) Deficiency
- Hypomagnesemia and Mineral Metabolism
- Fundic Gland Polyps

In the original Integrated Review, the review team concluded that data relating to hepatotoxicity and cytopenia did not support a WARNING AND PRECAUTIONS and instead recommended including the terms of increased liver function test and anemia in the ADVERSE REACTIONS section under a heading of "Less Common Adverse Reactions" in the Voquezna PI.

The original NDA included 4-year summary data from Study Vonoprazan-4003, an ongoing 5-year randomized, double-blind safety trial of vonoprazan compared to lansoprazole for long-term maintenance of healed EE conducted in Japan (hereafter referred to as VISION). In the resubmission, which included the final study report (translated from Japanese) and legacy datasets for the completed 5-year study, no new safety findings for SAEs, TEAEs, or AESIs were identified. The occurrence of gastric polyps by 5-years in VISION was quantified at approximately 50% of subjects in both the vonoprazan and lansoprazole (PPI comparator) groups. Therefore, the WARNINGS and PRECAUTIONS subsection on fundic gland polyps in the Voquezna PI was expanded to indicate that polyps have been reported with vonoprazan in clinical trials and the risk increases with long-term use, especially beyond one year. Refer to Appendix for details of the safety analysis of the completed study.

In addition to results from VISION, the resubmission also included a safety update, including clinical study reports, from four completed studies (two pharmacokinetic studies, a phase 2 study in subjects with episodic heartburn and symptomatic gastroesophageal reflux disease (sGERD), and a phase 3 clinical study of quadruple therapy for *H. pylori*) and two ongoing clinical studies (a pharmacokinetic study in adolescents with sGERD, VPED-102, (b) (4) The Division of Anti-infectives (DAI) was consulted to review the safety data from the *H. pylori* pharmacokinetic and clinical studies in the resubmission. The DAI review did not identify any new signals.

In summary, the new safety data submitted in the NDA were consistent with the previous findings of safety from the original NDA review, with no new safety signals identified.

8. Pediatrics

No pediatric studies were conducted as part of this NDA. As noted in the original NDA submission, Voquezna is subject to study requirements under the Pediatric Research Equity Act (PREA) because vonoprazan for healing of EE and relief of heartburn and maintenance of healed EE and relief of heartburn introduces new indications and a new dosing regimen. Because of the Complete Response issued during the previous review cycle, no PMRs were issued. Refer to Section 8.3 Plans for Pediatric Drug Development in the original Integrated Review.

On August 10, 2023, the Applicant submitted an Amended iPSP to IND 079212. The Applicant reached agreement with the Division, with concurrence of the Pediatric Review Committee (PeRC), on an Amended Agreed iPSP on September 7, 2023, superseding the study plan included in the resubmission. (b) (4)

The Division of Anti-Infectives granted a full waiver for PREA requirements for the treatment of *H. pylori* infection for NDAs 215152/215153 on May 3, 2022. The pediatric study(ies) requirement was waived because necessary studies are impossible or highly impracticable. The prevalence of *H. pylori* infection that

requires treatment is low in the pediatric population. Therefore, a waiver of pediatric studies under PREA for the treatment of *H. pylori* for NDA 215151 will also be granted.

Pediatric studies for healing of EE/maintenance of healed EE are waived for ages birth to less than 1 month of age because studies in this age group are impossible or highly impracticable. The number of pediatric patients with erosive esophagitis in this age group is limited.

Pediatric studies for healing of EE/maintenance of healed EE are deferred in pediatric patients 1 month to less than 18 years of age because the drug is ready for approval for use in adults before pediatric studies are complete. The deferred assessment includes a plan to conduct four pharmacokinetic studies and one clinical trial in pediatric patients 1 month to less than 18 years of age (see Postmarketing section for a description of these studies/trial). The proposed PMRs were discussed with PeRC on October 3, 2023.

(b) (4)

9. Other Relevant Regulatory Issues

None.

10. Labeling

Prescribing Information

The FDA agreed the Applicant could include the *H. pylori* indication in this NDA with a cross-reference to NDAs 215152/212153 for the safety and efficacy information on the use of Voquezna co-packaged with clarithromycin and/or amoxicillin (Voquezna Triple Pak/ /Dual Pak). The language for the *H. pylori* indication throughout the PI aligns with the approved labeling for NDAs 215152/212153.

Although the CMC deficiencies in the original NDA precluded approval, labeling was negotiated with the Applicant during the first review cycle. Refer to Section 21 Labeling Summary of Considerations and Key Additional Information in the original Integrated Review.

The following additional revisions were made during the resubmission:

DOSAGE AND ADMINISTRATION

Recommended Dosage

- The recommended dosage regimens was revised (b) (4) to text and the specific dosing recommendations for the treatment of *H. pylori* infection were added for both the dual and triple therapy regimens (timing of administration in the morning and evening, 12-hours apart) to align with the approved labeling for NDAs 215152/215153.

- The statement [redacted] was removed from the description of the healing of EE and relief of heartburn indication. [redacted]

Recommended Dosage in Patients with Renal Impairment/ Recommended Dosage in Patients with Hepatic Impairment

- The recommendation to [redacted] in patients being treated for *H. pylori* infection with an estimated GFR of < 30 mL/ minute or with Child-Pugh Class B and C hepatic impairment was revised to "use is not recommended" to align with the draft Guidance for Industry (2023): *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.

WARNINGS AND PRECAUTIONS

Fundic Gland Polyps

- This subsection was revised to indicate that vonoprazan is associated with a risk of fundic gland polyps that increases with long-term use, especially beyond one year.

ADVERSE REACTIONS

Clinical Trials Experience

- The tabular listing of the most common adverse reactions in the maintenance of healed EE phase of Study EE-301 was revised to those reported in at least 3% of patients in the Voquezna group. This revision removed [redacted] Headache was added to the less common listing of adverse reactions in 1% or less in Voquezna-treated patients.

DRUG INTERACTIONS

- A subsection was added to the drug interactions table "Drug Interactions Affecting Drugs Co-Administered with VOQUEZNA and Interactions with Diagnostics" for co-administration of Voquezna with clarithromycin and/or amoxicillin for the treatment of *H. pylori* infection. Some adverse reactions are potentially fatal. Reference is added to the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections of the clarithromycin and amoxicillin labeling.

CLINICAL STUDIES

Maintenance of Healed Erosive Esophagitis and Relief of Heartburn

- The rate of healed EE through Week 24 in the subgroup of with baseline LA Grade C or D severity of EE was revised from [redacted]%" to "61%" to correct a rounding error. In Study EE-301 the rate of healed EE to the nearest hundredth of a percentage is 61.46% and the value is listed as 61.5% in original Integrated Review, dated February 7, 2023.

Patient Labeling

As discussed in the original NDA submission, the PPIs have a Medication Guide due to the risks of acute tubulointerstitial nephritis, *Clostridiodes difficile*-associated diarrhea, (CDAD), bone fracture, and lupus erythematosus. A Medication Guide is not deemed necessary at this time for Voquezna; however, Patient Information (PPI) was recommended for Voquezna to convey these same risks as the PPIs, with the exception of lupus erythematosus which has not been reported with vonoprazan. These, and additional risks of vitamin

B12 deficiency and hypomagnesemia, will be a part of routine pharmacovigilance monitoring post-approval of Voquezna. Should cases be reported, the need for a Medication Guide will be reassessed.

Carton and Container Labeling

There were no comments on the carton and container labeling in the resubmission. The recommendations from the previous review cycle were incorporated by the Applicant.

11. Postmarketing

Postmarketing Requirements and Commitments

Under FDAAA, two postmarketing requirements (PMRs) will be issued for pregnancy registries (a prospective study and an additional study that uses a different design) to obtain data on use of vonoprazan in pregnant women. These registries were previously agreed to by the Applicant under NDAs 215152/25153 and are designed to enroll patients exposed to vonoprazan monotherapy.

Vonoprazan is the first-in-class of potassium-competitive acid blocking agents. Despite the lack of a safety signal in animal reproductive toxicology studies for vonoprazan alone, the lack of human safety data with vonoprazan exposure in pregnancy is a safety issue. Vonoprazan is anticipated to be used in females of reproductive potential, wherein exposure to the drug may occur before the female is aware of the pregnancy. Data are needed on the safe use of vonoprazan-containing products during pregnancy as there is currently no available human data to inform the safety of vonoprazan combination products during pregnancy, and the small number of pharmacovigilance reports on pregnancy exposure to vonoprazan monotherapy are missing information to assess for a causal relationship between the drug and maternal/fetal outcomes. The goal of the second registry is to evaluate the safety of vonoprazan-containing products in females exposed during pregnancy, including assessing risks of pregnancy complications, major congenital malformations, and other adverse effects on the developing fetus and neonate. The study may provide data regarding rare pregnancy outcomes and corroborate findings from the prospective pregnancy registry.

Under PREA, five PMRs will be issued (four studies and development of an age-appropriate formulation will be issued. Refer to section on **Pediatrics** for discussion of the PREA PMRs.

All PMRs and milestone dates were communicated to the Applicant on October 13, 2023. The Applicant responded on October 23, 2023, agreeing to the pregnancy registry studies and proposed dates for the interim reports, study completion, and final study report harmonized with NDAs 215152/25153. The Applicant also agreed with the proposed timelines for the four pediatric studies. (b) (4)

On October 23, 2023, the Applicant agreed to all PMRs and milestone dates.

FDAAA PMRs

Study 1 (PMR 4367-1)

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.

- Final Protocol Submission: December 2023
- Interim Report(s): July 2024 – July 2035 (Annual)
- Study Completion: July 2035
- Final Report Submission: April 2036

Study 2 (PMR 4367-2)

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.

- Draft Protocol Submission: December 2023
- Final Protocol Submission: July 2024
- Interim Report(s): July 2024 – July 2031 (Annual)
- Study Completion: July 2031
- Final Report Submission: April 2032

PREA PMRs

Study 1 (PMR 4367-3)

Complete the ongoing randomized, parallel-group, multiple-dose, 14-day dose-ranging study to evaluate the pharmacokinetics and safety of Voquezna (vonoprazan) in pediatric patients 12 to <18 years of age with gastroesophageal reflux disease, with or without erosive esophagitis.

- Final Report Submission: February 2024

Study 2 (PMR 4367-4)

Conduct a randomized, parallel-group, multiple-dose, 14-day, dose ranging study to evaluate the pharmacokinetics, and safety of Voquezna (vonoprazan) in pediatric patients ≥ 6 to <12 years of age with gastroesophageal reflux disease (GERD) with or without erosive esophagitis.

- Final Protocol Submission: December 2023
- Study Completion: January 2025
- Final Report Submission: July 2025

Study 3 (PMR 4367-5)

Conduct a randomized, parallel-group, multiple-dose, 14-day, dose ranging study to evaluate the pharmacokinetic and safety of Voquezna (vonoprazan) in pediatric patients ≥ 1 month to <1 year of age with

erosive esophagitis and pediatric patients ≥ 1 year to < 6 years of age with gastroesophageal reflux disease (GERD) with or without erosive esophagitis.

- Final Protocol Submission: January 2025
- Study Completion: December 2026
- Final Report Submission: June 2027

Study 4 (PMR 4367-6)

Conduct a trial to evaluate the efficacy and safety of Voquezna (vonoprazan) for the healing of endoscopically confirmed erosive esophagitis and relief of heartburn symptoms and the maintenance of healed erosive esophagitis and relief of heartburn symptoms in pediatric patients ≥1 month to <18 years of age with endoscopically confirmed erosive esophagitis. The trial will include two study periods: an 8-week healing phase and a randomized, blinded, placebo-controlled 24-week maintenance phase.

- Final Protocol Submission: August 2024
- Study Completion: August 2030
- Final Report Submission: February 2031

Formulation Development (PMR 4367-7)

Develop an age-appropriate formulation for pediatric patients 1 month to < 6 months of age.

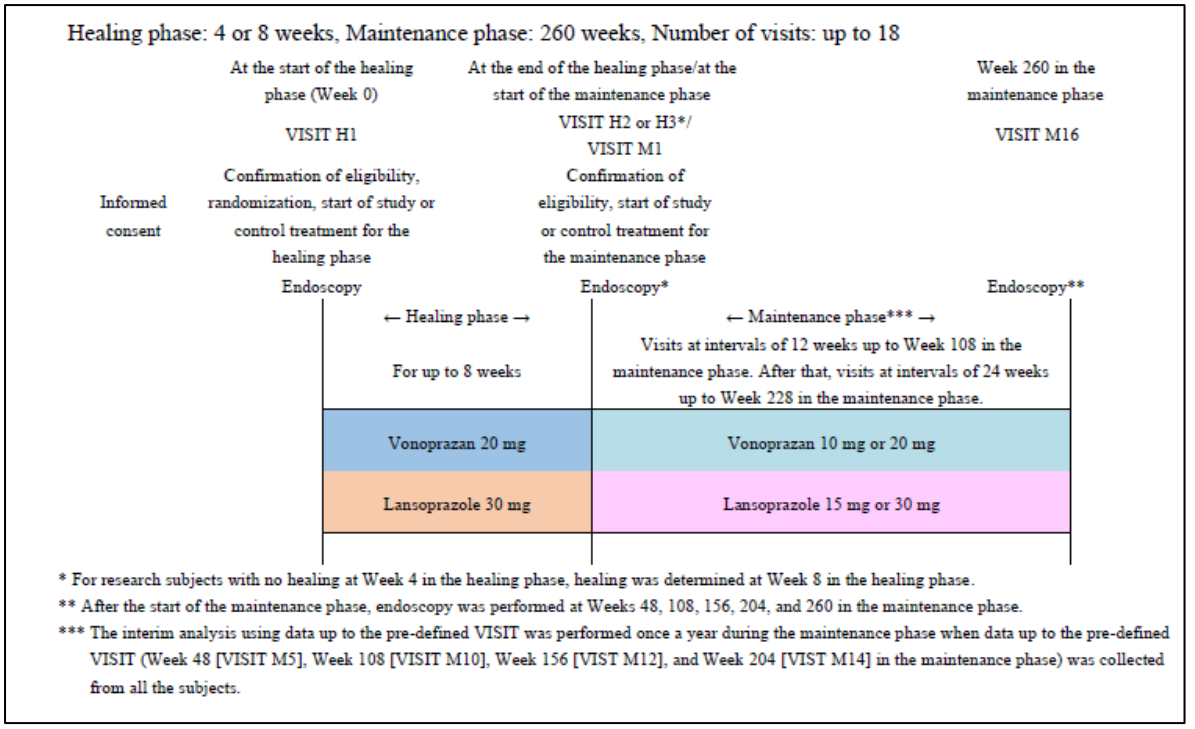
- Final Report Submission: January 2025

12. Appendix

Safety Review of Vonoprazan-4003 (VISION) Study

Vonoprazan-4003, titled "Vonoprazan study in patients with erosive esophagitis to evaluate long-term safety: A study to evaluate the safety of long-term administration of vonoprazan in maintenance treatment in patients with erosive esophagitis (EE)" (hereafter referred to as "VISION") was a phase 4, open-label, randomized, parallel-group study in 202 adult Japanese subjects with healing of EE. Subjects with endoscopically confirmed EE of any LA Grade were enrolled and randomized 2:1 to receive treatment with vonoprazan 20 mg once daily or lansoprazole 30 mg once daily for up to 8 weeks. Subjects with confirmation of healing of EE on endoscopy performed at 4 or 8 weeks continued vonoprazan 10 or lansoprazole 15 mg once daily for five years for maintenance of healed EE. See **Figure 1**. The investigator could increase the respective daily dose of vonoprazan (20 mg) or lansoprazole (30 mg) if the investigator judged that there was insufficient effect for maintenance of healed EE at the randomized dosage.[1] Study visits were conducted every 3 months, with laboratory studies and physical examinations performed. Repeat endoscopy was performed annually (i.e., at Weeks 48, 108, 156, 204, and 260).

Figure 1: Study Design Schema, Vonoprazan-4003 (VISION)



Source: Study Protocol, Vonoprazan-4003 Version 5, June 10, 2021, p.24

The safety review of the NDA resubmission focused on data from VISION to assess the safety of vonoprazan with long-term use and to support the findings of safety from the original NDA submission.

[1] Seventeen subjects in the vonoprazan group (12.2%) had their maintenance dose increased from 10 mg to 20 mg once daily. Twelve subjects in the lansoprazole group (17.4%) had their maintenance dose increased from 15 mg to 30 mg once daily. Refer to **Table 1**.

Approach to the Safety Review

The Applicant conducted their safety analysis considering only the data from subjects who entered the maintenance phase (i.e., 202 subjects, 135 in vonoprazan group and 67 in lansoprazole group). The review team assessed data from both the healing and maintenance phases of VISION (i.e., 208, 139 in vonoprazan group and 69 in lansoprazole group) to consider all available safety data. A high percentage of subjects in each healing phase treatment group continued into the maintenance phase (99%). The review focused primarily on safety data from the group of subjects who received vonoprazan. The design of the study and the small sample size did not allow for comparative assessment of safety between vonoprazan and lansoprazole.

The review analyzed serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs). The review also considered the Adverse Events of Special Interest (AESIs) previously described in the original NDA review.

- Hepatoxicity was assessed as an AESI for vonoprazan based on identification of an important potential safety risk at the time of marketing approval in Japan and a risk for hepatotoxicity in the earlier development of other PCAB drugs outside of the U.S. (i.e., linaprazan). During drug development of Voquezna, the review team requested that the Applicant evaluate hematologic abnormalities as an AESI, based upon the postmarketing addition of pancytopenia, agranulocytosis, leukocytopenia, and thrombocytopenia to the Japanese prescribing information for vonoprazan (Takecab®).
- AESIs related to long-term acid suppression include: *Clostridiodes difficile*-associated diarrhea (CDAD), hypomagnesemia, vitamin B12 (cobalamin) deficiency, and fundic gland polyps.
- Prescribing information for the proton pump inhibitors (PPIs) includes Warnings and Precautions for the adverse reactions that are not known to be related to acid suppression, including serious cutaneous adverse reactions (SCARs), acute tubulointerstitial nephritis (AIN), and cutaneous/systemic lupus erythematosis (CLE/SLE).

Vonoprazan-4003 (VISION)

Study Population and Disposition

The disposition of subjects is summarized in **Table 1.**

Few subjects discontinued the study in the healing phase (1.4% in each treatment group). Although the overall discontinuation/interruption rate in the maintenance phase was similar between treatment groups (24% for vonoprazan group versus 22% for lansoprazole group), a larger proportion of subjects in the vonoprazan group discontinued or interrupted study drug due to adverse events (8.9% for vonoprazan group versus 3.0% for lansoprazole group). Overall, 29 subjects had their dose of study drug increased during the maintenance phase, including 17 vonoprazan-treated subjects (12.2%) and 12 lansoprazole-treated subjects (17.4%).

Table 1 Patient Disposition, Healing Phase (HP) and Maintenance Phase (MP), Vonoprazan-4003 (VISION)

	Vonoprazan n (%)	Lansoprazole n (%)
Safety/analysis population, HP	**Vonoprazan 20 mg N = 139**	**Lansoprazole 30 mg N = 69**
Discontinued study drug	2 (1.4)	1 (1.4)
Protocol deviation	1 (0.7)	1 (1.4)
Lost to follow up	1 (0.7)	0
Safety/analysis population, MP	**Vonoprazan 10 mg N=135**	**Lansoprazole 15 mg N=67**
Discontinued/interrupted study drug	32 (23.7)	15 (21.7)
Protocol deviation	1 (0.7)	1 (1.5)
Lost to follow up	1 (0.7)	1 (1.5)
Adverse event	12 (8.9)	2 (3.0)
Withdrawal by subject	15 (11.1)	8 (11.9)
Other	3 (2.2)	3 (4.5)
Dose increased for any reason	17 (12.2)	12 (17.4)

Source: Reviewer-generated, JMP; datasets: ae.xpt; app.xpt, demo.xpt, stat.xpt
Abbreviations: HP, healing phase; MP, maintenance phase; N, number of patients in treatment group; n, number of patients in specified population or group

All enrolled subjects were Japanese and there were no Hispanic or Latino subjects. The treatment groups were generally similar with respect to body mass index (BMI), age group, and tobacco use. Use of alcohol was generally comparable, with a slight trend toward more frequent alcohol use in the vonoprazan group. There was a slight imbalance in sex with slightly more male subjects versus female subjects in the vonoprazan group compared to the lansoprazole group (70.5% versus 60.9%, respectively). A slightly greater proportion of subjects reported caffeine use in the vonoprazan group compared to the lansoprazole group (80.6% versus 72.4%, respectively). Refer to **Table 2**. Overall, a greater proportion of subjects in the vonoprazan group had factors associated with increased risk of GERD and increased severity of GERD symptoms. However, this imbalance does not impact the interpretability of the safety data.

Table 2 Demographics, Vonoprazan-4003 (VISION)

	Vonoprazan N=139		Lansoprazole N=69	
	n	%	n	%
All[1]	139	66.8	69	33.2
Sex				
Female	41	29.5	27	39.1
Male	98	70.5	42	60.9
Age, years				
Mean (SD)	61.7 (11.9)		61.8 (10.9)	
Median (min, max)	61 (35, 84)		63 (38, 87)	
Age Group				
<65 years	82	59.0	35	50.7
≥65 years[2]	57	41.0	34	49.2
BMI				
< 18.5	2	1.4	1	1.4
≥ 25.0	66	47.4	29	42.0
18.5 ≤ to < 25.0	71	51.2	39	56.5
Tobacco Use				
Current Smoker	25	18.0	9	13.0
Former Smoker	62	44.6	29	42.0
Never Smoked	52	37.4	31	44.9
Alcohol Use				
Daily	44	31.6	17	24.6
Few Times / Week	27	19.4	16	23.2
Few Times / Month	22	15.8	19	27.5
None	46	33.1	17	24.6
Caffeine Use				
Caffeine use	112	80.6	50	72.4
No caffeine use	27	19.4	19	27.5

Source: Reviewer-generated, JMP; Dataset: demo.xpt
[1] Subjects randomized into healing phase
[2] Included 28 subjects ≥75 years (vonoprazan 17 [12.2%], lansoprazole 11 [15.9%])
Abbreviations: BMI, body mass index; N, number in treatment group; n, number in demographic group

The study enrolled more subjects with severe EE (i.e., Los Angeles [LA] Grade C/D) compared to mild EE (i.e., LA Grade A/B). Refer to **Table 3**. Treatment groups were balanced with respect to baseline severity of EE.

Table 3 Baseline Erosive Esophagitis, Los Angeles (LA) Grade, Randomized Subjects, Vonoprazan-4003 (VISION)

	Vonoprazan		Lansoprazole	
	n	%	n	%
Total (N)*	**139**	**66.8**	**69**	**33.2**
Baseline LA Grade				
A	5	3.0	1	1.4
B	50	36.0	25	36.2
C	20	14.4	10	14.5
D	64	46.0	33	47.8
Grade A-B	55	39.6	26	37.7
Grade C-D	84	60.4	43	62.3

Source: Reviewer-generated, JMP; Dataset: demo.xpt
*Subjects randomized into healing phase
Abbreviations: N, number in treatment group; n, number in demographic group

Overall Adverse Event Summary

Serious Adverse Events (SAEs) were low and balanced between the two treatment groups. Treatment Emergent Adverse Events (TEAEs) leading to permanent discontinuation or interruption of study drug

were low but slightly higher in the vonoprazan group compared to the lansoprazole group (**Table 4**). See further discussion below.

TEAEs were common in VISION, with more than 90% of subjects in either treatment group experiencing at least one during the 5-year study (vonoprazan 92% versus lansoprazole 94%). Severity of TEAEs was similar in both treatment groups, with most events in the vonoprazan group considered mild (88% mild, 11% moderate, 1% severe in vonoprazan group).

Table 4 Overview of Treatment-Emergent Adverse Events, Safety Population, Vonoprazan-4003 (VISION)

Event Category	Vonoprazan 20 mg/10 mg* N=139 n (%)	Lansoprazole 30 mg/15 mg* N=69 n (%)
SAE	50 (36.0)	27 (39.1)
SAEs with fatal outcome	0	1 (1.4)
Subjects with TEAE leading to permanent discontinuation of study drug[1]	6 (4.3)	1 (1.4)
Subjects with TEAE leading to interruption of study drug	16 (11.5)	5 (7.2)
Any TEAE	128 (92.1)	65 (94.2)

Source: Reviewer-generated, datasets: ae.xpt; app.xpt, demo.xpt; Software: JMP
*Includes one subject in vonoprazan group and two subjects in lansoprazole group had maintenance dose increased to 20 mg and 30 mg, respectively
[1] All occurred during the maintenance phase
Abbreviations: N, number in treatment group; n, number of subjects with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Deaths

No deaths were reported in the vonoprazan group. One death due to myocardial infarction was reported in a subject who received lansoprazole.

Serious Adverse Events

Overall, 130 SAEs were reported in 77 subjects: 89 SAEs in 50 subjects in the vonoprazan group and 41 SAEs in 27 subjects in the lansoprazole group. Some SAEs were reported more than once in the same subject. Overall, SAEs were reported in a similar percentage of subjects in each treatment group, with 36% in the vonoprazan group versus 39% in the lansoprazole group. **Table 5** shows the SAEs reported by treatment group and occurring in more than one vonoprazan-treated subject.

Table 5 Serious Adverse Events Occurring in More than One Subject in the Vonoprazan Group, Safety Population, Vonoprazan-4003 (VISION)

SAE Preferred Term**	Vonoprazan 20 mg/10 mg* N=139 n (%)	Lansoprazole 30 mg/15 mg* N=69 n (%)
Number of subjects with at least one SAE	50 (36.0)	27 (39.1)
Large intestine polyp	5 (3.6)	4 (5.8)
Cataract[1]	4 (2.9)	6 (8.7)
Carpal tunnel syndrome	3 (2.2)	1 (1.4)
Diverticulum intestinal hemorrhagic	3 (2.2)	0
Inguinal hernia	2 (1.4)	2 (2.9)
Cholangitis[2]	2 (1.4)	1 (1.4)
Breast cancer	2 (1.4)	0
Diverticulitis	2 (1.4)	0
Lumbar spinal stenosis	2 (1.4)	0
Renal cell carcinoma	2 (1.4)	0
Spondylolisthesis	2 (1.4)	0

Source: Reviewer-generated, JMP; datasets: ae.xpt; app.xpt, demo.xpt
*Includes one subject in vonoprazan group and two subjects in lansoprazole group had maintenance dose increased to 20 mg and 30 mg, respectively
**Some subjects may have reported the same SAE more than once.
[1] Includes: cataract, cataract nuclear
[2] Includes: cholangitis, cholangitis acute, cholangitis infective
Abbreviations: N, number in treatment group; n, number of subjects reporting each SAE; SAE, serious adverse event; TEAE, treatment-emergent adverse event

SAEs Reported in Two or More Vonoprazan-Treated Subjects

SAEs of large intestine polyps, cataracts, carpal tunnel syndrome, diverticulitis/hemorrhagic diverticulum, and breast cancer in the vonoprazan group likely represent background incidence in these disorders that are common in the general population. Both subjects with renal cell carcinoma (RCC) had a risk factor of a history of current or previous tobacco use that confounded the assessment.[2] Inguinal hernia is not plausibly associated to use of vonoprazan. Both cases of spondylolisthesis represented exacerbations of previous diagnosed conditions and unlikely to be related to vonoprazan.

Of the two cases of lumbar spinal stenosis, one (Subject ID (b) (6)) was an exacerbation of a previously diagnosed condition and therefore association with vonoprazan cannot be determined. The other case was reported in a 56 year old non-smoking male subject (Subject ID (b) (6)) who was diagnosed and underwent surgery for a lumbar spinal stenosis, identified after 902 days of treatment with vonoprazan (20 mg once daily for 97 days, then 10 mg once daily). The investigator determined age-related changes to be the primary factor in the condition and assigned no causal relationship to study drug and the Applicant did not consider this event related to study drug. Given that middle age is a predisposing factor, a relationship to vonoprazan is unclear, although a contribution of vonoprazan to the lumbar spinal stenosis cannot be excluded.

Of the two cases of cholangitis that occurred in vonoprazan-treated subjects, one (Subject ID (b) (6)) was attributed to choledocholithiasis and was unlikely to be related to study drug. The other case is presented below:

[2] Subject (b) (6) experienced SAEs of renal cell carcinoma and cholangitis acute. Refer to narrative.

- Subject (b) (6) experienced two SAEs: RCC and cholangitis acute. As previously noted, the association of his RCC is confounded by prior history of tobacco use. The case discussion focuses on the SAE of cholangitis.

  The subject was 76 year old male subject with prior history of tobacco use and reported use of alcohol 2-3 days per week. He entered the maintenance phase after 35 days of vonoprazan 20 mg once daily. Prior medications included pitavastatin calcium, carvedilol, tamsulosin HCl, zolpidem tartrate. Intercurrent medications during the study included mecobalamin, limaprost alfadex, indomethacin transdermal patch and pregabalin for exacerbation of prior lumbar spinal stenosis which was ultimately treated surgically on maintenance day 657: (2) cefcapene pivoxil[3] and dexamethasone valerate for an ingrown toenail on maintenance day 340. He was diagnosed with T1a left renal cell carcinoma (SAE) on maintenance Day 707 and was treated surgically on maintenance day 776.

  On maintenance day 951 he presented with fever and was diagnosed on day 952 with cholangitis. based on elevated liver function tests and magnetic resonance cholangiopancreatography (MRCP) suspicious for 7 mm stone in the common bile duct. An SAE of "cholangitis acute" was recorded. He received cefazolin initially, then cefoperazone/sulbactam on Day 953. Of note, no stone was seen on endoscopic retrograde cholangiopancreatography (ERCP) done on Day 953. Vonoprazan, mexiletine, carvedilol and clostridium butyricum were recorded as discontinued by MD 958. Cholangitis was reported as resolved on maintenance day 995.

  None of the concomitant or prior medications is known to be associated with cholangitis or bile duct stones and the subject had no identified risk factors for cholangitis.[4] However, several of the concomitant medications are associated with abnormal liver function tests, including hyperbilirubinemia (e.g., carvedilol). Additionally, a stone was not confirmed on ERCP, which raises the possibility that the case represents primary biliary cholangitis. The prevalence of primary biliary cholangitis is estimated to be approximately 34 per 100,000 individuals (Tanaka, 2021) which makes it unlikely that this case represents the background rate of cholangitis in the Japanese population. Further, based on the temporal relationship and positive de-challenge, a relationship between cholangitis and vonoprazan cannot be fully excluded.

To further clarify the relationship between vonoprazan use and cholangitis, the review team also assessed data from previously conducted studies of vonoprazan for EE and other indications. An analysis of clinical trial data from the Applicant's original Integrated Summary of Safety (ISS) identified two cases of cholangitis due to cholelithiasis in vonoprazan-treated subjects. Both cases were confounded by prior medical history or concomitant medication use.

SAEs Reported in a Single Vonoprazan-Treated Subject

[3] RAD-AR Council Japan, Cefcapene pivoxil hydrochloride hydrate Drug Information Sheet, May 2009, retrieved August 28, 2023 from: https://rad-ar.or.jp/siori/english/search/result?dj0yNSZyPWkmaz10JnA9MSZnPTAmaT04JmkyPTImbj0xNjQ4NA=&n=38981#:~:text=Dosing%20schedule%20(How%20to%20take%20this%20medicine)&text=For%20adults%20(patients%20who%20cannot,the%20disease%2C%20age%20or%20symptoms.

[4] Refer to current prescribing information at Drugs at FDA: https://www.accessdata.fda.gov/scripts/cder/daf/

Of the SAEs occurring in a single subject (data not shown), most had alternative etiologies identified, were not plausibly related to vonoprazan, represented common diagnoses in the general population, or were confounded by pre-existing medical conditions, existing risk factors or concomitant medication use. One SAE of gastric cancer is presented:

- Subject (b) (6) was a 52-year old non-smoking male subject with prior history of hypertension and hyperlipidemia and no history of smoking or alcohol use, tested negative for *H. pylori*, and had pre-existing fundic gland polyps noted on screening endoscopy. He entered the maintenance phase after receiving 33 days of vonoprazan 20 mg for healing. He was diagnosed with gastric cancer (foveolar-type gastric adenocarcinoma) during study endoscopy on maintenance day 1083 (Week 156). Retrospective review of the Week 130 endoscopy (on maintenance day 765) showed an early lesion. Given the development of the cancer during treatment with vonoprazan, the investigator considered the event as related to vonoprazan.

  No other cases of gastric cancer were reported in previous studies of vonoprazan. Additionally, gastric cancer occurs more commonly in eastern Asian countries, accounting for half of cases worldwide (Hamashima 2015). Therefore, it is unclear whether this TEAE was related to vonoprazan or represents background incidence of gastric cancer in the population.

TEAEs Leading to Permanent Discontinuation or Interruption of Study Drug

A slightly higher proportion of subjects permanently discontinued study drug due to TEAEs in the vonoprazan group compared to the lansoprazole group (six subjects, 4.3% vs. one subject, 1.4%) and had interruptions of study drug (16 subjects, 11.5% vs 5 subjects, 7.2%) Refer to **Table 4**.

Of the six vonoprazan-treated subjects who discontinued study drug, three subjects had SAEs previously discussed (Subject IDs (b) (6)). The remaining three subjects had other risk factors or concomitant medications associated with the reported TEAEs.

Of the 16 vonoprazan-treated subjects with interruption of study drug, one subject had an SAE previously discussed (Subject (b) (6)). The remaining subjects had TEAEs that were confounded.

Treatment-Emergent Adverse Events

Table 6 presents the TEAEs reported by treatment group and in >5% of subjects in the vonoprazan group. Most of the events were generally similar between treatment groups, with none of the differences being clinically meaningful. However, dyslipidemia was reported more frequently with vonoprazan (7.2%) compared to lansoprazole (1.4%) in VISION. Of the ten subjects with dyslipidemia recorded, two had previous medications prescribed for hyperlipidemia, suggesting dyslipidemia prior to treatment with vonoprazan; six cases were confounded by obesity (i.e., BMI of 25 or higher). The remaining four subjects represent only 2.9% rate, which is not a meaningful imbalance. Therefore, a relationship between vonoprazan and hyperlipidemia cannot be established.

In general, the most common TEAEs in VISION in the vonoprazan group are consistent with TEAEs in Study EE-301. There is some overlap in TEAEs with the terms recommended for inclusion in labeling based upon the results of Study EE-301 either as common or less common adverse reactions (terms shown as **bold** in **Table 6**. Other common TEAEs in Table 9 are not considered to be adverse reactions associated with vonoprazan and some may be similar to the background rate of such adverse events occurring in the population over a 5-year period, with the exception of gastric polyps and a case of bacterial enterocolitis (discussed under Adverse Events of Special Interest).

Table 6 Treatment Emergent Adverse Events Reported in Vonoprazan-4003 (VISION) by Treatment Group and in > 5 % of Vonoprazan-Treated Subjects, Safety Population

	Vonoprazan 20 mg/10 mg* N=139	Lansoprazole 30 mg/15 mg* N=69
TEAE Grouped Term	**n (%)**	**n (%)**
Subjects reporting at least one TEAE	**128 (92.1)**	**65 (94.2)**
Gastric polyps [A]	99 (71.2)	50 (72.5)
Upper respiratory tract infection [B]	56 (40.3)	35 (50.7)
Gastritis [C]	18 (12.9)	10 (14.5)
Osteoarthritis [D]	18 (12.9)	8 (11.6)
Eczema [E]	16 (11.5)	19 (27.5)
Large intestine polyp	16 (11.5)	9 (13.0)
Diarrhea [F]	15 (10.8)	6 (8.7)
Hypertension	15 (10.8)	6 (8.7)
Bronchitis	13 (9.4)	7 (10.1)
Back pain	13 (9.4)	3 (4.3)
Influenza	13 (9.4)	1 (1.4)
Vertigo [G]	12 (8.6)	9 (13.0)
Rhinitis [H]	11 (7.9)	10 (14.5)
Dyslipidemia [I]	10 (7.2)	1 (1.4)
Gastrointestinal mucosal disorder	10 (7.2)	6 (8.7)
Sinusitis [J]	10 (7.2)	0
Enterocolitis [K]	9 (6.5)	5 (7.2)
Gastroenteritis [L]	9 (6.5)	4 (5.8)
Constipation	8 (5.8)	5 (7.2)
Contusion	8 (5.8)	3 (4.3)
Cystitis [M]	8 (5.8)	3 (4.3)
Dental caries [N]	8 (5.8)	3 (4.3)

Source: Reviewer-generated, JMP; datasets: ae.xpt; app.xpt, demo.xpt
*Includes one subject in vonoprazan group and two subjects in lansoprazole group who had maintenance dose increased to 20 mg and 30 mg, respectively
[A] includes gastric polyp, gastric mucosal lesion, gastric mucosal hypertrophy, duodenal polyp
[B] includes nasopharyngitis, upper respiratory infection
[C] includes gastritis erosive, gastric mucosa erythema, chronic gastritis
[D] Includes arthritis, osteoarthritis, periarthritis, spinal osteoarthritis
[E] Includes, dermatitis, dermatitis allergic, dermatitis contact, eczema, stasis dermatitis
[F] includes diarrhea, feces soft
[G] Includes dizziness, Meniere's disease, vertigo, vertigo positional
[H] Includes rhinitis allergic, rhinitis, seasonal allergy, upper respiratory tract inflammation
[I] Includes dyslipidemia, hypercholesterolemia, hyperlipidemia
[J] includes sinusitis, sinusitis acute, sinusitis chronic
[K] Includes enteritis viral, enterocolitis, enterocolitis bacterial enterocolitis viral; Section 5.3 of the proposed PI includes a Warning and Precaution for *Clostridiodes difficile*-Associated Diarrhea
[L] Includes gastroenteritis, gastroenteritis viral
[M] includes cystitis, cystitis interstitial
Abbreviations: N, number in treatment group; n, number of subjects reporting each term; TEAE, treatment-emergent adverse event
Bold indicates terms that were identified in EE-301 and proposed for inclusion in the Prescribing Information either as common or less common adverse reactions.

Laboratory Findings

Review of the laboratory assessments did not identify any new safety concerns.

In the original Integrated Review, Study EE-301 demonstrated that vonoprazan had a more pronounced effect on serum gastrin levels than lansoprazole. The results from VISION show a similar treatment effect. A more pronounced effect of vonoprazan compared to lansoprazole was also reported for Chromogranin A, Pepsinogen I and Pepsinogen II levels in VISION (data not shown).

Analysis of the laboratory data did not show a clinically meaningful change in the mean aspartate aminotransferase (AST) or alanine transaminase (ALT) over time (data not shown). However, the mean AST and ALT increased over time in the vonoprazan group compared to relatively little change in the lansoprazole group, which supports the possibility that vonoprazan increases hepatic enzymes.

Adverse Events of Special Interest Associated with Vonoprazan

Hepatotoxicity

In the original NDA, review of data from Study EE-301 and ex-U.S. EE studies did not identify any cases of drug-induced liver injury (DILI). TEAEs related to hepatotoxicity were reported in 1.7% of subjects who received vonoprazan 10 mg in the maintenance phase of EE-301, including three subjects increased transaminases and two with hepatic steatosis.

In VISION, TEAEs related to hepatotoxicity were reported in eight subjects (5.8%), all in the vonoprazan group. There were six subjects with "hepatic function abnormal" (not otherwise defined by the Applicant), one subject with gamma-glutamyltransferase increased, and one subject with hepatic steatosis. . All of these subjects with hepatic abnormalities had either (1) medical conditions associated with abnormal liver function (i.e., hepatic steatosis); or concomitant medications known to be associated with liver toxicity or changes in liver function (e.g., pitavastatin, metformin, febuxostat, rosuvastatin).

Four subjects (including two of the abovementioned subjects reporting TEAEs leading to discontinuation) had transaminase levels greater than 3x the upper limit of normal. None of these subjects met criteria for DILI, based on normal bilirubin levels. All subjects had potential explanation for abnormal hepatic enzymes, including hepatic steatosis (2) and alcoholic liver disease (1), or concomitant medications that are associated with increased hepatic enzymes (i.e., itopride, domperidone, aspirin).

As previously recommended, the term "increased liver function test" will be included as a less common adverse reaction in the ADVERSE REACTIONS, *Clinical Trials Experience* subsection of the Voquezna PI, as recommended in the original Integrated Review.

Hematologic Abnormalities

In the original Integrated Review, anemia was reported in less than 1% of Voquezna-treated subjects in Study EE-301

In VISION, hematologic abnormalities were reported uncommonly, occurring at a similar rate in both treatment groups (vonoprazan 3.6% versus lansoprazole 2.9%). The most reported hematologic TEAE was anemia in three subjects in the vonoprazan group (2.2%) and two subjects in the lansoprazole group (2.9%). One case each of leukopenia (Subject (b) (6)) and myelodysplastic syndrome (Subject (b) (6)) was reported in the vonoprazan group. Both cases were confounded by use of concomitant medications known to be associated with hematologic abnormalities. No cases of thrombocytopenia were reported as TEAEs. The laboratory assessments in the study did not include blood counts.

The reports of anemia TEAEs in VISION support the inclusion of anemia as a less common adverse reaction in the ADVERSE REACTIONS, *Clinical Trials Experience* subsection of the Voquezna PI, as recommended in the original Integrated Review.

Adverse Events of Special Interest Associated with Suppression of Acid Secretion

Bone Fracture

In the original Integrated Review, bone fracture was reported in less than 1% of Voquezna-treated subjects in Study EE-301. **Table 7** shows the TEAEs related to bone fracture in VISION. The occurrence of any bone fracture was similar between the treatment groups, occurring in 10.8% of subjects who received Voquezna compared to 10.1% of subjects who received lansoprazole. Both groups reported fractures considered to be associated with acid suppression (i.e., spinal compression, hip and wrist) in 4.3% of subjects.

Table 7 Adverse Events of Special Interest: Bone Fracture, Vonoprazan-4003 (VISION)

Subjects Reporting TEAE	Vonoprazan 20mg/10 mg N=139 n (%)	Lansoprazole 30 mg/15 mg N=69 n(%)
Subjects reporting at least one fracture	**15 (10.8)[1]**	**7 (10.1)**
Subjects reporting at least one fracture previously associated with acid suppression	***6 (4.3)***	***3 (4.3)***
Spinal Compression Fracture	*3 (2.2)*	*2 (3.0)*
Tooth Fracture	2 (0.7)	0
Patella Fracture	1 (0.7)	1 (1.4)
Wrist Fracture	*1 (0.7)*	*1 (1.4)*
Hand Fracture	1 (0.7)	1 (1.4)
Facial Bone Fracture	1 (0.7)[1]	0
Acetabulum Fracture	*1 (0.7)[1]*	*0*
Compression Fracture	*1 (0.7)*	*0*
Lumbar Vertebral Fracture	*1 (0.7)*	*0*
Lower Limb Fracture	1 (0.7)	0
Ankle Fracture	1 (0.7)	0
Rib Fracture	1 (0.7)	0

Source: Reviewer-generated, JMP; ae.xpt, app.xpt, demo.xpt
*Subjects randomized into maintenance phase
[1] Eighteen events were reported in fifteen subjects, including 3 reports of facial fracture and acetabulum fracture in the same subject (ID (b) (6))
Abbreviations: N, number in treatment group; n, number of subjects reporting fracture
Italics indicated fracture considered to be associated with acid suppression.

The reports of bone fracture TEAEs in VISION are supportive of the reports of bone fracture as a less common adverse reaction in Study EE-301. Bone fracture will be included in the ADVERSE REACTIONS, *Clinical Trials Experience* subsection of the Voquezna PI, as recommended in the original Integrated Review.

Clostridiodes difficile-Associated Diarrhea (CDAD)

In the original Integrated Review, there were no events related to CDAD in clinical trials. There were foreign postmarketing reports of CDAD with vonoprazan when used in combination with antibacterials. In VISION, there were no reported cases of CDAD. However, each treatment group reported one case of bacterial enterocolitis with no data provided to identify the organism involved.

CDAD will be included in the ADVERSE REACTIONS, *Postmarketing Experience* subsection of the Voquezna PI, as recommended in the original Integrated Review.

Hypomagnesemia

In the original Integrated Review, there were no events of hypomagnesemia in the clinical trials but there were a limited number of foreign postmarketing cases. In VISION, there were no cases of hypomagnesemia reported as a TEAE. Five subjects, all in the vonoprazan group (3.6%), had serum magnesium levels below the lower limit of normal. All these subjects completed the study. However, serum magnesium levels in these subjects fluctuated over the course of the study and did not show a consistent trend based on duration of treatment. The mean change from baseline at the end of the treatment period (i.e., Week 260) was not clinically meaningful in either treatment group (data not shown).

One of the subjects with hypomagnesemia (Subject ID (b) (6)) received supplemental magnesium during the trial after a recorded serum level of 1.7 mg/dL, with normalization of lab values, but discontinued supplementation during the trial with subsequent drop of magnesium level below normal by the end of the trial.[5] It is unknown whether the subject's magnesium levels returned to normal after the trial ended. However, given the temporal association with vonoprazan, an association cannot be excluded.

Hypomagnesemia will be included as class labeling, similar to the PPIs, in the WARNINGS AND PRECAUTIONS section and in the ADVERSE REACTIONS, *Postmarketing Experience* subsection of the Voquezna PI, as recommended in the original Integrated Review.

Vitamin B12 (Cobalamin) Deficiency

In the original Integrated Review, there were no events of vitamin B12 deficiency in clinical trials or postmarketing.

In VISION, there were no TEAEs related to Vitamin B12 deficiency reported (e.g., no Vitamin B12 deficiency, no megaloblastic anemia, no RBC macrocytosis). The study included laboratory testing of Vitamin B12 levels at all study visits and there were no recorded levels below the normal range. No change in the assessment of safety was identified based on the data from VISION. Vitamin in B12 deficiency will be included as a subsection in the WARNINGS AND PRECAUTIONS section of the Voquezna PI based upon the mechanism of acid suppression similar to the PPIs.

Fundic Gland Polyps

In the original Integrated Review, there were fundic gland polyps reported in 1.7 % of Voquezna-treated subjects by six months of treatment in Study EE-301 (compared to 1.6% of lansoprazole-treated subjects).[6]

In VISION, the presence or absence of fundic gland polyps was a secondary safety endpoint. Of the subjects who entered the maintenance phase (135 subjects in the vonoprazan group and 67 subjects in

[5] The precise timing of magnesium supplementation was not reported. The Subject first recorded a concomitant medication of Magnesium oxide at the Week 156 Visit (~Day 1092). The subject did not report magnesium as a concomitant medication at the time the last (low) magnesium level was recorded at the Week 260 visit (~Day 1820).

[6] Subjects were included in this analysis if they had a TEAE of gastric polyps reported in the healing phase or if they had gastric polyps reported in the maintenance phase and received Voquezna or lansoprazole for both study phases. Because of treatment cross-over, which limited the interpretability of the data, two subjects (both randomized to Lansoprazole 30 mg in the healing phase and Voquezna 10 mg in the maintenance phase) with gastric polyps reported during the maintenance phase were not included in this analysis.

the lansoprazole group), the number who had endoscopically confirmed fundic gland polyp (as assessed by the Investigator/Sub-Investigator at each study visit) were as follows:

- Start of the healing phase: 59 subjects (43.7%) in the vonoprazan group and 29 subjects (43.3%) in the lansoprazole group
- Week 48 of the maintenance phase: 67 (54.5%) in the vonoprazan group and 29 (46.8%) in the lansoprazole group
- Week 156 of the maintenance phase: 72 (66.1%) in the vonoprazan group and 44 (77.2%) in the lansoprazole group
- Week 260 of the maintenance phase: 75 (72.1%) in the vonoprazan group and 45 (84.9%) in the lansoprazole group

The Applicant did not comment on the high percentage of patients with baseline gastric polyps but it could be postulated patients had been exposed to PPIs in the past. The percentage of patients with fundic gland polyps increased over the 5-years of the study.

In the original Integrated Review, fundic gland polyps was recommended as a subsection in the WARNINGS AND PRECAUTIONS section of the Voquezna PI. Based on the longer-term data from VISION, the WARNINGS and PRECAUTIONS subsection on fundic gland polyps will indicate that polyps have been reported with vonoprazan in clinical trials and that the risk increases with long-term use, especially beyond one year.

Adverse Events of Special Interest Associated with PPIs, Not Known to be Related to Acid Suppression

Severe Cutaneous Adverse Reactions

In the original Integrated Review, there was no clear risk for SCARs identified in Study EE-301 or the Applicant's ISS. However, an analysis of foreign post-marketing data by the Applicant identified potential risk to patients from cutaneous hypersensitivity reactions. In VISION, there were no TEAEs related to SCARs in vonoprazan-treated subjects. Based on the previous Integrated Review, SCARs will be included as a subsection in the WARNINGS AND PRECAUTIONS section of the Voquezna PI with the individual terms added to the ADVERSE REACTIONS, *Postmarketing Experience* subsection.

Hypersensitivity

In the original Integrated Review, there was a case of hypersensitivity reported in a subject who received Voquezna in Study EE-301 and an additional case of hypersensitivity from a clinical trial of symptomatic non-erosive GERD. In VISION, there were six subjects (4.3%) with TEAEs related to hypersensitivity, including five with urticaria (3.6%), in the vonoprazan group. Given the seriousness of the reaction, known hypersensitivity to vonoprazan or any component of Voquezna tablets will be included as CONTRAINDICATIONS in the PI, as recommended in the original Integrated Review.

Acute Tubulointerstitial Nephritis (AIN/TIN)

In the original Integrated Review, one case of AIN was reported in a Voquezna-treated subject in Study EE-301. In VISION, no TEAEs of AIN or related adverse events were reported.[7] Given the seriousness of the reaction, AIN will be included as a subsection in the WARNINGS AND PRECAUTIONS with the individual term added to the ADVERSE REACTIONS, *Clinical Trials Experience* subsection as a less common adverse reaction, as recommended in the original Integrated Review.

Cutaneous Lupus Erythematosus (CLE)/Systemic Lupus Erythematosus (SLE)

There were no cases of SLE, CLE or associated terms in the original Integrated Review or in VISION. Therefore, CLE and SLE will not be included in the Voquezna PI.

Other Safety Considerations

Erectile Dysfunction

On April 14, 2023, Applicants of PPI products were notified of Safety Labeling Change (SLC) for new safety information that should be included in the ADVERSE REACTIONS, *Postmarketing Experience* of the PPI labels related to the risk of erectile dysfunction. On July 18, 2023, the class labeling changes were approved. The class SLC did not include NDAs 215152/215153 (VOQUEZNA Triple/Dual Pak for *H. pylori*).

The Applicant was asked to provide postmarketing cases of erectile dysfunction in the resubmission for NDA 215151.

The Applicant searched their clinical trials and global safety database for cases of ED following exposure to vonoprazan, as of March 31, 2023. There were no cases identified in clinical trials of vonoprazan. Four cases were reported postmarketing in Japan and China. The Division of Pharmacovigilance (DPV) I evaluated the cases of erectile dysfunction associated with vonoprazan from the FDA Adverse Event Reporting System (FAERS) database, published literature, and cases the Applicant identified in clinical trials and their global safety database. DPV considered the four cases identified (one from FAERS, three applicant-submitted) were confounded due to underlying medical conditions predisposing to or medications known to be associated with ED. The review concluded that there was insufficient evidence to support an association between vonoprazan and erectile dysfunction and no labeling revisions are needed. Refer to the Pharmacovigilance memo, dated August 8, 2023 (Reference ID 62222792).

[7] There was a single case of hematuria reported (Subject ID (b) (6)) in a subject with renal cancer, which is the likely cause of the hematuria.

References

Cazan D, Klimek L, Sperl A, Plomer M, Kölsch S. Safety of ambroxol in the treatment of airway diseases in adult patients. Expert Opin Drug Saf. 2018 Dec;17(12):1211-1224. doi: 10.1080/14740338.2018.1533954. Epub 2018 Nov 22. PMID: 30372367.

EAU Guidelines. Edn. presented at the EAU Annual Congress Milan 2023. ISBN 978-94-92671-19-6, retrieved October 25, 2023 from: https://uroweb.org/guidelines/renal-cell-carcinoma/chapter/epidemiology-aetiology-and-pathology

Hamashima C, Shabana M, Okada K, Okamoto M, Osaki Y. Mortality reduction from gastric cancer by endoscopic and radiographic screening. Cancer Sci. 2015 Dec;106(12):1744-9. doi: 10.1111/cas.12829. Epub 2015 Nov 11. PMID: 26432528; PMCID: PMC4714659.

Hashimoto S, Ikegami S, Nishimura H, Uchiyama S, Takahashi J, Kato H. Prevalence and Risk Factors of Carpal Tunnel Syndrome in Japanese Aged 50 to 89 Years. J Hand Surg Asian Pac Vol. 2020 Sep;25(3):320-327. doi: 10.1142/S2424835520500356. PMID: 32723040.

Isohata N, Nagata K, Utano K, Nozaki R, Nozu S, Kato T, Kijima S, Matsumoto H, Majima K, Ryu Y, Hirayama M, Endo S. Recent trends in the prevalence and distribution of colonic diverticula in Japan evaluated using computed tomography colonography. World J Gastroenterol. 2021 Jul 21;27(27):4441-4452. doi: 10.3748/wjg.v27.i27.4441. PMID: 34366615; PMCID: PMC8316905.

Kawakami M, Takeshita K, Inoue G, Sekiguchi M, Fujiwara Y, Hoshino M, Kaito T, Kawaguchi Y, Minetama M, Orita S, Takahata M, Tsuchiya K, Tsuji T, Yamada H, Watanabe K; Structured abstract preparation team. Japanese Orthopaedic Association (JOA) clinical practice guidelines on the management of lumbar spinal stenosis, 2021 - Secondary publication. J Orthop Sci. 2023 Jan;28(1):46-91. doi: 10.1016/j.jos.2022.03.013. Epub 2022 May 19. PMID: 35597732.

Tada K, Kumamaru H, Miyata H, Asaga S, Iijima K, Ogo E, Kadoya T, Kubo M, Kojima Y, Tanakura K, Tamura K, Nagahashi M, Niikura N, Hayashi N, Miyashita M, Yoshida M, Ohno S, Imoto S, Jinno H. Characteristics of female breast cancer in japan: annual report of the National Clinical Database in 2018. Breast Cancer. 2023 Mar;30(2):157-166. doi: 10.1007/s12282-022-01423-4. Epub 2022 Dec 22. PMID: 36547868; PMCID: PMC9950166.

Tanaka. Pbc: No Longer a Western Disease? Clinical Liver Disease. 2020;16(6):227-230. doi: https://doi.org/10.1002/cld.903.

Washio M, Mori M. Risk factors for renal cell cancer in a Japanese population. Clin Med Oncol. 2009 Jun 15;3:71-5. doi: 10.4137/cmo.s2669. PMID: 20689612; PMCID: PMC2872592.

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US Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	215151
SERIAL NO.:	S-035
DATE RECEIVED BY OB:	07/10/2023
DRUG NAME:	Vonoprazan tablets
SPONSOR:	Phathom Pharmaceuticals, Inc.
INDICATION:	Healing of all grades of erosive esophagitis and relief of heartburn
DOSAGE FORM:	Tablets
STRENGTHS:	10 mg and 20 mg
REVIEW FINISHED DATE:	07/25/2023
CMC STATISTICAL REVIEWER:	Shaobo Liu, Ph.D.
PROJECT MANAGER:	Megan Nguyen

Secondary Reviewer:

Meiyu Shen, Ph.D., Team Leader, Mathematical Statistician, CDER/OTS/OB/DB VI

Concur:

Yi Tsong, Ph.D., Division Director, DBVI, CDER/OTS/OB/DB VI

Distribution: NDA 215151
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CDER/OTS/OB/DBVI/ Atiar Mohammad Rahman
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CDER/OPQ/OPRO/DRBPMIII/RBPMB7/ Megan Nguyen

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1 EXCUTIVE SUMMARY

On February 15, 2023, Office of Pharmaceutical Quality (OPQ) requested the Biology and Chemical Statistical Team in DB VI, Office of Biostatistics (OB) evaluating Phathom Pharma (Applicant)'s type C meeting's Question 4 regarding the adequacy of the proposed stability data package to support the proposed 24-month shelf-life and the benefit of conducting the proposed an Accelerated Stability Assessment Program (ASAP) stability study in shelf-life projections. Our comments regarding to the applicant's Question 4 of the proposed stability data package and conducting the ASAP stability study are as followed:

- We suggest the Applicant include the following test points, 0, 1, 2, 3 and 6 months to conduct the statistical analysis for predict shelf life. We recommend the Applicant provide statistical analyses for both strengths packaged in all the to-be-marketed configurations.
- The study design of Applicant's separated ASAP stability study should have scientific justification for its intended purpose of the prediction of shelf shelf-life of your products. We recommend the Applicant include at least three testing time points under multiple temperatures and humidity conditions per strength per package configuration. The storage conditions in the ASAP study should be under the stressed conditions, e.g., the temperatures should be higher than the accelerated conditions (40°C). The testing parameters should be stability indicating. The Applicant should also provide statistical analyses for their ASAP model.
- To validate ASAP predictions, we suggest the Applicant should provide the post-action commitment to continue updating the long-term stability data up to the granted shelf life.

On May 19th, 2023, the Applicant submitted Amendment 035 to the New Drug Application for vonoprazan tablets 10 mg and 20 mg to provide a response to the Agent Complete Response Letter dated 07 February 2023. On July 10th, 2023, Office of Pharmaceutical Quality (OPQ) requested the Biology and Chemical Statistical Team in DB VI, Office of Biostatistics (OB) evaluating Applicant's submission of a statistical analysis of 3-month long-term and accelerated stability of the drug product vonoprazan (b) (4) and 24-month long-term stability study (b) (4) to support the Applicant's proposed 24-month shelf-life of the (b) (4) formulation vonoprazan tablets at long-term term storage condition (25℃/60% RH). Our analysis will only focus on the stress conditions and long-term condition study for (b) (4) formulation. The long-term stability predictions of (b) (4) formulation at 24-month are summarized below **Table 1**.

Table 1. Predicted values (b) (4) at 24-month Long-Term Storage Condition

(b) (4)

Our comments regarding the Applicant's proposed 24-month shelf-life for (b) (4) formulation 20 mg vonoprazan tablets are as followed:

- Our independent statistical stability analysis based on ASAP modelling the Applicant's stability data of 20 mg vonoprazan tablets stored under target ASAP stress conditions and 3-month long term condition (25℃/60% RH) supports the 24-month shelf-life at long-term storage condition (25℃/60% RH).
- To validate ASAP predictions, we continue recommending that the Applicant should provide the post-action commitment to provide the stability data under long-term storage condition up to the granted shelf life (24-month).

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4. SUMMARY AND RECOMMENDATIONS

Based on our statistical review on Applicant provided analysis, our comments regarding to the Applicant's proposed 24-month shelf-life for 20 mg vonoprazan tablets are as followed:

- Our independent statistical stability analysis based on ASAP modelling the Applicant's stability data of 20 mg vonoprazan tablets stored under target ASAP stress conditions and 3-month long term condition (25℃/60% RH) supports the 24-month shelf-life at long-term storage condition (25℃/60% RH).
- To validate ASAP predictions, we continue recommending that the Applicant should provide the post-action commitment to provide the stability data under long-term storage condition up to the granted shelf life (24-month).

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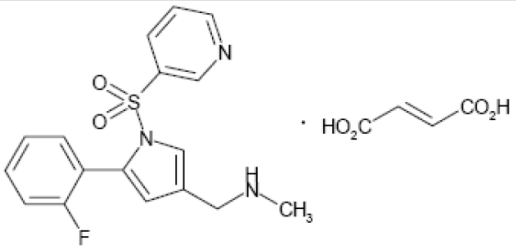
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application Number*:	NDA 215151
Supporting Document Number/s:	0035
CDER Receipt Date:	May 19, 2023
Sponsor:	Phathom Pharmaceuticals, Inc., USA
Product:	Vonoprazan (TAK-438)
Pharmacologic Class:	Potassium competitive acid blocker (PCAB)
Indication:	Treatment of erosive esophagitis (EE) and heartburn.
Therapeutic area:	Gastroenterology
Clinical Review Division:	Division of Gastroenterology (DG)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Dinesh Gautam, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Project Manager:	Maureen Dewey, MPH, RAC

Nonclinical Summary

Drug Information[+]

Type of Product:	Tablet
Code/ Generic Name:	TAK-438/ Vonoprazan
Chemical Name (optional):	1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methylmethanamine monofumarate.
CAS# or UNII (if available):	CAS: 881681-01-2 UNII:N/A
Structure or Biochemical Description:	
Molecular Formula/ Molecular Weight:	$C_{17}H_{16}FN_3O_2S \cdot C_4H_4O_4$/461.46

Executive Summary

Introduction

TAK-438 belongs to a class of compounds referred to as potassium competitive acid blockers (ACABs), that suppress gastric acid secretion by inhibiting gastric hydrogen-potassium-adenosine triphosphatase (H^+,K^+-ATPase). TAK-438 is being developed for the treatment of healing and maintenance of all grades of erosive esophagitis and relief of heartburn.

In the current submission (May 19, 2023), the Applicant has submitted pharmacokinetic studies (Absorption: Study # PRE-DDA-438-004; Metabolism: studies # TKD-BCS-01698-R1 and # PRE-DDA-438-006) and Juvenile toxicology studies (# TKD-BCS-00941, # TKD-BCS-00940 and TKD-BCS-01178). These studies were previously reviewed under IND 79212. Key findings of the studies are summarized below.

Pharmacokinetics/ADME/Toxicokinetics

Absorption

Study Title: Permeability Study of [^{14}C]TAK-438 and 20 Model Drugs across Caco-2 Cells (Study # PRE-DDA-438-004).

This *in vitro* study was conducted to determine the permeability of [^{14}C]-TAK-438F compared with 20 model drugs using Caco-2 cells. The study showed that TAK-438 is highly permeable with a permeability coefficient of 17.8.

Metabolism

Study Title: Assessment of relative contribution of phase 1 and phase 2 metabolic enzymes to TAK-438 metabolism and cytochrome p450/sulfotransferases phenotyping (Study # TKD-BCS-01698-R1).

The *in vitro* non-GLP exploratory study was conducted to determine the relative contributions of cytochrome P450 enzymes (CYPs) and sulfotransferase (SULTs) enzymes to the metabolism of TAK-438 using human liver S9 (HS9) fractions, and to determine the relative contributions of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 to TAK-438 metabolism using human complementary deoxyribonucleic acid (cDNA)-expressed recombinant CYPs (rCYPs). In addition, CYP2B6, 2C19, 2D6, and 3A4 were used to confirm the metabolism of TAK-438 in the presence of human liver microsomes (HLMs).

In human liver S9 incubations, the CYP-mediated metabolism accounted for 69.6% of total clearance of TAK-438 in human liver S9 (HS9), and SULTs mediated metabolism accounted for the remaining 30.4%. In recombinant CYP (rCYPs) incubations, TAK-438 was mainly metabolized by CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. In human liver microsomes incubations, TAK-438 was predominantly metabolized by CYP2C19, 2D6, and 3A4 and to a lesser extent by CYP2B6.

In conclusion, CYP-mediated metabolism of TAK-438 accounted for 69.6% of total clearance while conjugation mediated by SULTs accounted for the remaining 30.4%. The CYP-mediated metabolism of TAK-438 was principally catalyzed by CYP2B6 (7.6-9.6%), CYP2C19 (16.0-20.0%), CYP2D6 (16.2-17.3%), and CYP3A4 (13.0-37.1%).

Study Title: Stability of [^{14}C]TAK-438 in artificial human gastrointestinal fluid (Study # PRE-DDA-438-006).

The stability of [^{14}C]TAK-438 free base ([^{14}C]TAK-438F) in the artificial gastric fluids (fasted state simulated gastric fluid, FaSSGF) and the artificial intestinal fluids (fasted state simulated intestinal fluid, FaSSIF) was investigated. The results showed that TAK-438F at the concentration of 0.04 and 0.08 mg/mL was stable at 37^{0}C in the FaSSGF up to 60 minutes and in the FaSSIF up to 8 hours.

Toxicology

Study Title: A Single-Dose Tolerability Study of TAK-438 by Oral (Gavage) in Juvenile Sprague Dawley Rats (Study # TKD-BCS-00941).

TAK-438 was administered at doses of 0 (0.5% w/v methylcellulose), 1, 3, 10, 30 or 100 mg/kg by oral gavage to juvenile SD rats (5/sex/group) on Postnatal Days (PNDs) 4, 12, and 21. The experimental design is shown in the table below.

Group No.	Test Material	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)	No. of Juvenile Animals					
					Subset 1 (PND 21)		Subset 2 (PND 12)		Subset 3 (PND 4)	
					M	F	M	F	M	F
1	TAK-438	1	0.2	5	5	5	5	5	5	5
2	TAK-438	3	0.6	5	5	5	5	5	5	5
3	TAK-438	10	2	5	5	5	5	5	5	5
4	TAK-438	30	6	5	5	5	5	5	5	5
5	TAK-438	100	20	5	5	5	5	5	5	5

The animals in Subset 1 were administered a single dose on PND 21 and observed for 7 days until euthanized on PND 28. The animals in Subset 2 were administered a single dose on PND 12 and observed for 7 days until euthanized on PND 19. The animals in Subset 3 were administered a single dose on PND 4 and observed for 7 days until euthanized on PND 11.

All doses of TAK-438 were well tolerated in male and female pups at all ages. There were no TAK-438-related mortalities or clinical signs. Only mild decreases in mean body weights and/or mean body weight gains were observed in both males and females at 100 mg/kg following a single administration on PND 21 or on PND 4. A mild decrease in female mean body weight gain was also observed at 30 mg/kg following a single administration on PND 21. The results showed that up to 100 mg/kg TAK-438 was well tolerated in juvenile SD rats following a single oral administration on PNDs 4, 12, and 21.

Study Title: A Dose Range-Finding Study of TAK-438 by Oral Administration (Gavage) in Juvenile Sprague Dawley Rats (Study: # TKD-BCS-00940).

TAK-438 was administered to juvenile SD rats orally at 0 (0.5% methylcellulose in water), 3, 10, 30 or 100 mg/kg once daily from postnatal day (PND) 4 to 21. A satellite group of animals was dosed in a similar fashion to assess toxicokinetics (TK, 3/sex/timepoint) on PNDs 4, 14, and 21. Mortalities occurred in all dose groups, including the control group. Between the main and TK study groups, 4, 6, 8, 7, and 14 animals were found dead in 0, 3, 10, 30, and 100 mg/kg/day dose groups, respectively. In the main study group, there were 0, 0, 1, 1, and 6 mortalities in 0, 3, 10, 30, and 100 mg/kg/day dose groups, respectively. Most mortality occurred by PND9. Animals in the high dose group were terminated on PND10 due to high mortality. No TAK-438-related clinical signs were observed. Decreases in mean body weight gains relative to vehicle controls at ≥3 mg/kg/day in males and at ≥10 mg/kg/day in females were noticed. In males, mean body weight gains during the overall dosing period (PNDs 4 through 21) were 4.9%, 17%, and 27% lower than vehicle controls at 3, 10, and 30 mg/kg/day, respectively. In females, mean body weight gains during the overall dosing period (PNDs 4 through 21) were 0.07% above vehicle controls at 3 mg/kg/day and 6.3% and 25.4% lower than vehicle controls at 10 and 30 mg/kg/day, respectively.

Systemic exposures to TAK-438 and its metabolites (M1 and M2) were observed at all doses. Exposures (AUC_{last}) to TAK-438 and its metabolites were similar in males and

females. Exposures to TAK-438, M1, and M2, in terms of AUC_{last} and C_{max}, increased as TAK-438 dose level increased from 3 to 30 mg/kg/day. The increases in exposure to TAK-438 ranged from approximately linear to greater than dose proportional. Exposure to M1 and M2 metabolites exhibited less than dose proportional increases to the increase in TAK-438 dose.

Study Title: A 6-Week Study of TAK-438 Administered by Oral (Gavage) in Juvenile Rats with a 8-week Recovery Period (Study # TKD-BCS-01178).

Male and female juvenile SD rats were dosed once daily via oral gavage from postnatal days (PNDs) 7 to 50 with the vehicle (0.5% w/v methylcellulose) or with TAK-438 as a suspension at 3, 10, or 24 mg/kg for 6 weeks followed by 8-week recovery period. Male and female rats were assigned to groups of 24/sex/group: 12/sex/group were designated for terminal necropsy on PND 51, and 12/sex/group were designated for evaluation after an 8-week recovery period, with terminal necropsy on PND 108. An additional 6 rats/sex (control group) and 24 rats/sex (TAK-438 groups) were used to evaluate TK parameters. Following key findings were noted.

- There were 3 early deaths (1 from main study group and 2 from recovery group) on the study, none of which were attributed to TAK-438.
- No TAK-438-related clinical observations were observed.
- No test article-related effect on sexual maturity was noticed in males.
- In females, sexual maturation was delayed at ≥10 mg/kg when compared to controls, however, were within the historical control data of the test facility.
- No test article-related changes in clinical chemistry, coagulation parameters, macroscopic observations and organ weights at any dose level were noticed.
- Lower mean body weight gain was observed in TAK-438 treated males than in the controls on PND 28 to 35 at ≥3 mg/kg and through PND 66, at ≥10 mg/kg, . By the end of recovery period (PND 105), body weights had fully recovered at 10 mg/kg and partially recovered at 24 mg/kg. However, the body weight remained lower throughout the recovery period in males at 24 mg/kg/day.
- In females, the mean body weight gains on PNDs 19 to 21 were significantly lower than the controls at each dose level. Differences in mean body weight gain were significantly lower on PNDs 24 to 28 at 3 mg/kg and from PNDs 21 to 24 and PNDs 28 to 31 in 10 and 24 mg/kg dose groups. At the end of the recovery period, the body weights of females remained comparable to the controls at each dose level.
- In females, the food intake was decreased in a dose-dependent manner between PNDs 21 to 35 at 3, 10 and/or 24 mg/kg doses, compared to the controls; however, no differences in food intake were observed at the end of the recovery period.
- Histopathological examinations revealed a minimal to moderate eosinophilic globules in the chief cells of the stomach in ≥3 mg/kg dose groups, and minimally increased mitoses in the liver of a few males at ≥10 mg/kg. These changes were no longer evident at the end of the recovery period.

- Test article-related effects were observed on bone size/geometry (i.e., femur metaphysis, diaphysis, and in females only, lumbar vertebrae), bone mass, bone density at 10 and 24 mg/kg males and females. Femur length decreased in females in the 24 mg/kg dose group.
    - At the end of the recovery period, there was partial recovery at all dose levels.
    - Complete reversibility was observed at the femur metaphysis site, and no meaningful TAK-438-related changes were observed in femur length.
- The NOAEL was determined to be 10 mg/kg/day for both males and females based on the effects of the test article on body weight and bone mass and density in the high dose groups. The C_{max} and $AUC_{(last)}$ values for males at 10 mg/kg/day were 90.9 ng/mL and 236 ng.h/mL, and for females at 10 mg/kg/day were 129 ng/mL and 391 hr.ng/mL, respectively.

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/

DINESH C GAUTAM
07/20/2023 11:47:33 AM

SUSHANTA K CHAKDER
07/20/2023 11:51:15 AM

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215151
Priority or standard	Standard
Submit date(s)	3/11/2022
Received date(s)	3/11/2022
PDUFA goal date	1/11/2023
Division/office	Division of Gastroenterology (DG)
Review completion date	2/7/2023
Established/proper name	Vonoprazan
(Proposed) proprietary name	Voquezna
Pharmacologic class	Potassium-competitive acid blocker (PCAB)
Code name	TAK-438
Applicant	Phathom Pharmaceuticals
Dosage form(s)/formulation(s)	Oral tablets, 10 mg, and 20 mg
Proposed Dosing regimen	20 mg once daily for (b) (4) 8 weeks (Healing of EE); 10 mg once daily for up to 24 weeks (Maintenance of Healed EE); 20 mg twice daily for 2 weeks (Treatment of *H. pylori*)
Applicant proposed indication(s)/ population(s)	Voquezna is indicated for the following indications: healing of all grades of erosive esophagitis (EE) and relief of heartburn in adults for up to eight weeks; to maintain healing of all grades of EE and relief of heartburn in adults up to six months; in combination with amoxicillin plus clarithromycin as triple therapy for the treatment of *Helicobacter pylori* (*H. pylori*) infection in adults; in combination with amoxicillin as dual therapy for the treatment of *H. pylori* infection in adults
Proposed SNOMED indication	40719004: Erosive Esophagitis
Regulatory action	Complete response
Approved dosage (if applicable)	Click or tap here to enter text.
Approved indication(s)/ population(s) (if applicable)	Click or tap here to enter text.
Approved SNOMED term for indication (if applicable)	Click or tap here to enter text.

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AIN	acute tubulointerstitial nephritis
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
CDAD	*Clostridiodes difficile*-associated diarrhea
CI	confidence interval
CLE	cutaneous lupus erythematosis
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COVID-19	Coronavirus Disease of 2019
CYP	cytochrome P450 isoenzyme
DDI	drug-drug interaction
DILI	drug-induced liver injury
DPV	Division of Pharmacovigilance
ECG	electrocardiogram
EE	erosive esophagitis
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GD	gestation day
GERD	gastroesophageal reflux disease
GLP	good laboratory practice
HCV	hepatitis C virus
HTR	holding time ratio
IC_{50}	half maximal inhibitory concentration
IND	investigational new drug
ISS	Integrated Summary of Safety
ITT	intent-to-treat
LA	Los Angeles
MCV	mean corpuscular volume
MITT	modified intent-to-treat
MOA	mechanism of action
NDA	new drug application
NI	non-inferiority
NOAEL	no observed adverse effect level
NRI	Non-Responder Imputation
OSI	Office of Scientific Investigations

PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
PI	Prescribing Information
PK	pharmacokinetic
PMR	postmarketing requirement
popPK	population pharmacokinetic
PP	per protocol
PPI	proton pump inhibitors
PREA	Pediatric Research Equity Act
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCARS	severe cutaneous adverse reactions
SCF	spinal compression fracture
SD	standard deviation
sGERD	symptomatic non-erosive gastroesophageal reflux disease
SLE	systemic lupus erythematosis
SOC	system organ class
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time to maximum concentration
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

Phathom Pharmaceuticals submitted new drug application (NDA) 215151 for Voquezna (vonoprazan) 10 mg and 20 tablets under the 505(b)(1) pathway on March 11, 2022, seeking the following indications: healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *H. pylori* infection. Voquezna Triple Pak and Voquezna Dual Pak (NDA 215152, co-package of vonoprazan/amoxicillin/clarithromycin and NDA 215153, co-package of vonoprazan/amoxicillin) for the treatment of *H. pylori* infection were approved on May 5, 2022, by the Division of Anti-Infectives. A cross-reference letter to NDA 215152 supported the safety and efficacy information for the use of vonoprazan for treatment of *H. pylori* infection, and relevant portions of Module 3 (e.g., quality 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).

A single adequate, and well-controlled study (Study EE-301) was conducted to support the safety and effectiveness of Voquezna for the proposed indications. Two additional studies each of healing and maintenance of healed erosive esophagitis (EE), conducted outside the United States, served as confirmatory studies of efficacy and also provided supportive safety data.

The primary endpoint in in Study EE-301 for the healing and maintenance of healed EE was non-inferiority (NI) to the active comparator lansoprazole, a proton pump inhibitor. A prespecified, multiplicity-controlled secondary endpoint of percentage of 24-hour heartburn-free days was also assessed.

In the healing phase, the efficacy results demonstrate noninferiority of Voquezna 20 mg once daily compared to lansoprazole 30 mg once daily for the healing of all LA grades of EE at Week 2 or Week 8 and for the percentage of 24-hour heartburn-free days through Week 8.

In the maintenance phase, the efficacy results demonstrate noninferiority of both Voquezna 10 mg and 20 mg compared to lansoprazole 15 mg once daily for the maintenance of healed EE (all grades) and the percentage of 24-hour heartburn-free days through Week 24. Voquezna 20 mg did not demonstrate greater efficacy than the 10 mg dosage and the applicant did not request approval of that dosage regimen for maintenance of healed EE.

The review of the clinical safety database supports the overall safety of Voquezna 20 mg once daily for healing of erosive esophagitis and Voquezna 10 mg once daily for maintenance of healed erosive esophagitis in subjects with all LA grades of EE at baseline. In the review of data from Study EE-301 and the ex-U.S. phase 3 trials, low overall rates were observed for TEAEs, SAEs and AEs resulting in discontinuation with no imbalance evident between subjects treated with the recommended dosage of Voquezna and lansoprazole comparator. Adverse reactions reported in >1% of Voquezna-treated subjects in the healing phase of Study EE-301 were gastritis, diarrhea, abdominal distension, abdominal pain, and nausea. In the maintenance of healed EE phase of Study EE-301, adverse reactions reported in ≥2% of Voquezna-treated subjects were gastritis, abdominal pain, dyspepsia, hypertension, and urinary tract infection.

Adverse Events of Special Interest (AESI), related to vonoprazan itself or the closely related class of proton pump inhibitors (PPI) were infrequently reported.

Although there were no observed safety or efficacy concerns with the nonclinical or clinical data in the NDA, the applicant identified the presence of [redacted] during the review cycle. [redacted]

On October 5, 2022, the applicant submitted a Chemistry Manufacturing and Controls (CMC) Prior Approval Supplement to NDA 215152 (cross-referenced to NDAs 215153 and 215151) proposing [redacted] test and acceptance criteria in the drug substance and drug product specifications, and to add the associated analytical testing sites, analytical methods, analytical method validations, stability testing commitments and supportive data to justify [redacted]) as a surrogate to derive an acceptable intake (AI) [redacted].

The assessment of the quality data revealed that the stability data for both strengths of vonoprazan tablets cannot consistently meet the acceptance criterion [redacted], resulting in a lack of CMC information to support a viable shelf life for both the 10 mg and 20 mg tablets for this NDA.

On December 19, 2022, it was communicated to the applicant (NDA 215152, cross-referenced to NDA 215151) that FDA agreed to the proposal to use [redacted] as a read-across surrogate for the derivation of an AI for [redacted] in the drug product. In addition, a teleconference was held with the applicant on December 22, 2022 (see internal meeting minutes dated December 29, 2022 in DARRTS) and an advice letter was sent to the applicant on December 23, 2022 further communicating that the corresponding acceptance criterion for [redacted] in the drug product in parts per million (ppm), based on the AI [redacted] and the maximum daily dose (MDD) of the product (40 mg/day), is [redacted] ppm. Therefore, the proposed acceptance criteria of not more than (NMT) [redacted] ppm for release and NMT [redacted] ppm for stability for [redacted] in the drug product specifications in the NDA are not acceptable because the daily intake [redacted], if present, at both limits exceeds the AI [redacted] and, therefore, the data do not support a viable shelf life for vonoprazan 10 mg or 20 mg tablets. In response to the December 23, 2022, advice letter, the applicant submitted an amendment on January 23, 2023, discussing a proposed plan to submit data in the future for six reformulated batches of drug product (three batches for each dosage strength). This amendment was not reviewed in detail in the current review cycle as the deficiencies are not addressed by this amendment. The review team will continue to engage with the applicant to resolve these issues.

Of note, the Division of Anti-Infectives issued a Complete Response (CR) for supplemental NDAs 215152/S-002 and 215153/S-002 on February 3, 2023. The CR Letter explained that the proposed specification limits [redacted], of [redacted] ppm at release and [redacted] ppm for end of shelf life, are not acceptable specified limits [redacted] in vonoprazan because they would lead to a daily intake greater than the AI limit [redacted] for the maximum labeled dose of 40 mg/day.

There are potential risks of long-term carcinogen exposure and erosive esophagitis is a chronic condition for which use of acid suppression over many months (or longer) is often warranted. Multiple other products are available for the healing and maintenance of healed erosive esophagitis and relief of heartburn symptoms. The proposed acceptance criteria for release and stability (b) (4) in the drug product specifications in this NDA are not acceptable because the daily intake (b) (4) exceeds the acceptable intake limit. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. The review team does not recommend approval.

I, the signatory authority, for this application concur with the recommendation to take a Complete Response (CR) action.

I concur that the identified risks cannot be mitigated through labeling or further evaluated during routine pharmacovigilance or by a risk evaluation and mitigation strategy, etc.

The overall benefit-risk is not favorable as described in the Benefit-Risk Framework below. For detailed information supporting the basis for this CR action, refer to the detailed reviews included in this Interdisciplinary Assessment document and the Product Quality Review.

The following will be communicated to the applicant in the CR Letter:

(b) (4)

To address these deficiencies:

1. Revise the acceptance criterion (b) (4) for the drug product release and stability specifications.

2. Perform a root cause investigation [redacted] (b) (4)

3. Submit long term, intermediate (if applicable), and accelerated stability data for at least three batches for each strength (i.e., 10 mg and 20 mg tablets) representative of the to-be-marketed product demonstrating that the stability data meet the updated specifications, including acceptance criterion [redacted] (b) (4). Refer to the guidance for industry, *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).

We encourage you to request a meeting to discuss your plans to address these deficiencies prior to resubmission.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

This assessment focuses on the benefit-risk assessment for Voquezna for the proposed indications of (1) healing of all grades of EE and relief of heartburn associated with EE in adults and (2) maintenance of healing of all grades of EE and relief of heartburn associated with EE in adults. Refer to NDA 215152 and NDA 215153 for the benefit-risk assessment of Voquezna for the treatment of *Helicobacter pylori.*

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GERD comprises a spectrum of acid-related disorders, including sGERD and EE. The pathophysiology of GERD is multifactorial and different mechanisms may result in symptoms, including gastric composition and motility, anti-reflux barrier, refluxate characteristics, clearance mechanisms, mucosal integrity and symptom perception. Erosive esophagitis is a complication/manifestation of severe GERD, defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms (e.g., heartburn). • The severity of GERD symptoms may be associated with the extent and duration of gastric acid exposure in the esophagus (Holloway and Dent 1990; Orlando 1997). However, the presence of GERD symptoms poorly correlates with severity of esophagitis, quantitative measures of reflux frequency or esophageal pH. • The global prevalence of GERD is estimated at approximately 14% of the population, with North American prevalence estimated at nearly 20%. Erosive esophagitis is diagnosed during endoscopy in up to 50% of patients with GERD symptoms. (Fennerty 1997) • Patients who do not receive treatment, or in whom acid reflux is not effectively controlled, are at risk of developing significant complications, such as bleeding, strictures, and the premalignant condition of Barrett's esophagus. (Hillman et al. 2004)	• GERD, along with EE, represents a significant disease burden globally, with the U.S. population being highly affected. Persisent erosions can lead to morbidity associated with complications such as bleeding and strictures, and failure to control EE symptoms can have a significant impact on patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In adults, many patients with EE, especially those with LA Grade C or D erosions, will have recurrence erosions within 6 months of discontinuation of therapy, and most will have recurrence of symptoms. (Katz et al. 2022)	
Current Treatment Options	• Medical management of EE is focused on healing of erosions and control of symptoms, either by pharmacological or surgical means, with surgery usually reserved for intractable cases. • Pharmacological management of GERD includes: (1) drugs to suppress acid production, including H2RAs antagonists, and PPIs; (2) prokinetic agents (e.g., metoclopramide); (3) acid-neutralizing drugs (e.g., antacids) and (4) mucosal barrier agents (e.g. carafate). (Freston 2004) • The substituted benzimidazole proton pump inhibitors (PPIs), along with lifestyle changes are considered standard of care for EE in clinical practice guidelines. Multiple PPIs are currently available for both the healing and maintenance of healed EE. • An 8-week course of a PPI is currently recommended a first line for treatment of EE (healing of erosions and symptom control) followed by maintenance therapy at a lower dosage. • While PPIs are highly effective for healing of esophageal erosions and maintenace of healed erosions, many patients will experience recurrence of symptoms/erosions off PPI therapy, often within a few weeks, which leads to use of higher doses, more frequent dosing, and long-term, chronic use. • PPIs are generally well-tolerated for short-term use (6 months or less). However post-marketing surveillance has revealed safety risks with some adverse reactions related to long-term acid-suppression (e.g., bone fracture, hypomagnesemia, vitamin B12 deficiency).	• Although PPIs are effective at healing EE and controlling the associated symptoms of GERD, including heartburn, additional therapies are needed as some patients may continue to have erosions or symptoms despite treatment with available therapies. • Long-term maintenance therapy is needed to prevent recurrence of EE and symptoms in adults. • Post-marketing surveillance has revealed safety risks with use of PPIs.
Benefit	• A single adequate, and well-controlled study (Study EE-301), with a healing phase and maintenance of healed EE	• The results from Study EE-301, supported by the ex-U.S. studies, demonstrate effectiveness of: o Voquezna 20 mg once daily for 8 weeks for the healing of all grades of EE and relief of heartburn associated with EE in adults

	phase, was conducted to support the safety and effectiveness of Voquezna for the proposed EE indications. • Two additional studies each of healing and maintenance of healed erosive esophagitis (EE), conducted outside the United States, served as confirmatory evidence of effectiveness and also provided supportive safety data. • The primary endpoint for both the healing and maintenance of healed EE in Study EE-301 was non-inferiority (NI) to the active comparator lansoprazole, a PPI. • Secondary endpoints of percentage of 24-hour heartburn-free days and healing/maintenance of healed EE in the subgroup of patients with more severe disease (LA Grades C or D) were prespecified and multiplicity-controlled. • In the healing phase of Study EE-301, the efficacy results demonstrate NI of Voquezna 20 mg once daily compared to lansoprazole 30 mg once daily for the healing of all LA grades of EE at Week 2 or Week 8 (8% treatment difference; 95% CI 4.5, 12.2) and for the percentage of 24-hour heartburn-free days through Week 8 (3% treatment difference; 95% CI -1.6, 7.0). • For the endpoint of complete healing of erosive esophagitis at Week 2, superiority was demonstrated for Voquezna compared to lansoprazole in the subgroup of patients with LA Grade C or D disease (18% treatment difference; 95% CI 7.4, 27.4). • In the maintenance phase, the efficacy results demonstrate NI of both Voquezna 10 mg and 20 mg once daily compared to lansoprazole 15 mg once daily for the maintenance of healed EE (all grades) (7% treatment difference; 95% CI 0.2, 14.1) and the percentage of 24-hour heartburn-free days (2% treatment difference; 95% CI -2.3, 6.8) through Week 24. • In the maintenance phase, Voquezna 20 mg did not demonstrate greater efficacy than the 10 mg dosage and the applicant did not request approval of that dosage regimen for maintenance of healed EE. • Superiority was also demonstrated through Week 24 for maintenance of healed EE for Voquezna compared to lansoprazole in the subgroup of patients with LA Grade C	o Voquezna 10 mg once daily for up to 6 months to maintain healing of all grades of EE and relief of hearburn assoicated with EE in adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	or D disease (13% treatment difference; 95% CI 0.02, 26.1). • The phase 3 ex-U.S. studies also demonstrated non-inferiority of vonoprazan 20 mg once daily compared to lansoprazole 30 mg once daily for healing and vonoprazan 10 mg once daily compared to lansoprazole 15 mg once daily for maintenance of healed EE (all grades).	
Risk and Risk Management	• The nonclinical safety profile of vonoprazan and its metabolites was extensively studied and reviewed under NDAs 215152 and 215153 for the treatment of *Helicobacter pylori* infection in adults. In the current NDA, no additional nonclinical studies have been provided. No nonclinical deficiency or safety concersn were identified. • Low rates of SAEs, AEs leading to discontinuation and TEAEs were reported in Study EE-301 and the ex-U.S. phase 3 trials. Rates for vononprazan were similar overall to the active comparator, lansoprazole, a PPI. • The most common adverse reactions in patients treated with: o Vonoprazan 20 mg once daily for 2 to 8 for healing of EE (>1%) were: gastritis, diarrhea, abdominal distension, abdominal pain, and nausea. o Vonoprazan 10 mg once daily for up to 24 weeks for maintenance of healed EE (>2%) were: gastritis, abdominal pain, dyspepsia, hypertension, and urinary tract infection. • Adverse Events of Special Interest (AESI) were infrequently reported. • No new safety signals were identified in the available postmarketing data from FAERS or the published literature. • Although there were no reported adverse reactions or laboratory abnormalities observed in the NDA would preclude approval, the OPQ review identified deficiencies in the drug product due to the presence of a (b) (4) impurity, identified by the applicant during the review cycle. (b) (4)	• The clinical database supports the overall safety of o Voquezna 20 mg once daily for 8 weeks for the healing of all grades of EE and relief of heartburn associated with EE in adults o Voquezna 10 mg once daily for up to 6 months to maintain healing of all grades of EE and relief of hearbutn assoicated with EE in adults. • Safety issues due to acid suppression that are seen with the drug class of PPIs may also be a potential concern with vonoprazan. • While no safety or efficacy concerns were noted with nonclinical or clinical data in the NDA, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. o The identified risks cannot be mitigated through labeling, byfurther evaluation during routine pharmacovigilance, or by a risk evaluation and mitigation strategy, etc. o The review team recommends a Complete Response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(b) (4) The applicant's proposed (b) (4) acceptance criteria for the impurity in the drug product specifications exceed the acceptable intake limit resulting in a lack of CMC information to support a viable shelf life for both the 10 mg and 20 mg tablets. See Section 9 Product Quality.	

Abbreviations: AESI, adverse event of special interest; AWC, adequate, well-controlled study; CLE, cutaneous lupus erythematosis; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; H_2RAs, histamine 2-receptor; HP, healing phase; LA, Los Angeles; MOHEE, maintenance of healed erosive esophagitis; MP, maintenance phase; NI, non-inferiority; PMR, postmarking requirement; PPI, protein pump inhibitors; REMS, risk evaluation and mitigation strategy; sGERD, symptomatic non-erosive gastroesophageal reflux disease; SLE, systemic lupus erythematosis

2.2. Conclusions Regarding Benefit-Risk

The identified CMC deficiencies in the drug product preclude approval and a Complete Response action is recommended by the review team.

II. Interdisciplinary Assessment

3. Introduction

Phathom Pharmaceuticals submitted new drug application (NDA) 215151 for Voquezna (vonoprazan) tablets. Vonoprazan is a potassium-competitive acid blocker, a new pharmacologic class of gastric acid suppressant, with a mechanism of action similar to the substituted benzimidazoles known as proton pump inhibitors (PPIs). Vonoprazan competitively inhibits the binding of potassium ions to hydrogen potassium (H+K+)-ATPase (also known as the proton pump) in the final step of gastric acid secretion in gastric parietal cells, resulting in suppression of acid secretion.

Vonoprazan was first approved in Japan in 2014. Since then, vonoprazan has been approved in 15 additional countries (Philippines, Singapore, Thailand, Argentina, Peru, Taiwan, Korea, Malaysia, Ecuador, Indonesia, China, Russian Federation, Brazil, Mexico, and Colombia) with an estimated post-authorization exposure in over (b) (4) patients as of June 2021. The approved indications include healing and maintenance of healed erosive esophagitis (EE), treatment of *Helicobacter pylori (H. pylori)*, and other various gastrointestinal conditions (e.g., treatment and prevention of gastric and duodenal ulcer).

Vonoprazan was approved in the United States on May 3, 2022, as Voquezna Triple Pak (NDA 215152) and Voquezna Dual Pak (NDA 215153), co-packaged products of vonoprazan 20 mg tablets with clarithromycin 500 mg tablets and amoxicillin 500 mg capsules (Triple Pak) or amoxicillin 500 mg capsules (Dual Pak), for the treatment of *H. pylori*.

Voquezna is supplied as tablets containing 10 mg and 20 mg of vonoprazan, equivalent to 13.36 mg and 26.72 mg, respectively, of vonoprazan fumarate.

The Applicant proposes the following indications for Voquezna under NDA 215151:

- For healing of all grades of EE and relief of heartburn associated with EE in adults
- To maintain healing of all grades of EE and relief of heartburn associated with EE in adults
- In combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori (H. pylori)* infection in adults.
- In combination with amoxicillin for the treatment of *H. pylori* infection in adults.

PPIs are the current standard-of-care treatment for healing of EE and maintenance of healed EE. Refer to Section 2.1 (Benefit-Risk Framework) for additional details.

The Applicant's proposed dosage regimen is shown in Table 3.

Table 3. Applicant's Proposed Dosage Regimen

Indication	Recommended Dosage	Duration
Healing of EE and Relief of Heartburn	20 mg once daily	(b) (4) 8 weeks
Maintenance of Healed EE and Relief of Heartburn	10 mg once daily	Up to 6 months
Treatment of *H. pylori* Infection		
Triple Therapy		
VOQUEZNA	20 mg twice daily†	14 days
Amoxicillin	1,000 mg twice daily†	14 days
Clarithromycin	500 mg twice daily†	14 days
Dual Therapy		
VOQUEZNA	20 mg twice daily‡	14 days
Amoxicillin	1,000 mg three times daily§	14 days

†To be taken in the morning and evening (12 hours apart).
‡To be taken in the morning and evening.
§To be taken in the morning, mid-day and evening.
Abbreviations: EE, erosive esophagitis

The indications for Voquezna in combination with amoxicillin and clarithromycin (NDA 215152) or amoxicillin (NDA 215153) were previously reviewed by the Division of Anti-infectives. This review will only discuss the new data submitted in support of the indications for healing and maintenance of healed EE.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Non-Inferiority Margin for the Primary Endpoint of Healing of EE at Week 8 in the Healing Phase of Study EE-301

3.1.1.2. Non-Inferiority Margin for the Primary Endpoint of Maintenance of Healed EE Through Week 24 in the Maintenance Phase of Study EE-301

3.1.1.3. Non-Inferiority Margin for the Secondary Endpoint of 24-Hour Heartburn Free Days in the Healing Phase of Study EE-301

3.1.1.4. Non-Inferiority Margin for the Secondary Endpoint of 24-Hour Heartburn-Free Days Through Week 24 in the Maintenance Phase of Study EE-301

3.1.1.5. Impact of a Single Site (Site ID: 10010) on Superiority of Voquezna 10 mg Once Daily Over Lansoprazole 15 mg Once Daily for the Endpoints of Maintenance of Healed EE for All Grades (Primary Endpoint) and Grades C or D (Secondary Endpoint) in Study EE-301

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Adverse Events of Special Interest Related to Vonoprazan

3.1.2.2. Adverse Events of Special Interest Related to Suppression of Acid Secretion

3.1.2.3. Adverse Events of Special Interest, Reported With Proton Pump Inhibitors, Not Known to be Related to Acid Suppression

3.2. Approach to the Review

The primary evidence of efficacy and safety for Voquezna for the proposed indications of healing of EE and maintenance of healed EE is provided by a single adequate and well-controlled trial conducted in the U.S. and Europe (Study EE-301). Study EE-301 is a randomized, double-blind, active-controlled phase 3 study. Recommendations from FDA during protocol development were incorporated into the study design. The active comparator in Study EE-301 is lansoprazole, a PPI. In addition to Study EE-301, four phase 3 trials conducted in Asia (Japan, China, Malaysia, Taiwan and Korea) provide confirmatory evidence of vonoprazan effectiveness to substantiate the results of Study EE-301, and supportive safety data. All of the phase 3 studies were conducted according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 Good Clinical Practice.(December 2016)

The ex-U.S. trials are considered confirmatory trials. In general, these studies included similar subject populations, dosage regimens for vonoprazan and active comparator (lansoprazole), primary endpoint definitions, and timing of assessments as in Study EE-301. Refer to Section 6.2.4 for additional details regarding the ex-U.S. trials. The Applicant provided additional information to support the applicability of the data from the four ex-U.S. trials to the U.S. population and provided full clinical study reports and data sets.

Additional supportive safety information from ex-U.S. phase 2 and 3 trials conducted in other gastrointestinal-related indications, and ex-U.S. post-marketing safety surveillance data, including pharmacovigilance reports, literature publications, and a long-term active-controlled safety trial were reviewed (see Section 7.4 Assessment of Safety).

Table 4 provides an overview of the U.S. clinical trial (Study EE-301).

Table 4. Clinical Study Submitted[1] in Support of Efficacy and Safety Determinations for Voquezna (EE-301)

Study Identifier	Study (Phase) Population	Study Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints (Healing Phase)	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
EE-301						
Healing phase	Subjects with endoscopically confirmed EE of LA Classification Grades A to D as assessed by a central adjudicator	Control Type: Active concurrent Randomization: Stratified randomization Blinding: Double-blind Analysis: non-inferiority	Vonoprazan 20 mg tablet (N=514) Active Control: Lansoprazole 30 mg capsule (N=513) Oral, once daily Duration: 2 to 8 weeks	Primary: • percentage of subjects who have complete healing of EE (i.e., all grades) at Week 2 or Week 8 as assessed by endoscopy. Secondary (arranged per testing hierarchy): • percentage of 24-hour heartburn-free days over the healing period (i.e., through Week 8) as assessed by daily diary • percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D • percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution was defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary). • percentage of subjects who have complete healing of EE at Week 2 or Week 8 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D • percentage of subjects who have complete healing of all grades of EE at Week 2 as assessed by endoscopy	Planned: 1000 Actual: 1027	111 centers in US and 6 European countries[2]
Maintenance Phase	Subjects completing the healing phase with endoscopically confirmed healed EE either at Week 2 or Week 8		Vonoprazan (N=592): 10 mg tablet (N=298) 20 mg tablet (N=298) Active control: Lansoprazole 15 mg capsule (N=297) Oral, once daily Duration: 24 weeks	Primary: • percentage of subjects who maintained complete healing of EE (i.e., all grades) through Week 24 (Voquezna 20 mg and 10 mg) Secondary: • percentage of Grade C or D subjects who maintained healing of EE through Week 24 (Voquezna 20 mg) • percentage of 24-hour heartburn-free days through Week 24 (Voquezna 20 mg) • percentage of Grade C or D subjects who maintained healing through Week 24 (Voquezna 10 mg) • percentage of subjects who maintained healing through Week 24 (Voquezna 10 mg) • percentage of 24-hour heartburn-free days through Week 24 (Voquezna 10 mg)	Planned: 800 Actual: 893	

Source: Clinical Study Report and adsl.xpt
Source: Reviewer
[1] A single adequate and well-controlled study was submitted in support of NDA 215151.
[2] Participating countries: United States (approximately 63% of subjects), Bulgaria, Czechia, Great Britain, Hungary, Poland.
Abbreviations: EE, erosive esophagitis; LA, Los Angeles; PC, placebo-controlled

4. Patient Experience Data

Study subjects completed an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms throughout the study. Subjects also completed the Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM), Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL), and the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) during each site visit.

Only the symptom data recorded in the daily diary were used to support the claim of "relief of heartburn" for the indications of healing of EE and maintenance of healed EE in labeling based on the secondary efficacy endpoints in Study EE-301 of percentage of 24-hour heartburn-free days. (Sections 6.2.2.3 and 6.2.3.4) The PAGI-SYM, PAGI-QoL and the EQ-5D-5L instruments measure a subject's general well-being and may capture effects that may be influenced by factors beyond the study drug effect. Therefore, data from these tools were considered as exploratory and will not be discussed further in this review.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☒	Patient-reported outcome	Sections 6.2.2.3 and 6.2.3.4
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The majority of the clinical pharmacology information supporting Voquezna for the indications of healing of EE and maintenance of healed EE (NDA 215151) was reviewed previously under NDAs 215152 and 215153 for the indication of treatment of *H. pylori* infection in combination with amoxicillin and clarithromycin (NDA 215152) or clarithromycin (NDA 215153) and reflected in the approved labeling (refer to the Integrated Review of NDAs 215152/215153, DARRTS date May 3, 2022, and the Prescribing Information (PI) for Voquezna Triple Pak and Dual Pak) (Phathom 2022). A pharmacokinetic (PK) and pharmacodynamic (PD) study of vonoprazan 20 mg once daily compared to lansoprazole 30 mg once daily (Study VONO-103) was additionally conducted and submitted to support this NDA. Table 6 summarizes the general clinical pharmacology and pharmacokinetics of vonoprazan.

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

	Drug Information
Characteristic	**Pharmacologic Activity**
Established pharmacologic class	Potassium-competitive acid blocker (PCAB)
Mechanism of action	Vonoprazan suppresses basal and stimulated gastric acid secretion at the secretory surface of the gastric parietal cell through inhibition of the H+, K+-ATPase enzyme system in a potassium competitive manner. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, vonoprazan has been characterized as a type of gastric proton-pump inhibitor, in that it blocks the final step of acid production.
Active moieties	vonoprazan
QT prolongation	At a dose 6 times the maximum recommended dose, vonoprazan does not prolong the QT interval to any clinically relevant extent. The Applicant conducted a thorough QT study aimed at determining the QTc effect of vonoprazan exposures following single doses of 20 mg and 120 mg (Study TAK-438_111), indicating no effect of vonoprazan plasma concentrations on the QTc intervals up to 120 mg dose, i.e., 6-fold the maximum proposed dose.
Acid secretion inhibition	Following a single dose of vonoprazan 10 to 40 mg in healthy subjects (Study TAK-438_101), intragastric pH began increasing within 2 to 3 hours. The elevated intragastric pH compared to placebo is maintained for over 24 hours after dosing. The mean time% with intragastric pH >4 increases with increasing doses. Following multiple doses of vonoprazan 10 to 40 mg in healthy subjects (Study TAK-438_107), the inhibitory effect of vonoprazan on acid secretion reached steady state by Day 4 and increased dose-dependently (see Table below). The antisecretory effect of vonoprazan decreases following drug discontinuation although intragastric pH remains elevated compared to placebo for 24 to 48 hours following the last dose. **Table 7. Mean (SD) 24-Hour Intragastric pH and Mean Time% With pH >4 Following Once-Daily Administration of Vonoprazan 10, 20, 30 or 40 mg on Day 7** **Parameter** **Vonoprazan Dosage**

Characteristic	Drug Information
	Pharmacologic Activity

	10 mg QD	20 mg QD	30 mg QD	40 mg QD
N	9	9	9	9
24-hr intragastric pH	4.6 (0.91)	5.9 (0.73)	5.9 (0.49)	6.2 (0.81)
Time Intragastric pH >4	60.2 (19.08)	85.2 (12.26)	90.1 (7.85)	93.2 (10.51)

Source: Study Report TAK-438_107, Table 15.2.8.1
Abbreviations: QD, once daily; SD, standard deviation

General Information

Bioanalysis

Adequately validated HPLC/MS/MS methods were used to determine the concentrations of vonoprazan and its inactive metabolites (M-I, M-II, M-III, and M-IV-Sul) in human plasma.

Healthy subjects versus patients

A population PK analysis was performed based on data from 1179 subjects including 589 subjects with EE and 157 subjects with symptomatic GERD. Although disease status (EE or GERD) was identified as a covariate associated with vonoprazan PK parameters such as absorption rate, clearance, and volume of distribution, EE or GERD is not expected to have a clinically meaningful impact on vonoprazan exposure.

Pharmacokinetic parameters at single dose and steady state

Table 8. Mean (%CV) Pharmacokinetic Parameters for Vonoprazan at a Single Dose or Steady State Following Once Daily Dosing

	Vonoprazan 10 mg		Vonoprazan 20 mg		Vonoprazan 40 mg	
Parameter	**Single Dose**	**Steady State**	**Single Dose**	**Steady State**	**Single Dose**	**Steady State**
N	44	30	108	68	96	33
T_{max}(h)[1]	1.5 (0.75, 4.0)	1.5 (0.75,3.0)	2.0 (0.75, 5.0)	2.0 (0.75, 5.0)	1.5 (0.75, 5.0)	3 (0.75, 6.0)
C_{max} (ng/mL)	9.6 (36.6)	11.7 (27.5)	21.3 (38.5)	26.1 (35.2)	52.2 (36.0)	37.3 (36.6)
AUC (ng·h/mL)[2]	75.0 (37.4)	92.9 (33.1)	196.1 (42.4)	230.9 (41.3)	484.5 (36.8)	269.7 (31.0)
$t_{1/2}$ (h)	7.5 (18.9)	7.7 (27.1)	7.3 (23.1)	7.9 (22.6)	7.5 (16.8)	6.8 (22.4)
CL/F (L/h)	149.8 (33.3)	120.2 (35.2)	118.3 (38.1)	100.2 (38.3)	94.6 (38.3)	82.2 (35.3)
Vz/F (L)	1578.5 (32.0)	1270.7 (26.6)	1202.8 (35.9)	1114.0 (39.6)	995.4 (34.2)	789.9 (33.9)

Source: Tables 6.p and 6.q. in Section 2.7.2. Summary of Clinical Pharmacology Studies,
The results of TAK-438_101, TAK-438_107, TAK-438_109, TAK-438_111, TAK-438_114, TAK-438/CPH-002, and VONO-103 were pooled.

1. T_{max} are presented in median (min, max)
2. AUC_{inf} for single dose; $AUC_{0\text{-}24}$ for steady-state

Abbreviations: AUC_{0}-24, area under the plasma concentration-time curve from time 0 to end of the dosing interval, 24 hours; AUC_{∞}, area under the plasma concentration-time curve from time 0 to infinite; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life; T_{max}, time to reach C_{max}; V_z/F, apparent oral volume of distribution

Characteristic	Drug Information Pharmacologic Activity
Range of effective dosage(s) or exposure	Healing of EE: In the phase 2 dose-ranging study (TAK-438/CCT-001) over the vonoprazan dosage range of 5 mg QD to 40 mg QD, the proportion of subjects achieving EE healing at Week 4 was >90% in all dosage groups and did not significantly differ between dosage groups. In phase 3 studies (Studies EE-301, TAK-438/CCT-002 and TAK-439_303), the only dosage of Voquezna evaluated was 20 mg QD compared to lansoprazole 30 mg QD for up to 8 weeks. Maintenance of Healed EE: In the phase 3 trials for maintenance (Studies EE-301, TAK-438/CCT-003 and TAK-438_305), Voquezna 10 mg QD and 20 mg QD were evaluated compared to lansoprazole 15 mg QD, and both Voquezna dosages showed similar rates of maintenance of healed EE through Week 24 compared to lansoprazole. For example, in the phase 3 Study EE-301 conducted in the US, the difference from lansoprazole in response rate was numerically greater with 20 mg QD than 10 mg QD but the difference from lansoprazole between Voquezna 10 mg QD and 20 mg QD was not clinically meaningful (i.e., 7.2% and 8.7%, respectively). See Section 6.1.
Maximally tolerated dosage or exposure	The maximally tolerated vonoprazan dosage is unknown. The highest evaluated doses in humans were 120 mg as a single dose and 40 mg as total daily dose (20 mg BID and 40 mg QD) (Data source: Study TAK-438_111).
Bridge between to-be-marketed and clinical trial formulations	Not needed as the formulation used in the phase 3 clinical trial (i.e., EE-301) is the same as the to-be-marketed formulation.
	Absorption
Bioavailability	Absolute bioavailability of vonoprazan is unknown.
T_{max}	Median T_{max} =1.5 to 2.0 hours in healthy subjects with a dosage of Voquezna 10 mg and 20 mg QD.
Time to steady state	Steady state of vonoprazan plasma concentrations was achieved by Day 3 to 4.
Dosage proportionality	Following a single dose of vonoprazan doses ranging from 1 to 120 mg, mean C_{max} and AUC_{inf} increased in a greater than dose-proportional manner, with slopes of 1.30 and 1.24, respectively (Study TAK-438_101). At steady state, vonoprazan C_{max} and AUC_{0-24} increased in approximately dose proportional manner over the dosage range of 10 to 40 mg QD, with slopes of 1.16 and 1.15 (Study TAK-438_107).
Accumulation	After once daily doses, an accumulation index ratio of AUC was <1.2 over the dose range of 10 to 40 mg.
Food effect (fed/fasted)	In a food effect study in healthy subjects receiving a single dose of vonoprazan 20 mg (Study TAK-438_109), a high-fat meal 30 minutes before dosing resulted in a 5% increase in C_{max}, a 15% increase in AUC, and a delay in median T_{max} of 2 hours. In the phase 3 clinical trial of EE in the United States (Study EE-301), subjects were instructed to take vonoprazan 30 minutes before breakfast whereas in the other phase 2 and 3 trials of vonoprazan for EE, subjects were instructed to take vonoprazan after breakfast. The Applicant proposes that Voquezna can be taken with or without food and the food effect study supports administration of vonoprazan without regard to food.
	Distribution
Plasma protein binding	Vonoprazan protein binding in human plasma is 85% to 88% over the concentration range of 100 to 1000 ng/mL.
Drug as substrate of transporters	Vonoprazan is not a substrate of P-gp, BCRP, organic anion transporting polypeptide (OATP)1B1, or OATP1B3.

Characteristic	Drug Information
	Pharmacologic Activity
	Elimination
Primary excretion pathways (% dosage)	In the mass balance study, the overall mean recovery of radioactivity was 98.5% over 120 hours following a single 20 mg oral dose of [14C]-vonoprazan (Study TAK-438_103). In total, 67.4% (8% as unchanged vonoprazan) and 31.1% (1.4% as unchanged vonoprazan) of the total radioactive dose was recovered in the urine and feces, respectively. The predominant route of excretion of radioactivity was via urinary excretion.
Metabolic pathway(s)	Vonoprazan is mainly metabolized by CYP3A4/5 and to a lesser extent CYP2B6, CYP2C19, and CYP2D6 to metabolites M-I, M-II, and M-III. Vonoprazan is also metabolized by SULT2A1 followed by CYP2C9 to form M-IV-Sul and glucuronidation of M-I and M-II to form M-I-G and M-II-G. In the mass balance study (Study TAK-438_103), M-I-G was the primary characterized component in plasma at all timepoints, followed by M-IV-Sul and vonoprazan. Exposure to vonoprazan, M-I, M-II, M-III, M-IV-Sul, and M-I-G represented 13.9%, 8.2%, 6.8%, 4.3%, 16.9%, and 19.2% of the total radioactivity, respectively.
	Intrinsic Factors and Specific Populations
Body weight and age	Population PK model identified body weight and age as a significant covariate associated with vonoprazan clearance and volume of distribution, respectively. However, the observed effects of weight or age on vonoprazan exposure is not considered clinically relevant.
Renal impairment	In the dedicated renal impairment study at single dose of vonoprazan 20 mg (Study TAK-438_113), the mean vonoprazan AUC_{inf} was 1.7-, 1.3- and 2.4- times greater in subjects with mild (eGFR 60 to <90 mL/min/1.73m^2), moderate (eGFR 30 to <60 mL/min/1.73m^2), and severe renal impairment (eGFR 15 to <30 mL/min/1.73m^2), respectively, compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73m^2). In subjects requiring dialysis (N=8), AUC_{inf} estimates were 1.3-fold greater compared to estimates from subjects with normal renal function. See Section 8.1 regarding the recommended dosage adjustment in patients with renal impairment.
Hepatic impairment	In the dedicated hepatic impairment study at single dose of vonoprazan 20 mg (Study TAK-438_112), the mean vonoprazan AUC_{inf} was 1.2-, 2.4- and 2.6-times higher in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to subjects with normal liver function. See Section 8.1 regarding the recommended dosage adjustment in patients with hepatic impairment.
CYP2C19 polymorphism	Effect of CYP2C19 genotype and the associated CYP2C19 metabolizer status on PK have been evaluated in clinical studies and there are no considerable differences in the pharmacokinetics of vonoprazan based on CYP2C19 metabolizer status.
	Drug Interaction Potential (Drug as Victim)
Effect of CYP3A4 inhibitor on vonoprazan	When a single dose of vonoprazan 40 mg was administered with clarithromycin (a strong CYP3A inhibitor) 500 mg twice daily for 7 days (N=16), vonoprazan AUC_{inf} increased 58% compared to administration of vonoprazan alone (TAK-438_110). See Section 8.2.
Effect of CYP3A4 inducer on vonoprazan	The PBPK model predicted that vonoprazan exposures (AUC_{inf}) will be approximately 50% and 80% lower when co-administered with a moderate CYP3A4 inducer (i.e., efavirenz) and a strong CYP3A4 inducer (e.g., rifampin), compared to when vonoprazan is administered alone. See Section 8.2.

Characteristic	Drug Information Pharmacologic Activity Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism enzymes	In vitro studies: • In vitro, vonoprazan inhibits CYP2B6, CYP2C19, and CYP3A4/5 in time- and concentration-dependent manner. The PBPK predictions of potential clinical DDIs using in vitro findings and static mechanistic models suggest that vonoprazan weakly inhibits CYP2B6 and CYP2C19, i.e., a 47% increase in AUC of a CYP2B6 substrate (bupropion) and a 49% increase in AUC of a CYP2C19 substrate (proguanil). • The metabolite TAK-438 M-III showed induction potency for CYP2B6 and CYP3A4 at concentrations higher than the clinically relevant concentrations. Clinical studies: • The clinical DDI study (Study VONO-101) showed that midazolam (sensitive CYP3A4 substrate) C_{max} and AUC increased by 1.9-fold when midazolam was administered after repeated doses of Voquezna 20 mg BID compared to administration alone.
Inhibition/induction of transporters	Vonoprazan does not inhibit transporters (P-gp, BCRP, MATE1, OCT1, OATP1B1/1B3) in vitro at clinically relevant concentrations.
Alteration of gastric pH dependent drug absorption	Vonoprazan reduces intragastric acidity, which may alter the absorption of oral drugs that is absorbed depending on gastric pH such as antiretrovirals (rilpivirin, atazanavir, nelfinavir, etc.), iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole.

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; CYP, cytochrome isoenzyme; DDI, drug-drug interaction; EE, erosive esophagitis; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; PBPK, physiologically based pharmacokinetic; PCAB, potassium-competitive acid blocker; P-gp, P-glycoprotein; PK, pharmacokinetic; QTc, QT corrected for heart rate

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. In Vitro Studies

In vitro studies with vonoprazan demonstrated potassium competitive inhibition of gastric acid production in porcine (half maximal inhibitory concentration [IC_{50}] =19.3 to 29.9 nmol/L) and rabbit (IC_{50}=0.3 μmol/L) gastric glands in a noncovalent and reversible manner by selective inhibition of the H+, K+-ATPase enzyme. Vonoprazan metabolites, M-I, M-II, and MIII did not inhibit this enzyme at the concentrations up to 10 μmol/L, and metabolite, M-IV-Sul only weakly inhibited the enzyme (IC_{50}=4120 μmol/L).

5.1.2. In Vivo Studies

In an in vivo study, the inhibitory effects of vonoprazan and lansoprazole were assessed on aspirin- and indomethacin-induced gastric mucosal lesions in rats. Vonoprazan (0.5 to 4 mg/kg) and lansoprazole (0.5 to 16 mg/kg) were given orally. Vonoprazan and lansoprazole both inhibited aspirin-induced gastric mucosal lesions in rats, with 50% inhibitory dose (ID50) values of 0.73 and 0.77 mg/kg, respectively. Vonoprazan and lansoprazole both inhibited indomethacin-induced gastric mucosal lesions with ID50 values of 1.65 and 4.38 mg/kg, respectively. In another study, indomethacin-induced gastric bleeding in rats was inhibited following IV injections of vonoprazan (0.2, 0.4 and 0.8 mg/kg) or lansoprazole (0.1, 0.3 and 1 mg/kg), with ID50 values of 0.32 and 0.29 mg/kg, respectably. The preventive actions of vonoprazan and lansoprazole was also assessed against experimental reflux esophagitis in rats. Rats were administered vonoprazan at 0.5, 1, 2 and 4 mg/kg or lansoprazole at 1, 2, 4 and 8 mg/kg orally. The ID50 values of vonoprazan and lansoprazole were 1.27 and 3.20 mg/kg, respectably. Intravenous administration of vonoprazan (2 mg/kg) caused a marked increase in gastric perfusate pH under histamine-stimulated acid secretion in anesthetized rats. Vonoprazan (0.1-0.8 mg/kg) administered IV resulted in a dose-dependent inhibition of histamine-induced gastric acid secretion with an ID50 value of 0.15 mg/kg. Vonoprazan (0.5-4 mg/kg, oral) inhibited basal acid secretion in conscious rats and histamine- and 2-deoxy-D-glucose-stimulated acid secretion in anesthetized rats, with ID50 values of 0.83 to 1.26 mg/kg.

5.1.3. In Vitro and In Vivo Summary/Conclusions

Vonoprazan has been shown to be a reversible potassium competitive inhibitor of H+, K+-ATPase in vitro. Vonoprazan metabolites did not show H+, K+-ATPase inhibitory activity at concentrations up to 10 μmol/L, except metabolite, M-IV-Sul, which showed very weak inhibitory activity. Oral administration of vonoprazan inhibited aspirin and indomethacin-induced gastric lesions in rats. Vonoprazan also inhibited experimental reflux esophagitis in rats. Intravenous vonoprazan caused a dose-dependent inhibition of histamine-stimulated acid secretion in anesthetized rats. Thus, the findings of the nonclinical pharmacology studies conducted with vonoprazan support the proposed indications under the current NDA.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

6.1.1. Healing of EE

The proposed dosage for healing of all grades of EE is Voquezna 20 mg once daily for (b) (4) 8 weeks, administered without regard to food.

Voquezna dosage of 20 mg once daily was selected for the healing phase of Study EE-301 based on data from a phase 2 dose ranging trial conducted in Japan (TAK-438/CCT-001) and two previously conducted phase 3 trials in Japan and Asia (Studies TAK-438/CCT-002 and TAK-439_303) for healing of EE.

A double-blind phase 2 dose-ranging trial in Japan (TAK-438/CCT-001) in subjects with EE of Los Angeles (LA) Classification Grades A to D informed the dose-response relationship for healing of EE and supported selection of Voquezna 20 mg once daily for the healing phase of Study EE-301. In the phase 2 study, four dose groups were administered vonoprazan (5, 10, 20, and 40 mg once daily) or lansoprazole 30 mg once daily for 8 weeks in a 1:1:1:1:1 ratio. Endoscopy was performed at baseline, Week 2, Week 4, and Week 8 (only when healing was not observed on endoscopy at Week 4). The active-comparator lansoprazole 30 mg once daily is approved for up to 8 weeks for the treatment of EE (Prevacid NDA 20406).

At Week 2, the proportion of subjects with healed EE in the vonoprazan 10 mg, 20 mg, and 40 mg groups tended to be greater than in the vonoprazan 5 mg group or lansoprazole group. The proportions of subjects who achieved endoscopic healing at Weeks 4 and 8 were generally similar between all vonoprazan dose groups and the lansoprazole group. Although the healing rate at Weeks 4 and 8 numerically increased according to dose over the range from 5 mg to 40 mg, the difference in the rates between the vonoprazan dose groups was small (see Table 9).

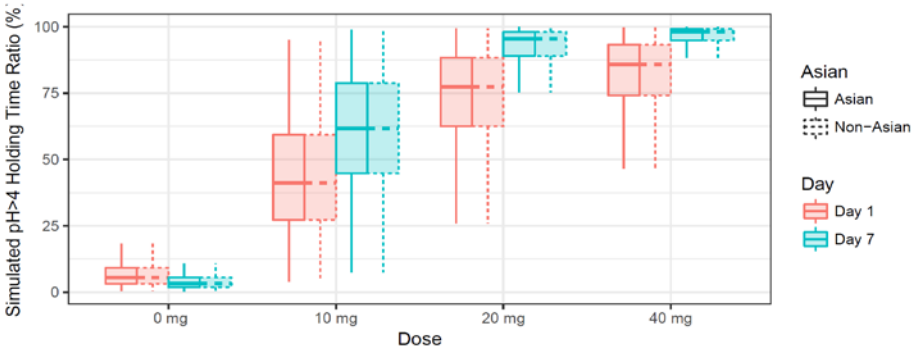
Table 9. Healing Rate of EE in Phase 2 Dose-Ranging Study (Study TAK-438/CCT-001, Full Analysis Set)

	Vonoprazan				Lansoprazole
Parameter	**5 mg QD**	**10 mg QD**	**20 mg QD**	**40 mg QD**	**30 mg QD**
N	148	145	154	145	139
EE healing rate at Week 2, n (%)	123/143 (86.0)	124/133 (93.2)	135/144 (93.8)	127/134 (94.8)	117/132 (88.6)
Difference from lansoprazole, %	-2.6	4.6	5.1	6.1	-
95% CI	-10.5, 5.2	-2.3, 11.5	-1.6, 11.8	-0.5, 12.7	
EE healing rate at Week 4, n (%)	132/143 (92.3)	123/133 (92.5)	136/144 (94.4)	130/134 (97.0)	123/132 (93.2)
Difference from lansoprazole, %	-0.9	-0.7	1.3	3.8	-
95% CI	-7.0, 5.3	-6.9, 5.5	-4.4, 7.0	-1.3, 9.0	
EE healing rate at Week 8, n (%)	138/143 (96.5)	127/133 (95.5)	139/144 (96.5)	130/134 (97.0)	126/132 (95.5)
Difference from lansoprazole, %	1.0	0.0	1.1	1.6	
95% CI	-3.6, 5.7	-5.0, 5.0	-3.6, 5.7	-3.0, 6.1	

Source: Study TAK-438/CCT-001 CSR Section 15.1 Tables 2.1.2, 2.4.1.1.1.1, 2.4.1.1.2.1.1, 2.4.1.2.2.1, 2.4.1.2.2.2, 2.4.1.2.1.1, 2.4.1.2.1.2
A missing result was treated as not healed. Grades O (no mucosal break) and X (unable to judge) at baseline were excluded from analysis.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; QD, once daily

The observed dose-response relationship for vonoprazan in the phase 2 study is generally aligned with the PK-PD relationship following an E_{max} model. Figure 1 presents simulated time% gastric pH >4 over 24 hours by vonoprazan dose based on the PK-PD model developed using pooled data from 6 studies in healthy subjects in the U.K. and Japan. The results suggest that time% intragastric pH >4 increases dose-dependently but does not increase further at vonoprazan doses greater than 20 mg once daily, supporting the selection of the 20 mg vonoprazan dose. It also indicates that there is no significant racial difference in the PK-PD relationship of vonoprazan between Asian and non-Asian (primarily White) subjects, which supports the applicability of efficacy results from Asian subjects to patients in the United States. See Section 14.1 for further information of the PK-PD modeling and simulation.

Figure 1. Model-Predicted Time% Intragastric pH >4 Over 24 Hours on Day 1 and Day 7 (Steady State) by Vonoprazan Dose



Source: The Population PK-PD report, Figure 7.2
Day 1 (red) and 7 (cyan) are grouped by Dose and Asian/Non-Asian (solid/dashed). The band inside the box is the median of predicted values. The lower and upper hinges correspond to the 25th and 75th percentiles. Whiskers represent 1.5 times the interquartile range.

In two subsequent phase 3 healing studies conducted in Asia (Studies TAK-438/CCT-002 and TAK-439_303), vonoprazan 20 mg once daily showed a similar healing rate for all grades of EE by Week 8 compared to lansoprazole 30 mg once daily as shown in Table 20. The results of these clinical trials also informed the dose selection for healing phase in Study EE-301 in the United States. A dosage of Voquezna 20 mg once daily was the only dosage studied for the healing phase of Study EE-301 in the United States. See further Section 6.2.2 for the efficacy assessment of vonoprazan 20 mg once daily for healing of EE in phase 3 trials.

6.1.2. Maintenance of Healed EE

The proposed dosage for the maintenance of healed EE (all grades) is Voquezna 10 mg once daily, administered without regard to food.

The Voquezna dosage selected for the maintenance phase of Study EE-301 was based on data from two previously conducted phase 3 trials in Asia for maintenance of healed EE (Studies TAK-438/CCT-003 and TAK-438_305). In both of these ex-U.S. phase 3 trials, vonoprazan 10 mg and 20 mg once daily showed numerically higher rates of maintenance of healed EE (all grades) through Week 24 (92.6% and 96.6% for Study TAK-438/CCT-003, 75.8% and 76.9% for Study TAK-438_305) compared to lansoprazole 15 mg once daily (81.1% for Study TAK-438/CCT-003, 65.9% for Study TAK-438_305) as shown in Table 22. The rates of maintenance of healed EE (all grades) in both studies were similar in the two vonoprazan dose arms (Table 14 and Table 16 in Section 6.2). The active comparator lansoprazole 15 mg once daily is approved for maintenance of healing of EE in the United States (Prevacid NDA 20406).

In the maintenance phase of Study EE-301, two dosage levels of Voquezna (10 and 20 mg once daily) were evaluated in comparison to lansoprazole 15 mg once daily. The proportion of subjects with maintenance of healed EE (all grades) was similar between the Voquezna 10 mg and 20 mg dose groups in the overall population and in a subgroup of subjects with more severe grades of erosive esophagitis (LA Grades C or D) (Table 16 and Table 17 in Section 6.2.3). See Section 6.2 for details of the efficacy assessment of vonoprazan 10 mg and 20 mg once daily (QD) for maintenance of healed EE.

6.2. Clinical Trials Intended to Demonstrate Efficacy

Results from Study EE-301 serves as the primary basis of the benefit evaluation of Voquezna for the indications of healing of EE and maintenance of healed EE. Study EE-301 was phase 3, two-stage, randomized, double-blind, non-inferiority, active comparator trial in approximately 1000 adult subjects with EE. The overall design of the trial is discussed in this section. EE-301 included an 8-week healing phase and a 24-week maintenance phase, which are discussed separately in subsequent sections. The complete protocol synopsis for Study EE-301 is in Section 15.1 of the review.

Subjects were randomized 1:1 to Voquezna 20 mg once daily or active comparator, lansoprazole 30 mg once daily, for up to 8 weeks in the healing phase.

The randomization was stratified by LA Classification Grade (A or B versus C or D). A central adjudication process confirmed the subject's screening endoscopy in order to determine whether

the subject met the eligibility for criterion for EE and the assigned LA Grading for stratification. The adjudicators were independent experts who were experienced in endoscopic grading of EE. The central adjudicator also reviewed images from all other study-defined endoscopies to assess the presence or absence of EE. Adjudicators were blinded to treatment assignment at the time of review of endoscopy images.

Healing was defined as endoscopically confirmed healed EE. Subjects underwent endoscopy at Week 2 of the healing phase. If healing was confirmed at Week 2, the subject was immediately rerandomized into the maintenance phase. If healing was not confirmed, the subject continued to receive randomized treatment until Week 8. If healing was confirmed at Week 8, the subject was rerandomized into the maintenance phase. If healing of EE was not confirmed at Week 8, the subject was considered as completed for the healing phase but was discontinued from the study without entering the maintenance phase.

The primary efficacy endpoint in the healing phase of Study EE-301 was healing of all grades of EE at Week 2 or Week 8. The study was a non-inferiority design with a margin of -10% for this endpoint in the healing phase. (Section 6.3.1.) As noted previously, lansoprazole 30 mg once daily is approved for up to 8 weeks for the treatment of EE (Prevacid NDA 020406).

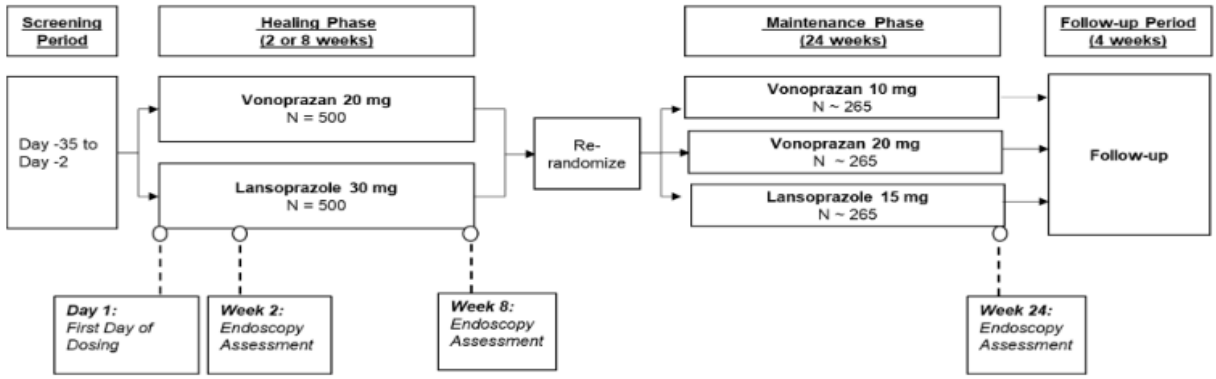
Randomization into the maintenance phase was stratified based on LA Classification Grade (A or B versus C or D) at baseline of the healing phase. Subjects were randomized into the maintenance phase in a 1:1:1 ratio to receive Voquezna 20 mg, Voquezna 10 mg, or active comparator, lansoprazole 15 mg, once daily for 24 weeks in the maintenance phase. An endoscopy was to be performed at Week 24 to assess the maintenance of healing of EE. Additional, unscheduled endoscopies based on the subject's symptoms were allowed in the healing and maintenance phases if deemed warranted by the investigator.

Subjects completed an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms throughout the study. A safety follow-up visit was planned at four weeks after the last dose of study drug to assess adverse events and the serum gastrin level. Subjects who did not have EE healing at Week 8, and therefore discontinued the study after the healing phase, underwent the safety follow-up period. The electronic diary continued to be completed twice daily during the follow-up phase and was reviewed at the follow-up visit.

The primary endpoint for the maintenance phase was maintenance of healed EE (all grades) through Week 24. The study was a non-inferiority design with a margin of -10% for this endpoint in the maintenance phase. (Section 6.3.2.) Lansoprazole 15 mg once daily is approved for maintenance of healing of EE in the United States (Prevacid NDA 20406).

Study schematic is shown in Figure 2. See Section 15.2 for the complete schedule of assessments.

Figure 2. Study Design For Study EE-301



Source: Figure 3-1 in the Clinical Study Protocol for Study EE-301
Abbreviations: EE, erosive esophagitis; N, planned sample size in treatment group

Eligibility Criteria, Study EE-301

Key eligibility criteria for the healing phase are summarized below. The complete list of eligibility criteria is available in Section 15.

- Inclusion criteria
  - Men and non-pregnant women ≥18 years of age
  - Endoscopically confirmed EE of LA Classification Grades A to D during the Screening Period (Visit 1) as assessed by a central adjudicator.[1]
- Exclusion criteria
  - Positive for *Helicobacter pylori* or has had a *Helicobacter pylori* infection within 45 days of randomization.
  - Endoscopic Barrett's esophagus (>1 cm of columnar-lined esophagus) and/or definite dysplastic changes in the esophagus.
  - Any other condition affecting the esophagus, including eosinophilic esophagitis; esophageal varices; viral or fungal infection; esophageal stricture; a history of radiation therapy, radiofrequency ablation, endoscopic mucosal resection, or cryotherapy to the esophagus; or any history of caustic or physiochemical trauma (including sclerotherapy or esophageal variceal band ligation). However, subjects diagnosed with Schatzki's ring (mucosal tissue ring around lower esophageal sphincter) were eligible to participate.
  - Scleroderma (systemic sclerosis), cutaneous lupus erythematosus, or systemic lupus erythematosus.

[1] A central adjudication committee assessed the subject's screening endoscopy in order to determine whether the subject met the LA grade eligibility criterion. The adjudicators were independent experts experienced in endoscopic grading of EE. During the screening endoscopy procedure, the investigator/endoscopist took pictures documenting the investigator's/endoscopist's visual assessment of the subject's EE LA grade. These pictures were sent electronically to a blinded central adjudicator for an independent standardized review. Both the investigator and adjudicator assessments were entered into the clinical database. The adjudicator's assessment was used as the final determination of presence or absence of EE for study eligibility, as well as which strata (LA Grade A or B or C or D) to assign the subject.

- History of surgery or endoscopic treatment affecting gastroesophageal reflux, including fundoplication and dilation for esophageal stricture (except Schatzki's ring) or a history of gastric or duodenal surgery (except endoscopic removal of benign polyps).
- Active gastric or duodenal ulcer at the start of the Screening Period. Subjects with gastric or duodenal erosions were permitted to participate.
- Clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to randomization.
- Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.
- History of malignancy (including MALToma) or had been treated for malignancy within 5 years prior to the start of the Screening Period (Visit 1). (The subject might be included in the study if he/she had cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
- Acquired immunodeficiency syndrome or human immunodeficiency virus infection or tested positive for the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or HCV-RNA. However, subjects who tested positive for HCV antibody but negative for HCV-RNA were permitted to participate.
- Laboratory evidence of hepatic or renal impairment

6.2.1. Results of Analyses, Study EE-301 (Healing and Maintenance Phases)

Table 10 shows the overall screening and enrollment for Study EE-301. Of the 4167 subjects screened, 1027 were randomized into the trial, and 1024 received at least one dose of treatment (safety population). Of the 964 subjects who completed the healing phase, 893 were re-randomized to enter the maintenance phase, with 889 receiving at least one dose of study drug.

Table 10. Subject Screening and Enrollment, Study EE-301

Disposition	Study EE-301
Subjects screened	4167
Screening failures	3140
Healing phase	
Subjects randomized	1027
Subjects treated	1024
Subjects completed	964
Maintenance phase	
Subjects randomized[1]	893
Subjects treated	889
Subjects completed	812

Source: Reviewer-generated; adsl.xpt; Software: JMP Clinical
[1]Patients who were healed at the end of healing phase were re-randomized at entry into Maintenance Phase.
Abbreviations: EE, erosive esophagitis

Table 11 shows the disposition of subjects by treatment group for the healing and maintenance phases of trial EE-301.There were 514 subjects randomized to Voquezna 20 mg once daily and 513 to lansoprazole 30 mg once daily in the healing phase, with a similar rate of completion between treatment arms. The safety population and the mITT population were the same for the healing phase; the difference in these two populations for the maintenance phase was due to several subjects who did not have healed EE at the end of the healing phase and were incorrectly

re-randomized into the maintenance phase (3 in Voquezna 10 mg treatment arm, 5 in Voquezna 20 mg treatment arm, and 3 in lansoprazole 15 mg arm). These 11 subjects were included in the safety population but not in the mITT population for the maintenance phase analyses.

Table 11. Subjects Disposition by Treatment Group, Study EE-301

	Healing Phase		Maintenance Phase		
Disposition Outcome	Voquezna 20 mg n (%[a])	Lansoprazole 30 mg n (%[a])	Voquezna 10 mg n (%[a])	Voquezna 20 mg n (%[a])	Lansoprazole 15 mg n (%[a])
Subjects randomized	514	513	296	296	297
MITT population	514	510	293	291	294
Per-protocol population	488	474	259	246	251
Safety population	514	510	296	296	297
Completed	483 (94.0)	481 (94.3)	274 (92.6)	269 (90.9)	269 (90.6)
Discontinued study; Safety Population[b]	31 (6.0)	29 (5.7)	22 (7.4)	27 (9.1)	28 (9.4)
Pretreatment event, AE or SAE	3 (0.6)	7 (1.4)	3 (1.0)	5 (1.7)	4 (1.3)
Lost to follow-up	5 (1.0)	4 (0.8)	7 (2.3)	8 (2.7)	9 (3.0)
Other	8 (1.6)	7 (1.4)	1 (0.3)	2 (0.7)	4 (1.3)
Significant protocol deviation	0	1 (0.2)	3 (1.0)	0	0
Voluntary withdrawal	10 (1.9)	7 (1.4)	3 (1.0)	6 (2.0)	5 (1.7)
Pregnancy	0	0	0	1 (0.3)	0
Lack of efficacy	0	0	0	0	1 (0.3)
Withdrawal of consent	5 (1.0)	3 (0.6)	5 (1.7)	5 (1.7)	5 (1.7)

Source: ds.xpt and adsl.xpt; Software: R
Duration is 2 weeks or 8 weeks.
Risk difference (with 95% confidence interval) is shown between Voquezna and lansoprazole.
[a] Percentage is calculated based on the safety population.
[b] Reasons for discontinuation
Abbreviations: EE, erosive esophagitis; MITT, modified intent-to-treat; n, number of patients in specified population or group; N, number of patients in treatment arm; AE, adverse event; SAE, serious adverse event

Table 12 shows the baseline characteristics of the mITT population for EE-301. Approximately half of subjects were female (53.0%). Mean age was 51 years, with a range of 18 to 84 years. Subjects ≥65 years of age comprised 19.5% of the population. A majority of subjects self-identified as White (90.7%) with approximately 6% of the study population identifying as Black/African American (6.2%) and 3% identified as another racial group. A total 12.2% of subjects identified as Hispanic or Latino (87.8%). Among all subjects, 62.6% were enrolled in the United States and 37.4% were enrolled in Europe.

Half of the subjects had a BMI ≥30 (50.8%). The mean BMI for the study was 31.2 (SD 6.35) with a median of 30.1 (min 18, max 64). The study had a higher prevalence of obesity than the United States in general, which is estimated at approximately 41.9% (CDC 2022a). However, the rate is consistent with suspected rate of obesity among patients with GERD (52%, (Magallen and Sollano 2013)).

The protocol had a target enrollment goal of 30% of subjects with LA Grades C or D. The majority of subjects in the study overall had an adjudicated LA Classification Grade A or B for EE (66.7%) and 34.3% had Grade C or D. Similar proportions for Grade A or B and Grade C or D were reflected in all analysis populations (safety, modified intent-to-treat [MITT], intent-to-treat [ITT]), in both phases and between treatment groups.

Demographic and other baseline characteristics were similar between treatment groups.

Table 12. Baseline Demographic and Clinical Characteristics, MITT Population, Study EE-301

	Healing Phase			Maintenance Phase		
Characteristic	**Voquezna 20 mg N = 514 n (%)**	**Lansoprazole 30 mg N = 510 n (%)**	**Total N = 1024 n (%)**	**Voquezna 10 mg N = 293 n (%)**	**Voquezna 20 mg N = 291 n (%)**	**Lansoprazole 15 mg N = 294 n (%)**
Sex, n (%)						
Female	256 (49.8)	287 (56.3)	543 (53.0)	159 (54.3)	146 (50.2)	171 (58.2)
Male	258 (50.2)	223 (43.7)	481 (47.0)	134 (45.7)	145 (49.8)	123 (41.8)
Age, years						
Mean (SD)	51 (13.4)	51.7 (14.1)	51.3 (13.8)	52.3 (13.8)	51.0 (14.5)	51.0 (13)
Median (min, max)	52 (18, 84)	53 (19, 84)	53 (18, 84)	54 (18, 84)	53 (20, 84)	52 (19, 83)
Age group 1, years, n (%)						
<45	166 (32.3)	163 (32.0)	329 (32.1)	81 (27.6)	101 (34.7)	95 (32.3)
≥45 to <65	255 (49.6)	240 (47.1)	495 (48.3)	151 (51.5)	128 (44.0)	152 (51.4)
≥65 to <75	83 (16.1)	91 (17.8)	174 (17.0)	48 (16.4)	57 (19.6)	43 (14.5)
≥75	10 (1.9)	16 (3.1)	26 (2.5)	13 (4.4)	5 (1.7)	5 (1.7)
Age group 2, years, n (%)						
<65	421 (81.9)	403 (79.0)	824 (80.5)	232 (79.2)	229 (78.7)	246 (83.7)
≥65 to <75	83 (16.1)	91 (17.8)	174 (17.0)	48 (16.4)	57 (19.6)	43 (14.5)
≥75	10 (1.9)	16 (3.1)	26 (2.5)	13 (4.4)	5 (1.7)	5 (1.7)
Race, n (%)						
American Indian or Alaska Native	2 (0.4)	1 (0.2)	3 (0.3)	1 (0.3)	0	1 (0.3)
Asian	7 (1.4)	6 (1.2)	13 (1.3)	4 (1.4)	3 (1.0)	3 (1.0)
Black or African American	23 (4.5)	41 (8.0)	64 (6.3)	15 (5.1)	17 (5.8)	20 (6.8)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.2)	2 (0.2)	0	0	1 (0.3)
Not Reported	1 (0.2)	0	1 (<0.1)	0	0	1 (0.3)
Other	5 (1.0)	5 (1.0)	10 (1.0)	4 (1.4)	2 (0.7)	3 (1.0)
Unknown	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.7)	0	0
White	474 (92.2)	455 (89.2)	929 (90.7)	267 (91.1)	269 (92.4)	265 (90.1)
Ethnicity, n (%)						
Hispanic or Latino	62 (12.1)	58 (11.4)	120 (11.7)	31 (10.6)	33 (11.3)	31 (10.5)
Not Hispanic or Latino	450 (87.5)	449 (88.0)	899 (87.8)	261 (89.1)	257 (88.3)	261 (88.8)
Not reported	1 (0.2)	1 (0.2)	2 (0.2)	0	1 (0.3)	0
Unknown	1 (0.2)	2 (0.4)	3 (0.3)	1 (0.3)	0	2 (0.7)
Country of participation, n (%)						
Bulgaria	24 (4.7)	23 (4.5)	47 (4.6)	16 (5.5)	14 (4.8)	16 (5.4)
Czech Republic	38 (7.4)	32 (6.3)	70 (6.8)	23 (7.8)	21 (7.2)	17 (5.8)
Great Britain	19 (3.7)	12 (2.4)	31 (3.0)	7 (2.4)	9 (3.1)	13 (4.4)
Hungary	13 (2.5)	9 (1.8)	22 (2.1)	10 (3.4)	8 (2.7)	2 (0.7)
Poland	95 (18.5)	118 (23.1)	213 (20.8)	59 (20.1)	80 (27.5)	51 (17.3)
United States	325 (63.2)	316 (62.0)	641 (62.6)	178 (60.8)	159 (54.6)	195 (66.3)
Body Mass Index, n (%)[a]						
≥30	253 (49.3)	267 (52.4)	520 (50.8)	153 (52.2)	143 (49.1)	147 (50.0)
≥25 to <30	183 (35.7)	170 (33.3)	353 (34.5)	100 (34.1)	100 (34.4)	100 (34.0)

Characteristic	Healing Phase Voquezna 20 mg N = 514 n (%)	Lansoprazole 30 mg N = 510 n (%)	Total N = 1024 n (%)	Maintenance Phase Voquezna 10 mg N = 293 n (%)	Voquezna 20 mg N = 291 n (%)	Lansoprazole 15 mg N = 294 n (%)
<25	77 (15.0)	73 (14.3)	150 (14.6)	40 (13.7)	48 (16.5)	46 (15.6)
Mean (SD)	30.8 (6.0)	31.5 (6.6)	31.2 (6.4)	31.6 (6.8)	31.0 (6.7)	31.0 (6.1)
Median (min,max)	30 (18, 52)	30 (18, 64)	30 (18, 64)	30 (20, 64)	30 (18, 55)	30 (20, 53)
LA Grade						
A	168 (32.7)	184 (36.1)	352 (34.4)	110 (37.5)	106 (36.4)	101 (34.4)
B	169 (32.9)	152 (29.8)	321 (31.3)	88 (30.0)	93 (32.0)	97 (33.0)
C	154 (30.0)	156 (30.6)	310 (30.3)	86 (29.4)	81 (27.8)	92 (31.3)
D	23 (4.5)	18 (3.6)	41 (4.0)	9 (3.1)	11 (3.8)	4 (1.4)
LA Grade Category						
Grades A or B	337 (65.6)	336 (65.9)	673 (65.7)	198 (67.6)	199 (68.4)	198 (67.3)
Grades C or D	177 (34.4)	174 (34.1)	351 (34.3)	95 (32.4)	92 (31.6)	96 (32.7)

Source: adsl.xpt; Software: R
[a] One subject (ID (b) (6)) in the vonoprazan 20 mg group did not have baseline. N for the % calculation is 513.
Abbreviations: EE, erosive esophagitis; MITT, modified intent-to-treat; LA, Los Angeles; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

6.2.2. Study EE-301, Healing Phase

6.2.2.1. Design, EE-301, Healing Phase

A complete description of the EE-301 study design is presented in the introduction to Section 6.2 Clinical Trials Intended to Demonstrate Efficacy, and Figure 2. The full protocol synopsis is in Section 15.1.

6.2.2.2. Statistical Analysis Plan, EE-301, Healing Phase

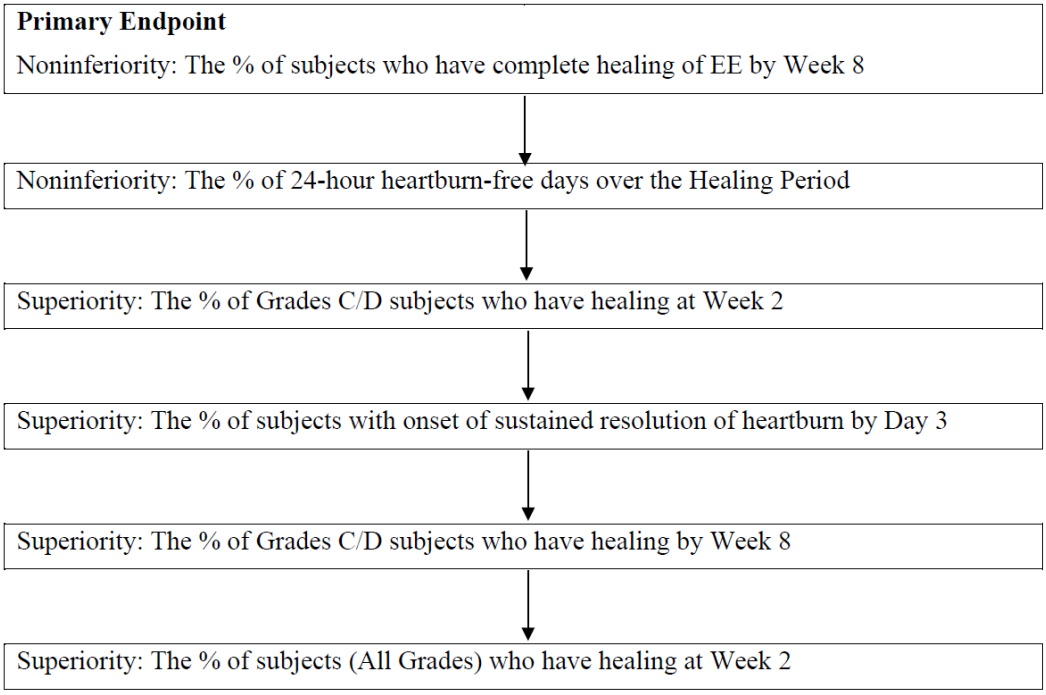
The Applicant's statistical analysis plans for Study EE-301 were reviewed by the statistical and clinical teams prior to the trial completion.

Primary and Ranked Secondary Endpoints

The primary efficacy endpoint was defined as the percentage of subjects who had complete healing of EE, as assessed by endoscopy, at Week 2 or Week 8. The secondary efficacy endpoint of percentage of 24-hour heartburn-free days was defined as the percentage of days with neither daytime or nighttime heartburn symptoms as assessed by the daily diary during treatment. The secondary efficacy endpoint of percentage of subjects with onset of sustained resolution of heartburn by day 3 defined sustained resolution of heartburn as the first occurrence of 7 consecutive days with neither daytime or nighttime heartburn as assessed by the daily diary during treatment.

The statistical testing hierarchy for the healing phase is shown in Figure 3. The hypothesis testing of the primary and secondary efficacy endpoints in the healing phase was adjusted for multiple comparisons using a fixed-sequence testing procedure to control the Type 1 error rate at the 0.05 level. The statistical tests were performed at α=0.05 in the sequential order shown in until a test was not significant.

Figure 3. Testing Hierarchy, Healing Phase



Source: Statistical Analysis Plan (Version 3.0), Figure 3, Page 31.
Abbreviations: EE, erosive esophagitis

Analysis Methods

The efficacy analyses for the healing phase were conducted in the MITT set, which included all subjects randomized into the healing phase who had documented EE at baseline and receive at least one dose of study drug during the healing phase. All tests were performed at the two-sided 0.05 α level.

The primary endpoint was analyzed for non-inferiority of Voquezna 20 mg compared to lansoprazole 30 mg using a Farrington and Manning test with a non-inferiority margin of -10% for the difference in EE rates at Week 2 or Week 8 between treatments (Voquezna 20 mg - lansoprazole 30 mg). The treatment difference and the 95% confidence interval (CI) were calculated via the Miettinen and Nurminen method. See discussion of non-inferiority margin justification in Section 6.3.1.

Superiority of Voquezna 20 mg to lansoprazole 30 mg was analyzed via the Farrington and Manning test the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

The percentage of 24-hour heartburn–free days over the healing phase as assessed by the daily diary was analyzed for non-inferiority using Welch's t-test with a non-inferiority margin of -15%. See non-inferiority margin justification in Section 6.3.2.

Potential intercurrent events considered in the healing phase include: 1) treatment discontinuation prior to completing the healing phase, 2) PPI or H2 receptor antagonist taken during the healing phase, 3) treatment non-compliance, 4) Coronavirus SARS-CoV (COVID-19)

impacts. Intercurrent events were handled using the following methods for the primary efficacy analysis:

- Treatment discontinuation: for binary endpoints, Non-Responder Imputation (NRI) was used to handle the occurrence of treatment discontinuation intercurrent events. For 24-hour heartburn-free days, data were collected while subjects were on treatment.
- Prohibited EE medication: data collected were used regardless of use of prohibited EE medication.
- Treatment non-compliance: data collected were used regardless of treatment compliance.
- COVID-19 impacts: missing data for subjects without a post-baseline endoscopy at a visit due to COVID-19 related reasons were imputed using a missing at random assumption.

Estimands and Missing Data Handling

The estimand corresponding to the primary efficacy objective for the maintenance phase was defined as the difference between treatments (Voquezna 20 mg – lansoprazole 30 mg) in rates of EE healing at Week 2 or Week 8 in subjects with endoscopically proven EE irrespective of whether they fully adhere to the treatment schedule or take prohibited EE medications (PPIs and H2 receptor antagonists).

If a subject took prohibited EE medications or did not fully adhere to the healing treatment schedule, all subsequent data were used.

For the primary analysis of binary efficacy endpoints, missing data were handled using multiple imputation, assuming missing at random, to handle missing data due to reasons related with COVID-19 and NRI was used to handle all missing data that were unrelated to COVID-19.

In addition, for binary endpoints, the following sensitivity analyses were performed:

- A sensitivity analysis was performed for binary endpoints on observed data only.
- A sensitivity analysis was performed using multiple imputation under missing at random assumption to handle all missing data regardless of the reasons for missing.
- A sensitivity analysis was performed using multiple imputation as described in 3). After imputations, subjects who had treatment compliance <80% or >120% or had any PPI or H_2RA use were considered as EE not healed.
- A sensitivity analysis was performed after data for subjects who had treatment compliance <80% or >120% or at time point after any PPI or H_2RA use were excluded, using multiple imputation as described in the above point).
- A sensitivity analysis where subjects were considered as EE not healed at time points after any PPI or H_2RA use.

For the percentage of 24-hour heartburn free days, all days with at least 1 morning or evening diary entry during the treatment period were used. Days with missing both entries were excluded from the denominator in calculation of percentage. If a subject had only one diary entry on a day and that entry did not indicate heartburn, the day was considered heartburn-free for the analysis. A sensitivity analysis was performed in which the days after a subject discontinued treatment

were imputed as having heartburn. For this sensitivity analysis, the denominator for subjects who dropped out of the study was based the number of planned days in the healing period.

6.2.2.3. Results of Analyses, EE-301, Healing Phase

Treatment Compliance Rate

The statistical analysis plan (SAP) defined treatment compliance as an overall study drug compliance within a range of 80% to 120% inclusive. The treatment compliance rate during the healing phase ranged from 48% to 250% with a mean rate of 99.1% (median: 100%).

Primary and Key Secondary Efficacy Results, EE-301, Healing Phase

Primary Endpoint

The Applicant's primary efficacy results for the endpoint of healing of all grades of EE at Week 2 or Week 8 in the MITT population were confirmed by the statistical review team, and the results demonstrate noninferiority of Voquezna 20 mg once daily compared to lansoprazole 30 mg once daily, as summarized in Table 13. The estimated differences in the EE healing rate for Voquezna 20 mg versus lansoprazole 30 mg was 8.3%. The lower bound of the 95% CI for the difference in healing rate was 4.49%, exceeding the non-inferiority (NI) margin, -10% (See Section 6.3.1 for NI margin justification). The p-value of non-inferiority was less than 0.0001.

Table 13. Primary Analysis: Healing of All Grades of EE at Week 2 or at Week 8, MITT, Study EE-301, Healing Phase

Parameter	Voquezna 20 mg (N=514)	Lansoprazole 30 mg (N=510)
EE Healing rate at Week 2 or Week 8, n (%)[1]	478 (92.9)	431 (84.6)
Treatment difference, % (CI[2])	8.3 (4.49, 12.23)	
P-value of noninferiority[3]	<0.0001	
Missing data, n (%)	14 (2.7)	15 (2.9)

Source: Reviewer generated analysis based on Applicant submitted data adeffiph.xpt for NDA 215151.
[1] n represents the average number of subjects who had complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated EE healing rate based on multiple imputation model.
[2] The 2-sided 95% confidence interval of the difference in EE healing rates between Voquezna 20 mg and lansoprazole 30mg was calculated via the Miettinen and Nurminen method.
[3] Noninferiority of Voquezna 20 mg to lansoprazole 30 mg p-value based on a Farrington and Manning test with a noninferiority margin of 10%.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm.

A total of 14 subjects (2.7%) in the Voquezna 20 mg group, and 15 subjects (2.9%) in the Voquezna 20 mg group had missing values. Most missing data were due to study dropout. The amount of missing data for subjects that were enrolled in the healing phase was small and the dropout rates were similar among the treatment groups. Multiple imputation was used to handle missing data due to COVID-19, while non-responder imputation was used to handle missing data for all other reasons. Pre-specified sensitivity analyses, including a sensitivity analysis using multiple imputation to handle all missing data regardless of the reasons for missing data and the per-protocol analysis, produced similar results and supported the conclusions from the primary analysis. Refer to Section 16.2 for additional information on the sensitivity analyses.

Key Secondary Endpoints

The efficacy results for the key secondary endpoints in the healing phase are shown in Table 14. The order of endpoints listed in Table 14 reflects the testing hierarchy.

- For the percentage of 24-hour heartburn-free days through Week 8, the noninferiority margin proposed by the Applicant was -15%. The historical studies used for NI margin justification were different from Study EE-301 in terms of study design and subject population (see Section 6.3.2 for NI margin justification). Upon review of the NI margin, the review team recommended a more conservative NI margin of -5%. The noninferiority of Voquezna 20mg versus lansoprazole 30 mg was demonstrated for the percentage of 24-hour heartburn-free days, with the lower confidence bound of -1.60% for the mean treatment difference being higher than the NI margin of -5%.
- The analysis for EE healing rate at Week 2 for subjects with EE of LA Grades C or D at baseline showed favorable results for the Voquezna 20 mg arm with a treatment difference versus lansoprazole 30 mg of 17.6 (95% CI: 7.44, 27.43) and a p-value of 0.0004.
- The secondary endpoint of percentage of subjects with onset of sustained heartburn resolution by Day 3 was similar between treatment groups (34.4% Voquezna 20 mg, 32.2% lansoprazole 30 mg) and did not achieve statistical significance (p-value=0.2196) based on the analysis. Failure of this endpoint ended the formal testing.
- Higher healing rates for Voquezna 20 mg versus lansoprazole 30 mg were also observed for the EE healing rate at Week 2 or Week 8 among subjects with Grade C or D EE at baseline (91.7% versus 72.0%, nominal p-value<0.0001) and for the EE healing rate at Week 2 among subjects with all grades of erosions (74.3% versus 68.2%, nominal p-value=0.0174). These two endpoints were not formally tested per the pre-specified fixed-sequence testing procedure.

The primary analysis of the percentage of 24-hour heartburn free days only included days with at least 1 morning or evening diary in the denominator. Therefore, days after a subject dropped out of the study would not be accounted for in the analysis. The results of this analysis might not be meaningful if one of the treatments had safety or tolerability issues that resulted in a higher dropout rate; however, dropout rates were similar in both arms. The sensitivity analysis in which the days after a subject discontinued treatment were imputed as having heartburn produced similar results to the primary analysis. In addition, allowing subjects with healing of EE at Week 2 to leave the healing phase and enter the maintenance phase could have an effect on the estimated treatment difference for the percentage of 24-hour heartburn-free days during the healing phase. The percentage of 24-hour heartburn-free days generally increased with longer exposure to treatment. Because of this, results might be biased against the treatment arm with a higher rate healing of EE at Week 2, which was the Voquezna 20 mg arm. As such, the primary analysis may underestimate the effect of Voquezna 20 mg compared to lansoprazole 30 mg on 24-hour heartburn-free days.

Table 14. Multiplicity-Controlled Secondary Endpoints Efficacy Results, MITT, Study EE-301, Healing Phase

Secondary Endpoint Parameter	Voquezna 20 mg (N=514)	Lansoprazole 30 mg (N=510)
Percentage of 24-hour heartburn-free days, %		
Median	81.3	78.3
Mean (SD)	66.8 (34.6)	64.1 (35.5)
Treatment difference in mean, % (CI[1])	2.7 (-1.6, 7.03)	
P-value of noninferiority[2]	<0.0001	
Percentage of subjects with baseline EE grades C or D who have complete healing of EE at Week 2		
n (%)[3]	(N=177)	(N=174)
	124 (70.2)	92 (52.6)
Treatment difference, % (CI[4])	17.6 (7.44, 27.43)	
P-value of superiority	0.0004	
Percentage of subjects with onset of sustained heartburn resolution by Day 3		
n (%)[3]	177 (34.4)	164 (32.2)
Treatment difference, % (CI[4])	2.3 (-3.5, 8.04)	
P-value of superiority	0.2196	
The percentage of Grade C or D subjects with healing of EE at Week 2 or Week 8		
n (%)[3]	(N=177)	(N=174)
	162 (91.7)	125 (72.0)
Treatment difference, % (CI[4])	19.6 (11.84, 27.58)	
P-value of superiority[5]	<0.0001	
The percentage of subjects (all grades) with healing of EE at Week 2		
n (%)[3]	382 (74.3)	348 (68.2)
Treatment difference, % (CI[4])	6.1 (0.53, 11.60)	
P-value of superiority[5]	0.0174	

Source: Reviewer generated analysis based on Applicant submitted data adeffish.xpt and adsd.xpt for NDA 215151.
[1] The 2-sided 95% CI of the difference in mean percentage of 24-hour heartburn-free days between Voquezna 20 mg and lansoprazole 30 mg was calculated from Welch's t-test.
[2] Reviewer calculated p-value.
[3] n represents the average number of subjects who had complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated EE healing rate based on multiple imputation model.
[4] The 2-sided 95% CI of the difference in EE healing rates between Voquezna 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.
[5] Nominal p-value. Hypothesis was not a formally test per the preplanned fixed-sequence testing procedure due to the failure to reject the null hypothesis for percentage of subjects with onset of sustained heartburn resolution by Day 3.
Abbreviations: SD, standard deviation; CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm.

Subgroup Analyses

Subgroup analyses by age, sex, race, ethnicity, and baseline EE grade category were performed to assess the consistency of the results observed from the primary efficacy analyses. The subgroup analyses results are shown in Table 15. Treatment group differences in healing of EE at Week 2 or Week 8 were generally consistent across subgroups defined by baseline age, sex, race, and ethnicity. Voquezna 20 mg showed higher healing rates compared to lansoprazole for most subgroups.

In the analysis results by subgroup of race, although the Voquezna 20 mg group had a lower observed healing rate than the lansoprazole 30 mg group for black or African American subjects, this directional difference is likely due to small sample size in this subgroup. The 95% CI for the

difference in this subgroup is wide, indicating there is a lot of uncertainty in the estimated treatment effect.

As for ethnicity, the treatment difference was 16.2% for the subjects who identified as Hispanic or Latino subjects while it was 6.5% for the subjects who identified as not Hispanic or Latino. This slightly differential treatment difference is mainly due to a higher observed healing rate in the lansoprazole 30 mg group. The observed response rates for the Voquezna 20 mg group were consistent across these two subgroups (90.3% for Hispanic or Latino versus 91.3% for not Hispanic or Latino).

As for EE grade category at baseline, differential treatment differences were identified across the EE severity categories (1.5% for Grade A or B and 18.6% for Grade C or D). Differential treatment difference is due to a lower observed healing rate in the lansoprazole 30 mg group for Grade C or D subjects. The observed response rates for the Voquezna 20 mg group were consistent across these two subgroups (91.4% for Grade A or B versus 90.4% for Grade C or D).

It is known that male sex correlates with increased severity of EE (Menon et al. 2011); therefore, an additional subgroup analysis for sex by EE grade was performed. Each subgroup was balanced between treatment groups. The treatment effects of Voquezna 20 mg were consistent in these subgroups. No differential effect by sex and EE grade category was identified for Voquezna 20 mg.

Table 15. Treatment Group Differences in Healing of EE at Week 2 or Week 8 by Subgroups of Age at Baseline, Sex, Race, Ethnicity, and EE Grade Category, MITT, Healing Phase

Characteristic	Voquezna 20 mg n/N (%)	Lansoprazole 30 mg n/N (%)	Treatment Difference (Voquezna 20 mg – Lansoprazole 30 mg) (95% CI[1])
Sex			
Female	237/256 (92.6)	245/287 (85.4)	7.2 (1.96, 12.55)
Male	231/258 (89.5)	182/223 (81.6)	7.9 (1.68, 14.44)
Age group, years			
<45	151/166 (91.0)	130/163 (79.8)	11.2 (3.66, 19.01)
≥45 to <65	230/255 (90.2)	207/240 (86.2)	3.9 (-1.75, 9.81)
≥65	87/93 (93.5)	90/107 (84.1)	9.4 (0.6, 18.47)
Race			
White	435/474 (91.8)	379/455 (83.3)	8.5 (4.28, 12.80)
Black or African American	18/23 (78.3)	35/41 (85.4)	-7.1 (-29.41, 11.70)
Asian	6/7 (85.7)	5/6 (83.3)	2.4 (-41.43, 47.97)
American Indian or Alaska Native	2/2 (100)	1/1 (100)	NA (NA, NA)
Native Hawaiian or Other Pacific Islander	0	1/1 (100)	-100 (-100.00, 58.69)
Ethnicity			
Hispanic or Latino	56/62 (90.3)	43/58 (74.1)	16.2 (2.63, 30.17)
Not Hispanic or Latino	411/450 (91.3)	381/449 (84.9)	6.5 (2.27, 10.78)
EE Grade Category			
A or B	308/337 (91.4)	302/336 (89.9)	1.5 (-2.95, 6.02)
C or D	160/177 (90.4)	125/174 (71.8)	18.6 (10.59, 26.64)
Sex by EE Grade Category			
Female, A or B	173/190 (91.1)	190/209 (90.9)	0.1 (-5.74, 5.89)
Male, A or B	135/147 (91.8)	112/127 (88.2)	3.6 (-3.52, 11.33)
Female, C or D	64/66 (97.0)	55/78 (70.5)	26.5 (15.59, 37.88)

Characteristic	Voquezna 20 mg n/N (%)	Lansoprazole 30 mg n/N (%)	Treatment Difference (Voquezna 20 mg – Lansoprazole 30 mg) (95% CI[1])
Male, C or D	96/111 (86.5)	70/96 (72.9)	13.6 (2.68, 24.74)

Source: Reviewer generated analysis based on Applicant submitted data adeffipm.xpt for NDA 215151.
[1] The 2-sided 95% confidence interval of the difference in EE healing rates between Voquezna 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm

6.2.3. Study EE-301, Maintenance Phase

6.2.3.1. Design, Maintenance

A complete description of the Study EE-301 design is presented in the introduction to Section 6.2 Clinical Trials Intended to Demonstrate Efficacy, and Figure 2.

6.2.3.2. Eligibility Criteria, EE-301, Maintenance Phase

Subjects with EE who had confirmed endoscopic healing of EE either at Week 2 or at Week 8 of the healing phase were rerandomized into the maintenance phase.

6.2.3.3. Statistical Analysis Plan, EE-301, Maintenance Phase

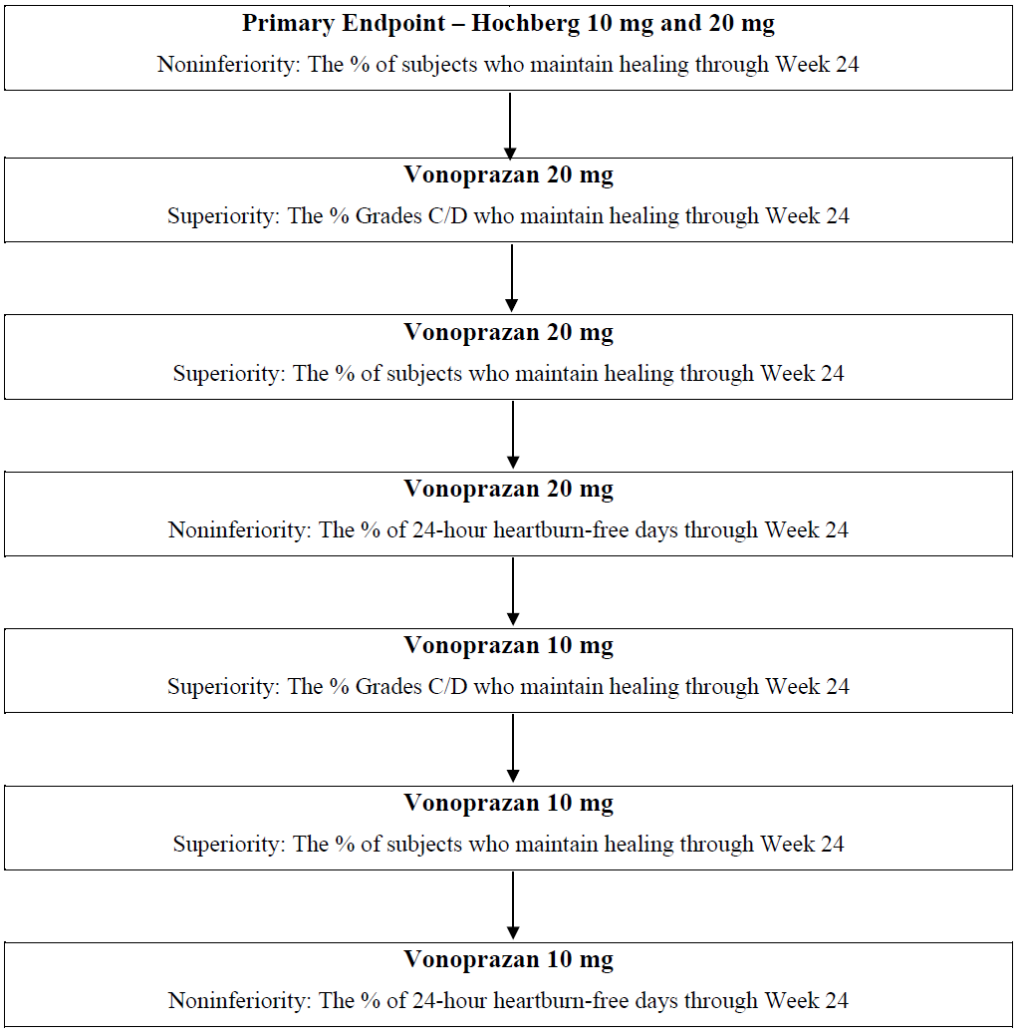
Primary and Ranked Secondary Endpoints

The primary efficacy endpoint was defined as the percentage of subjects who maintained complete healing of EE, as assessed by endoscopy, through Week 24. The hypothesis-testing of the primary endpoint of the maintenance phase was adjusted using Hochberg's multiple comparisons method to control the overall 0.05 level of significance to test the non-inferiority of each dose group of Voquezna (i.e., 20 mg once daily and 10 mg once daily) to lansoprazole. If both Voquezna dose groups had p-value ≤0.05, both dose groups were found to be non-inferior to lansoprazole 15 mg. Otherwise, if one dose group has p-value >0.05 and the other dose group has p-value ≤0.025, the dose group with p-value ≤0.025 was found to be non-inferior to lansoprazole 15 mg.

If non-inferiority was declared for both Voquezna dose groups from the primary efficacy analysis, the comparisons to lansoprazole 15 mg for the secondary efficacy endpoints would be performed using a fixed-sequence testing procedure shown in Figure 4 to control the Type 1 error rate at the 0.05 level until a test was not significant.

If non-inferiority was not declared for either Voquezna dose group from the primary efficacy analysis, the testing procedure would end.

Figure 4. Testing Hierarchy, Maintenance Phase



Source: Statistical Analysis Plan (Version 3.0), Figure 3, Page 32.

Analysis Method

The efficacy analyses for the maintenance phase were conducted in MITT set, defined as all subjects randomized into the maintenance phase who have healed EE at the end of the healing phase and receive at least one dose of study drug during the maintenance phase.

The primary endpoint of maintenance of healed EE (all grades) through Week 24 was analyzed for non-inferiority using a Farrington and Manning test with a NI margin of -10% for the difference in maintenance of healing rates after 24 weeks between treatment arms (Voquezna 20 mg – lansoprazole 15 mg, Voquezna 10mg – lansoprazole 15 mg). For a discussion of the justification to support the non-inferiority margin for the primary endpoint in the maintenance phase see Section 6.3.2. The treatment difference and the 95% CI were calculated via the Miettinen and Nurminen method. Binary secondary endpoints for testing superiority of Voquezna over lansoprazole 15 mg were analyzed via the Farrington and Manning test with the null hypothesis of difference ≤0 versus the alternative hypothesis of difference >0. The percentage of 24-hour heartburn–free days over the maintenance phase as assessed by the daily

diary was analyzed for non-inferiority with a NI margin -15% (see Section 6.3.3 for NI margin justification of the secondary endpoint in the maintenance phase) using Welch's t-test.

Estimands and Missing Data Handling

The estimand corresponding to the primary efficacy objective for the maintenance phase was defined as difference between maintenance treatments (Voquezna 10 or 20 mg – lansoprazole 15 mg) in rates of maintained EE healing through Week 24 in subjects healed from an episode of endoscopically proven EE irrespective of whether they fully adhere to the maintenance treatment schedule or take prohibited EE medications (PPIs and H2 receptor antagonists).

If a subject discontinued the study drug prior to completing 24 weeks maintenance phase, the subject was considered a non-responder. If a subject took prohibited EE medications or did not fully adhere to the maintenance treatment schedule, all subsequent data were used.

For the primary analysis of binary efficacy endpoints, missing data were handled using multiple imputation, assuming missing at random, to handle missing data due to reasons related with COVID-19 and NRI was used to handle all missing data that were unrelated to COVID-19.

In addition, the following sensitivity analyses were performed.

- A sensitivity analysis was performed for binary endpoints on observed data only.
- A sensitivity analysis was performed using multiple imputation under missing at random assumption to handle all missing data regardless of the reasons for missing.
- A sensitivity analysis was performed using multiple imputation as described earlier. After imputations, subjects who had treatment compliance <80% or >120% or had any PPI or H_2RA use were considered as EE recurred.
- A sensitivity analysis was performed after data for subjects who had treatment compliance <80% or >120% or at time point after any PPI or H_2RA use were excluded, using multiple imputation as described above in 3).
- A sensitivity analysis where subjects were considered as EE recurred at time points after any PPI or H_2RA use.

For the percentage of 24-hour heartburn free days, all days with at least 1 morning or evening diary entry during the treatment period were used. Days with missing both entries were excluded from the denominator in calculation of percentage. If a subject had only one diary entry on a day and that entry did not indicate heartburn, the day was considered heartburn-free for the analysis. A sensitivity analysis was performed in which days after a subject discontinued treatment were imputed as having heartburn.

6.2.3.4. Results of Analyses, EE-301, Maintenance Phase

There were 893 subjects who completed the healing phase and were randomized to enter the maintenance phase; 4 subjects did not take study drug. Of the remaining 889 subjects who received at least one dose of study drug, 296 received Voquezna 10 mg, 296 received Voquezna 20 mg, and 297 received lansoprazole 15 mg. A total of 77 subjects (22 vonoprazan 10 mg, 27 vonoprazan 20 mg, 28 lansoprazole 15 mg) discontinued treatment (Table 11 in Section 6.2.1).

The population who entered the maintenance phase were similar in demographics and overall characteristics to the population of the study as a whole (see Table 12, Section 6.2.1) Demographics and physical characteristics were similar across randomized treatment groups. Approximately half of subjects were female (54.2%). Mean age was 52 years, with a range of 18 to 84 years. Subjects ≥65 years of age comprised 19.6% of the population. Most subjects were White (91.2%) with approximately 6% of the study population Black/African American (6.0%) and other groups making up the remaining 3%. A total 88.6% of subjects identified as not Hispanic or Latino. Among all subjects, 60.1% were enrolled in the United States and 39.9% were enrolled in Europe. Approximately half (50.5%) of subjects were obese. Baseline (pre-healing phase) LA Grade was similar to the study overall and between maintenance phase treatment groups.

Primary and Major Secondary Efficacy Results, EE-301, Maintenance Phase

Primary Endpoint

The Applicant's primary efficacy results for the endpoint of maintenance of healed EE (all grades) through Week 24 in the MITT population were confirmed by the statistical review team, and the results demonstrate noninferiority of both Voquezna 10 mg and 20 mg compared to lansoprazole, as summarized in Table 16. The estimated difference in the percentage of subjects who maintained healed EE (all grades) through Week 24 was 7.2% for Voquezna 10 mg and 8.7% for Voquezna 20 mg compared to lansoprazole. The lower bound of the 95% CI for the difference in maintenance of healing rates exceeded the NI margin of -10% for both doses compared to lansoprazole 15 mg, with p-values less than 0.0001.

Table 16. Primary Analysis: Maintenance of Healed EE (All Grades) Through Week 24, MITT, Study EE-301, Maintenance Phase

Parameter	Voquezna 10 mg (N=293)	Voquezna 20 mg (N=291)	Lansoprazole 15 mg (N=294)
EE maintenance rate through Week 24, n (%)[1]	232 (79.2)	235 (80.7)	212 (72.0)
Treatment difference, % (CI[2])	7.2 (0.21, 14.09)	8.7 (1.80, 15.53)	
P-value of noninferiority[3]	<0.0001	<0.0001	
Missing data, n (%)	28 (10.6)	34 (11.7)	32 (10.9)

Source: Reviewer generated analysis based on Applicant submitted data adeffipm.xpt for NDA 215151.
[1] n represents the average number of subjects who maintained complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated maintenance of EE healing rate based on multiple imputation model.
[2] The 2-sided 95% confidence interval of the difference in rates of maintenance of healed EE (all grades) between Voquezna (10mg, 15 mg) and lansoprazole 15 mg was calculated via the Miettinen and Nurminen method.
[3] Noninferiority of Voquezna (10mg, 15 mg) to lansoprazole 15 mg p-value based on a Farrington and Manning test with a noninferiority margin of 10%.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm

A total of 28 subjects (10.6%) in the Voquezna 10 mg group, 34 subjects (11.7%) in the Voquezna 20 mg group, and 32 subjects (10.9%) in the lansoprazole 15 mg group had missing values. Most missing data were due to study dropout. The amount of missing data for subjects that were enrolled in the maintenance phase was very small. The dropout rates were similar across treatment groups. Only one subject who was in the lansoprazole 15 mg group discontinued from treatment due to reasons related to COVID-19. NRI was used to handle all missing data that were unrelated to COVID-19. Note that NRI could make the compared treatments appear more similar if there is a large amount of missing data, possibly biasing results

towards noninferiority. Additional sensitivity analyses were performed, including a sensitivity analysis using multiple imputation to handle all missing data regardless of the reasons for missing and a per-protocol analysis, to assess the impact of missing data on the conclusions. The results of the sensitivity analyses supported the conclusions from the primary analysis. Refer to Section 16.2 for the results from the sensitivity analyses.

Multiplicity-Controlled Secondary Endpoints

The efficacy results for the key secondary endpoints in the maintenance phase are shown in Table 17. The order of endpoints listed in Table 17 reflects the testing hierarchy.

Both doses of Voquezna (10 mg once daily and 20 mg once daily) met statistical significance for each of the multiplicity-controlled secondary endpoints, as summarized in Table 17.

Table 17. Multiplicity-Controlled Secondary Endpoints Efficacy Results, MITT, Study EE-301, Maintenance Phase

Secondary Endpoint Parameter	Voquezna 10 mg (N=293)	Voquezna 20 mg (N=291)	Lansoprazole 15 mg (N=294)
The percentage of Grade C or D subjects who maintained healing of EE through Week 24			
n/N (%)[1]	71/95 (74.7)	71/92 (77.2)	59/96 (61.5)
Treatment difference, % (CI[2])	13.3 (0.02, 26.14)	15.7 (2.50, 28.44)	
P-value of superiority	0.0245	0.0098	
The percentage of subjects who maintained healing of EE through Week 24			
n (%)[1]	232 (79.2)	235 (80.7)	212 (72.0)
Treatment difference, % (CI[2])	7.2 (0.21, 14.09)	8.7 (1.80, 15.53)	
P-value of superiority	0.0218	0.0068	
The percentage of 24-hour heartburn-free days through Week 24, %			
Median	94.6	95.2	89.3
Mean (SD)	80.9 (28.6)	80.6 (30.0)	78.6 (27.5)
Treatment difference in mean, % (CI[3])	2.3 (-2.27, 6.84)	2.0 (-2.63, 6.72)	
P-value of noninferiority[4]	<0.0001	<0.0001	

Source: Reviewer generated analysis based on Applicant submitted data adeffish.xpt and adsd.xpt for NDA 215151.
[1] n represents the average number of subjects who maintained complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated maintenance of EE healing rate based on multiple imputation model.
[2] The 2-sided 95% confidence interval of the difference in rates of maintenance of healed EE between Voquezna (10mg, 15 mg) and lansoprazole 15 mg was calculated via the Miettinen and Nurminen method.
[3] The 2-sided 95% CI of the difference in mean percentage of 24-hour heartburn-free days between Voquezna (10 mg, 15 mg) and lansoprazole 15 mg was calculated from Welch's t-test.
[4] Reviewer calculated p-values.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm.

The primary analysis of the percentage of 24-hour heartburn free days only included days with at least 1 morning or evening diary in the denominator. Therefore, days after a subject dropped out of the study would not be accounted for in the analysis. The results of this analysis might not be meaningful if one of the treatments had safety or tolerability issues that resulted in a higher dropout rate. The dropout rates were similar between treatment arms; however, the sensitivity analysis in which the days after a subject discontinued treatment were imputed as having heartburn produced more favorable results for the lansoprazole 15 mg arm with an estimated treatment difference of -2.5% (95% CI of -7.87 to 2.94) for Voquezna 10 mg compared to

lansoprazole 15 mg and -1.9% (95% CI of -7.35 to 3.51) for Voquezna 20 mg compared to lansoprazole 15 mg. This analysis may be sensitive to early dropouts who would be imputed as having very few 24-hour heartburn-free days and may skew the distribution 24-hour heartburn free days. Given the dropout rates were similar between arms, the primary analysis of the percentage of 24-hour heartburn-free days appears to be reasonable.

Subgroup Analyses

Subgroup analyses by age, sex, race, ethnicity, and baseline EE grade category were performed to assess the consistency of the results for the maintenance phase observed from the primary efficacy analyses. The subgroup analyses results are shown in Table 18. Treatment group differences in the rates of maintenance of healed EE through Week 24 were generally consistent across subgroups defined by age group at baseline, sex, race, ethnicity. Both Voquezna 10 mg and 20 mg arms showed numerically higher rates of maintenance of healed EE compared to lansoprazole 15 mg for most subgroups.

Table 18. Treatment Group Differences in Maintenance of Healed EE (All Grades) Through Week 24 by Subgroups of Age Group at Baseline, Sex, Race, Ethnicity, and EE Grade Category, MITT, Maintenance Phase

Characteristic	Voquezna 10 mg n/N (%)	Voquezna 20 mg n/N (%)	Lansoprazole 15 mg n/N (%)	Treatment Difference (Voquezna 10 mg – Lansoprazole 30 mg) (95% CI[1])	Treatment Difference (Voquezna 20 mg – Lansoprazole 30 mg) (95% CI[1])
Sex					
Female	127/159 (79.9)	118/146 (80.8)	127/171 (74.3)	5.6 (-3.54, 14.64)	6.6 (-2.77, 15.64)
Male	105/134 (78.4)	114/145 (78.6)	82/123 (66.7)	11.7 (0.78, 22.53)	12.0 (1.28, 22.65)
Age group, years					
<45	54/81 (66.7)	78/101 (77.2)	63/95 (66.3)	0.4 (-13.71, 14.18)	10.9 (-1.71, 23.39)
≥45 to <65	127/151 (84.1)	105/128 (82.0)	109/151 (72.2)	11.9 (2.62, 21.18)	9.8 (-0.13, 19.53)
≥65	51/61 (83.6)	49/62 (79.0)	37/48 (77.1)	6.5 (-8.43, 22.34)	1.9 (-13.5, 18.2)
Race					
White	209/267 (78.3)	216/269 (80.3)	194/265 (73.2)	5.1 (-2.23, 12.35)	7.1 (-0.08, 14.25)
Black or African American	14/15 (93.3)	14/17 (82.4)	10/20 (50.0)	43.3 (13.41, 65.77)	32.4 (1.10, 57.59)
Asian	4/4 (100)	1/3 (33.3)	2/3 (66.7)	33.3 (-31.36, 81.14)	-33.3 (-82.66, 44.96)
American Indian or Alaska Native	1/1 (100)	0	1/1 (100)	NA	NA
Native Hawaiian or Other Pacific Islander	0	0	0/1 (0)	NA	NA
Ethnicity					
Hispanic or Latino	23/31 (74.2)	28/33 (84.8)	21/31 (67.7)	6.5 (-16.35, 28.72)	17.1 (-3.95, 37.60)

Characteristic	Voquezna 10 mg n/N (%)	Voquezna 20 mg n/N (%)	Lansoprazole 15 mg n/N (%)	Treatment Difference (Voquezna 10 mg – Lansoprazole 30 mg) (95% CI[1])	Treatment Difference (Voquezna 20 mg – Lansoprazole 30 mg) (95% CI[1])
Not Hispanic or Latino	208/261 (79.7)	203/257 (79.0)	186/261 (71.3)	8.4 (1.05, 15.77)	7.7 (0.27, 15.13)
EE grade category					
A or B	161/198 (81.3)	161/199 (80.9)	150/198 (75.8)	5.6 (-2.56, 13.66)	5.1 (-2.99, 13.28)
C or D	71/95 (74.7)	71/92 (77.2)	59/96 (61.5)	13.3 (0.02, 26.14)	15.7 (2.50, 28.44)

Source: Reviewer generated analysis based on Applicant submitted data adeffipm.xpt for NDA 215151.
[1] The 2-sided 95% confidence interval of the difference in EE healing rates between Voquezna and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm.

6.2.4. Confirmatory Evidence from Trials Conducted Outside the United States

The Applicant submitted four phase 3 trials conducted in Asia (Japan, China, Malaysia, Taiwan, and Korea), 2 healing trials and 2 maintenance trials, to provide confirmatory evidence of vonoprazan effectiveness and supportive safety data.

The ex-U.S. trials are considered confirmatory trials. However, as described below, these studies included similar subject populations, dosage regimens for vonoprazan and active comparator (lansoprazole), primary endpoint definitions, and timing of assessments as in Study EE-301.

The consensus definition of GERD is widely accepted, including in Japan, European Union, Philippines, Korea, and the United States. While the prevalence of GERD-related disorders is higher in the U.S. and European populations (approximately 18 to 28% and 9 to 26, respectively) compared to East Asia (approximately 3 to 8%) (El-Serag et al. 2014), the endoscopic grading of EE using the LA Classification is also used globally.

The Applicant justified the applicability of the data from these studies to the U.S. population by the (1) similarity in the etiology of EE across ethnic groups; (2) similarity across treatment guidelines and clinical practice for the management of EE between Asian and European countries and the United States; and (3) lack of impact on PK or PD (i.e., time% gastric pH >4) of vonoprazan by ethnicity or race (Asian versus non-Asian) (see Figure 1 and Section 6.1).

6.2.4.1. Ex-U.S. Phase 3 Healing Trials (TAK-438/CCT-002, TAK-438_303)

The Applicant submitted data from two (2) clinical trials conducted outside of the United States as confirmatory evidence for healing of EE. The clinical trials (TAK-438/CCT-002, TAK-438_303) were similar in design to EE-301 with regard to study design, enrollment criteria, vonoprazan regimen (20 mg once daily), active comparator (lansoprazole 30 mg once daily), stratification of randomization by LA Classification of EE (Grades A or B and Grades C or D), primary endpoint, and treatment duration. The primary differences among studies were region

(Western versus Asian countries), use of central adjudication for the endoscopies in the U.S. trial but not in the ex-U.S. trials, and inclusion of an endoscopy at Week 4 (in addition to Weeks 2 and 8) in the ex-U.S. trials. In addition, the assessment of heartburn was conducted using different methodology and is not directly comparable between Study EE-301 and the ex-U.S. trials (see Table 19).

In Studies TAK-438/CCT-002 and TAK-438_303, all subjects were Asian with a mean age of approximately 55 years, the majority were male (approximately 70%), baseline LA Grade of C or D was reported in approximately 30% of subjects, and the mean body mass index was approximately 25 kg/m^2. Approximately 20% of subjects in Study TAK-438/CCT-002. Metabolizer status for CYP2C19 was not collected in Study TAK-438_303.

In Study EE-301, 91% of subjects self-identified as White, the mean age was 51 years, approximately 50% of the subjects were male, and EE of LA Grade C or D was reported at baseline in 34%, and the mean body mass index was approximately 30 kg/m^2. Approximately 2% of the subjects in were poor metabolizers of CYP2C19.

No clinically significant differences in the pharmacokinetics of vonoprazan were identified by race/ethnicity, age, sex, body weight, baseline LA Grade of EE, or CYP2C19 phenotype. See Section 8.1 Intrinsic Factors.

Table 19. Clinical Trial Design, Studies for Healing of EE

Design Feature	Study EE-301	Study TAK-438/CCT-002	Study TAK-438_303
Design	Randomized, multicenter, double-blind, active-control, parallel-group	Randomized, multicenter, double-blind, active-control, parallel-group	Randomized, multicenter, double-blind, active-control, parallel-group
Diagnosis	Endoscopically confirmed EE of LA Classification Grades A to D	Endoscopically confirmed EE of LA Classification Grades A to D	Endoscopically confirmed EE of LA Classification Grades A to D
Age at informed consent	≥18 years	≥20 years	≥18 years
Vonoprazan regimen	20 mg QD	20 mg QD	20 mg QD
Control regimen	Lansoprazole 30 mg QD	Lansoprazole 30 mg QD	Lansoprazole 30 mg QD
Treatment duration	Up to 8 weeks	Up to 8 weeks	Up to 8 weeks
Strata for randomization	LA Classification Grade at baseline (A or B, C or D)	LA Classification Grade at baseline (A or B, C or D)	LA Classification Grade at baseline (A or B, Cor D)
Randomization ratio for treatments	1:1	1:1	1:1
Endoscopic evaluations	Weeks 2 and 8	Weeks 2, 4, and 8	Weeks 2, 4, and 8
Centrally adjudicated endoscopy used for efficacy analyses	Yes	No	No
Prespecified primary efficacy endpoint	EE healing rate by Week 8	EE healing rate by Week 8	EE healing rate by Week 8
Region	United States, Europe[a]	Japan	China, Malaysia, Taiwan, Korea
Number treated	514 Vono 510 Lanso	207 Vono 202 Lanso	244 Vono 235 Lanso

Source: Derived from table 1.b.in section 2.5 (Clinical Overview) in the applicant's NDA submission
[a]Europe was defined as the countries of Bulgaria, Czechia, Hungary, Poland, and United Kingdom.
Abbreviations: EE, erosive esophagitis; LA, Los Angeles; QD, once daily; Vono, vonoprazan.

The statistical methods used to analyze Study TAK-438/CCT-002 and Study TAK-438_303 were aligned with those for Study EE-301. Efficacy analyses were based on the MITT Set, which was defined as including all subjects who were randomized to the study treatments and received at least one dose of study drug. The original efficacy analysis excluded subjects with no endoscopy during the healing phase. As part of the ad hoc analysis, missing values were imputed as EE not healed for consistency with Study EE-301.

The primary efficacy endpoint was the EE healing rate by Week 8. Secondary efficacy endpoints were the EE healing rates at Week 2 and at Week 4. Analyses of the EE healing rate were based on the investigator's assessment.

A subgroup analysis of the EE healing rates at Week 2 and by Week 8 was performed in the subset of subjects with baseline EE Grades C or D.

In the ad hoc analysis for each study, the noninferiority of vonoprazan 20 mg to lansoprazole 30 mg was evaluated with a Farrington and Manning test with a noninferiority margin of 10% for the difference in EE healing rates by Week 8 between treatments (vonoprazan 20 mg minus lansoprazole 30 mg). The point estimate and 2-sided 95% CI of the difference in endoscopic healing rate between vonoprazan 20 mg and lansoprazole 30 mg were calculated via the Miettinen and Nurminen method. The superiority of vonoprazan 20 mg to lansoprazole 30 mg was assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

All three trials (i.e., EE-301 and the ex-U.S. trials) demonstrated non-inferiority to the active comparator with respect to healing of EE at week 8 (primary endpoint) and week 2 (secondary endpoint) for all grades of EE and for subject with baseline LA Grade C or D. All three trials demonstrated superiority of vonoprazan over lansoprazole for healing in all grades of EE at 2 weeks, but TAK-438_303 failed to show superiority of vonoprazan over lansoprazole (p-value 0.3860) at 8 weeks. For subjects with baseline LA Grade C or D, superiority to lansoprazole was demonstrated in both EE-301 and TAK-438/CCT-002, but not in Study TAK-438_303, for healing at Week 2 and Week 8 (see Table 20). However, the results for these endpoints still numerically favored vonoprazan for Study TAK-438_303 and the statistical power to detect differences between treatment arms could have been affected by the smaller number of subjects with baseline LA Grade C or D compared to Study EE-301.

Table 20. Healing of EE at Week 2 or by Week 8 for All Grades and for Subjects With Baseline LA Grade C or D in Studies TAK-438/CCT-002, and TAK-438_303, MITT, Healing Phase

	Study TAK-438/CCT-002		Study TAK-438_303	
Parameter	**Vonoprazan 20 mg QD**	**Lansoprazole 30 mg QD**	**Vonoprazan 20 mg QD**	**Lansoprazole 30 mg QD**
Week 2, All Grades				
N	207	202	244	235
EE Healing rate, (%)	89.4	80.7	72.5	65.5
Treatment difference, % (95% CI[1])	8.7 (1.80, 15.72)		7.0 (-1.28, 15.24)	
P-value of superiority[2]	0.0069		0.0485	
Week 8, All Grades				
N	207	202	244	235
EE Healing rate, (%)	98.1	94.1	90.2	89.4
Treatment difference, % (95% CI[1])	4.0 (0.27, 8.40)		0.8 (-4.72, 6.40)	
P-value of superiority[2]	0.0183		0.3860	

Parameter	Study TAK-438/CCT-002		Study TAK-438_303	
	Vonoprazan 20 mg QD	Lansoprazole 30 mg QD	Vonoprazan 20 mg QD	Lansoprazole 30 mg QD
P-value of non-inferiority[3]	<0.0001		0.0001	
Week 2, Grade C or D				
N	75	73	76	68
EE Healing rate, (%)	88.0	63.0	60.5	50.0
Treatment difference, % (95% CI[1])	25.0 (11.44, 38.16)		10.5 (-5.75, 26.32)	
P-value of superiority[2]	0.0002		0.1022	
Week 8, Grade C or D				
N	75	73	76	68
EE Healing rate, (%)	98.7	86.3	82.9	79.4
Treatment difference, % (95% CI[1])	12.4 (4.66, 22.31)		3.5 (-9.41, 16.72)	
P-value of superiority[2]	0.0021		0.2965	

Source: Healing ISE Table 4.c; Table 4.d; Table 4.e.
[1] Miettinen and Nurminen method.
[2] Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.
[3] Farrington and Manning test with a noninferiority margin of -10%
Abbreviations: CI, confidence interval; EE, erosive esophagitis; ISE, Integrated Summary of Effectiveness; LA, Los Angeles; MITT, modified intent-to-treat; N, number of patients in treatment arm; QD, once daily

6.2.4.2. Ex-U.S. Phase 3 Maintenance Trials (TAK-438/CCT-003 and TAK-438_305)

The Applicant submitted data from two (2) clinical trials conducted outside of the United States as confirmatory evidence for maintenance of healed EE. The clinical trials (TAK-438/CCT-003 and TAK-438_305) were similar to EE-301 with respect to study design, enrollment criteria for the trial population, vonoprazan regimen (vonoprazan 10 mg or 20 mg once daily), active-comparator (lansoprazole 15 mg once daily), stratification by baseline LA Classification (Grades A or B and Grades C or D), primary endpoint, and treatment duration. The primary differences among studies were region (Western versus Asian countries) and the use of central adjudication for the endoscopies (see Table 21).

In Studies TAK-438/CCT-003 and TAK-438_305, all subjects were Asian with a mean age of approximately 55 years, the majority were male (approximately 70%), baseline LA Grade of C or D was reported in approximately 20% of subjects, and the mean body mass index was approximately 25 kg/m^2. Approximately 18% of subjects in Study TAK-438/CCT-003 were poor metabolizers of CYP2C19. Metabolizer status for CYP2C19 was not collected in Study TAK-438_305

In Study EE-301, 91% of subjects self-identified as White, the mean age was 51 years, approximately 50% of the subjects were male, and EE of LA Grade C or D was reported at baseline in 34%, and the mean body mass index was approximately 30 kg/m^2. Approximately 2% of the subjects in were poor metabolizers of CYP2C19.

No clinically significant differences in the pharmacokinetics of vonoprazan were identified by race/ethnicity, age, sex, body mass index, baseline LA Grade of EE, or CYP2C19 phenotype. See Section 8.1 Intrinsic Factors.

The primary endpoint for the ex-U.S. trials measured recurrence by Week 24 instead of maintenance; however, results for the endpoint of recurrence are mathematically equivalent to results for maintenance and we are presenting the results for maintenance for consistency with how results for EE-301 were presented.

Table 21. Clinical Trial Design, Studies for Maintenance of Healed EE

Design Feature	Study EE-301	Study TAK-438/CCT-003	Study TAK-438_305
Design	Randomized, multicenter, double-blind, active-control, parallel-group	Randomized, multicenter, double-blind, active-control, parallel-group	Randomized, multicenter, double-blind, active-control, parallel-group
Diagnosis	Endoscopically confirmed healed EE of LA Classification Grades A to D	Endoscopically confirmed healed EE of LA Classification Grades A to D	Endoscopically confirmed healed EE of LA Classification Grades A to D
Age at informed consent	≥18 years	≥20 years	≥18 years
Vonoprazan regimen	10 mg QD 20 mg QD	10 mg QD 20 mg QD	10 mg QD 20 mg QD
Control regimen	Lansoprazole 15 mg QD	Lansoprazole 15 mg QD	Lansoprazole 15 mg QD
Treatment duration	24 weeks	24 weeks	24 weeks
Strata for randomization	LA Classification Grade at baseline (A or B, C or D)	LA Classification Grade at baseline (A or B, C or D)	LA Classification Grade at baseline (A or B, C or D)
Randomization ratio for treatments	1:1:1	1:1:1	1:1:1
Endoscopic evaluations during maintenance	Week 24	Weeks 12 and 24	Weeks 12[a] and 24
Centrally adjudicated endoscopy used for efficacy analyses	Yes	No	No
Prespecified primary efficacy endpoint	Maintenance of EE healing by Week 24	Recurrence of EE by Week 24	Recurrence of EE by Week 24
Region	United States, Europe[b]	Japan	China, Malaysia, Taiwan, Korea
Number treated during maintenance	296 Vono 10 mg 296 Vono 20 mg 297 Lanso 15 mg	202 Vono 10 mg 204 Vono 20 mg 201 Lanso 15 mg	235 Vono 10 mg 226 Vono 20 mg 242 Lanso 15 mg

Source: Table 1.c in Section 2.5 (Clinical Overview) in the Applicant's NDA submission.
[a]An endoscopy was performed at Week 12 if relapse of EE was suspected in the subject because of subjective symptoms or changes in clinical laboratory values.
[b]Europe was defined as the countries of Bulgaria, Czechia, Hungary, Poland, and United Kingdom.
Abbreviations: EE, erosive esophagitis; LA, Los Angeles; QD, once daily; Vono, vonoprazan.

All three studies demonstrated both non-inferiority and superiority to lansoprazole with respect to maintenance of healing (i.e., not recurred) in all grades of EE and the non-inferiority of vonoprazan compared to lansoprazole for maintenance of healing in subjects with baseline LA Grade C or D. While TAK-438_305 did not demonstrate superiority of the lower dose of vonoprazan (10 mg) over lansoprazole for subjects with baseline LA Grade C or D, the vonoprazan 10 mg dose still showed numerically higher maintenance of healed EE rates compared to lansoprazole and the small sample size for subjects with baseline LA Grade C or D may have affected the power to detect statistically significant differences between arms. The

estimated treatment difference between vonoprazan 10 and lansoprazole for this endpoint was consistent with the estimated treatment difference for Study EE-301.

Table 22. Maintenance of Healed EE Through Week 24 for All Grades and for Subjects with Baseline LA Grade C or D in Studies TAK-438/CCT-003, and TAK-438_305, MITT, Maintenance Phase

	Study TAK-438/CCT-003			Study TAK-438_305		
Parameter	Vonoprazan 10 mg QD	Vonoprazan 20 mg QD	Lansoprazole 15 mg QD	Vonoprazan 10 mg QD	Vonoprazan 20 mg QD	Lansoprazole 15 mg QD
Week 24, All Grades						
N	202	204	201	207	195	208
Rate of maintenance of healed EE, (%)	92.6	96.6	81.1	75.8	76.9	65.9
Treatment difference, % (95% CI[1])	11.5 (5.01, 18.23)	15.5 (9.73, 21.82)		10.0 (1.23, 18.62)	11.1 (2.22, 19.73)	
P-value of superiority[2]	0.0003	<0.0001		0.0127	0.0071	
P-value of non-inferiority[3]	<0.0001	<0.0001		<0.0001	<0.0001	
Week 24, Grade C or D						
N	40	43	41	43	39	42
EE Healing rate, (%)	82.5	95.3	61.0	65.1	71.8	50.0
Treatment difference, % (95% CI[1])	21.5 (1.81, 39.94)	34.4 (18.08, 50.57)		15.1 (-5.99, 34.98)	21.8 (0.36, 41.27)	
P-value of superiority[2]	0.0159	0.0001		0.0792	0.0225	

Source: Maintenance ISE Table 4.c; Table 4.d.
[1] Miettinen and Nurminen method.
[2] Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.
[3] Farrington and Manning test with a noninferiority margin of -10%
Abbreviations: CI, confidence interval; EE, erosive esophagitis; ISE, Integrated Summary of Effectiveness; LA, Los Angeles; MITT, modified intent-to-treat; N, number of patients in treatment arm; QD, once daily

6.2.4.3. Summary of Efficacy in Ex-U.S. Trials

The population and design of the 4 phase 3 trials conducted outside of the United States in Asia was similar to the population and design of Study EE-301, and the results are considered applicable to the U.S. population based upon the rationale provided by the applicant for the generalizability to the US population.

The results of the two ex-U.S. healing phase trials (Study TAK-438/CCT-002 and Study TAK-438_303) demonstrated that vonoprazan 20 mg QD was non-inferior to lansoprazole 30 mg QD for healing in all grades of EE by Week 8 and superior to lansoprazole 30 mg QD for healing in all grades of EE at Week 2. The results showed numerically higher rate of healing of EE for Grade C or D at Week 2 or by Week 8 in the vonoprazan group compared to the lansoprazole group.

Similarly, the two ex-U.S. maintenance phase trials (Study TAK-438/CCT-003 and Study TAK-438_305) provided evidence of the effectiveness of both the 10 mg QD and 20 mg QD

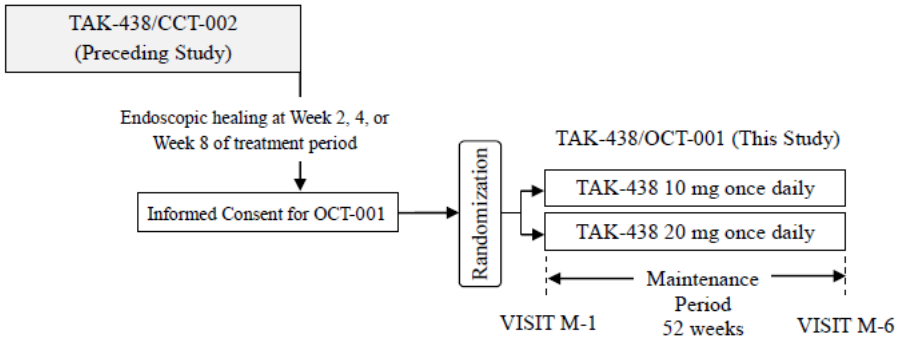
vonoprazan doses. The results for each dose were statistically superior to lansoprazole 15 mg QD for the endpoint of maintenance of healed EE (all grades) through Week 24. The results showed a numerically higher rate for the vonoprazan 10 mg QD group compared to the lansoprazole 15 mg QD group for the endpoint of maintenance of healed EE for Grade C or D through Week 24.

In summary, the results from these trials are considered confirmatory to support the effectiveness of vonoprazan for the healing of EE and maintenance of healed EE.

6.2.5. Maintenance of Effect from Long-Term Study Conducted Outside the United States

The vonoprazan clinical development program included one long-term extension study in subjects with healed EE conducted outside the U.S. with follow-up for up to 52 weeks. Study TAK-438/OCT-001 was a phase 3 randomized, double-blind, uncontrolled trial in 305 adult subjects who achieved endoscopically confirmed healing of EE in Study TAK-438/CCT-002. Randomization was stratified by baseline LA Grade (i.e., A or B, B or C). Subjects were randomized 1:1 to vonoprazan 10 mg or 20 mg once daily for 52 weeks. The primary objective was to evaluate the safety of long-term administration of two doses of vonoprazan over a 52-week period, with a primary endpoint of descriptive analysis of adverse events. The secondary endpoint was the EE recurrence rate to assess persistence of maintenance of healed EE. The trial did not include scheduled endoscopic assessments. Recurrence rate was determined based on endoscopy performed as needed when recurrence of EE was suspected based on symptoms or other clinical criteria. Given that recurrence of EE is poorly correlated with symptoms, it is possible that the study did not capture all recurrence events and may exaggerate the treatment effect of vonoprazan.

Figure 5. Study Schematic, TAK-438/OCT-001



Source: Clinical Study Report, TAK-438/OCT-001, March 2014

The recurrence rate reported in Study TAK-438/OCT-001 was similar for both doses of vonoprazan (9.4% and 9.0% for 10 mg and 20 mg, respectively). The rate of maintenance of healed EE can be calculated as 90.6% for vonoprazan 10 mg and 91% for vonoprazan 20 mg.

This study provides supportive descriptive information that the effect of vonoprazan is maintained for up to 52 weeks; however, any conclusions are limited because the study did not include a comparator or scheduled endoscopic assessments. Given that recurrence of EE is poorly correlated with symptoms, it is possible that the study did not capture all recurrent events and may exaggerate the treatment effect of vonoprazan.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. Non-Inferiority Margin for the Primary Endpoint of Healing of EE at Week 8 in the Healing Phase of Study EE-301

Issue

The primary endpoint of percentage of subjects with healing of all grades of EE at Week 2 or Week 8 in Study EE-301 was assessed for NI between Voquezna 20 mg once daily and lansoprazole 30 mg once daily. The Applicant proposed a NI margin of -10% based on two placebo-controlled historical studies of lansoprazole 30 mg once daily (Studies M87-092 and M92-721). The review team assessed the acceptability of this study to support the Applicant's proposed NI margin of -10% for this endpoint in support of the indication of healing of EE for Voquezna.

Background

In the NDA submission, the Applicant based the NI margin of -10% for the primary endpoint of percentage of subjects with healing of all grades of EE on publications (Earnest et al. 1998) and (Castell et al. 1996) describing the results of Studies M87-092 and M92-721, respectively, conducted by Takeda during the development of Prevacid (lansoprazole) delayed-release capsules (NDA 020406). In the 74-day letter sent on May 24, 2022, the Agency requested the Applicant provide an integrated assessment of the available data to support the proposed margin for this endpoint and the associated data calculations. On June 14, 2022, the Applicant submitted their response.

Assessment

Support for an NI margin of -10% for the primary endpoint of percentage of subjects with healing of all grades of EE at Week 2 or Week 8 in Study EE-301 was based on the estimated treatment effect of lansoprazole 30 mg once daily compared to placebo in Studies M87-092 and M92-721.

The Applicant stated that they used a conservative approach and only used results from Study M87-092 because this study had the smallest sample size and treatment difference between lansoprazole 30 mg once daily and placebo and the 95% CI of the difference from placebo was lower. The Applicant used the intent-to-treat (ITT) analysis population, as described in the Earnest publication (Earnest et al. 1998), which they considered more applicable to the MITT analysis conducted in Study EE-301 than the per protocol (PP) population for this study reported in the approved the PI for Prevacid (lansoprazole) delayed-release capsules (NDA 020406) supporting the indication of healing of all grades of EE. The 2-sided 95% CI was calculated by the Applicant using the Wald method.

Although Study M92-721 was not used by the Applicant to support the NI margin, the data from this study provides additional evidence. The difference in the healing rate of all grades of EE in Studies M87-092 and M92-721 is shown in Table 23.

Table 23. Healing Rates at Week 8 for Lansoprazole 30 mg Once Daily vs. Placebo in Studies M87-092 and M92-721 in Subjects With Erosive Esophagitis– Intent-to-Treat Populations

Study Parameter	Lansoprazole 30 mg	Placebo
M87-092		
N	71	66
Healing Rate, %	87.3	47.0
Diff to Placebo (95% CI[a])	40.3 (26.0, 54.6)	
M92-721		
N	421	213
Healing Rate, %	87.2	31.9
Diff to Placebo (95% CI[a])	55.3 (48.3, 62.3)	

Source: Reviewer's analysis based on (Earnest et al. 1998) and (Castell et al. 1996) publications in the Applicant's response to information request submitted on June 14, 2022.
[a] The 2-sided 95% confidence interval of the difference in healing rate between lansoprazole and placebo was calculated via the Wald method.
Abbreviations: CI, confidence interval; Diff, difference; N, number of subjects in treatment arm

The lower limits of the 2-sided 95% CI for the difference in healing rate for Study M87-092 and Study M92-721 were 26.0% and 48.3%, respectively. A conservative assumption of the treatment effect of lansoprazole 30 mg once daily compared to placebo is 26.0%. Therefore, the Applicant proposed that a NI margin of -10% assures that Voquezna 20 mg once daily retains at least 60% of the treatment effect of lansoprazole 30 mg once daily compared with placebo (60% ≈ [26-10]/26) for the healing rate at Week 2 or Week 8 in Study EE-301.

While Studies M87-092 and M92-721 were similar in design to the healing phase of Study EE-301, there were some differences from Study EE-301 in design and subject populations. One difference in study design was that in Studies M87-092 and M92-721 subjects remained in the healing phase for an entire 8 weeks and received the healing dose of lansoprazole (30 mg once daily), whereas in Study EE-301 subjects were allowed to enter the maintenance phase at Week 2 if their esophageal erosions were healed on endoscopy and received the lower maintenance dosage of lansoprazole (15 mg once daily). However, the difference in exposure to lansoprazole in the historical studies should not have much impact on the overall proportion of subjects who were healed at the end of the healing phase (Week 8) because subjects were required to achieve complete healing of erosions at Week 2 prior to entering the maintenance phase in Study EE-301, and thus would likely have remained healing with continued treatment to Week 8.

The analysis population also differed slightly between the historical studies and Study EE-301. The percentage of subjects with healing of all grades of EE in Studies M87-092 and M92-721 was based upon the ITT population versus the MITT population for Study EE-301. The MITT population in Study EE-301 was defined as all subjects randomized into the healing phase who had documented EE at baseline and received at least one dose of study drug during the healing phase. Three out of 1027 subjects were excluded from the ITT population in Study EE-301 because they did not receive any dose of study drug. Since the proportion of excluded subjects was small, the slight difference in analysis population should not impact the NI margin justification.

Finally, the subject populations for Studies M87-092 and M92-721 were defined using different grading scales for severity of esophageal erosions than used in Study EE-301. Study M87-092 enrolled subjects with Grade 2 or higher "erosive reflux esophagitis" defined using a Kauls-modified Savary-Miller Scale (adapted by Takeda), whereas the LA classification scale (Grades A to D) was used in Study EE-301.

In Study M87-092, subjects with baseline EE Grade 2 (36.3% of subjects) would not have been classified as having EE using the LA criteria. Subjects with Grade 3 (53.1%) and Grade 4 (10.6%) roughly correspond to LA Grades A or B and C, respectively. No subjects were enrolled that would have been classified as having LA Grade D (see Table 110). In Study EE-301, 66% of subjects had EE of LA Grades A or B and 34% of subjects had EE of Grades C or D at baseline. The baseline grade of EE has implications for healing rates. In Study EE-301, the healing rate for lansoprazole 30 mg once daily was approximately 20% lower for subjects with LA Grades C or D (71.8%) compared to LA Grades A or B (89.9%).

In order to determine if the lansoprazole treatment effect would have been different if Study M87-092 included more subjects with baseline EE grades similar to LA Grades C or D, the review team considered information about the placebo healing rate in the historical studies. However, the data were limited because of the enrollment criteria and the grading scale.

Placebo data were identified in a publication by (Hetzel et al. 1988) of omeprazole (a (PPI similar to lansoprazole) in subjects with "erosive peptic esophagitis" of Grade 2 or greater defined using the investigator's own grading scale of 0 to 4 (see Table 110). Subjects in the placebo arm had EE of Grade 2 to Grade 4 (which roughly corresponds to LA Grades B or C) at baseline and the healing rate at Week 8 was 9% (3 of 32 subjects). The 9% healing rate is considerably lower than the observed placebo healing rates in the less severe EE populations enrolled in Studies M87-092 and M92-72 with approximately 47% and 32% placebo healing rates, respectively.

Therefore, based on data with a similar PPI (omeprazole), the treatment effect of lansoprazole 30 mg once daily in Study M87-092 likely would have been larger if the study population had been more similar to Study EE-301. In addition, the Applicant selected the worse result from the two available studies (i.e., Study M87-092 and not Study M92-72) for the estimated treatment effect. Therefore, the estimated treatment effect of lansoprazole 30 mg once daily used to justify the NI margin in the healing phase is likely a conservative approach and should apply to Study EE-301, despite the differences in the study population.

Other aspects of the historical studies and Study EE-301 were similar.

Conclusion

An NI margin of -10% for the primary endpoint of percentage of subjects with healing of all grades of EE in Study EE-301 at Week 2 or Week 8 can be supported based on the treatment effect of lansoprazole 30 mg once daily compared to placebo in Studies M87-092 and M92-721.

As discussed in Section 6.2.2.3 Results of Analyses, EE-301, Healing Phase, the lower bound of the 95% CI of the treatment difference for Voquezna 20 mg once daily compared to lansoprazole 30 mg once daily for percentage of subjects with healing of all grades of EE at Week 2 or Week 8 in Study EE-301 was 4.49%. The lower bound of the CI exceeds zero, therefore, Voquezna would demonstrate NI to lansoprazole at any margin.

The results of Study EE-301 for the primary endpoint of percentage of subjects with healing of all grades of EE at Week 2 or Week 8, along with the results for the same primary endpoint in the ex-US confirmatory studies, also supports granting the indication of healing of EE for Voquezna.

6.3.2. Non-Inferiority Margin for the Primary Endpoint of Maintenance of Healed EE Through Week 24 in the Maintenance Phase of Study EE-301

Issue

The primary endpoint of percentage of subjects with maintenance of healed EE (all grades) through Week 24 of the maintenance phase in Study EE-301 was assessed for NI between Voquezna 10 mg once daily and lansoprazole 15 mg once daily. The Applicant proposed a NI margin of -10% based on two placebo-controlled historical studies of lansoprazole 15 mg once daily, as described in the PI for Prevacid (lansoprazole) delayed-release capsules (NDA 020406).

The review team assessed the acceptability of these studies to support the Applicant's proposed NI margin of -10% for this endpoint in support of the indication of maintenance of healed EE for Voquezna.

Background

In the NDA submission, the Applicant based the NI margin of -10% for the primary endpoint of percentage of subjects with maintenance of healed EE (all grades) through Week 24 at the end of the maintenance phase in Study EE-301 on the results of two studies conducted by Takeda and reported in the PI for Prevacid (lansoprazole) delayed-release capsules (NDA 020406). In the 74-day letter sent on May 24, 2022, the Agency requested the Applicant provide an integrated assessment of the available data to support the proposed margin for this endpoint and the associated data calculations. On June 14, 2022, the Applicant submitted their response.

Assessment

The Applicant stated that they selected the two historical studies (Study 1: M88-271 and Study 2: M89-350) because they were the studies that supported the approval of Prevacid (lansoprazole) delayed-release capsules for the indication of maintenance of healed EE (NDA 020406). These studies were also published by (Robinson et al. 1996) (M88-271) and (Sontag et al. 1996) (M89-350). Similar to their rationale for not using the results of both studies to support the NI margin for this endpoint in the healing phase, the Applicant selected Study M88-271 (Study 1) as the most conservative for estimating the effect size.

The rates for percentage of subjects with maintenance of healed EE (all grades) are reported as endoscopic remission rates in the Prevacid PI (Takeda 2018). The Applicant obtained the maintenance rates by subtracting from 100 and the 2-sided 95% CI was calculated using the Wald method. The results were verified by the statistical review team (See Table 24).

Table 24. Rates for Maintenance of Healed EE for Lansoprazole 15 mg Once Daily vs. Placebo in Studies M88-271 and M89-350 in Subjects With Erosive Esophagitis Healed Through Week 24 (Calculated by the Statistical Reviewer From Endoscopic Remission Rates in the Prevacid PI)

Study Parameter	Lansoprazole 15 mg	Placebo
M88-271		
N	59	55
MOH Rate, %	81	27
Diff to Placebo (95% CI[1])	54 (38.6, 69.4)	
M89-350		
N	50	47
MOH Rate, %	72	13
Diff to Placebo (95% CI[1])	59 (43.3, 74.7)	

Source: Reviewer's analysis based on Prevacid PI (Table 21) in the Applicant's response to information request submitted on June 14, 2022.
[1] The 2-sided 95% confidence interval of the difference in healing rate between lansoprazole and placebo was calculated via the Wald method.
Abbreviations: CI, confidence interval; Diff, difference; MOH, maintenance of healing; N, number of subjects in treatment arm; PI, Prescribing Information

The lower limits of the 2-sided 95% CI for the difference in the rates of maintenance of healed EE for Study M88-271 and Study M92-721 were 38.6% and 43.3%, respectively. A conservative assumption for the treatment effect of lansoprazole 15 mg once daily compared to placebo is 38.6%. Therefore, the Applicant proposed that a NI margin of -10% assures that Voquezna 10 mg once daily retains at least 74% of the treatment effect of lansoprazole 15 mg once daily compared with placebo (74% ≈ [38.6-10]/38.6) for the rate of maintenance of healed EE through Week 24 in Study EE-301.

While Study M88-271 and Study M89-350 were similar in design to the maintenance phase of Study EE-301, there were some differences from Study EE-301 in analysis and subject populations.

One difference between the historical studies and Study EE-301 is the analysis population. In Studies M88-271 and M89-350 an PP analysis was used, whereas in Study EE-301 an MITT analysis, which included all randomized subjects who received study drug, was used and missing data due to reasons not related to COVID-19 were imputed as non-responders. A treatment policy strategy, where data will be collected after intercurrent events, was applied to handle intercurrent event of prohibited EE medication use.

In the (Robinson et al. 1996) publication of Study M88-271, 173 subjects (57 placebo recipients, 60 recipients of lansoprazole 15 mg once daily, and 56 recipients of lansoprazole 30 mg once daily) with healed EE at Week 8 entered the maintenance phase of the study. Three subjects were excluded from the analysis population (2 in the placebo group and 1 in the lansoprazole 15 mg group). Of these two subjects had no evaluable endoscopy and one subject received additional acid-suppressive medication. The proportion of subjects excluded from the analysis was small compared to the total number of subjects enrolled; therefore, the exclusion of subjects should not have much impact on the overall proportion of subjects who achieved maintenance of healed EE through Week 24.

In the (Sontag et al. 1996) publication of Study M89-350, 163 subjects (56 placebo recipients, 53 recipients of lansoprazole 15 mg once daily, and 54 recipients of lansoprazole 30 mg once daily) with healed EE at Week 8 entered the maintenance treatment phase. Seventeen subjects were

excluded from the analysis population (9 placebo recipients, 3 recipients of lansoprazole 15 mg once daily, and 5 recipients of lansoprazole 30 mg once daily). The reasons for exclusion were no evaluable endoscopy (n=9), use of prohibited medications (n=7), and one subject did not fulfill the initial entry criterion. As the PP analysis excluded more placebo subjects compared to the lansoprazole 15 mg once daily group (9 versus 3 subjects), a MITT analysis that included all randomized subjects who took study drug and used non-responder imputation to handle missing data (as was done in the Study EE-301 analysis) would likely have produced even more favorable results for the lansoprazole 15 mg dose compared to placebo.

Finally, the subject populations for the historical studies were defined using a different grading scale for esophageal erosions than used in Study EE-301. Study M88-271 and Study M89-350 enrolled subjects with Grade 2 or higher "erosive reflux esophagitis" defined using a Kauls-modified Savary-Miller Scale (adapted by Takeda,), whereas as Study EE-301 used the LA classification scale for grading of EE (Grades A through D).

In Study M88-271, subjects with EE of Grade 2 (41.2% of subjects) would not have been classified as having EE using the LA criteria. Subjects with Grade 3 (50.6%) and Grade 4 (8.2%) roughly correspond to LA Grades A and B, respectively. No subjects were enrolled that would have been classified as having LA Grade D. (see Table 110). The baseline grade of EE has implications for maintenance of healed EE rates. In Study EE-301, the rate of maintenance of healed EE for lansoprazole was lower in subjects with LA Grades C or D compared to LA Grades A or B (61% versus 75%), indicating a potential slight differential in healing for subjects with more severe EE.

In order to determine whether the lansoprazole treatment effect would have been different if the historical studies included more subjects with baseline EE grades similar to LA Grades C or D, the review team considered information about the placebo healing rate in the historical studies. However, the data was limited because of the enrollment criteria and the grading scale.

The statistical team explored whether the treatment effect of lansoprazole in the historical studies would be impacted if the subject populations were more similar to the study population in Study EE-301 (i.e., 66% of subjects with LA Grades A or B and 34% of subjects with LA Grades C or D). Using a hypothetical assumption that the treatment difference between lansoprazole 15 mg once daily and placebo is 0 (i.e., lansoprazole 15 mg once daily does not have effect on subjects with LA Grades C or D), the overall rate of healed EE would be 25.5% (i.e., a difference in the rate of maintenance of healed EE of $38.6\% \times 0.66+0 \times 0.34 \approx 25.5\%$). In this extreme case, a -10% noninferiority margin would assure that Voquezna retains at least 60% (60% = [25.5%-10%]/25.5%) of the treatment effect of lansoprazole 15 mg once daily. Therefore, the difference in subject population in EE severity does not impact the NI margin justification. In addition, the Applicant selected the worse result from the two available studies (i.e., Study M88-271 and not Study M89-350) for the estimated treatment effect.

Other aspects of the historical studies and Study EE-301 were similar.

Conclusion

A NI margin of -10% for the primary endpoint of percentage of subjects with maintenance of healed EE (all grades) through Week 24 in Study EE-301 is supported by the treatment effect of lansoprazole 15 mg once daily compared to placebo in Studies M88-271 and M89-350.

As discussed in Section 6.2.3.4, the lower bound of the 95% confidence interval of the treatment difference for Voquezna 10 mg once daily compared to lansoprazole 15 mg once daily for the percentage of subjects with maintenance of healed EE (all grades) through Week 24 in Study EE-301 was 0.21%. The lower bound of the CI exceeds zero, therefore Voquezna would demonstrate NI to lansoprazole at any margin. Furthermore, as part of the pre-specified multiple testing procedure, the Applicant tested the endpoint of maintenance of healed EE for superiority and was able to demonstrate superiority for Voquezna 10 mg once daily compared to lansoprazole 15 mg once daily.

The results of Study EE-301 for the percentage of subjects with maintenance of healed EE (all grades) through Week 24, along with the results for the same endpoint in the ex-US confirmatory studies, also supports granting the indication of maintenance of healed EE for Voquezna.

6.3.3. Non-Inferiority Margin for the Secondary Endpoint of 24-Hour Heartburn Free Days in the Healing Phase of Study EE-301

Issue

The secondary endpoint of percentage of 24-hour heartburn-free days through Week 8 of the healing phase in Study EE-301 was assessed for NI between Voquezna 20 mg once daily and lansoprazole 30 mg once daily. The Applicant proposed a NI margin of -15% based on a placebo-controlled historical study of lansoprazole 30 mg once daily (Study M92-721). The review team assessed the acceptability of this study to support the Applicant's proposed NI margin of -15% for this endpoint in support of a labeling claim of "relief of heartburn" for the indication of healing of EE for Voquezna.

Background

In the NDA submission, the Applicant based the NI margin of -15% for the secondary endpoint of percentage of 24-hour heartburn-free days during the healing phase on a publication by (Castell et al. 1996) describing the results of Study M92-721 conducted by Takeda. Study M92-721 was a randomized, double-blind study that evaluated healing of EE with placebo, lansoprazole 15 mg once daily, lansoprazole 30 mg once daily, and omeprazole 20 mg once daily through Week 8. In the 74-day letter sent on May 24, 2022, the Agency requested further information from Study M92-721 to support the NI margin that were not provided in the Castell publication. On June 14, 2022, the Applicant submitted their response.

Assessment

The Applicant's submission contained information from the Takeda Clinical Study Report for Study M92-721 that was not reported in the Castell et al publication. Study M92-721 was not used to support approval of Prevacid (NDA 020406) and has not been previously reviewed by FDA.

The mean percentage of 24-hour heartburn-free days through Week 8 in the PP population was calculated by the statistical team using the submitted data and is shown in Table 25. The results indicate that the treatment effect of lansoprazole 30 mg compared to placebo is 35.8%.

Therefore, the Applicant proposes that a NI margin of -15% assures that Voquezna 20 mg once daily retains at least 58% of the treatment effect of lansoprazole 30 mg once daily compared with placebo (58% = [35.8-15]/35.8) for the percentage of 24-hour heartburn-free days through Week 8 of the healing phase in Study EE-301.

Table 25. Mean Percentage of 24-Hour Heartburn-Free Days for Lansoprazole 30 mg Once Daily vs. Placebo in Study M92-721 in Subjects With Erosive Esophagitis Through Week 8 – Per Protocol Population (Takeda Clinical Study Report)[a]

Parameter	Lansoprazole 30 mg	Placebo	Treatment Difference (Lansoprazole 30 mg - Placebo) (95% CI[b])
N	417	206	
Mean (SD), %	72.6 (31.1)	31.6 (31.5)	41 (35.8, 46.2)

Source: Reviewer's analysis based on Applicant's response to information request submitted on June 14, 2022.
[a] Study not previously reviewed by FDA in support of an NDA
[b] The 2-sided 95% confidence interval of the difference in percentage of 24-hour heartburn-free days between lansoprazole 30 mg and placebo was calculated via the Wald method.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; SD, standard deviation.

While Study M92-721 was similar in design to Study EE-301, there were some notable differences that the statistical review team explored to determine whether the study was sufficiently similar to Study EE-301 in design and conduct to support the NI margin.

One notable exception in study design was that in Study M92-721 subjects remained in the healing phase for an entire 8 weeks, whereas in Study EE-301 subjects were allowed to enter the maintenance phase at Week 2 if their esophageal erosions were healed on the Week 2 endoscopic assessment. Subjects in both studies randomized to lansoprazole, received 30 mg once daily during the healing phase and 15 mg once daily during the maintenance phase. The longer duration of exposure to lansoprazole 30 mg once daily in Study M92-721 could affect the assessment of the percentage of 24-hour heartburn-free days through Week 8 in the healing phase.

The statistical review team performed a post-hoc analysis of Study EE-301 to assess whether duration of exposure to the higher dosage of Voquezna or lansoprazole in the healing phase was associated with the percentage of 24-hour heartburn-free days. For both the treatment arms in Study EE-301, subjects healed at Week 8 had a higher proportion of 24-hour heartburn-free days than subjects healed at Week 2. Furthermore, subjects in the Voquezna 20 mg arm who were healed at Week 2 and entered the maintenance phase and randomized to receive the same dose of Voquezna (20 mg once daily) had a similar percentage of 24-hour heartburn-free days during 8 weeks of dosing (Week 2 of healing through Week 6 of maintenance) compared to subjects who received Voquezna 20 mg once daily for eight weeks in the healing phase. (See Table 26).

Table 26. Percentage of 24-Hour Heartburn-Free Days for Voquezna 20 mg vs. Lansoprazole 30 mg in Subjects With Erosive Esophagitis Healed at Week 2 and at Week 8 in Study EE-301- Modified Intent-to-Treat Population (Statistical Reviewer's Post-Hoc Analysis; NDA 215151)

	Percentage of 24-Hour Heartburn-Free Days (95% Confidence Interval)	
Parameter	**Voquezna 20 mg N=514**	**Lansoprazole 30 mg N=510**
Subjects healed at Week 2	(n=382) 64.3 (60.7, 67.8)	(n=348) 63.5 (59.7, 67.3)
Subjects healed at Week 8	(n=96) 78.4 (73.0, 83.8)	(n=83) 71.0 (64.4, 77.6)
Subjects healed at Week 2, went into the maintenance study, and stayed on the same dose through maintenance Week 6	(n=122) 78.3 (72.8, 83.9)	NA

Source: Reviewer's analysis based on Applicant's submitted adsd.xpt dataset for Study EE-301 in NDA 215151.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects assessed at each time point; NA, not available; NDA, new drug application

Therefore, duration of exposure to the study treatments appears to have affected the percentage of 24-hour heartburn-free days, as subjects with longer exposure reported more 24-hour heartburn-free days. The impact that the duration of the healing phase in Study M92-721 would have on the estimated percentage of 24-hour heartburn-free days for the placebo arm is unclear. It is unknown whether the percentage of 24-hour heartburn-free days changes over time in the placebo arm; however, the design of the study could affect missing data and dropout rates. It should be noted that fewer placebo subjects had healed EE at Week 2 (24%) compared to lansoprazole 30 mg (61%) in Study M92-721, and, therefore, the estimated percentage of 24-hour heartburn-free days for subjects in the placebo arm is less likely to have been impacted because of missing data or dropouts.

Another important difference between Study M92-721 and Study EE-301 is the analysis population. The percentage of 24-hour heartburn-free days was based on the PP population for Study M92-721 versus the MITT population for Study EE-301. While results for the PP population analysis were similar to the MITT analysis for Study EE-301, the PP populations across studies may not be directly comparable as treatment assignment could affect adherence to the protocol. Analyses based on the PP population could overestimate the effect of a treatment over placebo compared to an intent-to-treat or MITT analysis if there is poor subject adherence to study drug due to safety or tolerability issues. However, results from Study EE-301 generally showed good subject adherence to treatment for the lansoprazole 30 mg dosage. In this instance, the PP analysis in Study M92-721 may underestimate the benefit for lansoprazole 30 mg compared to a MITT analysis, as the placebo arm had a higher dropout rate (16.75% versus 1.25%).

The subject population for Study M92-721 was defined using a different grading scale for assessing the severity of esophageal erosions than the severity scale used in Study EE-301. Study M92-721 enrolled subjects with Grade 2 or higher "erosive reflux esophagitis" defined using a Kauls-modified Savary-Miller Scale (adapted by Takeda). The LA classification scale (Grade A to D) was used in Study EE-301. The LA Classification was proposed in 1994 and grades EE based upon the extent of break in the mucosa from adjacent normal tissue. Subjects with EE of Grade 2 (65% of subjects) or Grade 3 (28% of subjects) in Study M92-721 would have been classified as having EE of Grade A using the LA criteria. In Study M92-721, Grade 4 (7% of subjects) roughly corresponds to LA Grades B or C (see Table 110). Study M92-721 did not

include a definition of EE severity that would identify the equivalent of LA Grade D. In Study EE-301, based on the Los Angeles classification, 66% of subjects had EE of Grades A or B and 34% of subjects had EE of Grades C or D at enrollment. However, the severity of EE is poorly correlated with heartburn symptoms (Isshi et al. 2021) and thus differences in EE grading between the two studies were unlikely to be clinically relevant for the purposes of supporting the NI margin for the percentage of 24-hour heartburn-free days. Furthermore, the baseline symptom data were described as comparable between lansoprazole and placebo groups in Study M92-721.

Other aspects of Study M92-721 and Study EE-301 were similar. A twice daily subject diary was used to collect daytime and nighttime heartburn symptoms in both Study M92-721 and Study EE-301. The diary in Study M92-721 was very similar to diary used in Study EE-301, except that the diary in Study M92-721 used a 4-point severity scale (none, mild, moderate, severe) and the diary in Study EE-301 used 5-point severity scale (none, mild, moderate, severe, very severe). Given that the secondary endpoint of percentage of 24-hour heartburn-free days is based on presence or absence of any degree of heartburn, differences in the scales used in the two studies were not felt to be clinically relevant for the purpose of establishing the NI margin for the 24-hour heartburn-free days endpoint.

Conclusion

Support for an NI margin of -15% for the secondary endpoint of percentage of 24-hour heartburn-free days during the healing phase of Study EE-301 was based on the estimated treatment effect of lansoprazole 30 mg once daily compared to placebo in Study M92-721. As discussed in Section 6.2.2.3, the lower bound of the 95% confidence interval of the treatment difference for Voquezna 20 mg once daily compared to lansoprazole 30 mg once daily for the percentage of 24-hour heartburn-free days in the healing phase of Study EE-301 was -1.6%, which would still demonstrate NI at a much more conservative margin than the Applicant's proposed -15% NI margin. Given the uncertainty of the treatment effect of lansoprazole 30 mg in Study M92-721 compared to Study EE-301, due to the differences in study design and analysis populations, a more conservative margin (i.e., -5%) is recommended than the -15% NI margin proposed by the Applicant. A more conservative margin would provide assurance that Voquezna has a clinically acceptable effect compared to lansoprazole and other approved PPIs, which are accepted as standard of care for healing of EE and highly effective. The percentage of 24-hour heartburn-free days during the healing phase of Study EE-301 for subjects assigned to lansoprazole 30 mg who were healed at Week 2 was slightly lower compared to subjects that continued through Week 8 (64.5% versus 71.0%). Even conservatively assuming the treatment effect for lansoprazole versus placebo when using the same study design used in Study EE-301 is 15% (less than half of the lower bound for the effect of lansoprazole in Study M92-721), a -5% margin would still guarantee that at least 66% of the treatment effect of lansoprazole was preserved.

In conclusion, an NI margin for the secondary endpoint of percentage of 24-hour heartburn-free days in Study EE-301 through Week 8 can be justified and the results support the "relief of heartburn" claim in the label for the indication of healing of EE for Voquezna.

6.3.4. Non-Inferiority Margin for the Secondary Endpoint of 24-Hour Heartburn Free Days Through Week 24 in the Maintenance Phase of Study EE-301

Issue

The secondary endpoint of percentage of 24-hour heartburn-free days through Week 24 of the maintenance phase in Study EE-301 was assessed for NI between Voquezna 10 mg once daily and lansoprazole 15 mg once daily. The Applicant proposed a NI margin of -15% based on a placebo-controlled historical study of dexlansoprazole 30 mg once daily (Study T-EE05-135). Dexlansoprazole is the R-enantiomer of lansoprazole (a racemic mixture of the R- and S-enantiomers) and Dexilant (dexlansoprazole) delayed-release capsules are approved for the indication of maintenance of healed EE and relief of heartburn (NDA 022287). The review team assessed the acceptability of this data to support the Applicant's proposed NI margin of -15% for the endpoint of percentage of 24-hour heartburn-free days through Week 24 in Study EE-301 and a labeling claim of "relief of heartburn" for the indication of maintenance of healed EE for Voquezna.

Background

In the NDA submission, the Applicant based the NI margin of -15% for the secondary endpoint of percentage of 24-hour heartburn-free days through Week 24 at the end of the maintenance phase in Study EE-301 on a publication by (Metz et al. 2009) describing the results of a dexlansoprazole study (Study T-EE05-135) conducted by Takeda that supported approval of Dexilant for relief of heartburn in maintenance of healed EE. Study T-EE05-135 was a randomized, double-blind study that evaluated placebo, dexlansoprazole 30 mg once daily, and dexlansoprazole 60 mg once daily for the endpoint of percentage of 24-hour heartburn-free days through Week 24 in subjects with healed EE. In the 74-day letter sent on May 24, 2022, the Agency requested further information from Study T-EE05-135 that were not provided in the Metz publication to support the NI margin in Study EE-301. Although it may be reasonable to rely on data from dexlansoprazole to support the NI margin, the NDA submission did not include a rationale to bridge the results for dexlansoprazole 30 mg once daily to lansoprazole 15 mg once daily through Week 24. In the 74-day letter sent on May 24, 2022, the Agency advised the Applicant to submit data to support that lansoprazole would be expected to have a similar magnitude of effect as dexlansoprazole for the endpoint of percentage of 24-hour heartburn-free days through Week 24. On June 14, 2022, the Applicant submitted their response.

Assessment

The Applicant's submission contained information from Study T-EE05-135 that was not reported in the Metz et al publication or the approved labeling for Dexilant.

The Applicant submitted results from Study T-EE05-135 found in the publicly available FDA medical review of Dexilant (NDA 022287) for the placebo and dexlansoprazole 30 mg once daily treatment groups. Additional information on dexlansoprazole dosage of 60 mg and 90 mg once daily from the study can also found in the FDA statistical review for NDA 022287.

Study T-EE05-135 used the same twice daily diary with the same 5-point heartburn severity scale (none, mild, moderate, severe, and very severe) used in Study EE-301 to measure heartburn symptoms. The secondary endpoint of percentage of 24-hour heartburn-free days through Week 24 in Study T-EE05-135 was also the same secondary endpoint as in Study EE-301.

The lower bound of the 95% CI of the mean treatment difference between dexlansoprazole 30 mg once daily and placebo for the percentage of 24-hour heartburn-free days through Week 24, verified by the review team, in Study T-EE05-135 was 40.3%. Additionally, the review team calculated the treatment difference and 95% CI for the other dexlansoprazole dosage in Study T-EE05-135 (60 mg once daily) and dexlansoprazole dosages of 60 mg and 90 mg once daily in a similarly designed study (T-EE04-086), also from the FDA statistical review for NDA 022287, as shown in See Table 27.

Table 27. Cross-Study Comparison[a] Mean Percentage of 24-Hour Heartburn-Free Days for Dexlansoprazole 30 mg, 60 mg, and 90 mg Once Daily vs. Placebo in Studies T-EE05-135 and T-EE04-086 in Subjects With Healed Erosive Esophagitis Through Week 24 - MITT Populations

Study Parameter	Dexlansoprazole 30 mg	Dexlansoprazole 60 mg	Dexlansoprazole 90 mg	Placebo
T-EE05-135				
N	132	147		141
Mean (SD), %	83.3 (26.6)	78.4 (28.3)		36 (32.0)
Diff to Placebo (95% CI[1])	47.3 (40.3, 54.3)	42.4 (35.4, 56.6)		
T-EE04-086				
N		157	147	133
Mean (SD), %		79.7 (30.7)	79.2 (30.0)	29.5 (29.3)
Diff to Placebo (95% CI[b])		50.2 (32.2, 57.2)	49.7 (42.7, 56.7)	

Source: Adapted from FDA Statistical Review of NDA 022287 and verified by reviewer compared to Applicant's response to information request submitted on June 14, 2022.
[a] Because clinical trial results are dependent on the subject population and study design, conclusions on the comparative efficacy of each treatment cannot be made by comparing results obtained in one trial to results in another trial
[b] The 2-sided 95% confidence interval of the difference in percentage of 24-hour heartburn-free days between dexlansoprazole and placebo was calculated via the Wald method.
Abbreviations: CI, confidence interval; Diff, difference; MITT, modified intent-to-treat; N, number of subjects in treatment arm; SD, standard deviation

Studies T-EE05-135 and T-EE04-086 were similar in design to the maintenance phase of Study EE-301. The Los Angeles grading scale was used to assess EE severity (Grade A through D) in Studies T-EE05-135 and T-EE04-086 and Study EE-301. In Studies T-EE05-135 and T-EE04-086, about 70% of subjects were enrolled with baseline EE, Grade A or B, and 30% of subjects were enrolled with baseline Grade C or D, which was similar to the subject population in EE-301 (66% and 34%, respectively). In addition, Studies T-EE05-135 and T-EE04-086 used the same twice daily subject diary with a 5-point severity scale (none, mild, moderate, severe, very severe) to collect daytime and nighttime heartburn symptoms that was used in EE-301.

In support of using the dexlansoprazole treatment effect of relief of heartburn to estimate the lansoprazole treatment effect to justify the NI margin in Study EE-301, the Applicant noted the following information:

- There is a lack of dose-response for dexlansoprazole 30 mg, 60 mg and 90 mg once daily compared to placebo for the endpoint of percentage of 24-hour heartburn-free days through Week 24. (Studies T-EE-305-135 and T-EE04-086)

- The effect of lansoprazole 30 mg, dexlansoprazole 60 mg and dexlansoprazole 90 mg once daily were directly compared to placebo in a publication of two placebo-controlled studies through Week 8 in subjects with EE ((Sharma et al. 2009)). These studies used the same twice daily diary with the same 5-point scale as utilized in Study EE-301 to assess heartburn symptoms. Of note, lansoprazole 30 mg once daily had a slightly lower efficacy results compared to both doses of dexlansoprazole as shown in Table 28. Because symptom severity does not generally correlate with the severity of erosions ((Isshi et al. 2021)), it may be reasonable to use heartburn data obtained through Week 8 (end of the healing phase) to inform the assessment of heartburn through Week 24 (end of the maintenance phase).

Table 28. Median Percentage of 24-Hour Heartburn-Free Days for Dexlansoprazole 30 mg, and 60 mg Once Daily vs. Lansoprazole 30 mg in Sharma et al Study 1 and Study 2 in Subjects With Erosive Esophagitis through Week 8

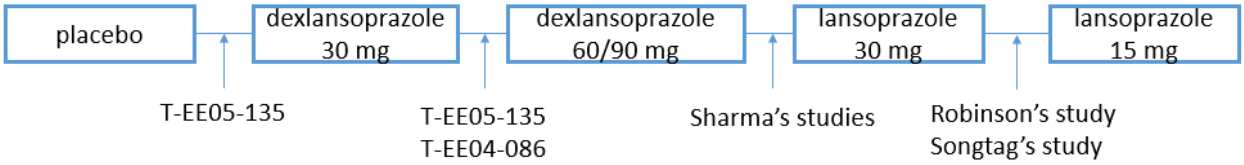
Study	Parameter	Dexlansoprazole 30 mg	Dexlansoprazole 60 mg	Lansoprazole 30 mg
Sharma et al Study 1	Median Percentage of 24-Hour Heartburn-Free Days	82.1	84.2	80.0
Sharma et al Study 2	Median Percentage of 24-Hour Heartburn-Free Days	83.0	80.8	78.3

Source: Reviewer generated table based on (Sharma et al. 2009) publication in the Applicant's response to information request submitted on June 14, 2022.

- Although not direct evidence, lansoprazole 15 mg and 30 mg once daily did not show a dose response at 6 months for relief of heartburn symptoms in two published placebo-controlled studies. Both doses were superior to placebo ((Robinson et al. 1996; Sontag et al. 1996)). These studies used an endpoint that was assessed differently from the 24-hour heartburn-free endpoint in Study EE-301 and the other studies discussed above, and cannot be used to justify the NI margin, but provides supportive evidence of a treatment effect of lansoprazole during the maintenance phase. At 6 months, in both studies, there was no difference between the two lansoprazole doses, and both were superior to placebo (data not shown).

Overall, there are no direct data to support the treatment effect of lansoprazole 15 mg once daily compared to placebo for the endpoint of percentage of 24-hour heartburn-free days during the maintenance phase. The lack of direct evidence of the treatment effect of lansoprazole 15 mg once daily compared to placebo for the endpoint of percentage of 24-hour heartburn-free days through Week 24 could introduce additional uncertainties in the estimate of the treatment effect during maintenance (See Figure 6).

Figure 6. Diagram of the Evidence Submitted by the Applicant to Support the NI Margin for the Endpoint of 24-Hour Heartburn-Free Days Over the Maintenance Phase (Statistical Reviewer's Interpretation)



Source: Reviewer generated figure.
Abbreviations: NI: non-inferiority.

Therefore, to provide additional support for the Applicant's position, the statistical review team compared the dose response of various doses of dexlansoprazole for the endpoint of percentage of 24-hour heartburn-free days in healing (through Week 8) and maintenance phases (through Week 24) across studies as shown in Table 29. The median results for dexlansoprazole 60 mg across studies indicate the efficacy is slightly better in the maintenance phase than in the healing phase.

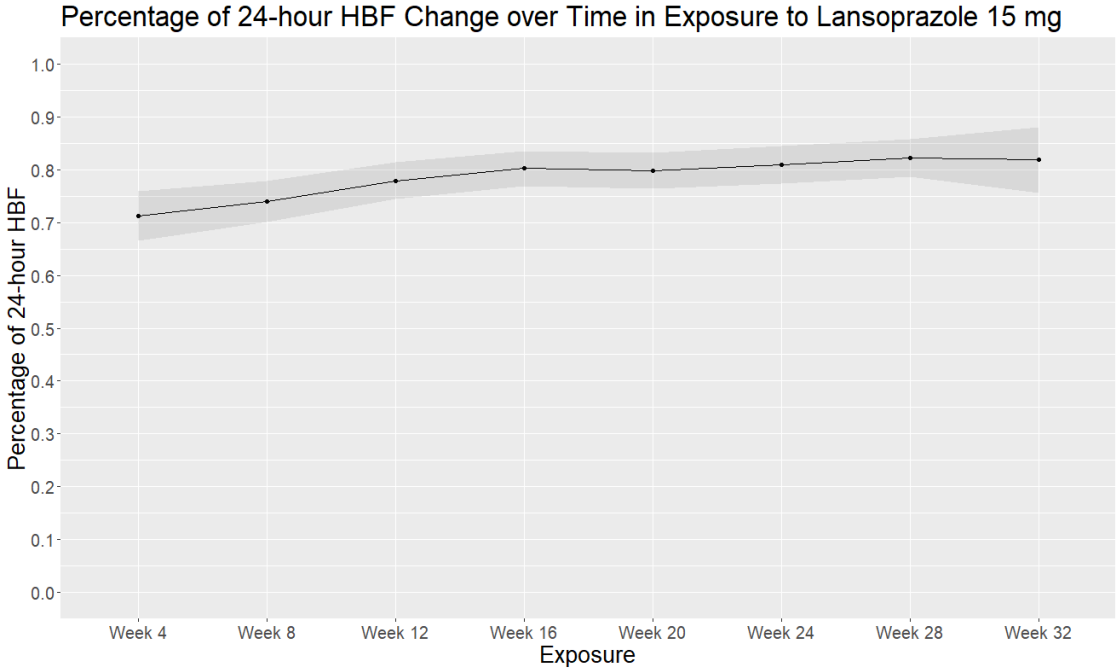
Table 29. Cross-Study Comparison[a] of Mean and Median Percentage of 24-Hour Heartburn-Free Days for Dexlansoprazole 30 mg, and 60 mg, and 90 mg Once Daily in Studies of Erosive Esophagitis

Study	Phase	Percentage of 24-Hour Heartburn-Free Days, %	Dexlansoprazole 30 mg	Dexlansoprazole 60 mg	Dexlansoprazole 90 mg
Sharma Study 1[b]	Healing	Median		82.1	84.2
Sharma Study 2[b]	Healing	Median		83.0	80.8
T-EE04-086[c]	Maintenance	Median		95.8	94.4
		Mean		79.7	79.2
T-EE05-135[c]	Maintenance	Median	96.1	90.9	
		Mean	83.3	78.4	

Source: Reviewer generated table based on Applicant's response to information request submitted on June 14, 2022. Adapted From (Sharma et al. 2009) and FDA Statistical Review of NDA 022287
[a] because clinical trial results are dependent on the subject population and study design, conclusions on the comparative efficacy of each treatment cannot be made by comparing results obtained in one trial to results in another trial
[b] data from (Sharma et al. 2009); study not reviewed by FDA
[c] data from NDA 022287, as found in the FDA statistical review

In addition, using the lansoprazole data in Study EE-301 the statistical review team explored the change over time in the mean percentage of 24-hour heartburn-free days with exposure to lansoprazole 15 mg once daily in Study EE-301 over the healing (lansoprazole 30 mg once daily for 2 to 8 weeks) and maintenance phases (lansoprazole 15 mg once daily for 24 weeks) combined. As shown in Figure 7, the effect of lansoprazole seen in the healing phase is maintained in the maintenance phase and provides further support for the Applicant's position that the treatment effect of lansoprazole 30 mg once daily reported through Week 8 in the healing phase in the literature is similar to the effect expected with lansoprazole 15 mg once daily through Week 24 in the maintenance phase.

Figure 7. Percentage of 24-Hour Heartburn-Free Days Change Over Time in Exposure to Lansoprazole 15 mg Once Daily in Study EE-301 (Statistical Reviewer's Post-Hoc Analysis; NDA 215151)



Source: Reviewer's analysis based on Applicant submitted data adds.xpt for Study EE-301 in NDA 215151.
Abbreviation: HBF, heartburn-free; NDA, new drug application

Finally, in a cross-study comparison of the results for the endpoint of percentage of 24-hour heartburn-free days for the lansoprazole 15 mg once daily arm in the maintenance phase of Study EE-301 and dexlansoprazole 30 mg once daily in the maintenance phase of Study T-EE05-135, lansoprazole 15 mg once daily had a numerically similar (but slightly smaller) percentage of 24-hour heartburn-free days to dexlansoprazole 30 mg once daily (see Table 30).

Table 30. Cross-Study Comparison[a] of Mean and Median Percentage of 24-Hour Heartburn-Free Days for Lansoprazole 15 mg Once Daily in Study EE-301 (NDA 215151) and Dexlansoprazole 30 mg Once Daily in Study T-EE05-135 (NDA 022287)

		Percentage of 24-Hour Heartburn-Free Days Over the Maintenance Phase	
Study	**Treatment**	**Mean**	**Median**
EE-301	Lansoprazole 15 mg	78.6	89.3
T-EE05-135[b]	Dexlansoprazole 30 mg	83.3	96.1

Source: Reviewer generated table based on Applicant's submitted data adds.xpt and Applicant's response to information request submitted on June 14, 2022.
[a] Because clinical trial results are dependent on the subject population and study design, conclusions on the comparative efficacy of each treatment cannot be made by comparing results obtained in one trial to results in another trial
[c] data from NDA 022287, as found in the FDA statistical review
Abbreviations: NDA, new drug application

Conclusion

A NI margin of -15% for the secondary endpoint of percentage of 24-hour heartburn-free days during the maintenance phase in Study EE-301 is supported indirectly by the treatment effect of dexlansoprazole 30 mg once daily from placebo-controlled trials of dexlansoprazole and additional supportive information from studies of lansoprazole for the relief of heartburn in

healing and maintenance studies. Other available data support a similar treatment effect of lansoprazole and dexlansoprazole for the endpoint of percentage of 24-hour heartburn-free days in healing and maintenance of healed EE.

As discussed in Section 6.2.3.4, the lower bound of the 95% confidence interval of the treatment difference for Voquezna 10 mg once daily compared to lansoprazole 15 mg once daily for the percentage of 24-hour heartburn-free days in the Maintenance phase of Study EE-301 was -2.3%, which would still demonstrate NI at a much more conservative margin than the Applicant's proposed -15% NI margin. Given the uncertainty of the treatment effect of lansoprazole 15 mg compared to placebo during maintenance of healed EE (Week 24) and the possibility that lansoprazole 15 mg once daily may not be as effective as dexlansoprazole 30 mg once daily, a more conservative NI margin (i.e., -5%) is recommended than the -15% NI margin proposed by the Applicant. A more conservative margin would provide assurance that Voquezna has a clinically acceptable effect compared to compared to lansoprazole and other approved PPIs, which are accepted as standard of care for maintenance of healed EE and highly effective. The lower bounds for the 95% CIs of the treatment difference between dexlansoprazole and placebo all exceeded 30%. Even conservatively assuming the treatment effect for lansoprazole is 15% (less than half of the lower bounds for the effect of dexlansoprazole), a -5% margin would still guarantee that at least 66% of the treatment effect of lansoprazole was preserved.

In conclusion, an NI margin for the secondary endpoint of percentage of 24-hour heartburn-free days through Week 24 in Study EE-301 can be justified and the results support a "relief of heartburn" claim in the label for the indication of maintenance of healed EE for Voquezna.

6.3.5. Impact of a Single Site (Site ID: 10010) on Superiority of Voquezna 10 mg Once Daily Over Lansoprazole 15 mg Once Daily for the Endpoints of Maintenance of Healed EE for All Grades (Primary Endpoint) and Grades C or D (Secondary Endpoint) in Study EE-301

Issue

For the primary endpoint of maintenance of healed EE (all grades) through Week 24 in the maintenance phase of Study EE-301, the results demonstrate noninferiority of both Voquezna 10 mg QD and 20 mg QD compared to lansoprazole. Furthermore, as part of the pre-specified multiple testing procedure, the Applicant tested the endpoint of maintenance of healed EE for superiority and was able to demonstrate superiority for Voquezna 10 mg QD compared to lansoprazole 15 mg QD for both the primary endpoint and the multiplicity-controlled secondary endpoint of maintenance of healed EE in LA Grades C or D as summarized in Table 16 and Table 17. Removal of a single study site (i.e., Site 10010; Dr. Kopp located in the United States (Anderson, SC)) alters the statistical conclusion of superiority of Voquezna over lansoprazole in both analyses.

The review team performed analyses to investigate the robustness of the superiority claim for these endpoints to determine whether labeling claims can be supported based on these data.

Background

Site 10010 is a site in the United States that enrolled 35 subjects in the healing phase. Thirty-one (31) out of 35 subjects had documentation on endoscopy of complete healing of EE at Week 2 or Week 8 and entered the maintenance phase, with 10 subjects (5 with EE of LA Grades C or D at baseline) re-randomized into the Voquezna 10 mg once daily (QD) group, 11 (4 with EE of LA Grades C or D at baseline) into the Voquezna 20 mg QD group, and 10 (5 with EE of LA Grades C or D at baseline) into the lansoprazole 15 mg QD group. The exclusion of Site 10010 from the analysis affected the statistical conclusions of superiority for Voquezna 10 mg QD compared to lansoprazole 15 mg QD for maintenance of healed EE in both the overall population and in the subgroup of subjects with baseline EE of LA Grades C or D; however, the superiority for Voquezna 20 mg QD compared to lansoprazole 15 mg QD for this endpoint was not impacted by the removal of the site from the analysis. The rate of maintenance of healed EE (all grades) through Week 24 for site 10010 was 100% for Voquezna 10 mg QD, and 40% for lansoprazole 15 mg QD, respectively. The rates of maintenance of healed EE from this site were more favorable for Voquezna 10 mg QD compared to the rates in the overall study, leading to a non-significant treatment difference (i.e., lack of superiority) for Voquezna 10 mg QD compared lansoprazole 15 mg QD for maintenance of healed EE (all grades) through Week 24 when Site 10010 is excluded from the analysis. Furthermore, the rates of maintenance of healed EE for LA Grades C or D at site 10010 was 100% for Voquezna 10 mg QD, and 40% for lansoprazole 15 mg QD. Removal of site 10010 changes the statistical conclusion of superiority of Voquezna 10 mg QD over lansoprazole 15 mg QD for maintenance of healed EE for LA Grades C or D.

The review team performed several different types of sensitivity analyses for both the primary and secondary endpoints as described below:

Assessment of Primary Endpoint

Reviewer's Non-Responder Imputation for COVID-19

The endpoint of the rate of maintenance of healed EE (all grades) through Week 24 was assessed based on a Farrington Manning test with non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C). The estimates from multiple imputation were pooled using Rubin's Method. The review team performed a sensitivity analysis based on a non-responder imputation incorporating no special data handling due to COVID-19 (NRI-NC). The analysis results on this endpoint with site 10010 removed are shown in Table 31. The nominal p-value for the treatment difference in the rate of maintenance of healed EE (all grades) through Week 24 between Voquezna 10 mg QD and Lansoprazole 15 mg QD was greater than 0.05 (p-value=0.0706) if NRI-C is performed, while the p-value of superiority is less than 0.05 (p-value=0.0419) when NRI-NC is performed, regardless of the reasons for missing data.

The review team identified six subjects with missing data due to COVID-19 in the maintenance phase. Three of six subjects received lansoprazole 15 mg QD, while the other three received Voquezna 20 mg QD. None of these subjects were treated with Voquezna 10 mg QD. Therefore, the rate of maintenance of healed EE for Voquezna 10 mg QD (78.5%) remains the same for both missing data handling methods. However, the rates of maintenance of healed EE (all grades) for lansoprazole 15 mg QD change from 73.1% for NRI-C to 72.2% for NRI-NC,

respectively. This less than 1% difference in the rates of maintenance of healed EE for the lansoprazole arm using the two different methods changed the statistical significance of the endpoint from superiority to non-significance when site 10010 was excluded.

On October 28, 2022, the review team sent an information request to the Applicant regarding the reasons for missing data for the six subjects impacted by COVID-19. On November 8, 2022, the Applicant submitted a response stating that 2 subjects who received lansoprazole 15 mg QD in the maintenance phase missed the visits at Week 16 and 20 because of site staff unavailability due to COVID-19 and the endoscopy pictures taken at Week 24 were not adequate/readable and could not be sent for adjudication. The review team performed a sensitivity analysis where these two subjects were imputed as non-responders while multiple imputation was applied to handle missing data for other subjects impacted by COVID-19 (NRI-C2).

The review team conducted a tipping point analysis for the overall MITT population to explore the robustness of the overall results. The tipping point analysis showed that if 5 subjects out of 32 (16%) with missing data in the lansoprazole 15 mg QD group switched from imputed non-responder to imputed responder, the p-value will be greater than 0.05, indicating some degree of robustness in the analysis result for the overall population.

Table 31. Analysis Results for Voquezna 10 mg QD Versus Lansoprazole 30 mg QD With Site 10010 Removed: Maintenance of EE Healing Through Week 24, Study EE-301, Maintenance Phase, MITT

Analysis Parameter	Voquezna 10 mg QD (N=283)	Lansoprazole 15 mg QD (N=284)
NRI-C[1] (MITT)		
n (%)[2]	222 (78.4)	208 (73.1)
Treatment difference, % (CI[3])	5.3 (-1.76, 12.33)	
P-value of superiority[4]	0.0706	
NRI-NC[5] (MITT)		
n (%)	222 (78.4)	205 (72.2)
Treatment difference, % (CI[1])	6.3 (-0.85, 13.34)	
P-value of superiority[4]	0.0419	
NRI-C2 (MITT)		
n (%)[2]	222 (78.4)	206 (72.5)
Treatment difference, % (CI[3])	5.9 (-1.15, 12.99)	
P-value of superiority[4]	0.0504	

Source: Reviewer's analysis based on Applicant submitted data adeffipm.xpt, and adeff.xpt.
[1] Multiple imputation was performed to handle missing data due to reasons related with COVID-19. Non-responder imputation was used to handle all missing data that were unrelated to COVID-19. The estimates from multiple imputation were pooled using Rubin's Method.
[2] n represents the average number of subjects who maintained complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated maintenance of EE healing rate based on multiple imputation model.
[3] The 2-sided 95% CI of the difference in maintenance rates between Voquezna 10 mg once daily group and lansoprazole 30 mg once daily group was calculated via the Miettinen and Nurminen method.
[4] Superiority of Voquezna 10 mg QD group to lansoprazole 30 mg QD group p-value based on a Farrington and Manning test.
[5] Non-responder imputation was performed to handle all missing data regardless of the reasons for missing.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRI-NC, non-responder imputation incorporating no special data handling due to COVID-19; QD, once daily

Applicant's Pre-Specified Sensitivity Analyses

In the SAP for Study EE-301, the Applicant pre-specified several sensitivity analyses for the primary endpoint of maintenance of healed EE (all grades) through Week 24 (see Section 6.2 for the description of the sensitivity analyses Section 16.2 for the results of the analyses for the

overall population). The review team performed the same analyses with Site 10010 removed (see Table 32). The nominal p-values of superiority for these sensitivity analyses are all less than 0.05.

Table 32. Sensitivity Analyses Pre-Specified by the Applicant for Voquezna 10 mg QD vs. Lansoprazole 30 mg QD With Site 10010 Removed: Maintenance of EE Healing Through Week 24, Study EE-301, Maintenance Phase

Analysis Parameter	Voquezna 10 mg QD (N=283)	Lansoprazole 15 mg QD (N=284)
Observed data at Week 24 (MITT)		
n (%)	(N=255) 222 (87.1)	(N=254) 205 (80.7)
Treatment difference, % (CI[1])	6.4 (0, 12.81)	
P-value of superiority[2]	0.0257	
Multiple imputation method 1[3] (MITT)		
n (%)[4]	246 (87.1)	228 (80.4)
Treatment difference, % (CI[1])	6.7 (0.67, 12.86)	
P-value of superiority[2]	0.0214	
Multiple imputation method 2[5] (MITT)		
n (%)[4]	245 (86.4)	218 (76.7)
Treatment difference, % (CI[1])	9.8 (3.40, 16.14)	
P-value of superiority[2]	0.0022	
Multiple imputation method 3[6] (MITT)		
n (%)[4]	249 (88.0)	229 (80.6)
Treatment difference, % (CI[1])	7.5 (1.50, 13.50)	
P-value of superiority[2]	0.0119	
Per Protocol Set		
n (%)	(N=249) 221 (88.8)	(N=243) 196 (80.7)
Treatment difference, % (CI[1])	8.1 (1.76, 14.55)	
P-value of superiority[2]	0.0062	

Source: Reviewer's analysis based on Applicant submitted data adeff.xpt, adeffi4.xpt, adeffi5.xpt, and adeffi6.xpt.
[1] The 2-sided 95% CI of the difference in maintenance rates between Voquezna 10 mg once daily group and lansoprazole 30 mg once daily group was calculated via the Miettinen and Nurminen method.
[2] Superiority of Voquezna 10 mg once daily group to lansoprazole 30 mg once daily group p-value based on a Farrington and Manning test.
[3] Multiple imputation was performed for subjects without post-baseline endoscopy under missing at random assumption. The MCMC method was first used to produce a monotone missing data pattern, and then a subsequent imputation using logistic regression with treatment effect and LA Classification grade at screening as predictor variables was used for imputation of remaining missing data at Week 24. The estimates from multiple imputation were pooled using Rubin's Method.
[4] n represents the average number of subjects who maintained complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated maintenance of EE healing rate based on multiple imputation model.
[5] Multiple imputation was performed as described above in (3). After imputations, subjects who did not maintain healing through Week 24, had treatment compliance <80% or >120%, or had any PPI or H2RA use were considered as EE recurred. The estimates from multiple imputation were pooled using Rubin's Method.
[6] Post-baseline endoscopy assessments for subjects who had treatment compliance <80% or >120%, or at time point after any proton pump inhibitor (PPI) or histamine-2 receptor antagonist (H_2RA) use were excluded. After excluding such data, multiple imputation was performed as described above in (3). The estimates from multiple imputation were pooled using Rubin's Method.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; NRI, non-responder imputation; QD, once daily

Reviewer's Non-Responder Imputation for Prohibited Medications

In the primary estimand, data after use of prohibited medication were collected, corresponding to the treatment policy strategy. Use of prohibited medication could influence the maintenance of healed EE, so the review team performed a sensitivity analysis with Site 10010 removed to assess the effect of the intercurrent event of prohibited medication. In the analysis, subjects who used prohibited medication during the maintenance phase were treated as non-responders. Eleven

subjects used prohibited medication during the maintenance phase, four receiving Voquezna 10 mg QD, five receiving Voquezna 20 mg QD, and two receiving lansoprazole 15 mg QD. The nominal p-value of superiority of Voquezna 10 mg QD over lansoprazole 15 mg QD for this analysis is 0.0716 with a treatment difference of 5.3 and was similar to the analysis based on NRI-C, indicating use of prohibited medication had little impact on the evaluation of maintenance of healed EE.

Reviewer's Analysis for Site 10010 Based on Site Inspection Results

The review team performed additional analyses based on the results of an inspection for Site 10010, identified as a high enrolling site in Study EE-301. See Section 10 Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure. The Inspector noted that source records documenting who performed the endoscopy and the local endoscopy assessments were not available for 87% (90 of 103) of endoscopies performed in the 35 randomized subjects at this site. Dr. Kopp, the principal investigator at this site who does not have formal specialized training in gastroenterology, independently reviewed the endoscopy photos, and submitted his assessment to the clinical database rather than the assessments made by a sub-investigator at this site with formal specialized training in gastroenterology who performed the endoscopies. Therefore, the assessment performed by the central reader was compared to Dr. Kopp's assessment and was included as the final reading used in the data line listings if the two readings aligned. If the two readings did not align, a second central reader adjudicated the results, and that result was used for the data line listing.

During the inspection, the investigator did not locate source records for the sub-investigator's assessment. Response to information request from the Office of Scientific Investigations (OSI) sent October 18, 2022, was received from the Applicant on October 26, 2022, and contained certified copies of the local endoscopy source records that documented the local assessments performed by the sub-investigator.

OSI identified 14 discrepancies among 103 endoscopy assessments at various timepoints in the study (Weeks 2, 8 and 24) among the 35 subjects enrolled at this site when comparing the certified copies of the endoscopy source records with the Applicant's data line listings submitted to the NDA. At noted above, this site enrolled 35 subjects in the healing phase.

Of the 14 discrepancies, two in the lansoprazole 15 mg QD group had an impact on the analysis of the primary endpoint of maintenance of healed EE (all grades) through Week 24 for Voquezna 10 mg QD versus lansoprazole 15 mg QD. In one subject, an endoscopy at Week 24 was adjudicated centrally as EE of LA Grade C (Dr. Kopp reported as Grade A) while the local read by the sub-investigator was healed ([redacted] (b) (6)). Therefore, in the sensitivity analysis, the data for that endoscopy was replaced with "not recurred". Another subject ([redacted] (b) (6)) had discrepancies in the endoscopy assessments at multiple timepoints between the sub-investigator, Dr. Kopp, and the central reader. Central adjudication was not implemented but needed for Weeks 8 and 24 based on the sub-investigator's reading based on the process outlined in the protocol. Thus, that subject was removed by the review team from the sensitivity analysis of the primary endpoint of maintenance of healed EE (all grades). The results of the sensitivity analysis demonstrated a nominal p-value of superiority for Voquezna 10 mg QD over lansoprazole 15 mg QD, 0.0315 with a treatment difference of 6.6, indicating use of local endoscopy readings versus central readings for site 10010 in the overall analysis of the primary endpoint does not change the statistical conclusion.

Additional Information from Confirmatory Trials

The Applicant submitted data from two phase 3 trials conducted outside of the United States as supportive evidence for maintenance of healed EE. The two trials (TAK-438/CCT-003 and TAK-438_305) were similar to Study EE-301 in terms of overall design, subject population, study drug doses, and treatment duration. Both non-U.S. studies demonstrated superiority of vonoprazan 10 mg QD over lansoprazole 15 mg QD for the endpoint of maintenance of healed EE (see Section 6.2.4).

Assessment of Secondary Endpoint

Reviewer's Non-Responder Imputation for COVID-19

The endpoint of the rate of maintenance of healed EE through Week 24 for subjects with EE of Grade C or D at baseline was assessed based on a Farrington Manning test with non-responder imputation incorporating no special data handling due to COVID-19 (NRI-NC). The review team performed a sensitivity analysis based on a non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C). Although the review team identified six subjects with missing data due to COVID-19 in the maintenance phase, these subjects all had EE of Grade A or B at baseline. Therefore, analysis results based on NRI-C and NRI-NC are the same. The results for NRI-NC results for this endpoint with site 10010 removed are shown in Table 33. The p-value of superiority was 0.0616, which is slightly greater than 0.05. The rate of maintenance of healed EE for subjects with EE of Grade C or D at baseline for Voquezna 10 mg QD was numerically greater compared to lansoprazole 15 mg QD (73.3% versus 62.6%).

Table 33. Analysis Results for Voquezna 10 mg QD vs. Lansoprazole 15 mg QD With Site 10010 Removed: Maintenance of EE Healing Through Week 24 for Subjects with EE of Grade C or D at Baseline, Study EE-301, Maintenance Phase, MITT

Analysis Parameter	Voquezna 10 mg QD (N=90)	Lansoprazole 15 mg QD (N=91)
NRI-NC[1] (MITT)		
n (%)	66 (73.3)	57 (62.6)
Treatment difference, % (CI[2])	10.7 (-2.95, 24.00)	
P-value of superiority[3]	0.0616	

Source: Reviewer's analysis based on Applicant submitted data adeffipm.xpt, and adeff.xpt.
[1] Non-responder imputation was performed to handle all missing data regardless of the reasons for missing.
[2] The 2-sided 95% CI of the difference in maintenance rates between Voquezna 10 mg QD group and lansoprazole 15 mg QD group was calculated via the Miettinen and Nurminen method.
[3] Superiority of Voquezna 10 mg QD group to lansoprazole 15 mg QD group p-value based on a Farrington and Manning test.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; NRI-C, non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19; NRI-NC, non-responder imputation incorporating no special data handling due to COVID-19; QD, once daily

Applicant's Pre-Specified Sensitivity Analyses

In the SAP for Study EE-301, the Applicant pre-specified several sensitivity analyses for the endpoint of maintenance of healed EE through Week 24 (see Section 6.2 for the description of the sensitivity analyses Section 16.2 for the results of the analyses for the overall population). The review team performed the same analyses with site 10010 removed for subjects with EE of Grade C or D at baseline (see Table 34). Most analyses did not demonstrate statistical

significance, which may have been attributed to the small sample size when site 10010 is removed.

Table 34. Sensitivity Analysis Results for Voquezna 10 mg QD vs. Lansoprazole 15 mg QD With Site 10010 Removed: Maintenance of EE Healing Through Week 24 for Subjects with EE of Grade C or D at Baseline, Study EE-301, Maintenance Phase

Analysis Parameter	Voquezna 10 mg QD (N=90)	Lansoprazole 15 mg QD (N=91)
Observed data through Week 24 (MITT)		
n (%)	(N=82) 66 (80.5)	(N=77) 57 (74.0)
Treatment difference, % (CI[1])	6.5 (-6.65, 19.64)	
P-value of superiority[2]	0.1653	
Multiple imputation method 1[3] (MITT)		
n (%)[4]	72 (80.4)	67 (73.2)
Treatment difference, % (CI[1])	7.2 (-5.15, 19.48)	
P-value of superiority[2]	0.1466	
Multiple imputation method 2[5] (MITT)		
n (%)[4]	72 (80.4)	62 (68.2)
Treatment difference, % (CI[1])	12.2 (-0.51, 24.73)	
P-value of superiority[2]	0.0403	
Multiple imputation method 3[6] (MITT)		
n (%)[4]	74 (81.7)	66 (72.6)
Treatment difference, % (CI[1])	9.0 (-3.25, 21.20)	
P-value of superiority[2]	0.0901	
Per Protocol Set		
n (%)	(N=80) 66 (82.5)	(N=73) 53 (72.6)
Treatment difference, % (CI[1])	9.9 (-3.37, 23.27)	
P-value of superiority[2]	0.0707	

Source: Reviewer's analysis based on Applicant submitted data adeff.xpt, adeffi4.xpt, adeffi5.xpt, and adeffi6.xpt.
[1] The 2-sided 95% CI of the difference in maintenance rates between Voquezna 10 mg QD group and lansoprazole 15 mg QD group was calculated via the Miettinen and Nurminen method.
[2] Superiority of Voquezna 10 mg QD group to lansoprazole 15 mg QD group p-value based on a Farrington and Manning test.
[3] Multiple imputation was performed for subjects without post-baseline endoscopy under missing at random assumption. The MCMC method was first used to produce a monotone missing data pattern, and then a subsequent imputation using logistic regression with treatment effect and LA Classification grade at screening as predictor variables was used for imputation of remaining missing data at Week 24. The estimates from multiple imputation were pooled using Rubin's Method.
[4] n represents the average number of subjects who maintained complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated maintenance of EE healing rate based on multiple imputation model.
[5] Multiple imputations were performed as described above in (3). After imputations, subjects who did not maintain healing through Week 24, had treatment compliance <80% or >120%, or had any PPI or H2RA use were considered as EE recurred. The estimates from multiple imputation were pooled using Rubin's Method.
[6] Post-baseline endoscopy assessments for subjects who had treatment compliance <80% or >120%, or at time point after any PPI or H2RA use were excluded. After excluding such data, multiple imputation was performed as described above in (3). The estimates from multiple imputation were pooled using Rubin's Method.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; NRI, non-responder imputation; QD, once daily

To assess whether the non-significant result with site 10010 removed for subjects with EE of Grade C or D at baseline was due to the reduced sample size or due to a large treatment effect at the site, the review team performed a post-hoc analysis replacing the data for site 10010 with 4 outcomes of EE not recurred and 1 outcome of EE recurred for the Voquezna 10 mg QD group and 3 outcomes of EE not recurred and 2 outcomes of EE recurred for lansoprazole 15 mg QD group. The analysis using hypothetical data for Site 10010 was based on the most likely outcome given the overall rate of maintenance of healed EE for subjects with EE of Grade C or D at baseline by treatment arm (74.7% for Voquezna 10 mg QD versus 61.5% for lansoprazole 15 mg

QD). Analysis based on NRI-NC showed a treatment difference of 11.2% with a p-value of superiority of 0.0487, indicating that the reduced sample size among the subgroup of subjects with EE of Grade C or D at baseline may be a contributing factor to the change in statistical significance for this endpoint when Site 10010 is removed.

Additional Information from Confirmatory Trials

The review team performed post-hoc analysis on the data from two phase 3 trials conducted outside of the United States submitted by the Applicant as supportive evidence of maintenance of healed EE. The two trials (TAK-438/CCT-003 and TAK-438_305) were similar to Study EE-301 in terms of overall design, subject population, study drug doses, and treatment duration (see Section 6.2.4). The post-hoc analysis results are shown in Table 35. In both post-hoc analyses, the rate of maintenance of healed EE for subjects with EE of Grade C or D at baseline for vonoprazan 10 mg QD was numerically greater compared to lansoprazole 15 mg QD (82.5% versus 61.0% for TAK-438/CCT-003 and 65.1% versus 50.0% for TAK-438_305). Only results for Study TAK-438/CCT-003 showed a nominal p-value of superiority less than 0.05. However, testing of superiority could be underpowered given the small sample size for this subgroup. Based on the magnitude of the treatment difference, there is evidence to support that vonoprazan 10 mg QD is superior to lansoprazole 15 mg QD with respect to maintenance of healed EE through Week 24 for subjects with EE of Grade C or D at baseline.

Table 35. Analysis Results for Vonoprazan 10 mg QD vs. Lansoprazole 15 mg QD: Maintenance of EE Healing Through Week 24 for Subjects with EE of Grade C or D at Baseline, Study TAK-438/CCT-003 and Study TAK-438_305, Maintenance Phase, MITT

Study Parameter	Vonoprazan 10 mg QD	Lansoprazole 15 mg QD
TAK-438/CCT-003		
n (%)	(N=40) 33 (82.5)	(N=41) 25 (61.0)
Treatment difference, % (CI[1])	21.5 (1.81, 39.94)	
P-value of superiority[2]	0.0159	
TAK-438_305		
n (%)	(N=43) 28 (65.1)	(N=42) 21 (50.0)
Treatment difference, % (CI[1])	15.1 (-5.99, 34.98)	
P-value of superiority[2]	0.0792	

Source: Adapted from Maintenance ISE ad hoc Table 2.3.1 and 2.4.1, verified by the review team.
[1] The 2-sided 95% CI of the difference in maintenance rates between Voquezna 10 mg once daily group and lansoprazole 15 mg once daily group was calculated via the Miettinen and Nurminen method.
[2] Superiority of Voquezna 10 mg QD group to lansoprazole 15 mg QD group p-value based on a Farrington and Manning test.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; QD, once daily

Reviewer's Analysis Replacing Data for Site 10010 Based on Site Inspection Results

See discussion above of the OSI findings at site 10010. Of the 14 discrepancies identified by OSI at this site, three had an impact on the analysis of the endpoint of maintenance of healed EE for subjects with EE of Grade C or D at baseline. Two of the subjects are discussed above ((b) (6)). The third subject's ((b) (6)) endoscopy at Week 24 was read as EE of LA Grade B at baseline by the sub-investigator, LA Grade C by Dr. Kopp, and LA Grade C by the central reader. No central adjudication was implemented but needed based on the sub-investigator's read based on the process outlined in the protocol. Thus, this subject was removed

by the review team from the sensitivity analysis for the secondary endpoint of maintenance of healed EE for Grade C or D. The results of the sensitivity analysis demonstrated a nominal p-value of superiority of Voquezna 10 mg QD over lansoprazole 15 mg QD, 0.0467 with a treatment difference of 11.3, indicating use of local endoscopy readings versus central readings for site 10010 in the overall analysis of the secondary endpoint does not change the statistical conclusion.

Conclusion

Superiority of Voquezna 10 mg QD over lansoprazole 15 mg QD for the endpoint of maintenance of healed EE for all grades (primary endpoint) and Grade C or D (secondary endpoint) has been demonstrated in Study EE-301. The statistical robustness of these results is supported by the results on similar endpoints in the phase 3 trials conducted outside of the United States.

In addition, the review team evaluated the impact of site 10010 on the results, given the discrepancies noted by OSI during their inspection. Although removing site 10010 changed the results for the primary endpoint from superiority to non-significance, various sensitivity analyses showed little impact on the treatment difference of Voquezna 10 mg QD versus lansoprazole 15 mg QD when site 10010 was removed. For the secondary endpoint, although several sensitivity analyses did not demonstrate statistical significance when site 10010 was removed, the reduced sample size may be a contributing factor to the change in statistical significance. Other sensitivity analyses using the local endoscopy reading instead of the central reading for several subjects treated with lansoprazole with discrepant results between readers showed the results for the primary and secondary endpoints were robust even when the local reading was used for the analyses.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of vonoprazan (TAK-438) and its metabolites has been studied extensively and reviewed under NDAs 215152 and 215153 for the treatment of *Helicobacter pylori* infection in adults. In the current NDA, no additional nonclinical studies have been provided.

The following is a summary of the data previously reviewed by the FDA Nonclinical reviewer under NDAs 215252/215153.

Safety Pharmacology and Pharmacokinetics

The IC_{50} for the inhibitory effect of vonoprazan on human Ether-à-go-go-Related Gene (hERG) current was 4.8 mcg/mL, which is more than 100-fold higher than the mean maximum plasma concentration (C_{max}) for the 20 mg dose vonoprazan in humans. No treatment-related effects were noted on cardiovascular function (blood pressure, heart rate and ECG) at up to 20 mg/kg vonoprazan in dogs. In rats, there were no significant changes in respiratory rate, tidal volume, or

minute volume at up to 100 mg/kg/dose. There were deaths in animals (4 of 8) and changes in respiratory parameters (bronchoconstriction, decreased tidal volume and minute volume) at 600 mg/kg. In a functional observational battery in rats, animals in the 600 mg/kg group exhibited decreased muscle resistance, decreased locomotor activity, partially closed palpebra, difficulty in hopping and a decrease in body temperature. Animals in the 100 mg/kg dose group showed mydriasis which returned to normal at 22 hours after dosing. No treatment-related findings were noted at 30 mg/kg. In rats and dogs, the $t_{1/2}$ were 1.3 and 1.1 hours, respectively. The oral bioavailability of vonoprazan was 52.4% in dogs and 10.3% in rats.

In rats and dogs, absorption following a single oral dose of [14C] vonoprazan, was as high as 92.2% and 86.3%, respectively. In rats, vonoprazan and its metabolites were widely distributed with higher concentration in the liver, kidney, intestine, lung, and stomach wall than in the plasma, and were low in the brain and the spinal cord. After oral administration of [14C] vonoprazan, the primary route of excretion was feces (96.4%) in rats and urine (93.9%) in dogs.

Vonoprazan is mainly metabolized by CYP3A4/5 and to a lesser extent by CYP2B6, CYP2C19, and CYP2D6. An in vitro study showed that vonoprazan was metabolized to M-I, M-II, M-III, M-IV-Sul and N-demethylated TAK-438 in the multiple species (humans, mice, rats, dogs, and monkeys). Major human metabolites (>10% of the active pharmaceutical ingredient) are M-II and M-IV-Sul. The M-IV-Sul metabolite is in greater proportion in humans compared to rats and dogs; in rats M-IV -Sul was approximately 1% of the total radioactivity in the plasma following a dose of [14C] vonoprazan. In both rats and dogs, the M-IV-Sul metabolite accounted for <1% of the dose excreted in urine and plasma. Vonoprazan and its metabolites do not significantly induce or inhibit cytochrome isoenzymes.

Target Organs of Toxicity in Toxicology Studies

In repeated dose toxicology studies in rats and dogs, the stomach, liver, thyroid, and adrenal glands were identified as target organs of toxicity following oral administration of vonoprazan. Table 36 below shows a summary of organ toxicity in rats and dogs.

Table 36. Target Organs of Toxicity in Nonclinical Studies

Toxicology Study	Doses (mg/kg/day)	NOAEL (mg/kg/day)	Organs of Toxicity
4-week rat	0, 10, 30, and 100	10	Stomach: Males and females at ≥30 mg/kg/day dose levels showed increased stomach weight and histopathology changes including eosinophilic changes in the chief cells, vacuolation of the parietal cells, hyperplasia of the mucus neck cells, increased globule leucocytes, increased eosinophils in the mucosa/submucosa, squamous epithelial hyperplasia in the limiting ridge, and atrophy of the parietal cells. Liver: Males at 100 mg/kg/day dose had minimal vacuolation of the midlobular hepatocytes. Thyroid: Males at 100 mg/kg/day dose showed follicular cell hypertrophy.
13-week rat	0, 1, 10, 100 and 300	10	Stomach: Increased stomach weights and inflammatory cell Infiltration at ≥100 mg/kg/day doses. Thickening of the glandular stomach in males with mucous metaplasia at 300 mg/kg/day. Adrenal gland: Hypertrophy in the zona glomerulosa in males (≥100 mg/kg/day) and females (300 mg/kg/day). Liver: vacuolation of midlobular hepatocytes in males (≥100 mg/kg/day) and females (300 mg/kg/day).
26-week rat	0, 1, 5, 10, and 30	5	Stomach: Increased stomach weights at ≥5 mg/kg/day. Thickening of the glandular stomach wall in males at ≥10 mg/kg, red patch in the stomach at 30 mg/kg, atrophy of parietal cells (≥10 mg/kg), mucosal fibrosis (≥10 mg/kg males and 30 mg/kg females), mucosal angiectasis and inflammatory cell infiltration (30 mg/kg). Liver: Increased liver weights at ≥5 mg/kg/day. Vacuolation of hepatocytes in males at 30 mg/kg and centrilobular hypertrophy of the hepatocytes in males at 10 and 30 mg/kg and in females at 30 mg/kg.
4-week dog	0, 0.6, 2, 6, and 20	0.6	Stomach: Minimal single cell necrosis of parietal cells, minimal to mild vacuolization of parietal cells, minimal atrophy of parietal cells, and inflammatory cell infiltration of the fundus mucosa at ≥2 mg/kg/day.

Toxicology Study	Doses (mg/kg/day)	NOAEL (mg/kg/day)	Organs of Toxicity
13-week dog	0, 1, 1.3, 1.6 and 2	1.0	Stomach: Inflammatory cell infiltration in the fundic mucosa, single cell necrosis in the fundic gland, degeneration of the tunica muscularis, hyperplasia of the fundic mucosa and vacuolization of the parietal cells were observed at 1 mg/kg and above.
39-week dog	0, 0.3, 0.6 and 2	0.6	Stomach: Thickening of stomach wall in both sexes at 2 mg/kg. Vacuolation of the parietal cells in both sexes at 0.3 mg/kg and above. Hyperplasia of the fundic mucosa, single cell necrosis in the fundic gland and inflammatory cell infiltration in the fundic gland in both sexes at 2 mg/kg. Degeneration of the muscular layer of the stomach in males at 2 mg/kg. Plasma gastrin values were increased in 1 male at 0.6 mg/kg and 2 females at 2 mg/kg.

Source: FDA Nonclinical review NDAs 215252 and 215153
Abbreviations: NOAEL, no observed adverse effect level

Genetic Toxicology and Carcinogenicity

Vonoprazan was not genotoxic in the bacterial reverse mutation assay, an in vitro chromosomal aberration assay in Chinese Hamster lung cells, and an in vivo rat bone marrow micronucleus test.

In a 2-year carcinogenicity study in mice, there were drug-related increases in hepatocellular adenomas and carcinomas in male mice dosed at ≥20 mg/kg/day and female mice dosed at ≥60 mg/kg/day. Additionally, there were drug-related increases in benign and malignant neuroendocrine cell tumors in the stomachs of male mice at ≥20 mg/kg/day and in female mice at ≥60 mg/kg/day.

In a 2-year carcinogenicity study in rats, there were drug-related increases in hepatocellular adenomas and carcinomas in male and female rats dosed at ≥50 mg/kg/day. Additionally, there were drug-related increases in benign and malignant neuroendocrine cell tumors in the stomachs of male rats at ≥150 mg/kg/day and in female rats at ≥5 mg/kg/day.

Reproduction and Developmental Toxicology

In a fertility and early embryonic development study in rats, no changes in fertility parameters measured were reported up to the highest dose tested (300 mg/kg/day). In an embryo-fetal developmental study in rats, maternal toxicity was reported at 300 mg/kg (death, clinical signs, reduced weight gain). At 300 mg/kg/day (133-times higher than the expected clinical exposure based on area under concentration-time curve (AUC) exposure data extrapolated from nonpregnant rats), visceral malformations (ventral septal defect and malpositioned subclavian branch) were reported in 38 fetuses (28% fetal incidence) across 19 litters (79% litter incidence), and external malformations (small anus and tail malformations) were reported in 3 fetuses (1.2% fetal incidence) in 3 litters (16% litter incidence). The incidences of visceral malformations were statistically significant compared to concurrent controls and above the historical control range.

No treatment-related fetal malformations or variations were reported at the 100 mg/kg dose (27-fold higher exposure than the expected clinical exposure based on exposure data extrapolated from nonpregnant rats). Based on the very large margins both to the effect and no adverse effect dose, these findings are clinically of minimal concern.

In the rabbit embryo-fetal development study, feed consumption and body weights of the high dose group were reduced compared to controls in the 30 mg/kg dose group. No treatment-related fetal malformations or other developmental effects were reported in any dose group.

In the rat pre- and post-natal development study, findings in the F1 animals in the 100 mg/kg dose group included liver discoloration in postnatal day 4 pups, and reduced body weights from birth past weaning, and increased copulatory interval. These effects were not seen at the next lower dose of 10 mg/kg (approximately equivalent to the clinical exposure on an AUC basis). The white and black liver lesions had also been seen in pups in the preliminary dose-range finding study in which dams were dosed during gestation and through lactation up to doses of 100 mg/kg from gestation day 6 to lactation day 13 and were associated with hemorrhage and necrosis in the liver.

To determine if the liver discoloration was due to vonoprazan exposure during gestation or lactation, a follow-up study where the dams were treated during gestation, lactation, or both was conducted with vonoprazan. In this study, the liver lesions were found in the pups of dams treated both during gestation and lactation, and lactation alone.

Summary/Conclusions

In the in vitro hERG assay, vonoprazan inhibited hERG currents with an IC_{50} of 4.8 mcg/mL. The 4.8 mcg/mL concentration is more than 100-fold higher than the mean maximum plasma concentration in humans at the 20 mg dose. In the in vivo cardiovascular safety pharmacology study in dogs, no adverse cardiovascular findings were observed. Following oral administration, the bioavailability of vonoprazan was 52.4% in dogs and 10.3% in rats. Vonoprazan is mainly metabolized by CYP3A4/CYP3A5 and to a lesser extent by CYP2B6, CYP2C19, and CYP2D6. None of the metabolites are either inducer or inhibitor of CYP450 enzymes. In repeated dose toxicology studies in rats, the stomach, liver, thyroid, and adrenal glands were identified as target organs of toxicity. In dogs, the stomach was the main target organ of toxicity. The adverse findings in the stomach are related to the pharmacological actions of the drug. Vonoprazan was not genotoxic in a standard battery of genotoxicity studies. In a 2-year carcinogenicity study in mice and rats, hepatocellular adenomas and carcinomas and drug-related increases in benign and malignant neuroendocrine cell tumors in the stomachs were noted. The carcinogenicity findings in rats and mice should be included in labeling of vonoprazan. In the embryofetal development study in rats, fetal abnormalities were limited to the 300 mg/kg/day dose and included ventricular septal defect and mal-positioned subclavian artery in fetuses, as well as tail abnormalities and small anal opening. No adverse embryo-fetal effects were observed at the 100 mg/kg/day. In the embryofetal development study in rabbits, no embryo-fetal mortality or toxicity occurred, and there were no external, visceral, or skeletal abnormalities. In the pre- and post-natal developmental study in rats, decreased body weight gain compared to controls was observed in the offspring from dams in the high dose group. Liver discoloration occurred in offspring from the high dose group at lactation day 4 but was not present in animals examined after weaning. In a follow-up mechanistic study in rats, the liver lesions were found in the pups of dams treated

both during gestation and lactation, and lactation alone. The clinical relevance of the liver findings is uncertain.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Safety issues due to acid suppression that are seen with the drug class of PPIs may also be a potential concern with vonoprazan. Although vonoprazan is a potassium-competitive acid blocker, it demonstrates a similar pharmacologic effect as the PPI drug class through suppression of acid production at the H+K+ATPase ("proton pump") at the luminal surface of the gastric parietal cell.

Serious or clinically significant adverse reactions (ARs) have been identified for the PPI drug class and added to the WARNINGS AND PRECAUTIONS section of the PI as Safety Labeling Changes (SLCs) since original marketing. These ARs are:

- Acute tubulointerstitial nephritis (AIN/TIN)
- *Clostridiodes difficile*-associated diarrhea (CDAD), especially in hospitalized patients.
- Bone fracture, particularly osteoporosis-related fractures of the hip, wrist, or spine, associated with high dose (i.e., multiple daily doses) and long-term (one year or longer) PPI therapy.
- Severe cutaneous adverse reactions (SCARs)
- Cutaneous and systemic lupus erythematosis (CLE, SLE)
- Vitamin B12 deficiency reported with PPI use longer than 3 years.
- Hypomagnesemia: reported with PPI use for at least 3 months.
- Fundic gland polyps: associated with long-term PPI use (over one year).

All of the class WARNINGS AND PRECAUTIONS for the PPIs were assessed for a relationship to vonoprazan by the review team. See additional discussion in Section 0 and 0.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Vonoprazan received regulatory approval, first in Japan in 2014 and then in 17 other countries for indications of EE healing and maintenance, gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of a gastric or duodenal ulcer during use of nonsteroidal anti-inflammatory drugs or aspirin.

Given the postmarketing use of vonoprazan in foreign countries, the Division of Pharmacovigilance (DPV) evaluated postmarketing reports in the FDA Adverse Event Reporting System (FAERS) database and the medical literature for an association between vonoprazan and adverse events associated with the PPI class of drugs, as described in Section 7.2, many of which were identified by the Applicant as adverse events of special interest (AESIs), see Section 7.4.

Other AESIs of hepatotoxicity and hematologic abnormalities (i.e., cytopenias) were also reviewed along with serious hypersensitivity reactions.

DPV incorporated data obtained from the Applicant's response to an Information Request issued by FDA on September 29, 2022, into the analysis. A brief summary of the review is discussed below. Refer to the completed DPV review for additional details. The review team agreed with DPV's recommendations for labeling.

The Applicant proposed WARNINGS AND PRECAUTIONS, similar to the PPI drug class, for AIN/TIN, *Clostridiodes difficile*-associated diarrhea, bone fracture, severe cutaneous ARS, vitamin B12 deficiency, hypomagnesemia and fundic gland polyps. No new safety information was identified by DPV to support additional changes to the proposed Voquezna WARNINGS AND PRECAUTIONS section for these ARs.

The Applicant did not propose WARNINGS AND PRECAUTIONS subsections for cutaneous and systemic lupus erythematosus or hypomagnesemia. DPV concluded that there is insufficient evidence to support a WARNINGS AND PRECAUTIONS subsection for CLE/SLE unless evidence exists from clinical trials. DPV identified a limited number of postmarketing cases of hypomagnesemia (including other electrolyte abnormalities) that were deemed plausibly associated with vonoprazan use and recommended addition of AR terms to the to the proposed Voquezna PI in the ADVERSE REACTIONS *Postmarketing Experience* subsection. One case of vitamin B12 deficiency in a patient with underlying risk factors for the event was identified by DPV, but DPV supports including this AR in the WARNINGS AND PRECAUTIONS subsection for consistency with PPI labeling and a similar mechanism of action.

DPV agrees with the Applicant to include hypersensitivity reactions in CONTRAINDICATIONS because of one case of anaphylactic shock possibly associated with vonoprazan use.

DPV reviewed a case of clinically significant drug-induced liver injury resulting in liver failure submitted by the Applicant in their IR response possibly related to vonoprazan and confounded by concomitant medications and alcohol use. DPV determined a single case is not sufficient to elevate liver failure to the WARNINGS AND PRECAUTIONS section of the Voquezna PI at this time but does suggest that close pharmacovigilance monitoring is needed.

DPV review of FAERS reports did not identify any cases of cytopenia plausibly associated with vonoprazan use. However, a literature search identified two cases with suspected immune-associated thrombocytopenia induced by vonoprazan.

Adverse reactions of thrombocytopenia, vitamin B_{12} deficiency, and hypomagnesemia identified by DPV and accompanying recommendations for labeling are discussed in detail below.

Thrombocytopenia

DPV identified one Japanese publication containing two cases (summarized below) of suspected drug-induced immune thrombocytopenia from the medical literature with possible causal association with vonoprazan use; both cases noted positive dechallenge to vonoprazan, although one case was also treated with a short course of steroids. DPV suggested addition of the term,

thrombocytopenia, to the *Postmarketing Experience* subsection of ADVERSE REACTIONS in the Voquezna PI based on these few cases.

- Case 1: A 72-year-old male with a baseline platelet count of 299,000/microL received vonoprazan for 14 days. He developed thrombocytopenia with a nadir platelet count of 4,000 /microL. His immature platelet fraction was 20.9% and bone marrow aspiration showed primary immune thrombocytopenia-like features. Vonoprazan was discontinued, and he was treated with dexamethasone for 4 days; his platelet count improved immediately.
- Case 2: A 54-year-old female with an initial platelet count of 153,000 /microL received vonoprazan for 106 days. She developed thrombocytopenia with a nadir platelet count of 28,000/microL. Vonoprazan was discontinued and her platelet count improved immediately. A bone marrow biopsy was not performed.

Vitamin B_{12} Deficiency

DPV identified one well-documented case (summarized below) of vitamin B_{12} deficiency possibly associated with vonoprazan use. Although the patient was elderly with atrophic gastritis, which represent risk factors for the event, vonoprazan could have contributed to the event particularly in a vulnerable patient. Inhibition of gastric acid secretion could theoretically promote malabsorption of cobalamin by multiple mechanisms and for consistency with PPI product labeling, vitamin B_{12} deficiency will be added as a subsection to the WARNINGS AND PRECAUTIONS section of the Voquezna PI.

- Case 1: An 88-year-old female on galantamine for Alzheimer's disease for an unknown duration and vonoprazan for 217 days (20 mg daily for 63 days followed by 10 mg daily for 154 days) presented to the hospital; laboratory tests revealed hemoglobin 7, mean corpuscular volume (MCV) 114, and platelet count of 173,000 (units not reported). The patient declined examination for the cause of anemia. She underwent laboratory testing 182 days later; hemoglobin decreased slightly to 5.9, MCV was 124, and platelet count decreased to 106,000. Her labs were drawn again 99 days later (hemoglobin 5.5, MCV 131, platelet count 119,000). She was noted to have exertional dyspnea and lower leg edema and was treated with furosemide 20 mg/day. Another 19 days later, she was hospitalized. Her vitamin B_1 was 12 ng/mL, vitamin B_{12} was 52 pg/mL, and folic acid was 1.9 ng/mL; pernicious anemia was suspected. Endoscopy revealed atrophy predominantly in the gastric fundus and body and she was diagnosis with type A gastritis. She was treated with intramuscular vitamin B_{12} and supplemented with vitamin B_1 and folic acid. The next day, vonoprazan was discontinued. Her hemoglobin improved 19 days later from 4.5 to 6 and platelet count improved from 129,000 to 360,000. The next day, she was given intramuscular mecobalamin. She was discharged 4 days later, and thrombocytopenia and macrocytic anemia had resolved.

Hypomagnesemia

DPV identified three cases in which patients experienced hypomagnesemia and other related electrolyte abnormalities (hypokalemia n=3, hypocalcemia n=2) possibly associated with vonoprazan use. Although it is difficult to assess the response to dechallenge in these cases, all three cases described resolution of the electrolyte abnormalities after electrolyte replacement and

vonoprazan discontinuation; two cases explicitly mentioned that there was no further recurrence. Two cases were noteworthy as the patients presented with critically low magnesium levels (0.2-0.4 mg/dL) with clinically significant sequelae (seizures n=1, disturbances in gait/consciousness n=1). The remaining case was limited because the patient's actual electrolyte values were not reported, but the patient did experience neuromuscular manifestations with the reported electrolyte abnormalities. Based on the seriousness of the cases, hypomagnesemia will be added as a subsection to the WARNINGS AND PRECAUTIONS section of the Voquezna PI, consistent with PPI class labeling. In addition, other electrolyte abnormalities, such as hypokalemia and hypocalcemia, will be added to the *Postmarketing Experience* subsection of ADVERSE REACTIONS.

The two cases describing patients with critically low magnesium levels (0.2-0.4 mg/dL) with clinically significant sequelae are summarized below.

- **FAERS Case #19725016/19902587, other important medical event, JPN, 2021:** This published case report describes a 71-year-old female admitted for the treatment of diffuse large B-cell lymphoma of the ileum; treatment consisted of pirarubicin, cyclophosphamide, vincristine, prednisone, and rituximab. She was taking lansoprazole to prevent gastric mucosal injury but was switched to vonoprazan due to epigastric discomfort and heartburn. Three weeks later, she visited an outpatient clinic for poor physical condition and experienced a convulsive seizure with loss of consciousness. She was admitted to the hospital for investigation of the cause. Laboratory tests revealed hypomagnesemia (0.4 mg/dL) and hypokalemia (2.8 me/L) as well as slightly elevated bilirubin (1.3 mg/dL) and transaminase levels (aspartate aminotransferase [AST] 51 U/L, alanine aminotransferase [ALT] 70 U/L). Hypomagnesemia was considered the cause of the seizure and magnesium 40 mEq was given intravenously. The next day, her magnesium level improved to 2.2 mg/dL, and magnesium therapy was stopped. However, her magnesium level decreased gradually; on hospital day 7, it was approximately 1 mg/dL. Vonoprazan was discontinued. By hospital day 10, her magnesium level improved to 2.1 mg/dL. She was discharged after receiving her chemotherapy regimen for lymphoma. She was switched to famotidine and continued to receive outpatient treatment for lymphoma without recurrence of hypomagnesemia.
- **FAERS Case #21106338, hospitalization/other important medical event, JPN, 2022:** This published case report describes a 66-year-old male with a history of myocardial infarction and cerebral infarction admitted to the hospital because of disturbances in gait and consciousness. Approximately 2 years prior, he underwent endovascular aortic repair for abdominal aortic aneurysm; at that time, he was taking a PPI, which was changed to vonoprazan. Approximately 4 months after the procedure, he experienced a sudden clonic convulsion diagnosed as symptomatic epilepsy associated with old cerebral infarction and treated with levetiracetam. At that time, his serum calcium was slightly low at 7.2 mg/dL (albumin-corrected calcium 7.5 mg/dL), but his magnesium level was not measured.

  Two months before his current admission, he had diarrhea and appetite loss; approximately 2 weeks later (43 days before the current admission), he went to the emergency department for convulsions and altered consciousness. His serum magnesium was 0.4 mg/dL, potassium was 2.66 mEq/L, and albumin-corrected calcium was 6.9 mg/dL. His symptoms improved spontaneously, and he left the hospital.

He gradually became unable to walk and was ultimately admitted to the hospital with disturbance in consciousness. He was taking vonoprazan, levetiracetam, clopidogrel, diltiazem, telmisartan, amlodipine, nicorandil, bisoprolol, and isosorbide dinitrate. Electroencephalogram and head computed tomography scan were normal, however, serum electrolytes were abnormal. His serum magnesium was 0.2 mg/dL, potassium was 3 mEq/L, and albumin-corrected calcium was 5.7 mg/dL. Serum intact-parathyroid hormone, 1,25-dihydroxyvitamin D, and calcitonin levels were all within normal ranges. Intravenous magnesium and oral calcium were given, and his serum magnesium increased to 2 mg/dL of day 2 of admission with improvement in consciousness. His serum calcium levels improved steadily, but his magnesium levels rapidly declined once intravenous administration was discontinued, even though he had a sufficient intake after hospitalization. It was suspected that he had experienced magnesium malabsorption induced by long-term treatment with an antacid drug and vonoprazan, which had been used for over 2 years; therefore, vonoprazan was stopped on day 5 of hospital admission. Although temporary intravenous administration of magnesium was needed again as serum magnesium decreased to 1.1 mg/dL on day 10 of admission, his serum magnesium level increased naturally to 1.6 mg/dL on day 20 after discontinuation of vonoprazan. An H_2 antagonist was started instead of vonoprazan on the same day, and serum magnesium has not decreased again.

For additional safety information on all the ARs described in this section see Sections 7.7.2 and 7.7.3.

See also Section 21 Labeling Summary of Considerations and Key Additional Information.

Other Adverse Events

DPV also identified events of gastric adenocarcinoma, select endoscopic/histopathologic findings (e.g., gastric erythema, parietal cell protrusions, oxyntic gland dilatation), and gastrointestinal candidiasis from their high-level overview of FAERS and the medical literature. However, there was insufficient evidence to includes these terms as ARs in the Voquezna PI.

7.4. FDA Approach to the Safety Review

7.4.1. Sources of Data for Clinical Safety Assessment

Data from the adequate and well-controlled Study EE-301 evaluating vonoprazan for healing and maintenance of healed erosive esophagitis (EE) forms the primary basis of the clinical safety evaluation for Voquezna.

The safety database also includes safety data from the following trials conducted outside of the United States in subjects with EE:

- Four phase 3 trials: two (2) for healing of EE (TAK438/CCT-002, TAK438/CCT-303), and two (2) for maintenance of healed EE (TAK438/CCT-003, TAK438/CCT-305).
- 52-week uncontrolled safety data for maintenance of healed EE (Study TAK-438/OCT-001).

In addition, the safety database also included data from:

- Phase 2/3 trials conducted outside of the United States for various GI indications other than EE. Refer to Section 17.6.
- Vonoprazan-4003 (VISION) trial (a 5-year randomized, double-blind safety trial of vonoprazan versus lansoprazole for long-term maintenance of healed EE).
- Post-marketing pharmacovigilance reports and published safety data.

7.4.2. Safety Analysis Plan and Definitions

The applicant defined adverse events as any untoward medical occurrence in a subject enrolled in this study regardless of its relationship to study drug.

The investigator recorded any clinically significant changes occurring during the study as an adverse event. Abnormal laboratory findings that were expected with the underlying disease were not to be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition. Treatment Emergent Adverse Events (TEAEs) were defined by the applicant as any event that occurred after the first dose of study drug in that study phase or any event at baseline that worsened in either intensity or frequency after the first dose of study drug in that study phase. Serious adverse events defined as adverse event that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect. Disease severity was determined by the investigator and rated mild, moderate, or severe using the following criteria: (1) mild, the event is transient and easily tolerated by the subject; (2) moderate, the event causes the subject discomfort and interrupts the subject’s usual activities; (3) severe, the event causes considerable interference with the subject’s usual activities. All adverse events were coded using the Medical Dictionary for Regulatory Activities version 23.0.

For this NDA, the Applicant identified the following treatment emergent adverse events (TEAEs) of special interest based on previously identified events related to gastric acid suppression, published reports from previous PCABs developed outside of the United States, idiosyncratic reactions, or based on ex-U.S. post-marketing safety data:

- Hepatotoxicity, reported for PCABs previously developed outside of the U.S. (AZD0865, SCH28080)
- Hematologic abnormalities, per FDA request, based on updates to the package insert for vonoprazan approved in Japan (Takecab®)
- Bone fracture, reported with the related drug class of PPIs
- *Clostridiodes difficile*-enteric infection, related to long-term acid suppression
- Severe cutaneous adverse reactions, as reported idiosyncratic reactions
- Gastric cancer, based on the possible relationship of elevated serum gastrin on the development of gastric malignancy and the effect of long-term acid suppression on serum gastrin levels

At FDA's request, the applicant included two additional TEAEs as TEAEs of special interest for Voquezna Triple and Duel-Packs for the treatment of *H. pylori* infection. Refer to the review for NDA 215152/NDA 215153.

- Hypersensitivity reactions (due to the antibacterial components of the *H. pylori* regimen)
- QT prolongation (due to the pro-arrhythmogenic clarithromycin component of the *H. pylori* regimen)

In NDA 215151, the Applicant also reviewed other TEAEs potentially related to acid suppression, and reported with PPIs, including vitamin B12 deficiency, hypomagnesemia and fundic gland polyps, and potential idiosyncratic events related to acute tubulointerstitial nephritis. The Applicant did not discuss events of cutaneous/systemic lupus erythematosus, which has also been identified as a PPI class effect.

For the purposes of this review, the term Adverse Events of Special Interest (AESI) will be used to describe the overall combined group of events of:

- TEAEs of special interest
- TEAEs related to acid suppression
- events related to cutaneous/systemic lupus erythematosus

7.4.3. Reviewer's Approach to the Safety Evaluation

Clinical trial safety data were independently analyzed using R, JMP, and JMP Clinical software. All safety assessments and conclusions are those of the review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

Study EE-301

The safety data for the healing phase and maintenance phases for Study EE-301 were analyzed individually and was used primarily to inform the safety profile of vonoprazan in the intended population of patients with EE. An additional review was conducted of safety data from subjects who received only Voquezna at the recommended dosages for both healing and maintenance of healed EE (i.e., 20 mg QD for 2 or 8 weeks followed by 10 mg QD for 24 weeks) compared to lansoprazole (i.e., 30 mg QD for 2 or 8 weeks followed by 15 mg QD for 24 weeks), (see Section 7.6.3).

The following types of data were assessed for Study EE-301: exposure, demographics and baseline characteristics, assessment of overall TEAEs (including serious adverse events [SAEs]), AEs leading to discontinuation, physical examinations including vital sign measurements, 12-lead electrocardiogram, and clinical laboratory testing (hematology, chemistry, and urinalysis), and AESIs.

Supportive Trials

Safety data from the four phase 3 EE trials conducted outside of the United States (two (2) for healing of EE (TAK438/CCT-002, TAK438/CCT-303), and two (2) for maintenance of healed

EE (TAK438/CCT-003, TAK438/CCT-305)) were used to support the assessment of safety results from Study EE-301.

The following trials supported the longer-term safety of vonoprazan in patients with EE:

- 52-week uncontrolled safety data for maintenance of healed EE (Study TAK-438/OCT-001)
- Vonoprazan-4003 (VISION) trial (a 5-year randomized, double-blind safety trial of vonoprazan versus lansoprazole for long-term maintenance of healed EE)

The following types of data were assessed for the supportive trials: assessment of overall TEAEs (including serious adverse events [SAEs])), and AEs leading to discontinuation. The only data available from VISION was TEAEs in >1% of subjects.

AESIs were assessed across all studies.

The safety review also included information available from post-marketing data (see Section 7.3 Potential Safety Concerns Identified Through Postmarket Experience).

7.5. Adequacy of Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of Voquezna for the proposed indications, patient populations, dosage regimens, and duration of use.

A total of 8355 subjects have been exposed to at least one (1) dose of vonoprazan across the clinical development program, including phase 1 studies. Mean vonoprazan exposure for the 460 healthy subjects who participated in phase 1 trials was 7 days. A total of 307 subjects received vonoprazan 10 mg for at least 52 weeks in trials for any indication.

Overall, 1764 subjects with erosive esophagitis (EE) were enrolled in phase 3 trials, with 1602 unique subjects exposed to at least one dose of vonoprazan at any dose level.

- 477 subjects received the proposed regimen for erosive esophagitis (i.e., vonoprazan 20 mg for healing and vonoprazan 10 mg for maintenance)
- 965 subjects received vonoprazan 20 mg QD for healing of EE (2 to 8 weeks) in the double-blind, randomized, comparative phase 3 EE healing studies (EE-301, TAK-438/CCT-002, TAK-438_303)
- 733 subjects received vonoprazan 10 mg QD for maintenance of healed EE for at least 24 weeks in the phase 3 double-blind, randomized, comparative maintenance studies (EE-301, TAK-438/CCT-003, TAK-438_305). An additional 154 subjects received vonoprazan 10 mg once daily for 52 weeks in an uncontrolled randomized trial of two doses of vonoprazan (TAK-438/OCT-001). All subjects in maintenance of healed EE studies were also exposed to either vonoprazan or a PPI for healing of EE prior to beginning maintenance treatment
- 135 subjects received vonoprazan 10 mg once daily for up to five (5) years in the long-term safety study, Vonoprazan-4003 (VISION)

Table 37 shows the exposure to vonoprazan at doses ranging from 5 mg to 40 mg per day across all ISS study pools. Voquezna 20 mg once daily is the proposed dosage for healing of EE and Voquezna 10 mg once daily is the proposed dosage for maintenance of healed EE.

Table 37. Overall Vonoprazan Exposure Across All ISS Studies

	Vonoprazan Total Daily Dose				
Parameter	**5 mg N=148**	**10 mg N=1968**	**20 mg N=3773**	**40 mg N=249**	**Overall N=566**
Mean Duration of treatment (days)	54.5	166.5	99.4	44.3	127.6
(SD)	(4.88)	(137.17)	(120.92)	(13.74)	(130.48)
Median	55.0	167.0	35.0	54.0	55.0
Min, Max	6, 58	1, 684	1, 623	3, 59	1, 684
Person-years of exposure	22.08	896.95	1027.25	30.23	1976.70
Duration of treatment (mutually exclusive categories[a])					
1 day to <2 weeks	1 (0.7)	24 (1.2)	229 (6.1)	5 (2.0)	191 (3.4)
≥2 weeks to <4 weeks	0	101 (5.1)	1057 (28.0)	16 (6.4)	818 (14.5)
≥4 weeks to <8 weeks	102 (68.9)	546 (27.7)	1025 (27.2)	184 (73.9)	1825 (32.2)
≥8 weeks to <24 weeks	45 (30.4)	343 (17.4)	395 (10.5)	44 (17.1)	677 (12.0)
≥24 weeks to <36 weeks	0	532 (27.0)	668 (17.7)	0	1325 (23.4)
≥36 weeks to <52 weeks	0	115 (5.8)	94 (2.5)	0	181 (3.2)
≥52 weeks	0	307 (15.6)	305 (8.1)	0	643 (11.4)

Source: Adapted from ISS Table 1.m
[a] Mutually exclusive categories includes each subject once, according to total duration of exposure.
[b] Non-mutually exclusive categories count each subject exposed for at least the categorized duration of exposure (e.g., subjects who were exposed for 8 weeks are also included in the counts for 4 weeks, 2 weeks, 1-day)
Abbreviations: ISS, Integrated Summary of Safety; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

The review of the clinical safety database supports the overall safety of Voquezna 20 mg once daily for healing of erosive esophagitis and Voquezna 10 mg once daily for maintenance of healed erosive esophagitis in subjects with all LA grades of EE at baseline. In the review of data from Study EE-301 and the ex-U.S. phase 3 trials, low overall rates were observed for TEAEs, SAEs and AEs resulting in discontinuation with no imbalance evident between subjects treated with the recommended dosage of Voquezna and active comparator (lansoprazole). There were no deaths deemed attributable to Voquezna.

The most common adverse reactions in Study EE-301 for the healing of EE (>1%) with Voquezna 20 mg once daily were gastrointestinal in nature and consisted of gastritis, diarrhea, abdominal distension, abdominal pain, and nausea.

The most common adverse reactions in Study EE-301 for the maintenance of healed EE (>2%) with Voquezna 10 mg once daily were gastritis, abdominal pain, dyspepsia, hypertension, urinary tract infection, diarrhea, and headache.

A maintenance dosage of Voquezna 20 mg once daily had numerically higher numbers of SAEs and TEAEs leading to discontinuation than Voquezna 10 mg once daily, but these events, in general, were not considered plausibly related to vonoprazan. There did not appear to be a consistent dose-related increase in adverse events with the higher dosage.

Adverse events of special interest (AESIs), as defined previously, were infrequently reported, or not reported, in Study EE-301.

The 120-Day Safety Update provided safety data from four clinical trials that were ongoing at the time of the NDA submission: Vonoprazan-4003 (VISION) long-term study of maintenance of EE in Japan and Europe, the NERD-201 clinical trial of sGERD in the United States, one clinical trial of *H. pylori* and one PK study, both in China. These trials are now complete. The Update also reports on two additional U.S. GERD studies that have been initiated and are ongoing (NERD-301, sGERD in adults, and VPED-102, PK study in adolescent subjects with GERD). As agreed, the applicant provided deaths and SAEs from these studies in addition to a preliminary report of adverse events from the first 4-years of the VISION trial. There were no additional deaths and very few new SAEs. The additional data do not change the benefit risk profile for vonoprazan from what is in the initial NDA submission.

7.6.1. Safety Findings and Concerns, EE-301, Healing Phase

As previously described, in the healing phase of Study EE-301 subjects were randomized to receive Voquezna 20 mg once daily or lansoprazole 30 mg once daily for up to eight (8) weeks. Endoscopic assessment was performed at 2 weeks and 8 weeks. Subjects with confirmed healing were re-randomized directly into the maintenance phase.

Table 38 shows the duration of exposure to study drug during the healing phase of Study EE-301. Most subjects in either treatment arm received >14 to ≤ 28 days of treatment (65% and 61% for vonoprazan and lansoprazole, respectively). Exposure to lansoprazole and Voquezna during the healing phase was similar, with no difference likely to affect interpretation of the safety data.

Table 38. Duration of Exposure, Safety Population, Study EE-301- Healing Phase

Parameter	Voquezna 20 mg N=514 n (%)	Lansoprazole 30 mg N=510 n (%)
Duration of treatment, days		
Mean (SD)	29.5 (17.4)	31.2 (18.6)
Median (Q1, Q3)	22 (18, 34)	22 (18, 49.8)
Min, Max	2, 85	2, 83
Total exposure (person years)	41	44
Subjects treated, by duration, n (%)		
≤14 days	34 (6.6)	34 (6.7)
>14 to ≤28 days	334 (65.0)	310 (60.8)
>28 to ≤56 days	59 (11.5)	52 (10.2)
>56 days	87 (16.9)	114 (22.4)

Source: adex.xpt and adsl.xpt; Software: R
The study healing phase duration is up to 8 weeks. Patients with endoscopic healing at week 2 left the study healing phase and were re-randomized into the study maintenance phase (and were not further included in the study healing phase).
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6.1.1. Overall Adverse Event Summary, EE-301, Healing Phase

Table 39 provides a summary of treatment-emergent adverse events (TEAEs) reported during the healing phase of Study EE-301. Overall, there were few SAEs, AEs leading to discontinuation or interruption of study drug. All subjects who permanently discontinued study drug also discontinued the study. Most TEAEs were classified as mild to moderate in severity by the investigator. The protocol did not include any option for dose reduction or delayed dosing.

The proportion of AEs in each category were comparable between the Voquezna and lansoprazole treatment groups.

Table 39. Overview of Adverse Events, Safety Population, Study EE-301, Healing Phase

Event Category	Voquezna 20 mg N=514 n (%)	Lansoprazole 30 mg N=510 n (%)
SAE	3 (0.6)	3 (0.6)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	0
AE leading to permanent discontinuation of study drug	5 (1.0)	11 (2.2)
AE leading to interruption of study drug	8 (1.6)	7 (1.4)
Any TEAE	155 (30.2)	149 (29.2)
Severe	2 (0.4)	4 (0.8)
Moderate	51 (9.9)	53 (10.4)
Mild	102 (19.8)	92 (18.0)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between vonoprazan and lansoprazole.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

7.6.1.2. Deaths, EE-301, Healing Phase

There were no deaths among subjects in either treatment group during the healing phase of Study EE-301.

7.6.1.3. Serious Adverse Events, EE-301, Healing Phase

Table 40 shows the serious adverse events (SAEs) reported during the healing phase of Study EE-301. Seven serious adverse events were reported in six subjects: four SAEs in three subjects in the Voquezna group and three SAEs (one in each subject) in the lansoprazole group. No patterns were detected in the number or types of SAEs reported between study arms. Each SAE occurred only once.

Table 40. Serious Adverse Events, Safety Population, EE-301, Healing Phase

SAE Preferred Term	Voquezna 20 mg N=514 n(%)	Lansoprazole 30 mg N=510 n(%)
Number of subjects with at least one serious AE	3 (0.6)	3 (0.6)
Serious Adverse Event (PT)		
Cerebrospinal fluid leakage	1 (0.2)	0
Chest pain[a]	1 (0.2)	0
Peripheral edema[a]	1 (0.2)	0
Covid-19	1 (0.2)	0
Animal bite	0	1 (0.2)
Breast cancer stage I	0	1 (0.2)
Influenza	0	1 (0.2)

Source: adae.xpt; Software: R
[a] Chest pain and peripheral edema were reported in the same subject ((b) (6)) see narrative below.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event; PT, MedDRA preferred term

The SAEs in subjects in the Voquezna group are summarized below:

- Subject (b) (6) experienced two of the serious adverse events (chest pain and peripheral edema), resulting in a single hospitalization. This 43-year-old woman experienced left leg edema on Day 7 of vonoprazan 20 mg during the EE-301 healing phase. On Day 15 (Visit 3), the investigator recommended an emergency department visit and study drug was held. The subject presented to the emergency department on (b) (6) (Day 16) with leg swelling and chest pain. Evaluation for a deep venous thrombosis did not identify a cause of leg swelling. Chest pain resolved without treatment. Vonoprazan dosing resumed on (b) (6). Chest pain did not recur. The subject completed the healing phase on Day 63. She was randomized for the maintenance phase to the vonoprazan 10 mg arm, but voluntarily withdrew from the study without receiving maintenance treatment or completing a safety follow up visit. Given the spontaneous resolution and lack of recurrence with rechallenge, it is unlikely that the chest pain was related to vonoprazan. However, due to the timing and persistence of the peripheral edema relationship to treatment with vonoprazan cannot be excluded. Peripheral edema was reported in several subjects as a TEAE and will be included as a less common adverse reaction in labeling.
- Subject (b) (6) was hospitalized for Covid-19 during the global pandemic. This is unlikely to be related to vonoprazan.
- Subject (b) (6) underwent an unscheduled surgery for a herniated lumbar disc on (b) (6) (study day -1). The next day, she was randomized to the vonoprazan 20 mg daily arm on (b) (6). She was hospitalized on (b) (6) (day 3) for a cerebrospinal fluid leak and was treated with enoxaparin. The cerebrospinal fluid leak appears to be directly attributable to the surgical procedure and unlikely to be related to vonoprazan.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events, EE-301, Healing Phase

Table 41 shows the subjects with adverse events that led to discontinuation of study drug and discontinuation from the study. Overall, the proportion of subjects who discontinued due to an AE was small (1.6% of the study population) with no more than a single occurrence of any AE leading to discontinuation.

In the Voquezna group, five subjects experienced six AEs that led to discontinuation of Voquezna and discontinuation from the study. The TEAEs were mild or moderate in intensity, and all were recorded as recovered/resolved. Only nausea and abdominal pain/discomfort appear likely related to vonoprazan in the cases reported and described below.

In the lansoprazole group, 11 subjects experienced 15 AEs that led to discontinuation of lansoprazole and discontinuation from the study, with three AEs occurring in one subject and two occurring in another. Two serious TEAEs (influenza, breast cancer stage 1) were assessed by the investigator as not related to study drug. Three subjects had TEAEs that led to discontinuation that were reported as not recovered/not resolved (colitis, microscopic colitis, flatulence).

Table 41. Adverse Events Leading to Treatment Discontinuation, Safety Population, Study EE-301 (Healing Phase)

Adverse Events Leading to Discontinuation Preferred Term	Voquezna 20 mg N=514 n (%)	Lansoprazole 30 mg N=510 n (%)
Subjects with adverse events leading to treatment discontinuation	5 (1.0)	11 (2.2)
Adverse events leading to treatment discontinuation (PT)		
Abdominal pain [A,C]	2 (0.4)	1 (0.2)
Chest discomfort [C]	1 (0.2)	0
Fluid retention	1 (0.2)	0
Nausea	1 (0.2)	0
Rash maculo-papular	1 (0.2)	0
Diarrhea [D,E]	0	3 (0.6)
Colitis [B]	0	2 (0.4)
Abdominal distention	0	1 (0.2)
Breast cancer stage I	0	1 (0.2)
COVID-19	0	1 (0.2)
Dizziness [D]	0	1 (0.2)
Gastroesophageal reflux disease	0	1 (0.2)
Flatulence [E]	0	1 (0.2)
Headache [D]	0	1 (0.2)
Influenza	0	1 (0.2)
Malaise	0	1 (0.2)

Source: adae.xpt; Software: R
[A] includes abdominal pain, abdominal discomfort
[B] includes colitis, colitis microscopic
[C] abdominal discomfort and chest discomfort were reported in the same subject ((b) (6)). See narrative below.
[D] diarrhea, headache and dizziness were reported in the same subject ((b) (6))
[E] diarrhea, flatulence was reported in the same subject ((b) (6)) reported
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; PT, MedDRA preferred term

The AEs leading to treatment discontinuation in subjects in the Voquezna group are summarized below:

- Subject (b) (6) experienced both abdominal and chest discomfort beginning on Day 1 of receiving Voquezna 20 mg. Symptoms continued until Day 9, and the subject discontinued treatment with study drug. At the early termination visit on Day 43, the symptoms were resolved. The investigator assessed the events as related to study drug. Given the timing of symptoms with initiation of Voquezna, it is possible that the events were related to drug; however, there was no rechallenge and the precise timing of resolution of symptoms relative to stopping study drug is not known. Abdominal pain was observed as a TEAE in >1% of subjects in the study and will be included in labeling.
- Subject (b) (6), a 42-year-old male with endoscopically confirmed erosive esophagitis (Grade D), was randomized to receive Voquezna 20 mg QD for up to 8 weeks. The subject received study drug on treatment days 1 and 2. On treatment day 1, the subject experienced moderate nausea and vomiting. The investigator assessed the symptoms as related to study drug. The subject discontinued study drug due to the nausea event with the last dose was received on treatment day 2. No treatment was reported for either event. The events were noted as recovered/resolved on treatment day 4. Given the timing of the event and resolution with discontinuation of Voquezna, the events may have been related to treatment. Nausea and vomiting were also reported in several other subjects as TEAEs and both terms will be included in labeling.
- Subject (b) (6), a 19-year-old female with endoscopically confirmed erosive esophagitis (LA Grade A), was randomized to receive Voquezna 20 mg QD for up to 8 weeks. On treatment day 4, she experienced abdominal pain, mild fever, and mild malaise. The next day, treatment day 5, she developed a maculo-papular rash on her trunk. Pain, fever, and malaise resolved without treatment on day 6. Study drug was discontinued due to the rash, with the last dose on day 7. The rash had resolved by Day 10. The investigator assessed the rash as related to study drug. The abdominal pain, fever, and malaise that resolved while the subject continued study drug are most consistent with a viral infection, which is unlikely to be related to vonoprazan; however, it is unclear whether the rash in this subject is related to vonoprazan or to the viral illness. Rash was also observed as a TEAE in several other subjects and will be included in labeling.
- Subject (b) (6), a 35-year-old female with endoscopically confirmed erosive esophagitis (Grade B) and prior history of thyroiditis and allergic disorders, randomized to receive Voquezna 20 mg QD for up to 8 weeks, experienced fluid retention. She was considered healed at the Week 2 visit and entered the maintenance phase, where she was randomized to receive Voquezna 10 mg daily. The fluid retention began on an unspecified day near at the end of the healing phase or beginning of maintenance phase. The fluid retention continued until the subject discontinued treatment on maintenance phase Day 67 (treatment day 85). Fluid retention was resolved at the early termination visit (treatment day 113). The investigator assessed the fluid retention as related to study drug. Given the presence of concomitant disorders associated with fluid retention (hypothyroidism, requiring levothyroxine), the contribution of vonoprazan to her symptoms remains unclear. Peripheral edema was observed as a TEAE in several subjects and will be included in labeling.

- Subject (b) (6) experienced upper abdominal pain on treatment Day 8 with Voquezna 20 mg, with subsequent diarrhea the following day. The symptoms resolved without treatment by Day 11 and without interruption of study drug, but the subject discontinued the study on Day 14 due to the abdominal pain. The investigator assessed the abdominal pain as related to study drug. However, given the resolution of symptoms without discontinuation of treatment, it is unlikely that vonoprazan is related to the abdominal pain or diarrhea in this subject.

7.6.1.5. Treatment-Emergent Adverse Events, EE-301, Healing Phase

This section describes the treatment emergent adverse events (TEAEs), reported during the healing phase of Study EE-301.

TEAEs Reported in >1% of Subjects

Overall, 48.4% of subjects in the Voquezna 20 mg arm and 40.6% of subjects in the lansoprazole arm reported at least one TEAE during the healing phase. Table 42 shows the TEAEs that were reported in more than 1% of subjects exposed to either study drug during the healing phase of Study EE-301. Related terms were grouped together. For list of grouped terms, see Appendix, Table 97. There was no meaningful difference between rates in subjects assigned to the Voquezna and lansoprazole treatment arms for these TEAEs.

The review team determined that TEAEs reported in more than 1% of subjects in either treatment arm, after rounding to the nearest whole number, represented the appropriate cut-point to capture the adverse reactions plausibly related to vonoprazan in the healing phase for inclusion in labeling as a table of common adverse reactions (see terms in bold and italics in the table).

While gastroesophageal reflux disease (GERD) and Barrett's esophagus were TEAEs reported in more than 1% of subjects in either treatment arm after rounding, they were not considered adverse reactions for inclusion in labeling as they were likely related to the subject's underlying condition and not plausibly related to vonoprazan.

Table 42. Treatment-Emergent Adverse Events Occurring in >1% of Subjects in Either Treatment Arm, EE-301, Healing Phase

	Voquezna 20 mg N=514		Lansoprazole 30 mg N=510	
Dictionary-Derived Term	**n**	**(%)**	**n**	**(%)**
Any TEAE [f]	249	(48.4)	207	(40.6)
Gastritis[a]	***14***	***(2.7)***	***8***	***(1.6)***
Abdominal pain [b]	***10***	***(2.0)***	***6***	***(1.2)***
COVID-19[c]	11	(2.1)	9	(1.8)
Diarrhea[d]	***11***	***(2.1)***	***13***	***(2.5)***
Nausea	***9***	***(1.8)***	***5***	***(1.0)***
Abdominal distension	***8***	***(1.6)***	***3***	***(0.6)***
Barrett's esophagus	8	(1.6)	7	(1.2)
Constipation	6	(1.2)	2	(0.4)
Gastroesophageal reflux disease	6	(1.2)	2	(0.4)
Headache	6	(1.2)	6	(1.2)
Urinary tract infection	6	(1.2)	4	(0.8)

Source: Reviewer-generated, EE-301, ADAE.xpt, JMP Clinical, Additional Filter to Include Adverse Events "Healing Phase"
*Rounded based on 4 decimal places
a Includes gastritis, chronic gastritis, erosive gastritis, gastric erythema
b Includes: abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain
c Includes: COVID-19, coronavirus infection, COVID, COVID pneumonia
d Includes diarrhea, frequent bowel movement
f Total includes any TEAE occurring during healing phase occurring in either treatment arm at least once
Terms in ***bold italics*** recommended for inclusion in Table in Section 6.1 of the Prescribing Information.
Abbreviations: N, number of subjects; n, number of subjects with adverse event; MedDRA, Medical Dictionary for Regulatory

TEAEs Reported in 1% or Fewer Subjects

TEAEs reported in 1% or less of subjects in the healing phase of Study EE-301 are shown in Table 106 in the Appendix.

TEAEs Related to Adverse Events of Special Interest

The following subsections address TEAEs reported during the healing phase of Study EE-301 that relate to the AESIs, as defined in Section 7.4.2. Overall, there was no imbalance between Voquezna and lansoprazole groups.

Hepatotoxicity

Investigators were instructed in the protocol that any clinically significant laboratory abnormalities should be recorded as adverse events. The Applicant performed a broad search for hepatotoxicity preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hepatic enzyme increased, hepatic steatosis, non-alcoholic steatohepatitis, transaminases increased.

The Applicant also reviewed the liver-related laboratory results and defined liver function tests as abnormal if they met any of the following criteria: AST and/or ALT >3 x upper limit of normal (ULN), total bilirubin > 2 x ULN or alkaline phosphatase > 1.5 X ULN. The protocol had criteria for temporary or permanent study drug discontinuation based on pre-specified laboratory criteria.

There were six (1.2%) subjects in the Voquezna group and four (1.0%) subjects in the lansoprazole group with reported TEAEs associated with hepatotoxicity as defined by the broad search criteria. There were five terms in the Voquezna group related to any transaminase increase, including three of hepatic enzymes increased and one each of ALT and AST increased (in the same subject). There were two terms in the lansoprazole group related to transaminase increase, including GGT increased and transaminases increased. Terms related to hepatic steatosis (grouped term of hepatic steatosis, hepatic steatohepatitis, and non-alcoholic steatohepatitis) were reported in one subject in each treatment group. One case of esophageal varices was reported in the lansoprazole group. The investigator considered three events of hepatic enzyme increased in three subjects in the Voquezna group and two events (one each of ALT increased, transaminases increased) in subjects in the lansoprazole group as related to study drug. All events were assessed as mild or moderate severity by the investigator. None of the TEAEs were considered serious or resulted in temporary or permanent study drug discontinuation. One subject in the vonoprazan 20 mg group had an increase in ALT that was >3 × ULN and an alkaline phosphatase value that was >1.5 × ULN. None of the other subjects had elevations in ALT or AST >3 × ULN, alkaline phosphatase >1.5 × ULN, or total bilirubin >2 × ULN.

Hematologic Abnormalities

TEAEs associated with changes in hematology parameters (anemia, hemoglobin decreased, hematocrit increased, lymphocytosis, platelet count increased, white blood cell count decreased, and thrombocytosis) were reported by the applicant for 2 subjects in the vonoprazan 20 mg group and 7 subjects in the lansoprazole 30 mg group.

None of the hematologic TEAEs in either group was serious, led to discontinuation from study drug, or considered related to study drug by the investigator. All of the hematologic TEAEs were mild or moderate in intensity with the exception of 1 subject in the lansoprazole 30 mg group who had a severe TEAE of anemia.

One subject ((b) (6)) in the Voquezna group was recorded as not recovered/not resolved for the TEAE "hemoglobin decreased" at the end of the study. However, no clinically relevant decrease in hemoglobin can be attributed to Voquezna. The subject's baseline hemoglobin was 111 g/L and remained essentially stable through the healing phase, with a minimal decrease to 108 g/L at Week 8. Although below the LLN (110 g/L) the decrease is not clinically meaningful. During the maintenance phase, the subject was re-randomized to the lansoprazole group, with continued decreasing hemoglobin recorded through the end of the study at maintenance Week 24, with a nadir of 96 g/L.

Bone Fracture

A forearm fracture was reported in a postmenopausal female subject with prior history of osteoporosis who received three days of Voquezna. Given the limited duration of drug exposure, it is unlikely that Voquezna contributed to the fracture. There were no fractures reported in the lansoprazole group in the healing phase.

***Clostridiodes difficile*-associated Diarrhea (CDAD)**

There were no events related to *Clostridiodes-difficile* enteral infection (including *C. difficle* enterocolitis, bacterial enterocolitis attributable to *C. difficle*, and CDAD) in the healing phase.

Hypomagnesemia

There were no TEAEs related to hypomagnesemia in the healing phase.

Cobalamin (Vitamin B12) Deficiency

There were no cases of vitamin B12 deficiency reported in the healing phase.

Fundic Gland Polyps

Five subjects in the Voquezna group and six subjects in the lansoprazole group reported fundic gland polyps as a grouped term, which included the individual TEAEs of gastric polyps, benign gastric neoplasm, and duodenal polyp, representing ≤1% of subjects in each treatment group. None of the TEAEs were reported as serious. TEAEs were generally mild in intensity, with a single event of gastric polyps noted as moderate intensity in the lansoprazole group and no events marked as severe in either group. Two of the gastric polyp cases and the duodenal polyp case in the lansoprazole group were recorded as recovered/resolved, with the remaining eight

TEAEs recorded as not recovered/not resolved (five in the Voquezna group; three in the lansoprazole group). Overall, no imbalance was noted between treatment groups.

Severe Cutaneous Adverse Reactions

There were no cases of serious cutaneous adverse reactions (SCARs), including toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), or drug reaction with eosinophilia and systemic symptoms (DRESS) reported during the healing phase.

In addition to SCARs, the other cutaneous adverse reactions were evaluated. Overall, rashes were uncommon, occurring in approximately 0.5% of subjects. Rashes were reported in two subjects in the Voquezna group, compared to three subjects in the lansoprazole group. None of the events were reported as serious or severe, with the remaining events reported as mild or moderate severity (1 each mild and moderate in Voquezna group; 2 mild and 1 moderate in lansoprazole group). Only one event (pruritic rash) in a subject in the lansoprazole group was recorded as not recovered/not resolved at the end of the study. One subject in the lansoprazole group had study drug interrupted due to allergic dermatitis and one subject (in the Voquezna group discontinued study drug and withdrew due to maculopapular rash. Refer to Section 7.6.1.4 for full narrative of this case.

Hypersensitivity Reactions

There were no cases of drug hypersensitivity reactions reported in the healing phase in either treatment group.

Acute Tubulointerstitial Nephritis

There were no cases of ATN (including tubulointerstitial nephritis, TIN) reported in either treatment group in the healing phase. A single case of hematuria was reported in one subject ([redacted] (b) (6)) in the lansoprazole group compared to none in the Voquezna group. However, there are many potential causes of hematuria, and this case is not reported as related specifically to ATN.

Cutaneous/Systemic Lupus Erythematosus

There were no cases of cutaneous/systemic lupus erythematosus (CLE/SLE) or associated terms reported in the healing phase.

7.6.1.6. Laboratory Findings, EE-301, Healing Phase

Safety assessments in Study EE-301 included laboratory assessments, vital signs, and electrocardiograms (EGCs) according to the Schedule of Events (see Section 15.2). Overall, no clinically meaningful changes from baseline were seen in routine laboratory parameters (e.g., electrolytes, renal function) or vital signs in either the Voquezna or lansoprazole treatment groups in Study EE-301. Magnesium, vitamin B12, vitamin D, albumin, and phosphorus were not assessed.

Electrocardiograms

Vonoprazan is not associated with clinically relevant QT prolongation based on a previously conducted thorough QT study which was reviewed under IND 143190 (treatment of *H. pylori*). The study was determined to be adequate in design to characterize the effect of vonoprazan on the QTc interval and the results showed that at a dose 6 times the maximum recommended dose, vonoprazan does not prolong the QT interval to any clinically relevant extent (see integrated review for NDA 215152).

Electrocardiograms were obtained at baseline in all subjects in Study EE-301; however, EGCs were not obtained in all subjects at the end of the healing phase. Also, subjects were not excluded from the trial for an abnormal QT interval at baseline. At baseline in the Voquezna group there were 4 subjects with QTcF > 450 msec and 2 subjects with QTcF > 480 msec. Only subjects who discontinued during the healing phase or whose EE was not healed at the end of the healing phase had ECGs performed post-baseline in the healing phase, including 16 subjects in the Voquezna group

Of the subjects with an available ECG at the end of the healing phase in the Voquezna 20 mg group, including those with abnormal QT values at baseline, one subject in the (b) (6) had a post-baseline QTcF value greater than 450 msec. The subject's QTcF was 458 msec at baseline and 467 msec at the early termination visit after voluntarily withdrawing from the study. No other QTcF abnormalities were reported in this group.

No subject had a reported TEAE associated with these changes.

Selected Laboratory Findings

This subsection includes the discussion of selected laboratory findings relevant to AESIs:

- Liver biochemistry (as related to AESI of hepatotoxicity (clinical chemistries, DILI analysis)
- Hematologic assessments (as related to AESI of hematologic abnormalities).

For a discussion of gastrin (as related to AESI of fundic gland polyps), see Section 7.6.2.6 Laboratory Findings, EE-301, maintenance phase.

Liver Biochemistry

Few subjects had any elevation of liver biochemistry exceeding specified levels defined by the applicant during the healing phase. Results were comparable between subjects receiving Voquezna or lansoprazole. There were no discontinuations due to elevated hepatic enzyme assessments or suspected drug-induced liver injury (DILI) during the healing phase. In the Voquezna group, there were two subjects with alkaline phosphatase > 2x ULN and one subject with alanine aminotransferase > 5x ULN. No subject in either group had alkaline phosphatase > 3x ULN, alanine aminotransferase > 10x ULN, aspartate aminotransferase > 10x ULN.

Table 43 shows subject-level data from the DILI analysis (Figure 17), including four Temple's corollary and two cholestasis cases. There were no Hy's Law cases. There were three Temple's corollary cases in the Voquezna group compared to one in the lansoprazole group.

Table 43. DILI Analysis, Individual Subject Listing, EE-301, Healing Phase

Subject ID	Treatment Arm	Maximum ALT/AST (xULN)	Maximum Bilirubin (xULN)
Temple's Corollary Cases			
(b) (6)	Vonoprazan 20 mg	3	0.78
*	Vonoprazan 20 mg	5.97	0.38
*	Vonoprazan 20 mg	4.12	0.56
	Lansoprazole 30 mg	3.11	0.33
		Maximum ALP (xULN)	**Maximum Bilirubin (xULN)**
Cholestasis Cases			
(b) (6)	Vonoprazan 20 mg	0.44	2.15
	Vonoprazan 20 mg	0.49	2.03

Source: adlb.xpt; Software: R
* Also reported as a TEAE of hepatoxicity due to transaminase >3x ULN
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

A summary of cases involving Temple's corollary cases in subjects treated with Voquezna follows:

- Subject (b) (6) had an elevation of ALT to 3x ULN noted at the Week 2 visit. At that time, his AST was slightly elevated to 1.7x ULN. He continued to receive study drug and was re-randomized into the maintenance phase to receive Voquezna 10 mg daily. His AST and ALT decreased to baseline values by the maintenance Week 4 visit, but then showed gradually increasing levels over the maintenance phase, with levels approaching 2.7x ULN and 1.6x the ULN for ALT and AST, respectively. Although the ALT and AST levels fluctuated while on Voquezna, a relationship cannot be excluded, a relationship to Voquezna cannot be excluded. Increased liver function tests were observed as a TEAE in <1% of subjects and recommended for inclusion in labeling.
- Subject (b) (6) is a 48-year-old male subject who developed a mild venous thrombosis on Day 20 of Voquezna 20 mg daily. He was treated with low-molecular weight heparin (nadroparin and bemparin) through Day 42. On Day 34, the subject had an ALT >5x ULN and AST 1.6x ULN and the investigator reported an AE of elevated transaminases. The values decreased without alteration of Voquezna dosing by the end of the healing phase. Elevated transaminases have been reported with nadroparin (Drugbank 2022). Therefore, a relationship between Voquezna and transaminase elevation cannot be confirmed.
- Subject (b) (6) was a 32-year-old male who developed a toothache on Day 11, associated with mild fatigue. On Day 20, the subject was noted to have ALT >3x ULN, alkaline phosphatase >1.5x ULN and AST and GGT above the normal range. A mild lymphocytosis was also reported (5K cells/uL, normal range 0.9-3.6). The laboratory abnormalities all normalized by Day 53 without alteration of Voquezna treatment, making it unlikely that the laboratory changes were related to Voquezna treatment.

Hematologic Assessments

No clinically significant decreases in hematologic parameters were seen in any subject in the healing phase.

In the healing phase, the number of subjects with decreases in hemoglobin levels were similar in both treatment arms: fourteen subjects treated with Voquezna (2.9%) and fifteen subjects treated with lansoprazole (3.1%). None of the reported decreases resulted in clinically meaningful anemia.

With respect to other hematologic parameters, neither treatment group reported clinically significant decreases (i.e., platelets <100,000 cells/uL; WBC <1000 cells/uL; lymphocytes, neutrophils < 500 cells/uL). Lower severity decreases in hematologic indices were reported in both treatment groups, with similar occurrence in both groups (lymphocytes, neutrophils) or a numerically greater number in the lansoprazole group compared to Voquezna (WBC, platelets).

Overall, there were no clinically meaningful decreases in hematologic indices during the healing phase and no imbalance of Voquezna relative to lansoprazole.

Serum Gastrin (Related to Fundic Gland Polyps/Gastric Cancer)

Serum gastrin is a trophic factor, and it has been proposed that elevated serum gastrin may lead to increased risk of development of gastric neoplasm and benign gastric polyps.

PPIs are known to increase serum gastrin levels. Given similar effect on acid suppression, it was expected that Voquezna might show a similar effect on serum gastrin levels.

A full discussion of laboratory assessments related to serum gastrin is found in Section 7.6.2 (Safety Findings and Concerns, EE-301, Maintenance Phase).

7.6.2. Safety Findings and Concerns, EE-301, Maintenance Phase

As previously described, subjects who achieved healing at either the week 2 or week 8 endoscopic assessment during the healing phase of Study EE-301 were re-randomized into the maintenance phase to receive Voquezna 10 mg, Voquezna 20 mg or lansoprazole 15 mg once daily for 24 weeks.

Table 44 shows the duration of exposure to study drug during the maintenance phase of Study EE-301. Most subjects in either treatment arm received more than 140 days (20 weeks) of treatment (94% and 92% for vonoprazan 10 mg and 20 mg and 95% for lansoprazole, respectively) with approximately 60% completing more than 168 days. There is no meaningful difference in exposure to study drug between treatment groups.

Table 44. Duration of Exposure, Safety Population, Study EE-301-Maintenance Phase

Parameter	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Duration of treatment, days			
Mean (SD)	165.4 (25.5)	164.2 (29.2)	165.3 (27.1)
Median (Q1, Q3)	170 (167, 174)	170 (167, 173)	170 (168, 174)
Min, Max	20, 203	5, 212	4, 212
Total exposure (person years)	134	133	134
Subjects treated, by duration, n (%)			
≥1 to ≤28 days	4 (1.4)	4 (1.4)	5 (1.7)

Parameter	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
>28 to ≤56 days	2 (0.7)	3 (1.0)	2 (0.7)
>56 to ≤84 days	6 (2.0)	10 (3.4)	5 (1.7)
>84 to ≤112 days	1 (0.3)	1 (0.3)	3 (1.0)
>112 to ≤140 days	4 (1.4)	4 (1.4)	3 (1.0)
>140 to ≤168 days	106 (35.8)	91 (30.7)	97 (32.7)
>168 days	173 (58.4)	183 (61.8)	182 (61.3)

Source: adex.xpt and adsl.xpt; Software: R
Duration is 24 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6.2.1. Overall Adverse Event Summary, EE-301, Maintenance Phase

Table 45 provides a summary of treatment-emergent adverse events (TEAEs) reported during the Maintenance Phase of Study EE-301. Overall, there were few SAEs or AEs leading to discontinuation/interruption of study drug. The protocol did not include any option for dose reduction or delayed dosing. Most TEAEs were classified as mild to moderate in severity by the investigator. There were no meaningful differences between Voquezna 10 mg, the recommended maintenance dosage, versus lansoprazole in the percentage of subjects who experienced SAEs, TEAEs leading to study drug interruption or study discontinuation. In addition, the severity of TEAEs was similar in these groups.

In the group of subjects who received the 20 mg dosage of Voquezna, a larger proportion of subjects discontinued due to TEAEs compared to lansoprazole and a larger proportion reported severe AEs. See also Section 7.6.2.4.

Table 45. Overview of Adverse Events, Safety Population, Study EE-301, Maintenance Phase

Event Category	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
SAE	10 (3.4)	14 (4.7)	7 (2.4)
SAEs with fatal outcome	0	2 (0.7)	0
AE leading to permanent discontinuation of study drug	2 (0.7)	8 (2.7)	2 (0.7)
AE leading to interruption of study drug	5 (1.7)	8 (2.7)	9 (3.0)
Any AE	160 (54.1)	167 (56.4)	150 (50.5)
Severe [a]	8 (2.7)	17 (5.7)	8 (2.7)
Moderate	80 (27.0)	86 (29.1)	66 (22.2)
Mild	72 (24.3)	64 (21.6)	76 (25.6)

Source: adae.xpt; Software: R
[a]Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, EE-301, Maintenance Phase

Two subjects died during the maintenance phase of Study EE-301. Both were assigned to the Voquezna 20 mg treatment group. Death was attributed by the applicant to complications of

SARS-CoV2 infection/COVID-19 in both cases. The investigator determined the deaths as unrelated to study drug.

7.6.2.3. Serious Adverse Events, EE-301, Maintenance Phase

Serious TEAEs (SAEs) are shown in Table 46. Ten subjects (3.4%) in the Voquezna 10 mg group reported eleven SAEs. Fourteen subjects (3.4%) in the Voquezna 20 mg group reported thirteen SAEs, including the two subjects who died due to complications of COVID-19. Eight subjects (4.7%) in the lansoprazole 15 mg group experienced nine SAEs. COVID-19 was the only SAE reported in more than one subject.

Table 46. Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study EE-301-Maintenance Phase

Preferred Term	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Subjects experiencing any SAE	10 (3.4)	14 (4.7)	8 (1.6)
SAE cases (PT) [verbatim term, where appropriate]			
COVID-19[a]	2 (0.7)	4 (1.4)	0
Aortic aneurysm [worsening of aortic aneurysm]	1 (0.3)	0	0
Diverticulitis [worsening of diverticulitis]	1 (0.3)	0	0
Gastric bypass	1 (0.3)	0	0
Intervertebral disc protrusion	1[c] (0.3)	0	0
Large intestine polyp	1 (0.3)	0	0
Lower limb fracture	1 (0.3)	0	0
Melena	1[c] (0.3)	0	0
Rotator cuff syndrome	1 (0.3)	0	0
Sinusitis	1 (0.3)	0	0
Anemia	0	1 (0.3)	0
Chest discomfort	0	1 (0.3)	0
Edema peripheral	0	1 (0.3)	0
Follicular thyroid cancer	0	1 (0.3)	0
Myocardial infarction	0	1 (0.3)	0
Pancreatitis [post-ERCP pancreatitis]	0	1 (0.3) [d]	0
Pancreatolithiasis	0	1 (0.3) [d]	0
Peritonsillar abscess	0	1 (0.3)	0
Presyncope	0	1 (0.3)	0
Small intestine adenocarcinoma	0	1 (0.3)	0
Tubulointerstitial nephritis	0	1 (0.3)	0
Acute respiratory distress syndrome	0	0	1 (0.3)
Adenocarcinoma [mucocellular carcinoma]	0	0	1 (0.3)[e]
Ileus	0	0	1 (0.3)[e]
Diabetes mellitus [worsening of DM type 2]	0	0	1 (0.3)
Traumatic hemothorax	0	0	1 (0.3)
Ligament injury	0	0	1 (0.3)
Stress urinary incontinence	0	0	1 (0.3)
Umbilical hernia	0	0	1 (0.3)

Source: adae.xpt; Software: R
[a] Includes Covid-19, Covid-19 pneumonia
[b] Includes AEs occurring reported during the maintenance and follow-up periodics
[c] Subject (b) (6) reported both melena and intervertebral disc protrusion.
[d] Subject (b) (6) reported both pancreatitis and pancreatolithiasis
Abbreviations: DM, diabetes mellitus; ERCP, Endoscopic retrograde cholangiopancreatography; N, number of patients in treatment arm; n, number of patients with adverse event; NR = not related

The treatment with study drug was unlikely to contribute to the SAEs related to infectious diseases (Covid-19, diverticulitis, or sinusitis), given that neither vonoprazan nor lansoprazole is likely to cause immunosuppression that would increase the risk of infections (except *C. difficile* enterocolitis). Gastric bypass is a surgical procedure, unrelated to drug treatment. Additionally, the traumatic AEs, including intervertebral disc protrusion, traumatic hemothorax, ligament injury, and rotator cuff syndrome appear unlikely to be due to study drug. One subject in the Voquezna 10 mg group experienced an SAE of lower extremity fracture, which is discussed elsewhere (Refer to Section 7.7.2.1). One subject in the Voquezna 20 mg group reported an SAE of anemia, which is discussed elsewhere. Refer to Section 7.7.1.

Among the SAEs reported, three subjects, all in the Voquezna 20 mg group, had serious TEAEs considered related to study drug by the applicant, including follicular thyroid cancer in one subject, small intestine adenocarcinoma in one subject, and tubulointerstitial nephritis in one subject. These cases are discussed below.

- Subject (b) (6) (50-year-old, male, healing phase Voquezna 20 mg, maintenance phase Voquezna 20 mg). The subject was found to have EE healing after receiving Voquezna 20 mg for 64 days and was randomized to receive Voquezna 20 mg for maintenance. On day 157 of maintenance, he experienced a TEAE of follicular thyroid cancer. The investigator assessed the TEAE as serious, severe, and related to study drug. He continued study treatment and completed the study after 203 total days of maintenance (Voquezna 20 mg for 267 total days). The SAE was recorded as resolved/recovered with end of occurrence 39 days after last dose of Voquezna.

  Thyroid cancers of all types have an incidence of 13 cases/100,000 people/year, with most cases occurring in white patients, age 50-59, like Subject (b) (6). (U.S. Cancer Statistics Working Group 2022) Follicular thyroid cancer accounts for approximately 10-15% of all thyroid cancers. (Aschebrook-Kilfoy et al. 2013) Therefore, it is possible that this case represents the background rate of thyroid cancers. Whether use of Voquezna is associated with the event is unclear. Routine postmarketing surveillance is adequate to assess thyroid cancer as a possible safety signal. A single case does not support including thyroid cancer in labeling at this time.

- Subject (b) (6) (73-year-old, male, healing phase Voquezna 20 mg, maintenance phase Voquezna 20 mg). His end-of-treatment endoscopy showed a duodenal mass. According to the case report submitted by the Applicant, previous endoscopic assessments at screening, Weeks 2 and 8 of the healing phase had not demonstrated any duodenal abnormalities at that anatomic region. Biopsy of the mass revealed a tubulo-villous adenoma, the subject discontinued participation in the study to obtain medical treatment. Subsequent biopsy confirmed poorly differentiated adenocarcinoma and possible lung metastases. The investigator assessed the TEAE as serious, severe, and related to study drug.

Small bowel adenocarcinomas (SBA) are rare, with an incidence estimated between 0.4 to 0.7 per 100,000 people in Europe and the United States. SBA occurs most often in men in their sixth decade. (Aparicio et al. 2022) No additional reports of small bowel adenocarcinomas have been reported by the Applicant since the original case report submitted to IND 079212. A single case does not support including small bowel adenocarcinoma in the labeling. Routine post-marketing surveillance is adequate to monitor this event.

- Subject (b) (6), a 64-year-old male with prior history of omeprazole treatment for eight years prior to study enrollment, was assessed as healed after 23 days of lansoprazole 30 mg in the healing phase. At an unreported time during the healing phase, he started on sertraline for depression and atorvastatin for hypercholesterolemia. He was randomized to receive Voquezna 20 mg during the maintenance phase. On Maintenance Day 37, the subject was hospitalized due to acute tubulointerstitial nephritis confirmed on biopsy. The investigator considered the event to be related to study drug, as a causal association could not be excluded based on the temporal relationship to study drug exposure.

  Electron microscopy revealed minimal change disease. Treatment for the event included dialysis, intravenous fluids, and intravenous solumedrol followed by oral prednisone. His laboratory studies, including serum chemistries, urinalysis, and serum eosinophils, remained normal throughout the study. The study drug and atorvastatin were withdrawn. The subject was discharged from the hospital and followed by a nephrologist. Dialysis continued until Maintenance Day 62. The event was considered severe in intensity and was noted as recovered/resolved on Maintenance Day 101.

Acute tubulointerstitial nephritis (AIN) may be due to autoimmune disease, infections, drug-induced or idiopathic. The precise pathophysiology of drug-induced AIN is unknown but may be antibody mediated or related to direct drug toxicity or a delayed Type IV hypersensitivity reaction. (Sanchez-Alamo et al. 2022) AIN is reported with PPIs, occurring between 1 week to 9 months following drug exposure.

The role of vonoprazan in the subject's AIN is unclear. The subject was treated with PPIs, including omeprazole, prior to enrolling in the study and received lansoprazole 30 mg daily for 23 days during the healing phase. Atorvastatin was started during the healing phase, continued into the maintenance phase, and was discontinued prior to AIN recovery. Renal failure has been reported with atorvastatin. Therefore, the assessment of AIN with vonoprazan cannot be conclusively established based on this case. However, given the importance of this event as an AESI, since AIN has been previously associated with PPIs, tubulointerstitial nephritis was included in the less common adverse reactions in the labeling.

Although the Applicant did not assess any SAEs in the Voquezna 10 mg group as being related to study drug, a brief summary of the cases follows:

- Subject (b) (6) was a 68-year-old female (healing phase lansoprazole; maintenance phase Voquezna 10 mg) with an SAE of a large intestine polyp, identified following hospitalization for an unscheduled colonoscopy that occurred on Maintenance Day 101. Given high background rates of large intestine polyps in patients over age 60, it is unlikely that the colon polyp was related to Voquezna treatment.
- Subject (b) (6), a 59-year-old male, received Voquezna 20 mg for 8 weeks during the healing phase and was re-randomized to maintenance treatment with Voquezna 10 mg. On Day 173 of the maintenance phase, he was found to have worsening of a pre-existing aortic aneurysm, requiring hospital admission for surgical repair. No change was made to his treatment regimen. This subject had a pre-existing aortic aneurysm and although a non-serious TEAE of aortic aneurysm (verbatim "aortic artery enlargement") was reported in another subject ((b) (6), a 70-year-old male) on Day 10 of the maintenance phase, after having received Voquezna 20 mg for 16 days in the healing

phase, there does not appear to be a plausible pathophysiologic mechanism to link this drug to the development of aortic aneurysm.

- Subject (b) (6), a 46-year-old male with a prior history of hypertension, unspecified non-infectious colitis, and low back pain, and previously treated with pantoprazole for GERD, received Voquezna 20 mg for 27 days during the healing phase and was re-randomized to receive Voquezna 10 mg in the maintenance phase. During the healing phase (study day unknown) he started nebivolol hydrochloride for hypertension. On day 162 of maintenance, the subject was hospitalized for low back pain and diagnosed with an intervertebral disc protrusion. He was treated with dexamethasone, dexketoprofen, etodolac, baclofen, mannitol and metamizole sodium. He was discharged from the hospital on Day 167. On day 168 of maintenance, the subject underwent the EOT endoscopy and discontinued study drug. The following day, he was hospitalized for melena, with weakness, easy fatigue, upper abdominal pain, and tarry black stools. The Investigator assessed the event as serious and moderate in intensity and unrelated to study drug. He was treated with famotidine, and intravenous fluids. A second endoscopy was performed, showing gastric erythema and erosive gastritis as the cause of the melena. He was discharged from the hospital on Day 172 and the SAE was reported as recovered/resolved on maintenance day 172. The Investigator assess the event as not related based on concomitant medications (i.e., NSAIDs) and post-procedural status (upper endoscopy with gastroscopy). The Applicant assessed the event as not related to study dose.

There are multiple confounding elements that preclude assigning causality to vonoprazan, as noted by the Applicant. Further support that the gastritis and resulting melena were unrelated to vonoprazan includes the lack of gastritis on the end of treatment endoscopy while the subject was on study drug. Therefore, this case does not likely represent gastritis caused by vonoprazan. However, gastritis was observed in the study as a common adverse reaction and therefore is recommended for inclusion in labeling.

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, EE-301, Maintenance Phase

Table 47 shows the TEAEs that led to discontinuation of study drug and discontinuation from the study in the maintenance phase of Study EE-301. Two subjects (0.7%) in the Voquezna 10 mg group, eight subjects (2.7%) with ten TEAEs in the Voquezna 20 mg group and 2 subjects (0.7%) in the lansoprazole 15 mg group experienced TEAEs that lead to drug/study discontinuation. There was no apparent trend observed for individual TEAEs that led to discontinuation. The only TEAEs that led to discontinuation of treatment that were experienced by more than one subject in any treatment group were gastroesophageal reflux disease (GERD) and COVID-19, reported for 2 subjects each in the Voquezna 20 mg group. Although a larger proportion of subjects in the Voquezna 20 mg group experienced drug/study discontinuation compared to either the Voquezna 10 mg and lansoprazole 15 mg groups, this is driven by TEAEs of COVID-19, GERD, and pregnancy (total of 5 subjects) which are not plausibly attributable to Voquezna.

Table 47. Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study EE-301-Maintenance Phase

Preferred Term	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Subjects with Any AE leading to Discontinuation	2 (0.7)	8 (2.7)	2 (0.7)
AE (PT)			
Abdominal pain upper	1 (0.3)	1 (0.3)	0
Rash maculo-papular	1 (0.3)	0	0
COVID-19	0	2 (0.7)	1 (0.3)
Gastroesophageal reflux disease	0	2 (0.7)	0
Depressed mood	0	1 (0.3) [A]	0
Dizziness	0	1 (0.3) [B]	0
Pregnancy	0	1 (0.3)	0
Rash macular	0	1 (0.3) [A]	0
Tubulointerstitial nephritis	0	1 (0.3)	0
Vomiting	0	1 (0.3) [B]	0
Colitis microscopic	0	0	1 (0.3)

Source: adae.xpt; Software: R, JMP Clinical
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug in that study phase or any event at baseline that worsened in either intensity or frequency after the first dose of study drug in that study phase.
Duration is 24 weeks.
[A] Subject (b) (6) reported depressed mood and macular rash
[B] Subject (b) (6) reported dizziness and vomiting.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Brief narratives of TEAEs leading to treatment discontinuation for the subjects treated with Voquezna 10 mg or Voquezna 20 mg follows. The narrative for Subject (b) (6), a 64-year-old male who discontinued due to tubulointerstitial nephritis (also an SAE) was previously discussed. Refer to Section 7.6.2.5.

Voquezna 10 mg

- Subject (b) (6), a 74-year-old female, was considered healed on Day 35 of Voquezna 20 mg in the healing phase. She was re-randomized to receive Voquezna 10 mg in the maintenance phase. On Maintenance Day 54, she experienced mild abdominal pain, recorded as resolved on Maintenance Day 70 without treatment. On Maintenance Day 92 she experienced mild abdominal distention which was recorded as resolved on Maintenance Day 112 without treatment. The Investigator considered both events to be related to study drug. On Maintenance Day 125, she again experienced mild abdominal pain. The subject discontinued the study drug due to the event, with the last dose on Maintenance Day 131. No treatment was recorded, and the event was noted as recovered/resolved on Maintenance Day 134.

  Concurrent medical conditions reported were arrhythmia, spinal osteoarthritis, hypertension, hypothyroidism, type 2 diabetes mellitus, and osteoarthritis; concomitant medications included verapamil, levothyroxine sodium, losartan potassium, indapamide, and thioctic acid.

  The subject's abdominal pain was intermittent in nature and resolved without withdrawal of treatment in the earlier reported episode. Further, there is confounding due to her complex medical history and use of concomitant medications that are reported to be

associated with abdominal pain (i.e., indapamide). Abdominal pain was reported as a TEAE in other subjects in the maintenance phase of the study and is recommended for inclusion in labeling.

- Subject (b) (6), a 30-year-old male, was considered healed by endoscopy on Day 21 of lansoprazole 30 mg in the healing phase. He was re-randomized to receive Voquezna 10 mg in the maintenance phase. On Day 20 of maintenance treatment, he experienced a maculopapular rash. No treatment was given. Study drug was discontinued on Maintenance Day 23. The event was recorded as resolved on Maintenance Day 27. The Investigator considered the event to be of moderate severity and likely related to study drug due to temporal relationship. The reviewer concurs with this assessment. Rash was reported as a TEAE in other subjects in the trial and is recommended for inclusion in labeling.

Voquezna 20 mg

- Subject (b) (6), a 47-year-old male, withdrew from the trial due to the TEAE of depressed mood. Concurrent medical conditions reported were hyperlipidemia, dyspepsia, irritable bowel syndrome, hepatic cyst (benign), anal pruritus, blood glucose abnormal, and back pain; concomitant medication included topical diclofenac diethylamine and corticosteroids in combination with antibiotics for treatment of anal itching.

  He was considered healed after 15 days of lansoprazole 30 mg in the healing phase and was re-randomized to receive Voquezna 20 mg in the maintenance phase. On Maintenance Day 96, exostosis and serum uric acid increase were noted. The Investigator considered both events to be of moderate severity and unrelated to study drug. He was treated with allopurinol and meloxicam. The exostosis was reported as recovered/resolved on Maintenance Day 128. The elevated uric acid was reported as ongoing.

  On Maintenance Day 123, he experienced abdominal pain, dyspepsia and worsening of GERD. The Investigator considered all events to be of moderate severity and unrelated to study drug. The subject was treated with antacids and drotaverine (a phosphodiesterase-4 inhibitor anti-spasmodic). The abdominal pain was recovered/resolved on Maintenance Day 155, but GERD and dyspepsia were noted as ongoing.

  On Maintenance Day 146, the subject reported mild back pain, considered unrelated to study drug. He was treated with paracetamol/tramadol on Maintenance Day 148, but the event was recorded as ongoing.

  On Maintenance Day 150, the subject experienced depressed mood and a macular rash. The Investigator considered these events to be mild in intensity and unrelated to study drug. The subject discontinued study drug due to these events and received his last dose of study drug on Maintenance Day 150.

  He underwent the Week 24 endoscopy on Maintenance Day 168 and was diagnosed with mild erythematous gastropathy. The investigator considered the event to be mild intensity and unrelated to study drug, given temporal relationship.

The prescribing information for tramadol/acetaminophen (paracetamol) includes a Warning and Precaution for suicide risk, and the temporal relationship supports an association between the analgesic and the TEAE of depression. Although this case appears unrelated to vonoprazan, depression was observed in other subjects as a TEAE in the study overall and is recommended for inclusion in labeling.

- Subject (b) (6), a 72-year-old female, withdrew from the trial due to abdominal pain. Concurrent medical conditions reported were scoliosis, headache, osteoarthritis, hyperlipidemia, hypertension, hypothyroidism, obesity, intervertebral disc disorder, type 2 diabetes mellitus, gastritis, hiatus hernia, eye pain, hepatic steatosis, duodenogastric reflux, autoimmune thyroiditis, exostosis, chondromalacia, myocardial ischemia, arteriosclerosis, gastroesophageal sphincter insufficiency, acquired esophageal web, and gastric disorder; concomitant medications included gliclazide, atorvastatin calcium, nebivolol hydrochloride, metformin hydrochloride, ramipril, indapamide, and levothyroxine sodium.

  She received Voquezna 20 mg for 21 days during the healing phase, with an AE reported of worsening of GERD on Day 20. The Investigator considered the event to be severe and unrelated to study drug. Of note, the subject was considered healed on her Week 2 endoscopy. She was re-randomized to receive Voquezna 20 mg daily during the maintenance phase. On Maintenance Day 8, she reported severe abdominal pain. Her abdominal pain and GERD were treated with calcium carbonate/magnesium carbonate with decrease in intensity from severe to mild reported on Day 18. However, she discontinued the study due to these events, receiving her last dose of study drug on Maintenance Day 20. She began treatment with pantoprazole on Maintenance Day 22, with both events noted as recovered/resolved on Maintenance Day 28.

  Although treatment failure (for reflux symptoms) may explain the subject's abdominal pain, it is possible that vonoprazan may have contributed to her symptoms. However, there are other confounding elements including concomitant medications that are associated with abdominal pain (indapamide, metformin, ramipril). Therefore, the association between vonoprazan and her abdominal pain remains inconclusive. However, as previously noted, abdominal pain was observed as a common adverse reaction in the maintenance phase and is recommended for inclusion in labeling.

- Subject (b) (6), a 73-year-old female, withdrew from the trial due to vomiting and dizziness. Concurrent medical conditions reported were obesity, osteoarthritis, hypertension, diverticulum intestinal, varicose veins, dyspepsia, gastric polyps, and hiatus hernia; concomitant medications included nebivolol, indapamide, and telmisartan. The subject had never smoked and never drank alcohol.

  She received Voquezna 20 mg daily for 16 days in the healing phase. She was considered healed at Week 2 and was re-randomized to receive Voquezna 20 mg daily during the maintenance phase. On Maintenance Day 174, she experienced vomiting and dizziness. The Investigator considered both events to be moderately severe and not related to study drug. The subject discontinued the study, with the last dose on Day 174. The events were recorded as recovered/resolved on Day 177.

  Although there is a temporal association between vonoprazan treatment and vomiting/dizziness, there is confounding due to multiple concomitant medications that

are associated with these either dizziness, vomiting, or both (e.g., nebivolol, indapamide, telmisartan). Therefore, the association between vonoprazan and vomiting or dizziness remains inconclusive. However, both vomiting and dizziness were observed as less common adverse reactions in the study and both terms are recommended for inclusion in labeling.

7.6.2.5. Treatment-Emergent Adverse Events, EE-301, Maintenance Phase

This section describes the treatment emergent adverse events (TEAEs), reported during the maintenance phase of EE-301.

TEAEs Reported in >2% of Subjects

Table 48 shows the TEAEs that were reported in more than 2% of subjects in any treatment arm during the maintenance phase of Study EE-301, including TEAEs reported during the 4 weeks after the last dose of study drug (i.e., the "Safety Follow-Up Period"). For list of grouped terms, see Appendix, Table 97. There was no meaningful difference between rates in subjects assigned to any treatment arm for these TEAEs.

The review team determined that TEAEs reported in more than 2% of subjects in Voquezna 10 mg and lansoprazole groups, after rounding, represented the appropriate cut-point to capture the adverse events plausibly related to vonoprazan in the maintenance phase for inclusion in labeling as a table of adverse reactions (i.e., gastritis, abdominal pain, dyspepsia, hypertension, urinary tract infection, diarrhea, and headache). COVID-19 infection was deemed unlikely to be related to use of study drug and gastroesophageal reflux disease (GERD) were likely related to the subject's underlying condition and not plausibly related to vonoprazan; therefore, these terms were not included in labeling, although they were reported in more than 2% of subjects, after rounding.

In the higher 20 mg Voquezna dose group, TEAEs plausibly related to vonoprazan reported in more than 2% of subjects, after rounding were abdominal pain, gastritis, dyspepsia, back pain, hypertension, arthralgia, and diarrhea. Although there were numerically greater numbers of subjects with TEAEs overall in the Voquezna 20 mg group compared to the Voquezna 10 mg group, there was not a clear dose-related increase in TEAEs that are thought to represent adverse reactions. Given that the Voquezna 20 mg dose did not show increased efficacy compared to Voquezna 10 mg dose, there is no benefit to justify the additional exposure, and therefore it is not recommended for approval.

In the analysis, the TEAE group term of hepatic enzyme increased was reported in 0.7% of subjects treated with Voquezna 10 mg, 1.7% of subjects treated with Voquezna 20 mg, 3.4% of subjects treated with lansoprazole. Although >2% of the subjects in the lansoprazole group reported hepatic enzyme elevation, the percentage of subjects in the Voquezna 10 mg group was less than 1%.

Table 48. Treatment-Emergent Adverse Events Occurring in >2% of Subjects in Any Treatment Arm, Safety Population, Study EE-301-Maintenance Phase

Preferred Term	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Subjects experiencing any TEAE	162 (54.7)	166 (56.1)	152 (51.2)
Gastritis [A]	***19 (6.4)*** [G]	8 (2.7)	***8 (2.7)***
Coronavirus infection [B]	18 (6.1)	30 (10.1)	20 (6.7)
Abdominal pain [C]	***12 (4.1)***	16 (5.4)	***6 (2.0)***
Dyspepsia	***11 (3.7)***	12 (4.1)	***8 (2.7)***
Hypertension [D]	***10 (3.3)***	10 (3.3)	***6 (2.0)***
Gastroesophageal reflux disease [E]	9 (3.0)	9 (3.0)	6 (2.0)
Urinary tract infection	***8 (2.7)***	1 (0.3)	***7 (2.4)***
Back pain [F]	7 (2.4)	10 (3.4)	6 (2.0)
Sinusitis	7 (2.4)	4 (1.4)	1 (0.3)
Nausea	6 (2.0)	3 (1.0)	3 (1.0)
Hepatic enzyme increased [H]	3 (1.0)	7 (2.4)	9 (3.0)
Diarrhea	***3 (1.0)***	7 (2.4)	***13 (4.4)***
Headache	***2 (0.7)***	2 (0.7)	***9 (3.0)***
Arthralgia	2 (0.7)	5 (3.0)	7 (2.4)
Bronchitis	2 (0.7)	1 (0.3)	7 (2.4)
ALL	132	193	116

Source: adae.xpt; Software: R, JMP Clinical
[A] Includes PTs: acute gastritis, chronic gastritis, gastritis, gastric mucosal erythema
[B] Includes PTs: coronavirus infection, COVID-19, COVID-19 pneumonia
[C] Includes PTs: abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness, abdominal pain
[D] Includes PTs: elevated blood pressure, hypertension, hypertensive emergency
[E] Includes PTs: erosive esophagitis, gastroesophageal reflux disease
[F] Includes PTs: back pain, spinal pain
[G] TEAEs of abdominal pain and abdominal pain upper were recorded in a single patient (Subject (b) (6)). Analysis counted only one of these events.
[H] Includes PTs: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hypertransaminemia, liver function test increased
Abbreviations: N, number of subjects; n, number of subjects with adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term
Terms in ***bold italics*** recommended for inclusion in Table in Section 6.1 of the Prescribing Information

TEAEs Reported in 2% or Fewer Subjects

TEAEs reported in 2% or less of subjects in the maintenance phase of Study EE-301 are shown in Table 107 in the Appendix.

TEAEs Related to Adverse Events of Special Interest

The following subsections address TEAEs reported during the maintenance phase of EE-301 that relate to the AESIs as defined in Section 7.4.2.

Hepatotoxicity

As discussed earlier in the review for the healing phase, investigators were instructed to report any clinically significant laboratory abnormalities as adverse events and the Applicant performed a broad search for hepatoxicity preferred terms. The reviewer's evaluation of potential hepatotoxicity with vonoprazan in the maintenance phase was based on both the TEAEs and analysis of hepatic laboratory data. TEAEs associated with hepatotoxicity were comparable between treatment groups. In each of the treatment groups, all hepatoxicity-related events were

mild or moderate in intensity, none was serious, and none led to discontinuation from treatment. The Investigator considered the events were related to drug study in two subjects in the Voquezna 10 mg group, one subject in the Voquezna 20 mg group, and six subjects in the lansoprazole 15 mg group.

Table 49. Adverse Events of Special Interest Assessment (Hepatotoxicity), Safety Population, Study EE-301-Maintenance Phase

Preferred Term	Voquezna 10 mg N=296 n (%)	Voquezna 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Subjects with at least one TEAE	5 (1.7)	8 (2.7)	9 (3.0)
Hepatic steatosis	2 (0.7) [A]	1 (0.3)	0
Alanine aminotransferase increased	1 (0.3)	4 (1.4)	2 (0.7)
Hepatomegaly	1 (0.3) [A]	1 (0.3)	0
Elevated transaminase [B]	1 (0.3)	0	0
Liver function test increased	1 (0.3)	0	0
Aspartate aminotransferase increased	0	1 (0.3)	0
Gamma-glutamyl transferase increased	0	0	1 (0.3)
Hepatic enzyme increased	0	1 (0.3)	5 (1.7)
Liver function test abnormal	0	0	1 (0.3)

Source: Reviewer-adapted from Clinical Study Report, EE-301, Table M12.p; confirmed by reviewer: adae.xpt, Software: JMP Clinical
[A] Subject (b) (6) reported both hepatomegaly and hepatic steatosis
[B] Appears in dataset as hypertransaminasemia.
Abbreviations: N, number of subjects; n, number of subjects with adverse event; MedDRA, Medical Dictionary for Regulatory Activities

Hematologic Abnormalities

Overall, hematologic TEAEs were uncommon. At least one hematologic TEAE was reported in two subjects in the Voquezna 10 mg group (0.7%), 3 subjects in the Voquezna 20 mg group (1.0%) and six subjects in the lansoprazole group (2.0%). One case of anemia in the Voquezna 20 mg group was considered serious and severe. One subject in the Voquezna 20 mg group reported three TEAEs (hematocrit and hemoglobin increased, red blood cell count increased), which were counted as one TEAE in the analysis. The remaining TEAEs were assessed as mild or moderate severity. Only one subject reported a polycythemia related TEAE. One case of thrombocytopenia, one case of leukopenia and one case of anemia in the lansoprazole group was considered related to study drug. No hematologic TEAEs in Voquezna subjects were considered related to study drug by the Applicant.

One subject in the Voquezna 20 mg group reported a serious TEAE of anemia that was not considered to be related to study drug by the investigator. The subject had a prior history of anemia and the hospital evaluation of his anemia revealed bleeding hemorrhoids. Platelet count was normal. Given plausible etiology as bleeding hemorrhoids with a normal platelet count and prior history of anemia, it is unlikely that the event is related to vonoprazan.

Bone Fracture

In the maintenance phase, two (0.7%) subjects in the Voquezna 10 mg group, five (1.7%) subjects in the Voquezna 20 mg group, and one (0.3%) subject in the lansoprazole 15 mg group experienced a TEAE associated with bone fracture. None of the bone fracture events was

considered related to study drug by the Applicant. One TEAE of lower limb fracture in the Voquezna 10 mg group was reported as serious.

The relationship between individual cases of bone fracture and treatment with Voquezna were assessed:

Voquezna 10 mg

- Subject (b) (6) was a 71-year-old male with a history of gastritis, liver steatosis and asthma, who had a severe TEAE of lower limb fracture reported on Maintenance Day 37. The subject was considered healed after fifteen days of healing phase treatment with lansoprazole 30 mg and re-randomized to receive Voquezna 10 mg in the maintenance phase. On Maintenance Day 37, he was hospitalized with TEAE of lower limb fracture (verbatim: left leg fracture), due to a fall, which required surgical reduction. He was discharged after six days. The subject continued in the study. The Investigator considered the TEAE not related to study drug. An association between vonoprazan and the fracture cannot be determined due to lack of information about prior treatment with acid suppressive medications prior to the study, limited information about the nature of the fall; however, it seems unlikely that a short duration of treatment with Voquezna contributed to the fracture.
- Subject (b) (6) is a 68-year-old female ((b) (6)), with a history of osteoarthritis, who reported a moderate event of hand fracture on Maintenance Day 73. Concomitant medications included torsemide. The subject was considered healed after sixteen days of healing phase treatment with lansoprazole 30 mg and was re-randomized to receive Voquezna 10 mg in the maintenance phase. On Maintenance Day 73, a TEAE of hand fracture (verbatim: fracture of the left metacarpal bone) was reported. The event was recorded as resolved on Maintenance Day 154. The Investigator considered the TEAE not related to study drug. Due to the concurrent treatment with a diuretic known to cause calcium and magnesium depletion, the association between vonoprazan and the fracture is unclear; however, a potential contribution of vonoprazan to the event cannot be excluded.

Voquezna 20 mg

- Subject (b) (6) was a 49-year-old female with history of ankylosing spondylitis who reported a TEAE of fractured sacrum. She was considered healed after 24 days of lansoprazole in the healing phase and was re-randomized to receive Voquezna 20 mg in the maintenance phase. On Maintenance Day 83, a severe TEAE of fractured sacrum (verbatim: bilateral sacral insufficiency fracture) was reported. The subject continued in the study. The event was recorded as recovering/resolving at the treatment follow-up visit. The event was considered not related to study drug by the Investigator. Sacral insufficiency fractures occur in approximately 10% of patients with ankylosing spondylitis; therefore, the association between vonoprazan and the fracture is unclear, however a potential contribution of vonoprazan to the event cannot be excluded.
- Subject (b) (6) was a 36-year-old male with a history of Raynaud's phenomena and hepatic steatosis, who reported a TEAE of ankle fracture. He was considered healed after 23 days of Voquezna 20 mg in the healing phase and was re-randomized to receive

Voquezna 20 mg in the maintenance phase. On Maintenance Day 161, he reported a moderate TEAE of ankle fracture (verbatim: right ankle fracture). He continued in the study and the event was recorded as not recovered/not resolved at the end of the study. The Investigator assessed the event as not related to study drug. The subject had no predisposing risk factors for fracture and received 184 days of Voquezna 20 mg during the trial; therefore, a potential association between the ankle fracture and vonoprazan cannot be excluded.

- Subject (b) (6) was a 54-year-old female with a relevant history of rheumatoid arthritis, hypertonic bladder, fibromyalgia, anxiety, insomnia, xerostomia, nausea, type 2 diabetes mellitus who reported a foot fracture. Concomitant medications included: methotrexate, hydrocortisone, folic acid, gabapentin, hydroxychloroquine, trazadone, linaclotide, pilocarpine, and ondansetron. She received 17 days of Voquezna 20 mg and was re-randomized to receive Voquezna 20 mg in the maintenance phase. On Maintenance Day 36 a moderate TEAE of foot fracture (verbatim: right foot fracture) was reported. She was treated with intraarticular cortisone. The event was recorded as recovered/resolved on Maintenance Day 58. The Investigator assessed the event as not related to study drug. Methotrexate carries a labeled risk of stress fractures; therefore, the association between vonoprazan and the fracture is unclear.
- Subject (b) (6) was a 28-year-old male with history of dyspepsia, spinal osteoarthritis and duodenitis. No concomitant medications were reported. He received 16 days of Voquezna 20 mg in the healing phase and was re-randomized to receive Voquezna 20 mg in the maintenance phase. On Maintenance Day 138, a moderate TEAE of radius fracture (verbatim: fracture of the right radial bone in the area of the elbow joint) was reported. He continued in the study. The fractured was recorded as not recovered/not resolved at the end of the trial. The Investigator assessed the event as not related to study drug. The subject had no predisposing risk factors for fracture and received had received 154 days of Voquezna 20 mg at the time of the TEAE. Therefore, a potential association between the ankle fracture and vonoprazan cannot be excluded.
- Subject (b) (6) was a 30-year-old female with history of intermittent abdominal bloating. Concomitant medications included levonorgestrel intrauterine device. She received 16 days of lansoprazole 30 mg in the healing phase and was re-randomized to receive Voquezna 20 mg in the maintenance phase. On Maintenance Day 56, a moderate TEAE of dental fracture (verbatim: microfracture left upper molar) was recorded. The event was reported recovered/resolved on Maintenance Day 70. The Investigator considered the TEAE not related to study drug. The potential association between vonoprazan and the fracture is unclear.

An association between Voquezna treatment and bone fracture cannot be conclusively established based on the cases reported during the maintenance phase of Study EE-301; however, a numerically greater number of events were reported in subjects receiving Voquezna 20 mg than in subjects receiving either Voquezna 10 mg or lansoprazole, including subjects who were treated with Voquezna 20 mg in both the healing and maintenance phase. This supports that Voquezna 10 mg may have a more favorable safety profile than Voquezna 20 mg and the selection of Voquezna 10 mg as the recommended dosage for the maintenance of healed EE indication. A WARNING AND PRECAUTIONS subsection for bone fracture is recommended for inclusion in labeling.

***Clostridiodes difficile*-associated Diarrhea (CDAD)**

There were no events related to *Clostridiodes-difficile* enteral infection (including *C. difficile* enterocolitis, bacterial enterocolitis attributable to *C. difficile*, and *C. difficile*-associated diarrhea) in the maintenance phase.

Hypomagnesemia

There were no TEAEs related to hypomagnesemia in the maintenance phase.

Cobalamin (Vitamin B12) Deficiency

There were no cases of vitamin B12 deficiency reported in the maintenance phase.

Fundic Gland Polyps

To assess the AESI of fundic gland polyps, the reviewer focused on TEAEs that related to polyps arising in gastric epithelium. Because polyps arising in the duodenum may occur in ectopic gastric epithelium, duodenal polyps were included. Gastric or duodenal polyps were reported in six subjects in the Voquezna 10 mg group versus two subjects in Voquezna 20 mg group and one subject in the lansoprazole group. All events were reported as mild (asymptomatic) and were identified incidentally on the end of treatment endoscopy. The TEAE reported in one subject in the Voquezna 10 mg group was recorded as recovered/resolved. The remaining TEAEs were recorded as not recovered/not resolved. The TEAE reported in the lansoprazole subject was considered related to study drug. None of the cases in Voquezna-treated subjects was considered related to study drug by the Investigator. No additional information was available regarding how the causality determination was made. In the absence of a plausible alternative explanation and the numerically greater number of gastric polyps seen in subjects treated with any dose of Voquezna compared to lansoprazole, it is possible that the TEAEs were related to vonoprazan. The rate of gastric polyps does not appear to be a dose-dependent, as more TEAEs were seen in the Voquezna 10 mg group than the Voquezna 20 mg group.

Severe Cutaneous Adverse Reactions

There were no cases of severe cutaneous adverse reactions (SCARs) (i.e., Stevens-Johnson Syndrome, toxic epidermal necrolysis, or drug-rash with eosinophilia and systemic symptoms) in the maintenance phase. In addition to SCARs, other cutaneous adverse events were evaluated. Rash (including related terms) was observed as a less common adverse reaction in the study and is included in labeling.

In general, few dermatologic TEAEs were reported in the maintenance phase and rates were similar across treatment groups. Ten TEAEs were reported in nine subjects in each of the Voquezna arms compared to twelve subjects in the lansoprazole arm. None of the events were serious. All TEAEs were assessed as mild or moderate in severity. Two subjects, one in the Voquezna 10 mg treatment arm and one in the Voquezna 20 mg treatment arm discontinued study drug and withdrew from the study due to the TEAE. Narrative summaries were presented previously. Refer to Section 7.6.2.4.

No Voquezna subjects reported alopecia (reported in one lansoprazole subject) or skin ulcer (reported in two lansoprazole subjects). The reviewer considered that contact dermatitis, actinic

keratosis, seborrheic dermatitis, and psoriasis were unlikely to be associated with Voquezna, given the lack of a biologically plausible mechanism that would explain an association. The Investigator considered two TEAEs of rash and one case of eczema (recorded as dermatitis allergic) reported in the Voquezna 10 mg group, one case of hyperhidrosis in the Voquezna 20 mg group and one case of eczema (recorded as dermatitis atopic) in the lansoprazole group to be related to study drug. Notably, none of the urticaria TEAEs were considered related to study drug, which is reasonable given that urticaria due to drug hypersensitivity typically occurs shortly after drug introduction (cases occurred on Maintenance Days 24 and 135 for the Voquezna 20 mg subjects and Maintenance Day 70 for the lansoprazole subject). Despite the investigator assessment, it is plausible that there may be an association between rashes associated with hypersensitivity (including urticaria and atopic dermatitis/eczema) and Voquezna, in a non-dose dependent manner, with a similar incidence to lansoprazole. The terms of eczema, rash and urticaria are recommended for inclusion in labeling.

Hypersensitivity Reactions

There were no cases of anaphylaxis reported in the maintenance phase. However, there were two drug reactions reported in the maintenance phase, both of which the Investigator considered not related to study drug. An assessment of the relationship between individual cases and treatment with Voquezna follows:

- Subject (b) (6), a 47-year-old female with history of Ehlers-Danlos syndrome and hypertension, assigned to the Voquezna 10 mg group, reported a TEAE of adverse drug reaction on Maintenance Day 167, reported as recovered/resolved on Maintenance Day 168. She continued in the study, with last dose of study drug on Maintenance Day 194. Of note, the subject was started on ramipril eight days prior to entering the study. Ramipril was discontinued when the drug reaction was identified, and she was started on valsartan. Given the resolution of the drug reaction with discontinuation of ramipril without discontinuation of Voquezna, it is likely that the event was not related to Voquezna.
- Subject (b) (6), a 72-year-old female assigned to the Voquezna 20 mg group reported a moderate TEAE of drug hypersensitivity on Maintenance Day 124. No end date was reported for the event and there is no information regarding challenge or rechallenge. Study drug was not interrupted. Of note, the subject started amlodipine on Maintenance Day 109. Therefore, it is unclear whether the drug reaction is associated with vonoprazan due to confounding but seems unlikely given the temporal relationship of the TEAE to amlodipine.

Acute Tubulointerstitial Nephritis

As previously discussed, one case of acute tubulointerstitial nephritis (AIN) was reported as an SAE in a subject treated with Voquezna 20 mg during the maintenance phase.

Cutaneous/Systemic Lupus Erythematosus

There were no cases of cutaneous/systemic lupus erythematosis (CLE/SLE) or associated terms reported in the maintenance phase.

7.6.2.6. Laboratory Findings, Study EE-301, Maintenance Phase

No clinically important differences were observed among the treatment groups in evaluations of routine clinical laboratory, vital sign, and electrocardiogram parameters in the maintenance phase.

Electrocardiogram Findings

QTcF results were summarized based on the incidence of subjects who met prespecified abnormal QTcF criteria (see Section 17.3). The study included 59 subjects with elevated QTcF at baseline. As previously noted, scheduled ECGs were performed at baseline (Screening Phase) and at end of treatment. No ECG data was obtained at the end of the healing phase for subjects continuing into the maintenance phase which might be used as a "maintenance baseline" QTcF interval.

Because ECGs were not obtained at the end of the healing phase for subjects who entered maintenance, there were no available "maintenance baseline" ECG intervals.

The Applicant conducted their analysis, summarizing only abnormalities for subjects with at least one post-baseline abnormal QTcF result, and the test value was higher than the available baseline. However, this approach does not capture data on subjects with post-baseline values that increased by more than 30 or 60 msec from baseline, if that post-baseline value remained in the normal range. Therefore, the review team analyzed the highest post-baseline QTcF intervals in two ways: (1) including all subjects, regardless of baseline value; and (2) including only subjects who had a post-baseline QTcF higher than baseline.

In the review team's analysis, a larger proportion of subjects in the lansoprazole group (7%) had an absolute QTcF above 450 msec compared to subjects in either Voquezna group. Of the subjects with recorded QTcF increase, with abnormal post-baseline QTcF, only one subject in the Voquezna 10 mg group and none in the Voquezna 20 mg group had a post-baseline QTcF over 480 msec compared to three subjects in the lansoprazole group of whom two had post-baseline QTcF of over 500 msec. No Voquezna subjects had prolongation greater than 500 msec. Fifteen subjects treated with Voquezna 10 mg (5.1%), twelve subjects treated with Voquezna 20 mg (4.0%) and 12 subjects treated with lansoprazole (4.0%) had an increase from baseline in QTcF values of >30 msec. Five subjects treated with Voquezna 10 mg (1.7%), four subjects treated with Voquezna 20 mg (0.2%), and three subjects treated with lansoprazole (1.0) had an increase from baseline in QTcF values of >60 msec.

Both the review's team and the applicant's analyses showed similar rates across treatment arms for any abnormal post-baseline QTcF (i.e., greater than 450 msec), with no dose-dependent patterns evident between the Voquezna 10 mg and 20 mg groups

Liver Biochemistry

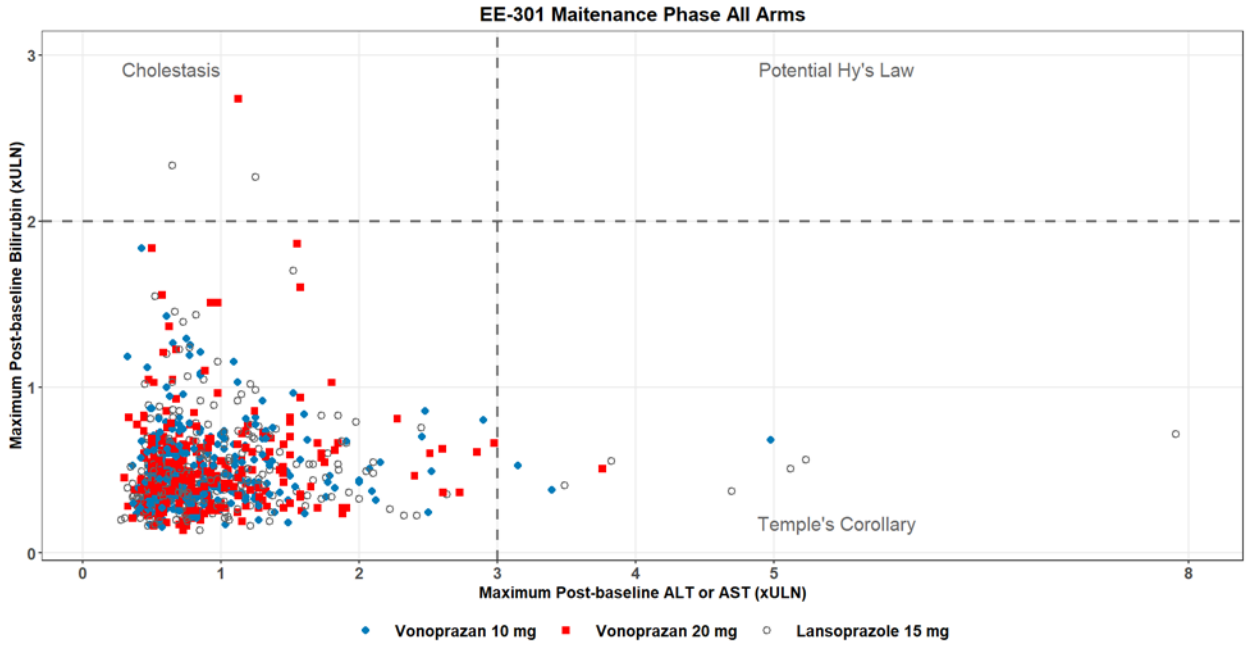
Of the subjects with liver testing performed, fewer than 1% of subjects in any group had transaminase elevations greater than 3 x ULN. No subject in any treatment group had an elevation of ALT or AST > 10 x ULN, a total bilirubin > 3 x ULN, or alkaline phosphatase > 2 x ULN. Results were comparable between subjects receiving Voquezna 10 mg or lansoprazole. A numerically larger proportion of subjects treated with Voquezna 20 mg (2.4%) had elevated total

bilirubin levels compared to the Voquezna 10 mg or lansoprazole groups (0.1% and 1.4% respectively).

There were no discontinuations due to elevated hepatic enzyme assessments or suspected drug induced liver injury (DILI) during the maintenance phase.

Figure 8 show the drug induced liver injury (DILI) analysis. There were no Hy's Law cases in the maintenance phase. Three subjects in the Voquezna 10 mg group (1.0%), one subject in the Voquezna 20 mg group (0.3%) and six subjects in the lansoprazole group (2.0%) met criteria for Temple's corollary. No subjects in the Voquezna 10 mg group were identified as having risk of cholestatic injury, compared to one subject in the Voquezna 20 mg group (0.1%) and two subjects in the lansoprazole group (0.7%).

Figure 8. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study EE-301-Maintenance Phase



Source: adlb.xpt; Software: R
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All patients with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Refer to Table 108 for summary of DILI analysis subject data. A brief summary of Temple's corollary cases in subjects treated with Voquezna follows:

- Subject (b) (6) was a 72-year-old male with no relevant past medical history or concomitant medications. He received Voquezna 20 mg in the healing phase (16 days) and was re-randomized to receive Voquezna 10 mg in the maintenance phase. His transaminase levels were stable during the healing phase. On Maintenance Day 28, his ALT (199) and AST (123) were elevated, as was alkaline phosphatase (117) and GGT (354). No action was taken with respect to study drug. All hepatic laboratories had normalized by Maintenance Day 82 and remained normal with an isolated ALT of 42 on

Maintenance Day 194; the elevation is not clinically meaningful. Given the spontaneous resolution of abnormalities without alteration of study drug treatment, it is unlikely that the laboratory changes were related to vonoprazan.

- Subject (b) (6) was a 29-year-old male with history of overweight and intermittent rhinorrhea on concomitant medications that included ibuprofen/pseudoephedrine from Study Day 9 to 14 and nutritional supplementation with "sea water" from Study Day 9 to 50. He was assigned to Voquezna 20 mg in the healing phase. On Day 19, his ALT was elevated (89 U/L). On Day 23, he was considered healed, and was re-randomized to receive Voquezna 10 mg in the maintenance phase. His ALT continued to increase, reaching a peak of 126 U/L on Maintenance Day 81 with recording of a TEAE of alanine aminotransferase increased. No action was taken with respect to study drug. His ALT again fluctuated but remained above the normal range at the time of the last recorded lab value on Maintenance Day 179. An association between the ALT elevation and treatment with Voquezna is possible, given the temporal relationship. However, the fluctuations in level without alterations in study drug make alternative etiologies or other contributing factors possible. The term increased liver function test is recommended for inclusion in labeling.
- Subject (b) (6) was a 43-year-old male with history of hepatitis C, hypertension, migraine, dyspepsia, and sleep apnea with concomitant medications including aspirin, caffeine, paracetamol (acetaminophen). He was assigned to the Voquezna 20 mg arm in both the healing and maintenance phases. His baseline ALT was slightly elevated (54 U/L) but had normalized by the end of the healing phase. On Maintenance Day 43, his ALT increased to 161 U/L, along with elevations of AST (84 U/L) and total bilirubin (19.2 mcmol/L). A mild TEAE of alanine aminotransferase elevated was recorded. No action was taken with respect to study drug. On Maintenance Day 51, all hepatic labs had normalized and the TEAE was considered resolved/recovered. At the Week 12 study visit (Maintenance Day 92) all hepatic laboratories were normal and an additional concomitant medication of olmesartan was recorded. At the end of the study, his ALT was mildly elevated to 59 U/L. Given multiple confounding factors: that the subject had a disease that predisposes to liver injury (i.e., Hepatitis C); took concomitant medications known to cause liver injury (i.e., paracetamol); and the history of previous transaminase elevations, an association between vonoprazan and the laboratory abnormalities remains unclear.
- Subject (b) (6) was a 64-year-old woman with history of Type 2 diabetes mellitus, hypertension, hypercholesterolemia, hepatic cirrhosis and hepatic encephalopathy with concomitant medications including enalapril, metformin, and intermittent paracetamol (acetaminophen). She was randomized to receive lansoprazole 30 mg in the healing phase (24 days) and Voquezna 20 mg in the maintenance phase. Her hepatic laboratory parameters were normal at baseline and through the healing phase. On Maintenance Day 83, she was started on a 7-day course of amoxicillin for a tooth infection. On Maintenance Day 90, her ALT, alkaline phosphatase and GGT were elevated. A moderate TEAE of alanine aminotransferase increased was recorded. All hepatic laboratory parameters normalized by Maintenance Day 154 without a change in study drug. She received her last dose of Voquezna on Maintenance Day 161. It is extremely likely that her elevated hepatic function tests were associated with amoxicillin, given the temporal relationship. Additionally, her ongoing use of potentially hepatotoxic

medications (metformin, paracetamol) and history of cirrhosis may also have contributed to her risk of hepatic dysfunction. Therefore, it is unlikely that the abnormal hepatic labs were associated with vonoprazan.

Hematologic Abnormalities

The baseline for maintenance phase laboratory analyses was the last measurement during the healing phase prior to the first dose of study drug in the maintenance phase. Analysis of the changes in hematologic parameters over time excludes the Week 16 and Week 18 visits because the number of subjects with laboratory studies performed at those visits was too low to provide interpretable information (26 and 15 subjects, respectively).

A similar and low number of subjects experienced hematologic indices below normal across all treatment groups. Platelet counts <140k was reported in four subjects (1.4%) in each Voquezna group, compared to eight subjects (2.7%) in the lansoprazole group. Platelet counts < 125K were reported in three subjects (1.0%) in both the Voquezna 10 mg and lansoprazole groups. No subject had a platelet count < 100k.

A small numeric difference was seen in the proportion of subjects with a decrease in hemoglobin below baseline. Five subjects in the Voquezna 10 mg group (1.7%) had hemoglobin levels that decreased more than 2 g/dL from baseline, compared to nine in the Voquezna 20 mg group (2.8%) and two in the lansoprazole group (0.7%). The suggests that vonoprazan may have a greater effect on hemoglobin than lansoprazole, and that effect may be dose dependent. The term anemia is recommended for inclusion in labeling.

Brief narratives for the subjects in the Voquezna 10 mg group with a decrease in hemoglobin >2 g/dL follows:

- Subject (b) (6) was a 47-year-old male randomized to receive lansoprazole 30 mg in the healing phase (29 days) and Voquezna 10 mg in the maintenance phase. He had history of diabetes mellitus, hypertension, myopia with corrective corneal surgery. He reported prior medications as amlodipine and omeprazole. Concomitant medications continued during the trial included hydrochlorothiazide and triamterene. Triamterene was reported as discontinued and olmesartan started on Maintenance Day 71. Neither changes in hemoglobin nor anemia are associated with any of his concomitant medications. His hemoglobin dropped to 15.1 g/dL (trial baseline was 17.2 g/dL) at the end of the healing phase. Nadir was 14.7g/dL on maintenance day 89. Given the temporal relationship in the healing phase with lansoprazole, the decrease in hemoglobin is not attributed to Voquezna.
- Subject (b) (6) was a 63-year-old male randomized to receive Voquezna 20 mg in the healing phase (16 days) and Voquezna 10 mg in the maintenance phase. He had history of hypertension, gout, and renal failure. Concomitant medications included lisinopril. Amlodipine was recorded as added on Maintenance Day 42, and lisinopril discontinued. He received a short course of prednisone for an unrecorded indication on Maintenance Day 86-90, concurrent with the recording of a TEAE of renal impairment. His study and maintenance baseline hemoglobin measurements were both 16.0 g/dL. His hemoglobin started to decrease by Maintenance Day 29 and reached the nadir of 13.2 (more than 2 g/dL below baseline) on Maintenance Day 90. The subject's hemoglobin did not return to baseline during the study. It is possible that the hemoglobin change was

related to a cumulative effect from sequential treatment with vonoprazan. This supports the inclusion of the term anemia in labeling.

- Subject (b) (6) was a 65-year-old male randomized to receive Voquezna 20 mg in the healing Phase (29 days) and Voquezna 10 mg in the maintenance phase. Prior history included hypogonadism, depression, eczema, hepatic steatosis, and allergic rhinitis. Concomitant medications include testosterone (unknown route of administration or formulation) and calcium carbonate/simethicone. A TEAE of cellulitis was recorded on Maintenance Day 105 and he received treatment with cefdinir and topical mupirocin for 20 days. His baseline hemoglobin was 18.2 g/dL, which may be related to use of testosterone which can be associated with polycythemia. His hemoglobin showed a steady decline initially reaching a nadir of 15.3 g/dL on Maintenance Day 87, then stabilizing, within the normal range. Although the decrease was not clinically meaningful, given the temporal relationship, the subject's decreased hemoglobin may be associated with vonoprazan, providing further support for including anemia as a term in labeling.
- Subject (b) (6) was a 39-year-old male randomized to receive Voquezna 20 mg in the healing phase (20 days) and Voquezna 10 mg in the maintenance phase. Prior history included depression, type 2 diabetes mellitus, hyperthyroidism, chronic neck pain and hyperlipidemia. Concomitant medications included: dapagliflozin, bupropion, exenatide, methadone, propranolol, tapentadol, thiamazole, and venlafaxine. Both study and maintenance baseline hemoglobin were 17.2 g/dL. Atorvastatin was started on Maintenance Day 82 for hyperlipidemia. He underwent gastric bypass surgery on Maintenance Day 166. At the start of the maintenance phase, his hemoglobin decreased to 15.9 g/dL by maintenance day 19 (less than 1.5 g/dL below baseline) and then remained stable at 16.4 g/dL through maintenance day 57. By the end of the study, his hemoglobin level was 14.7 (>2 g/dL below baseline). An association between vonoprazan and decreased hemoglobin in this subject cannot be established or excluded, given the presence of multiple confounders (e.g., medications, surgery).
- Subject (b) (6) was a 69-year-old female who received lansoprazole 30 mg in the healing phase (16 days) and Voquezna 10 mg in the maintenance phase. Prior history included hypertension, hyperlipidemia, asthma, dizziness, intercostal neuralgia, obesity, osteoarthritis, lumbosacral/cervical radiculopathy. Concomitant medications included betahistine (for vertigo), indapamide/perindopril, nebivolol, pregabalin, rosuvastatin, tizanidine. Inhaled ciclesonide was started on Maintenance Day 99 for asthma. She had no TEAEs reported during the study. Her baseline hemoglobin was normal (14.2 g/dL) and increased to slightly above the normal range at the end of the healing phase (18.8 g/dL). Over the course of the maintenance phase, her hemoglobin decreased close to baseline (13.8 g/dL) and then continued to decrease to just below the normal range on Maintenance Day 85 (13.6). Her hemoglobin level was 13.4 g/dL at the end of the study. Given that her Week 2/Maintenance Baseline level was disproportionately elevated compared to her other hemoglobin assessments, it is possible that this measurement represents a laboratory error. If so, the effect of vonoprazan on her hemoglobin level cannot be assessed, given lack of a Maintenance Baseline. Assuming the laboratory assessment was accurate, the temporal relationship between the beginning of vonoprazan exposure and decreasing hemoglobin levels suggests a possible association. However,

there are multiple confounders, including concomitant medications associated with anemia (i.e., perindopril, pregabalin, rosuvastatin). Therefore, the role of vonoprazan either alone or in association with co-administered medications known to cause anemia, cannot be determined for this subject.

Serum Gastrin

Elevated serum gastrin has a potential role in the development of fundic gland polyps. Inhibition of gastric acid secretion leads to hypergastrinemia, which leads to increased mucosal stimulation and subsequent hypertrophy and hyperplasia of gastric mucosa. (Spiegel et al. 2010). PPI use has been associated with an increased risk of fundic gland polyps. Therefore, an analysis of serum gastrin levels was conducted.

Refer to Figure 18 in the Appendix. In the healing phase, serum gastrin increased from baseline in both the Voquezna 20 mg and lansoprazole 30 mg groups, with a more pronounced elevation in the Voquezna subjects. The average serum gastrin remained in the normal range during treatment with lansoprazole, including a decrease to normal in subjects who were re-randomized from Voquezna 20 mg in healing phase to lansoprazole in the maintenance phase. Average serum gastrin in subjects treated with Voquezna showed a marked increase above normal, in a dose-dependent manner, including an increase seen in the maintenance phase for subjects who received lansoprazole in the healing phase. Given the association between serum gastrin level and fundic gland polyps, and the known association between use of PPI therapy and increased risk for fundic gland polyps, a subsection in WARNINGS AND PRECAUTIONS for fundic gland polyps is recommended for the labeling.

7.6.3. Safety Findings and Concerns, EE-301, Healing and Maintenance Phases, Recommended Regimen Analysis

The safety data were assessed for the subgroup of subjects who received the recommended dosage of Voquezna in both the healing and maintenance phases (20 mg QD, followed by 10 mg QD) and subjects who received the approved dosage of lansoprazole in both the healing and maintenance phases (30 mg QD, followed by 15 mg QD).

Table 50 shows the overview of AEs for subjects who received the recommended dosage regimen of Voquezna (20 mg in the healing phase, 10 mg in the maintenance phase) or the labeled dose of lansoprazole (30 mg for healing, 15 mg for maintenance). There were no deaths reported among subjects who received the recommended dosage regimens of Voquezna or lansoprazole. Overall, the proportion of subjects who reported the various types of AEs was similar between the two regimens.

Table 50. Overview of Treatment-Emergent Adverse Events, Controlled Study Safety Population, EE-301, Healing and Maintenance Phases, Recommended Regimen Analysis

Event	Voquezna H 20mg, M 10mg N=147 n (%)	Lansoprazole H 30mg, M 15mg N=134 n (%)
Subjects with at least one TEAE	77 (52.4)	87 (64.9)
Moderate or severe TEAEs	89 (36.2)	79 (34.6)
SAEs (non-fatal)*	6 (4.1)	3 (2.2)
AEs leading to discontinuation of study drug	1 (0.7)	3 (2.1)
AEs leading to interruption of study drug	7 (4.8)	10 (7.5)

Source: adae.xpt; Software: JMP
*There were no fatal events in subjects who received the recommended regimen of Voquezna or labeled regimen of lansoprazole.
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; H, Healing Dose; M, Maintenance Dose; N, number of subjects in group; n, number of subjects with at least one event

There were seven SAEs reported in six subjects in the Voquezna group (4.1%) compared to three SAEs in three subjects in the lansoprazole group (2.2%). No single SAE was reported more than once (data not shown). Of the SAEs reported in the Voquezna group, only peripheral edema was considered possibly related to Voquezna by the review team and is recommended for inclusion in labeling. Narratives for the SAEs in Voquezna subjects were already presented.

Table 51 shows the TEAEs that occurred in more than 2% of subjects who received either the recommended Voquezna regimen or the labeled lansoprazole regimen in both healing and maintenance phases of Study EE-301. This list of terms is similar to the terms identified in the analysis of the healing and maintenance phases analyzed separately. TEAEs that were not previously reported in the separate analyses of healing and maintenance, and which showed more than a two-subject difference between groups (i.e., sinusitis, IBS) are unlikely to be attributable to Voquezna.

Table 51. Treatment-Emergent Adverse Events Occurring in >2% of Subjects[1] who Received Voquezna, Safety Population, EE-301, Voquezna versus Lansoprazole, Recommended Regimen

Preferred Term [2]	Voquezna H 20mg, M 10mg N=146 n (%)	Lansoprazole H 30mg, M 15mg N=134 n (%)
COVID-19 [A]	13 (9%)	11 (8%)
Abdominal pain [B]	11 (9%)	6 (5%)
Gastritis [C]	10 (7%)	5 (4%)
Diarrhea	8 (5%)	6 (5%)
Dyspepsia	8 (5%)	6 (5%)
Nausea	6 (4%)	1 (1%)
Constipation	5 (3%)	4 (3%)
Upper respiratory tract infection [D]	5 (3%)	3 (2%)
Gastroesophageal reflux disease	5 (3%)	2 (2%)
Sinusitis	5 (3%)	1 (1%)
Irritable bowel syndrome	5 (3%)	0
Urinary tract infection	4 (3%)	3 (2%)
Dizziness	4 (3%)	2 (2%)
Gastroesophageal sphincter insufficiency	4 (3%)	2 (2%)
Hypertension	4 (3%)	2 (2%)
Hepatic enzyme increased	4 (3%)	2 (2%)

Source: Reviewer-generated adae.xpt;,Software:JMP.
[1] Rounded to nearest whole number
[2] Coded as MedDRA preferred terms
[A] includes coronavirus infection, COVID-19
[B] includes abdominal discomfort, abdominal pain, abdominal pain upper
[C] includes chronic gastritis, gastric mucosa erythema, gastritis, gastritis erosive
[D] includes nasopharyngitis, upper respiratory tract infection
Abbreviations: COVID-19, SARS-CoV2 illness; N, number of subjects; n, number of subjects with adverse event; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities

An analysis was conducted of TEAEs related to AESIs in subjects who received either the recommended Voquezna regimen or the labeled lansoprazole regimen in both healing and maintenance phases (data not shown). No new imbalances were identified, and findings were consistent with the safety analysis of the healing and maintenance phases separately.

7.6.4. Additional Supportive Safety Analysis

Data from the following trials were used to support the assessment of safety results from Study EE-301:

- Four phase 3 EE trials conducted outside of the United States: two for healing of EE (TAK438/CCT-002, TAK438/CCT-303), and two for maintenance of healed EE (TAK438/CCT-003, TAK438/CCT-305).
- 52-week uncontrolled safety data for maintenance of healed EE (Study TAK-438/OCT-001).
- Vonoprazan-4003 (VISION) trial (a 5-year randomized, double-blind safety trial of vonoprazan versus lansoprazole for long-term maintenance of healed EE).

7.6.4.1. Phase 3 Ex-U.S. EE Trials

Healing of EE Trials (TAK-438_303 and TAK-438/CCT-002)

Overall, safety of vonoprazan 20 mg compared to lansoprazole 30 mg was similar in the pooled analysis of the two phase 3 ex-US healing studies (TAK-438_303 and TAK-438/CCT-002) when compared to the healing phase of Study EE-301. There were no deaths in the vonoprazan group. Serious Adverse Events were infrequent and reported at a similar frequency to the healing phase of Study EE-301. No SAE was reported in more than one subject in the vonoprazan group, with two subjects in the lansoprazole group reporting large intestine polyps. No SAEs were deemed related to study drug by the investigator. TEAEs leading to study drug discontinuation occurred infrequently, at a similar frequency as in the healing phase of Study EE-301, with no term reported more than once in either treatment group.

There were no cases of Hy's law reported in these studies. Refer to Figure 19. One case of Temple's corollary was identified in the vonoprazan 20 mg group in Study TAK-438/CCT-002, with maximum ALT/AST 3.2 x ULN but without bilirubin elevation. The subject was a 53-year-old Japanese female, randomized to receive vonoprazan 20 mg (12 days). She had a prior history of dyslipidemia and fatty liver, and concomitant use of atorvastatin. Given her preexisting risk factors including fatty liver and concomitant use of a drug known to be associated with hepatic dysfunction, the relationship of her transaminase elevation to vonoprazan remains unclear, but unlikely given her short duration of exposure to vonoprazan.

TEAEs were similar between the healing phase of Study EE-301 and the pooled phase 3 ex-U.S. healing studies. Table 52 shows the TEAEs that occurred in > 1% of subjects in either treatment group in the pooled studies. TEAEs shown as bolded and italics in the table were also reported as TEAEs >1% in the healing phase of Study EE-301. TEAEs of nasopharyngitis, hepatic enzyme increased, constipation, headache, and rash were also reported in Study EE-301. Of the other TEAEs in the table, pepsinogen increased and blood gastrin increased are known effects of acid suppression and were observed in laboratory tests conducted during Study EE-301. Other reported TEAEs were not considered clinically informative.

An analysis of the TEAEs occurring in ≤ 1% of subjects in the pooled phase 3 ex-U.S. healing studies was generally similar to Study EE-301 and there were no reported TEAEs that were considered clinically informative (data not shown).

Table 52. Treatment Emergent Adverse Events Occurring in >1% of Subjects in Either Treatment Arm, Integrated Summary of Safety, ex-U.S. EE Healing Trials[A]

Preferred Term	Vonoprazan 20 mg N=451 n (%)	Lansoprazole 30 mg N=437 n (%)
Pepsinogen increased [B]	19 (4.2)	3 (0.7)
Blood gastrin increased	13 (2.9)	5 (1.1)
Nasopharyngitis	11 (2.4)	9 (2.1)
Hepatic enzyme increased [C]	10 (2.2)	17 (3.9)
Diarrhea	**10 (2.2)**	**8 (1.8)**
Abdominal pain [D]	**9 (2.0)**	**7 (1.6)**
Abdominal distention	**8 (1.8)**	**7 (1.6)**
Constipation	6 (1.3)	5 (1.1)
Gastritis	**5 (1.1)**	**6 (1.4)**
Serum lipids increased [E]	5 (1.1)	6 (1.4)
Nausea	**5 (1.1)**	**3 (0.7)**
Helicobacter test positive	4 (0.9)	5 (1.1)
Headache	2 (0.4)	8 (1.8)
Rash [F]	2 (0.4)	7 (1.6)
Protein urine present	2 (0.4)	6 (1.4)
Blood creatine phosphokinase increased	1 (0.2)	5 (1.1)

Source: Reviewer generated; ISS adae.xpt; Software: JMP Clinical
[A] EE Healing Pool includes Studies EE-301, TAK-438_303 and TAK-438/CCT-002. Results from EE-301 are excluded from this table.
[B] Includes enzyme level increased (all reported terms consistent), pepsinogen increased
[C] includes ALT increased, AST increased, GGT increased, liver enzyme increased, liver function test abnormal, liver function test increased
[D] Includes abdominal discomfort, abdominal pain, abdominal pain upper, epigastric discomfort
[E] includes blood cholesterol increased, blood triglycerides increased, hyperlipidemia, lipid metabolism disorder, serum lipids increased
[F] includes eczema, urticaria, rash, rash pruritic
TEAEs shown in bold and italics in the table were also reported as TEAEs >1% in the healing phase of Study EE-301
Abbreviations: EE, erosive esophagitis

Maintenance of Healed EE Phase 3 Ex-U.S. Trials (TAK-438/CCT-003and TAK-438/CCT-305)

Safety of vonoprazan 10 mg compared to lansoprazole 15 mg was also similar in the pooled analysis of the two phase 3 ex-U.S. maintenance of healed EE (Studies TAK-438/CCT-003 and TAK-438/CCT-305) when compared to the maintenance phase of Study EE-301. Subjects participating in these ex-U.S. studies were identified as healed in a previous study, after receiving either vonoprazan or a PPI comparator (usually lansoprazole, with esomeprazole used in only one trial). There were no deaths in the vonoprazan group. Serious Adverse Events were reported at a similar frequency to the maintenance phase of Study EE-301, with no SAE reported in more than one subject in a treatment group. No SAEs in the vonoprazan 10 mg group were assessed as related to study drug. TEAEs leading to study drug discontinuation were reported at a similar frequency to the maintenance phase of Study EE-301, and included those related to gastrointestinal disorders, and increased liver function tests.

There were no cases of Hy's law in these studies. Refer to Figure 20. Three cases of Temple's corollary were identified in the vonoprazan 10 mg group, compared to three cases in the vonoprazan 20 mg group and two cases in the lansoprazole group. The review team considered

all cases as likely related to vonoprazan. The term of increased hepatic enzymes was reported also reported in subjects in Study EE-301 and will be included in the Voquezna labeling.

Narratives for the vonoprazan 10 mg subjects follows:

- Subject TAK-438/CCT-003-(b) (6) was a 53-year-old Japanese male randomized to receive vonoprazan 10 mg for maintenance after receiving 11 days of vonoprazan 20 mg for healing. He had a prior history of dyslipidemia and treatment for *H. pylori.* On Maintenance Day 55 a TEAE of nasopharyngitis was recorded. On Maintenance Day 57, he received concomitant medications of clarithromycin, dextromethorphan, carbocisteine, dequalinium chloride and tulobuterol for four days. On the final study day (Maintenance Day 163) a serious TEAE of liver function test abnormal was recorded, with elevated transaminases of ALT 10.4 x ULN (467 IU/L) and AST 14.3 x ULN (571 IU/L) without total bilirubin increase. At the end-of-treatment follow-up (Maintenance Day 180) the ALT had decreased to 5 x ULN (222 IU/L) and AST had decreased to 2 x ULN (83 IU/L). The TEAE was considered related to study drug by the Investigator. The temporal relationship to vonoprazan and the positive de-challenge suggest that the transaminase elevation was related to vonoprazan, and not the concomitant medications.
- Subject TAK-438/CCT-003-(b) (6) was a 42-year-old Japanese male randomized to receive vonoprazan 10 mg for maintenance after receiving 14 days of vonoprazan 20 mg for healing. He had a prior history of fatty liver and treatment for *H.pylori*, with no recorded concomitant medications. On Maintenance Day 158 at his end-of-treatment visit, a mild TEAE of liver function test abnormal was recorded, with elevated transaminases of ALT 7.24 x ULN (326 IU/L) and AST 3.2 x ULN (127 IU/L) without bilirubin elevation. No follow up laboratory studies were recorded. Given his prior history of fatty liver disease, the relationship of the TEAE to vonoprazan is unclear, however a potential role of vonoprazan cannot be excluded.
- Subject TAK 438_305-(b) (6) was a 48-year-old Chinese male randomized to receive vonoprazan 10 mg for maintenance after receiving an unknown duration of lansoprazole 30 mg in Study TAK-438/ for healing. He had a prior history of gastric polyps, hypertension, hyperthyroidism, rash, and treatment for *H.pylori*. Concomitant medications include ebastine, tacrolimus ointment, valsartan, and amlodipine. On Maintenance Day 86, mild TEAEs of muscle injury and liver function test increased were recorded, not considered related to study drug by the Investigator. Elevated transaminases were 3.2 x ULN, with ALT 130 IU/L and AST 137 IU/L without elevation of bilirubin above ULN. Study drug was discontinued. Follow up laboratory studies on Maintenance Day 99 normalized with ALT 41 IU/L and AST 25 IU/L. Because some of his concomitant medications are associated with hepatic adverse reactions (i.e., amlodipine, valsartan) and elevated ALT may be associated with muscle injury, the relationship of the transaminase elevation to vonoprazan is unclear. However, a relationship cannot be excluded given the unexplained AST elevation and the positive de-challenge.

TEAEs were similar between the maintenance phase of Study EE-301 and the pooled phase 3 ex-U.S. maintenance of healed EE studies. Table 53 shows the TEAEs that occurred in more than 2% of subjects in any treatment group, after rounding. TEAEs shown as bolded and italics in the table were also reported as TEAEs >2% in the healing phase of Study EE-301. TEAEs of hepatic enzyme increased, gastric polyp, gastritis and abdominal distention were also reported in Study

EE-301. The proportion of subjects who reported hepatic enzyme increased was reported more in the ex-U.S. studies than in the maintenance phase of Study EE-301 (7% versus 0.7% of subjects who received vonoprazan 10 mg). However, there are racial and ethnic difference between study populations which include factors associated with risk of liver disease in the Asian population, including a higher rate of chronic hepatitis B infection (CDC 2006) and more common use of herbal/dietary supplements associated with liver injury (Real et al. 2019). Therefore, the review team concluded that the higher occurrence of elevated hepatic enzymes in the ex-U.S. trials did not change the overall assessment of safety. Other reported TEAEs were not considered clinically informative.

An analysis of the TEAEs occurring in ≤ 2% of subjects in the pooled phase 3 ex-U.S. maintenance studies was generally similar to Study EE-301 and there were no reported TEAEs that were considered clinically informative (data not shown).

Table 53. Treatment Emergent Adverse Events Occurring in >2% of Subjects in Any Treatment Group (After Rounding), Integrated Summary of Safety EE, Ex-U.S. Maintenance Trials [A]

Preferred Term	Vonoprazan 10 mg N=437 n (%)	Vonoprazan 20 mg N=430 n (%)	Lansoprazole 30 mg N=443 n (%)
Nasopharyngitis	53 (12.1)	52 (12.1)	54 (12.2)
Upper respiratory tract infection	44 (10.1)	41 (9.5)	35 (7.9)
Hepatic enzyme increased [B]	31 (7.1)	46 (10.7)	36 (8.1)
Diarrhea [C]	**24 (5.5)**	27 (6.3)	**32 (7.2)**
Dyspepsia	**18 (4.1)**	10 (2.3)	**12 (2.7)**
Abdominal pain [D]	**17 (3.9)**	14 (3.3)	**25 (5.6)**
Gastric polyp [E]	15 (3.4)	17 (3.9)	10 (2.3)
Vertigo/dizziness [F]	13 (3.0)	14 (3.3)	10 (2.3)
Back pain	12 (2.7)	7 (1.6)	7 (1.6)
Hypergastrinemia [G]	12 (2.7)	10 (2.3)	1 (0.2)
Pepsinogen level increased [H]	12 (2.7)	13 (3.0)	4 (0.9)
Blood lipids elevated [I]	11 (2.5)	12 (2.8)	17 (3.8)
Eczema [J]	11 (2.5)	11 (2.6)	8 (1.8)
Gastritis [K]	**10 (2.3)**	10 (2.3)	**14 (3.2)**
Gastroenteritis [L]	8 (1.8)	12 (2.8)	7 (1.6)
Gastroesophageal reflux disease	8 (1.8)	6 (1.4)	12 (2.7)
Abdominal distention	6 (1.4)	8 (1.9)	17 (3.8)
Hyperuricemia/Gout [M]	5 (1.1)	11 (2.6)	6 (1.3)

Source: Reviewer generated; ISS adae.xpt; Software: JMP Clinical
[A] Data derived from ISS, Pool 2 which includes Studies EE-301, TAK-438_305 and TAK-438/CCT-003. Results from EE-301 are excluded from this table.
[B] Includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma glutamyl-transferase increased, hepatic enzyme increased hepatic function abnormal, liver function test abnormal, liver function test increased
[C] includes bowel movement irregularity, diarrhea, frequent bowel movements
[D] includes abdominal pain, abdominal discomfort, abdominal pain lower, abdominal pain upper, epigastric discomfort
[E] includes duodenal polyp, gastric polyps, gastric mucosal lesion [verbatim: gastric cardia mucosal elevated lesion]
[F] includes dizziness, Meniere's disease, vertigo, vertigo positional
[G] includes blood gastrin elevated, hypergastrinemia
[H] includes enzyme level increased [verbatim terms related to pepsinogen], pepsinogen increased
[I] includes blood cholesterol increased, blood cholesterol abnormal, blood lipids elevated, blood triglycerides increased, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, lipids abnormal
[J] includes dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, eczema, rash, rash pruritic
[K] includes chronic gastritis, gastritis, gastritis erosive, gastritis hemorrhagic, reflux gastritis
[L] includes enterocolitis [verbatim term: acute enteritis], gastroenteritis
[M] includes blood uric acid increased, gout, hyperuricemia
TEAEs shown in ***bold and italics*** in the table were also reported as TEAEs >2% in the healing phase of Study EE-301
Abbreviations: EE, erosive esophagitis

TEAEs from subjects who received the recommended regimen of vonoprazan (20 mg for healing, 10 mg for maintenance) were analyzed to provide confirmatory evidence of safety (data not shown). No new safety signals were identified, and the results are consistent with the safety profile of Voquezna in Study EE-301.

7.6.4.2. Long-Term Safety Data

Study TAK-438/OCT

Study TAK-438/OCT-001 (hereafter referred to as OCT-001) was a phase 3 randomized, double-blind, uncontrolled trial in 305 adult subjects with endoscopically confirmed healing of EE in Study TAK-438/CCT-002. Patients were randomized 1:1 to vonoprazan 10 mg or 20 mg once

daily for 52 weeks. The primary objective was to evaluate the safety of long-term administration of one of two doses of vonoprazan over a 52-week period, with a primary endpoint of descriptive analysis of adverse events.

Limitations of the trial include the lack of an active comparator.

Table 54 shows the high-level summary of TEAEs reported in the trial. There were no deaths reported in either dosage group. The number of subjects with any TEAE, moderate or severe TEAEs, and TEAEs leading to interruption of study drug were similar in both dose groups. A slightly higher proportion of subjects in the vonoprazan 20 mg group compared to the 10 mg group reported TEAEs that were considered serious and TEAEs that led to discontinuation of study drug.

Table 54. Summary of Treatment-Emergent Adverse Events, Long-Term Safety Study, TAK-438/OCT-001

Event	Vonoprazan 10 mg N=154 n (%)	Vonoprazan 20 mg N=151 n (%)
Subjects with at least one TEAE	118 (76.6)	119 (78.8)
Moderate or severe TEAEs	20 (13.0)	19 (12.6)
SAEs (non-fatal) *	9 (5.8)	12 (7.9)
AEs leading to discontinuation of study drug	8 (5.2)	13 (8.6)
AEs leading to interruption of study drug	3 (1.9)	3 (2.0)

Source: Reviewer generated, ISS adae.xpt; Software: JMP with supplemental data from Applicant, Clinical Study Report, TAK-438/OCT-001, March 2014.
* No deaths were reported
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of subjects in group; n, number of subjects with at least one event

Serious Adverse Events were reported in eight subjects in the vonoprazan 10 mg group (5.2%) and eleven subjects in the vonoprazan 20 mg group (7.3%). All SAEs were reported only once per treatment group, with the exception of pneumonia (one subject in the 10 mg group and 2 subjects in the 20 mg group). Overall, the SAEs were not considered to be plausibly related to vonoprazan.

Table 55 shows the TEAEs that occurred by treatment arm that were reported in more than 2% of subjects in the vonoprazan 10 mg arm. TEAEs of gastritis and hypertension were reported in >2% of subjects in the maintenance phase of Study EE-301. TEAEs of dizziness, hepatic enzymes increased, gastric polyps, constipation, insomnia, and urticaria were also reported in Study EE-301. A numerically greater percentage of subjects in the vonoprazan 20 mg group compared to the vonoprazan 10 mg group experienced TEAEs related to hepatic enzyme increased, consistent with Study EE-301. Hyperuricemia/gout was not reported in Study EE-301. However, this TEAE occurred in greater frequency in the low-dose compared to high-dose group, which suggests that this TEAE is unlikely to be related to vonoprazan and most likely represents background rate (up to 6.8% of adults). (Dehlin et al. 2020)

An analysis of the TEAEs occurring in ≤ 2% of subjects in the vonoprazan 10 mg arm in Study OCT-001 was generally similar to the maintenance phase of Study EE-301 and there were no reported TEAEs that were considered clinically informative.

Table 55. Treatment-Emergent Adverse Events Occurring in More than 2% of Subjects in the Vonoprazan 10 mg Arm, Long Term Safety Study, TAK-438/OCT-001

Preferred Term	Vonoprazan 10 mg N=154 n (%)	Vonoprazan 20 mg N=151 n (%)
Vertigo/Dizziness	6 (3.8)	1 (0.7)
Back pain*	6 (3.9)	3 (2.0)
Hepatic enzyme increased [A]	5 (3.2)	8 (5.3)
Gastric Polyps	5 (3.2)	7 (4.6)
Insomnia	5 (3.2)	7 (4.6)
Gastritis [B]	5 (3.2)	6 (4.0)
Musculoskeletal pain* [C]	5 (3.2)	4 (2.6)
Hypertension [D]	4 (2.6)	5 (3.3)
Constipation	4 (2.6)	2 (1.3)
Fall*	4 (2.6)	2 (1.3)
Hyperuricemia/Gout	4 (2.6)	2 (1.3)
Urticaria	4 (2.6)	1 (0.7)

Source: reviewer-generated; ISS adam.xpt; Software: JMP Clinical
[A] includes alanine aminotransferase increased, gamma-glutamyltransferase increased, hepatic function abnormal, liver function test abnormal, liver function test increased
[B] includes chronic gastritis, gastritis, gastritis erosive
[C] includes arthralgia, extremity pain, musculoskeletal pain, myalgia
[D] includes blood pressure increased, hypertension
*TEAE not considered to be related to vonoprazan, due to lack of plausible physiologic mechanism

Study Vonoprazan-4003 (VISION)

Study Vonoprazan-4003 (VISION) was a phase 4, multicenter, randomized, blinded, active comparator-controlled, long-term safety study of vonoprazan for maintenance of healed EE. (Uemura et al. 2018) VISION included 202 subjects with confirmed healing of EE following 8 weeks of treatment with vonoprazan or lansoprazole, who were randomized 2:1 to receive vonoprazan 10 mg or lansoprazole 15 mg once daily for up to five years. While the Applicant's focus was primarily on hypergastrinemia and neuroendocrine tumors, other TEAEs and laboratory data were also assessed. The study concluded in March 2022 and the Applicant anticipates that the full study report will be available in 2023. Line listings of TEAEs >1%, without laboratory or additional subject-level data, were included in this submission. The submission did not include information on deaths, SAEs, or AEs leading to discontinuation of study drug.

Limitations of the study include a small sample size.

Table 56 summarizes TEAEs reported in >2% of subjects in the vonoprazan arm. Rates of most TEAEs were similar between the vonoprazan and lansoprazole groups. TEAEs of gastritis, hypertension, urinary tract infection, and abdominal pain were reported in >2% of Voquezna-treated subjects in the maintenance phase of Study EE-301. TEAEs of upper respiratory infection, gastric polyps, nasopharyngitis, dizziness, fracture, constipation, insomnia, hepatic function abnormal, and diabetes mellitus were also reported in Study EE-301. Gastric polyps were reported in 46% of subjects in each treatment group, which suggests a strong association with chronic acid suppressive therapy. Other possibly related changes in gastric mucosa (i.e., gastric mucosal lesions and gastric mucosal hypertrophy) were also reported at high frequency. This observation supports inclusion of a WARNINGS AND PRECAUTIONS subsection in labeling for fundic gland polyps, as previously discussed. TEAEs related to bone fracture were

reported in VISION, in 7% of vonoprazan subjects, compared with 12% of lansoprazole subjects. This observation supports inclusion of a WARNINGS AND PRECAUTIONS subsection in labeling for bone fracture. No other AESIs were listed as occurring in >1% of subjects. The available data do not suggest new safety signals with long-term use of vonoprazan for up to 5 years.

Table 56. TEAEs Reported in >2% of Vonoprazan Subjects, Vonoprazan-4003 (VISION) Study

	Vonoprazan 10 mg		Lansoprazole 15 mg	
Preferred Term	**N=135**	**%**	**N=67**	**%**
Upper respiratory infection [A]	63	46.7	44	65.7
Gastric polyps	62	45.9	31	46.3
Nasopharyngitis	46	34.1	29	43.3
Gastric mucosal lesion	30	22.2	17	25.4
Gastritis [B]	18	13.3	10	14.9
Large intestine polyp	16	11.9	9	13.4
Hypertension	15	11.1	6	9.0
Back pain	13	9.6	3	4.5
Bronchitis	12	8.9	7	10.4
Influenza	12	8.9	1	1.5
Osteoarthritis [C]	12	8.9	7	10.4
Dermatitis [D]	12	8.9	17	25.4
Gastrointestinal mucosal disorder	10	7.4	6	9.0
Sinusitis, acute or chronic	10	7.4	0	
Dyslipidemia	10	7.4	1	1.5
Vertigo/Dizziness	11	8.1	7	10.4
Fracture [E]	9	6.7	8	11.9
Constipation	8	5.9	4	6.0
Diverticulum intestinal [F]	8	5.9	3	4.5
Urinary tract infection/cystitis	8	5.9	4	6.0
Upper respiratory tract infection	7	5.2	6	9.0
Dental caries	7	5.2	2	3.0
Gastroenteritis	7	5.2	4	6.0
Ligament sprain	7	5.2	2	3.0
Arthralgia	7	5.2	6	9.0
Insomnia	7	5.2	0	
Asthma (includes cough-variant)	7	5.2	3	4.5
Gastric mucosal hypertrophy	6	4.4	1	1.5
Abdominal pain [G]	6	4.4	4	6.0
Periodontal disease [H]	6	4.4	3	4.5
Hepatic function abnormal	6	4.4	0	
Seasonal allergy/allergic rhinitis	6	4.4	5	7.5
Contusion	6	4.4	3	4.5
Hyperuricemia	6	4.4	1	1.5
Diabetes mellitus	6	4.4	0	
Headache	6	4.4	3	4.5
Skin bacterial infection [I]	6	4.4	6	9.0
Pharyngitis	5	3.7	5	7.5
Lumbar spinal stenosis	5	3.7	1	1.5
Benign prostatic hyperplasia	5	3.7	0	
Stomatitis	4	3.0	3	4.5
Hemorrhoids [J]	4	3.0	4	6.0
Colitis	4	3.0	1	1.5
Conjunctivitis	4	3.0	3	4.5
Enteritis infectious	4	3.0	3	4.5

Preferred Term	Vonoprazan 10 mg N=135	%	Lansoprazole 15 mg N=67	%
Tenosynovitis	4	3.0	0	
Urticaria	4	3.0	3	4.5
TOTAL (average TEAE per Subject)*	598	(4.4)	387	(5.8)

Source: Reviewer-generated from data extracted from Applicant Response to Labeling Information Request Dated 29 September 2022-Postmarketing Information, 14 October 2022; Software: Excel
[A] includes nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, upper respiratory tract inflammation
[B] includes gastritis erosive, gastric mucosal erythema, chronic gastritis
[C] includes osteoarthritis, spinal osteoarthritis, arthritis
[D] includes eczema, dermatitis contact, dermatitis allergic, dermatitis, hand dermatitis, rash
[E] includes spinal compression fracture, rib fracture, hand fracture, patella fracture, tooth fracture, wrist fracture, ankle fracture, coccyx fracture
[F] includes diverticulum intestinal hemorrhagic, diverticulitis
[G] includes abdominal pain upper, abdominal pain, abdominal pain lower, abdominal discomfort
[H] includes periodontal disease, periodontitis, gingivitis
[I] includes dermatitis infective, cellulitis
[J] includes hemorrhoids, hemorrhoidal hemorrhage, hemorrhoids thrombosed
*Total derived from full data submitted, including TEAEs excluded from the table.
Abbreviations: TEAE, treatment-emergent adverse event

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Adverse Events of Special Interest Related to Vonoprazan

This section describes the AESIs that relate specifically to vonoprazan, including liver toxicity and hematologic disorders.

- Drug-related liver function test abnormalities have been reported for other drugs (SCH28080 and AZD0865) classified as potassium-competitive acid-blockers (PCABs) during development outside of the United States. These compounds contained an imidazopyridine ring structure which may be implicated in their hepatotoxic effects. Liver effects of vonoprazan, which does not contain a non-imidazopyridine ring structure, were identified by the Applicant as a key area for safety monitoring during development in the United States and postmarketing outside the United States.
- During drug development of Voquezna, the review team requested that the Applicant evaluate hematologic abnormalities as an AESI, based upon the postmarketing addition of pancytopenia, agranulocytosis, leukocytopenia, and thrombocytopenia to the Japanese prescribing information for vonoprazan (Takecab®).

7.7.1.1. Hepatotoxicity

Background

In 2014, at the time of the marketing approval for vonoprazan in Japan, the Japanese Pharmaceuticals and Medical Devices Agency (PDMA) identified hepatic impairment as an important potential risk (PMDA, 2014). Assessment strategies included early postmarketing surveillance, which ultimately identified 39 cases of hepatic impairment with vonoprazan

monotherapy which led to a safety labeling update in 2020 to include a "Clinically Significant Adverse Reaction" (CSAR) of hepatic impairment in the Takecab® label. The Applicant reports that as of December 25, 2021, 727 cases related to hepatotoxicity were reported from post-marketing sources, of which 218 were serious.

In the NDA, the Applicant evaluated SAEs, AEs leading to discontinuation, TEAEs, and laboratory abnormalities in the clinical studies of vonoprazan across treatment indications to assess hepatotoxicity.

Assessment

For the hepatotoxicity analysis, the review team assessed terms related to increased hepatic enzymes, liver injury, and hepatic steatosis, using the grouped terms listed in Table 97.

Study EE-301

In Study EE-301, there were no hepatic TEAEs that were serious, fatal, led to discontinuation of study drug, or severe in intensity, in either the healing or maintenance phases. The percentage of subjects with hepatotoxicity TEAEs were generally similar between Voquezna and lansoprazole groups. There were no cases of Hy's law in either the healing or maintenance phase

In the healing phase, as described in Section 7.7.1.1, there were six (1.2%) subjects in the Voquezna group and four (1.0%) subjects in the lansoprazole group with reported TEAEs associated with hepatotoxicity as defined by the broad search criteria. Two of the subjects with hepatotoxicity TEAEs also met criteria for Temple's corollary. The review team noted confounding factors (e.g., hepatotoxic concomitant medications or herbal supplements, medical comorbidities) or temporal relationships that suggested causes other than vonoprazan in the Temple's corollary cases. Therefore, review team did not consider any of the TEAEs or laboratory abnormalities to be associated with vonoprazan.

In the maintenance phase, hepatoxicity TEAEs were reported in 5 subjects (1.7%) in the Voquezna 10 mg group, 8 subjects (2.7%) in the Voquezna 20 mg group and 9 subjects (3%) in the lansoprazole group. Two cases in subjects treated with Voquezna 10 mg were considered by the review team to be potentially related to vonoprazan. One of the cases met criteria for Temple's corollary. Two additional subjects in the Voquezna 10 mg group (3 subjects total, 1.0%) and one subject in the Voquezna 20 mg group (0.3%) met criteria for Temple's corollary. These cases are described in Section 7.6.2.6.

Ex-U.S. Phase 3 EE Studies

In the ex-US healing and maintenance studies, there were no SAEs, severe AEs, or AEs leading to discontinuation in subjects receiving the recommended dose of vonoprazan (20 mg for healing, 10 mg for maintenance).

Hepatotoxicity TEAEs in the healing studies were reported in 2.2% of subjects in the vonoprazan group and 3.9% of subjects in the lansoprazole group. In the maintenance studies, hepatotoxicity TEAEs in the maintenance studies were reported in 7.1% of subjects in the vonoprazan 10 mg group, 10.2% of subjects in the vonoprazan 20 mg group and 8.6% of subjects in the lansoprazole groups.

One subject in the vonoprazan 20 mg group in a maintenance study (Study TAK-438/CCT-003) met Hy's law criteria; however, the subject had a confirmed diagnosis of acute cholecystitis explaining liver function abnormalities, which makes DILI unlikely.

One case of Temple's corollary was identified in a vonoprazan-treated subject in a healing study (Study TAK-438/CCT-002), with maximum ALT/AST 3.2 x ULN but without bilirubin elevation. The relationship of the event to vonoprazan remains unclear but is considered unlikely due to a short duration of exposure to vonoprazan (12 days).

Three cases of Temple's corollary were identified in the vonoprazan 10 mg group in the maintenance studies. The relationship between transaminase elevations and vonoprazan 10 mg cannot be excluded in any of cases. See narratives in Section 7.6.4.1.

ISS All-Subjects Pool

The All-Subjects pool in the NDA consists of twenty-one phase 2/3 studies of vonoprazan (doses ranging from 5 mg to 40 mg) across various indications with lansoprazole or placebo as the comparator, not including studies for the treatment of *H. pylori*. See Table 109 for a list of the studies included. TEAEs associated with hepatotoxicity were assessed in a subgroup of the All Subjects pool (i.e., limited to subjects who received vonoprazan (10 or 20 mg), lansoprazole (15 mg or 30 mg), or placebo AND excluding EE-301 and the ex-U.S. phase 3 EE healing and maintenance studies. The proportion of subjects with a hepatic TEAE was similar between subjects in vonoprazan and lansoprazole groups (3.3% to 4.0% of subjects in any group) compared to placebo (1.1%). Elevated hepatic enzymes were the most frequently reported hepatic TEAE in all groups.

There were no serious or severe events. There were no cases of Hy's law in Voquezna-treated subjects in this pool.

Hepatic TEAEs leading to discontinuation were uncommon in the vonoprazan groups and similar to lansoprazole and placebo groups.

Vonoprazan-4003 (VISION)

In the line listings of TEAEs occurring in more than 1% of subjects in the VISION study, six hepatic TEAEs (reported as "hepatic function abnormal") were reported in the vonoprazan 10 mg group (4.4%) compared to none in the lansoprazole group. Patient level data and laboratory data are not yet available at the time of this review.

Postmarketing Data

One case of clinically significant DILI resulting in liver failure was identified by DPV in their postmarketing review, but the review concluded that the case was confounded by concomitant alcohol and medication use.

Conclusion

Overall, the safety data in the NDA do not suggest a signal of hepatotoxicity with vonoprazan beyond elevations in liver function tests, reported in 1% of subjects in both the healing and maintenance phases of Study EE-301. Overall, in the NDA the events are reported in a similar percentage of subjects as those treated with lansoprazole. Therefore, inclusion of a subsection in

the WARNINGS AND PRECAUTIONS section of the Voquezna labeling for hepatotoxicity is not needed based on the currently available data; however, the term “increased liver function tests” is recommended for inclusion as a reported adverse reaction.

7.7.1.2. Cytopenias

Background

In 2019, the Japanese PMDA issued a Revision of Precautions to add “Pancytopenia, agranulocytosis, leukopenia, and thrombocytopenia” to Section 11.1 Clinically Significant Adverse Reactions of the label for Takecab® (vonoprazan). Action was taken based on cases reported between September 2017 and June 2019 for which a causal relationship between the drug and the event could not be ruled out, including two cases of thrombocytopenia, four cases of agranulocytosis/leukopenia and two cases of pancytopenia, none of which was associated with patient fatality.

In the NDA, the Applicant evaluated SAEs, AEs leading to discontinuation, TEAEs, and laboratory abnormalities in the clinical studies of vonoprazan across treatment indications to assess hematologic abnormalities.

Assessment

The review focused on adverse events and laboratory assessments related to cytopenia (i.e., anemia, thrombocytopenia, lymphopenia, leukopenia and neutropenia). Abnormalities related to increased hematologic parameters were discussed previously. Refer to Table 97 for grouped terms.

Study EE-301

In Study EE-301, there were no hematologic TEAEs that were serious or led to discontinuation of study drug. In the healing phase, hematologic TEAEs were reported in two Voquezna subjects and seven lansoprazole subjects. In the maintenance phase, hematologic TEAEs were reported in two subjects in the Voquezna 10 mg group, three subjects in the Voquezna 20 mg group and six subjects in the lansoprazole group. One subject in the maintenance phase Voquezna 20 mg group who discontinued the study had an SAE of anemia. The subject had a prior history of anemia and bleeding hemorrhoids; therefore, it is unlikely that the event was related to vonoprazan.

Overall, hematologic TEAEs were uncommon, and anemia was the only TEAE that was reported in more than one subject in a treatment group. In the healing phase, two subjects in the Voquezna group and seven subjects in the lansoprazole 30 mg group reported TEAEs.

In the maintenance phase, at least one hematologic TEAE was reported in two subjects in the Voquezna 10 mg group (0.7%), three subjects in the Voquezna 20 mg group (1.0%) and six subjects in the lansoprazole group (2.0%).

There were no clinically meaningful decreases in hematologic indices in any treatment group in either the healing or maintenance phases, except for hemoglobin, and observed changes in parameters were similar across treatment group with no consistent trends.

Ex-U.S. Studies

In the ex-U.S. EE studies, there were no SAEs or AEs leading to discontinuation for cytopenia-related events. In the healing studies, cytopenia-related TEAEs were reported in two vonoprazan-treated subjects and two lansoprazole treated subjects.

In the maintenance studies, cytopenia-related TEAEs were reported in two vonoprazan 10 mg subjects, one vonoprazan 20 mg subject and none in the lansoprazole group.

TEAEs associated with cytopenia were assessed in a subgroup of the All Subjects pool (i.e., limited to subjects who received vonoprazan (10 or 20 mg), lansoprazole (15 mg or 30 mg), or placebo. The proportion of subjects with a hematologic TEAE was similar between subjects in vonoprazan, and lansoprazole groups compared to placebo. Anemia was the most frequently reported cytopenia.

In Study OCT-001, no cytopenia related TEAEs were reported in subjects receiving the recommended maintenance dose of vonoprazan.

In the line listings for Study Vonoprazan-4003 (VISION), TEAEs of anemia were reported in 1.5% of vonoprazan subjects and 3.0% of lansoprazole subjects (two subjects in each group).

Postmarketing

No cases of cytopenia plausibly associated with vonoprazan use were identified. A literature search identified two cases with suspected immune-associated thrombocytopenia induced by vonoprazan.

Conclusion

There is no clear association between vonoprazan and cytopenia or other hematologic abnormalities based upon the available clinical trial data. Leukocytosis, leukopenia, and neutropenia are included in the list of less common adverse drug reactions in the approved label for Voquezna Dual/Triple Pak for the treatment of *H. pylori* infection.

A WARNINGS AND PRECAUTIONS subsection on hematologic abnormalities is not warranted because of the lack of SAEs or otherwise clinically significant AEs and laboratory abnormalities in clinical trials.

The literature suggestions a possible association between drug-induced immune thrombocytopenia and vonoprazan and the review team recommends including the thrombocytopenia as a term in the postmarketing section of labeling.

7.7.2. Adverse Events of Special Interest Related to Suppression of Acid Secretion

Potassium-competitive acid blockers, including Voquezna, and PPIs act to suppress acid secretion through interaction with the gastric H+/K+ ATPase (“proton pump”) to treat disorders associated with excessive gastrointestinal acid secretion (e.g., gastric and duodenal ulcers, GERD). This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Due to similarities in mechanism of action, some of the

risks associated with PPI use may be seen with Voquezna. These risks will be discussed individually.

7.7.2.1. Bone Fracture

Background

Biologic evidence suggests that drugs that result in gastric acid suppression, including PPIs, may influence bone mineral homeostasis and therefore affect bone health, which may increase the risk of fracture; however, the process remains uncertain and is likely multifactorial. (Briganti et al. 2021; Staines et al. 2021)

In 2010 FDA added safety information as part of a Safety Labeling Change to the product labels for prescription PPIs, based on several epidemiologic studies suggesting an increased risk of fractures of the hip, wrist, and spine with PPI use, with the greatest risk among older individuals who have used PPIs for at least one year or who took high doses of PPIs. (FDA 2010) All prescription single-ingredient PPI product labels currently have language about bone fractures.

Bone fracture was included as an AESI by the Applicant in the NDA, given similarities in mechanism of action (MOA) to PPIs.

Assessment

Study EE-301

Eight TEAEs of bone fracture were reported during Study EE-301. One event was reported in a Voquezna subject in the healing phase. In the maintenance phase, six events were reported in Voquezna subjects, after receiving either Voquezna or lansoprazole in the healing phase. One subject received lansoprazole in both the healing and maintenance phases. None of the subjects with fractures received the recommended regimen of Voquezna in both the healing and maintenance phases.

Brief narratives of cases follow:

Healing phase:

- In the healing phase, a forearm fracture was reported in a postmenopausal female subject with prior history of osteoporosis after receiving 3 days of Voquezna 20 mg in the healing phase. In addition to confounding by her history of osteoporosis, the limited duration of drug exposure makes it unlikely that Voquezna contributed to the fracture.

Maintenance phase:

- Two subjects received lansoprazole for 15 days during the healing phase and then Voquezna 10 mg once daily for 36-days and 73-days, respectively, during the maintenance phase. The role of Voquezna in contributing to the fractures (lower leg and hand) in these subjects cannot be determined due to confounding from use of lansoprazole during the healing phase and other risk factors (i.e., trauma and concomitant medications).

- Three subjects with limb fractures (foot, ankle, and radius), received Voquezna 20 mg for both the healing and maintenance phases with exposures from 52 to 184 days. Two of the subjects had risk factors (i.e., age, medical conditions and/or other concomitant medications) that may have increased the risk of fracture.
- One subject ((b) (6)) received lansoprazole for 24 days during the healing phase and then Voquezna 20 mg once daily during the maintenance phase. She sustained a sacral fracture (verbatim term "sacral insufficiency fracture") after 83 days of Voquezna. The role of Voquezna in contributing to this fracture cannot be determined, due to confounding from use of lansoprazole during the healing phase and pre-existing risk factors (i.e., up to 10% of patients with ankylosing spondylitis may develop sacral stress fractures. (Lukasiewicz et al. 2016))

Ex-U.S. Phase 3 EE Studies

In the Ex-U.S. phase 3 healing and maintenance studies, bone fractures were reported infrequently. In the healing studies, bone fractures were reported in one subject in the vonoprazan 20 mg group (tooth fracture) and two subjects in the lansoprazole group.

In the maintenance studies, bone fractures were reported in one subject (0.2%) in the vonoprazan 10 mg group (spinal compression fracture), six subjects (1.4%) in the vonoprazan 20 mg group (tooth fracture, rib fracture (2), upper limb fracture (2), and humerus fracture) and two subjects (0.4%) in the lansoprazole group (displaced fracture, stress fracture).

Of these events, only three (both rib fractures and one spinal compression fracture) were reported in subjects who received the recommended regimen of vonoprazan (20 mg for healing, 10 mg for maintenance). Given the traumatic etiology of rib fractures, an association between rib fractures and vonoprazan is unlikely. The spinal compression fracture was reported in a 77 year-old woman with prior history of osteoporosis who received healing dose of vonoprazan 20 mg for 14 days then maintenance dose vonoprazan 10 mg for 5 days when the event was recorded. Given the short duration of treatment with any dose of vonoprazan and existing risk factors, it is unlikely that vonoprazan is related to this injury.

ISS All-Subjects Pool

In the All-Subjects Pool, bone fractures were reported at low frequency and at similar rates in all treatment groups: 1.5% of vonoprazan 10 mg subjects, 1.0% of vonoprazan 20 mg subjects, 2.0% of lansoprazole 15 mg subjects and 2.0% of lansoprazole 30 mg subjects. No factures were reported in placebo subjects.

Spinal Compression Fractures

Because SCFs are often due to loss of bone density and therefore suggestive of changes in bone mineralization, specific attention was given to the occurrence of spinal compression and femoral neck fractures.

Sixteen cases of SCF/femoral neck fracture were reported in the subset of the All-Subjects pool. All subjects were 65 years of age or older. All were receiving vonoprazan at the time of the reported event. Ten of the events were reported in subjects with previous osteoporosis. Five of the remaining subjects had conditions other than osteoporosis that increased risk of SCF,

including previous SCF, spondylosis, or rheumatoid arthritis. (Chen et al. 2016; Jacob and Kostev 2021)

The remaining case was reported in a 77-year-old male subject with no identified risk factors, enrolled in study TAK_438/CCT-201 for sGERD. Given the short duration of the trial it appears unlikely that vonoprazan was related, however an association cannot be excluded in this case.

Long-Term Extension (OCT-001)

One fracture was reported in each of the vonoprazan 10 mg and 20 mg groups. Given small numbers of cases and lack of active comparator, no conclusions can be reached regarding the role of vonoprazan.

Vonoprazan-4003 (VISION)

In the VISION trial, TEAEs of bone fracture were reported in 9 subjects (6.7%) in the vonoprazan group and 8 subjects (11.9%) in the lansoprazole group. Subject level data is not yet available to allow assessment of the relationship of these events to study drug.

No imbalance was apparent in the reported rates of SCF between the vonoprazan (1.5%; 2 of 125) and lansoprazole groups (3%; 2 of 67). There is no additional data available on the specific cases to identify pre-existing risk factors or circumstances of injury.

Postmarketing

No cases of fracture plausibly associated with vonoprazan use were identified in FAERS.

Conclusion

Given the known risk of long-term acid suppression contributing to osteoporosis-related fractures of the hip, wrist and spine identified postmarketing with the PPIs, and included as PPI class labeling, there is biologic plausibility that vonoprazan may also increase the risk of fractures due to similar effects on acid-suppression. Bone fracture was reported infrequently in clinical trials and at a similar rate between vonoprazan and lansoprazole treatment groups.

A WARNINGS AND PRECAUTIONS subsection is recommended in labeling to describe the risk of bone fracture. Because bone fracture, including osteoporosis-related spinal compression fracture, has been reported in clinical trials of other indications, the following sentence will be added to the WARNINGS AND PRECAUTIONS section “Bone fracture, including osteoporosis-related fracture, has been reported with vonoprazan.” The term bone fracture is also recommended for inclusion in labeling as a term reported in Study EE-301.

7.7.2.2. Clostridiodes difficile-Associated Diarrhea

Background

Acid-suppressive therapies are associated with an increased risk of *Clostridiodes difficile*-associated diarrhea (including enterocolitis and pseudomembranous colitis). The precise etiology is unknown, but acid suppression may predispose to *C. difficile* infection. (Nerandzic et al. 2009) Use of antibacterials is the most important risk factor for CDAD. Concurrent use of PPIs along

with antibacterials could exacerbate the risk of CDAD. (Hebert et al. 2013; Hebert and Robicsek 2014) In February of 2012, the FDA issued a Drug Safety Communication that the use of PPIs may be associated with an increased risk of *C difficile*–associated diarrhea based on a review of FAERS and the medical literature and risk of CDAD was included as a WARNINGS AND PRECAUTIONS in labeling for all marketed PPIs. (FDA 2012)

Assessment

No TEAEs associated with *C. difficile* infection were reported in Study EE-301, in the ex-US phase 3 healing and maintenance studies, or the All Subjects pool in the ISS. Six reports of *C. difficile* infection were reported with vonoprazan use in FAERS. All cases were confounded by use of concomitant antimicrobials or use of chemotherapy. No relevant cases were reported in the published literature.

For a discussion to TEAEs related to *C. difficile* infection in clinical trials of vonoprazan with amoxicillin, with or without clarithromycin, for the treatment of *H. pylori infection*, refer to the review of NDA 215152 and NDA 215153. The approved labeling for Voquezna Triple/Dual Pak includes a WARNINGS AND PRECAUTIONS for CDAD to address the risks associated with use of acid-suppressing therapy and antibacterials.

The Applicant was requested to submit postmarketing cases of serious/severe adverse events of *C. difficile* infection deemed plausibly associated with vonoprazan use, not confounded by use of other medications known to be independently associated with *C. difficile* (e.g., antibacterial agents). The Applicant was not able to identify any cases meeting those criteria and concluded the risk of *C. difficile* infection with vonoprazan monotherapy appears low.

Conclusion

The available data on the use of vonoprazan as monotherapy does not suggest an increased risk of *C. difficile* infection; however, there is a potential risk of CDAD with vonoprazan due to its MOA as an acid-suppressant similar to the PPIs. Given that CDAD poses a significant risk to patients, the review team recommended that the risk of CDAD be included as a subsection in the WARNINGS AND PRECAUTIONS section of labeling to address the risks associated with use of acid-suppressing therapy and antibacterials.

7.7.2.3. Hypomagnesemia

Background

Hypomagnesemia occurs with alteration of magnesium (Mg^{2+}) homeostasis involving the kidney, small intestine, or bone. The precise mechanism of the PPI effect on magnesium metabolism has not been determined, although renal excretion and reabsorption of magnesium appear to be normal in patients receiving PPI therapy. It has been suggested that PPIs may affect intestinal absorption of magnesium through alteration of TRPM6/7 channel affinity for magnesium, secondary to decrease in intestinal pH (increase in protons). (Perazella 2013)

Serum levels of less than 1.7 mg/dL are associated with serious outcomes involving neuromuscular (tremor, tetany, seizures, weakness), cardiovascular (ECG changes, prolonged

QTc, dysrhythmias), and metabolic systems (i.e., secondary hypokalemia, altered calcium metabolism).

Case reports of hypomagnesemia in patients taking PPIs for more than one year were identified in post-marketing surveillance. A Safety Labeling Change (SLC) was made in 2022 to add hypomagnesemia to the WARNINGS AND PRECAUTIONS of the prescribing information for the PPIs. Given similarities in MOA, Voquezna is expected to have a similar effect on magnesium absorption compared to PPIs.

Assessment

No cases of hypomagnesemia were reported as AEs in EE-301, the ex-U.S. phase 3 healing and maintenance studies or in the All Subjects pool in the ISS. However, magnesium levels were not included in the laboratory assessments in Study EE-301 or in any of the clinical trials included in the ISS. A limited number of postmarketing cases of hypomagnesemia (including other electrolyte abnormalities) were identified that were deemed plausibly associated with vonoprazan use.

Conclusion

Given that hypomagnesemia poses a serious risk to patients, the review team recommends including a hypomagnesemia as a subsection in the WARNINGS AND PRECAUTIONS section of the labeling, mainly based on the risks reported with PPIs and the limited number of postmarketing cases associated with vonoprazan use.

7.7.2.4. Vitamin B12 (Cobalamin) Deficiency

Vitamin B12 (cobalamin) is a water-soluble essential vitamin required for the formation of hematopoietic stem cells. Because dietary B12 is protein bound, absorption depends on cleavage from dietary protein, dependent on pepsin (activated by gastric acid from pepsinogen). Therefore, chronic acid suppression may predispose to B12 deficiency. Vitamin B12 deficiency is more common in older compared to younger adults. (Lindenbaum et al. 1994)

Deficiency of vitamin B12 may lead to serious health consequences including megaloblastic anemia and neuropsychiatric sequelae (e.g., paresthesia, depressed mood, irritability, cognitive impairment). The prescribing information for the PPI class includes a WARNINGS AND PRECAUTIONS subsection for vitamin B12 deficiency.

Assessment

No cases of vitamin B12 deficiency were reported as AEs in Study EE-301. Vitamin B12 levels were not reported in the study.

In the All-Subjects Pool, four cases of vitamin B12 deficiency were reported in subjects who received vonoprazan versus only one subject in subjects who received active comparator, but overall incidence was extremely low (i.e., fewer than 0.1% of all subjects). Three subjects in the vonoprazan group had increased vitamin B12 levels. Analysis of the laboratory assessments did not suggest a trend for decreasing Vitamin B12 levels, with average vitamin B12 level remaining above the lower limit of normal over the analysis period.

Conclusion

Clinical trials of vonoprazan did not identify a safety signal for Vitamin B12 deficiency. However, given the plausible risk of Vitamin B12 deficiency associated with to chronic acid suppression, especially in patients with other risks for deficiency (e.g., older adults), the review team recommends that Vitamin in B12 deficiency be included as a subsection in the WARNINGS AND PRECAUTIONS section based upon the MOA of acid suppression similar to the PPIs.

7.7.2.5. Fundic Gland Polyps

Background

It is well established that the risk of fundic gland polyps (FGPs) may be increased up to 4-fold with long-term use of PPIs, with an overall incidence of 7.3% of patients after a mean duration of use of 32.5 month. (Spiegel et al. 2010) Discontinuation of acid suppression therapy generally results in regression of polyps. The etiology of the effect is uncertain but there is evidence that hypergastrinemia resulting from acid suppression leads to mucosal stimulation resulting in hypertrophy and hyperplasia of the fundic mucosa. Given that potassium-competitive acid blockers have a similar effect to PPIs on acid suppression, it is plausible that increased risk of FGP might be associated with use of vonoprazan.

Assessment

Study EE-301

There were 17 cases of gastric polyps or benign gastric neoplasms reported in Study EE-301. During the healing phase of the trial, five cases were reported in each treatment arm. During the maintenance phase, including follow-up, six cases were reported in subjects who received any maintenance dose of Voquezna, compared to only one case in a subject who received lansoprazole. In the study the effect of vonoprazan on serum gastrin levels suggests more sustained hypergastrinemia compared to the effect from lansoprazole, which may reflect a greater potential to promote development of FGPs.

ISS All-Subjects Pool

The trend toward greater occurrence of gastric polyps among subjects receiving vonoprazan is not seen in the All Subjects Pool in the NDA.

Vonoprazan-4003 (VISION)

Gastric polyps were reported in 62 subjects (45.9%) of vonoprazan-treated subjects and 31 (46.3%) of lansoprazole-treated subjects in the 5-year VISION trial.

Conclusion

There is evidence from both Study EE-301 that gastric polyps are associated with the use of vonoprazan up to 24 weeks, with comparable rates to lansoprazole. Therefore, the review team

recommends that fundic gland polyps be included as a subsection in the WARNINGS AND PRECAUTIONS section in the labeling.

7.7.3. Adverse Events of Special Interest, Reported with Proton Pump Inhibitors, Not Known to be Related to Acid Suppression

PPI use has been associated with several ARs that appear to be unrelated to acid suppression. Therefore, it is unclear whether use of Voquezna poses similar risk. The review team evaluated each of these AESIs to assess whether there is evidence that Voquezna carries risk similar to PPIs.

7.7.3.1. Severe Cutaneous Adverse Reactions

Background

The Applicant reported that severe cutaneous adverse reactions (SCARs) was identified as a potential safety signal during routine signal evaluation from an empirical statistical data mining tool by Takeda in 2018. In 2019, toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme were added to the Japanese drug label.

Case reports of SCARs, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), in patients taking were identified in post-marketing surveillance. A Safety Labeling Change (SLC) was made in 2022 to add SCARs to the WARNINGS AND PRECAUTIONS of the prescribing information for the PPIs.

Assessment

There were no SCARs reported in Study EE-301.

In the ISS All-Subjects pool, there were three cases of SCARs reported. However, all cases had confounding with concomitant medications or concurrent risk factors that provide alternative explanation rather than vonoprazan.

Conclusion

There was no clear safety signal for SCARs identified in Study EE-301 or the All Subjects pool. However, given the evidence from post-marketing sources and the overall risk to patients from cutaneous hypersensitivity reactions, the review team recommends including SCARs as a subsection in the WARNINGS AND PRECAUTIONS section of labeling with the individual terms added to the postmarketing adverse reactions.

7.7.3.2. Hypersensitivity Reactions

Background

Hypersensitivity reactions (e.g., anaphylaxis, urticaria, angioedema) have been reported with the PPIs; however, the chemical structures of vonoprazan and PPIs are different such that the risk of hypersensitivity reactions may also be different for vonoprazan. Clinical trial data, the ISS, and available ex-U.S. postmarketing information were evaluated to assess the risk of hypersensitivity reactions with vonoprazan.

Assessment

In Study EE-301, there was a single case of hypersensitivity reported.

In the 120-day safety report, the Applicant reported a single case of anaphylaxis related to vonoprazan. The subject was a 42-year-old woman with a previous history of multiple food allergies and Hashimoto's thyroiditis who experienced a severe intensity anaphylactic reaction following the first dose of vonoprazan 20 mg during the open-label run-in period. She developed a rash within an hour of ingestion of study drug, with subsequent facial swelling, throat tightness and respiratory distress. Based on the temporal relationship, vonoprazan or other excipients in the formulation are likely to be the cause of the anaphylactic reaction.

Conclusion

Cases of serious hypersensitivity reactions, including anaphylaxis, have been reported with vonoprazan use. Therefore, a Contraindication for subjects with known hypersensitivity to vonoprazan or any component of Voquezna tablets, is recommended for inclusion in labeling.

7.7.3.3. Acute Tubulointerstitial Nephritis

Background

Acute tubulointerstitial nephritis (AIN) may be due to autoimmune disease, infections, drug-induced or idiopathic. The precise pathophysiology of drug-induced AIN is unknown but may be antibody mediated or related to direct drug toxicity or a delayed Type IV hypersensitivity reaction. (Sanchez-Alamo et al. 2022) AIN is reported with PPIs, occurring between 1 week to 9 months following drug exposure.

Assessment

One case of AIN was reported in a subject treated with Voquezna 20 mg in the maintenance phase of Study EE-301. No other cases were reported in the NDA.

Conclusion

Although there was no clear safety signal for AIN identified in the NDA, one case has been reported. Therefore, the review team supports including AIN as a subsection in the WARNINGS AND PRECAUTIONS section of labeling with the individual term added to the adverse reactions reported in Study EE-301.

7.7.3.4. Cutaneous/Systemic Lupus Erythematosis

Background

Worsening and new onset of lupus erythematosis (LE) has been reported with PPIs. Cutaneous LE (CLE) represents most of the cases, although systemic LE (SLE) has also been reported. (Lin et al. 2021) The underlying mechanism of drug-induced LE is not known and no single chemical structure has been identified that increases the risk, but genetic predisposition, drug biotransformation, epigenetic dysregulation and neutrophil extracellular traps are suspected contributors. (He and Sawalha 2018) Therefore, LE does not appear to be related to acid-suppression and the association with vonoprazan is not known.

Assessment

There were no cases of SLE, CLE or associated terms reported in Study EE-301. Review of the All-Subjects Pool did not reveal any cases of SLE/CLE or TEAE terms that might be associated with LE (e.g., cutaneous vasculitis).

No cases of SLE/CLE were identified in FAERS or the published literature for any type of lupus in association with vonoprazan use.

Conclusion

There is no evidence suggesting an association between vonoprazan and SLE/CLE in clinical trials, postmarketing experience, or published literature; therefore, it will not be included in labeling at this time.

8. Therapeutic Individualization

8.1. Intrinsic Factors

No clinically significant differences in the PK of vonoprazan were identified by sex, age, body weight, race/ethnicity, disease state of GERD or EE, or CYP2C19 phenotype.

The Applicant's population pharmacokinetic (popPK) analysis was performed based on pooled vonoprazan PK data from 1179 subjects in 13 studies of healthy subjects (180 Asians and 253 Europeans), 1 study in 589 Japanese subjects with EE (Study TAK-438/CCT-001), and 157 European subjects with GERD (Study Vonoprazan-2001). Although the popPK analysis identified that sex, age (18 to 92 years old), body weight (38 to 153 kg), race/ethnicity (Asian versus non-Asian, primarily White), disease state (healthy volunteer versus patients with GERD or EE) as covariates affecting PK parameters, none of them had a clinically meaningful impact on vonoprazan systemic exposure. In the dataset of 1179 subjects, there were 651 CYP2C19 extensive metabolizers, 37 intermediated metabolizers, and 109 poor metabolizers and the popPK analysis indicated that CYP2C19 phenotypes (extensive metabolizers, intermediated metabolizers, or poor metabolizers) did not affect the PK of vonoprazan.

The popPK report was submitted in NDAs 215152/215153 for *H. pylori* infection, which were deemed acceptable by the FDA reviewers and the findings from the popPK report are reflected in

the approved labeling of Voquezna Triple Pak/Duel Pak. Refer to the Integrated Review of NDA 215152/215153 dated May 3, 2022, Section 14.3.

In addition to the popPK analysis revealing no PK difference by ethnicity/race (Asian versus non-Asian), the Applicant's PK-PD analysis based on 6 studies in healthy subjects in the U.K. and Japan confirmed no significant difference by race or ethnicity (Asian versus non-Asian, primarily White) in the PK-PD relationship of vonoprazan, i.e., AUC versus Time% gastric pH >4 (See Figure 1 in Section 6.1). See further information of the PK-PD modeling and simulation in Section 14.2.

Renal Impairment

The effect of renal impairment on vonoprazan exposure was evaluated in a dedicated renal impairment study (Study TAK-438_113) and reviewed in NDA 215152/215153. Following a single 20 mg oral dose, the AUC of vonoprazan was 1.7-, 1.3-, and 2.4-times greater in subjects with mild, moderate, and severe renal impairment (defined as estimated GFR [eGFR] 60 to <90, 30 to <60, and 15 to <30 mL/min/1.73 m^2, respectively), respectively, compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2). In subjects requiring dialysis, the AUC of vonoprazan was 1.3-fold greater compared to subjects with normal renal function. Refer to the Integrated Review of NDA 215152/215153 dated May 3, 2022, Section 14.2. for further details.

As shown in Table 57, for healing of EE, the Applicant proposed dosage adjustment of vonoprazan from 20 mg once daily to 10 mg once daily in patients with severe renal impairment (eGFR <30 mL/min, which is acceptable given the 2.4-fold increase in exposure observed. Dosage adjustment in patients with mild to moderate renal impairment or receiving dialysis is not necessary; the recommended dosage is 20 mg QD (same as normal renal function).

For maintenance of healing of EE, dosage adjustment is not necessary in patients with mild, moderate, or severe renal impairment given that safety was evaluated up to 2-fold of the proposed dosage (i.e., 20 mg QD) in phase 3 trials. Therefore, the recommended dosage is 10 mg QD (same as normal renal function).

Table 57. Recommended Dosage Adjustment for Patients with Renal Impairment

Indication	Mild to Moderate RI eGFR 30 mL/min or Greater	Severe RI eGFR Less than 30 mL/min	Patients Requiring Dialysis
Healing of EE	20 mg QD (no adjustment; same as normal renal function)	10 mg QD	20 mg
Maintenance of healed EE	10 mg QD (no adjustment; same as normal renal function)	10 mg QD (no adjustment; same as normal renal function)	10 mg
*H. pylori**	20 mg BID	Avoid use	Avoid use

Source: created by the reviewer, Drug label of Voquezna Triple Pak/Duel Pak
*The indication approved in NDA 215152/215153
Abbreviations: BID, twice daily; EE, erosive esophagitis; eGFR, estimated glomerular filtration rate; QD, once daily; RI, renal impairment

Hepatic Impairment

The effect of hepatic impairment on the PK of vonoprazan was evaluated in a dedicated hepatic impairment study (Study TAK-438_112) and reviewed in NDA 215152/215153. The study

findings showed that the AUC of vonoprazan after a single 20 mg oral dose were 1.2-, 2.4-, and 2.6- times greater in subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment, respectively, compared to subjects with normal hepatic function. Refer to the Integrated Review of NDA 215152/215153 dated May 3, 2022, Section 14.2. for further details.

As shown in Table 58, for healing of EE, the Applicant proposed dosage adjustment from 20 mg once daily to 10 mg once daily in patients with mild to moderate hepatic impairment (Child-Pugh Class B and C), which is acceptable given the 2.4- and 2.6-fold exposure increase observed. Dosage adjustment in patients with mild hepatic impairment is not required so the recommended dosage is 20 mg QD.

For maintenance of healed EE, dosage adjustment is not necessary in patients with mild, moderate, severe hepatic impairment given that safety was evaluated up to 2-fold of the proposed dose (i.e., 20 mg QD) in phase 3 trials. Therefore, the recommended dosage is 10 mg QD.

Table 58. Recommended Dosage Adjustment for Patients With Hepatic Impairment

Indication	Mild HI Child-Pugh Class A	Moderate HI Child-Pugh Class B	Severe HI Child-Pugh Class C
Healing of EE	20 mg QD (no adjustment; same as normal renal function)	10 mg QD	10 mg QD
Maintenance of healing	10 mg QD (no adjustment; same as normal hepatic function)	10 mg QD (no adjustment; same as normal hepatic function)	10 mg QD (no adjustment; same as normal hepatic function)
*H. pylori**	20 mg BID	Avoid use	Avoid use

Source: created by the reviewer based upon Prescribing Information for Voquezna Dual Pak/Triple Pak (Phathom 2022)
*The indication approved in NDA 215152/215153
Abbreviations: BID, twice daily; EE, erosive esophagitis; HI, hepatic impairment; QD, once daily

Of note, in this NDA, for the treatment of *H. pylori infection*, (b) (4) This recommendation (b) (4) is inconsistent with the approved recommendation in the labeling for Voquezna Triple Pak/duel Pak which recommends these patients should avoid use of vonoprazan. (b) (4) the recommendations in the labeling for Voquezna for the treatment of *H. pylori* infection with antibiotics should state "avoid use of vonoprazan" in patients with severe renal impairment and patients with moderate to severe hepatic impairment to align with Voquezna Triple Pak/Duel Pak. Refer to the Integrated Review of NDA 215152/215153 dated May 3, 2022, Section 8.1.

8.2. Drug Interactions

In vitro drug-drug interaction (DDI) studies, clinical DDI studies, and the physiologically based pharmacokinetic (PBPK) analysis provided in this NDA were previously submitted and reviewed in NDA 215152/215153 to support the DDI information of Voquezna Triple Pak/Duel Pak for the treatment of *H.pylori* infection and its approved labeling reflects the information. The

proposed labeling of this NDA as to the DDI potential of vonoprazan was consistent with the approved labeling of NDA 215152/215153 and there was no DDI information newly added.

The maximum proposed dose of vonoprazan for EE is 20 mg QD (for healing of EE), which is covered by the approved dose for the treatment of *H.pylori* infection, 20 mg BID. Therefore, the DDI liability as a perpetrator in the proposed labeling of Voquezna as a single agent for EE is consistent with those of the approved labeling for Voquezna Triple Pak/Duel Pak for *H. pylori* infection. Additionally, we recommend adding DDI information between vonoprazan and aspirin/NSAIDs to the labeling based on a clinical DDI study (Study TAK-438/CPH-003).

The DDI potential of vonoprazan is summarized as below and please refer to the Integrated Review of NDA 215152/215153 dated 05/03/2022, Sections 8.2, 14.1, 14.2, 14.4, for further detail.

8.2.1. Effect of Other Drugs on Vonoprazan (as a Victim Drug)

Vonoprazan is metabolized via multiple pathways by a combination of cytochrome P450 (CYP) isoforms (CYP3A4/5, and to a lesser extent CYP2B6, CYP2C19, CYP2C9, and CYP2D6) along with sulfo-transferases (SULT) and glucuronosyl-transferases (UGT). Vonoprazan is not a substrate of P-gp, breast cancer resistance protein (BCRP), OATP1B1, or OATP1B3.

CYP3A Inhibitors

The effect of CYP3A inhibitors on vonoprazan exposure is not deemed clinically meaningful to require dose adjustment in patients who concomitantly use CYP3A4 inhibitors.

In Study TAK-438_110, a single 40 mg dose of vonoprazan was administered with clarithromycin (a strong CYP3A inhibitor) 500 mg twice daily for 7 days (N=16), which resulted in vonoprazan AUC_{inf} increase by 58% compared to administration of vonoprazan alone.

Strong or Moderate CYP3A Inducers

Concomitant use of vonoprazan with strong or moderate CYP3A4 inducers is not recommended due to potential loss of therapeutic benefit.

Based on the PBPK model, vonoprazan AUC are predicted to be 72-78% lower when co-administered with rifampin (a strong CYP3A4 inducer) and 44-54% lower when co-administered with efavirenz (a moderate CYP3A4 inducer). No clinical DDI studies were conducted to evaluate the effect of CYP3A4 inducers on vonoprazan exposure.

Given the lack of effect of CYP2C19 phenotype on vonoprazan exposures, coadministration of CYP2C19 inhibitors is unlikely to affect vonoprazan exposure. In addition, since contribution of CYP2D6 to vonoprazan metabolism is lesser than CYP3A4, CYP2D6 inhibitors are not likely to significantly affect vonoprazan exposure. Of note, an in vitro postmarketing requirement (PMR) study is pending under NDA 215152/215153, which is to conduct in vitro reaction phenotyping to assess the extent of contribution of CYP enzymes (including CYP2D6) to vonoprazan metabolism.

Aspirin/NSAIDs (i.e., Loxoprofen, Diclofenac, Meloxicam)

When a single dose of vonoprazan 40 mg was co-administered following repeated administrations of aspirin 100 mg QD, loxoprofen 60 mg three times a day, diclofenac 25 mg three times a day, or meloxicam 10 mg QD for 6 days, AUC or C_{max} of vonoprazan was not altered compared to administration of vonoprazan alone (Study TAK-438/CPH-003). Of note, loxoprofen is not approved in the United States.

8.2.2. Effect of Vonoprazan on Other Drugs (as a Perpetrator Drug)

Vonoprazan inhibits CYP3A4/5, CYP2C19, and CYP2B6 in time- and concentration-dependent manner in vitro. Vonoprazan had little or no inhibitory effect on P-gp, BCRP, OATPB1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 at the clinically relevant concentrations (IC_{50}>30 μmol/L).

CYP3A Substrates

Vonoprazan is a weak CYP3A inhibitor.

In a clinical DDI study (Study VONO-101) that evaluated the effect of 20 mg BID doses on the PK of oral midazolam (sensitive index CYP3A4 substrate), midazolam C_{max} and AUC increased 1.9-fold when administered after repeated doses of vonoprazan compared to when administered alone. In a separate clinical DDI study (TAK-438_110), compared with the use of clarithromycin (CYP3A4 substrate and strong inhibitor) alone, clarithromycin exposures increased approximately 1.6-fold when co-administered with vonoprazan.

As vonoprazan may increase exposure of CYP3A substrates, when sensitive CYP3A substrates with narrow therapeutic index (e.g., tacrolimus, cyclosporine) is concomitantly used with vonoprazan, frequent monitoring is warranted.

CYP2C19 Substrates

The PBPK model predicted that vonoprazan increases AUC of proguanil (a sensitive CYP2C19 substrate) by 1.5-fold when vonoprazan is co-administered with proguanil, which suggests that vonoprazan is a weak CYP2C19 inhibitor. No clinical DDI studies were conducted to evaluate the effect of vonoprazan on exposure of CYP2C19 substrates.

As vonoprazan may increase exposure of CYP2C19 substrates, if sensitive CYP2C19 substrates with narrow therapeutic index (e.g., clopidogrel, citalopram, cilostazol) is concomitantly used with vonoprazan, frequent monitoring is warranted.

CYP2B6 Substrates

The PBPK model predicted that vonoprazan increases AUC of bupropion (a CYP2B6 substrate) by 1.5-fold when vonoprazan is co-administered with bupropion, suggesting CYP2B6 might be a weak CYP2B6 inhibitor. However, given that there are no known sensitive CYP2B6 substrates, DDI mitigation strategy is not necessary for CYP2B6 substrates.

Drugs With Gastric pH-Dependent Absorption

Vonoprazan increases gastric pH over 24 hours, which may alter the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., antiretrovirals including rilpivirine, atazanavir, or nelfinavir, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole). Although no clinical DDI studies have been conducted, concomitant use of vonoprazan with other drugs that are absorbed gastric pH-dependently may result in changes in their safety and effectiveness.

As such, patients who take such drugs whose bioavailability is likely affected by gastric pH elevation should follow the recommendation in the prescribing information of each drug. For example, the erlotinib label states that concomitant use of proton pump inhibitors with erlotinib should be avoided if possible. Given the comparable pharmacologic action of vonoprazan to PPIs, the concomitant use of vonoprazan with erlotinib should be avoided as well.

Aspirin and NSAIDs (i.e, Loxoprofen, Diclofenac, Meloxicam)

When a single dose of aspirin 100 mg, loxoprofen 60 mg, diclofenac 25 mg, or meloxicam 10 mg was co-administered with vonoprazan 40 mg QD, no clinically relevant PK changes were observed in aspirin, loxoprofen, diclofenac, or meloxicam (Study TAK-438/CPH-003). Loxoprofen is not approved in the United States.

Of note, no significant changes were observed in inhibition of platelet aggregation activity following a single dose of aspirin 100 mg with vonoprazan 40 mg QD, compared to aspirin alone.

8.3. Plans for Pediatric Drug Development

Voquezna is subject to study requirements under the Pediatric Research Equity Act (PREA) because vonoprazan for healing and maintenance of healed EE introduces new indications and a new dosing regimen. NDA 215151 also includes proposed indications for the treatment of *H. pylori* in adults. Vonoprazan was approved on May 3, 2022, for the treatment of *H. pylori* infection in combination with clarithromycin and/or amoxicillin, as co-packaged products (Voquezna Triple/Dual Pak; NDAs 215152/215153). The proposed indication for treatment of *H. pylori* in NDA 215151 is for vonoprazan with the clarithromycin and/or amoxicillin prescribed separately. The Division of Anti-Infectives granted a full waiver for PREA requirements for the treatment of *H. pylori* infection for NDAs 215152/215153 on May 3, 2022.

Outside of the neonatal period, EE is not considered to be a rare disease in pediatric patients. EE is rarely identified during the neonatal period, given the time needed to recognize, diagnosis and attempt non-pharmacologic treatment of GERD symptoms.

The Division issued an Agreed initial Pediatric Study Plan (iPSP) for the EE indications to the Applicant on September 24, 2020 and agreed to amend the iPSP on July 14, 2021. The Agreed Amended iPSP included the following:

- A plan to request a (b) (4) waiver of PREA requirements in pediatric patients from birth to <1-month of age because the required studies are impossible or highly impracticable given the current treatment guidelines and the low prevalence of EE in neonates.

- A plan to request a deferred assessment in pediatric patients 1-month to less than 17 years of age with EE because the drug is ready for approval for use in adults before pediatric studies are complete. The deferred assessment included:
  - A plan to develop an age-appropriate formulation for pediatric patients down to 1 month of age.
  - A plan to conduct a juvenile toxicity study in rats.
  - A plan to conduct the following clinical trials in pediatric patients 1-month to 17 years of age:
    - Study 1: A randomized, parallel-group, multiple-dose, 14-day dose-ranging study to evaluate the pharmacokinetics and safety of Voquezna (vonoprazan) in pediatric patients 12 to <17 years of age with gastroesophageal reflux disease (GERD), with or without erosive esophagitis
    - Study 2: A randomized, parallel-group, multiple-dose, 14-day, dose ranging study to evaluate the pharmacokinetics, and safety of Voquezna (vonoprazan) in pediatric patients ≥ (b) (4) month to < 12 years of age with gastroesophageal reflux disease (GERD) wi or without erosive esophagitis.
    - Study 3: A (b) (4) trial to evaluate the efficacy and safety of Voquezna (vonoprazan) for the healing of endoscopically confirmed erosive esophagitis and heartburn symptoms for 8 weeks and the maintenance of healed of erosive esophagitis and heartburn symptoms for 24 weeks in pediatric patients 1 month to 17 years of age with endoscopically confirmed erosive esophagitis.
- (b) (4), (b) (5)
- A plan to request a full waiver for the *H. pylori* indications for NDA 215151.

The Applicant included an Agreed Amended iPSP in the submitted NDA application (dated September 9, 2022) and proposed the following changes to the deferred pediatric studies:

- Revise the clinical study timelines based on current enrollment for Study 1.
- Separate Study 2 into two studies:

(b) (4)

(b) (4)

(b) (4)

Therefore, the Applicant will need to develop an age-appropriate formulation (b) (4) for patients (b) (4) to 6 months of age.

(b) (4)

As discussed elsewhere in this review, the review team identified product quality approvability concerns that will impact the pediatric development timeline for EE as outlined in the Agreed Amended iPSP. Therefore, the decision about the final PREA PMRs will be deferred for this review cycle and will be negotiated with the Applicant in the next cycle, assuming the product quality deficiencies have been addressed.

8.4. Pregnancy and Lactation

8.4.1. Non-Clinical Experience

The nonclinical information used in support of the pregnancy and lactation subsections of labeling for Voquezna are shown in the Table 59 below. There are no pregnancy signals of concern in the animal studies of vonoprazan at relevant doses.

The reproductive and developmental toxicology studies with vonoprazan are also summarized in Section 7.1 of this review and additional details are available in Section 13.

Table 59. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical data
8.1 Pregnancy	In an orally dosed rat embryo-fetal development study, fetuses in the 300 mg/kg* vonoprazan dose group had increased rates of ventral septal defects, malpositioned subclavian branch, tail malformations and small anus. This dose was associated with maternal toxicity. The NOAEL in this study was 100 mg/kg. In a rabbit embryo-fetal development study, there were no treatment-related fetal malformations up to the highest dose tested, 30 mg/kg vonoprazan. In a rat GLP pre- and postnatal development study, liver discoloration associated with necrosis, hemorrhage and/or fibrosis was seen in PND 4 pups from the 100 mg/kg vonoprazan dose group, with a NOAEL of 10 mg/kg in this study. While this effect was not seen in lower dose groups in the GLP rat PPND study, liver discoloration was seen in lower

	doses (3, 10 and 30 mg/kg) in a non- GLP rat dose-range finding study, dosed from GD 6 to LD 13.
8.2 Lactation	Vonoprazan and its metabolites are present in rat milk.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	In an orally dosed fertility and early embryonic development study in rats, no effects of fertility parameters were seen up to the highest dose tested, 300 mg/kg/day vonoprazan.

Source: FDA Nonclinical review of Voquezna Triple Pak (NDA 215152)
*Doses in the animal studies were calculated based on the free vonoprazan molecule
Abbreviations: GD, gestation day; GLP, good laboratory practice; LD, lactation day; N, number of patients in treatment arm; n, number of patients with adverse event; NOAEL, no observed adverse effect level; PND, post-natal day; PPND, peri- and postnatal development; SD, standard deviation

8.4.2. Clinical Experience

Pregnancy

Clinical experience with vonoprazan among pregnant and breast-feeding individuals is limited. There are no human pregnancy outcome data for vonoprazan identified in the published English language literature. The Applicant's pharmacovigilance database (from approvals outside the United States) was limited by a high percentage of unknown outcomes. Study EE-301 excluded subjects who were pregnant or lactating. No subject became pregnant during the healing phase of the study. One subject became pregnant during the maintenance phase of Study EE-301; however, no follow-up information is available as the subject did not provide additional information regarding the pregnancy and outcome. There were no pregnancy or pregnancy-related events in the confirmatory evidence studies (TAK-438/CCT-002, TAK-438_303, TAK-438/CCT-003, TAK-438_305).

Lactation

It is not known whether vonoprazan is present in human milk. There are no reports in the published literature or in the Applicant's pharmacovigilance database of human infant exposure via lactation.

Vonoprazan is found in rat milk. As describe above in Section 8.4.1, in a rat good laboratory practice pre- and postnatal development study liver discoloration and necrosis, hemorrhage and/or fibrosis was observed in rat pups exposed to vonoprazan only through lactation.

A PMR for a "milk only" clinical lactation study to assess whether vonoprazan is present in clinically relevant quantities in human milk was issued to the Applicant with approval of NDAs 215152/215153. Further lactation studies may be needed to assess vonoprazan levels in infants exposed to the product via lactation, if vonoprazan is found to be present in human milk.

Females and Males of Reproductive Potential

As described above in Section 8.4.1, no adverse findings with regard to fertility were observed in animals exposed to vonoprazan during a fertility and early embryonic development study. No additional information in the published human literature were identified. Therefore, subsection 8.3 (Females and Males of Reproductive Potential) will not be included in Voquenza labeling.

Conclusions

Available data from pharmacovigilance reports with vonoprazan use in pregnant women are not sufficient to evaluate for a drug-associated risk for major birth defects, miscarriage or other adverse maternal or fetal outcomes.

The recommended lactation labeling language will advise patients not to breastfeed during treatment.

There is no need for pregnancy testing or contraception with use of Voquezna.

There are already existing PMRs for a pregnancy exposure registry and a postmarketing pregnancy study of a different design issued with the approval of NDAs 215152/215153. The protocols for these two PMRs should be revised with approval of NDA 215151 to add subjects with EE who become pregnant during treatment with Voquezna. There is already an existing PMR for a "milk only" clinical lactation study for NDAs 215152/215153 to assess whether vonoprazan is present in clinically relevant quantities in human milk. It is not necessary to require a milk only clinical lactations study for NDA 215151.

9. Product Quality

In NDA 215151 the Applicant is seeking approval for vonoprazan 10 mg and 20 mg tablets for oral administration for the treatment of healing of erosive esophagitis (EE), maintenance of healed EE, and treatment of *H. pylori* infection (in combination with the antibacterials clarithromycin and/or amoxicillin, provided separately). Vonoprazan 20 mg tablets was previously submitted by the Applicant, and approved May 3, 2022, as part of a co-packaged product with 500 mg amoxicillin capsules (Voquezna Dual Pak; NDA 215153) and 500 mg clarithromycin tablets and 500 mg amoxicillin capsules (Voquezna Triple Pak; NDA 215152) for the treatment of *H. pylori* infection.

In the pre-NDA meeting for NDA 215151, it was agreed that CMC documents related to the drug substance, 20 mg strength tablet, development pharmaceutics, and analytical methods applicable to both 10 mg and 20 mg tablets would be cross-referenced from NDAs 215152/215153 to NDA 215151.

Drug Substance

For the drug substance, vonoprazan fumarate, the synthetic scheme, control of materials, control of critical steps, and intermediates, process validation studies, manufacturing process and development, characterization, impurities/degradant characterization, specifications, the analytical procedures, reference standards, container closure system, and stability data have all been cross-referenced to NDAs 215152/NDA 215153 and found adequate for the drug substance. See Drug Substance Review by K. Zuck dated January 20, 2022, in the OPQ review platform.

In a submission to NDA 215152 (Supplement 2, Manufacturing (CMC), submitted October 5, 2022, an (b) (4) impurity (b) (4) was detected in the drug product Voquezna.

Additional analytical analysis of several batches of the drug substance, vonoprazan fumarate, by the applicant has shown the level of this (b) (4) impurity to be approximately (b) (4) ppm. A control for the (b) (4) impurity has been added to the drug substance specification for vonoprazan fumarate by the applicant with retest period of (b) (4) months for the drug substance to ensure that the limit (b) (4) in the drug substance is met. The drug substance specification is adequate to ensure the quality of vonoprazan as it relate to the safety and efficacy of the eventual drug product. A limit of (b) (4) ppm for vonoprazan fumarate would translate to a daily exposure (b) (4), which is well below the limit of concern (b) (4) in drug products (b) (4).

The stability data for vonoprazan fumarate drug substance while stored at long-term (b) (4) supports the proposed retest period of (b) (4) months while packaged in the proposed commercial packaging configuration.

Drug Product

Voquezna (vonoprazan) tablets are intended to be supplied as two dosage strengths: 10 mg of vonoprazan (equivalent to 13.36 mg of vonoprazan fumarate) and 20 mg of vonoprazan (equivalent to 26.72 mg of vonoprazan fumarate) for oral administration.

Each film-coated tablet contains the following inactive ingredients: croscarmellose sodium, ferric oxide red (only in 20 mg tablets), ferric oxide yellow (only in 10 mg tablets), fumaric acid, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

Voquezna tablets 10 and 20 mg are packaged in 30-count high-density polyethylene (HDPE) bottles (b) (4). A 5-count HDPE bottle presentation is a professional sample and not for resale.

The formulation of the vonoprazan 20 mg strength tablets for NDA 215151 is identical to that of NDAs 215152/215153. (b) (4)

The applicant's request for a categorical exclusion from the requirement to submit an Environmental Assessment per 21 CFR 25.31(b) is acceptable.

The proposed drug product specification included in the original NDA submission includes testing for appearance, identification (HPLC and UV), assay (HPLC), degradation products (HPLC), dissolution, (b) (4), and uniformity of dosage units. In the October 5, 2022, CMC submission to NDA 215151, the applicant added (b) (4) to the specifications (LC-SRM-MS).

On December 19, 2022, FDA agreed to the proposal to use (b) (4) a read-across surrogate for the derivation of an acceptable intake (AI) for (b) (4) in the drug product.

The corresponding acceptance criterion (b) (4) in the drug product in parts per million (ppm), based on the AI (b) (4) (February 2021) and the maximum daily dose (MDD) of the product (40 mg/day), is (b) (4) ppm as calculated per the following equation:

(b) (4)

The Applicant's proposed acceptance criteria of not more than (NMT) (b) (4) ppm for release and NMT (b) (4) ppm for stability (b) (4) in the drug product specifications are not acceptable because the daily intake (b) (4), if present, at both limits exceeds the AI (b) (4).

Twelve months long-term stability data (25°C/60% RH) were provided for four batches of 10 mg and 20 mg tablets packaged in (b) (4) HDPE bottles to bracket the commercial package size of 30-ct bottles. These stability batches were manufactured at the proposed commercial manufacturing site, i.e., Catalent Winchester, using the drug substance from the non-commercial site (b) (4). In addition, twelve months long term stability data were provided for 12 batches manufactured at (b) (4), which includes eight batches manufactured with the drug substance from the proposed commercial manufacturing site, (b) (4). Six months accelerated stability data (40°C/75% RH) were also provided for each of these lots. Even though other stability data are acceptable to support the proposed expiration dating period of 24 months when stored at 20°C to 25°C, the limited stability data (b) (4) show that both strengths of vonoprazan tablets cannot consistently meet the acceptance criterion (b) (4).

In summary, the applicant's proposed limits of NMT (b) (4) ppm for release and NMT (b) (4) ppm for stability (b) (4) in the drug product specifications are not acceptable. The CMC data in the NDA do not support a viable shelf life for vonoprazan 10 mg and 20 mg tablets.

(b) (4)

A paper review of the analytical method and the method validation report for the quantitation (b) (4) in vonoprazan tablets was conducted by the Office of Testing and Research (ORT review dated November 28, 2022). OTR comments on the method were communicated to the applicant

on December 6, 2022, under NDA 215152. The applicant's responses provided to NDA 215152 addressed OTR's concerns and OTR considers the method adequate for quality purposes (OTR review dated January 19, 2023).

Manufacturing

The manufacturing process review for vonoprazan 20 mg (b) (4) tablets was conducted as part of NDA 215152 and found to be adequate. The assessment covered information specific to Vonoprazan tablets 10 mg and packaging of Vonoprazan tablets 10 mg and 20 mg in high-density polyethylene (HDPE) bottles.

The vonoprazan tablets will be manufactured at Catalent Pharma Solutions, LLC (FEI# 1000122400) located at Winchester, KY, USA. Based on the experience and compliance history, acceptable profile for the tablets (TCM), and approval of the facility for the 20 mg strength tablet (cross-referenced from NDA 215152/215153), the facility is recommended for approval to support the application.

The commercial manufacturing of vonoprazan drug substance will be conducted at (b) (4) . Based on the experience and compliance history, acceptable profile for the non-sterile active pharmaceutical ingredient (CSN), and approval for drug substance manufacturing responsibility for the 20 mg strength tablet (cross-referenced from NDA 215152/215153), the site is recommended for approval to support the application.

Biopharmaceutics

The proposed dissolution method and acceptance criteria for the 10 mg and 20 mg tablets are acceptable and adequately bridged the formulation used during development to the commercial tablets.

Labeling

Issues on the container labels and carton labeling have been satisfactorily resolved and the container labels and carton labeling provided in SDN-22 (dated October 14, 2022) are acceptable. Issues on Prescribing Information have been satisfactorily resolved. The Prescribing Information labeling provided in SDN-32 (dated January 24, 2023) is adequate.

Conclusion

Based on OPQ's evaluation of the available information, the applicant has not provided adequate chemistry, manufacturing, and controls (CMC) information to ensure the identity, strength, purity, and quality of the proposed drug product and the product is not recommended for approval.

The following deficiencies need to be addressed:

(b) (4)

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The Office of Scientific Investigations (OSI) inspected three clinical sites that participated in Study EE-301 and the contract research organization responsible for critical study-related activities and concluded the study appears to have been conducted adequately and the data generated by the three clinical sites appears acceptable in support of the respective indications of healing of EE and maintenance of healed EE. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. See Section 20 for a summary of inspection findings and Section 23 for financial disclosures.

11. Advisory Committee Summary

Not applicable. An Advisory Committee meeting was not held because no unexpected significant safety or efficacy issues were identified, and no other issues arose that would benefit from advisory committee discussion.

III. Appendices

12. Summary of Regulatory History

On October 11, 2007, pre-investigational (PIND) application 079212 was submitted by Takeda Global Research & Development Center, Inc. for the development of vonoprazan immediate-release tablets (10 and 20 mg), an acid-inhibitory agent belonging to a new class of potassium-competitive acid blockers for: healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, (b) (4) On November 20, 2007, a Special Protocol Assessment was submitted for 24-month rat and mouse carcinogenicity studies. The Carcinogenicity Assessment Committee concurred with the proposed doses in the protocols.

In 2009, two pre-IND guidance meetings were granted to discuss the nonclinical toxicology and overall clinical development program and planned in vitro and in vivo drug-drug interaction studies. On May 13, 2019, the Division of Gastroenterology was notified of a change in ownership of PIND 079212 from Takeda to Phathom Pharmaceuticals Inc. Phathom licensed the rights from Takeda to develop vonoprazan in the United States to initiate a clinical development program for the treatment of *Helicobacter pylori* (*H. pylori*) infection, 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 July 10, 2019, a type B pre-IND meeting was held to discuss key aspects of the clinical pharmacology program and the phase 3 clinical development program in support the planned new drug application (NDA) for EE. An Investigational New Drug (IND 079212) was activated on August 8, 2019, for the protocol for Study EE-301, intended to serve as a phase 3 adequate and well-controlled trial in the United States and Europe to support the NDA, and the trial was determined safe to proceed on September 10, 2019. FDA requested the Applicant include in the protocol for Study EE-301 justifications with data to support the proposed non-inferiority margins for the primary and secondary endpoints in which a non-inferiority assessment was proposed.

On August 23, 2019, IND 143190 for vonoprazan, amoxicillin, and clarithromycin tablets and IND 144399 for vonoprazan and amoxicillin tablets for the treatment of *H. pylori* infection became active in the Division of Anti-Infectives (DAI).

On February 7, 2020, the Applicant submitted an End of Phase 2 chemistry, manufacturing, and controls (CMC) meeting request, granted by FDA, and subsequently canceled by the Applicant on April 14, 2020, after receiving preliminary responses.

The Applicant requested a type C guidance meeting on February 13, 2020, to which FDA issued written responses on March 31, 2020, containing agreements on the overall design of the proposed drug-drug interaction studies with additional comments to be provided upon submission of the full protocols to the IND.

On March 12, 2020, the Applicant submitted their proposed Initial Pediatric Study Plan (iPSP) for the indications of healing of EE and relief of heartburn and maintenance of healed EE with

relief of heartburn. On September 24, 2020, FDA issued the agreed initial Pediatric Study Plan. On December 18, 2020, the Applicant submitted an amended iPSP (b) (4). The FDA issued an amended agreed iPSP on July 14, 2021. See also Section 8.3 Plans for Pediatric Drug Development.

An additional type C meeting was requested to gain clarification on the proposed dissolution methods provided in the CMC End of Phase 2 meeting preliminary comments. The FDA issued Written Responses on September 1, 2020.

On April 22, 2021, the FDA granted a meeting to discuss the Applicant's proposed strategy for the Integrated Summary of Effectiveness and the Integrated Summary of Safety and related data requirements for an NDA for vonoprazan for the healing and maintenance of healing of all grades of EE and relief of heartburn. Written Responses were issued on July 1, 2021. The Applicant proposed to submit the results of Study EE-301, conducted in the United States and Europe, and four "supportive" phase 3 trials (TAK-438/CCT-002, TAK-438/CCT-003, TAK-438_303, TAK-438_305), conducted by Takeda in Japan and Asia (outside of Japan) and not under a U.S. IND, as evidence of the efficacy and safety of vonoprazan to support the proposed indications. FDA stated the primary determination of safety and effectiveness will be based upon the results of Study EE-301. Data from the other four trials will be considered as supportive. In addition, the Applicant proposed to designate the following as adverse events of special interest (AESIs) as they appear correspond to the safety profile identified during development of vonoprazan outside the United States: hepatoxicity, severe cutaneous adverse reactions, *Clostridioides difficile* infection and pseudomembranous colitis, hypergastrinemia, and bone fracture. FDA noted that in 2019, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) added "pancytopenia, agranulocytosis, leukopenia, and thrombocytopenia" to the Japanese product label. Therefore, FDA requested the Applicant also include hematologic abnormalities as an AESI.

The Applicant was asked to impute data missing due to the COVID-19 pandemic using a missing at random assumption and to submit an updated Statistical Analysis Plan for review prior to the NDA submission. August 18, 2021, the Applicant submitted an updated Statistical Analysis Plan for Study EE-301 to address comments from FDA issued July 2, 2021.

In response to a type C meeting request received July 15, 2021, to obtain feedback on the pediatric development plan, including juvenile toxicity, and pharmacokinetic studies the FDA issued written responses on September 28, 2021.

On September 24, 2021, a type B pre-NDA meeting request was received and was subsequently granted as a teleconference scheduled for November 18, 2021, to discuss the key aspects of the Applicant's submission strategy of the clinical and CMC sections in support of an NDA 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. FDA preliminary comments were provided to the Applicant on November 15, 2021 and based on the agreements outlined for the future NDA submission, the Applicant canceled the meeting. (b) (4)

The preliminary comments issued on November 15, 2021, in advance of the pre-NDA meeting for NDA 215151 stated that the Applicant could include the proposed *H. pylori* indication statement(s) in the labeling submitted to NDA 215151. A cross-reference letter to NDA 215152 could be submitted for the safety and efficacy information supporting the use of vonoprazan for

treatment of *H. pylori* infection. The FDA agreed with the Applicant's plan to cross-reference NDA 215152 for other portions of NDA 215151 (e.g., 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).

On September 3, 2021, the Applicant submitted two NDAs (215152, co-package of vonoprazan/amoxicillin/clarithromycin and 215153, co-package of vonoprazan/amoxicillin) to DAI for the treatment of *H. pylori* infection. NDAs 215152/215153 were approved on May 5, 2022, as Voquezna Triple Pak and Voquezna Dual Pak.

NDA 215151 (the subject of this document) for Voquezna (vonoprazan) immediate-release tablets was submitted to the Agency under the 505(b)(1) pathway on March 11, 2022, seeking the following indications: healing of all grades of EE and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *H. pylori* infection.

During the review of NDA 215151, a type B meeting was held (September 6, 2022, under NDAs 215152/215153) to discuss the finding of (b) (4) a (b) (4) impurity, in the vonoprazan fumarate drug substance and vonoprazan tablets.

On October 5, 2022, the applicant submitted a Chemistry Manufacturing and Controls (CMC) Prior Approval Supplement to NDA 215152 (cross-referenced to NDAs 215153 and 215151) proposing to add (b) (4) test and acceptance criteria in the drug substance and drug product specifications, and to add the associated analytical testing sites, analytical methods, analytical method validations, stability testing commitments and supportive data to justify (b) (4) a surrogate to derive an acceptable intake (AI) (b) (4). The recommended acceptable intake (b) (4)

On December 19, 2022, it was communicated to the applicant (NDA 215152, cross-referenced to NDA 215151) that FDA agreed to the proposal to use (b) (4) surrogate for the derivation of an acceptable intake for (b) (4) in the drug product. In addition, as communicated on December 23, 2022, the corresponding acceptance criterion for (b) (4) in the drug product in parts per million (ppm), based on the AI (b) (4) and the maximum daily dose (MDD) of the product (40 mg/day), is (b) (4) ppm as calculated per the following equation:

(b) (4)

The applicant's proposed acceptance criteria of not more than (NMT) (b) (4) ppm for release and NMT (b) (4) ppm for stability for (b) (4) in the drug product specifications in the NDA are not acceptable because the daily intake of (b) (4), if present, at both limits exceeds the acceptable intake (b) (4) and, therefore, the data do not support a viable shelf life for vonoprazan 10 mg or 20 mg tablets. See Section 9 for additional discussion of the deficiencies.

The applicant submitted an amendment on January 23, 2023, discussing a proposed plan to submit data in the future for six reformulated batches of drug product (three batches for each dosage strength) (b) (4). This amendment was not reviewed in the current review cycle as the deficiencies stated in Section 9 are not addressed by this amendment. Information on the proposed reformulated drug product will be assessed outside of the review cycle.

On February 3, 2023, DAI issued a CR for the CMC Prior Approval Supplement (NDA 215152/S-02 and NDA 215153/S-02) citing the following:

> The proposed specification limits [redacted], of [redacted] ppm at release and [redacted] ppm for end of shelf life, are not acceptable specified limits [redacted] because they would lead to a daily intake greater than the AI limit [redacted] for the labeled 40 mg/day dose of vonoprazan for treatment of *H. pylori*. The AI [redacted] was derived using [redacted] surrogate, for which [redacted] is the acceptable AI.
>
> As the levels [redacted] in your drug products are above the AI limit, we recommend that you perform a root cause investigation to identify the source [redacted] and take appropriate measures to reduce or prevent the formation [redacted].

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

The Applicant is seeking approval of vonoprazan tablets (10 mg and 20 mg) for the treatment of healing of EE and relief of heartburn, maintenance of healed EE and relief of heartburn. The Applicant did not submit any nonclinical study reports in the current NDA, and a letter of reference to NDAs 215152 and 215153 has been provided for the nonclinical study reports. The nonclinical studies were reviewed under NDAs 215152 and 215153 for the treatment of *H. Pylori* infection in combination with amoxicillin and/or clarithromycin.

13.2. Individual Reviews of Studies Submitted to the NDA

The Applicant did not submit any nonclinical study reports in the current NDA and referred to NDAs 215152 and 215153 for nonclinical safety of vonoprazan. The nonclinical studies were reviewed under NDAs 215152 and 215153 for the treatment of *H. Pylori* infection in combination with amoxicillin and/or clarithromycin.

The nonclinical studies reviewed previously under different INDs and NDAs are summarized in the following sections.

13.3. Pharmacology

The inhibitory effects on acid production of vonoprazan were evaluated in isolated rabbit gastric glands at concentrations of 0.01, 0.03, 0.1, 0.3, 1 and 3 micromolar/L. TAK-438 is a potent inhibitor of forskolin-induced acid formation in isolated rabbit gastric glands with half maximal inhibitory concentration (IC_{50}) of 0.3 µmol/L (Study # TAK-438-00067-001R). TAK-438

metabolites (M-III and M-IV-Sul) did not show any inhibitory effect on forskolin-induced acid formation in isolated gastric glands at concentrations of 0.01 to 3 μmol/L (Study # TAK-438-10130). In vitro studies at pH 6.5 demonstrated that TAK-438 is a potent inhibitor of K^+-stimulated porcine gastric H^+, K^+-ATPase activity with IC_{50} of 19.3 to 29.9 nanomolar/L. M-IV-Sul (a TAK-438 metabolite) weakly inhibited gastric H^+, K^+-ATPase activity with an IC_{50} of 4120 nmol/L. Metabolites M-I, M-II, and M-III did not inhibit K^+-stimulated porcine gastric H^+, K^+-ATPase at the highest concentration tested (10000 nmol/L), and TAK-438 did not inhibit the highly homologous sodium, potassium-adenosine triphosphatase (Na^+, K^+-ATPase) at 10000 nmol/L (Studies # TAK-438-00115, #TAK-438-11415, #TAK-438-11416). TAK-438 is a reversible inhibitor of K^+-stimulated porcine gastric H+, K+-ATPase activity (Studies # TAK-438-00139 and TAK-438-00116). TAK-438 metabolites, M-I and M-II did not inhibit H^+, K^+-ATPase at 100 nmol/L without dilution (Study # TAK-438-00139). The enzyme kinetic analysis demonstrated that TAK-438 is a K^+-competitive inhibitor for H^+, K^+-ATPase activity in isolated porcine gastric vesicles (Studies # TAK-438-00117 and TAK-38-00140.001R).

The inhibitory effects of gastric acid secretion of TAK-438 were assessed in rats and dogs following oral and intravenous administration. Rats were administered TAK-438 (0.5, 1, 2, and 4 mg/kg) by oral gavage. One-hour post-dose, the pylorus was ligated, and stomach was removed 3 hours after ligation and the total acid output of the gastric contents was measured. Tak-438 at doses of 2 and 4 mg/kg significantly decreased total acid output with a 50% inhibitory dose (ID_{50}) value of 1.26 mg/kg (Study # TAK-438-00071). Similarly, in vivo studies were conducted in pylorus ligated rats to determine the inhibitory effects of TAK-438 on histamine-stimulated (30 mg/kg subcutaneous [SC]) and 2-deoxy-D-glucose-stimulated (200 mg/kg/10 mL SC) acid secretion. In both studies, TAk-438 inhibited histamine- and 2-deoxy-D-glucose-stimulated acid secretion in a dose-dependent manner with ID_{50} values of 0.86 and 0.83 mg/kg, respectively (Studies # TAK-438-00072 and TAK-438-00073). The inhibitory effects of TAK-438 (0.5, 1, 2 and 4 mg/kg, oral gavage) on aspirin- and indomethacin-induced gastric mucosal lesions were assessed in rats following oral administration of the drug. One hour after TAK-438 administration, aspirin (200 mg/kg/5 mL) or indomethacin (30 mg/kg/2 mL) was administered orally, and 4 hours later the stomach was removed, and gastric corpus counted under a microscope. TAK-438 significantly inhibited aspirin- and indomethacin-induced lesion formation in a dose-dependent manner with ID_{50} values of 0.73 and 1.65 mg/kg, respectively (Studies # TAK-438-10002 and TAK-438-10003). The preventive actions of TAK-438 was also assessed against experimental reflux esophagitis in rats at dose levels of 0.5, 1, 2 and 4 mg/kg orally. TAK-438 significantly inhibited esophageal lesion formation at the 2 and 4 mg/kg dose levels with an ID_{50} value of 1.27 mg/kg (Study # TAK-438-10004).

Intravenous administration of TAK-438 (2 mg/kg) in anesthetized stomach cannulated rats caused a marked increase in gastric perfusate pH under histamine-stimulated acid secretion for up to 5 hours (Study # TAK-438-10863). In rats, the histamine (30 mg SC) stimulated gastric acid secretion and indomethacin (30 mg/kg, IV) induced gastric bleeding in pylorus ligated rats was inhibited following IV injections of TAK-438 (0.1, 0.2, 0.4 and 0.8) with ID_{50} values of 0.15 and 0.32 mg/kg, respectively (Studies # TAK-438-10957and TAK-438-10864). The heidenhain pouch beagle dogs were used to study the effects of TAK-438 on gastric acid output following oral administration of TAK-438 at 0.1, 0.3, and 1 mg/kg doses. Gastric secretion was stimulated with SC injections of histamine HCl (30 μg/kg) on one day before and 1, 3, 6, 24, and 48 hours after TAK-438 or vehicle administration. After each histamine stimulation, gastric juice from the heidenhain pouch was collected continuously during 3 consecutives 30-minute periods and both

the gastric juice volume and total acid output was measured. The study showed that TAK-438 inhibited histamine-stimulated total acid output in a dose-dependent manner, exhibited complete inhibition at 1-, 3-, and 6-hours post-dose at the 1 mg/kg dose and continued inhibition of acid secretion for more than 48 hours post-dose at all dose levels (Study # TAK-438-00074).

In in vitro secondary pharmacology studies, TAK-438 was evaluated for receptor binding affinities, ion channel effects, and enzyme inhibition. Among 133 functional proteins (receptors, ion channels, enzymes, transporters) tested, TAK-438 inhibited L-type calcium channels, muscarinic receptors (M_1, M_2 or M_3), serotonin 5-HT2 receptor, sigma receptor, and sodium channel by 50% or more at a concentration of 10 μmol/L. The IC_{50} values were 2.27, 1.49, 0.80, and 1.43 μmol/L for L-type calcium channels, muscarinic M_1 receptors, muscarinic M_3 receptors, and serotonin 5-HT_2 receptors, respectively (Study # TAK 438-00005).

13.3.1. Safety Pharmacology

Potential effects of TAK-438 on the cardiovascular, respiratory and central nervous systems were investigated in in vitro and in vivo studies. In summary, TAK-438 was tested at concentrations of 0.5, 5, and 50 μg/mL for potential effects on the human Ether-à-go-go-Related Gene (hERG) current in HEK293 cells using the whole-cell patch-clamp method. TAK-438 inhibited hERG currents at concentrations of 0.5 μg/mL and higher, with an IC_{50} value of 4.8 μg/mL (Study # TAK-438-00063). In dogs, cardiovascular effects (blood pressure, heart rate and ECG) of TAK-438 was assessed in 4 conscious, telemetered male dogs receiving either vehicle or a single oral dose of TAK-438 at 2, 6 or 20 mg/kg. TAK-438 had no effect on any evaluated cardiovascular parameters up to a dose of 20 mg/kg (Study # TAK-438-00081). Potential effects of TAK-438 on the respiratory system was assessed in conscious free-moving male Crl:CD(SD) rats (n=8). TAK-438 was administered orally at doses of 30, 100 and 600 mg/kg. Four out of 8 animals in the 600 mg/kg dose group died. An increase in bronchoconstriction was noted in one of four animals before death occurred. Animals in the 600 mg/kg dose group showed decreased tidal volume (TV), minute volume (MV), at 4 and 8 hours after dosing. The respiratory parameters were unaffected in 30 and 100 mg/kg dose groups (Study # TAK-438-00082). Effects of TAK-438 on the central nervous system (CNS) was assessed in conscious free-moving male Crl:CD(SD) rats. TAK-438 was administered orally at doses of 30, 100 and 600 mg/kg. Death was noted in 1 animal in the 600 mg/kg group between 2 and 4 hours after dosing. The animals in the 600 mg/kg group exhibited the following signs at 1-4 hours after dosing: decreased muscle resistance, decreased locomotor activity, partially closed palpebra, difficulty in hopping and decrease in body temperature. In addition, these animals exhibited an increase in the pupil size at one to eight hours after dosing. Animals in the 100 mg/kg dose group showed an increase in the pupil size (mydriasis) at 1 to 8 hours after dosing which returned to normal at 22 hours after dosing. No treatment-related findings were noted in general physical condition or behavior of the animals at 30 mg/kg (Study # TAK-438-00080).

13.3.2. ADME/PK

The ADME profile of TAK-438 and related compounds have been studied in vivo in rats and dogs and in vitro (plasma protein binding, partitioning into blood cells, in vitro metabolism using hepatic microsomes, cytosols, and hepatocytes from several species, as well as in vitro

cytochrome (CYP) P450 isoenzyme inhibition and induction, human colon carcinoma cell line (Caco-2) permeability).

Absorption

After single oral dose of [^{14}C]-TAK-438, TAK-438F (TAK-438 free base) in rats (2 mg/kg) and dogs (0.3 mg/kg), the oral bioavailability of TAK-438 was 52.4% in dogs and 10.3% in rats (Studies # TAK-438-00103, TAK-438-00086 and TAK-438/00105). The apparent absorption (F_{app}) ratio of TAK-438 was 92.2% in rats and 86.3% in dogs as calculated from the ratio of AUC after oral administration to that of intravenous administration (Studies # TAK-438/00103 and TAK-438-00112). TAK- 438 was primarily absorbed from the portal vein. This was determined after single injection of [^{14}C]-TAK-438 (TAK-438F 2 and 18 mg/kg) into the jejunal loop of fasted male rats. The ratio of unchanged TAK-438F to the total radioactivity in the portal vein plasma was 89.1% (2 mg/kg) and 92.7% (18 mg/kg) at 2 hours after dosing (Studies #TAK-438-11280 and TAK-438-11281). After oral administration of [^{14}C]-TAK-438F to rats (2 to 18 mg/kg) and dogs (0.1 to 1.0 mg/kg), the plasma concentrations of TAK-438F increased more than a dose proportional manner (Studies # TAK-438/00103, TAK-438-00112 and TAK-438-11277).

In vitro studies were conducted to determine the permeability of [^{14}C]-TAK-438 using human colon adenocarcinoma (Caco-2) cells, and in another study, the permeability of [^{14}C]-TAK-438F was compared with 20 model drugs using Caco-2 cells. Both studies showed that TAK-438 is highly permeable with permeability coefficient of 17.8. (Studies # TAK-438-10811 and PRE-DDA-438-004).

Distribution

In rats, after single oral administration of [^{14}C]-TAK-438F (2 mg/kg), TAK-438 was widely distributed into tissues. The total radioactivity reached the maximum level at one hour in most tissues. The total radioactivity concentration was higher in the liver, followed in decreasing order by the kidneys, intestine, lungs, stomach, plasma, hypophysis, adrenals, spleen, blood, submaxillary glands, pancreas, heart, bone marrow, harderian glands, thyroid gland, brown fat, skin, thymus, skeletal muscle, testes, fat, eyes, brain, and spinal cord. The distribution of radioactivity into the blood cells at 0.25, 1, 2 and 24 hours after administration was 36.9%, 15.8%, 5.2% and 31.1%, respectively. At 168 hours no radioactivity was detected in the tissues except for the lung, liver, kidney, and gastric contents (Studies #TAK-438-00092 and TAK-438-11258). The distribution of TAK-438 metabolites (M-I, M-I-G, M-II and M-II-G) in the stomach wall was between 0.3% to 0.9% (Studies #TAK-438-00110, TAK-438-00111 and TAK-438-11038). In vivo plasma protein binding [^{14}C]-TAK-438F was conducted in rats (2 mg/kg) and dogs (0.3 mg/kg). In rats and dogs, the plasma protein binding ratios of the radioactivity were between 82.8%-95.1% and 88.5%-94%, respectively from 0.25 to 25 hour time points (Study #TAK-438-11249). In an in vitro study, the protein binding of [^{14}C]-TAK-438 ranged from 67.3% to 69.5% in rat plasma, from 71.7% to 83.3% in dog plasma, and from 85.2% to 88.0% in human plasma (Study #TAK-438-00087).

The feto-placental transfer of TAK-438F was determined after oral administration of [^{14}C]-TAK438F (2 mg/kg) to pregnant rats on 18th day of pregnancy. The concentrations of the radioactivity in the maternal plasma, placenta, in the fetuses and amniotic fluid were reached to

highest levels at 1 hour and decreased by 48 hours after oral administration (Studies #TAK-438-11240 and TAK-438-11247).

Metabolism

The metabolic profile of TAK-438 was assessed in vivo and in vitro studies.

In vivo studies showed that TAK-438 is extensively metabolized in rats and dogs. Profiling of plasma samples collected from the rat (2 mg/kg, orally) and dog (0.3 mg/kg, orally) studies showed the presence of unchanged TAK-438F, and the metabolites M-I, M-I-G, M-II, M-II-G, M-III, M-IV-Sul. In rats, M-I was the most predominant metabolite in plasma (52% of total radioactivity). In dogs, M-II-G was the major component (39% of total radioactivity); whereas M-III and M-IV-Sul were minor components (≤1.1% of total radioactivity) in plasma (Studies #TAK-438-00109, TAK-438-11243, TAK-438-00093 and TAK-438-11245). After oral administration of [^{14}C]-TAK-438 to rats and dogs, the metabolic profile was also assessed in the urine and feces collected during 24 and 48 hours after administration. In both species, parent drug and M-I, M-I-G, M-II, M-II-G, M-III, M-IV-Sul, and other unidentified metabolites were identified in urine and feces. In rats, M-I-G was the major component in the feces (8.5% of dose). In dogs, M-II-G was the major component (~43% of the dose) in the urine. In both species, M-III and M-IV-Sul were minor metabolites (<1% of the dose) in both urine and feces (Studies # TAK-438-00091, TAK-438-11244, TAK-438-00113 and TAK-438-11246).

In vitro metabolism using hepatic microsomes from mouse, rat, dog, monkey, and human showed that TAK-438 was metabolized to M-I, M-II, T-1641510 (*N*-demethylated TAK-438F), and up to six unidentified metabolites (UK-A, UK-B, UK-C, UK-D, UK-E, and UK-F). M-I and T-1641510 were major metabolites formed by human hepatic microsomes. (Study #TAK-438-00095). In another in vitro metabolism study, [^{14}C]-TAK-438 was incubated for up to six hours with hepatocytes from humans, rats, dogs, and monkeys. TAK-438 was mainly metabolized to M-I, M-II, M-III, M-IV-Sul, and N-demethylated TAK-438 in the hepatocytes from all the species. Whereas M-IV-Sul in the human hepatocytes were much higher than those in the other species (Study # TAK-438/00131). In vitro metabolism of vonoprazan (TAK-438) is shown in the Applicant's table below.

Table 60. In Vitro Metabolism of Vonoprazan by Hepatocytes

Animal species	Elimination amount (nmol/L)	Formation amount (nmol/L)				
	Vonoprazan	M-I	M-II	M-III	M-IV-Sul	*N*-demethylated TAK-438
Rat	3180	996	8	45	71	961
Dog	1324	241	5	13	25	595
Monkey	5560	2118	25	301	54	1585
Human (Lot No. 69)	1593	399	5	101	298	521
Human (Lot No. 85)	1496	192	6	46	469	473
Human (Lot No. IHR)	1021	143	13	25	381	251

Source: NDA file Module 2, Section 2.6.4 Pharmacokinetics Written Summary

The metabolic profile of [^{14}C]-TAK-438 was assessed in vitro by incubating with human microsome expressing cytochrome (CYP) isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). TAK-438 was metabolized by CYP2D6, CYP2C19, and CYP3A4. CYP2D6 and CYP2C19 mainly formed the N-

demethylated TAK-438, whereas CYP3A4 mainly formed M-I, M-III, and N-demethylated TAK-438. TAK-438 was also metabolized by CYP2B6 to form M-I, M-III, and N-demethylated TAK-438. The study suggests that TAK-438 is mainly metabolized by CYP3A4/5 and to a lesser extent by CYP2B6, CYP2C19, and CYP2D6. (Study # TAK-438-00097). In another study, [^{14}C]-TAK-438 incubated with human liver microsomes expressing CYP isoform substrates (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A11). TAK-438 was metabolized to M-I, M-II, N-demethylated TAK-438, and other seven unidentified metabolites (Study # TAK-438-00096).

Excretion

In rats, after oral administration of [^{14}C]-TAK-438 (2 mg/kg), the excretion of radioactivity in feces, urine and expired air were 79.8%, 16.7% and 0.6%, respectively at 72 hours after oral dosing (Study # TAK-438-00075). In another study, [^{14}C]-TAK-438 (2 mg/kg) was administered orally to male rats and the parent compound or the metabolites in urine and feces were measured. In the urine, TAK-438F, M-I, M-I-G, M-II, M-II-G and other unidentified metabolites comprised 2.1%, 0.1%, 1.3%, 0.7%, 1.4% and 10.2% of the dosed radioactivity, respectively. In the feces, TAK-438F, M-I, M-I-G, M-II, M-II-G and other unidentified metabolites comprised 0.8%, 1.6%, 8.5%, 0.4%, 0.6% and 65.0% of the dosed radioactivity, respectively (Study # TAK-438-00091). The biliary, urinary and fecal excretion of TAK-438 was determined after a single intraduodenal administration of [^{14}C]-TAK-438 at a dose of 2.67 mg/kg (2 mg/kg as the free base of TAK-438F) to bile duct-cannulated male rats. The excretion ratio of the radioactivity into the bile, urine and feces during 24 hours after administration was 88.0%, 8.7% and 2.1% of the dose, respectively. In another study in bile duct cannulated rats, at least 57.4% of TAK-438 and its metabolites in the bile were reabsorbed and subjected to enterohepatic circulation (Study # TAK-438-00088). Following a single intravenous administration of [^{14}C]-TAK-438 at a dose of 1.002 mg/kg (0.75 mg/kg as TAK-438F) to bile-duct cannulated male rats, excretion into the bile, urine and feces accounted for 79.8%, 15.9% and 1.0%, respectively of the dose within 24 hours after administration (Study # TAK-438-11037).

In dogs, after oral administration of [^{14}C]-TAK-438F (0.3 mg/kg), the excretion of radioactivity in feces and urine were 31.4% and 58.8%, respectively at 24 hours after oral dose. In the urine, TAK-438F, M-I, M-I-G, M-II, M-II-G and other unidentified metabolites comprised 0.5%, 0.6%, 0.8%, 1.0%, 42.6% and 13.3% of the dosed radioactivity, respectively. In the feces, TAK-438F, M-I, M-I-G, M-II, M-II-G and other unidentified metabolites comprised 0.5%, 0.7%, 0.6%, 0.5%, 0.1% and 28.9% of the dosed radioactivity, respectively. The major route of excretion in dog is via urine (Study # TAK-438-00113).

After oral administration of [14C]- TAK-438 at a dose of 2.67 mg/kg (2 mg/kg as TAK-438F) to fed lactating rats on the 14th day after parturition, distribution of total radioactivity in milk and the composition of radioactive components were examined. The concentrations of the radioactivity in the plasma and milk reached a maximum level of 208 ng/mL and 131 ng/mL at 1 and 4 hours post dosing, respectively, and then decreased to 17 and 36 ng/mL, respectively by 24 hours post dosing. The proportion of TAK-438 in total radioactivity in maternal plasma and milk at 0.25 to 24 hours post dosing was 0.0% to 7.7% and 0.0% to 22.7%, respectively (Studies #TAK-438-11241 and TAK-438-11248).

Toxicokinetics

Toxicokinetics (TK) of TAK-438 and its metabolites were measured in single and repeated-dose toxicity studies and pharmacokinetic (PK) parameters are included in the toxicology section below.

Drug-Drug Interactions

The PK of TAK-438 interactions with other possible drugs when co-administered are summarized below.

In vitro plasma protein binding study was conducted to determine the potential binding effects of [^{14}C]-TAK-438 in the presence of warfarin, ibuprofen, diazepam, phenytoin, propranolol, digoxin, diclofenac, loxoprofen, meloxicam, celecoxib, and SR26334 (clopidogrel metabolite). The ratios of the concentrations of the unbound drug concentration in the presence of [^{14}C]-TAK-438 was 92.5% to 111.1%. Therefore, these concomitant drugs were considered to not affect plasma protein binding of TAK-438 (Studies # TAK-438-11302, TAK-438-11301 and TAK-438-11317). Effects of vonoprazan on human plasma protein binding of concomitant drugs are shown in the Applicant's table below.

Table 61. Effects of Concomitant Drugs on Human Plasma Protein Binding of Vonoprazan

Concomitant Drug			
Compound	Concentration (μg/mL)	Unbound concentration[(a)] (ng/mL)	Relative concentration (%)
Control	-	19.9	100.0
Warfarin	1	18.4	92.5
Ibuprofen	20	22.1	111.1
Diazepam	0.3	19.3	97.0
Phenytoin	2	20.0	100.5
Propranolol	0.1	20.0	100.5
Diclofenac	1	19.5	98.0
Loxoprofen	5.5	21.6	108.5
Meloxicam	1	20.8	104.5
Celecoxib	1.5	21.2	106.5
SR26334	2.5[(b)]	20.3	102.0

Source: NDA file Module 2, Section 2.6.4 Pharmacokinetics Written Summary

In another in vitro study, the uptake of [^{14}C]-TAK-438 (0.3 μmol/L) was determined using cells expressing organic anion transporting polypeptide 1B1 and 1B3. As positive controls, the standard substrate for OATP1B1 and OATP1B3, [3H]-estradiol-17β-D-glucuronide (E217βG) was used. TAK-438 uptake by cells expressing OATP1B1 and OATP1B3 was similar to that by control cells, suggesting that TAK-438 is not a substrate for OATP1B1 or OATP1B3 (Study # TAK-438-11344).

The inhibitory effects of TAK-438 to various transporters (P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2, MATE1, MATE-2K and OCT1) were analyzed. The studies showed that TAK-438 inhibited transport activity of P-gp, with an IC_{50} value of 50.3 μmol/L. TAK-438 also weakly inhibited OAT3 and OCT2, with an IC_{50} value of 30 μmol/L or more. TAK-438 resulted in concentration dependent inhibition of MATE1 with a calculated IC_{50} value of 11.8

μM, and a concentration dependent inhibition of OCT1 with a calculated IC_{50} value of 2.2 μM. It did not inhibit any other transporters (BCRP, OATP1B1, OATP1B3, OAT1and MATE2-K) (Studies# TAK-438-10807, TAK-438-11346, TAK-438-11345 and TAKEDA-12-02Jan2020).

13.3.3. Toxicology

In the toxicology studies, doses administered were calculated as the free base of TAK-438F.

13.3.3.1. General Toxicology

Acute/Single-Dose Toxicology Studies

Single dose toxicology studies of TAK-438 (vonoprazan) were conducted in rats and dogs.

In rats, TAK-438 was administered at dose levels of 200, 600 and 2000 mg/kg once by oral gavage to 6-week-old Crl:CD(SD) rats (5/sex/group; Study # TAK-438-00053). The lethal dose of TAK-438 in rats was between 600 and 2000 mg/kg for males and between 200 and 600 mg/kg for females.

In dogs, TAK-438 was administered at dose levels of 10 and 60 mg/kg once by oral gavage to 9- or 11-month-old beagle dogs (2 sex/dose group; Study # TAK-438-00141). There were no mortalities. Animals in the 60 mg/kg dose group showed vomiting episodes within 1 hour after the test article administration. One male in the 10 mg/kg dose group, and all animals in the 60 mg/kg dose group showed increased levels of alanine aminotransferase (ALT). In another study, TAK-438 was administered orally to 2 male and 2 female beagle dogs at dose levels of 2, 10 and 60 mg/kg as the free base using an escalating dosage schedule (Study #TAK-438-00066). One male and 1 female died in the 60 mg/kg dose. Before death, clonic convulsions, tachypnea, cyanosis and mydriasis were observed in these animals. Histopathological examinations of the stomach of these animals showed vacuolization of the parietal cells. In surviving animals, increased plasma ALT, aspartate aminotransferase (AST), and lactate dehydrogenase (LDH), and decreased body temperature were observed at 60 mg/kg, and vomiting was observed at 10 mg/kg and higher dose levels.

Repeated-Dose Toxicology Studies

Study Title/Number: Four-Week Oral Gavage Toxicity Of TAK-438 In Rats With A 4-Week Recovery Period (Study # TAK-438-00085).

Key Study Findings

- The target organs of toxicity were the stomach (increased weight of stomach and histopathological findings of vacuolation of the parietal cells, hyperplasia of the mucous neck cells, increased globule leucocytes, increased eosinophils, squamous epithelial hyperplasia and the limiting ridge and atrophy of the parietal cells at 30 and 100 mg/kg dose groups in both sexes), liver (minimal vacuolation of the midlobular hepatocytes in males at 100 mg/kg and minimal to mild centrilobular hypertrophy of the hepatocytes in males in 30 and 100 mg/kg dose groups) and the thyroid gland (follicular cell

hypertrophy in males at 100 mg/kg). All these changes were likely related to the pharmacological actions of the drug.

- The no observed adverse effect level (NOAEL) was determined to be 10 mg/kg/day with corresponding area under concentration-time curve (AUC) of 482 and 658 ng.h/mL for males and females, respectively.

Conducting laboratory and location: (b) (4)

Good Laboratory Practice (GLP) compliance: Yes

Table 62. Study # TAK-438-00085 Methods

Methods	Details
Dose and frequency of dosing:	0, 10, 30 and 100 mg/kg/day (5 mL/kg), once daily for 28 days
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose solution.
Species/strain:	Crl:CD(SD) Rat
Number/sex/group:	20/sex in the control and high dose groups and 10/sex in the low and mid dose groups.
Age:	6 weeks
Satellite groups/ unique design:	For TK, 4/sex/group
Deviation from study protocol affecting interpretation of results:	None.

Source:
Abbreviations: TK, toxicokinetic

Table 63. Study # TAK-438-00085 Observations and Results

Parameters	Major Findings
Mortality	No deaths in any group.
Clinical signs	No treatment-related clinical signs.
Body weights	No adverse effects on body weight were observed.
Food consumption	No treatment-related changes in food consumption were observed.
Ophthalmoscopy	No ocular changes were observed.
Hematology	HD males: decreased hemoglobin (-6%), MCV (-6%), MCH (-8%), MCHC (-2%), fibrinogen (-9%) and increased WBC (+41%). At the end of the 4-week recovery period, decreased hemoglobin was reversed, other changes were not reversed.
Clinical chemistry	HD males: Increased AST (+7%), ALT (+27%), creatinine kinase (+18%) and ALP (+29%). HD female: increased ALP (+29%), and decreased creatinine (-17%) and AST (-10%). MD males: increased AST (+13%) and ALT (+12%). At the end of the recovery period, there was no treatment-related changes in males; in females decreased creatinine (-14%).

Parameters	Major Findings
Urinalysis	HD males: decreased pH, decreased sodium (-14%) and potassium (-16%) HD females: decreased pH MD and LD males: decreased sodium (-21%) MD and LD females: decreased sodium (-30%) At the end of the recovery period, a decrease in potassium was observed in females at HD.
Gross pathology	No treatment-related macroscopic findings.
Organ weights	Absolute (A) and relative (R) to body weight (%) HD males: increased liver weight (A= +20%; R= +23%) and stomach weight (A= +23%; R= +24%) and decreased adrenal gland weight (A= -15%; R= -11%). HD females: increased liver weight (A= +21%; R= +24%) and stomach weight (A= +22%; R= +25%) and decreased adrenal gland weight (A= -12%; R= -9%). MD males: increased liver weight (R= +7%) and stomach weight (A= +20%; R= +24%). MD females: increased liver weight (R= +10%) and stomach weight (A= +22%; R= +25%). LD males: increased stomach weight (A= +23%; R= +20%). LD females: increased liver weight (R= -6%) and stomach weight (A= +15%; R= +16%). At the end of the recovery period, slightly increased stomach weight (+11%) was still observed in females at 100 mg/kg/day.
Histopathology Adequate battery: Yes	<u>Stomach</u> • squamous epithelial hyperplasia in the limiting ridge (minimal and mild): - Male: LD: 3/10; MD: 5/10; HD: 5/10 - Female: LD: 6/10; MD: 8/10; HD: 9/10 • parietal cell vacuolation (minimal, mild, and moderate) - Male: LD: 6/10; MD: 9/10; HD: 10/10 - Female: LD: 7/10; MD: 10/10; HD: 10/10 • parietal cell atrophy (minimal or mild) - Male: MD: 6/10; HD: 10/10 - Female: MD: 1/10; HD: 10/10 • Increased globule leukocyte (mild and moderate) - Male: LD: 5/10; MD: 3/10; HD: 1/10 - Female: LD: 9/10; MD: 9/10; HD: 9/10 • Increased eosinophil, mucosal/submucosal (minimal or mild) - Male: LD: 6/10; MD: 7/10; HD: 6/10 - Female: LD: 6/10; MD: 5/10; HD: 8/10 • Eosinophilic change in chief cell (minimal or mild) - Male: HD: 6/10 - Female: MD: 2/10; HD: 5/10 • Hyperplasia of mucous neck cell (minimal or mild) - Male: LD: 9/10; MD: 10/10; HD: 10/10

Parameters	Major Findings
	- Female: LD: 7/10; MD: 10/10; HD: 9/10 Liver • Vacuolation of the midlobular hepatocytes (minimal) - Male: HD: 2/10 • Centrilobular hypertrophy of the hepatocytes (minimal or mild) - Male: MD: 6/10; HD: 10/10 - Female: HD: 10/10 Thyroid • Follicular cell hypertrophy (minimal) - Male: HD: 7/10 At the end of the recovery period, minimal hyperplasia of the squamous epithelium was observed in 2 females and 1 male in the 100 mg/kg group. All other changes were recovered.
Plasma gastrin concentration (pg/mL)	Male: 0: 283 pg/mL; LD: 303 pg/mL; MD: 759 pg/mL*; HD: 3343 pg/mL* Female: 0: 281 pg/mL; LD: 386 pg/mL; MD: 1188 pg/mL*; HD: 2652 pg/mL* At the end of the recovery period, there were no treatment-related changes in either sex.

Source:
* p<0.05 (significantly different from the control group)
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control
Abbreviations: 0, control; ACT, activated clotting time; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; HD, high dose; LD, low dose; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MD, mid dose; WBC, white blood cells

Toxicokinetics

For TK analysis, samples were collected at 0.5, 1, 2, 4, 8, and 24 hours after dosing on Day 1 and Week 4. The maximum plasma concentration (C_{max}) and AUC values for both males and females increased with dose. The C_{max} and AUC values in males and females on Day 1 were comparable to those on Day 28; however, the C_{max} and AUC values at 10 mg/kg/day on Day 28 were higher than those of Day 1 for both sexes. No gender differences in the C_{max} and AUC values were observed at any time. TK parameters for different groups are summarized in the Table below.

Table 64. Study #TAK-438-00085 TK Analysis

Sex	Male (n=3)			Female (n=3)		
Dose (mg/kg/day)	10	30	100	10	30	100
$AUC_{(0\text{-}24h)}$ ng.h/mL						
Day 1	277	4065	22730	419	2722	22590
Week 4 (27th dose)	482	2239	10656	658	3319	13375
C_{max} (ng/mL)						
Day 1	103.7	884.5	1705.3	126.2	772.6	2159.5
Week 4 (27th dose)	241.1	498.8	906.4	355.3	583.7	1392.6
T_{max} (h)						
Day 1	1.0	.0	3.7	1.0	0.7	0.7
Week 4 (27th dose)	0.5	0.8	2.3	0.5	0.8	0.8

Source: Sponsor study report TAK-438-00085
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Study Title/Number: Thirteen-Week Oral Gavage Toxicity Study of TAK-438 In Rats (Study # TAK-438-00143).

Key Study Findings

- Body weight was decreased in both sexes at the 300 mg/kg dose (males: 14%; females 10%).
- The target organs of toxicity were the stomach (atrophy and vacuolation of the parietal cells, eosinophilic change of the chief cells, squamous epithelial hyperplasia and increased globule leukocyte in both sexes at 10 mg/kg; hyperplasia of the chief cells, widening of the proliferative zone in the pylorus and inflammatory cell infiltration in both sexes in 100 and 300 mg/kg dose groups and mucous metaplasia in both sexes in 300 mg/kg dose groups), liver (vacuolation of the midlobular hepatocytes and centrilobular hypertrophy of the hepatocytes in both sexes in 100 and 300 mg/kg dose groups), thyroid gland (follicular cell hypertrophy in females at 300 mg/kg) and adrenal gland (hypertrophy of the zona glomerulosa in males at 100 and 300 mg/kg/day and females at 300 mg/kg). All these changes are likely related to the pharmacological effects of the drug.
- The NOAEL was determined to be 10 mg/kg/day with corresponding C_{max} values of 327.7 and 495.0 ng/mL and $AUC_{0\text{-}24h}$ values of 989 and 1343 ng.h/mL for males and females, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 65. Study # TAK-438-00143 Methods

Methods	Details
Dose and frequency of dosing:	0, 1, 10, 100 and 300 mg/kg/day (5 mL/kg), once daily for 13 weeks.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose solution.
Species/strain:	Crl:CD(SD) Rat
Number/sex/group:	10/sex/group.
Age:	6 weeks
Satellite groups/ unique design:	For TK, 4/sex/group
Deviation from study protocol affecting interpretation of results:	None.

Source:
Abbreviations: TK, toxicokinetic

Table 66. Study # TAK-438-00143 Observations and Results

Parameters	Major Findings
Mortality	No deaths in any group.
Clinical signs	No treatment-related clinical signs.
Body weights	Decreased body weight gains in males (14%) and females (10%) at the end of the dosing period at 300 mg/kg.
Food consumption	Decreased food consumption in males on days 4 (31%) and 7 (26%), and in females on Day 4 (18%) at 300 mg/kg. No treatment-related changes in food consumption were observed on other days.

Parameters	Major Findings
Ophthalmoscopy	No ocular changes were observed.
Hematology	Males at 300 mg/kg: decreased MCV (-4%), MCH (-5%), eosinophil ratio (-71%), monocyte ratio (-45%), APTT (-13%) and Fibrinogen (-18%). Males at 100 mg/kg: decreased eosinophil ratio (-41%) and monocyte ratio (-41%) Male at 1 and 10 mg/kg: decreased monocyte ratio (-38% and -7%, respectively). Females at 300 mg/kg; decreased platelet (-15%).
Clinical chemistry	Increases ALP in males at ≥10 mg/kg/day (+16-102%), and in females at 300 mg/kg/day (+109%), and increased ALT activity in males at 300 mg/kg/day (+79%). Increases cholesterol levels in females at 100 and 300 mg/kg/day (+23% and +55%), decreased triglyceride levels in males at 100 and 300 mg/kg/day (-73% and -92%), and increased phospholipid levels in females at 300 mg/kg/day (+20%). Males at the 300 mg/kg/day dose had increased BUN (+23%) and creatinine (+15%) levels; however, in females, the creatinine levels were decreased (-21%).
Urinalysis	Decrease in the urinary pH in males at 100 and 300 mg/kg (pH 6.75 and 7.0, respectively). Males at 300 mg/kg showed increased urinary volume (+89%), water intake (+60) and decreased osmotic pressure (-52%). Females at 300 mg/kg had increased urine volume (+167%), water intake (+54) and decreased osmotic pressure (-56%).
Gross pathology	300 mg/kg: thickening of the wall of the glandular stomach in males (2/10); and enlargement of liver in males (10/10) and females (8/10).
Organ weights	100 and 300 mg/kg: increased stomach weight in males (+14% and 26%) and females (+27% and 26%); increased liver weight in males (+30% and 91%) and females (+25% and 71%).
Histopathology Adequate battery: Yes	Stomach • Atrophy of the parietal cells (minimal to moderate) - Male: 10 mg/kg: 7/10 - Female: 10 mg/kg: 6/10; 100 mg/kg: 5/10 • Vacuolation of parietal cells (minimal or mild) - Male: 10 mg/kg: 1/10; 100 mg/kg: 2/10; 300 mg/kg: 3/10 - Female: 10 mg/kg: 1/10; 100 mg/kg: 6/10; 300 mg/kg: 2/10 • Hyperplasia of the chief cells (minimal or mild) - Male: 100 mg/kg: 10/10; 300 mg/kg: 10/10 - Female: 100 mg/kg: 10/10; 300 mg/kg: 10/10 • Eosinophilic changes of the chief cells (minimal to moderate) - Male: 10 mg/kg: 9/10; 100 mg/kg: 10/10; 300 mg/kg: 10/10 - Female: 10 mg/kg: 9/10; 100 mg/kg: 10/10; 300 mg/kg: 10/10 • Mucosal gland hyperplasia (minimal) - Male: 300 mg/kg: 3/10 - Female: 300 mg/kg: 2/10 • Infiltration of inflammatory cells (minimum) - Male: 100 mg/kg: 8/10; 300 mg/kg: 7/10 - Female: 100 mg/kg: 3/10; 300 mg/kg: 5/10 • Hyperplasia of the squamous epithelium in the limiting ridge (minimal or mild) - Male: 10 mg/kg: 5/10; 100 mg/kg: 10/10; 300 mg/kg: 10/10 - Female: 10 mg/kg: 6/10; 100 mg/kg: 7/10; 300 mg/kg: 7/10 Liver • Vacuolation of the midlobular hepatocytes (minimal, mild or moderate) - Male: 100 mg/kg: 8/10; 300 mg/kg: 10/10 - Female: 300 mg/kg: 6/10

Parameters	Major Findings
	• Centrilobular hypertrophy of the hepatocytes (minimal, mild or moderate) - Male: 100 mg/kg: 10/10; 300 mg/kg: 10/10 - Female: 100 mg/kg: 10/10; 300 mg/kg: 10/10 Thyroid gland • Follicular cell hypertrophy (minimal) - female: 300 mg/kg: 6/10 Adrenal gland • Hypertrophy of the zona glomerulosa (minimal) - Male: 100 mg/kg: 3/10; 300 mg/kg: 8/10 - Female: 300 mg/kg: 7/10
Plasma gastrin concentration (pg/mL)	Increased plasma gastrin levels in males at ≥100 mg/kg and females at ≥10 mg/kg. Male: 0 mg/kg: 176 pg/mL; 1 mg/kg: 174 pg/mL; 10 mg/kg: 276 pg/mL; 100 mg/kg: 1782 pg/mL*; 300 mg/kg: 5365 pg/mL* Female: 0 mg/kg: 156 pg/mL; 1 mg/kg:172 pg/mL; 10 mg/kg: 242 pg/mL*; 100 mg/kg: 3233 pg/mL*; 300 mg/kg: 3869 pg/mL*

Source:
* p<0.05 (significantly different from the control group)
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control
Abbreviations: 0, control; ACT, activated clotting time; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; HD, high dose; LD, low dose; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MD, mid dose; WBC, white blood cells

Toxicokinetics

For TK analysis samples were collected prior to dosing (week 13 only), 0.5, 1, 2, 4, 8, and 24 hours after dosing on Day 1 and Week 13. The C_{max} and AUC values for TAK-438 increased dose-dependently in both sexes after the first and ninety-first doses. The C_{max} and AUC values after repeated dosing for 91 days were similar to those after the first dose, with the exception that the C_{max} and AUC values after the 91st dose of 10 mg/kg/day in both sexes were higher than the values after the 1st dose. No significant gender differences in the C_{max} and AUC values were observed at any time. TK parameters for different groups are summarized in the Table below.

Table 67. Study #TAK-438-00143 TK Analysis

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	1	10	30	100	1	10	30	100
$AUC_{(0\text{-}24h)}$ ng.h/mL								
Day 1	4	218	28681	85475	5	376	20139	55290
Week 13 (91st dose)	4	989	26071	66567	17	1343	20190	63253
C_{max} (ng/mL)								
Day 1	1.2	84.9	2311.6	6858.0	1.3	116.6	2016.4	4113.5
Week 13 (91st dose)	0.9	327.7	1979.6	4169.7	10.8	495.0	3775.8	4272.7
T_{max} (h)								
Day 1	0.7	0.8	1.8	2.3	0.5	0.8	2.2	1.8
Week 13 (91st dose)	0.5	1.2	5.7	4.0	0.5	0.5	3.0	5.5

Source: Sponsor study report TAK-438-00143
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Study Title/Number: Twenty-Six-Week Oral Gavage Toxicity Study of TAK-438 In Rats With 13-Week Recovery period (Study # TAK-438-00212).

Key Study Findings

- The target organs of toxicity were the stomach (increased stomach weight in both sexes at ≥5 mg/kg, eosinophilic change of the chief cells and squamous epithelial hyperplasia in the limiting ridge, increased globule leukocyte in both sexes at 5 mg/kg and above; atrophy of the parietal cells in both sexes, vacuolation of the parietal cells in females and mucosal fibrosis in males at 10 and 30 mg/kg, mucosal fibrosis in females, vacuolation of parietal cells in males, mucosal angiectasis and inflammatory cell infiltration in both sexes were noticed at 30 mg/kg) and liver (vacuolation of the hepatocytes in males at 30 mg/kg and centrilobular hypertrophy of the hepatocytes in males at 100 and 300 mg/kg and females at 300 mg/kg).
- The NOAEL was determined to be 5 mg/kg/day in males and 10 mg/kg/day in females. The corresponding C_{max} and AUC_{0-24h} values were 72.7 ng/mL and 210 ng.h/mL for males, respectively, and the corresponding C_{max} and AUC_{0-24h} values were 584.8 ng/mL and 1615 ng.h/mL for females, respectively, at Week 26.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 68. Study # TAK-438-00212 Methods

Methods	Details
Dose and frequency of dosing:	0, 1, 5, 10 and 30 mg/kg/day (5 mL/kg), once daily for 26 weeks.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose solution.
Species/strain:	Crl:CD(SD) Rat
Number/sex/group:	Main study: 15/sex/group. Recovery group: 10/sex/group control and 30 mg/kg dose groups.
Age:	6 weeks
Satellite groups/ unique design:	For TK, 5/sex/group
Deviation from study protocol affecting interpretation of results:	None.

Source:
Abbreviations: TK, toxicokinetic

Table 69. Study # TAK-438-00212 Observations and Results:

Parameters	Major Findings
Mortality	No deaths in any group. One female at 10 mg/kg died due to gavage error.
Clinical signs	No treatment-related clinical signs.
Body weights	No test article-related effects on body weight.
Food consumption	No test article-related effects on food intake.
Ophthalmoscopy	No ocular changes were observed.
Hematology	Increased red blood cell count (up to 4%), hemoglobin (up to 5%) and hematocrit values (up to 5%) and decreased platelet count (up to 13%) in males at 10 and 30 mg/kg; decreased reticulocyte (14%) in females at 30 mg/kg. Increased monocyte count (up to 32%) in males at 30 mg/kg and in

Parameters	Major Findings
	females (up to 68%) at 10 and 30 mg/kg. These findings have no toxicological significance and recovered after the 13-weeks recovery period.
Clinical chemistry	Increased creatinine phosphokinase activity in males at 30 mg/kg (42%) and decreased creatinine in males at 5 mg/kg and above (up to 17%). These findings have no toxicological significance, and no treatment-related changes were observed following 13 weeks of recovery.
Urinalysis	Decreased urinary pH (7, compared to control pH of 8) and urinary sodium (27%) in males at 10 and 30 mg/kg dose groups; increased urine volume (43%) and decreased osmotic pressure (22%) in males at 30 mg/kg/day. These changes were recovered following 13-weeks recovery period.
Gross pathology	Thickening of the wall of the glandular stomach in males at 10 mg/kg (1/15) and 30 mg/kg (4/15); and red patch in glandular stomach in males (4/15) and females (1/15) at 30 mg/kg/day.
Organ weights	5, 10 and 30 mg/kg: increased stomach weight in males (19%, 19% and 20%) and females (26%, 33% and 30%); increased liver weight (16%), prostate weight (15%) and seminal vesicle weight (22%) in males at 30 mg/kg/day.
Histopathology Adequate battery: Yes	Stomach • Atrophy of the parietal cells (minimal to moderate) - Male: 10 mg/kg: 7/15; 30 mg/kg: 15/15 - Female: 10 mg/kg: 3/15; 30 mg/kg: 14/15 • Vacuolation of parietal cells (minimal) - Male: 30 mg/kg: 13/15 - Female: 30 mg/kg: 9/15 • Eosinophilic changes of the chief cells (minimal to moderate) - Male: 5 mg/kg: 15/15; 10 mg/kg: 15/15; 30 mg/kg: 15/15 - Female: 5 mg/kg: 15/15; 10 mg/kg: 14/15; 30 mg/kg: 15/15 • Mucosal gland hyperplasia (minimal) - Male: 10 mg/kg: 3/15; 30 mg/kg: 8/15 - Female: 30 mg/kg: 7/15 • Infiltration of inflammatory cells (minimum) - Male: 0 mg/kg: 2/15; 5 mg/kg: 1/15; 10 mg/kg: 4/15; 30 mg/kg: 12/15 - Female: 0 mg/kg: 1/15; 10 mg/kg: 2/15; 30 mg/kg: 10/15 • Hyperplasia of the squamous epithelium in the limiting ridge (minimal or mild) - Male: 5 mg/kg: 6/15; 10 mg/kg: 8/15; 30 mg/kg: 12/15 - Female: 5 mg/kg: 3/15; 10 mg/kg: 6/15; 30 mg/kg: 11/15 • Globule leukocyte hyperplasia (minimal to mild) - Male: 5 mg/kg: 1/15; 10 mg/kg: 1/15; 30 mg/kg: 4/15 - Female: 5 mg/kg: 1/15; 10 mg/kg: 0/15; 30 mg/kg: 3/15 • Mucosal angiectasis (minimal) - Male: 30 mg/kg: 3/15 - Female: 30 mg/kg: 1/15 At the end of the recovery period, minimal mucosal fibrosis was observed in 8 males and 5 females at 30 mg/kg, but this finding was also found in 1 male and 2 females in the control group. Minimal eosinophilic change of the chief cells was observed in 4 animals of each sex at 30 mg/kg. Minimal hyperplasia of the squamous epithelium in the limiting ridge was observed in 2 animals of each sex at 30 mg/kg, but this finding was also found in 2 females in the control group. Liver • Vacuolation of the hepatocytes (minimal to mild)

Parameters	Major Findings
	- Male: 0 mg/kg: 5/15; 1 mg/kg: 4/15; 5 mg/kg: 8/15; 10 mg/kg: 7/15; 30 mg/kg: 15/15 - Female: 0 mg/kg: 3/15; 1 mg/kg: 4/15; 5 mg/kg: 3/15; 10 mg/kg: 0/15; 30 mg/kg: 4/15 • Centrilobular hypertrophy of the hepatocytes (minimal, mild or moderate) - Male: 10 mg/kg: 9/15; 30 mg/kg: 15/15 - Female: 30 mg/kg: 10/15 Adrenal: • Hypertrophy of the zona glomerulosa - Female: 30 mg/kg: 6/15 At the end of the recovery period, histopathological changes in the liver and adrenal gland showed no treatment-related changes.
Plasma gastrin concentration (pg/mL)	• Increased plasma gastrin levels in males and females at 30 mg/kg/day. - Male: 0 mg/kg: 297 pg/mL; 1 mg/kg: 436 pg/mL; 5 mg/kg: 340 pg/mL; 10 mg/kg: 645 pg/mL; 30 mg/kg: 2545 pg/mL* - Female: 0 mg/kg: 345 pg/mL; 1 mg/kg:350 pg/mL; 5 mg/kg; 537 pg/mL; 10 mg/kg: 469 pg/mL*; 30 mg/kg: 4799 pg/mL*

Source:
* p<0.05 (significantly different from the control group)
-: indicates reduction in parameters compared to control; +: indicates increase in parameters compared to control
Abbreviations: 0, control; ACT, activated clotting time; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; HD, high dose; LD, low dose; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MD, mid dose; WBC, white blood cells

Toxicokinetics

Sample collection times: Prior to dosing (week 13 and 26 only) and 0.5, 1, 2, 4, 8, and 24 hours after dosing on Day 1, Week 13, and Week 26.

The C_{max} and AUC_{0-24h} values for TAK-438F, M-I and M-II increased dose-dependently in both sexes. With repeated daily dosing, the C_{max} and AUC_{0-24h} values for TAK-438F, M-I and M-II increased. The C_{max} and AUC_{0-24h} values for TAK-438F in females were higher than those in males except for at 30 mg/kg. However, the C_{max} and AUC_{0-24h} values for M-I and M-II in females were lower than those in males except for M-II at 1 and 5 mg/kg. The C_{max} and AUC_{0-24h} values for TAK-438F at 30 mg/kg and for M-II at 1 and 5 mg/kg were almost equal in both sexes. The time to maximum concentration (T_{max}) values in both sexes were 0.5 to 2.0 hours for TAK-438F, 0.5 to 4.0 hours for M-I, and 2.0 to 8.0 hours for M-II. TAK-438F, M-I and M-II were not detected in the control group. TK parameters for different groups are summarized in the Table below.

Table 70. TAK-438F TK Analysis

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	1	5	10	30	1	5	10	30
$AUC_{(0-24h)}$ ng.h/mL								
Day 1	3	38	239	4031	4	149	532	2633
Week 13 (85th dose)	3	243	814	6067	12	343	1303	5496
Week 26 (180th dose)	5	210	1054	8536	20	424	1615	6364
C_{max} (ng/mL)								
Day 1	0.7	16.0	89.3	769.5	1.6	93.2	265.1	1017.8
Week 13 (85th dose)	0.9	106.0	284.5	1062.0	5.3	125.5	537.8	1101.7
Week 26 (180th dose)	2.0	72.7	281.4	1027.7	8.8	181.5	584.8	1593.2

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	1	5	10	30	1	5	10	30
T_{max} (h)								
Day 1	0.5	0.5	1.0	1.0	0.5	1.0	1.0	0.5
Week 13 (85th dose)	0.5	0.5	1.0	2.0	1.0	1.0	0.5	0.5
Week 26 (180th dose)	1.0	0.5	1.0	2.0	0.5	1.0	0.5	0.5

Source: Sponsor study report TAK-438-00085
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Table 71. M-I TK Analysis

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	1	5	10	30	1	5	10	30
$AUC_{(0\text{-}24h)}$ ng.h/mL								
Day 1	285	2919	7469	29878	130	887	1882	5091
Week 13 (85th dose)	410	5342	12427	42116	173	1252	2193	10398
Week 26 (180th dose)	415	4921	12425	46144	214	1379	2671	9161
C_{max} (ng/mL)								
Day 1	61.4	511.9	1391.1	2531.4	44.5	210.2	354.3	605.3
Week 13 (85th dose)	111.7	1110.3	2198.2	3802.8	51.8	223.3	433.9	1090.6
Week 26 (180th dose)	130.4	909.4	2035.3	4011.7	69.4	296.7	427.6	1455.7
T_{max} (h)								
Day 1	1.0	1.0	1.0	4.0	1.0	1.0	1.0	1.0
Week 13 (85th dose)	1.0	2.0	1.0	2.0	1.0	0.5	0.5	2.0
Week 26 (180th dose)	1.0	2.0	1.0	2.0	1.0	1.0	0.5	0.5

Source:
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Table 72. M-II TK Analysis

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	1	5	10	30	1	5	10	30
$AUC_{(0\text{-}24h)}$ ng.h/mL								
Day 1	35	206	619	1348	43	218	281	726
Week 13 (85th dose)	79	498	1464	3629	82	445	591	2021
Week 26 (180th dose)	93	667	1794	5135	135	594	884	2484
C_{max} (ng/mL)								
Day 1	3.0	14.2	42.7	100.0	5.0	15.8	25.8	54.2
Week 13 (85th dose)	5.2	33.7	112.6	285.3	6.6	33.1	40.1	161.2
Week 26 (180th dose)	6.1	47.8	129.1	387.5	9.4	41.3	61.8	190.0
T_{max} (h)								
Day 1	4.0	8.0	8.0	8.0	2.0	8.0	4.0	8.0
Week 13 (85th dose)	4.0	8.0	8.0	8.0	2.0	8.0	8.0	8.0
Week 26 (180th dose)	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0

Source:
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Study Title/Number: Four-Week Oral Gavage Toxicity Study of TAK-438 In Dogs (Study # TAK-438-00084).

Key Study Findings

- TAK-438-related toxicological findings were noted as vomiting and decrease in chloride content at all dose groups.

- The target organ of toxicity was the stomach (atrophy, vacuolization and single cell necrosis of the parietal cells, and inflammatory cell infiltration in the fundic mucosa in males and/or females at 2 mg/kg and above).
- The NOAEL was determined to be 0.6 mg/kg/day with corresponding C_{max} and $AUC_{0\text{-}24h}$ values of 115-117 ng/mL and $AUC_{0\text{-}24h}$ averaging 492 ng*h/mL, respectively on Day 29.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 73. Study # TAK-438-00084 Methods

Methods	Details
Dose and frequency of dosing:	0, 0.6, 2, 6 and 20 mg/kg/day (5 mL/kg), once daily for 26 weeks.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose solution.
Species/strain:	Beagle dogs
Number/sex/group:	Main study: 3/sex/group.
Age:	12-months-old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None.

Source:

Table 74. Study # TAK-438-00084 Observations and Results

Parameters	Major Findings
Mortality	No deaths in any group.
Clinical signs	Vomiting was observed in ≥2 mg/kg dose groups and salivation was noted in ≥6 mg/kg dose groups.
Body weights	No test article-related effects on body weight.
Food consumption	No test article-related effects on food intake.
Ophthalmoscopy	No treatment-related abnormalities were observed.
Electrocardiography	No treatment-related changes were observed.
Hematology	No treatment-related abnormalities were seen in any animal.
Clinical chemistry	Decreased chloride in females at 2 mg/kg and both sexes at 6 and 20 mg/kg/day. Increase in ALT activity in females at ≥6 mg/kg/day and an increase in ALP activity in 1 male and 1 female at 20 mg/kg/day.
Urinalysis	No treatment-related effects on urinary parameters.
Gross pathology	No treatment-related changes were noticed.
Organ weights	6 and 20 mg/kg: increase in absolute liver weight up to 21% in males.
Histopathology Adequate battery: Yes	Stomach Minimal atrophy of the parietal cells, minimal to mild vacuolation of parietal cells, minimal inflammatory cell infiltration in the fundic mucosa and minimal single cell necrosis of the parietal cells at 2 mg/kg/day and above.
Hepatic drug metabolizing enzymes	Increases in aniline hydroxylase in males at 0.6 mg/kg and above, *p*-nitrophenol UDP-glucuronosyltransferase activity in females at 0.6 mg/kg and above and males at 20 mg/kg, and aminopyrine N-demethylase activity in both sexes at 6 and 20 mg/kg.

Source:
Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; UDP, uridine diphosphate

Toxicokinetics

Sample collection times: Sample collection times: prior to dosing (Day 29 only) and 0.5, 1, 2, 6, and 24 hours after dosing on Day 1 and Day 29.

The C_{max} and AUC_{0-24h} values after the first and dose 29 increased dose-dependently in both sexes. There were no apparent gender differences in the C_{max} and AUC_{0-24h} values between males and females. TK parameters for different groups are summarized in the Table below.

Table 75. Study # TAK-438-00084 TK Analysis

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	0.6	2	6	20	0.6	2	6	20
$AUC_{(0-24h)}$ ng.h/mL								
Dose 1	479	4150	12566	43230	421	3566	13151	33162
Dose 29	491	4473	12725	55471	493	3993	14268	65810
C_{max} (ng/mL)								
Dose 1	126.3	595.2	1562.7	3426.1	107.6	617.4	1329.6	2876.2
Dose 29	124.0	716.0	1855.1	6591.0	106.3	726.5	2012.9	6737.1
T_{max} (h)								
Dose 1	0.5	1.0	1.3	2.7	0.8	1.0	1.7	3.0
Dose 29	0.7	1.2	1.3	1.0	0.8	1.0	1.0	1.7

Source: Sponsor study report TAK-438-00084
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Study Title/Number: Thirteen-Week Oral Gavage Toxicity Study of TAK-438 In Dogs With a 4-Week Recovery Period (Study # TAK-438-10742).

Key Study Findings

- Vomiting in both sexes at 1.6 mg/kg and above.
- The target organ of toxicity was the stomach (inflammatory cell infiltration in the fundic mucosa, single cell necrosis in the fundic gland, degeneration of the tunica muscularis, hyperplasia of the fundic mucosa and vacuolization of the parietal cells at 1 mg/kg and above). At the end of the 4-week recovery period, degeneration of the tunica muscularis was observed at 2 mg/kg.
- There was no NOAEL established in the study. The lowest-adverse-effect level (LOAEL) determined to be less than 1 mg/kg/day because histopathological findings in the stomach were noted in both sexes at 1 mg/kg/day and above.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 76. Study # TAK-438-10742 Methods

Methods	Details
Dose and frequency of dosing:	0, 1, 1.3, 1.6 and 2 mg/kg/day (5 mL/kg), once daily for 13 weeks.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose solution.
Species/strain:	Beagle dogs
Number/sex/group:	Main study: 3/sex/group; 6 animals/sex for the control and high dose groups.
Age:	7 or 10-months-old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None.

Source:

Table 77. Study # TAK-438-10742 Observations and Results

Parameters	Major Findings
Mortality	No deaths in any group.
Clinical signs	Vomiting in both sexes at 1.6 mg/kg and above dose levels.
Body weights	No test article-related effects on body weight.
Food consumption	No test article-related effects on food intake.
Electrocardiography	No treatment-related changes were observed.
Hematology	No treatment-related abnormalities were seen in any animal.
Clinical chemistry	Increase in ALT activity in both sexes at ≥1 mg/kg/day.
Gross pathology	No treatment-related changes were noticed at the end of treatment and recovery periods.
Organ weights	Not determined.
Histopathology Adequate battery: Yes	Stomach Minimal or mild inflammatory cell infiltration in the fundic mucosa and minimal hyperplasia of the fundic mucosa, minimal single cell necrosis in the fundic gland, minimal degeneration of the tunica muscularis, and minimal or mild vacuolization of the parietal cells at 1 mg/kg/day and above. At the end of the 4-week recovery period, degeneration of the tunica muscularis was observed at 2 mg/kg.

Source:
Abbreviations: ALT, alanine aminotransferase

Toxicokinetics

Sample collection times: prior to dosing (day 28 and 90 only) and 0.5, 1, 2, 6, and 24 hours after dosing on Day 1, Day 28, and Day 90.

After the first dose in females, the C_{max} and $AUC_{0\text{-}24h}$ values for TAK-438F increased dose-dependently. After the first dose in males, the C_{max} and $AUC_{0\text{-}24h}$ values for TAK-438F increased between 1 and 1.3 mg/kg; however, the values for TAK-438F were almost equivalent at 1.3 mg/kg and above. With repeated dosing, the C_{max} and $AUC_{0\text{-}24h}$ values for TAK-438F after the dose 28 and 90 doses were almost comparable to those after the first dose at each dosage level.TK parameters for different groups are summarized in the Table below.

Table 78. Study # TAK-438-10742 TK Analysis

Sex	Male (n=3)				Female (n=3)			
Dose (mg/kg/day)	1	1.3	1.6	2.0	1	1.3	1.6	2.0
$AUC_{(0-24h)}$ ng.h/mL								
Day 1	787	1986	2064	1660	654	1212	1345	2412
Day 28	996	1854	1989	1703	903	1117	1125	2184
Day 90	981	2394	2094	1765	853	1055	1233	2494
C_{max} (ng/mL)								
Day 1	189.5	359.9	338.2	295.3	116.3	216.9	268.7	405.4
Day 28	195.4	332.9	341.6	280.5	148.3	230.0	209.8	363.5
Day 90	202.3	365.8	348.6	340.2	128.4	176.2	243.1	485.6
T_{max} (h)								
Day 1	0.8	1.0	1.0	1.2	1.3	1.0	1.0	1.2
Day 28	1.2	0.7	0.8	1.3	1.3	0.7	0.7	1.1
Day 90	0.8	0.8	1.0	0.9	1.0	1.0	1.0	1.0

Source: Sponsor study report TAK-438-10742
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Study Title/Number: Thirty-Nine-Week Oral Gavage Toxicity Study of TAK-438 In Dogs (Study # TAK-438-00217).

Key Study Findings

- Vomiting was noted in all dose groups.
- Thickening of stomach wall in both sexes at 2 mg/kg.
- The target organ of toxicity was the stomach.
  - Vacuolation of the parietal cells in both sexes at 0.3 mg/kg and above.
  - Hyperplasia of the fundic mucosa, single cell necrosis in the fundic gland and inflammatory cell infiltration in the fundic gland in both sexes at 2 mg/kg.
  - Degeneration of the muscular layer of the stomach in males at 2 mg/kg.
- The NOAEL was determined to be 0.6 mg/kg/day with corresponding AUC_{0-24} and C_{max} values of 381 ng.h/mL and 84.7 ng/mL for both sexes combined, respectively, on Week-39.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 79. Study # TAK-438-00217 Methods

Methods	Details
Dose and frequency of dosing:	0, 0.3, 0.6 and 2 mg/kg/day (5 mL/kg), once daily for 39 weeks.
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% methylcellulose solution.
Species/strain:	Beagle dogs
Number/sex/group:	3/sex/group.
Age:	7-months-old
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None.

Source:

Table 80. Study # TAK-438-00217 Observations and Results

Parameters	Major Findings
Mortality	No deaths in any group.
Clinical signs	Vomiting in both sexes at all dose levels.
Body weights	No test article-related effects on body weight.
Food consumption	No test article-related effects on food intake.
Ophthalmoscopy	No treatment-related changes were observed.
Electrocardiography	No treatment-related changes were observed.
Urinalysis	No treatment-related changes were observed.
Hematology	High values for the percentage and count of eosinophils in both sexes, and low values for the percentage and count of reticulocytes in males were noted at 2 mg/kg. However, these findings were not test article-related since the grade of the changes were slight and the values were within the range of normal variations.
Clinical chemistry	Increase in ALT activity in both sexes at 2 mg/kg/day.
Gross pathology	No treatment-related changes were noted at the end of treatment and recovery periods.
Organ weights	No treatment-related changes were observed in any dose groups.
Histopathology Adequate battery: Yes	Stomach Minimal vacuolation of the parietal cells in the stomach was noted in almost all animals in the test article-treated groups. Mild hyperplasia of the fundic mucosa, minimal single cell necrosis in the fundic gland and minimal or mild inflammatory cell infiltration in the fundic mucosa, mild degeneration of the muscular layer, and minimal atrophy of Peyer's patch in the ileum in the 2 mg/kg group.
Plasma gastrin	No treatment-related changes were observed in any animal in the 0.3 mg/kg group. Plasma gastrin values were high in 1 male at 0.6 mg/kg and 2 females at 2 mg/kg, which is related to the pharmacological effect of the drug.

Source:
Abbreviations: ALT, alanine aminotransferase

Toxicokinetics

Sample collection times: prior to dosing (all doses except first) and 0.5, 1, 2, 6, and 24 hours after dosing on Day Day1, Day 91, Day 182, and Day 273.

The C_{max} and $AUC_{0\text{-}24h}$ values for TAK-438, increased dose-dependently in both sexes. The values for TAK-438 increased more than the dosage ratio between the 0.6 and 2 mg/kg doses. The T_{max} values in both sexes were 0.7 to 1.5 hours. No apparent gender differences were observed in the C_{max}, $AUC_{0\text{-}24h}$ or T_{max} values. TK parameters for different groups are summarized in the Table below.

Table 81. Study # TAK-438-00217 TK Analysis

Sex	Male (n=3)			Female (n=3)		
Dose (mg/kg/day)	0.3	0.6	2.0	0.3	0.6	2.0
$AUC_{(0-24h)}$ ng.h/mL						
Day 1	97	263	2762	80	275	2865
Day 91	74	286	2673	80	253	3925
Day 182	162	426	3690	113	247	4199
Day 273	191	415	4481	134	346	4026
C_{max} (ng/mL)						
Day 1	40.3	92.3	496.6	29.9	83.4	492.9
Day 91	22.3	74.1	537.7	27.5	74.6	568.8
Day 182	46.0	105.3	636.8	37.2	91.1	579.4
Day 273	45.8	88.9	823.1	39.4	80.5	480.5
T_{max} (h)						
Day 1	0.7	0.8	0.8	0.8	0.7	1.0
Day 91	1.0	0.8	1.0	0.8	0.8	1.0
Day 182	0.7	1.0	1.5	0.8	0.8	1.0
Day 273	1.2	1.2	0.8	0.8	0.8	1.3

Source: Sponsor study report TAK-438-00217
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

Study Title/Number: Thirteen-Week Subcutaneous Toxicity Study of TAK-438 M-IV-Sul in Rats (Study # TAK-438-10049).

Key Study Findings

- In the 13-week subcutaneous toxicity study, TAK-438-M-IV-Sul (a metabolite of TAK-438) was administered subcutaneously to rats at 0, 6 and 20 mg/kg/day doses.
- No treatment-related adverse effects were noticed.
- The NOAEL was determined to be 20 mg/kg with corresponding AUC_{0-24h} values of 5233 ng.h/mL and 4366 ng.h/mL, respectively for males and females. The corresponding C_{max} values at 20 mg/kg dose were 10828.9 ng/mL and 16661.1 ng/mL for males and females, respectively.

Conducting laboratory and location: (b) (4) .

GLP compliance: Yes

Table 82. Study # TAK-438-10049 Methods

Methods	Details
Dose and frequency of dosing:	0, 6 and 20 mg/kg/day (5 mL/kg), once daily for 13 weeks.
Route of administration:	Subcutaneous injection
Formulation/vehicle:	Physiological saline and sodium hydroxide solution.
Species/strain:	Crl:CD(SD) rats
Number/sex/group:	10/sex/group.
Age:	6-week-old
Satellite groups/ unique design:	4 sex/group
Deviation from study protocol affecting interpretation of results:	None.

Source:

Table 83. Study # TAK-438-10049 Observations and Results

Parameters	Major Findings
Mortality	No deaths in any dose groups.
Clinical signs	No treatment-related clinical signs were observed at all dose levels.
Body weights	No treatment-related change in body weight was observed.
Food consumption	Food consumption was not affected at all doses.
Ophthalmoscopy	No treatment-related ophthalmologic abnormalities were observed in any group.
Electrocardiography	No treatment-related changes were observed.
Urinalysis	No treatment-related changes were observed.
Hematology	No treatment-related abnormalities were observed in any group. However, males in the 20 mg/kg group showed a significant increase in fibrinogen level (9%) and increase in monocyte ratio (15%). An increase in the ratio of eosinophil (54%) and monocytes (60%) were also observed in males at 6 mg/kg/day. Female rats in the 6 mg/kg group showed a shortening of APTT (8%), and large unstained cells (50%) at the high dose. All these changes were incidental and there was no dose-dependency.
Clinical chemistry	No treatment-related abnormalities were observed in any group.
Gross pathology	At the injection sites, dark red foci were observed in both sexes in both the control and treated groups. This was considered to be mechanical injury due to the injection.
Organ weights	No treatment-related changes in organ weight were observed in any dose group in both sexes. In males, significant decreases in the absolute and relative weights of adrenal (8-10%) and salivary gland (6-7%) were noted at 20 mg/kg/day. In addition, statistically significant increases in the absolute or relative weight of the liver (8%) and testes (6%) were noted in male rats. These changes were incidental and were minimal.
Histopathology Adequate battery: Yes	No treatment-related changes in any dose group in either sex. At the injection sites, subcutaneous hemorrhage, inflammatory cells infiltration, and/or subcutaneous fibrosis were observed in both sexes in both the control and treatment groups. These changes were considered to be mechanical injury due to injection.

Source:
Abbreviations: APTT, activated partial thromboplastin time

Toxicokinetics

Sample collection times: prior to dosing (all doses except first) and 0.5, 1, 2, 6, and 24 hours after dosing on Day 1, Day 91, Day 182, and Day 273.

The C_{max} and AUC_{0-24h} values increased dose-dependently in both sexes and were higher in males than in females (except for the C_{max} value after dose 90 at 20 mg/kg/day). The T_{max} value in both sexes was 0.25 hours. TK parameters for different groups are summarized in the Table below.

Table 84. Study # TAK-438-10049 TK Analysis

Sex	Male (n=3)		Female (n=3)	
Dose (mg/kg/day)	6	20	6	20
$AUC_{(0-24h)}$ ng.h/mL				
Day 1 (1st dose)	1553	5233	1108	4366
Week 13 (90th dose	3547	11278	2216	8183
C_{max} (ng/mL)				
Day 1 (1st dose)	3272.4	10828.9	2275.7	9762.6
Week 13 (90th dose)	4855.7	16571.4	3579.6	16661.1
T_{max} (h)				
Day 1 (1st dose)	0.25	0.25	0.25	0.25
Week 13 (90th dose	0.25	0.25	0.25	0.25

Source: Sponsor study report TAK-438-10049
Values indicated the mean
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; TK, toxicokinetic; T_{max}, time to reach maximum concentration

13.3.3.2. Genetic Toxicology

TAK-438 was negative in bacterial reverse mutation assay (Study # TAK-438-00052), the chromosomal aberration assay in Chinese hamster lung (CHL) cells (Study # TAK-438-00051) and the in vivo micronucleus assay in rats (Study # TAK-438-00083).

Tak-438-MIV-Sul (metabolite of TAK-438) was not genotoxic in the bacterial reverse mutation (Ames) assay (Study # TAK-438-00203), the in vitro Chinese hamster lung (CHL) chromosome aberration test (Study # TAK-438-00211), and the in vivo rat micronucleus test (Study # TAK-438-00202).

13.3.3.3. Reproductive Toxicology

TAK-438

Effects of TAK-438 on Fertility and Early Embryonic Development to Implantation in Rats (Study #TAK-438-00172).

To determine the effects of TAK-438 on fertility and early embryonic development in rats, TAK-438 was administered orally by gavage to male and female Crl:CD(SD) rats at dosage levels of 0 (0.5 w/v% methylcellulose solution), 30, 100 and 300 mg/kg/day. Males were treated daily for 14 days before mating, throughout the mating period and until the day before necropsy, for about 8 weeks in total. Females were treated daily for 14 days before mating, throughout the mating period and until Day 6 of gestation and were necropsied on Day 15 of gestation. In the 300 mg/kg group, 4 out of 20 males died between Day 2 and 4 of treatment; clinical signs included mydriasis, tremor, prone position, soiled (urine) perineal region, decreased locomotor activity, reddish eye mucus, decreased body weight in males for days 0-3 (-34.8±11.0 g; control: 6.2±4.5g); decreased food intake; at necropsy, red foci in the stomach and reddish rhinorrhea were observed in dead animals. In the 100 mg/kg dose group, mydriasis was observed, but there

were no treatment-related changes in body weight or food consumption. In the 30 mg/kg group, no treatment-related changes were observed in clinical signs, body weight or food consumption.

No treatment-related changes were noted in copulatory index, fertility index or mean copulatory interval in any dose group. No treatment-related changes were noted in the number of live embryos, the number of post-implantation losses or post-implantation loss rate in any treated group.

The NOAELs were determined to be 30 mg/kg/day for paternal and maternal toxicity and 300 mg/kg/day and above for reproductive function and embryonic development.

Effects of TAK-438 on Embryo-Fetal Development in Rats (Study # 438-00135).

To determine the potential embryo-fetal developmental effects of TAK-438 in rats, TAK-438 was administered orally by gavage to pregnant Crl:CD(SD) rats at the dosage levels of 0 (0.5 w/v% methylcellulose solution), 30, 100 and 300 mg/kg/day from gestation day (GD) 6 to 17 and euthanized and necropsied on day 20. In the 300 mg/kg dose group, one dam died on gestation day 15; clinical signs included mydriasis and decreased feces, prone position, tremors, soiled fur and salivation; body weights decreased during GD 6-8 and food consumption decreased on GD 6, 8, 10, and 12 and placenta weight decreased. Fetuses in the 300 mg/kg dose group showed reduced body weight, bent tail and thread-like tail, small anus in 2 fetuses, low sacro-caudal vertebra, supernumerary rib, membranous ventricular septal defect (28.2%) and malpositioned subclavian branch (3.7%), diaphragmatic hernia, absent adrenal, fused kidney and malpositioned subclavian artery in 1 fetus. In the 100 mg/kg dose group, decreased food consumption on GD 6, 8 and 10; bent tail and interrupted aortic arch was observed in 1 fetus. No treatment-related changes were noted in the macroscopic findings for the placentae in any treated group. No treatment-related effects were noted in the number of live fetuses, post-implantation loss rate or sex ratio in any group. The maternal NOAEL was 100 mg/kg/day based on death and clinical signs at the higher dose. The fetal NOAEL was 100 mg/kg/day based on an increase in malformations in fetuses at the 300 mg/kg dose.

Effects of TAK-438 on Embryo-Fetal Development in Rabbits (Study # 438-00137).

To determine the embryo-fetal developmental effects of TAK-438 in rabbits, TAK-438 was administered orally by gavage to pregnant Kbl:JW rabbits at the dosage levels of 0 (0.5 w/v% methylcellulose solution), 3, 10 and 30 mg/kg/day from GD 6 to 18 and euthanized and necropsied on GD 28. One control dam aborted on Day 22. In the 30 mg/kg dose group, two dams aborted on days 21 and 27; whole litter from one dam died; food consumption was decreased from GD 6-18; hydrothorax was noted in 1 dam that aborted her litter, and hemorrhage in the uterus was noted at necropsy in 1 dam whose whole litter died; no significant differences were noted in the incidences of skeletal abnormalities or variations or in the number of Sacro-caudal vertebrae. In the 10 mg/kg dose group, food consumption was decreased during GD 8-18. In the 3 mg/kg dose group, no adverse effects were noted in body weights, food consumption or necropsy findings.

No significant differences were noted in the number of corpora lutea or implants between the control and any treated groups. In the placental examinations, no significant differences were noted in the incidences of gross findings or placental weights between the control, and any treated group. On fetal examinations, no adverse effects were noted in fetal mortality, the

number of live fetuses, sex ratio, fetal weights, external abnormalities or visceral abnormalities or variations in any treated group. The maternal and fetal NOAELs were determined to be 10 mg/kg/day and 30 mg/kg/day, respectively.

Study for Effects of TAK-438 on Pre- and Postnatal Development, Including Maternal Functions, in Rats (Study # TAK-438-11215).

TAK-438 was administered orally by gavage to pregnant female Crl:CD(SD) rats at dosage levels of 0 (0.5 w/v% methylcellulose solution), 1, 3, 10, and 100 mg/kg/day from GD 6 to lactation day 21 (the period up to weaning of pups) to investigate adverse effects on dams and on the development of the offspring. The F_0 dams showed no test article-related abnormalities in clinical signs, delivery or nursing conditions, food consumption, duration of the gestation period, delivery index or necropsy findings (including the number of implantations) in dams in any test article group; reduced body weight gain at 3, 10 and 100 mg/kg/day. In the F_1 generation, reduced body weight in males from Days 11 to 56 after birth; decreased body weight in females from Days 11 to 42 after birth; pups in the 100 mg/kg/dose group showed discolored caudate lobes (white and black color) in the liver in culled pups on Day 4 after birth; no treatment-related change in the liver were observed on Day 21 after birth; increase in copulatory interval in the 100 mg/kg/day dose group; no test article-related changes were observed in clinical signs, birth index, viability index, weaning index, sex ratio, functional or physical development, external or skeletal findings, morphological development of reproductive organs, behavior, learning, or mating performance. No test article-related abnormalities were noted in survival, development, or growth in any test article group in the F_2 generation. Based on above findings, the NOAEL was determined to be 10 mg/kg/day for dams (F_0) and F_1 animals.

Metabolite

Effects of TAk-438 M-IV-Sul on Embryo-Fetal Development in Rats (Study # TAK-438-10069).

To determine the embryo-fetal developmental effects of TAK-438 M-IV Sul (metabolite of TAK-438), TAK-438 M-IV Sul was administered subcutaneously to pregnant Crl:CD(SD) rats at the dose levels of 0 (isotonic sodium chloride solution), 6, 20, and 60 mg/kg/day from GD 6 to 17 and euthanized and necropsied on day 20. No test article-related changes were observed in clinical signs, body weight, food intake, necropsy findings in the dam on cesarian section. No differences between control and treated groups were observed in the number of corpora lutea, implantations, live fetuses, pre- or post-implantation loss, sex ratio, body weights or placental weights of live fetuses. The maternal and fetal NOAEL was determined to be 60 mg/kg/day.

13.3.3.4. Carcinogenicity

Twenty-Four Month Oral Gavage Carcinogenicity Study of TAK-438 in Mice (Study # TAK-438-10883).

In the 2-year mouse carcinogenicity study, TAK-438 was administered by oral gavage to B6C3F1/Crlj mice at dose levels of 0 (control; 0.5% w/v methylcellulose solution), 6, 20, 60 and 200 mg/kg/day (n=55/sex/group) for 104 weeks. The numbers of mice surviving to their terminal

necropsy were 35 (63.6%), 31 (56.4%), 28 (50.9%), 25 (45.5%), and 14 (25.5%), in the vehicle control, 6, 20, 60, and 200 mg/kg/day dose groups for males, respectively, and 42 (76.4%), 34 (61.8%), 42 (76.4%), 41(74.5%), and 19 (34.5%), for females, respectively. TAK-438-related decreases in survival were observed in both male and female mice. The survival rate was significantly lower at the 200 mg/kg/day dose. Treatment was discontinued for males in the 200 mg/kg/day dose group after dosing for 88 weeks and 14 surviving males in this group were sacrificed in Week 90 after a withdrawal period of 10 days. The survival of females in the 200 mg/kg/day dose group was significantly lower (n=19), compared to controls (n=42) at the end of the study.

Treatment-related increases in tumor incidences were noted in the stomach and liver of both male and female mice. In the stomach, treatment with TAK-438 produced benign neuroendocrine cell tumors in males at 20, 60 and 200 mg/kg/day, and in females at 60 and 200 mg/kg/day. TAK-438 also produced malignant neuroendocrine cell tumors in the stomach of males at all doses and in females at 60 and 200 mg/kg/kg doses. In the liver, hepatocellular adenomas were increased in males in all dose groups and females in 20, 60, and 200 mg/kg/day dose groups; however, the incidences were significantly higher in males at 20, 60 and 200 mg/kg/day and females at 60 and 200 mg/kg/day, compared to controls. The incidences of hepatocellular carcinomas were also significantly higher in males at 60 and 200 mg/kg/day and in females at 200 mg/kg/day, compared to controls. The combined incidences of hepatocellular adenoma and carcinoma were significantly higher in males at ≥20 mg/kg and in females at ≥60 mg/kg, compared to controls. Males in 20, 60 and 200 mg/kg dose groups and females in 60 and 200 mg/kg dose groups had significantly higher combined incidences of benign and malignant neuroendocrine cell tumors in the stomach. Non-neoplastic findings included: fibrosis of the glandular stomach (males at 200 mg/kg), hyperplastic gastropathy (males at 6 mg/kg and higher and females at 60 and 200 mg/kg), diffuse neuroendocrine cell hyperplasia (males at 60 and 200 mg/kg and females at 200 mg/kg) and hyperkeratosis of the non-glandular regions of the stomach (males at 200 mg/kg and females at 60 and 200 mg/kg).

Twenty-Four Month Oral Gavage Carcinogenicity Study of TAK-438 in Rats (Study # TAK-438-10882).

In the 2-year rat carcinogenicity study, TAK-438 was administered once daily by oral gavage to male and female Crl:CD(SD) SPF rats for 104 weeks at doses of 0 (0.5 w/v% methylcellulose solution), 5, 15, 50 and 150 mg/kg/day (n=60 sex/dose). No TAK-438-related effects were observed on the survival in any dose group in either sex. The numbers of rats surviving to their terminal necropsy were 27 (45%), 36 (60%), 32 (53.3%), 25 (41.7%), and 35 (58.3%) in the vehicle control, 5, 15, 50, and 150 mg/kg/day dose groups male rats, respectively, and 24 (40%), 29 (48.3%), 23 (38.3%), 25 (41.7%), and 19 (31.7%) in the vehicle control, 5, 15, 50, and 150 mg/kg/day dose groups female rats, respectively.

TAK 438-related increased incidences of tumors were observed in the liver and stomach of both male and female rats. Males and females in 50 and 150 mg/kg dose groups showed significantly higher incidences of hepatocellular adenomas, compared to controls. Hepatocellular carcinomas were observed in 1 male at 50 mg/kg and 7 males and 1 female at 150 mg/kg. In addition, hepatocholangiocellular adenomas and carcinomas were observed in 1 male at 50 mg/kg and in 3 males at 150 mg/kg, respectively. The incidences of benign neuroendocrine cell tumors in the stomach at 5 mg/kg and higher doses were higher than controls in both males and females.

Malignant neuroendocrine cell tumors in the stomach were observed in males at 5 and 150 mg/kg doses and in females from all dose groups (statistically significant in females at all doses). In addition, malignant neuroendocrine cell tumors with eosinophilic changes were observed in one male at 15 mg/kg and 3 females each at 15 and 150 mg/kg.

Non-neoplastic findings were noted in the kidney, liver, lung, stomach, and thyroid. Pigmentation of the tubular cells in kidneys was observed at 15, 50 and 150 mg/kg in both sexes. In males, tubular dilatation in kidneys was observed at 150 mg/kg. In the liver, the following nonneoplastic findings were observed: centrilobular hypertrophy in both sexes in all dose groups, eosinophilic altered cell foci (males at 15 mg/kg and higher and females at 5 mg/kg and higher), midzonal vacuolation of the hepatocytes (males at 15 mg/kg and higher and females at 50 and 150 mg/kg), spongiosis hepatis (males at 50 and 150 mg/kg) and multinucleated hepatocytes (males at 150 mg/kg). In the lungs, accumulation of foamy alveolar macrophages and alveolar lipoproteinosis were observed in both sexes at 150 mg/kg. In the stomach, the following changes were noted: diffuse and focal neuroendocrine cell hyperplasia (both sexes at 5 mg/kg and higher doses), hyperplastic gastropathy (both sexes at 5 mg/kg and higher doses), glandular fibrosis (males at 15 mg/kg and higher and females at 5 mg/kg and higher doses), glandular atrophy (both sexes at 15 mg/kg and higher doses), focal foveolar cell hyperplasia (males at 15 mg/kg and females at 15 mg/kg and higher doses), intestinal metaplasia (both sexes at 50 and 150 mg/kg) and squamous hyperplasia of the limiting ridge (females at 50 and 150 mg/kg). In the thyroid, diffuse C cell hyperplasia (females at 15 mg/kg and higher) and diffuse follicular cell hypertrophy (females at 150 mg/kg) were observed.

14. Clinical Pharmacology: Additional Information and Assessment

The majority of in vitro and in vivo studies including bioanalysis methods, the population pharmacokinetic (popPK) analysis report submitted in NDA 215151 were previously reviewed in NDA 215152/215153. Refer to Section 14 of the Integrated Review of NDA 215152/215153 dated May 3, 2022.

The individual study reviews below are for the study reports that were submitted in NDA 215151, have impact on the clinical pharmacology assessment and labeling, and have not been previously reviewed in NDA 215152/NDA 215153.

14.1. In Vitro Studies

Study TAK-438/CPH-003 (Japan): Drug-Drug Interaction Study With Low-Dose Aspirin and Nonsteroidal Anti-inflammatory Drugs (Loxoprofen, Diclofenac, and Meloxicam)

Objectives: Study TAK-438/CPH-003 was an open-label, cross-over DDI study to investigate the effect of coadministration on the PK of vonoprazan and low-dose aspirin or NSAIDs (loxoprofen sodium, diclofenac sodium, or meloxicam) in 64 healthy Japanese male subjects.

Methods: The treatment phase consisted of a single dose of the substrate (Medication A in Table 85), initially administered alone, followed by a suitable washout period and then 6-day multiple doses of the interacting drug (Medication B in (Table 85) were administered. Medication A was

concomitantly administered on the 5th day of the multiple dose period. Cohorts 1 to 4, 6, and 7 had 7-day washout period whereas Cohort 5 and 8 had 14 days and 5 days for washout period.

Table 85. Study Drug Used and Daily Dose in Each Cohort in Study TAK-438/CPH-003

Cohort	Medication A (as Substrate [a])	Medication B (as Interacting Drug [a])
1	Vonoprazan (40 mg)	Aspirin (100 mg QD)
2	Vonoprazan (40 mg)	Loxoprofen sodium (60 mg TID)
3	Vonoprazan (40 mg)	Diclofenac sodium (25 mg TID)
4	Vonoprazan (40 mg)	Meloxicam (10 mg QD)
5	Aspirin (100 mg)	Vonoprazan (40 mg QD)
6	Loxoprofen sodium (60 mg)	Vonoprazan (40 mg QD)
7	Diclofenac sodium (25 mg)	Vonoprazan (40 mg QD)
8	Meloxicam (10 mg)	Vonoprazan (40 mg QD)

Source: Clinical Study Report TAK-438/CPH-003, Tables 9.a and 9.b
Abbreviations: TID, three times a day; QD, once daily

In Cohorts 1 to 4, pharmacokinetics of vonoprazan and its metabolites was assessed whereas in Cohorts 5 to 8, pharmacokinetics of each substrate or active metabolite as below.

- Cohorts 1 to 4: vonoprazan and its metabolites (M-I, M-II, M-III and M-IV-Sul)
- Cohort 5: aspirin and its metabolite (salicylic acid)
- Cohort 6: loxoprofen and its active metabolite (trans-OH metabolite)
- Cohort 7: diclofenac
- Cohort 8: meloxicam

Additionally, in Cohort 5, platelet aggregation inhibition activity was assessed by relative translucency, i.e., maximum change% in aggregation, using blood samples. Collagen 1 mcg/mL and arachidonic acid 1 mM was used as platelet aggregation inducing agents, respectively.

Results

Cohorts 1 to 4: Effect of NSAIDs and Aspirin on Vonoprazan

To assess the effect of concomitant administration of aspirin, loxoprofen sodium, diclofenac sodium or meloxicam on the PK of vonoprazan, C_{max} and AUC were compared using an analysis of covariance model, the results of which are summarized in Table 86.

No significant differences were observed in the exposure of vonoprazan when comparing vonoprazan administered alone to vonoprazan administered concomitantly with aspirin, loxoprofen sodium, diclofenac sodium, or meloxicam.

Table 86. Pharmacokinetic Parameters of Vonoprazan Following Coadministration of Vonoprazan With Low-Dose Aspirin or NSAIDs Compared to Vonoprazan Alone in Study TAK-438/CPH-003 (Cohorts 1 to 4)

		Geometric Means			
Cohort 1	**N**	**Vonoprazan Alone (R)**	**Vonoprazan + Aspirin (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	7	72.6	77.09	1.06	(0.90, 1.26)
AUC_{last} (h·ng/mL)	7	516.24	524.18	1.02	(0.95, 1.01)
Cohort 2	**N**	**Vonoprazan Alone (R)**	**Vonoprazan + Loxoprofen Sodium (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	8	69.2	57.8	0.8	(0.70, 1.00)
AUC_{last} (h·ng/mL)	8	447.18	437.69	0.98	(0.89, 1.07)
Cohort 3	**N**	**Vonoprazan Alone (R)**	**Vonoprazan + Diclofenac Sodium (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	8	85.3	85.7	1.0	(0.95, 1.07)
AUC_{last} (h·ng/mL)	8	528.47	516.27	0.98	(0.93, 1.02)
Cohort 4	**N**	**Vonoprazan Alone (R)**	**Vonoprazan + Meloxicam (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	7	74.0	72.0	1.0	(0.82, 1.16)
AUC_{last} (h·ng/mL)	7	459.30	454.37	0.99	(0.95, 1.03)

Source: Clinical Study Report TAK-438/CPH-003 Section 15.1, Tables 2.1.1.4.2.1.4.1_2, 2.1.1.4.2.1.3.1_2, 2.1.2.4.2.1.4.1_2, 2.1.2.4.2.1.3.1_2, 2.1.3.4.2.1.4.1_2, 2.1.3.4.2.1.3.1_2, 2.1.4.4.2.1.4.1_2, and 2.1.4.4.2.1.3.1_2
Abbreviation: AUC, area under concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; NSAID, nonsteroidal anti-inflammatory drug

Effect of Vonoprazan on NSAIDs (Cohorts 6 to 8)

To assess the effect of concomitant administration of vonoprazan on the PK of loxoprofen, diclofenac or meloxicam, C_{max} and AUC were compared using an analysis of covariance model, the results of which are summarized in Table 87.

No significant differences were observed in the PK of loxoprofen (and loxoprofen trans-OH), diclofenac, and meloxicam when loxoprofen, diclofenac, or meloxicam was co-administered with vonoprazan compared to each drug alone, respectively.

Table 87. Pharmacokinetic Parameters of Low-Dose Aspirin or NSAIDs Following Coadministration of Low-Dose Aspirin or NSAIDs With Vonoprazan Compared to Administration Alone in Study TAK-438/CPH-003 (Cohorts 5 to 8)

		Geometric Means			
Cohort 5	**N**	**Aspirin Alone (R)**	**Aspirin + Vonoprazan (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	8	227.9	418.1	1.8	(0.80, 4.)
AUC_{last} (h·ng/mL)	8	539.8	752.7	1.4	(0.74, 2.61)
Salicylic Acid					
C_{max} (ng/mL)	8	5068.0	5427.4	1.1	(0.804, 1.427)
AUC_{last} (h·ng/mL)	8	24140.2	23895.5	1.0	(0.739, 1.327)
Cohort 6	**N**	**Loxoprofen Sodium Alone (R)**	**Loxoprofen Sodium + Vonoprazan (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	8	3133.6	3056.7	1.0	(0.90, 1.06)
AUC_{last} (h·ng/mL)	8	7687.9	8195.7	1.1	(0.99, 1.15)
Cohort 7	**N**	**Diclofenac Sodium Alone (R)**	**Diclofenac Sodium + Vonoprazan (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	7	359.9	458.4	1.3	(0.92, 1.76)
AUC_{last} (h·ng/mL)	7	605.4	631.2	1.0	(0.93, 1.17)
Cohort 8	**N**	**Meloxicam Alone (R)**	**Meloxicam + Vonoprazan (T)**	**Mean Ratio (T/R)**	**90% CI of Ratio**
C_{max} (ng/mL)	8	1033.9	1080.8	1.0	(0.97, 1.12)
AUC_{last} (h·ng/mL)	8	21900.6	24948.7	1.1	(1.08, 1.21)

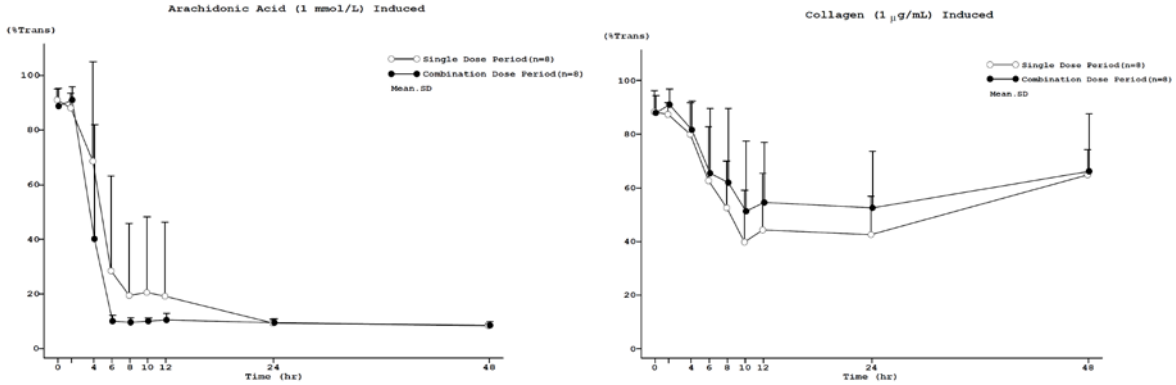
Source: Clinical Study Report TAK-438/CPH-003, Section 15.1, Tables 2.1.5.4.2.1.4.1_2, 2.1.5.4.2.1.3.1_2, 2.1.6.4.2.1.4.1_2, 2.1.6.4.2.1.3.1_2, 2.1.7.4.2.1.4.1_2, 2.1.7.4.2.1.3.1_2, 2.1.8.4.2.1.4.1_2, and 2.1.8.4.2.1.3.1_2
Abbreviation: AUC, area under concentration-time curve; CI, confidence interval; C_{max}, maximum concentration; NSAID, nonsteroidal anti-inflammatory drug

Effect of Vonoprazan on PK and PD of Aspirin (Cohort 5)

When aspirin was administered concomitantly with vonoprazan, there was an 83% increase in aspirin C_{max} and a 39% increase in AUC, but there was no meaningful difference in the PK of the major active metabolite, salicylic acid.

Inhibition of platelet aggregation activity was not significantly changed when coadministration of aspirin with vonoprazan compared to administration alone (Figure 9). No changes were observed in arachidonic acid-induced platelet aggregation activity when aspirin was administered concomitantly with vonoprazan compared to alone, whereas slight decreases in collagen-induced platelet aggregation inhibitory activity were noted when aspirin was administered concomitantly with vonoprazan compared to alone.

Figure 9. Time-Matched Difference of Ex-Vivo Inhibition of Platelet-Aggregating Activity Induced by Arachidonic Acid (Left Panel) and Collagen (Right Panel) in Blood Samples Collected From Healthy Subjects Following Administration of Aspirin Alone or Aspirin and Vonoprazan Concomitantly in Cohort 5 in Study TAK-438/CPH-003



Source: Clinical Study Report TAK-438/CPH-003, Figures 11.a and 11.b
Closed circle represents coadministration of low dose aspirin with vonoprazan; open circle represents administration of low dose aspirin alone
Abbreviations: SD, standard deviation

Conclusions: Concomitant administration of vonoprazan with aspirin, loxoprofen sodium, diclofenac sodium or meloxicam resulted in minor changes in plasma exposure of these agents, all of which are unlikely to be clinically significant.

Reviewer's Assessment:

Concomitant administration of vonoprazan with aspirin, loxoprofen sodium, diclofenac sodium, or meloxicam does not have clinically meaningful effect on the vonoprazan exposure.

Concomitant administration of vonoprazan with loxoprofen sodium, diclofenac sodium or meloxicam did not result in clinically meaningful changes in exposure of each drug.

Even though vonoprazan increased C_{max} and AUC of aspirin by 83% and 39%, respectively, when co-administered, it is unlikely clinically meaningful. Changes in systemic exposure (AUC) of aspirin and salicylic acid (i.e., the major metabolite of aspirin, active for COX-1 and -2 but inactive against TXA2) were not significant. Moreover, inhibition of platelet aggregation activity significantly differed between with and without vonoprazan. The complete inhibition of platelet aggregation induced by arachidonic acid was achieved within 24 hours following a single dose of aspirin alone, which was achieved slightly faster when co-administered with vonoprazan.

Considering aspirin's mechanism of anti-platelet aggregation activity (i.e., the irreversible inhibition of TXA2) and the chronic use of low dose aspirin as an anti-platelet inhibition agent, dose adjustment is deemed unnecessary when vonoprazan is concomitantly used with low dose aspirin.

The Applicant initially did not include this study results in the proposed labeling. However, given the potential for concomitant use of vonoprazan with aspirin and NSAIDs chronically, we recommend that this DDI study results be described in the labeling. Since loxoprofen is not currently approved in the United States, the DDI with loxoprofen will not be included in the labeling.

Study VONO-103 (US): Comparative Multiple Dose PK/PD Study of Vonoprazan to Lansoprazole

Objectives: Study VONO-103 was a phase 1, open-label, cross-over PK/ pharmacodynamic (PD) study to investigate the acid-inhibitory effect of vonoprazan 20 mg compared with lansoprazole 30 mg in healthy adult subjects. This study was conducted in the United States.

Methods: Subjects were randomized to one of two 7-day study drug administration periods (vonoprazan 20 mg once daily (QD) followed by lansoprazole 30 mg QD or the reverse order), separated by a washout period of at least 7 days. Study drug was given orally in the morning under fasting condition. On Days 1 and 7 of Periods 1 and 2, subjects continued the fast for 4 hours postdose when they were given a meal; the next meal was served at 9 hours postdose, and a snack was served at 12 hours postdose. Standard meals were provided. Gastric pH was measured continuously over a 24-hour period at baseline (Day -1 of Period 1 only) and on Days 1 and 7 of Periods 1 and 2. PK samples were collected at pre-dose and for 24 hours following dosing on Days 1 and 7 of Periods 1 and 2. There was a washout period of at least 7 days between the last dose in Period 1 and the first dose in Period 2.

Results

Pharmacokinetics

Mean PK parameters for vonoprazan on Days 1 and 7 are summarized in Table 88. Vonoprazan PK parameter estimates from this multiple dose study in U.S. subjects were generally similar to those observed in European subjects in Study TAK-438_107 and Japanese subjects in Study TAK-438/CPH-002. Mean accumulation ratios for C_{max} and AUC were 1.25 and 1.29, respectively, indicating an approximate 25% to 29% accumulation in plasma exposure following multiple once daily 20 mg doses of vonoprazan for 7 days.

Table 88. Mean (SD) Pharmacokinetic Parameter Estimates for Vonoprazan and Lansoprazole Following Oral Administration of Vonoprazan 20 mg or Lansoprazole 30 mg for 1 and 7 Days in Study VONO-103

Parameter (units)	Vonoprazan 20 mg (N = 40)	Lansoprazole 30 mg (N Day 1 =41) (N Day 7 = 38)
C_{max} (ng/mL)		
Day 1	21.8 (8.33)	1110 (411.88)
Day 7	27.4 (9.99)	1164 (506.53)
AUC_∞ (h·ng/mL)		
Day 1	229.5 (98.84)[a]	2679 (1361.0)
AUC_τ (h·ng/mL)		
Day 1	200.4 (80.86)	2665 (1352.3)
Day 7	261.4 (104.18)	3246 (2396.4)
t_{max} (h) median (min, max)		
Day 1	2.0 (1.00, 5.01)	1.5 (0.79, 4.00)
Day 7	2.0 (1.53, 5.00)	1.5 (0.75, 4.02)
$t_{1/2z}$ (h)		
Day 1	7.9 (1.94)[a]	1.4 (0.49)
Day 7	8.2 (1.89)	-

Source: Clinical Study Report VONO-103, Tables 14.2.1.1.2, 14.2.1.1.3, 14.2.1.2.2, 14.2.1.2.3
[a]N=39
Abbreviation: AUC, area under concentration-time curve; C_{max}, maximum concentration; SD, standard deviation; T_{max}, time to reach maximum concentration

Pharmacodynamics

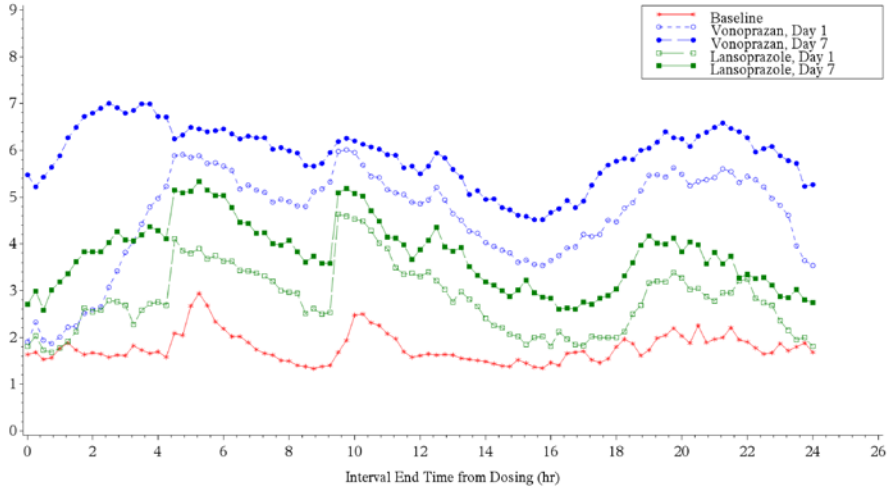
Intragastric pH was measured for 24 hours at Baseline, and on Days 1 and 7 of each Period. Mean intragastric pH profiles at baseline and following vonoprazan 20 mg or lansoprazole 30 mg on Days 1 and 7 are shown in Figure 10.

Mean gastric pH versus time profiles following a single dose of either vonoprazan 20 mg or lansoprazole 30 mg on Day 1 were higher than at baseline for most of the entire 24-hour interval.

Mean gastric pH began to rise above baseline during the 0 to 2 hour interval following either vonoprazan or lansoprazole but increased considerably more during the 2 to 4 hour interval for vonoprazan compared to lansoprazole. The mean gastric pH profile for vonoprazan on Day 1 was higher than that for lansoprazole starting at approximately 3 hours after dosing and continuing for the remainder of the 24-hour period. After seven days of once daily dosing the mean pH profiles for both vonoprazan and lansoprazole were higher than those observed after a single dose. Similar to Day 1, the mean pH profile for vonoprazan on Day 7 was considerably higher than that for lansoprazole and remained above pH 4 for nearly the entire 24-hour interval.

Mean 24-hour intragastric pH and percentage of time pH >4, 5 and 6 for vonoprazan 20 mg and lansoprazole 30 mg are presented in Table 89. On Day 1, pH increased to 4.6 in the vonoprazan 20 mg group compared to 2.8 in the lansoprazole 30 mg group. By Day 7, mean 24-hour intragastric pH for the vonoprazan 20 mg group was 5.9 compared to 3.8 in the lansoprazole 30 mg group (Table 89).

Figure 10. Mean Gastric pH vs. Time Profiles at Baseline and on Days 1 and 7 Following Vonoprazan 20 mg or Lansoprazole 30 mg Administered QD on Days 1 Through 7 in Study VONO-103



Source: Clinical Study Report VONO-103, Figure 14.2.4.13
Meals consumed at 4-, 9-, and 12-hours post-dose
Abbreviations: QD, once daily

Table 89. Mean (SD) 24-Hour Intragastric pH and Percent of Time pH >4, 5 and 6 at Baseline (Day 1) and Following Oral Administration of Vonoprazan, 20 mg or Lansoprazole 30 mg on Days1 and 7 in Study VONO-103

Parameter	Baseline	Vonoprazan		Lansoprazole	
	N = 43	Day 1	Day 7	Day 1	Day 7
		N = 40	N = 40	N = 41	N = 38
Mean pH	1.8 (0.26)	4.6 (1.09)	5.9 (0.85)	2.8 (0.80)	3.8 (1.20)
Mean (SD) % of Time Intragastric pH>4	3.9 (3.76)	62.4 (23.35)	87.8 (15.71)	22.6 (17.31)	42.3 (25.60)
Mean (SD) % of Time Intragastric pH>5	2.5 (2.73)	52.4 (25.21)	79.8 (19.95)	14.6 (13.80)	28.4 (24.17)
Mean (SD) % of Time Intragastric pH>6	1.3 (1.94)	33.1 (20.62)	62.5 (22.08)	7.4 (8.52)	16.4 (20.55)

Source: Clinical Study Report VONO-103 Tables 14.2.3.1.4, 14.2.3.1.5.1, 14.2.3.1.5.2, 14.2.3.1.6.1, and 14.2.3.1.6.2
Abbreviations: QD, once daily; SD, standard deviation

Conclusion: Vonoprazan showed gastric acid suppression effect following multiple administration of 20 mg once daily, which was greater than those of lansoprazole following multiple administration of 30 mg once daily.

Reviewer's Assessment

(b) (4)

the magnitude of acid suppression effect is not a quantitatively correlated with the healing rate of EE, e.g., the healing rate of EE was similar between vonoprazan 20 mg and 40 mg despite numerically greater % time > pH 4. Additionally, the % time gastric pH > 4 and the mean 24-hour pH for lansoprazole is lower in this study than the presented in Prevacid label (41% on Day 1 in Prevacid vs. 22.6% in this study for lansoprazole 30 mg; 4.9 on Day 5 in Prevacid vs. 3.8 in this study). It is unclear why the values for lansoprazole are notably lower in this study compared to those described in the Prevacid label.

(b) (4)

Bioanalytical Assay Methods

Vonoprazan: vonoprazan and its metabolites were quantitated in sodium heparin plasma using a validated bioanalytical method with liquid chromatography- mass spectrometry (LC-MS/MS) in Studies TAK-438/CPH-003 and VONO-103, respectively. The method validation reports were previously reviewed and deemed adequate. Refer to Section 14.5 of the Integrated Review of NDA 215152/215153 dated May 3, 2022.

Per the bioanalytical reports in Studies TAK-438/CPH-003 and VONO-103, the in-study performance of bioanalysis met the acceptance criteria including the incurred sample reanalysis

(ISR). All samples were analyzed following storage at -60 to -80°C within established long-term stability, 371 days.

NSAIDs and Aspirin: For Study TAK-438/CPH-003, the following analytes (validated quantitation range) in human plasma were measured using a validated bioanalytical method using LC-MS/MS:

- Aspirin: 2 to 1000 ng/mL
- Salicylic acid: 100 to 50000 ng/mL
- Diclofenac: 1 to 1000 ng/mL
- Loxoprofen: 10 to 10000 ng/mL
- Trans-OH metabolite: 2 to 2000 ng/mL
- Meloxicam: 3 to 3000 ng/mL

Per the bioanalytical reports of TAK-438/CPH-003, the bioanalytical method validations and bioanalyses of all analytes were acceptable to support the pharmacokinetics results of TAK-438/CPH-003. All samples were analyzed within the established long-term stability, 30 days at both -20°C and–80°C.

14.2. In Vivo Studies

Population PK-PD Analysis

Objectives

The objectives of the Applicant's analysis were to:

- Estimate individual AUC values using the previously developed popPK model.
- Develop a PK-PD model to characterize daily holding time ratios of pH >4 (HTR4: Percent time of gastric pH >4) and pH >5 (HTR5) as a response of vonoprazan exposure (AUC).
- Simulate the impact of covariates on the HTR4 and HTR5 response on Day 1 and 7.
- Simulate HTR4 and HTR5 response on Day 1 and Day 7 in Asian and non-Asian subjects at doses of 10, 20, and 40 mg.

Data

This analysis was based on PK and 24-hour intragastric pH from 5 phase 1 PK-PD studies in healthy subjects (i.e., Studies TAK-438_101, TAK-438_107, TAK-438_109, TAK-438/CPH-001, TAK-438/CPH-002, and TAK-438/CPH-010) (Table 90). In the two studies conducted in United Kingdom, subjects were primarily White while total nine Black subjects were included.

Table 90. Summary of Studies Included in the Population PK-PD Analysis

Study No.	Population	Region	Description
TAK-438_101	Healthy	United Kingdom	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Single- and

			Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK- 438 in Healthy Western Male Subjects, Preliminary Food Effect Analysis, and an Ethnic Comparison With Japanese Subjects
TAK-438_107	Healthy	United Kingdom	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential, Multiple Repeat Dose Study to Evaluate the Safety, Tolerability, and PK and PD of TAK-438 in Healthy Non-Japanese Male Subjects
TAK-438/CPH-001	Healthy	Japan	A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study of the Safety, Tolerability, PK and PD of TAK-438 in Healthy Male Subjects
TAK-438/CPH-002	Healthy	Japan	A Phase I, Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of the Safety, Tolerability, PK and PD of TAK-438 in Healthy Male Subjects
TAK-438/CPH-010	Healthy	Japan	Open-Label Crossover PD Study to Evaluate the Acid-inhibitory Effect of TAK-438 20 mg in Comparison with Esomeprazole 20 mg or Rabeprazole Sodium 10 mg in Healthy Adult Male Subjects

Source: Section 2.7.2. Summary of Clinical Pharmacology Studies, Table 6.b.
Abbreviations: PD, pharmacodynamic; PK pharmacokinetic

All studies but Study TAK-438/CPH-010 had individual AUC estimates from the previous popPK model. The AUC at steady state was set to either the individually estimated AUC (Studies TAK-438_101, TAK-438_107, TAK-438/CPH-001, and TAK-438/CPH-002) or the typical population predicted AUC (Study TAK-438/CPH-010) using the popPK model as below:

Figure 11. Population PK Model

$$AUC = F1 \cdot dose/CL \quad \text{with}$$

$$F1 = \left(\frac{dose}{20}\right)^{0.42} \quad \text{and}$$

$$CL = 119.7 \cdot \left(\frac{weight}{70}\right)^{0.51438} \cdot \left(\frac{creatinine}{72}\right)^{-0.45569}$$

(For the review of the previously developed population PK model, refer to Section 14.3 of the Integrated Review of NDA 215152/215153 dated 05/03/2022).
Abbreviations: AUC, area under the concentration-time curve; CL, clearance

The individual intragastric pH holding time ratios per day (24h) >4 (HTR4) was extracted from 5 studies. The dataset contained holding time ratios (HTR) up to 100.7% which would cause technical difficulties when using models based on a logistic-link function. Therefore, original HTR4 values were shrunk by 2% towards the center (50%), i.e., $HTR_{new} = (HTR-50)/102\%+50$, resulting in the final dataset had holding time ratios ranging from 1% to 99.7%. The final dataset contained 782 observations from 299 subjects Table 91 lists observation and subject counts and summary statistics for subject demographics included in the analysis.

Table 91. Summary of Baseline Demographics of Subjects in the Population PK-PD Analysis

Observations	N	782
Subjects	N	299
Study	101: N (%)	63 (21)
	107: N (%)	48 (16)
	CPH-001: N (%)	108 (36)
	CPH-002: N (%)	60 (20)
	CPH-010: N (%)	20 (7)
Dose	0 mg: N (%)	77 (26)
	1 mg: N (%)	15 (5)
	5 mg: N (%)	15 (5)
	10 mg: N (%)	41 (14)
	15 mg: N (%)	15 (5)
	20 mg: N (%)	53 (18)
	30 mg: N (%)	24 (8)
	40 mg: N (%)	41 (14)
	80 mg: N (%)	9 (3)
	120 mg: N (%)	9 (3)
Race	Asian: N (%)	197 (66)
	Black or African American: N (%)	9 (3)
	Multiracial: N (%)	1 (0)
	Native Hawaiian or Other Pacific Islande: N (%)	1 (0)
	White: N (%)	91 (30)
Age (years)	mean (SD)	27 (5.8)
	[min,max]	[18, 45]
Weight (baseline) (kg)	mean (SD)	68 (10)
	[min,max]	[50, 110]
Smoking	current: N (%)	40 (13)
	ex: N (%)	95 (32)
	never: N (%)	164 (55)
Asian	No: N (%)	102 (34)
	Yes: N (%)	197 (66)
Country	GB: N (%)	111 (37)
	JP: N (%)	188 (63)
Baseline HTR4	mean, median	6.9, 4.9
	[min,max]	[0, 42.4]
Baseline HTR5	mean, median	3.3, 2.1
	[min,max]	[0, 21.5]

Source: The Population PK-PD report, Table 5
Abbreviations: HTR, holding time ratio; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation

Base PD Model

To ensure that model predicted HTR remain within 0 to 100%, a logistic transformation was used, i.e. logit(HTR4) = log[HTR4/ (100−HTR4)]. It was modeled as dependent variable within a nonlinear mixed effects approach. Time-dependent changes in logit(HTR4) were described as an E_{max} model (structural model) where the maximum change from baseline over time (=T_{max}) was modeled as AUC dependent parameter using another nested E_{max} model (treatment effect model).

Over the modeling process, the placebo effect parameter (T_{max} value when AUC =0) was estimated close to 0; therefore, placebo effect was subsequently fixed to 0. There was a trend of HTR4 slightly decreasing over time in the lower dose groups and placebo, which was noticeable in the goodness-of-fit plots of residuals over time. Therefore, a slope parameter was added to the model to estimate treatment independent changes of HTR4 over time, which significantly reduced the unexplained variability of E_{max} and the half maximal effective concentration.

Figure 12. Base PD Model

$$\text{logit}(HTR4) = \left(base + \frac{day \cdot T_{\max}}{day + T_{50}}\right) \cdot (1 + slope \cdot day)$$

$$T_{\max} = \frac{AUC^{\gamma} \cdot E_{\max}}{AUC^{\gamma} + EC_{50}^{\gamma}}$$

Base: baseline estimate
Slope: treatment independent changes of HTR4 over time
γ: Hill-coefficient parameter
Abbreviations: AUC, area under the concentration-time curve; EC_{50}, AUC required to reach 50% of E_{max}; E_{max}, maximum effect over AUC; T_{50}, time required to reach 50% of T_{max}; T_{max}, maximum increase from base of logit(HTR4) over time

Covariate Analysis

Covariates effects on parameters such as E_{max} or the half maximal effective concentration were tested for age, body weight, smoking habits, baseline holding time ratios and Asian (versus non-Asian). Sex was not tested because all subjects were male. A standard stepwise covariate modeling procedure was followed with p-value thresholds of 0.1 for the univariate testing, 0.05 for the forward inclusion, and 0.01 for the backward deletion.

The full model contained the covariate effects Asian on E_{max}. Although Asian (versus non-Asian) was found statistically significant for E_{max} in logit(HTR4), it is important to note that there was no clinically relevant difference between E_{max} for Asian and Non-Asian subjects on the original scale, i.e., 99.84% for non-Asian versus 99.9% for Asian.

Final PD model

The final parameter estimates of the final PD model are listed in Table 92.

Table 92. Final Parameter Estimates for the Final PD Model (Left Panel, Population Estimates; Right Panel, Estimates of Variability)

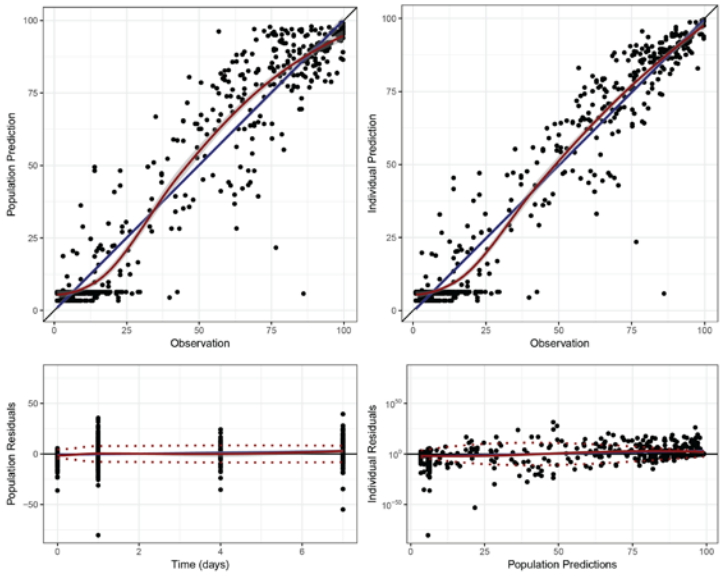
Parameter	Value	Std.Error	t-value	p-value
$E_{\max,\text{intercept}}$	6.42	0.357	18	$< 2 \cdot 10^{-16}$
$E_{\max,\text{Asian}}$	0.618	0.219	2.82	0.005
EC_{50}	0.0834	0.00533	15.6	$< 2 \cdot 10^{-16}$
γ	1.66	0.173	9.61	$< 2 \cdot 10^{-16}$
$base$	-2.69	0.0441	-60.9	$< 2 \cdot 10^{-16}$
T_{50}	0.37	0.0476	7.72	$6.8 \cdot 10^{-14}$
$slope$	0.0351	0.00819	4.28	$2.2 \cdot 10^{-5}$

Parameter	Variance	Std.Deviation
$E_{\max}$	0.858	0.926
EC_{50}	$2.45 \cdot 10^{-11}$	$4.95 \cdot 10^{-6}$
σ	0.741	0.861

Source: The Population PK-PD report, Table 6.3.
Abbreviations: EC_{50}, AUC required to reach 50% of E_{max}; E_{max}, maximum effect over AUC; PD, pharmacodynamic; PK, pharmacokinetic T_{50}, time required to reach 50% of T_{max}

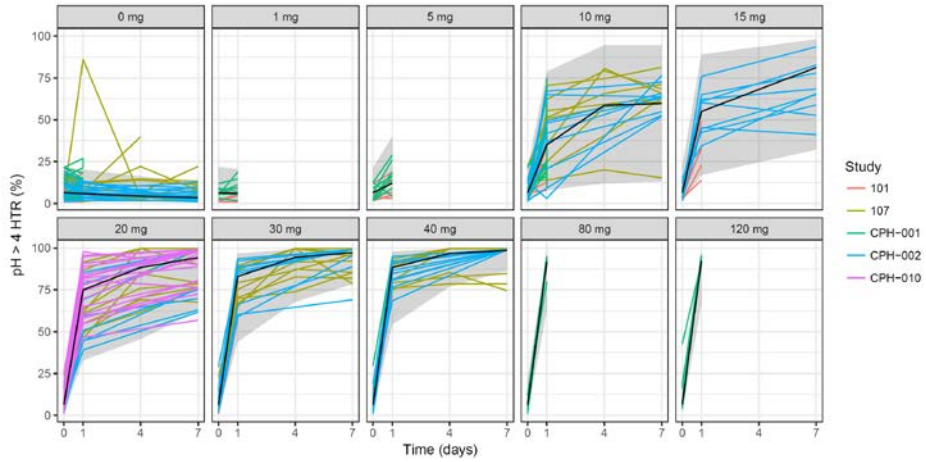
The goodness-of-fit plots for the final PD model for all data are shown in Figure 13 indicating that the base model adequately fits the data. Figure 14 shows a visual predictive check stratified by vonoprazan dose.

Figure 13. Goodness-Of-Fit Plots for Final PD Model



Source: The Population PK-PD report, Figure 6.8.
The solid red line shows a non-parametric smoother (loess) and the solid blue line shows a linear regression of the displayed data. The dotted red lines indicate a non-parametric smoother (loess) of ±|residuals| over time or predictions (to indicate possible trends of residual variability).
Abbreviations: PD, pharmacodynamic

Figure 14. Final Population PK-PD Model Visual Predictive Check, Stratified by Dose



Source: The Population PK-PD report, Figure 6.10.
Individual HTR4 profiles are shown as colored lines (by study). In addition, the black line shows typical model predictions, and the gray ribbon indicates the 90% prediction interval.
Abbreviations: HTR, holding time ratio; PD, pharmacodynamic; PK, pharmacokinetic

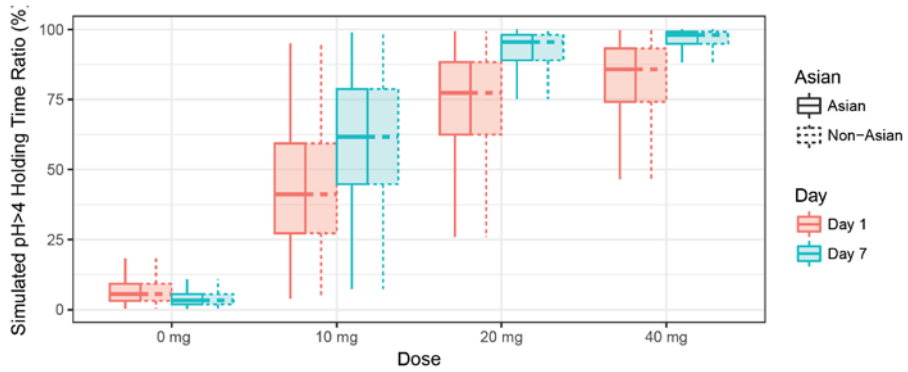
Simulation

The simulated dose-response relationship in HTR4 for doses ranging from 0 to 80 mg are presented in Figure 15. In this simulation, Asian subjects were defined as 63 kg body weight whereas non-Asian subjects were defined as 75 kg body weight.

The simulation suggests that HTR4 reaches the plateau at the vonoprazan dose ≥20 mg QD and further dose increase greater than 20 mg QD would not further increase HTR4. Additionally,

despite race (Asian versus non-Asian) was identified as a statistically significant covariate on E_{max}, the effect of race has minimal effect on the predicted HTR4.

Figure 15. Simulated Time% Intragastric pH >4 (HTR4) on Day 1 and 7 by Dose and Race



Source: The Population PK-PD report, Figure 7.2
HTR4 at Day 1 (red) and 7 (cyan) are grouped by Dose and Asian/Non-Asian (solid/dashed)
Abbreviations: HTR, holding time ratio

Reviewer's Summary/Assessment

The Applicant developed a population PK-PD model to characterize the relationship between systemic exposure (AUC) and the % time of intragastric pH >4 (i.e., daily holding time ratios of pH >4, HTR4) based on 5 PK-PD studies in healthy subjects conducted in Japan and United Kingdom. The model also evaluated the difference between and Asians and non-Asians (including White and Black but primarily White).

An E_{max} model was fit to describe the relationship between AUC and HTR4. The individual AUC were fixed with individual estimates from the previously developed popPK model (i.e., 'sequential' method).

The simulated dose-response relationship for HTR4 suggests that HTR4 would not further increase significantly by dose increase beyond vonoprazan dose 20 mg QD. Additionally, the results of the PK-PD analysis did not show significant effect of race between Asian and non-Asian subjects on HTR4.

In general, the Applicant's population PK-PD analysis is considered reasonable to support the dose selection for the phase 3 trials in subjects with EE for healing of EE and maintenance of healing of EE.

15. Trial Design: Additional Information and Assessment

15.1. Applicant's Protocol Synopsis

Table 93. Clinical Protocol Synopsis for EE-301 (NCT04124926) Study (Version 3, Amendment 2; October 1, 2019)

Protocol number:	EE-301
Title:	A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for

	Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis
Sponsor:	Phathom Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, CA 94025
Study phase:	3
Study sites:	Approximately 150 sites in the US and Europe
Indication:	Patients with Erosive Esophagitis
Rationale:	In a Phase 2 dose-ranging study of vonoprazan (TAK-438) in subjects with EE (TAK-438/CCT-001), vonoprazan was noninferior to lansoprazole 30 mg in healing at all doses tested (5 mg, 10 mg, 20 mg, and 40 mg), with good tolerability. The study demonstrated a dose response relationship with vonoprazan. Furthermore, the rate of endoscopic healing of EE in subjects with more severe disease (Los Angeles Classification [LA classification] grades C/D) was 96% or higher with vonoprazan at doses 20 mg or higher compared to 87% with lansoprazole 30 mg. Based on the results, 20 mg of vonoprazan was selected as the dose for the Japan Phase 3 EE healing study (TAK-438/CCT-002). Study TAK-438/CCT-002 confirmed the noninferiority and superiority (post-hoc) of vonoprazan 20 mg to lansoprazole 30 mg for the healing of EE. Study TAK-438/CCT-003 confirmed the noninferiority and superiority (post-hoc) of vonoprazan 10 and 20 mg to lansoprazole 15 mg for the maintenance of healed EE. Study EE-301 will further examine the effectiveness and safety of vonoprazan in subjects in the US and Europe in the healing and maintenance of healed EE.
Objectives:	<u>Healing Phase</u> • Primary - To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE over 8 weeks in subjects with endoscopically proven EE. - To assess the safety of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subjects with endoscopically proven EE. • Secondary - To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE over 2 weeks in subjects with endoscopically proven EE. - To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE in subjects with endoscopically proven EE LA Classification Grades C or D over 2 weeks and 8 weeks. - To assess relief of heartburn of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subjects with endoscopically proven EE over 8 weeks and within the first 3 days of treatment. <u>Maintenance Phase</u> • Primary - To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE. - To assess the safety of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE. • Secondary - To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE with baseline LA Classification Grades C or D. To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subject symptoms by subject daily diary.

Study population:	Subjects aged 18 years of age or older with endoscopically confirmed EE of LA classification Grades A to D during the Screening Period as assessed by a central adjudicator.
Study design:	This is a Phase 3, 2-phase multi-center, double-blind, noninferiority study of vonoprazan versus lansoprazole for the healing of all grades of EE and relief of heartburn and the maintenance of healing of all grades of EE and relief of heartburn. Subjects with EE (LA classification Grade A /B or C /D serving as a stratification at randomization) will be randomized to receive vonoprazan 20 mg or lansoprazole 30 mg QD for up to 8 weeks for the healing of EE. All subjects with endoscopic healing of EE at 2 or 8 weeks after the start of the study will enter a continuous 24-week maintenance phase. Subjects will be rerandomized to receive either vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg for 24 weeks. The subjects without confirmed endoscopic healing of EE at Week 8 will not be allowed to enter the maintenance phase. Subjects will complete an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms throughout the study. The study will include 4 main phases: Screening phase (Day -35 to Day -2): Subjects will provide informed consent and undergo screening assessments to determine study eligibility, and baseline assessment will be performed. If all eligibility criteria are met, the subject will enter the study. Healing phase (Healing Day -1 to Healing Day 15 or 57): Subjects with EE whose eligibility is confirmed will be randomized to receive vonoprazan 20 mg or lansoprazole 30 mg QD for up to 8 weeks. The date of the first dosing is defined as Day 1. An endoscopy will be performed at Week 2. If endoscopic healing of EE is confirmed at Week 2, the subject will enter the maintenance phase. If endoscopic healing is not confirmed, the subject will continue to receive randomized treatment until Week 8. If endoscopic healing is confirmed at Week 8, the subject will enter the maintenance phase. During the healing phase, if the investigator deems that an additional endoscopy is warranted based on the subject's symptoms prior to the window of the subject's next scheduled per-protocol endoscopy, an unscheduled endoscopy will be permitted whenever required as part of routine clinical care. If the subject's EE is found to have healed at this unscheduled endoscopy visit, the subject will be considered to have completed the healing phase and will undergo randomization for entry into the maintenance phase. If the subject is found to still have EE (of any grade) at the unscheduled endoscopy visit, the subject will be allowed to continue in the study within the healing phase and will undergo their subsequent per-protocol endoscopy. If endoscopic healing of EE is not confirmed at Week 8, the subject will discontinue the study without entering the maintenance phase and be considered as completed for the healing phase. Healing will be defined as endoscopically confirmed healed. Maintenance phase (Maintenance Day 1 to Maintenance Day 169): Subjects with EE who have confirmed endoscopic healing of EE either at Week 2 or at Week 8 of the healing phase (or during an unscheduled endoscopy) will enter the maintenance phase. Subjects will be rerandomized to receive either vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg daily for 24 weeks. Maintenance of healing will be assessed by endoscopy at Week 24 of the maintenance phase. If during the 24-week maintenance phase the investigator deems that an endoscopy is warranted, based on subject symptoms, an unscheduled endoscopy will be permitted whenever required. If the subject's EE is found to have relapsed at this unscheduled endoscopy visit, the subject will be discontinued from the maintenance phase of the study, considered a treatment failure, and will enter the follow-up

	Phase. If the subject is found to have maintained healing of EE at the unscheduled endoscopy visit, the subject will be allowed to continue in the study until Week 24. Follow-up Phase: A safety follow-up visit is planned at 4 weeks after the last dose of study drug to assess adverse events (AEs) and the serum gastrin level. Subjects who do not have EE healing at Week 8 and therefore discontinue the study after the healing phase will undergo the safety follow-up period.
Estimated study duration:	The total duration of the study is up to 41 weeks. Screening Period is up to 35 days, healing phase is up to 2 or 8 weeks depending on the healing of EE, maintenance phase is up to 24 weeks, and safety follow-up is at 4 weeks after last study drug administration.
Efficacy assessments:	Healing Phase • Primary - The percentage of subjects who have complete healing of EE at Week 2 or Week 8 as assessed by endoscopy • Secondary - The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy - The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D - The percentage of subjects who have complete healing of EE at Week 2 or Week 8 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D - The percentage of 24-hour heartburn-free days over the healing phase as assessed by the daily diary - The percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary) Maintenance Phase • Primary - The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy • Secondary - The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy for subjects with baseline LA Classification Grades C or D. - The percentage of 24-hour heartburn-free days over the maintenance phase as assessed by the daily diary.
Safety assessments:	Safety will be assessed by: • Adverse events • Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels • Gastric biopsy • Electrocardiogram (for maintenance phase only) • Vital signs
Study drug, dosage, and route of administration:	Healing Phase Blinded study drug (vonoprazan 20 mg QD or lansoprazole 30 mg QD) to be taken orally for up to 8 weeks. Maintenance Phase

	Blinded study drug (vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD) to be taken orally for 24 weeks.
Sample size:	Healing Phase A sample size of 500 subjects per treatment group provides at least 90% power to achieve noninferiority using a Farrington Manning test with a noninferiority margin of 10%, assuming EE healing rates at Week 2 or Week 8 of 80% and 80% for vonoprazan and lansoprazole, respectively. Maintenance Phase All subjects who have complete healing of EE during the healing phase will enter the maintenance phase. It is expected that approximately 800 subjects will enter the maintenance phase, but the actual number of subjects who enter will depend on the observed healing rates during the healing phase. During the study if less than 800 subjects are projected to enroll into the maintenance phase, additional subjects may be enrolled to ensure that a sufficient number of subjects enter the maintenance phase. For the maintenance of EE healing after 24 weeks, a sample size of 265 subjects per treatment group provides at least 90% power to achieve noninferiority with a noninferiority margin of 10% and at least 90% power to achieve superiority using the Farrington Manning test, assuming maintenance of EE healing rates of 82% and 70% for vonoprazan and lansoprazole, respectively.

Statistical methods:

Analysis of Primary Efficacy Endpoint

Healing Phase

The EE healing rate at Week 2 or Week 8 will be calculated along with 2-sided 95% CIs for each treatment group. A subject will be considered to have "complete healing of EE by Week 8" if the subject demonstrates healing at the Week 2 or Week 8 endoscopy.

The noninferiority of vonoprazan to lansoprazole will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in EE rates between treatments (vonoprazan minus lansoprazole). The point estimate and 2-sided 95% CI of the difference in endoscopic healing rate between vonoprazan and lansoprazole will be calculated via the Miettinen and Nurminen method.

If noninferiority is shown, superiority will also be assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

Maintenance Phase

The maintenance of healing rate during the 24-week maintenance phase will be calculated along with 2-sided 95% CIs for each treatment group. The noninferiority of each dose group of vonoprazan to lansoprazole will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in maintenance of healing rates between treatments (vonoprazan minus lansoprazole). The point estimate and 2-sided 95% CI of the difference in the maintenance of healing rate between each dose group of vonoprazan and lansoprazole will be calculated via the Miettinen and Nurminen method.
If noninferiority is shown for a vonoprazan dose group, superiority of that dose group compared to lansoprazole will also be assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0. An additional comparison will be made for superiority between the vonoprazan dose groups with no adjustment to the alpha level.

Analysis of Secondary Efficacy Endpoint

Healing Phase

The percentage of subjects who complete healing of EE at Week 2, who complete healing of EE at Week 2 for subjects with baseline LA Classification Grades C or D, and who complete healing of EE at Week 2 or Week 8 for subjects with baseline LA Classification Grades C or D will be analyzed for superiority of vonoprazan compared to lansoprazole similarly to the primary endpoint.

For the percentage of 24-hour heartburn-free days over the healing phase as assessed by daily diary, a 2-sided 95% CI will be calculated for the difference between the treatment groups in the mean percentage of 24-hour heartburn-free days (vonoprazan minus lansoprazole). If the lower bound of this CI is greater than -15%, noninferiority will be concluded. If noninferiority is shown, the percentage of 24-hour heartburn-free days over the healing phase will also be compared between treatment groups using a Wilcoxon rank-sum test.

The percentage of subjects with onset of sustained resolution of heartburn by Day 3 will be analyzed for superiority of vonoprazan compared to lansoprazole similarly to the primary endpoint. Sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary.

	Maintenance Phase The percentage of subjects who maintain complete healing of EE after 24 weeks for subjects with baseline LA Classification Grades C or D will be analyzed for superiority of each vonoprazan dose group compared to lansoprazole similarly to the primary endpoint. For the secondary endpoint of the percentage of 24-hour heartburn-free days over the maintenance phase as assessed by daily diary, a 2-sided 95% CI will be calculated for the difference between each vonoprazan dose group and the lansoprazole group in the mean percentage of 24-hour heartburn-free days (vonoprazan minus lansoprazole). If the lower bound of this CI is greater than -15%, noninferiority will be concluded. If noninferiority is shown for a vonoprazan dose group, superiority of that dose group compared to lansoprazole will also be assessed using a Wilcoxon rank-sum test. Safety Analyses For each phase, safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, and vital signs. Adverse Events will be coded using MedDRA. The number and percentage of subjects experiencing treatment-emergent AEs will be summarized by MedDRA system organ class and preferred term overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity. Clinical laboratory tests, pepsinogen I/II levels, gastrin levels, and vital signs will be summarized with descriptive statistics at each visit by treatment group. A summary of change-from-baseline at each visit will also be summarized by treatment group.

Source: Section 2.0 EE-301 Clinical Study Report, Final Version, 19 January 2022, NDA 215151, Source: Section 2.0 EE-301 Clinical Study Report, Final Version, 19 January 2022, NDA 215151,
Abbreviations: AE, adverse event; CI, confidence interval; EE, erosive esophagitis; LA, Los Angeles; MedDRA, Medical Dictionary for Regulatory Activities; QD, once daily

15.2. Schedule of Events Schema, Study EE-301

Table 94 shows the Schedule of Events for Study EE-301, Protocol Version 3, submitted on January 1, 2019

Table 94. Schedule of Events Schema, Study EE-301

	Screening Period (a)	Healing Phase				Maintenance Phase						
Timing		**Healing Day -1[b]**	**Healing Day 1[b]**	**Week 2[c] Healing Day 15**	**Week 8 [c m] Healing Day 57**	**Main Week 4 Main Day 29**	**Main Week 12 Main Day 85**	**Main Week 16 Main Day 113**	**Main Week 20 Main Day 141**	**Main Week 24 Main Day 169 Final Visit/ET (d)**	**Safety F/U[e]**	**Unscheduled Visit[f]**
Visit Windows (Days)	**Day-35 to -2**	**-**		**12 to 18**	**54 to 60**	**26 to 36**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**-**	**-**
Visit Number:	**1**	**2**		**3**	**4**	**M1**	**M2**	**M3**	**M4**	**M5**	**F/U**	**-**
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographic and medical history	X											
Smoking status and alcohol use	X											
Medication history	X											
Physical examination[g]	X	X		X	X	X	X			X	X	X
Vital signs	X	X		X	X	X	X			X	X	X
Weight and height	X											
Concomitant medications	X	X		X	X	X	X			X	X	X
Concurrent medical conditions	X											
FSH[h]	X											
Hepatitis B and C; HIV	X											
Urine drug screen	X											
Clinical laboratory test including hematology, serum chemistry, and urinalysis[i]	X			X	X	X	X			**X**		
^{13}C-UBT Breath Test	X											
CYP2C19 genotyping test				X								
Serum gastrin/pepsinogen I/II levels[j]	X			X	X	X	X			X	X	
Pregnancy test (serum HCG)[k]	X											
Pregnancy test (urine HCG)[k]		X		X	X	X	X			X		
Guidance on avoidance of pregnancy	X	X		X	X	X	X					
ECG	X									X		

	Screening Period (a)	Healing Phase				Maintenance Phase						
Timing		**Healing Day -1[b]**	**Healing Day 1[b]**	**Week 2[c] Healing Day 15**	**Week 8[c m] Healing Day 57**	**Main Week 4 Main Day 29**	**Main Week 12 Main Day 85**	**Main Week 16 Main Day 113**	**Main Week 20 Main Day 141**	**Main Week 24 Main Day 169 Final Visit/ET[d]**	**Safety F/U[e]**	**Unscheduled Visit[f]**
Visit Windows (Days)	**Day-35 to -2**	**-**		**12 to 18**	**54 to 60**	**26 to 36**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**-**	**-**
Visit Number:	**1**	**2**		**3**	**4**	**M1**	**M2**	**M3**	**M4**	**M5**	**F/U**	**-**
Subject s diary; distribute and/or review[l]	X[f]	X		X	X	X	X			X	X	
PAGI-SYM		X		X	X	X	X			X		
PAGI-QoL		X		X	X	X	X			X		
EQ-5D-5L		X		X	X	X	X			X		
Endoscopy	X			X	X					X		
Gastric biopsy[n]	X				X[s]					X		
Randomization		X		X[o]	X[o]							
Dispense study drug		X[p]		X[q]	X[q]		X					
First day of study drug administration			X									
Drug return/accountability/ review treatment compliance[q]				X	X	X	X			X		
Phone call to subject								X	X			
AE/pretreatment event assessment	X	X		X	X	X	X	X	X	X	X	X

[a] Visit window is Day -35 to Day -2 for assessment of *Helicobacter pylori*, serum gastrin and pepsinogen I/II values, ECG, and endoscopy in the Screening Period. However, given the invasive nature of an endoscopy, any endoscopic confirmation performed in a routine clinical setting before informed consent signing which would have included standard of care gastric mucosa sampling, endoscopy images available for adjudication and done within 7 days of randomization/dosing is acceptable to use for the purpose of fulfilling the Screening requirement, and repeat endoscopic examination during the Screening Period will not be required.

[b] The date of randomization is defined as Day -1. The date of first dosing day is defined as Day 1 for both the healing and maintenance phases.

[c] If the subject is confirmed as healed and rerandomized to the maintenance phase, this visit is considered the baseline visit for the maintenance phase, and subjects who prematurely discontinue from the healing phase or who are not healed at Week 8 should undergo maintenance phase Week 24/Final Visit/ET procedures (including gastric biopsy).

[d] For early discontinuations, the assessments mentioned for Week 24 are required to be performed.

[e] A safety follow-up visit is to be scheduled 4 weeks after the last dose of study drug administration. Subjects whose healing is not confirmed after Week 8 and who discontinued the study after the healing phase will undergo a safety follow-up visit 4 weeks after the last dose of study drug administration.

[f] At an unscheduled visit, the following procedures are to be completed with additional procedures at the investigator's discretion: a brief physical examination, vital sign measurements, concomitant medication assessment, and adverse event assessment. If the visit results in premature termination, then all procedures outlined for maintenance phase Week 24 /Final visit should be performed.

[g] Full physical examination is performed at baseline; a brief physical examination is performed at all other visits.

[h] If menopause is suspected.

[i] See Section 6.6 for all protocol-required laboratory assessments.

[j] Gastrin and pepsinogen I and II results will not be reported to investigative sites or other blinded personnel until the study blind is broken.

[k] Only female subjects with childbearing potential.

[l] Subjects should be instructed to complete the electronic diary every morning upon waking (for nighttime symptoms) and every evening before bedtime (for daytime symptoms) on each day of the study.
[m] Visit to be performed if not healed at Week 2.
[n] Four gastric mucosal biopsies (1 each from the greater and lesser curvature of the body and 1 each from the greater and lesser curvature of the antrum) should be obtained at each time point a gastric biopsy is done.
[o] Subjects with confirmed endoscopic healing at Week 2 or Week 8 will be rerandomized to the maintenance phase.
[p] Subjects are to start dose administration from Day 1.
[q] Subjects are to visit the study site without taking the study drug at Week 2 and Week 8 visits. For subjects without confirmed endoscopic healing of erosive esophagitis at Week 2, the daily dose of the study drug is to be administered after completion of assessments scheduled on that day. Subjects may need to return to the site a few days after Week 2 and Week 8 visits to receive a new allotment of study drug. No study procedures will be performed.
[r] Complete at least 7 days of diary during screening period
[s] only if EE not healed (follow Week 24 Final Visit/ET procedures)
Abbreviations: AE, adverse events; CYP2C19, cytochrome P450 2C19; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FSH, follicle- stimulating hormone; F/U, follow-up; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; Main, maintenance; PAGI-SYM, Patient Assessment of Gastrointestinal Disorders-Symptoms Severity Index; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; UBT, urea breath test

15.3. EE-301 Safety Assessments

Vitals signs included body temperature, resting seated blood pressure and pulse rate. When applicable, vital signs were to be measured within 30 minutes before or 30 minutes after any blood collection.

Physical examination

- Investigators were instructed to pay special attention to clinical signs related to previous serious illness. Height and weight were measured and recorded at baseline.
- A complete physical examination was performed at baseline including at minimum assessments of cardiovascular, respiratory, gastrointestinal, and neurologic systems.
- A brief physical examination was performed at all other visits including at minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver, spleen).

Endoscopic findings

- For safety evaluation, 4 biopsies (1 each from the greater and lesser curvature of the body, and 1 each from the greater and lesser curvature of the antrum) were taken during the baseline endoscopy of the healing phase, as well as the Week 24/final visit of the maintenance phase for all subjects. In addition, gastric biopsies were to be done on any subject who prematurely terminated from the study at any time, including those subjects whose EE was not healed at the Week 8 healing phase endoscopy.

  Biopsies were processed and analyzed at the central pathology laboratory. All biopsies were evaluated for the presence of active and chronic inflammation, atrophy, intestinal metaplasia, changes in endocrine cell density, and enterochromaffin-like (ECL) cell hyperplasia.

Electrocardiogram (ECG)

- A standard 12-lead ECG was recorded. The investigator (or a qualified interpreter) interpreted the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.
- Heart rate (HR), RR interval, PR interval, QT interval and QRS interval were recorded on the eCRF.
- Electrocardiograms were obtained at baseline and at the end of treatment; thus, only subjects who either discontinued during the healing phase or whose EE was not healed at the end of the healing phase had electrocardiograms performed post-baseline in the healing phase.
- Abnormal QTcF values were defined as electrocardiogram values that met at least 1 of the criteria listed below.
  - Absolute QTcF interval prolongation
    - QTcF interval >450 msec
    - QTcF interval >480 msec
    - QTcF interval >500 msec

  - Change from baseline in QTcF interval
    - QTcF interval increased from baseline >30 msec
    - QTcF interval increased from baseline >60 msec
  - QTcF interval >450 msec and increased from baseline >30 msec

Laboratory assessments

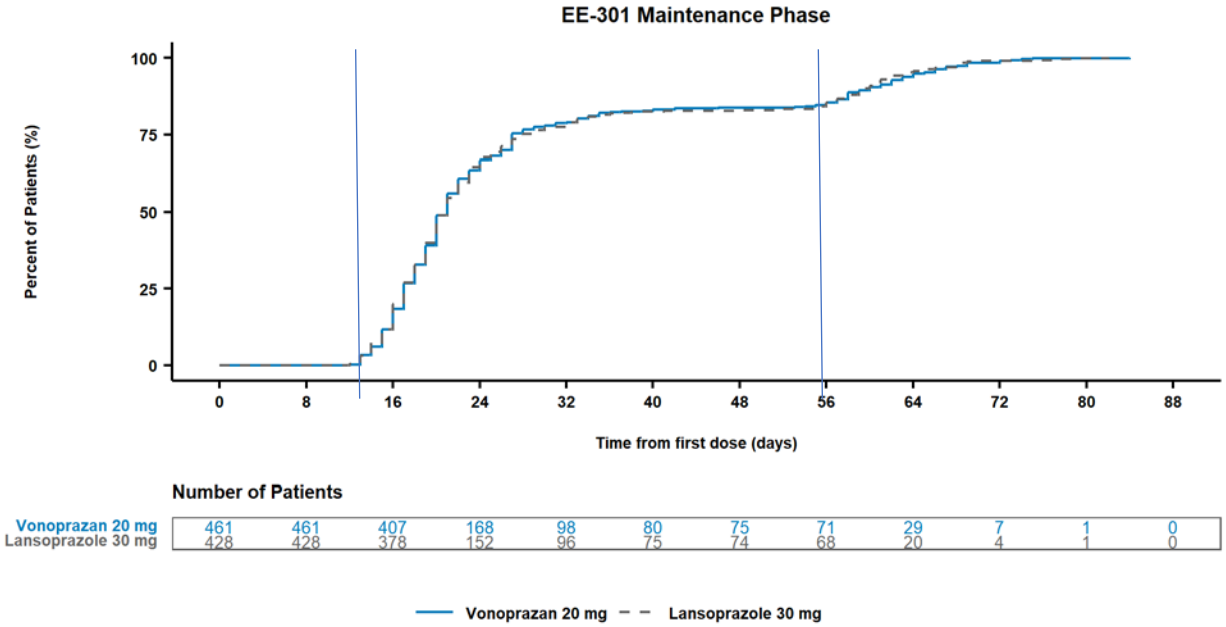
- Hematology: platelet count, red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), percent reticulocytes, white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
- Chemistry:
  - Clinical including blood urea nitrogen (BUN), creatinine, total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein (TP), potassium (K), sodium (Na), calcium (Ca), fasting glucose, and gamma-glutamyltransferase (GGT).
  - Serum gastrin and pepsinogen I and II levels were also evaluated as exploratory safety/pharmacodynamic biomarkers and were not reported to investigators until the study blind was broken
- Urinalysis: specific gravity, appearance, color, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein was abnormal).

16. Efficacy: Additional Information and Assessment

16.1. Study EE-301 Supplemental Efficacy Analyses

Figure 16 shows the number of subjects who had endoscopically confirmed healing of EE and entered the maintenance phase, over the time from first dosing in the healing phase of Study EE-301.

Figure 16. Time to Entry of Maintenance Phase, Safety Population, Study EE-301



Source: adsl.xpt, adae.xpt, adlb.xpt, advs.xpt, sv.xpt, and ds.xpt; Software: R
Time to entry of maintenance phase defined as the duration of time from first dose of healing phase to first dose of maintenance phase for each patient.
The study healing phase duration is up to 8 weeks. Patients with endoscopic healing at week 2 left the study healing phase and were re-randomized into the study maintenance phase (and were not further included in the study healing phase).

16.2. Study EE-301 Sensitivity Analysis

Table 95 displays the results for the pre-specified missing data sensitivity analyses as well as the per-protocol analysis on the primary efficacy endpoint in the healing phase. All sensitivity analyses show similar results and conclusions to the primary analysis, which had indicated that Voquezna 20 mg was noninferior to lansoprazole 30 mg for healing of EE.

Table 95. Sensitivity Analysis: Healing of EE at Week 2 or Week 8, Study EE-301, Healing Phase

Secondary Endpoint Parameter	Voquezna 20 mg (N=514)	Lansoprazole 30 mg (N=510)
Observed data at Week 2 or Week 8 (MITT)		
n (%)	(N=500) 468 (93.6)	(N=496) 427 (86.3)
Treatment difference, % (CI[1])	7.3 (3.65, 11.16)	
P-value of noninferiority[2]	<0.0001	
Multiple imputation method 1[3] (MITT)		
n (%)[4]	492 (95.7)	452 (88.6)
Treatment difference, % (CI[1])	7.1 (3.88, 10.50)	
P-value of noninferiority[2]	<0.0001	
Multiple imputation method 2[5] (MITT)		
n (%)[4]	480 (93.3)	433 (84.9)
Treatment difference, % (CI[1])	8.4 (4.62, 12.26)	
P-value of noninferiority[2]	<0.0001	

Secondary Endpoint Parameter	Voquezna 20 mg (N=514)	Lansoprazole 30 mg (N=510)
Multiple imputation method 3[6] (MITT)		
n (%)[4]	494 (96.1)	452 (88.7)
Treatment difference, % (CI[1])	7.4 (4.24, 10.78)	
P-value of noninferiority[2]	<0.0001	
NRI after use of prohibited medications		
n (%)[4]	476 (92.7)	431 (84.6)
Treatment difference, % (CI[1])	8.1 (4.27, 12.05)	
P-value of noninferiority[2]	<0.0001	
Per Protocol Set		
n (%)	(N=488) 462 (94.7)	(N=474) 410 (86.6)
Treatment difference, % (CI[1])	8.1 (4.53, 11.93)	
P-value of noninferiority[2]	<0.0001	

Source: Adapted from Clinical Study Report, Table M11.n, p176, verified by the review team.
[1] The 2-sided 95% CI of the difference in maintenance rates between Voquezna 20 mg group and lansoprazole 30 mg group was calculated via the Miettinen and Nurminen method.
[2] Noninferiority of Voquezna 20 mg group to lansoprazole 30 mg group p-value based on a Farrington and Manning test with a noninferiority margin of 10%.
[3] Multiple imputation was performed for subjects without post-baseline endoscopy under missing at random assumption. The MCMC method was first used to produce a monotone missing data pattern, and then a subsequent imputation using logistic regression with treatment effect and LA Classification grade at screening as predictor variables was used for imputation of remaining missing data at Week 2 and Week 8. The estimates from multiple imputation were pooled using Rubin's Method.
[4] n represents the average number of subjects who had complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated EE healing rate based on multiple imputation model.
[5] Multiple imputations were performed as described above in (3). After imputations, subjects who had EE not healed, had treatment compliance <80% or >120%, or had any PPI or H2RA use were considered as EE not healed. The estimates from multiple imputation were pooled using Rubin's Method.
[6] Post-baseline endoscopy assessments for subjects who had treatment compliance <80% or >120%, or at time point after any PPI or H2RA use were excluded. After excluding such data, multiple imputation was performed as described above in (3). The estimates from multiple imputation were pooled using Rubin's Method.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; NRI, non-responder imputation.

Sensitivity analyses for the primary endpoint in the maintenance phase are displayed in Table 96. All sensitivity analyses indicated that Voquezna 10 mg and 20 mg were noninferior to lansoprazole 15 mg for maintenance of healed EE (all grades) through Week 24.

Table 96. Sensitivity Analysis: Maintenance of Healed EE (All Grades) Through Week 24, Study EE-301, Maintenance Phase

Secondary Endpoint Parameter	Voquezna 10 mg (N=293)	Voquezna 20 mg (N=291)	Lansoprazole 15 mg (N=294)
Observed data at Week 24 (MITT)			
n (%)	(N=265) 232 (87.5)	(N=257) 232 (90.3)	(N=262) 209 (79.8)
Treatment difference, % (CI[1])	7.8 (1.48, 14.15)	10.5 (4.43, 16.69)	
P-value of noninferiority[2]	<0.0001	<0.0001	
Multiple imputation method 1[3] (MITT)			
n (%)[4]	256 (87.5)	263 (90.4)	234 (79.6)
Treatment difference, % (CI[1])	8.0 (1.98, 14.15)	10.9 (5.17, 16.69)	
P-value of noninferiority[2]	<0.0001	<0.0001	
Multiple imputation method 2[5] (MITT)			
n (%)[4]	255 (86.9)	252 (86.7)	223 (76.0)
Treatment difference, % (CI[1])	10.9 (4.63, 17.15)	10.7 (4.44, 17.00)	
P-value of noninferiority[2]	<0.0001	<0.0001	

Secondary Endpoint Parameter	Voquezna 10 mg (N=293)	Voquezna 20 mg (N=291)	Lansoprazole 15 mg (N=294)
Multiple imputation method 3[6] (MITT)			
n (%)[4]	259 (88.5)	265 (90.9)	234 (79.7)
Treatment difference, % (CI[1])	8.7 (2.83, 14.67)	11.2 (5.53, 16.95)	
P-value of noninferiority[2]	<0.0001	<0.0001	
NRI after use of prohibited medications			
n (%)[4]	231 (78.8)	230 (79.0)	211 (71.7)
Treatment difference, % (CI[1])	7.2 (0.17, 14.12)	7.3 (0.31, 14.26)	
P-value of noninferiority[2]	<0.0001	<0.0001	
Per Protocol Set			
n (%)	(N=259) 231 (89.2)	(N=246) 223 (90.7)	(N=251) 200 (79.7)
Treatment difference, % (CI[1])	9.5 (3.26, 15.89)	11.0 (4.80, 17.27)	
P-value of noninferiority[2]	<0.0001	<0.0001	

Source: Adapted from Clinical Study Report, Table M11.n, p176, verified by the review team.
[1] The 2-sided 95% CI of the difference in maintenance rates between each Voquezna group and lansoprazole 15 mg group was calculated via the Miettinen and Nurminen method.
[2] Noninferiority of each Voquezna group to lansoprazole 15 mg group p-value based on a Farrington and Manning test with a noninferiority margin of 10%.
[3]Multiple imputation was performed for subjects without post-baseline endoscopy under missing at random assumption. The MCMC method was first used to produce a monotone missing data pattern, and then a subsequent imputation using logistic regression with treatment effect and LA Classification grade at screening as predictor variables was used for imputation of remaining missing data at Week 24. The estimates from multiple imputation were pooled using Rubin's Method.
[4] n represents the average number of subjects who maintained complete healing of EE based on multiple imputation model rounded to the nearest integer; % represents the estimated maintenance of EE healing rate based on multiple imputation model.
[5] Multiple imputations were performed as described above in (3). After imputations, subjects who did not maintain healing up through Week 24, had treatment compliance <80% or >120%, or had any PPI or H2RA use were considered as EE recurred. The estimates from multiple imputation were pooled using Rubin's Method.
[6] Post-baseline endoscopy assessments for subjects who had treatment compliance <80% or >120%, or at time point after any PPI or H2RA use were excluded. After excluding such data, multiple imputation was performed as described above in (3). The estimates from multiple imputation were pooled using Rubin's Method.
Abbreviations: CI, confidence interval; EE, erosive esophagitis; MITT, modified intent-to-treat; N, number of patients in treatment arm; NRI, non-responder imputation.

17. Clinical Safety: Additional Information and Assessment

17.1. Grouped Adverse Event Terms for Safety Analyses

For the safety analyses the review team grouped related AE preferred terms as shown in Table 97:

Table 97. Summary of Grouped Terms Used in Safety Analysis

Group Term	Preferred Terms Included
Abdominal pain	abdominal discomfort, abdominal pain, lower abdominal pain, upper abdominal pain
Anemia	anemia, hematocrit decreased, hemoglobin decreased, blood iron decreased, iron-deficiency anemia
COVID-19	COVID-19, coronavirus infection, COVID,
Diarrhea	diarrhea, frequent bowel movement
Edema	Peripheral edema, fluid retention
Gastritis	gastritis, chronic gastritis, erosive gastritis, gastric erythema, acute gastritis
Hepatic enzyme increased	hepatic enzyme increased, alanine aminotransferase increased, hepatic steatosis, aspartate aminotransferase increased, gamma-glutamyl transferase increased, transaminases increased, hypertransaminasemia, transaminitis
Hepatic steatosis	hepatic steatosis, non-alcoholic steatosis, non-alcoholic steatohepatitis, steatosis
Leukocytosis	leukocytosis, white blood cells increased, polymorphonuclear leukocytes increased
Leukopenia	leukopenia, white blood cells decreased
Liver injury	liver injury, drug-induced liver injury, liver disorder
Lymphocytopenia	lymphocytopenia, lymphopenia,
Lymphocytosis	lymphocytosis, lymphocytes increased
Musculoskeletal pain	arthralgia, extremity pain, musculoskeletal pain, myalgia
Neutropenia	neutropenia, decreased polymorphonuclear leukocytes (PMNs)
Thrombocytopenia	thrombocytopenia, platelets decreased
Thrombocytosis	thrombocytosis, platelets increased

Source: Reviewer-generated

17.2. Study EE-301 Safety Analysis by Demographic Subgroup

In Study EE-301 the predominant demographic subgroups in the study included White race, non-Hispanic or Latino ethnicity and age less than 65. Overall, in both the healing and maintenance phases, no clinically meaningful trends were observed between Voquezna treatment arm(s) and lansoprazole when safety was assessed by demographic subgroups of race, ethnicity, sex and age.

The demographic comparisons described below for the maintenance phase of Study EE-301 are for the recommended dosage of Voquezna (10 mg once daily) compared to lansoprazole. The data for the higher Voquezna 20 mg dosage group are included only for descriptive purposes.

In the study, there were two deaths that occurred in the Voquezna 20 mg group during the maintenance phase. Both were attributed to COVID-19. The deaths occurred in male subjects less than 65 years of age (one White and one Asian subject: both non-Hispanic or Latino). Due to the few numbers of cases, deaths are not included in the tables below of demographic subgroups for the maintenance phase.

17.2.1. Race

In Study EE-301, the proportion of subjects who self-identified as races other than White was small compared to those that self-identified as White. Because there were a limited number of subjects in each of the non-white race categories (i.e., Black or African-American, Asian, American Indian/Alaskan Native, Native Hawaiian or Pacific Islander)) the analysis included two groups, White and All Other. As shown in Table 98, a treatment difference between Voquezna and lansoprazole in the All Other races category for AEs leading to discontinuation in the healing phase was observed, but not for other types of AEs, and the difference was not observed in the maintenance phase (see Table 99). A treatment difference between Voquezna and lansoprazole in All Other races category for subjects with at least one TEAE was observed in the maintenance phase, with a smaller treatment difference in the White race category. However, the small sample size in the All Other races demographic subgroup limits the ability to make meaningful comparisons. No clinically meaningful trends were identified in AEs between those who self-identified as White and all other races treated with Voquezna compared to respective race-matched lansoprazole cohorts.

Table 98. Summary of TEAEs by Race, Study EE-301, Healing Phase

	White			All Others[1]		
Race Parameter	V20 mg N=474 n (%)	L30 mg N= 455 n (%)	Treatment Difference[2]	V20 mg N=40 n (%)	L30 mg N=55 n (%)	Treatment Difference[2]
Subjects with at least one TEAE	136 (29)	125 (28)	+1 %	14 (35)	21 (38)	-3 %
SAEs (non-fatal)[3]	5 (1)	1 (2)	-1 %	0	2 (4)	-4 %
AEs leading to discontinuation	5 (1)	11 (2)	-1 %	11 (28)	3 (5)	+23 %

Source: Reviewer-generated; adsl.xpt, adae.xpt; software JMP Clinical
[1] Includes categories Black or African-American, Asian, American Indian/Alaskan Native, Native Hawaiian or Pacific Islander
[2] Treatment difference = Voquezna (%) - lansoprazole (%)
[3] There were no fatal events in the healing phase
Abbreviations: AE, adverse event; L, lansoprazole; N, number of subjects in treatment group; n, number reported; SAE, serious adverse event; TEAE, treatment-emergent adverse event; V, Voquezna

Table 99. Summary of TEAEs by Race[1], Study EE-301, Maintenance Phase

Race Parameter	White V10 mg N=270 n (%)	White V20 mg N=273 n (%)	White L15 mg N=268 n (%)	White Treatment Difference[3]	All Others[2] V10 mg N=26 n (%)	All Others[2] V20 mg N=23 n (%)	All Others[2] L15 mg N=29 n (%)	All Others[2] Treatment Difference[3]
Subjects with at least one TEAE	147 (54)	154 (56)	140 (52)	+2%	12 (46)	11 (48)	11 (38)	+8%
SAEs (non-fatal)	10 (4)	11 (4)	8 (4)	0	1 (4)	0	0	+4%
AEs leading to discontinuation	2 (1)	10 (4)	2 (1)	0	0	0	0	0

Source: Reviewer-generated; adsl.xpt, adae.xpt; Software JMP Clinical
[1] Table excludes subjects without race reported (1 subject, L15) or unknown (2 subjects, V10)
[2] Includes categories Black or African-American, Asian, American Indian/Alaskan Native, Native Hawaiian or Pacific Islander
[3] Treatment difference = Voquezna 10 mg (%) minus lansoprazole 15 mg (%)
Abbreviations: AE, adverse event; L, lansoprazole; N, number of subjects in group; n, number of subjects in event group; SAE, serious adverse event; TEAE, treatment-emergent adverse event; V, Voquezna

17.2.2. Ethnicity

In Study EE-301, the proportion of subjects who self-identified as Hispanic or Latino ethnicity was small compared to those that self-identified as non-Hispanic or Latino. As shown in Table 100, subjects with at least one TEAE showed a treatment difference of 15% for Voquezna compared to lansoprazole in Hispanic or Latino subjects in the healing phase, but not in the maintenance phase for Voquezna 10 mg (Table 101). However, the treatment difference was still present in the healing phase for Voquezna 20 mg compared to lansoprazole (13%) in the Hispanic or Latino subgroup. Similarly, SAEs showed a treatment difference between Voquezna and lansoprazole for Hispanic or Latino subjects compared to non-Hispanic or Latino subjects in both phases for the 20 mg Voquezna dose. The same trend was not observed for non-Hispanic or Latino subjects. The sample size in the Hispanic or Latino ethnic subgroup limits any meaningful conclusions about these trends. No clinically meaningful trends were identified in other types of AEs between those who self-identified as Hispanic or Latino and non-Hispanic or Latino treated with Voquezna compared to respective race-matched lansoprazole cohorts.

Table 100. Summary of TEAEs by Ethnicity[1], EE-301, Healing Phase

Ethnicity Parameter	Hispanic or Latino V 20 mg N=62 n (%)	Hispanic or Latino L 30 mg N= 58 n (%)	Hispanic or Latino Treatment Difference[2]	Non-Hispanic or Latino V 20 mg N=450 n (%)	Non-Hispanic or Latino L 30 mg N=449 n (%)	Non-Hispanic or Latino Treatment Difference[2]
Subjects with at least one TEAE	17 (27)	7 (12)	+15%	131 (29)	139 (31)	-2%
SAEs (non-fatal)[3]	4 (6)	0	+6%	1 (<1)	3 (1)	0
AEs leading to discontinuation	0	0	0	5 (1)	14 (3)	-2%

Source: reviewer-generated; adsl.xpt, adae.xpt; software JMP Clinical
[1]Table excludes subjects without ethnicity reported
[2] Treatment difference = Voquezna (%) - lansoprazole (%)
[3] There were no fatal events in the healing phase
Abbreviations: AE, adverse event; L, lansoprazole; N, number of subjects in treatment group; n, number reported; SAE, serious adverse event; TEAE, treatment-emergent adverse event: V, Voquezna

Table 101. Summary of TEAEs by Ethnicity[1], Study EE-301, Maintenance Phase

	Hispanic or Latino				Non-Hispanic or Latino			
Ethnicity Parameter	V 10 mg N=31 n (%)	V 20 mg N=34 n (%)	L 15 mg N=32 n (%)	Treatment Difference[2]	Vono 10 mg N=264 n (%)	Vono 20 mg N=261 n (%)	Lanso 15 mg N=263 n (%)	Treatment Difference[2]
Subjects with at least one TEAE	10 (32)	16 (47)	11 (34)	-2%	150 (57)	149 (57)	139 (53)	+4%
SAEs (non-fatal)	1 (3)	5 (15)	1 (3)	0	10 (4)	8 (3)	7 [4] (3)	+1%
AEs leading to discontinuation	0	0	1 (3)	0	1 (<1)	8 [3] (3)	2 (1)	0

Source: Reviewer-generated; adsl.xpt; Software JMP Clinical
[1]Table excludes subjects without ethnicity reported (V10, 1 subject; V20, 1 subject; L15, 2 subjects)
[2] Treatment difference = Voquezna 10 mg (%) minus lansoprazole 15 mg (%)
[3] Subjects (b) (6) each reported two AEs leading to discontinuation
[4] Subject (b) (6) reported two events
Abbreviations: AE, adverse event; L, lansoprazole; N, number of subjects in group; n, number of subjects in event group; SAE, serious adverse event; TEAE, treatment-emergent adverse event; V, Voquezna

17.2.3. Sex

As shown in Table 102 and Table 103, the proportion of male and female subjects was equally balanced in the study. SAEs were reported only in female subjects during the healing phase. However, the treatment difference between female Voquezna and lansoprazole cohorts for SAEs was +1%, which is not meaningfully greater than in male subjects. Overall, no clinically meaningful trends were identified in any type of AE between male and female subjects treated with Voquezna compared to respective sex-matched lansoprazole cohorts in the healing or maintenance phases.

Table 102. Summary of TEAEs by Sex, Study EE-301, Healing Phase

	Male			Female		
Sex Parameter	V20 mg N=258 n (%)	L30 mg N= 223 n (%)	Treatment Difference[1]	V20 mg N=256 n (%)	L30 mg N= 287 n (%)	Treatment Difference[1]
Subjects with at least one TEAE	71 (28)	61 (27)	+1%	78 (30)	85 (30)	0
SAEs (non-fatal)[2]	0	0	0	5 (2)	3 (1)	+1%
AEs leading to discontinuation	4 (2)	7 (3)	-1%	1 (<1)	7 (2)	-2%

Source: reviewer-generated; adsl.xpt, adae.xpt; software JMP Clinical
[1] Treatment difference = Voquezna (%) - lansoprazole (%)
[2] There were no fatal events in the healing phase
Abbreviations: AE, adverse event; L, lansoprazole; N, number of subjects in treatment group; n, number reported; SAE, serious adverse event; TEAE, treatment-emergent adverse event: V, Voquezna.

Table 103. Summary of TEAEs by Sex, Study EE-301, Maintenance Phase

Sex	Male				Female			
Parameter	V10 mg N=137 n (%)	V20 mg N=147 n (%)	L15 mg N=123 n (%)	Treatment Difference [1]	V10 mg N=159 n (%)	V20 mg N=149 n (%)	L15 mg N=174 n (%)	Treatment Difference [1]
Subjects with at least one TEAE	72 (52)	87 (59)	60 (49)	+3%	89 (56)	78 (52)	92 (53)	+3%
SAEs (non-fatal)	7 (5)[A]	11 (8)[B]	2 (2)	+3%	4 (2)	2 (1)	6 (3)[C]	-1%
AEs leading to discontinuation	2 (2)	5 (3)[D]	1 (1)	+1%	5 (3)[E]	3 (2)[F]	2 (1)	+2%

Source: Reviewer-generated; adsl.xpt; Software JMP Clinical
[1] Treatment difference = Voquezna 10 mg (%) minus lansoprazole 15 mg (%)
[A] 6 subjects; Subject (b) (6) reported two SAEs (intervertebral disc protrusion, melena)
[B] 12 subjects; Subject (b) (6) reported 2 SAEs (anemia, small intestine adenocarcinoma), Subject (b) (6) reported 2 SAEs (pancreatitis, pancreatolithiasis)
[C] 5 subjects; (b) (6) reported 2 SAEs (adenocarcinoma, ileus)
[D] 4 subjects; (b) (6) reported 2 AEs (depressed mood, rash macular)
[E] 4 subjects; subject (b) (6) reported 2 AEs (abdominal pain upper, abdominal distention)
[F] 2 subjects; subject (b) (6) reported 2 AEs (vomiting, dizziness)
Abbreviations: AE, adverse event; Lanso, lansoprazole; N, number of subjects in group; n, number of subjects in event group; SAE, serious adverse event; TEAE, treatment-emergent adverse event; Vono, Voquezna

17.2.4. Age

In Study EE-301, most subjects were < 65 years of age. Only a small number of subjects were 75 years of age and older. Ten subjects in the Voquezna group and sixteen subjects in the lansoprazole group were age 75 or older with four TEAEs and five TEAEs, respectively, and no SAEs reported. No AEs leading to discontinuation were reported in Voquezna subjects aged 75 years or older.

In the healing phase, as shown in Table 104, no clinically meaningful trends were identified in any type of AE between subjects < 65 years of age and 65 years of age and older treated with Voquezna compared to respective age-matched lansoprazole cohorts.

In the maintenance phase (Table 105), a treatment difference of 19% was observed between Voquezna 10 mg and lansoprazole subjects 65 years of age and older, with a smaller treatment difference (5%) in subjects less than 65 years of age for subjects experiencing at least one TEAE. However, TEAEs occurred in fewer subjects 65 years of age or older in the Voquezna 20 mg arm compared to the Voquezna 10 mg arm, but the small sample size of the older age subgroup may be contributing to the variability in the treatment difference across groups. No other trends in AEs were identified between subjects < 65 years of age and 65 years of age and older treated with Voquezna compared to respective age-matched lansoprazole cohorts in the maintenance phase.

Table 104. Summary of TEAEs by Age Group, EE-301, Healing Phase

Age Group Parameter	< 65 years V 20 mg N=421 n (%)	< 65 years L30 mg N= 403 n (%)	< 65 years Treatment Difference[1]	≥65 years1 V 20 mg N=93 n (%)	≥65 years1 L 30 mg N= 107 n (%)	≥65 years1 Treatment Difference[2]
Subjects with at least one TEAE	118 (28)	105 (26)	+2%	32 (34)	40 (37)	-3%
SAEs (non-fatal)[3]	5 (1)	1 (<1)	+1%	0	2 (2)	-2%
AEs leading to discontinuation	5 (1)	11 (3)	-2%	0	2 (2)	-2%

Source: reviewer-generated; adsl.xpt, adae.xpt; software JMP Clinical
[1] Subjects over 75 years were included in tabulation
[2] Treatment difference = Voquezna (%) - lansoprazole (%)
[3] There were no fatal events in the healing phase
Abbreviations: AE, adverse event; L, lansoprazole; N, number of subjects in treatment group; n, number reported; SAE, serious adverse event; TEAE, treatment-emergent adverse event: V, Voquezna

Table 105. Summary of TEAEs by Age Group, Study EE-301, Maintenance Phase

Age Group Parameter	< 65 years Vono 10 mg N=234 n (%)	< 65 years Vono 20 mg N=232 n (%)	< 65 years Lanso 15 mg N=249 n (%)	< 65 years Treatment Difference[1]	≥65 years[1] Vono 10 mg N=62 n (%)	≥65 years[1] Vono 20 mg N=64 n (%)	≥65 years[1] Lanso 15 mg N= 58 n (%)	≥65 years[1] Treatment Difference[2]
Subjects with at least one TEAE	121 (52)	128 (55)	126 (50)	+5%	40 (64)	37(58)	26 (45)	+19%
SAEs (non-fatal)	6 (3)	9 (4)	6 (2)	+1%	5 (8)	4 (6)	2 (3)	+5%
AEs leading to discontinuation	1 (<1)	6 (3)	2 (1)	-1%	3 (5)	2 (3)	0	+5%

Source: Reviewer-generated; adsl.xpt; Software JMP Clinical
[1] Tabulation includes subjects >75 years of age.
[2]Treatment difference = Voquezna 10 mg (%) minus lansoprazole 15 mg (%)
Abbreviations: AE, adverse event; Lanso, lansoprazole; N, number of subjects in group; n, number of subjects in event group; SAE, serious adverse event; TEAE, treatment-emergent adverse event; Vono, Voquezna

17.3. Study EE-301 Supplemental Safety Data and Analyses

This section includes supplementary data to support the analyses presented in Sections 7.6.1 and 7.6.2 of the review, including adverse events and laboratory assessments.

Laboratory assessments were conducted in Study EE-301 according to the schedule of assessments. See Section 15.2. Changes in serum gastrin, hepatic enzymes and hematologic indices are discussed in Section 7 of the review. Data are not shown for serum sodium, potassium, calcium, blood urea nitrogen and creatinine which remained generally stable during the trial with no clinically meaningful abnormalities identified. There was no pattern that suggested a difference between Voquezna and lansoprazole with respect to these laboratory assessments.

17.3.1. Study EE-301

Healing Phase

TEAEs reported in 1% or less of subjects in the healing phase of Study EE-301 are shown in Table 106. Referenced from Section 7.6.1.5.

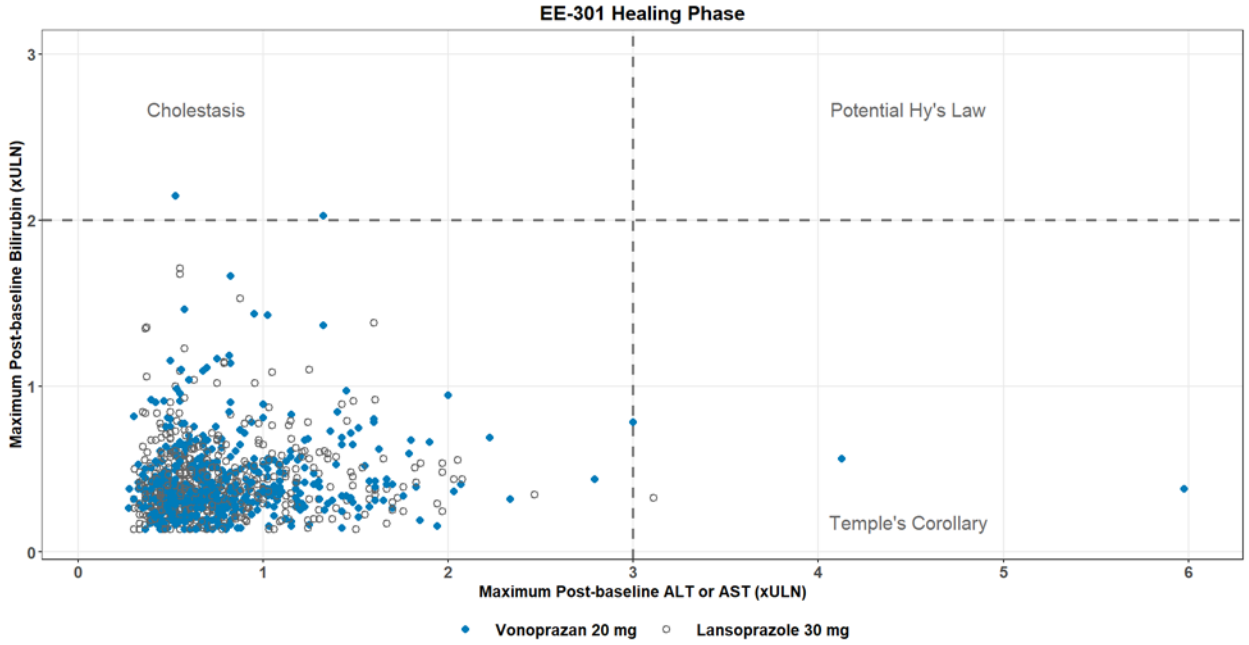
Table 106. Treatment-Emergent Adverse Events Reported in ≤1% of Subjects[1] in Either Treatment Arm, Study-EE-301, Healing Phase

Dictionary-Derived Term	Voquezna 20 mg N=514 n (%)	Lansoprazole 30 mg N=510 n (%)
Constipation	6 (1.2)	1 (0.2)
Hepatic enzyme increased [2]	5 (1.0)	3 (0.6)
Hiatus hernia	5 (1.0)	3 (0.6)
Flatulence	5 (1.0)	2 (0.4)
Cough	4 (0.8)	0
Irritable bowel syndrome	4 (0.8)	0
Nasopharyngitis	3 (0.6)	3 (0.6)
Gastroesophageal sphincter insufficiency	3 (0.6)	3 (0.6)
Gastric ulcer	3 (0.6)	2 (0.4)
Eructation	3 (0.6)	0
Benign gastric neoplasm	3 (0.6)	0
Esophageal disorder	3 (0.6)	0
Gastric polyps	2 (0.4)	5 (1.0)
Upper respiratory tract infection	2 (0.4)	2 (0.4)
Bronchitis	2 (0.4)	2 (0.4)
Dizziness	2 (0.4)	2 (0.4)
Vomiting	2 (0.4)	1 (0.2)
Dry mouth	2 (0.4)	1 (0.2)
Fatigue	2 (0.4)	1 (0.2)
Viral infection	2 (0.4)	1 (0.2)
Decreased appetite	2 (0.4)	1 (0.2)
Arthralgia	2 (0.4)	0
Insomnia	2 (0.4)	0
Ligament sprain	2 (0.4)	0
Diabetes mellitus	2 (0.4)	0
Tonsillitis	2 (0.4)	0
Muscle spasms	2 (0.4)	0

Source: Reviewer-generated; adae.xpt; software: JMP Clinical
[1] 1% or fewer after rounding.
[2] Includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, transaminases increased, hepatic enzyme increased
Table was truncated to include TEAEs occurring in at least two Voquezna subjects

Supporting data for DILI analysis in the healing phase of Study EE-301 is shown in Figure 17, referenced from Section 7.6.1.6.

Figure 17. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study EE-301- Healing Phase



Source: adlb.xpt; Software: R
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All patients with at least one post-baseline ALT or AST and bilirubin are plotted.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

17.3.1.1. Maintenance Phase

TEAEs reported in 2% or less of subjects in the maintenance phase of Study EE-301 are shown in Table 107. Reference from Section 7.6.2.5.

Table 107. Treatment-Emergent Adverse Events Occurring in ≤2% of Subjects in Any Treatment Arm[1], Safety Population, Study EE-301-Maintenance Phase

Dictionary-Derived Term	Vonoprazan 10 mg N=296 n (%)	Vonoprazan 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Pain in extremity	6 (2.0)	2 (0.7)	2 (0.7)
Vomiting	4 (1.4)	3 (1.0)	3 (1.0)
Musculoskeletal pain	4 (1.4)	3 (1.0)	2 (0.7)
Depression*	4 (1.4)	2 (0.7)	6 (2.0)
Nasopharyngitis	4 (1.4)	1 (0.3)	3 (1.0)
Gastric polyps	4 (1.4)	1 (0.3)	1 (0.3)
Upper respiratory tract infection	3 (1.0)	5 (1.7)	3 (1.0)
Osteoarthritis	3 (1.0)	4 (1.4)	2 (0.7)
Dizziness	3 (1.0)	3 (1.0)	3 (1.0)
Tooth abscess	3 (1.0)	2 (0.7)	3 (1.0)
Pharyngitis streptococcal	3 (1.0)	1 (0.3)	0
Renal colic / renal pain	3 (1.0)	0	0
Anxiety	2 (0.7)	3 (1.0)	3 (1.0)

Dictionary-Derived Term	Vonoprazan 10 mg N=296 n (%)	Vonoprazan 20 mg N=296 n (%)	Lansoprazole 15 mg N=297 n (%)
Anemia	2 (0.7)	3 (1.0)	1 (0.3)
Abdominal distension	2 (0.7)	2 (0.7)	3 (1.0)
Procedural pain	2 (0.7)	2 (0.7)	2 (0.7)
Ligament sprain	2 (0.7)	2 (0.7)	1 (0.3)
Irritable bowel syndrome	2 (0.7)	2 (0.7)	0
Hyperlipidemia*	2 (0.7)	2 (0.7)	1 (0.3)
Diabetes mellitus*	2 (0.7)	1 (0.3)	2 (0.7)
Hypothyroidism	2 (0.7)	1 (0.3)	1 (0.3)
Hepatic steatosis	2 (0.7)	1 (0.3)	0
Vertigo	2 (0.7)	1 (0.3)	0
Bursitis	2 (0.7)	1 (0.3)	0
Influenza like illness / Influenza	2 (0.7)	1 (0.3)	0
Constipation	2 (0.7)	0	5 (1.7)
Sciatica	2 (0.7)	0	2 (0.7)
Flatulence	2 (0.7)	0	1 (0.3)
Tonsillitis	2 (0.7)	0	1 (0.3)
Intervertebral disc protrusion	2 (0.7)	0	1 (0.3)
Ear infection	2 (0.7)	0	1 (0.3)
Migraine	2 (0.7)	0	1 (0.3)
Barrett's esophagus	2 (0.7)	0	0
Gastroesophageal sphincter insufficiency	2 (0.7)	0	0
Regurgitation	2 (0.7)	0	0
Aortic aneurysm	2 (0.7)	0	0
Dermatitis allergic	2 (0.7)	0	0
Paronychia	2 (0.7)	0	0
Rhinorrhea	2 (0.7)	0	0
Squamous cell carcinoma of skin	2 (0.7)	0	0

Source: Reviewer-generated; adae.xpt; software: JMP Clinical
[1] Table was truncated to include terms that were reported in two or more subjects in the Voquezna 10 mg group.
* MedDRA Dictionary-derived terms, includes grouped related terms. Refer to Section 17.1, Table 97.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects experiencing event

Supporting data for DILI analysis in the maintenance phase of Study EE-301 is shown in Table 108, referenced in Section 7.6.2.6.

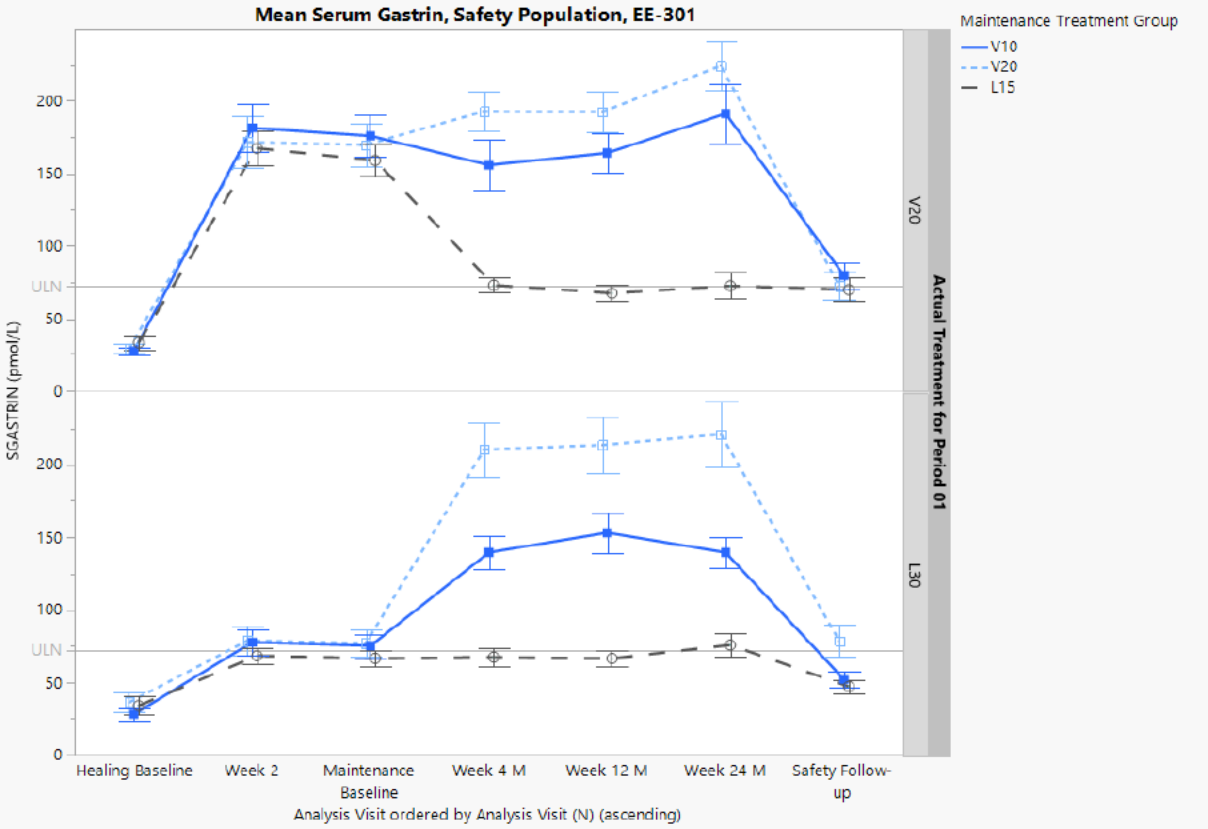
Table 108. Drug Induced Liver Injury Analysis, Individual Subject Listing, EE-301, Maintenance Phase

Patient ID	Treatment Arm		
Temple's Corollary Cases		**Maximum ALT/AST (xULN)**	**Maximum Bilirubin (xULN)**
(b) (6)	Voquezna 10 mg	4.98	0.68
[a]	Voquezna 10 mg	3.15	0.53
	Voquezna 20 mg	2.98	0.66
[a]	Voquezna 20 mg	3.76	0.51
[a]	Lansoprazole 15 mg	3.83	0.55
	Lansoprazole 15 mg	4.69	0.37
[a]	Lansoprazole 15 mg	5.12	0.51
[a]	Lansoprazole 15 mg	7.91	0.72
	Lansoprazole 15 mg	3.48	0.41
Cholestasis Cases		**Maximum ALP (xULN)**	**Maximum Bilirubin (xULN)**
(b) (6)	Voquezna 20 mg	0.83	2.74
	Lansoprazole 15 mg	0.66	2.34
	Lansoprazole 15 mg	0.52	2.27

Source: Reviewer-generated; adlb.xpt; Software: JMP Clinical
[a] Also included in TEAE tabulation.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; TB, total bilirubin; ULN, upper limit of normal

Figure 18 shows the mean serum gastrin level over both the healing and maintenance phases of Study EE-301 by treatment group in the healing phase, with plots for each maintenance phase treatment group. Referenced in Section 7.6.2.6.

Figure 18. Mean Serum Gastrin Level, EE-301



Source: Reviewer generated, adlb.sas.7, software: JMP Clinical
Abbreviations: L15, lansoprazole 15 mg daily; L30, lansoprazole 30 mg daily: M, maintenance; V10, Voquezna 10 mg daily; V20, Voquezna 20 mg daily

17.4. Determination of Less Common Adverse Reactions in Study EE-301 for Inclusion in Labeling (Section 6.1)

The following discussion focuses on TEAEs reported in 1% or less of patients treated with Voquezna 20 mg once daily in the healing phase or 10 mg once daily in the maintenance phase of Study EE-301. Additional discussion is provided for the subgroup of subjects who received the recommended dosage regimen (Voquezna 20 mg in healing followed by 10 mg in maintenance) and the labeled lansoprazole regimen (lansoprazole 30 mg in healing followed by 15 mg in maintenance). AEs were assessed by the reviewer for some basis of a causal relationship between vonoprazan and the event.

The Applicant submitted a list of the adverse reactions that were reported in Study EE-301 in subjects receiving the dose of Voquezna proposed for labeling (i.e., 20 mg for healing of EE; 10 mg for maintenance of healed EE) (b) (4)

(b) (4)

(b) (4)

(b) (4)

The following events were determined to be *less common adverse reactions* for inclusion in Section 6.1 of the Prescribing Information. The rationale for selection of these events is provided below. (b) (4)

A discussion of the rationale follows.

Blood and lymphatic system disorders: **anemia, lymphocytosis**

Cardiovascular disorders: **tachycardia**

Gastrointestinal disorders: duodenal polyp, dysphagia, eructation, flatulence, gastric polyps, vomiting, **dry mouth**

General disorders and administration site conditions: **asthenia, peripheral edema**

Infections: **Upper respiratory infection**

Investigations: increased liver function test

Metabolism and Nutrition Disorders: **diabetes mellitus**

Musculoskeletal system: bone fracture

Nervous system disorders: **dizziness,** syncope**, vertigo**

Psychiatric disorders: **depression, insomnia**

Renal and urinary disorders: tubulointerstitial nephritis

Skin and subcutaneous tissue disorders: eczema, rash, urticaria

Blood and Lymphatic System Disorders

(b) (4) one subject in the Voquezna 20 mg group in the healing phase reported a TEAE of low hemoglobin and one subject receiving both Voquezna 20 mg in the healing phase and 10 mg regimen of Voquezna in the maintenance phase reported a TEAE of anemia. Anemia was reported in four subjects who received the labeled dose of lansoprazole during the trial.

The review team notes that hematologic abnormalities have been reported with vonoprazan. Further, anemia may be seen associated with Vitamin B12 deficiency, which is a potential risk

with Voquezna. Finally, anemia is listed in the Prescribing Information less common adverse reactions list for the Voquezna Dual/Triple Pak.

Cardiac disorders

(b) (4)

. Although results of the thorough QT study did not demonstrate induction potential, an alteration in cardiac rhythm due to electrolyte variance due to Voquezna cannot be excluded. Three subjects who received the recommended regimen of Voquezna in the healing or maintenance phases experiencing tachycardia-related AEs, the review team concluded that "tachycardia" should be included in labeling to reflect this group of ARs.

Gastrointestinal Disorders

(b) (4)

the review team notes that xerostomia (i.e., dry mouth" may result from other causes, including direct effects (e.g., contact with astringents), systemic status (e.g., dehydration) and salivary hypofunction in disorders such as Sjogren's syndrome. Further, a role of active ionic transport in the oral mucosa has been proposed as a contributor to oral hydration. (Zhang and Castro 2015) The potential for Voquezna to interact with epithelial sodium-potassium pumps involved in mucosal ionic transport has not been investigated. Therefore, a lack of anticholinergic effect does not exclude the possibility that treatment with Voquezna may be related to dry mouth. Given that this AE was reported in four Voquezna subjects in the healing and/or maintenance phases (including one subject who received the recommended regimen in both healing and maintenance) and biologic plausibility, the review team recommends including xerostomia in labeling as "dry mouth".

Gastric polyps and the related TEAE of benign gastric neoplasm were reported in four subjects who received the recommended regimen of Voquezna, compared to three subjects who received the lansoprazole regimen. As previously discussed, gastric (fundic gland) polyps may occur in the setting of acid suppression as a response to increased gastrin levels. Duodenal polyps may occur through a similar mechanism in ectopic gastric mucosa. Duodenal polyp was reported at the follow-up visit in a subject who received Voquezna 10 mg during the maintenance phase. Given a likely biologic mechanism between vonoprazan treatment and gastric and duodenal polyps, these terms were included in the list of common ARs.

The remaining gastrointestinal terms (dysphagia, eructation, flatulence, and vomiting) were included because an association with Voquezna could reasonably considered due to temporal relationship. Dysphagia was reported in three subjects who received Voquezna during the maintenance phase of EE-301 (one in the Voquezna 10 mg group). Eructation was reported in two subjects who received the recommended Voquezna regimen versus none in subjects who received the labeled lansoprazole regimen. Flatulence was reported in three subjects in each treatment regimen group. Vomiting was reported in three subjects receiving the recommended Voquezna dosage regimen compared with two who received the labeled lansoprazole regimen.

General Disorders and Administration Site Conditions

(b) (4)
(b) (4), as a group, these terms were reported in seven subjects who received Voquezna in the trial (two in healing phase; four in the Voquezna 10 mg group in the maintenance phase) including three who received the recommended regimen in healing and maintenance. Two subjects receiving the labeled lansoprazole regimen reported this TEAE. Voquezna treatment cannot be excluded as contributing to the AE. Therefore, the review team recommended including "asthenia" in labeling.

(b) (4)
Given potential risk of renal and liver adverse effects from Voquezna discussed elsewhere (See AESIs) which may present with peripheral edema and five reported TEAEs of peripheral edema and peripheral swelling in Voquezna subjects, one in the healing phase and four in the maintenance phase (two in each Voquezna dose arm), including two subjects who received the recommended Voquezna regimen in both healing and maintenance, the review team recommended that "peripheral edema" be included in labeling.

Infections

TEAEs related to infections were generally not considered to be adverse reactions, given that events related to extra-gastrointestinal infection are unlikely to be related to Voquezna, which does not cause immunosuppression. No single infectious TEAE term was reported in more than a few subjects (except COVID-19) and background incidence of viral upper respiratory infections is high. However, multiple low-incidence TEAEs related to upper respiratory infections and symptoms were reported during EE-301 (e.g., nasopharyngitis, pharyngitis, tonsillitis, sinusitis). TEAEs related to upper respiratory tract infections were reported in twelve subjects who received the recommended Voquezna regimen in healing and maintenance compared to eleven subjects who received the labeled lansoprazole regimen. As a group, the incidence was high enough to justify inclusion in labeling.

Investigations

As noted above, the term of "increased liver function test" was included in the list because of the reports of increases in liver-related laboratory parameters and associated TEAEs in both the healing phase and maintenance phase.

Metabolic and Nutrition Disorders

(b) (4)
, five subjects treated with Voquezna in healing or maintenance experienced onset or worsening of diabetes or increased insulin levels, including two subjects receiving the recommended Voquezna regimen in both healing and maintenance. Therefore, the review team recommended including "diabetes mellitus" in the labeling.

Neurologic Disorders

(b) (4) Three Voquezna subjects in the trial experienced vertigo, including one subject receiving the recommended Voquezna regimen in healing and maintenance. Therefore, the review team recommended including the term in labeling.

(b) (4) TEAEs of dizziness were reported in four subjects who received the recommended regimen of Voquezna, compared to three who received the labeled lansoprazole regimen. Therefore, the review team recommended including dizziness in labeling.

Psychiatric Disorders

(b) (4), the reviewer noted that observations in animals may not reflect psychiatric and behavioral effects in humans. Further, the underlying cause of depressive symptoms are poorly understood. Five subjects in the trial who received the recommended Voquezna regimen in both healing and maintenance experienced either depression or depressed mood, compared to two who received the labeled lansoprazole regimen. Therefore, the review team recommended including "depression" in the labeling to address both terms.

(b) (4) observations in animals may not reflect psychiatric and behavioral effects in human and the etiology and pathophysiology of insomnia is poorly understood. Three subjects treated with Voquezna in the healing or maintenance phases in the trial experienced insomnia, including one who received the recommended Voquezna regimen in both healing and maintenance. Therefore, the review team recommended inclusion in labeling.

Renal Disorders

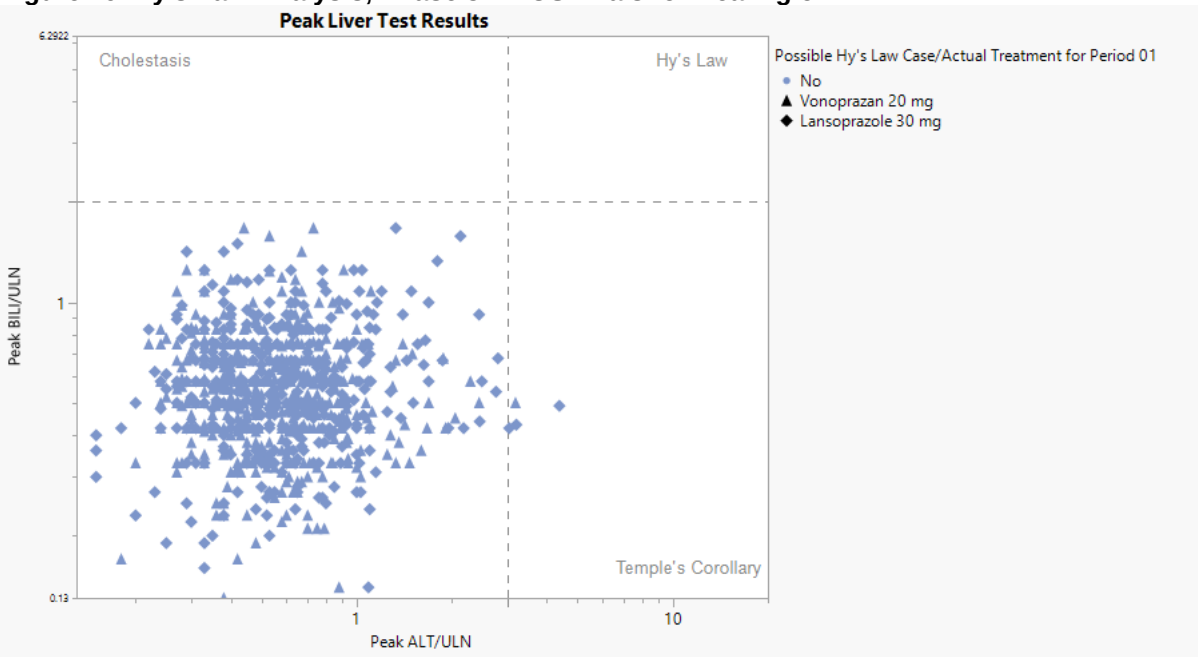
One case of acute tubulointerstitial nephritis (AIN) and one case of minimal change glomerulonephritis was reported during EE-301, both in the maintenance phase in subjects receiving Voquezna 20 mg. The narrative for Subject (b) (6), a 64-year-old male who discontinued due to tubulointerstitial nephritis was previously presented.

Although these cases were not reported in subjects who received the recommended Voquezna dosage in healing or maintenance, the term AIN was included in the less common listing of ARs in labeling because it represents an AESI and the risk may not be related to the dosage of vonoprazan.

17.5. Safety in Phase 3 Ex-U.S. Trials

Figure 19 shows the Hy's Law analysis of data from the ex-U.S. EE healing trials, referenced in Section 7.6.4.1. There were no Hy's law cases. One subject in the vonoprazan 20 mg group met criteria for Temple's Corollary.

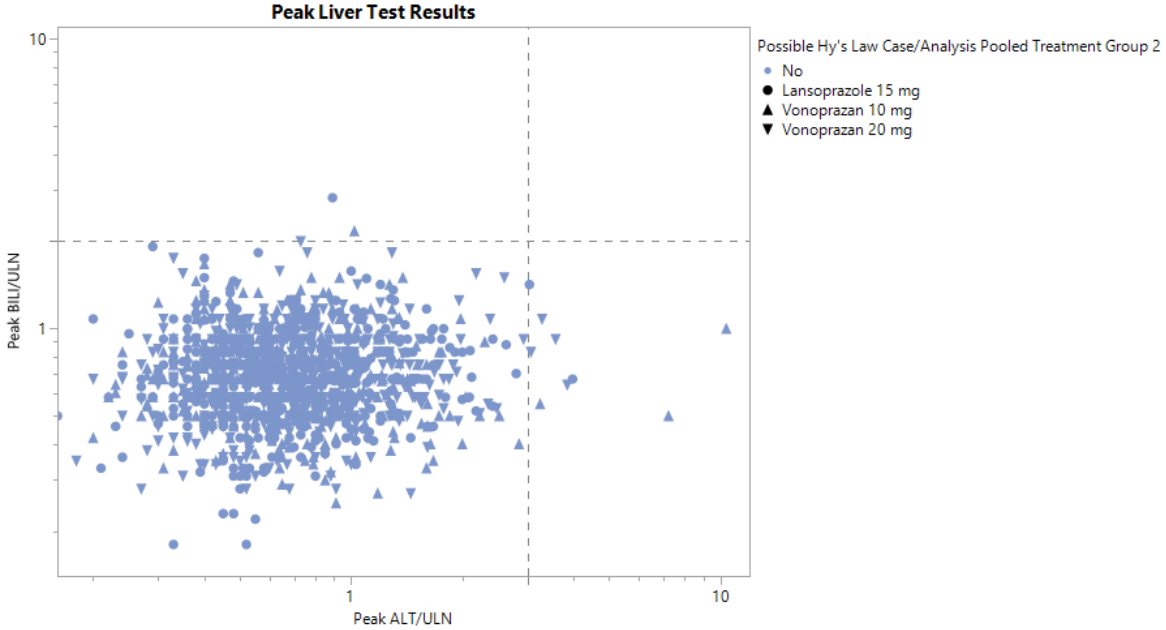
Figure 19. Hy's Law Analysis, Phase 3 Ex-US Trials for Healing of EE



Source: Reviewer-generated, ISS adlb.xpt, software: JMP clinical

Figure 20 shows the Hy's Law analysis of data from the phase 3 ex-U.S. EE maintenance trials. There was one Hy's law case in the vonoprazan 20 mg group. Nine subjects in the vonoprazan 20 mg group and one subject in the vonoprazan 10 mg group met criteria for Temple's Corollary.

Figure 20. Hy's Law Analysis, Phase 3 Ex-U.S. Trials for Maintenance of Healed EE



Source: Reviewer-generated, ISS adlb.xpt, software: JMP clinical

17.6. ISS All-Subjects Pool

For the analysis of AESIs, as described in Section 7.7, TEAEs were evaluated across all studies in the NDA. Table 109 provides a summary of the studies included in ISS Pool 3 (i.e., the "All-Subjects" pool), including the doses and subject sample size for each treatment group. There are twenty-one phase 2/3 studies in subjects treated with vonoprazan, PPI comparators (lansoprazole primarily, see footnote (a)), or placebo across multiple indications, including EE healing, maintenance of EE healing, symptomatic non-erosive gastroesophageal reflux disease (sGERD), gastric and duodenal ulcer healing, and prevention of ulcer recurrence during nonsteroidal anti-inflammatory drug (NSAID) or low dose aspirin treatment. Studies of vonoprazan for treatment of *H. pylori* are not included.

Table 109. Integrated Summary of Safety, All-Subjects Pool

	Study Drug Dose N						
	Vonoprazan				Lansoprazole		Placebo
Pool / Studies	40 mg	20 mg	10 mg	5 mg	30 mg	15 mg	PBO
All-EE Studies (Pool 3) Total	241	3799	1968	148	1983	1168	523
Non-EE Studies (listed below)	156	1853	1032	148	1086	740	-
TAK-438/CCT-101: Phase 3 GU		244			238		-
TAK-438_302: Phase 3 GU (*H. pylori* negative)		115			119		-
TAK-438/CCT-102: Phase 3 DU		183			186		-
TAK-438_304: Phase 3 DU		263			268		-
TAK-438/CCT-201: Phase 3 sGERD		271	278				278
Vonoprazan-2001: Phase 2 PPI partial responders	85	85			86 a		-
Vonoprazan-3001: Phase 3 sGERD			238				245
TAK-438/CCT-301/OCT-301: Phase 3 healed GU/DU receiving NSAIDs (extension)d		212	218			211	-
TAK-438/CCT-302/OCT-302: Phase 3 healed GU/DU receiving LDA (extension)		202	202			217	-
TAK-438/OCT-303: Phase 3 healed ulcer receiving NSAIDs		30					-
TAK-438/OCT-304: Phase 3 healed ulcer receiving LDA		27					-

Source: Reviewer Generated, based on ISS Tables 1.c, 1.1.g

[a] Esomeprazole was used as the comparator in a single study (Vonoprazan-2001) and data for these subjects are combined with the lansoprazole group for analysis in the All Subjects pool

Abbreviations: DU, duodenal ulcer; GU, gastric ulcer; LDA, low-dose aspirin; N, number of subjects in dose group; NSAID, non-steroidal anti-inflammatory drug; PPI, proton-pump inhibitor; sGERD, symptomatic non-erosive gastro-esophageal reflux disease

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

See consults from the review team for NDAs 215152/215153 dated January 26, 2022, and March 11, 2022 regarding the Established Pharmacologic Class of "potassium-competitive acid blocker" for vonoprazan.

19. Other Drug Development Considerations: Additional Information and Assessment

Table 110. Overview of Esophagitis Classification Scales

Los Angeles Rating Scale [A]		Hetzel-Dent [B]		Modified Savary–Miller system [C]		Kaul's Modified Savary-Miller Scale [D]		Takeda Modified Kauls Savary- Miller Scale [E]	
Grade	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**
		0	No Lesions			0	No abnormalities	0	Normal-appearing mucosa
		1	Erythema, hyperemia and/or friability			1	Mucosal edema, hyperemia	1	Mucosal edema, hyperemia and/or friability
						2	Friability of mucosa with bleeding under instrumentation		
A	One (or more) mucosal break 5 mm or less that does not extend between the tops of two mucosal folds	2	Superficial ulcerations or erosions involving <10% of the last 5 cm of the esophageal squamous mucosal surface	I, 1	Single or isolated erosive lesion(s) affecting only one longitudinal fold	3	isolated ulcerations ("mild esophagitis")	2	One or more erosions/ulcerations involving <10% of the distal 5 cm of the esophagus

Los Angeles Rating Scale [A]		Hetzel-Dent [B]		Modified Savary–Miller system [C]		Kaul's Modified Savary-Miller Scale [D]		Takeda Modified Kauls Savary- Miller Scale [E]	
Grade	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**
		3	Superficial ulcerations or erosions involving at least 10–50% of the last 5 cm of the esophageal squamous mucosal surface.					3	erosions/ulcerations involving 10-50% of the distal 5 cm of the esophagus, or an ulcer 3-5 mm in diameter
B	One (or more) mucosal break more than 5 mm-long that does not extend between the tops of two mucosal folds	4	Deep ulcerations anywhere in the esophagus or confluent erosions involving >50% of the last 5 cm of the esophageal squamous mucosal surface					4	multiple erosions involving >50% of the distal 5 cm of the esophagus or a single ulcer >5 mm in diameter
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves less than 75% of the circumference			II,2	Multiple erosive lesions, noncircumferential, affecting more than one longitudinal fold, with or without confluence	4	confluent ulcerations ("moderate esophagitis")		

Los Angeles Rating Scale [A]		Hetzel-Dent [B]		Modified Savary–Miller system [C]		Kaul's Modified Savary-Miller Scale [D]		Takeda Modified Kauls Savary- Miller Scale [E]	
Grade	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**	**Grade**	**Lesion**
D	One (or more) mucosal break that involves at least 75% of the esophageal circumference			III,3	Circumferential erosive lesions				
				IV,4	Chronic lesions: ulcer(s), stricture(s) and/or short esophagus. Alone or associated with lesions of grades 1 to 3				

Source: Reviewer-generated
[A] Used in Study EE-301
[B] (Hetzel et al. 1988; Richter and Bochenek 2000)
[C] (Robinson et al. 1996; Sontag et al. 1996)
[D] Study M87-0092
[E] Study M92-721 (Castell et al. 1996)

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Three clinical sites from Study EE-301 and an inspection of (b) (4) the contract research organization (CRO) who was responsible for performing critical study-related activities, were conducted to support NDA 215151. The Office of Scientific Investigations (OSI) concluded that the study appears to have been conducted adequately and the data generated by these sites appears acceptable in support of the respective indications of healing of EE and maintenance of healed EE.

Clinical Site Inspections

The clinical sites, shown in Table 111, were chosen primarily based on numbers of enrolled subjects, site-specific efficacy results, and inspection history.

Study records reviewed during the clinical site inspections included the study protocol and amendments; Ethics Committee submissions, approvals, and correspondence; subject eligibility criteria; informed consent process and forms; source records related to verification of the primary and key secondary efficacy endpoints of healing of EE and maintenance of healed EE

and 24-hour heartburn-free days over the healing and maintenance phases; adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures, Form FDA 1572).

Table 111. Clinical Sites Inspected by OSI for Study EE-301

Study Site Number	Number of Subjects Screened/Randomized in the Healing Phase	Principal Investigator	Location	PDUFA Inspection Dates
35006	104/39	Stefan Andrey Mitev, MD	Saharov 20A Sofia, 1784 Bulgaria	July 18 to 22, 2022
10004	198/70	John Lowe, MD	Ridgeline Drive Suite A Ogden, UT 84405	August 15 to 19, 2022
10010	85/35	James Kopp, MD	Greenville Street Anderson, SC 29621	August 23 to 25, 2022

During the clinical investigator inspections, the source records documenting the primary and key secondary efficacy endpoint data related to healing and maintenance of healing of erosive esophagitis (EE) (i.e., local endoscopy and central adjudicator's endoscopy reads at Screening/Baseline and Weeks 2, 8, and 24) were reviewed and verified against the applicant's data line listings for 90 of the 144 subjects randomized at these sites. There were no discrepancies in the endoscopy results noted between the central adjudicator's reads vs the data line listings at any of the 3 sites. Sites 35006 and 10004 also did not have any discrepancies noted between the local endoscopy reads vs. the data line listings.

Many of the local endoscopy source records were not available during the inspection at site 10010, but were subsequently submitted by the applicant, upon request, during the NDA review. An internal OSI review identified 14 discrepancies in 12 subjects between the certified copies of the local endoscopy reads vs. the data line listings that possibly resulted in deviations in the protocol-required central adjudication process. The discrepancies were between the principal investigator (Dr. Kopp), an internist without formal training in gastroenterology, and the sub-investigator with formal specialized training in gastroenterology who was delegated by Dr. Kopp to perform the endoscopies. Dr. Kopp read all endoscopies and submitted his reads to the applicant's database rather than submitting the sub-investigator's reads. According to the FDA Establishment Inspection Report (EIR), the inspection of site 10010 did not find objectionable conditions and the efficacy endpoint data were verified at this site. Discrepancies in endoscopy reads between the sub-investigator and Dr. Kopp for three subjects in the lansoprazole group had an impact on the efficacy analyses of maintenance of healed EE (subject ID (b) (6)). See a discussion of the efficacy results in Section 6.3.5.

During the clinical site inspections, the source records documenting the secondary efficacy endpoint of the incidence 24-hour heartburn-free days (i.e., daytime and nighttime heartburn entries in the subject's electronic diary) were reviewed and verified against the applicant's data line listings for 30 of the 144 randomized subjects at the 3 sites. During the NDA review, in response to an information request, the applicant reported that there was a programming error in the (b) (4) electronic patient-reported outcome (ePRO) application that allowed subjects to make duplicate electronic diary (eDiary) entries when documenting their morning or evening heartburn incidence. The eDiary audit trails in these 30 subjects were also reviewed to identify and assess the duplicate eDiary data reported to FDA. No issues or discrepancies were noted.

Inspection of the CRO

The Applicant contracted with [redacted] and transferred regulatory responsibilities to them to perform critical clinical trial activities.

Records reviewed during the inspection of [redacted], conducted [redacted] included investigator agreements; service provider agreements and contracts; written standard operating procedures; handling and processing of protocol deviations; validation and other documentation related to the operational use of electronic systems, including the electronic Systems used to manage endoscopy and ePRO data (e.g., [redacted] system and [redacted] ePRO application and online portal); adverse event reporting; drug accountability records; relevant communication and correspondence; and monitoring activities.

The programming error in the [redacted] ePRO application that allowed subjects to make duplicate electronic diary (eDiary) entries when documenting their morning or evening heartburn incidence was addressed during the NDA review in response to an information request. Only a small percentage of the total ePRO data was impacted by the programming error and the duplicate data entry by subjects was addressed by using the worst-case (i.e., the presence of heartburn with the highest severity grade entered by the subject).

21. Labeling Summary of Considerations and Key Additional Information

The FDA agreed the Applicant could include the *H. pylori* indication in this NDA with a cross-reference to NDAs 215152/212153 for the safety and efficacy information on the use of Voquezna with clarithromycin and/or amoxicillin (Voquezna Triple/Duel Pak). The language for the *H. pylori* indication throughout the Prescribing Information (PI) aligns with the approved labeling for Voquezna co-packaged with antibacterials.

The following discussion of the Voquezna PI focuses on the healing of erosive esophagitis (EE) and maintenance of healed EE indications.

Due to the CMC deficiencies in the NDA, as described in Section 9, labeling was not finalized with the applicant. On January 12, 2023, the review team sent comments on the PI and the Patient Package Insert (PPI) to the applicant (as reflected in the table below). The applicant resubmitted the PI and PPI on January 23, 2023, but the documents were not reviewed further during this cycle.

Table 112. Prescribing Information Voquezna (vonoprazan) Tablets, 10 mg, and 20 mg

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
HIGHLIGHTS	The Established Pharmacologic Class (EPC) for vonoprazan is potassium-competitive acid blocker, as determined for NDAs 215152/215153 (Voquezna Triple/Dual Pak). This is the first product in the class, which is similar to the Proton Pump Inhibitor (PPI) class in that both drug classes inhibit acid secretion at gastric parietal cell through inhibition of the H^+, K^+-ATPase enzyme system.

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
1 INDICATIONS AND USAGE	The indications in the PI are similar to those proposed by the applicant with the exception that the duration of therapy is not included. Per the Indications and Usage labeling guidance (July 2018), it is generally not necessary to limit the duration of use in this section unless it is essential to ensure the safe and effective use of the drug. In this case, the duration of use in the DOSAGE AND ADMINISTRATION section is sufficient.
2 DOSAGE AND ADMINISTRATION	The recommended dosage regimen for erosive esophagitis (EE) is: Voquezna 20 mg once daily for 8 weeks for healing of EE and relief of symptoms Voquezna 10 mg once daily for up to 24 weeks for maintenance of healed EE and relief of symptoms. The duration of treatment for the indication of healing of EE was revised from (b) (4) to "8 weeks". (b) (4) . Recommended dosages for patient with varying degrees of renal and hepatic impairment were included using estimated GFR (eGFR) cut-offs and Child-Pugh Classification to define degree of impairment. (b) (4) , the applicant agreed that (b) (4) the label will reflect the instruction "avoid use" in severe renal failure and moderate to severe hepatic impairment for the treatment of *H. pylori* to algin with Voquezna Dual/Triple Pak.
4 CONTRAINDICATIONS	Hypersensitivity reactions to vonoprazan or any component of the formulation are included as a contraindication due to a reported case of anaphylactic shock. The applicant provided literature data to support hypersensitivity reactions to various of the inactive ingredients in the tablets, including croscarmellose, mannitol, polyethylene glycol and titanium. See Section 7.3
5 WARNINGS AND PRECAUTIONS	The following serious or otherwise clinically significant adverse reactions were proposed by the applicant based upon class labeling for the proton pump inhibitors (PPIs), which have a similar mechanism of action to vonoprazan. Differences between the description of the adverse reactions in this PI compared to the PPI class are briefly summarized: • Presence of gastric malignancy: Follows PPI class labeling. • *Acute tubulointerstitial nephritis (TIN)*: (b) (4)

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
	[redacted] (b) (4) • *Clostridiodes difficile-associated diarrhea (CDAD)*: Data of increased risk of CDAD with PPIs is included along with a statement that Voquezna may also increase risk, especially with concomitant use of antibacterials. While there have not been serious cases plausibly related to vonoprazan in the absence of other medications that increase the risk of CDAD (e.g., antibacterials), the risk is potentially related to the mechanism of acid suppression and therefore vonoprazan would have similar risk to the PPIs. See Section 7.7.2. • *Bone fracture*: Epidemiologic data with PPIs suggests an increased risk of osteoporosis-related fractures in patients who received higher than recommended dosages, including multiple daily dosing and long-term therapy (1 year of longer). However, bone fracture, including osteoporosis-related fracture, was reported with vonoprazan in Study EE-301 and other clinical trials where lansoprazole was the comparator, but the cases were mostly confounded, and incidence rates were similar between the treatments. See Section 7.7.2. • *Severe cutaneous adverse reactions (SCARs)*: Single cases each of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported postmarketing. Other SCARs, reported with the PPIs have not been reported, with the exception of erythema multiforme, which was added to Section 6.2 Postmarketing Experience because of a less severe presentation than SJS/TEN. See Section 7.3. • Interactions with diagnostic investigations for neuroendocrine tumors: Follows PPI class labeling. • *Fundic gland polyps*: The PPI class labeling describes polyps increasing with long-term use, especially beyond 1 year. Polyps have been reported with vonoprazan in Study EE-301 and other clinical trials of up to 24 weeks. So, the phrase "[redacted] (b) (4)" was removed. In addition, in the VISION study with 5-years of follow-up, the rate of gastric polyps was similar to the lansoprazole comparator. See Section 7.7.2. • In addition to the above subsections proposed by the applicant, other PPI class warnings were added to this section based on review of postmarketing cases with vonoprazan outside of the US. Although there are limited cases plausibly associated with vonoprazan, the mechanism for development of these adverse reactions is related to malabsorption of nutrients as a result of acid suppression, the degree of which is similar between vonoprazan and the PPIs. See Section 7.3. • Vitamin B12 (cobalamin) deficiency • Hypomagnesemia and mineral metabolism No cases of cutaneous or systemic lupus erythematosus have been reported with vonoprazan. Therefore, unlike the PPIs, Voquezna will not contain lupus in this section. The mechanism of lupus is unknown and not thought to be related to acid suppression. See Section 7.7.3.
6 ADVERSE REACTIONS 6.1 Clinical Trials Experience	• Common adverse reactions in the healing phase of Study EE-301 were defined as > 1% of patients in either Voquezna 20 mg once daily or lansoprazole 30 mg once daily arm. No terms above this cut-off were excluded except for Barrett's esophagus which was considered related to EE disease and not to vonoprazan.

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
	• Common adverse reactions in the healing phase of Study EE-301 were defined as > 2% of patients in either Voquezna 10 mg once daily or lansoprazole 15 mg once daily arm. No terms above this cut-off were excluded except for gastroesophageal reflux disease which was considered lack of efficacy and not related to vonoprazan. • A description of cases of COVID-19 reported in the healing and maintenance phases is described separately from the tables of common adverse reactions, although the incidence in both the healing and maintenance phases for this adverse event meets the cut-off. Given the background prevalence of infection during the time period in which the study was conducted, disclosure of the rates of COVID in the trial are provided without implying as an adverse reaction. • Less common adverse reactions reported in 1% or less of patients who received the recommended dosage of Voquezna in the healing and/or maintenance phase of Study EE-301 were selected based on seriousness of the event and biologic plausibility. See Section 17.4..
6 ADVERSE REACTIONS 6.2 Postmarketing Experience	Adverse reaction terms reported post-approval of vonoprazan outside of the US are those described in CONTRAINDICATIONS (anaphylactic shock), and WARNINGS AND PRECAUTIONS (hypomagnesemia, vitamin B12 deficiency, SJS, and TEN) and others based upon pharmacovigilance cases or literature data, namely *C. difficile* (with concomitant use of antibacterials), hypokalemia and hypocalcemia (associated with hypomagnesemia), and thrombocytopenia. See Section 7.3.
7 DRUG INTERACTIONS	Follows the approved labeling for Voquezna Dual/Triple Pak
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy and 8.2 Lactation	• There are no pregnancy signals of concern in the animal studies of vonoprazan at relevant doses. • Available data from pharmacovigilance reports with vonoprazan use in pregnant women are not sufficient to evaluate for a drug-associated risk for major birth defects, miscarriage or other adverse maternal or fetal outcomes. • It is not known whether vonoprazan is present in human milk and it is found in rat milk; therefore, breast feeding is not recommended. • There is no need for pregnancy testing or contraception with use of Voquezna. See Section 8.4 for discussion of Postmarketing Requirements for pregnancy exposure registry and postmarketing pregnancy study and a "milk only" clinical lactation study.
8 USE IN SPECIFIC POPULATIONS 8.4 Pediatric Use	Safety and effectiveness have not been established in pediatric patients.
8 USE IN SPECIFIC POPULATIONS 8.5 Geriatric Use	No overall differences in safety or effectiveness were observed in Study EE-301 between patients aged 65 years of age and older and younger adult patients and other clinical experience has not identified differences in responses between older and younger patients. No pharmacokinetic differences based on age were predicted based on population PK.
8 USE IN SPECIFIC POPULATIONS 8.6 Renal Impairment 8.7 Hepatic Impairment	See discussion in DOSAGE AND ADMINISTRATION about dosage recommendations for patients by indication and degree of renal or hepatic impairment.

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
10 OVERDOSAGE	There are no available information on animal or human toxicities associated with overdose, so this section was removed.
11 DESCRIPTION	Per the Salt Policy guidance, an equivalency statement was added to indicate the amount of active moiety related to the amount of active ingredient (salt). (June 2015)
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action	Aligns with the approved labeling for Voquezna Dual/Triple Pak
12 CLINICAL PHARMACOLOGY 12.2 Pharmacodynamics	A discussion of the antisecretory effect of vonoprazan 10 mg and 20 mg after single doses and at steady state, including Time% pH>4, was included in included in tabular format (in place of a figure of 24-hour intragastric pH). (b) (4) was removed from labeling because (b) (4) A discussion of the enterochromaffin-line cell (ECL) effects in animals was moved to Section 13.2, as discussed below. Human data based on the 4-year interim analysis of the VISION study was added in place of shorter-term 6-month clinical data. Other subsections include cardiac electrophysiology (no effect on QTc at 6 times the maximum recommended dose) and effects on gastrin (increased while on treatment and then returned to baseline after vonoprazan was discontinued).
12 CLINICAL PHARMACOLOGY 12.3 Clinical Pharmacology	Aligns with the approved labeling for Voquezna Dual/Triple Pak. Pharmacokinetic parameters for single dose and steady state following Voquezna 10 mg and 20 mg once daily (EE regimen) are included in a table with the steady state parameters with 20 mg twice daily (*H. pylori* regimen). Results of a drug-drug interaction study with aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) was added. No clinically meaningful changes were observed with vonoprazan, or the concomitant drug compared to administration of each drug alone.
12 CLINICAL PHARMACOLOGY 12.4 Microbiology	Aligns with the approved labeling for Voquezna Dual/Triple Pak
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Neuroendocrine tumors developed in the stomach of rats and mice consistent with the mechanism of action of vonoprazan by inhibition of gastric acid secretion. Vonoprazan is negative for mutagenicity No effects on fertility or reproductive performance.
13 NONCLINICAL TOXICOLOGY 13.2 Animal Toxicology and/or Pharmacology	Increases in gastrin levels observed in mice and rats associated with formation of carcinoid tumors was moved to Section 13.2 from Section 12.2, as the findings are considered a rodent-specific phenomenon.
14 CLINICAL STUDIES	Healing of EE The primary endpoint in the healing phase (complete healing of all grades of erosive esophagitis [EE] at Week 2 or Week 8), along with the Week 2 results (secondary endpoint and component of the primary endpoint) in Study EE-301 are presented in tabular format. Although the Week 2 endpoint was not tested due to failure of an earlier endpoint in the statistical testing hierarchy, the Week 2 analysis is a component of the

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
	primary endpoint, the results were nominally significant, and the endpoint is considered clinically meaningful. Other secondary endpoints in the subgroup of patients with EE of LA Grade C or D are presented as text rather than in a table. The result for healing of EE at Week 2 in the subgroup of patients with LA Grade C or D was statistically significant and the label states that superiority was demonstrated for this endpoint. While the results of the endpoint at either Week 2 or Week 8 in the subgroup of patients with LA Grade C or D was not tested due to failure of an earlier endpoint in the statistical testing hierarchy, the results were nominally significant, the endpoint is considered clinically meaningful, and the results are included with descriptive statistics and a disclaimer ("The endpoint was not statistically significant under the prespecified multiple testing procedure"). Relief of heartburn in the healing phase, also a secondary endpoint, was included in another table. The results demonstrated non-inferiority of Voquezna to the comparator (lansoprazole). See Section 6.2.2.3. (b) (4) , were removed: (b) (4) A description of two randomized, active-controlled, double-blind studies conducted outside of the United States, which also demonstrated non-inferiority of vonoprazan 20 mg once daily compared to lansoprazole 30 mg once daily for the primary endpoint of healing of all grades of EE by Week 8, was added. Maintenance of Healed EE The primary endpoint in the healing phase (maintenance of healed EE (all grades) through Week 24 in Study EE-301 along with the secondary endpoint of maintenance of healed EE in the subgroup of patients with LA Grade C or D disease at baseline are presented together in a table of results. A statement that (b) (4) for the primary endpoint was removed, although a footnote to the table explains the results for the primary endpoint (non-inferiority and superiority to lansoprazole) and secondary endpoint (superiority to lansoprazole). Relief of heartburn in the maintenance phase, another secondary endpoint, was included in a second table. The results demonstrated non-inferiority of Voquezna to the comparator (lansoprazole). See Section 6.2.3.4. The following statement was removed because (b) (4) The description of the study design for the maintenance phase of Study EE-301 states that in addition to the treatment arms of Voquezna 10 mg once daily and lansoprazole 15 mg once daily, a third arm of "a higher dosage of Voquezna" was also included and that the higher dosage did not demonstrate additional treatment benefit. A description of two randomized, active-controlled, double-blind studies conducted outside of the United States, which also demonstrated non-inferiority of vonoprazan 10 mg once daily compared to lansoprazole 15

Full Prescribing Information Sections[1]	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI[2]
	mg once daily for the primary endpoint of maintenance of healed EE (all grades) through Week 24, was added. Treatment of *H. pylori* Infection Aligns with the approved labeling for Voquezna Dual/Triple Pak
17 PATIENT COUNSELING INFORMATION	The PPIs have a Medication Guide due to the risks of acute tubulointerstitial nephritis, *Clostridiodes difficile*-associated diarrhea (CDAD), bone fracture, and lupus erythematosus (as described in the section "What is the most important information that I should know"). The WARNINGS AND PRECAUTIONS section of the Voquezna PI contains many of the same adverse reactions as for the PPIs (with the exception of cutaneous and systemic lupus erythematosus). Although the vonoprazan cases are limited, the mechanism of action of both vonoprazan and the PPIs is to suppress acid secretion. Therefore, a Patient Package Insert (PPI) was recommended for Voquezna to convey the risks. A Medication Guide was not deemed necessary at this time. The risks of CDAD, bone fracture, vitamin B12 deficiency, and hypomagnesemia will be part of routine pharmacovigilance monitoring post-approval and should additional cases be reported, the need for a Medication Guide will be reassessed.

[1] Some sections may not be included because those sections may not have major issues (or changes).
[2] The finalized PI is the PI that will be approved or is close to being approved

22. Postmarketing Requirements and Commitments

Because the recommended action is a Complete Response, no postmarketing requirements or commitments will be issued. The identified deficiencies precluded discussions with the applicant of anticipated postmarketing requirements (PMRs) and postmarketing commitments (PMCs) during this review cycle.

During the review, the team discussed two potential postmarketing requirements (PMRs) for a pregnancy exposure registry and a postmarketing pregnancy study. Both PMRs were previously issued with the approval of NDAs 215152/215153.

PREA PMRs for pediatric patients 1 month to less than 17 years will be addressed at the time of approval.

23. Financial Disclosure

There were no financial disclosures that raised concern for potential bias for investigators participating in Study EE-301 (See Table 113).

Table 113. Covered Clinical Studies: EE-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 156 Investigators (605 sub-investigators) at 111 sites		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): n/a Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: n/a	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: n/a	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant received a financial disclosure certification from one investigator, (b) (6), in TAK-438_303 stating that he had a proprietary interest in the investigational product but did not disclose specific information regarding his interest. The Applicant made attempts to clarify details of the proprietary interest but was unsuccessful. The Applicant notes that (b) (6) enrolled (b) (4) subjects in the clinical trial which makes the impact of potential bias minimal.

The primary basis for the assessment of efficacy and safety of vonoprazan in the NDA was Study EE-301. Study TAK-438_303 was a randomized, double-blind, controlled, multicenter trial that was used as confirmatory evidence of the efficacy of vonoprazan in subjects with EE and for supportive safety information. Therefore, any potential bias from the data in four subjects in Study TAK-438_303 is unlikely to affect the evaluation of efficacy and safety of vonoprazan in the NDA, based on the totality of the submitted evidence.

24. References

Literature

Aparicio, T, A Pachev, P Laurent-Puig, and M Svrcek, 2022, Epidemiology, Risk Factors and Diagnosis of Small Bowel Adenocarcinoma, Cancers (Basel), 14(9).

Aschebrook-Kilfoy, B, RH Grogan, MH Ward, E Kaplan, and SS Devesa, 2013, Follicular thyroid cancer incidence patterns in the United States, 1980-2009, Thyroid, 23(8):1015-1021.

Briganti, SI, AM Naciu, G Tabacco, R Cesareo, N Napoli, P Trimboli, M Castellana, S Manfrini, and A Palermo, 2021, Proton Pump Inhibitors and Fractures in Adults: A Critical Appraisal and Review of the Literature, Int J Endocrinol, 2021:8902367.

Castell, DO, JE Richter, M Robinson, SJ Sontag, and MM Haber, 1996, Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group, Am J Gastroenterol, 91(9):1749-1757.

CDC, 2006, Travel-Related-Infectious-Diseases, online edition: Oxford Academic.

Chen, B, G Cheng, H Wang, and Y Feng, 2016, Increased risk of vertebral fracture in patients with rheumatoid arthritis: A meta-analysis, Medicine (Baltimore), 95(45):e5262.

Dehlin, M, L Jacobsson, and E Roddy, 2020, Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors, Nat Rev Rheumatol, 16(7):380-390.

Earnest, DL, E Dorsch, J Jones, DE Jennings, and PA Greski-Rose, 1998, A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis, Am J Gastroenterol, 93(2):238-243.

El-Serag, HB, S Sweet, CC Winchester, and J Dent, 2014, Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review, Gut, 63(6):871-880.

Fennerty, MB, 1997, Medical treatment of gastroesophageal reflux disease in the managed care environment, Semin Gastrointest Dis, 8(2):90-99.

Freston, JW, 2004, Therapeutic choices in reflux disease: defining the criteria for selecting a proton pump inhibitor, Am J Med, 117 Suppl 5A:14s-22s.

He, Y and AH Sawalha, 2018, Drug-induced lupus erythematosus: an update on drugs and mechanisms, Curr Opin Rheumatol, 30(5):490-497.

Hebert, C, H Du, LR Peterson, and A Robicsek, 2013, Electronic health record-based detection of risk factors for Clostridium difficile infection relapse, Infect Control Hosp Epidemiol, 34(4):407-414.

Hebert, C and A Robicsek, 2014, Reply to Daniell, Infect Control Hosp Epidemiol, 35(1):94-95.

Hetzel, DJ, J Dent, WD Reed, FM Narielvala, M Mackinnon, JH McCarthy, B Mitchell, BR Beveridge, BH Laurence, GG Gibson, and et al., 1988, Healing and relapse of severe peptic esophagitis after treatment with omeprazole, Gastroenterology, 95(4):903-912.

Hillman, LC, L Chiragakis, B Shadbolt, GL Kaye, and AC Clarke, 2004, Proton-pump inhibitor therapy and the development of dysplasia in patients with Barrett's oesophagus, Med J Aust, 180(8):387-391.

Holloway, RH and J Dent, 1990, Pathophysiology of gastroesophageal reflux. Lower esophageal sphincter dysfunction in gastroesophageal reflux disease, Gastroenterol Clin North Am, 19(3):517-535.

Isshi, K, N Matsuhashi, T Joh, K Higuchi, K Iwakiri, T Kamiya, N Manabe, T Nakada, M Ogawa, S Arihiro, K Haruma, and K Nakada, 2021, Clinical features and therapeutic responses to proton pump inhibitor in patients with severe reflux esophagitis: A multicenter prospective observational study, JGH Open, 5(1):99-106.

Jacob, L and K Kostev, 2021, Osteoarthritis and the incidence of fracture in the United Kingdom: a retrospective cohort study of 258,696 patients, Osteoarthritis Cartilage, 29(2):215-221.

Katz, PO, KB Dunbar, FH Schnoll-Sussman, KB Greer, R Yadlapati, and SJ Spechler, 2022, ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease, Am J Gastroenterol, 117(1):27-56.

Lin, SH, YS Chang, TM Lin, LF Hu, TY Hou, HC Hsu, YC Shen, PI Kuo, WS Chen, YC Lin, JH Chen, and CC Chang, 2021, Proton Pump Inhibitors Increase the Risk of Autoimmune Diseases: A Nationwide Cohort Study, Front Immunol, 12:736036.

Lindenbaum, J, IH Rosenberg, PW Wilson, SP Stabler, and RH Allen, 1994, Prevalence of cobalamin deficiency in the Framingham elderly population, Am J Clin Nutr, 60(1):2-11.

Lukasiewicz, AM, DD Bohl, AG Varthi, BA Basques, ML Webb, AM Samuel, and JN Grauer, 2016, Spinal Fracture in Patients With Ankylosing Spondylitis: Cohort Definition, Distribution of Injuries, and Hospital Outcomes, Spine (Phila Pa 1976), 41(3):191-196.

Magallen, MG and J Sollano, 2013, Obesity a Risk Factor in Gastroesophageal Reflux Disease in an Asian Population: 84, Official journal of the American College of Gastroenterology | ACG, 108:S28.

Menon, S, H Jayasena, P Nightingale, and NJ Trudgill, 2011, Influence of age and sex on endoscopic findings of gastrooesophageal reflux disease: an endoscopy database study, Eur J Gastroenterol Hepatol, 23(5):389-395.

Metz, DC, CW Howden, MC Perez, L Larsen, J O'Neil, and SN Atkinson, 2009, Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis, Aliment Pharmacol Ther, 29(7):742-754.

Nerandzic, MM, MJ Pultz, and CJ Donskey, 2009, Examination of potential mechanisms to explain the association between proton pump inhibitors and Clostridium difficile infection, Antimicrob Agents Chemother, 53(10):4133-4137.

Orlando, RC, 1997, The pathogenesis of gastroesophageal reflux disease: the relationship between epithelial defense, dysmotility, and acid exposure, Am J Gastroenterol, 92(4 Suppl):3S-5S; discussion 5S-7S.

Perazella, MA, 2013, Proton pump inhibitors and hypomagnesemia: a rare but serious complication, Kidney Int, 83(4):553-556.

Real, M, MS Barnhill, C Higley, J Rosenberg, and JH Lewis, 2019, Drug-Induced Liver Injury: Highlights of the Recent Literature, Drug Saf, 42(3):365-387.

Richter, JE and W Bochenek, 2000, Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group, Am J Gastroenterol, 95(11):3071-3080.

Robinson, M, F Lanza, D Avner, and M Haber, 1996, Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial, Ann Intern Med, 124(10):859-867.

Sanchez-Alamo, B, C Cases-Corona, and G Fernandez-Juarez, 2022, Facing the Challenge of Drug-Induced Acute Interstitial Nephritis, Nephron:1-13.

Sharma, P, NJ Shaheen, MC Perez, BL Pilmer, M Lee, SN Atkinson, and D Peura, 2009, Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation--results from two randomized controlled studies, Aliment Pharmacol Ther, 29(7):731-741.

Sontag, SJ, DG Kogut, R Fleischmann, DR Campbell, J Richter, and M Haber, 1996, Lansoprazole prevents recurrence of erosive reflux esophagitis previously resistant to H2-RA therapy. The Lansoprazole Maintenance Study Group, Am J Gastroenterol, 91(9):1758-1765.

Spiegel, A, P Stein, M Patel, R Patel, and E Lebovics, 2010, A report of gastric fundic gland polyps, Gastroenterol Hepatol (N Y), 6(1):45-48.

Staines, KA, K Myers, K Little, SH Ralston, and C Farquharson, 2021, Proton Pump Inhibitors Inhibit PHOSPHO1 Activity and Matrix Mineralisation In Vitro, Calcif Tissue Int, 109(6):696-705.

Uemura, N, Y Kinoshita, K Haruma, T Yao, R Kushima, and T Kanoo, 2018, Rationale and design of the VISION study: a randomized, open-label study to evaluate the long-term safety of vonoprazan as maintenance treatment in patients with erosive esophagitis, Clin Exp Gastroenterol, 11:51-56.

Zhang, GH and R Castro, 2015, Role of Oral Mucosal Fluid and Electrolyte Absorption and Secretion in Dry Mouth, Chin J Dent Res, 18(3):135-154.

Guidances

Guidance for Industry *International Council for Harmonisation Guidline for Good Clinical Practice E6(R2)* (December 2016)

(b) (4)

Guidance for Industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry* (July 2018)

Guidance for Industry *Naming of Drug Products Containing Salt Drug Substances* (June 2015)

Prescribing Information

Phathom, 2022, VOQUEZNA Triple/Dual Pak prescribing information, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215152s000,215153s000lbl.pdf.

Takeda, 2018, PREVACID SOLUTAB delayed-release capsule prescribing information, accessed, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020406s087s088,021428s034s035lbl.pdf.

Other

CDC, 2022a, Adult Obesity Facts, accessed November 7, 2022, https://www.cdc.gov/obesity/data/adult.html.

CDC, 2022b, When, What, and How to Introduce Solid Foods, accessed December 13, 2022, https://www.cdc.gov/nutrition/infantandtoddlernutrition/foods-and-drinks/when-to-introduce-solid-foods.html.

Drugbank, 2022, Nadroparin, accessed November 9, 2022, https://go.drugbank.com/drugs/DB08813.

FDA, 2010, FDA Drug Safety Communication: Possible increased risk of fractures of the hip, wrist, and spine with the use of proton pump inhibitors, accessed October 20, 2022, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-possible-increased-risk-fractures-hip-wrist-and-spine-use-proton-pump.

FDA, 2012, FDA Drug Safety Communication: Clostridium difficile associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs), accessed November 3, 2022, https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-clostridium-difficile-associated-diarrhea-can-be-associated-stomach.

HealthyChildren.org, 2022, Starting Solid Foods, accessed December 13, 2022, https://www.healthychildren.org/English/ages-stages/baby/feeding-nutrition/Pages/Starting-Solid-Foods.aspx.

U.S. Cancer Statistics Working Group, 2022, U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999–2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, accessed December 6, 2022, www.cdc.gov/cancer/dataviz.

25. Review Team

Table 114. Reviewers of Integrated Assessment

Role	Names
Regulatory Project Manager	Maureen Dewey
Nonclinical Reviewer	Dinesh Gautam
Nonclinical Team Leader	Sushanta Chakder
Office of Clinical Pharmacology Reviewer	Sojeong Yi
Office of Clinical Pharmacology Team Leader	Insook Kim
Clinical Reviewer	Laura H. Finkelstein
Clinical Team Leader	Joette Meyer
Statistical Reviewer	Dapeng Hu
Statistical Team Leader	Paul Imbriano
Supervisory Mathematical Statistician	Mohamed Alosh
Cross-Disciplinary Team Leader	Joette Meyer
Deputy Director for Safety	Joyce Korvick
Designated Signatory Authority Deputy Division Director	Juli Tomaino

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 115. Additional Reviewers of Application

Office or Discipline	Names
OPQ	ATL: Nina Ni Drug Product: Jane Chang, Nina Ni, Hong Cai Drug Substance: Fred Burnett, Lawrence Perez, Donna Christner RBPM: Melinda Bauerlien
Microbiology Microbiology Team Leader	Mesfin Abdi Vaikunth Prabhu, Yubing Tan
Biopharm Reviewer Biopharm Team Leader	Kamrun Nahar Tapash Ghosh
OPDP	Meeta Patel Adewale Adeleye, LaShawn Griffiths
Division of Pediatric and Maternal Health (DPMH)	Jane Liedtka, Tamara Johnson, Ramy Abdelrahman, Mona Khurana, Jacqueline Yancy
DMPP Patient Labeling	Nyedra Booker, Marcia Britt Williams
OSI	Cheryl Grandinetti, Phillip Kronstein
OSE/DEPI	Joel Weissfeld Benjamin Booth
OSE/DMEPA	Sherly Abraham Idalia Rychlik
OSE/DPV	Jamie Klucken Lisa Wolf
OSE/PM	Alvis Dunson, Alec Winiarski
DRM	Cristen Lambert Yasmeen Abou-Sayed
Clinical Data Science Staff	Ling Cao Jinzhong Liu
ODES: Division of Biomedical Informatics, Research and Biomarker Development	Veronica Pei
IAMA	Florence Moore, Nikia Morris, Robert Rust
Medical Editors	Pamela Hsieh, Katelyn Wakefield

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 116. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical Primary Reviewer	Dapeng Hu	OTS/OB/DBIII	6.2, 6.3, 16 ☒ Authored ☐ Approved
	Signature: Dapeng Hu -S Digitally signed by Dapeng Hu -S Date: 2023.02.06 15:34:55 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical Secondary Reviewer	Paul Imbriano	OTS/OB/DBIII	6.2, 6.3, 16 ☐ Authored ☒ Approved
	Signature: Paul M. Imbriano -S Digitally signed by Paul M. Imbriano -S Date: 2023.02.06 15:42:55 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical Tertiary Reviewer	Mohamed Alosh	OTS/OB/DBIII	6.2, 6.3, 16 ☐ Authored ☒ Approved
	Signature: Mohamed A. Alosh -S Digitally signed by Mohamed A. Alosh -S Date: 2023.02.06 17:01:07 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology Primary Reviewer	Sojeong Yi	OTS/OCP/DIIP	5, 6.1, 8.1, 8.2, 14 ☒ Authored ☐ Approved
	Signature: Sojeong Yi -S Digitally signed by Sojeong Yi -S Date: 2023.02.07 08:58:53 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Insook Kim	OTS/OCP/DIIP	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Insook Kim -S Digitally signed by Insook Kim -S Date: 2023.02.07 10:35:41 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Dinesh Gautam	OND/OII/DPTII	5.1, 7.1, 8.4, 13 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Dinesh C. Gautam -S Digitally signed by Dinesh C. Gautam -S Date: 2023.02.07 10:39:22 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Sushanta Chakder	OND/OII/DPTII	5.1, 7.1, 8.4, 13 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Sushanta K. Chakder -S Digitally signed by Sushanta K. Chakder -S Date: 2023.02.07 10:45:25 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Ramy Abdelrahman	OND/DPMH	8.3, 8.4 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Ramy A. Abdelrahman -S Digitally signed by Ramy A. Abdelrahman -S Date: 2023.02.07 11:08:04 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Mona Khurana	OND/DPMH	8.3, 8.4 ☐ Authored ☒ Approved
Secondary Reviewer	**Signature:** Mona Khurana -S Digitally signed by Mona Khurana -S Date: 2023.02.07 13:15:21 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Laura Finkelstein	OND/DG	6.2.1, 7.2, 7.4, 7.5, 7.6, 7.7, 10, 11, 15, 17, 19, 23 ☒ Authored ☐ Approved
Primary Reviewer	**Signature:** Laura H. Finkelstein -S Digitally signed by Laura H. Finkelstein -S Date: 2023.02.07 13:21:10 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Joette Meyer	OND/DG	2, 3, 21 ☒ Authored ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Joette M. Meyer -S Digitally signed by Joette M. Meyer -S Date: 2023.02.07 13:38:29 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Juli A. Tomaino	OND/DG	All Sections ☐ Authored ☒ Approved
Signatory Authority	**Signature:** Juli A. Tomaino -S Digitally signed by Juli A. Tomaino -S Date: 2023.02.07 13:48:32 -05'00'		

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/

JULI A TOMAINO
02/07/2023 02:11:23 PM