CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215152Orig1s000
215153Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215152/215153
Priority or standard	Priority
Submit date	9/3/2021
Received date	9/3/2021
PDUFA goal date	5/3/2022
Division/office	Division of Anti-Infectives (DAI)
Review completion date	4/29/2022
Established/proper name	NDA 215152: vonoprazan, clarithromycin, amoxicillin NDA 215153: vonoprazan, amoxicillin
(Proposed) proprietary name	Voquezna Triple Pak/Voquezna Dual Pak
Pharmacologic class	Potassium-competitive acid blocker
Code name	TAK-438
Applicant	Phathom Pharmaceuticals, Inc.
Dosage form(s)/formulation(s)	Voquezna Triple Pak: vonoprazan 20 mg tablets, clarithromycin 500 mg tablets, and amoxicillin 500 mg capsules, copackaged for oral use Voquezna Dual Pak: vonoprazan 20 mg tablets and amoxicillin 500 mg capsules, copackaged for oral use
Dosing regimen	Voquezna Triple Pak: vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily for 14 days. Voquezna Dual Pak: vonoprazan 20 mg twice daily plus amoxicillin 1,000 mg, three times a day for 14 days
Applicant proposed indication/ population	Treatment of *Helicobacter pylori* infection in adults
Proposed SNOMED indication	NDA 215152: triple therapy *Helicobacter pylori* NDA 215153: dual therapy *Helicobacter pylori*
Regulatory action	Approval
Approved dosage (if applicable)	Voquezna Triple Pak: vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily (morning and evening, 12 hours apart), with or without food, for 14 days Voquezna Dual Pak: vonoprazan 20 mg twice daily (morning and evening) plus amoxicillin 1,000 mg, three times a day (morning, mid-day, and evening), with or without food, for 14 days
Approved indication/ population	Treatment of *Helicobacter pylori* infection in adults
Approved SNOMED term for indication	NDA 215152: triple therapy *Helicobacter pylori* NDA 215153: dual therapy *Helicobacter pylori*

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1. Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATCC	American Type Culture Collection
AUC	area under the concentration-time curve
BID	twice daily
^{13}C-UBT	^{13}C-urea breath test
CI	confidence interval
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CP	Child-Pugh Class
CYP	cytochrome P450
DAI	Division of Anti-Infectives
DDI	drug-drug interaction
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DU	duodenal ulcer
FDA	Food and Drug Administration
GD	gestation day
GLP	good laboratory practice
GU	gastric ulcer
HCV	hepatitis C virus
HP	*Helicobacter pylori*
IC_{50}	half maximal inhibitory concentration
IND	investigational new drug
LD	lactation day
LTRI	lansoprazole triple therapy
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
mITTc	modified intent-to-treat clarithromycin-resistant
mITTp	modified intent-to-treat primary
MRHD	maximum recommended human dosage
NDA	new drug application
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
OATP	organic anion transporting polypeptide
PBPK	physiologically based pharmacokinetic
PD	pharmacodynamic
P-gp	P-glycoprotein
PIF	photo-irritation-factor
PIND	pre-investigational new drug
PK	pharmacokinetic
PMR	postmarketing requirement

PND	postnatal day
PPI	proton pump inhibitor
PPND	peri- and postnatal development
QD	once daily
QIDP	qualified infectious disease product
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TK	toxicokinetic
T_{max}	time to maximum concentration
ULN	upper limit of normal
UV	ultraviolet
VDUAL	vonoprazan dual therapy
VTRI	vonoprazan triple therapy

I. Executive Summary

1. Summary of Regulatory Action

New drug applications (NDA) 215152, Voquezna Triple Pak (vonoprazan tablets, amoxicillin capsules, and clarithromycin tablets) and 215153, Voquezna Dual Pak (vonoprazan tablets and amoxicillin capsules), both copackaged for oral use, were submitted by Phathom Pharmaceuticals, Inc., for the proposed indication of treatment of *H. pylori* infection in adults. Vonoprazan is a potassium-competitive acid blocker that suppresses gastric acid secretion, and amoxicillin and clarithromycin are components of other approved combination therapies for the treatment of *H. pylori* infection. These 505(b)(2) applications rely in part on the Food and Drug Administration (FDA)'s previous findings of safety and effectiveness for the listed drugs Amoxil (amoxicillin) capsules (NDA 050549) and Biaxin (clarithromycin) tablets (NDA 050662).

These applications were reviewed by the multidisciplinary review team, which recommended approval, and I, the signatory authority for this application, concur with those recommendations.

The Applicant submitted a three-arm trial comparing vonoprazan triple therapy and vonoprazan dual therapy with lansoprazole triple therapy (with clarithromycin and amoxicillin). This trial demonstrated that the vonoprazan combination therapies were effective for the treatment of *H. pylori* infection in adults. Additional support for the effectiveness of vonoprazan as part of a regimen to treat *H. pylori* infection is provided by a trial from Japan. The available safety data show that these therapies are safe for their intended use and that identified risks can be mitigated through labeling and further evaluated during routine pharmacovigilance.

Preclinical studies demonstrated that vonoprazan and its metabolites are present in rat milk, and postmarketing requirements (PMRs) include a lactation study to evaluate concentrations of vonoprazan in human breast milk. Because there are no adequate and well-controlled studies of vonoprazan-containing products in pregnant women to evaluate the drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes, additional PMRs include studies to evaluate pregnancy outcomes in women exposed to vonoprazan-containing products. PMRs will also further characterize the contribution of various cytochrome P450 (CYP) enzymes to the metabolism of vonoprazan, as well as to study the drug-drug interaction potential of vonoprazan's metabolite, M-I-G.The overall benefit-risk assessments are favorable for these NDAs as described in the Benefit-Risk Framework below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document and the Product Quality Review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *H. pylori* infection is usually asymptomatic but is an important cause of peptic ulcer disease (PUD) and gastric cancer. It may also have a role in functional dyspepsia (uninvestigated and functional), unexplained iron deficiency anemia, and other conditions. • Testing for *H. pylori* infection is recommended for adults with active PUD, a past history of PUD (unless previous cure of *H. pylori* infection has been documented), and certain gastric cancers. Patients who test positive should be treated. • Complications of *H. pylori* infection are infrequent in children, and "test and treat" strategies are not recommended.	*H. pylori* infection is an important cause of PUD and gastric cancer. Testing for *H. pylori* infection is recommended for adults with PUD and certain gastric cancers, and patients who test positive should be treated.
Current Treatment Options	• Currently approved treatments for *H. pylori* infection are multidrug regimens that include a proton pump inhibitor (PPI) with one or more antimicrobial agents. Recommended first-line therapies include clarithromycin triple therapy (with a PPI and amoxicillin), and bismuth quadruple therapy (with a PPI, metronidazole, and tetracyline). • *H. pylori* eradication rates in the U.S. have been declining because of increasing clarithromycin resistance.	Treatments for *H. pylori* infection include combinations of PPIs and antimicrobial agents. There are several approved first- and second-line therapies. *H. pylori* eradication rates in the U.S. have been declining because of increasing clarithromycin resistance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Vonoprazan is a potassium-competitive acid blocker that suppresses gastric acid secretion. In these new drug applications, it has been administered in combination with clarithromycin and amoxicillin or with amoxicillin alone for the treatment of *H. pylori* infection in adults. • Study HP-301 was a three-arm study comparing vonoprazan triple therapy and vonoprazan dual therapy with lansoprazole triple therapy (with clarithromycin and amoxicillin). The primary efficacy endpoint was the proportion of subjects with successful *H. pylori* eradication after the treatment period, as determined by ^{13}C-urea breath test (^{13}C-UBT), at 4 weeks after the last dose of study drug, in the modified intent-to-treat primary (mITTp) population (subjects who do not have a clarithromycin- or amoxicillin-resistant strain of *H. pylori* at baseline). • Vonoprazan triple therapy and vonoprazan dual therapy were non-inferior to lansoprazole triple therapy in the mITTp population. • In the mITTc population (subjects who had a clarithromycin-resistant strain of *H. pylori* at baseline), vonoprazan triple therapy and vonoprazan dual therapy were superior to lansoprazole triple therapy. • A supportive trial from Japan, CCT-401, compared vonoprazan triple therapy and lansoprazole triple therapy using different dosages and duration of therapy from those in HP-301. The eradication rate of vonoprazan triple therapy was significantly higher than lansoprazole triple therapy.	Vonoprazan triple therapy and dual therapy are effective for the treatment of *H. pylori* infection in adults. In subjects with clarithromycin-resistant *H. pylori* at baseline, vonoprazan triple therapy and vonoprazan dual therapy are superior to lansoprazole triple therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The most common adverse reactions reported in subjects treated with a vonoprazan-containing regimen were diarrhea, dysgeusia, abdominal pain, headache, and vulvovaginal candidiasis. • Treatment-emergent adverse events were less frequent in the vonoprazan dual therapy group than in the triple therapy groups. • There are no adequate and well-controlled studies of vonoprazan-containing products in pregnant women to evaluate the drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. • There are no data regarding the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. Vonoprazan and its metabolites are present in rat milk. • Liver lesions and increased stomach weights were noted in neonatal rats with gestational and/or lactational exposure to vonoprazan. • Characterization of the contribution of CYP enzymes to the metabolism of vonoprazan, as well as the inhibitory potential of the vonoprazan metabolite, M-I-G, on CYP enzymes and transporters is needed to further inform the potential for drug interactions.	The adverse reaction profile for vonoprazan-containing products is similar to that of other treatments for *H. pylori* infection. Findings from the animal studies are described in labeling. Postmarketing requirements include a pregnancy exposure registry to monitor pregnancy outcomes in women exposed to vonoprazan-containing products and an additional pregnancy study using a different design. A lactation study in lactating women who have received vonoprazan-containing products will assess concentrations of vonoprazan in breast milk using a validated assay. Additional postmarketing requirements include evaluating: (1) the contribution of CYP enzymes to the metabolism of vonoprazan, and (2) the inhibitory potential of the vonoprazan metabolite, M-I-G, on CYP enzymes and transporters. These assessments will inform the need for further clinical drug-drug interaction studies and/or labeling revisions.

Abbreviations: ^{13}C-UBT, ^{13}C-urea breath test; mITTc, modified intent-to-treat clarithromycin-resistant; mITTp, modified intent-to-treat primary; PPI, proton pump inhibitor; PUD, peptic ulcer disease

2.2. Conclusions Regarding Benefit-Risk

Vonoprazan is a potassium-competitive acid blocker that suppresses gastric acid secretion. In NDAs 215152 and 215153, it has been administered in combination with clarithromycin and amoxicillin or with amoxicillin alone, respectively, for the treatment of *H. pylori* infection in adults. These 505(b)(2) applications rely in part on FDA's previous findings of safety and effectiveness for the listed drugs Amoxil (amoxicillin) capsules (NDA 050549) and Biaxin (clarithromycin) tablets (NDA 050662).

The primary support for approval of these applications is from study HP-301, a three-arm study comparing vonoprazan triple therapy and vonoprazan dual therapy with lansoprazole triple therapy (with clarithromycin and amoxicillin). The primary efficacy endpoint was the proportion of subjects with successful *H. pylori* eradication after the treatment period, as determined by ^{13}C-urea breath test (^{13}C-UBT), at 4 weeks after the last dose of study drug, in the modified intent-to-treat primary (mITTp) population (subjects who do not have a clarithromycin- or amoxicillin-resistant strain of *H. pylori* at baseline). In this trial, vonoprazan triple therapy and vonoprazan dual therapy were non-inferior to lansoprazole triple therapy in the mITTp population. In addition, in the mITTc population (subjects who had a clarithromycin-resistant strain of *H. pylori* at baseline), vonoprazan triple therapy and vonoprazan dual therapy were superior to lansoprazole triple therapy. Additional support for the effectiveness of vonoprazan as part of a regimen to treat *H. pylori* infection is provided by a trial from Japan, CCT-401, comparing vonoprazan triple therapy and lansoprazole triple therapy using different dosages and duration of therapy from those in HP-301.

The safety profile of the vonoprazan-containing regimens studied is generally similar to that of currently approved proton pump inhibitor/antimicrobial drug combinations for the treatment of *H. pylori* infection. The most common adverse reactions reported in subjects treated with a vonoprazan-containing regimen were diarrhea, dysgeusia, abdominal pain, headache, and vulvovaginal candidiasis. Treatment-emergent adverse events were less frequent in the vonoprazan dual therapy group than in the triple therapy groups.

Preclinical studies demonstrated that vonoprazan and its metabolites are present in rat milk, and liver lesions and increased stomach weights were noted in neonatal rats with gestational and/or lactational exposure to vonoprazan. There are no data regarding the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. There are no studies of vonoprazan-containing products in pregnant women to evaluate drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Additionally, studies are needed to further characterize the contribution of various CYP enzymes to the metabolism of vonoprazan, as well as to evaluate the drug-drug interaction potential of vonoprazan's metabolite, M-I-G.

The benefit-risk assessments for vonoprazan triple therapy and dual therapy for the treatment of *H. pylori* infection in adults are favorable. Important safety information, including findings from the animal studies, is described in labeling, and routine postmarketing surveillance will be performed. Postmarketing requirements include a pregnancy exposure registry to monitor pregnancy outcomes in women exposed to vonoprazan-containing products, an additional pregnancy study using a different design, and a lactation study to assess concentrations of vonoprazan in breast milk in lactating women receiving vonoprazan-containing products.

II. Interdisciplinary Assessment

3. Introduction

Vonoprazan is a potassium competitive acid blocker, a new class of acid-inhibitory agent. 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. This results in suppression of acid secretion which enhances the replication of *H. pylori* bacteria and the effectiveness of antimicrobial drugs.

Voquezna Triple Pak (NDA 215152) copackages two vonoprazan 20 mg tablets, four amoxicillin 500 mg capsules, and two clarithromycin 500 mg tablets. Voquezna Dual Pak (NDA 215153) copackages two vonoprazan 20 mg tablets and six amoxicillin 500 mg capsules.

The proposed indication for both NDAs is treatment of *H. pylori* infection in adults. The recommended oral dosage of Voquezna Triple Pak is vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each given twice daily, and of Voquezna Dual Pak is vonoprazan 20 mg given twice daily plus amoxicillin 1,000 mg three times daily. The medications should be taken for 14 days with or without food.

H. pylori is a gram-negative bacterium that infects the epithelial lining of the stomach. It affects over 50% of the adult population worldwide (Lamb and Chen 2013) and 30 to 40% of the US population (Chey and Wong 2007). *H. pylori* infection is usually asymptomatic but may have clinically significant manifestations such as dyspepsia (non-ulcer or functional), peptic ulcer disease, atrophic gastritis, gastric adenocarcinoma, gastric mucosa-associated lymphoid tissue lymphoma, and iron deficiency anemia.

There is evidence for an etiologic role of *H. pylori* infection in peptic ulcer disease and gastric cancer. Treatment of *H. pylori* infection will reduce the risk of peptic ulcer recurrence and may reduce the incidence of gastric cancer.

Among the currently available treatment options, clarithromycin-based triple therapy or bismuth-based quadruple therapy are recommended first-line treatment options in North America. *H. pylori* eradication rates have been steadily diminishing in the United States as clarithromycin resistance has been increasing worldwide (Thung et al. 2016).

Currently available Food and Drug Administration (FDA)-approved treatment options for *H. pylori* infection are presented in Table 3.

Table 3. FDA-Approved Treatment Options for *H. pylori* Infection

Drug Regimens	Comment
Dual Therapy	Lower efficacy compared with triple/quadruple therapy
Omeprazole 40 mg QD + Clarithromycin 500 mg TID for 14 days	
Lansoprazole 30 mg TID + Amoxicillin 1 g TID for 14 days	Amoxicillin-based dual therapy is limited to patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.
Clarithromycin Triple Therapy	May not be an effective treatment option in regions where clarithromycin resistance exceeds 15%
Omeprazole 20 mg BID + Clarithromycin 500 mg BID + Amoxicillin in 1 g BID treatment option for 10 days (Omeclamox-Pak)	
Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 10-14 days	
Esomeprazole 40 mg QD + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 10 days	
Rabeprazole 20 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 7 days	
Bismuth Quadruple Therapy	
Omeprazole 20 mg BID + Pylera (bismuth subcitrate potassium 140 mg/ metronidazole 125 mg/tetracycline 125 mg) 3 capsules QID for 10 days	
Histamine-2 receptor antagonist+ copackaged bismuth subsalicylate 524.8 mg QID, metronidazole 250 mg QID, and tetracycline 500 mg QID for 14 days	
Triple therapy	
Talicia (fixed dose combination capsule contains 12.5 mg of rifabutin, 250 mg of amoxicillin, and 10 mg of omeprazole)- 4 capsules every 8 hours with food for 14 days	

Source: Adapted from NDA 213004,Multidisciplinary review Table 2-1.
Abbreviations: BID, twice daily; QD, once daily; QID, four times daily; TID, three times daily

The Division of Anti-Infectives (DAI) granted qualified infectious disease product designation for the copackaged double and triple therapy products on May 5, 2021. Vonoprazan was initially developed by Takeda in Japan, Asia (outside of Japan), and Europe. It is approved in Japan for treatment of *H. pylori* infection, reflux esophagitis, treating and preventing gastric ulcer (GU), and duodenal ulcer (DU). The current Applicant (Phathom) has licensed the exclusive rights to develop, manufacture, and commercialize vonoprazan in the United States, Europe, and Canada for treatment of *H. pylori* infection, (b) (4) Nineteen phase 1 studies (healthy subjects) and 22 phase 2/3 studies in acid-related indications, including *H. pylori*, have been conducted. This NDA contains the HP-301 pivotal phase 3 study in *H. pylori* as well as the CCT-401 supportive phase 3 study (different dosage and duration of treatment) in treatment of *H. pylori* infection.

Review Issue List

The review issues in Section 3.1 were identified and are discussed in Sections 6.3 and 7.7, respectively.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- COVID-19 Impact on Visit 4 Evaluations in HP-301
- Non-inferiority (NI) Margin Determination for HP-301

3.1.2. Key Review Issues Relevant to Evaluation of Risk

- Liver lesions and increased stomach weights in neonatal rats with gestational and/or lactational exposure to vonoprazan (TAK-438)
- Risk of Bone Fracture

3.2. Approach to the Review

Nineteen phase 1 studies (healthy subjects) and 22 phase 2/3 studies with vonoprazan have been conducted. This NDA contains the HP-301 pivotal phase 3 study in *H. pylori* as well as the CCT-401 supportive phase 3 study (different dosage and duration) for the indication of treatment of *H. pylori* infection. It was agreed with the Applicant at the pre-NDA stage that results of the HP-301 trial and the CCT-401 study would be analyzed separately.

Table 4 provides an overview of the clinical trials important to the review of Voquezna Triple and Dual Pak's efficacy and safety.

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Voquezna Triple Pak and Dual Pak

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
HP-301 (NCT 04167670)	Male and female patients with *H. pylori* infection *H. pylori* positive with at least 1 of: Dyspepsia lasting at least 2 weeks, functional dyspepsia, recent/new non-bleeding peptic ulcer, history of peptic ulcer not treated for *H. pylori* infection, need for long-term NSAID at a stable dose	Randomized (1:1:1), open-label dual therapy, double-blind, active-control, triple therapy parallel-group	Vonoprazan regimens: Triple therapy: vonoprazan 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg BID Dual therapy: vonoprazan 20 mg BID and amoxicillin 1000 mg TID Control regimen: lansoprazole 30 mg, amoxicillin 1000 mg, and clarithromycin 500 mg BID Number treated: 1039 Duration: 14 days	Primary: *H. pylori* eradication rate in subjects who did not have a clarithromycin or amoxicillin-resistant strain of *H. pylori* at baseline 4 weeks after end of treatment Secondary: Eradication rate in subjects infected with a clarithromycin-resistant strain of *H. pylori* and overall subjects, 4 weeks after end of treatment	975/ 1046 randomized 1039 treated	103 centers United States, United Kingdom, Bulgaria, Czech Republic, Hungary, Poland

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
TAK-438/CCT-401 (NCT 01505127)	Male and female patients with *H. pylori* infection with healed gastric ulcer or duodenal ulcer	Randomized (1:1:1:1), double-blind, double-dummy, active-control, parallel-group	1st-line eradication: Treatment: vonoprazan 20 mg, amoxicillin 750 mg,and clarithromycin 200 mg or 400 mg BID Control: lansoprazole 30 mg, amoxicillin 750 mg, and clarithromycin 200 mg or 400 mg BID 2nd-line eradication: vonoprazan 20 mg, amoxicillin 750 mg, and metronidazole 250 mg BID Number treated: 650 Duration 7 days	Primary: *H. pylori* eradication 4 weeks after end of first-line treatment Secondary: *H. pylori* eradication 4 weeks after end of second-line treatment	648/650	46 Japan

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled"
Abbreviations: BID, twice daily; DB, double-blind; LTE, long-term extension study; MC, multicenter; N, number of subjects; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized

4. Patient Experience Data

The primary endpoint for Study HP-301 was *H. pylori* eradication rate.

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	
☐	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 proposed drug products are copackaged products that contain vonoprazan/amoxicillin/clarithromycin (triple therapy) and vonoprazan/amoxicillin (dual therapy), respectively. Amoxicillin and clarithromycin are part of the FDA-approved combination treatments for *H. pylori* infection. Clarithromycin is a strong cytochrome P450 (CYP) 3A inhibitor as well as an inhibitor of P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATP1B1 and OATP1B3). Consequently, drug-drug interaction (DDI) potential with the triple therapy is significantly different and wide-ranging compared to the dual therapy. Refer to Section 8.2.2 for details on the DDI risk assessment and recommended mitigation for the use of dual and triple therapy. Clarithromycin exposures are known to be associated with QT prolongation. See Section 7.2 for the summary of QT related findings in the safety population of the pivotal phase 3 trial (HP-301). Refer to the FDA-approved amoxicillin and clarithromycin prescribing information for the overall summary of general clinical pharmacology and pharmacokinetics (PK) as well as for the complete details on the respective DDI risk assessment for these two drugs.

The following is the summary of general clinical pharmacology and PK for vonoprazan (Table 6). All vonoprazan PK information is from healthy adults receiving vonoprazan alone unless noted otherwise.

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Vonoprazan: potassium-competitive acid blocker (PCAB). The drug is the first member of a new EPC which shares a site of action with current proton pump inhibitors (PPIs), but differs in chemical structure and mechanism of inhibition of the H+, K+-ATPase enzyme system.
Mechanism of action	Vonoprazan inhibits the H+, K+-ATPase enzyme in the final step of acid secretion into the stomach. Vonoprazan binds to the active proton pumps in a noncovalent and reversible manner. Vonoprazan does not require activation by acid and may selectively concentrate in the parietal cells in both the resting and stimulated states.
Active moieties	The active moiety is vonoprazan.
QT prolongation	At a dose six 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. The study evaluated the mean difference in the post-dose, time-matched, baseline adjusted QTcF between vonoprazan and placebo and between moxifloxacin and placebo (ddQTcF). A by-time point analysis was also performed. Findings from the ddQTcF endpoint indicated no effect of vonoprazan plasma concentrations on ddQTcF and by-time analysis findings excluded the 10 msec threshold at both dose levels tested for ΔΔQTcF. See IRT-QT consult response dated 2/22/2022 for additional details.
	General Information

Characteristic	Drug Information
Bioanalysis	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	The available vonoprazan PK data from patients with *H. pylori* infection are too limited to allow PK comparison between healthy subjects versus patients.
Drug exposure at steady state following the therapeutic dosing regimen	**Parameter** / **Geometric Mean (GM) (CV%)[a]**: AUC_{0-12} (hour*ng/mL) 271 (30); C_{max} (ng/mL) 36 (31). [a] Based on the Reviewer's non-compartmental analyses in 21 healthy adult subjects receiving 20 mg vonoprazan BID. Data source: studies TAK-438_114 (n=10) and TAK-438/CPH-401 (n=11). With the proposed use of vonoprazan as triple therapy, i.e., with amoxicillin and clarithromycin (a strong CYP3A inhibitor), the mean vonoprazan C_{max} and AUC exposures are expected to increase at least 1.9- and 1.8-fold, respectively, compared to when vonoprazan is used alone. See the inhibition/induction of metabolism section in this table below.
Range of effective dosage(s) or exposure	The relationship between vonoprazan exposures and the efficacy endpoint of *H. pylori* eradication rates is unknown. The proposed vonoprazan 20 mg BID regimen is supported by the efficacy and safety results from the phase 3 trial (Study HP-301).
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).
Dosage proportionality	Vonoprazan C_{max} and AUC increased in an approximately dose proportional manner over the dose range of 10 mg to 40 mg.
Accumulation	At the proposed dosage (i.e., 20 mg BID), mean steady state vonoprazan C_{max} and AUC_{0-12} estimates were 1.5- and 1.8- fold higher, respectively, compared to the mean estimates from the same subjects on Day 1 (Data source: Study TAK-438_114, n=10).
Time to achieve steady-state	Steady-state vonoprazan plasma concentrations are achieved by Day 3 to 5.
Bridge between to-be-marketed and clinical trial formulations	The formulation used in the pivotal clinical trial is same as the to-be-marketed formulation.
	Absorption
Bioavailability	Absolute bioavailability of vonoprazan is unknown.
T_{max}	1.5 hours (Range: 0.8 hour to 4 hours)
Food effect (fed/fasted) Geometric least square mean ratio (GMR) and 90% confidence interval (CI)	**AUC GMR (90% CI)** / **C_{max} GMR (90% CI)** / **Delay in T_{max}**: 1.13 (1.09-1.18) / 1.05 (0.98-1.12) / Approximately 2 hours. The food effect was evaluated with a meal that provided approximately 884 calories, with 551 (62%) calories from fat, 203 calories (23%) from carbohydrate, and 124 calories (14%) from protein. The meal was started 30 minutes prior to dosing (Data source: Study TAK-438_109, n=24).

Characteristic	Drug Information
	Distribution
Volume of distribution	Mean (CV%) = 695 (35%) L
Plasma protein binding	Vonoprazan protein binding in human plasma is 85%-88% over the concentration range of 100-1000 ng/mL.
Drug as substrate of transporters	Vonoprazan is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, or OATP1B3.
	Elimination
Mass balance results	Following a single 20 mg oral dose of [^{14}C]vonoprazan, the overall mean recovery of radioactivity in urine + feces was 98.5% (67.4% of the dose excreted in urine and 31.1% excreted in feces). Of the total radioactivity in urine, vonoprazan and its metabolites M-I, M-I-G, M-II, M-III, and M-IV-Sul accounted for 12.0%, 2.8%, 20.6%, 0.1%, 1.1%, and 11.4%, respectively. The remaining 52% of the total radioactivity recovered in urine was attributed to other components (not specified). Of the total radioactivity in feces, vonoprazan and its metabolites M-I, M-I-G, M-II, M-III, and M-IV-Sul accounted for 4.4%, 1.0%, not detected, 0.2%, 2.4%, and 15.9%, respectively. The remaining 76.1% of the total radioactivity recovered in feces was attributed to other components (not specified).
Clearance (CL/F)	Mean (CV%) = 74 (32%) L/hour
Half-life	Mean (CV%) = 7 (27%) hour
Metabolic pathway(s)	Vonoprazan is metabolized by multiple enzymes, including CYP3A4/5, CYP2B6, CYP2D6, CYP2C19, and SULT2A1.
Primary excretion pathways (% dosage)	In a mass-balance study, the predominant route of excretion of total radioactivity was via urinary excretion. 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.
	Intrinsic Factors and Specific Populations
Body weight	POP-PK analyses concluded that body weight is a covariate associated with vonoprazan clearance. Compared to a reference subject of 70 kg body weight, the predicted AUC and C_{max} estimates were 11.2% and 22% higher in subjects with lower body weight (55 kg which is the 10th percentile of the analysis dataset) and 8.2% and 14.6% lower in subjects with higher body weight (85 kg which is the 90th percentile of the analysis dataset), respectively. Compared to a reference subject of 70 kg body weight, the predicted AUC estimates at steady state are 25% higher for a subject with 40 kg body weight and 25% lower for a subject with 120 kg weight. The observed effect of weight on vonoprazan PK is not considered clinically relevant for the proposed indication.
Age	POP-PK analyses concluded that age is a covariate associated with apparent volume of distribution estimates. The predicted C_{max} estimates were 27% higher in a 23-year-old subject (10th percentile of the analysis dataset) and 11.1% lower in an 85-year-old subject (90th percentile of the analysis dataset). The effect of age on vonoprazan AUC is not reported, likely due to expected minimal effect based on the available dataset. The observed effect of age on vonoprazan PK is not considered clinically relevant for the proposed indication.
Renal impairment	Vonoprazan is to be administered with clarithromycin and amoxicillin as triple therapy or amoxicillin as dual therapy as copackaged drug products. Based on the PK data from a dedicated renal impairment study, the proposal to avoid vonoprazan's use (as triple or dual therapy) in patients with severe renal impairment (GFR < 30 mL/min) is reasonable. In addition, this recommendation aligns with the use of clarithromycin and amoxicillin, as both drugs are not recommended in patients with severe renal impairment (GFR < 30 mL/min) without dosage adjustments.

<table>
<tr><th>Characteristic</th><th>Drug Information</th></tr>
<tr><td>Hepatic impairment</td><td>The use of vonoprazan (as triple or dual therapy) is not recommended in patients with moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment based on the PK data from a dedicated hepatic impairment study.</td></tr>
<tr><td>Genetics</td><td>CYP2C19: CYP2C19 polymorphisms have been evaluated in clinical studies and there were no considerable differences in the pharmacokinetics of vonoprazan based on CYP2C19 metabolizer status. In addition, a population PK analysis did not identify CYP2C19 metabolizer status as a significant covariate affecting vonoprazan exposures. See Section 8.1 for additional details.

CYP2D6: The role of CYP2D6 in vonoprazan metabolism is inconclusive. The effect of CYP2D6 genotype and the associated CYP2D6 metabolizer status on vonoprazan exposure is unknown.</td></tr>
<tr><td colspan="2">Drug Interaction Liability (drug as perpetrator)</td></tr>
<tr><td>Inhibition/induction of metabolism</td><td>In vitro, vonoprazan inhibits CYP2B6, CYP2C19, and CYP3A4/5 in a time- and concentration-dependent manner. Predictions of potential clinical DDIs using in vitro findings and static mechanistic models suggest that the vonoprazan 20 mg BID regimen when administered alone or with clarithromycin inhibits CYP2B6, CYP2C19, and CYP3A4/5 as summarized below:
<table>
<tr><th rowspan="2">Enzyme (Substrate)</th><th colspan="2">AUC Ratio Estimates (based on in vitro data and static mechanistic models)</th></tr>
<tr><th>Vonoprazan 20 mg BID Alone</th><th>Vonoprazan 20 mg BID with Clarithromycin</th></tr>
<tr><td>CYP2B6 (Bupropion)</td><td>1.47</td><td>1.49</td></tr>
<tr><td>CYP2C19 (Proguanil)</td><td>1.49</td><td>1.51</td></tr>
<tr><td>CYP3A4/5 (Midazolam)</td><td>2.49</td><td>3.32</td></tr>
</table>
Results from a clinical DDI study showed midazolam (sensitive CYP3A4 substrate) C_{max} and AUC increased 1.9-fold when midazolam was administered after repeated doses of vonoprazan compared to administration alone.

In a separate DDI study that evaluated the recommended vonoprazan (CYP3A4 substrate and inhibitor) dosing regimen, i.e., 20 mg BID, as a part of triple therapy with a lower clarithromycin (CYP3A4 substrate and strong inhibitor) dose of 400 mg BID (proposed dose of 500 mg BID) and lower amoxicillin dose of 750 mg BID for 7 days, and compared exposures to those when individual drug is administered alone at the same dosing regimens, vonoprazan C_{max} and AUC_{0-12} increased by 1.9-fold and 1.8-fold, whereas, clarithromycin C_{max} and AUC_{0-12} increased by 1.6-fold and 1.5-fold, respectively.

Publications with clinical data show that vonoprazan, when administered at doses lower than the recommended dose for the treatment of H. pylori, attenuates anti-platelet functions of clopidogrel (a prodrug of which the efficacy depends on conversion to the active metabolite primarily mediated by CYP2C19) (Kagami et al. 2018; Higuchi et al. 2022).

The metabolite TAK-438 M-III showed induction potency for CYP2B6 and CYP3A4 at concentrations higher than the clinically relevant concentrations (mean C_{max} at steady state is approximately 0.09 µM)</td></tr>
</table>

Characteristic	Drug Information
Inhibition/induction of transporter systems	Vonoprazan inhibits P-gp (IC_{50} of 50.3 µM), MATE1 (11.8 µM), and OCT1 (2.2 µM) in vitro at concentrations higher than the clinically relevant concentrations (mean vonoprazan C_{max} at steady state when administered as triple therapy is approximately 0.2 µM).

Source: Reviewer summarized data based on data from Sections 6, 8, and 14, as well as the Applicant-submitted in vitro and in vivo study reports.
Abbreviations: AUC, area under the curve; AUC_{tau}, area under the curve during a dosing interval; BCRP, breast cancer resistance protein; BID, twice daily; C_{max}, maximum plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; GMR, geometric mean ratio; HPLC, high performance liquid chromatography; GFR, glomerular filtration rate; IC_{50}, Half-maximal inh bitory concentration; MATE, Multidrug efflux transporters, MS, mass spectrometry; OCT, organic cation transporter; P-gp, P-glycoprotein, PK, pharmacokinetic; SD, standard deviation; SULT, Sulfotransferase; T_{max}, time to maximum plasma concentration.

5.1. Nonclinical Assessment of Potential Effectiveness

In vitro studies with vonoprazan demonstrated potassium competitive inhibition of gastric acid formation in porcine (half maximal inhibitory concentration [IC_{50}] =19.3 to 29.9 nmol/L) and rabbit gastric glands (IC_{50}=0.3 μmol/L) in a noncovalent and reversible manner by selective inhibition of the H+, K+-ATPase enzyme. The vonoprazan liver metabolites M-I, M-II, and M-III did not inhibit this enzyme at the concentrations tested (up to 10 μmol/L) and the metabolite M-IV-Sul only weakly inhibited the enzyme (IC_{50}= 4120 μmol/L). In animals in vivo, vonoprazan inhibited gastric acid in pylorus ligated rats and dogs with cannulated Heidenhain pouches. Complete inhibition of gastric acid secretion with vonoprazan was found in rats dosed with 4 mg/kg at 3 hours after dosing or 1 mg/kg (stimulated), and in dogs administered 1 mg/kg at 1, 3, and 6 hours post-dosing.

Vonoprazan has no known antibacterial activity. Vonoprazan was unable to inhibit the production of ammonia produced from *H. pylori* American Type Culture Collection (ATCC) 43504 urease sample. The minimum inhibitory concentration of amoxicillin and clarithromycin but not vonoprazan were calculated when amoxicillin, clarithromycin, or vonoprazan was incubated alone with six strains of *H. pylori*: ATCC 43504, ATCC 43526, ATCC 43579, ATCC 43629, ATCC 49503, and ATCC 700392. The minimum inhibitory concentration (MIC) range of amoxicillin was 0.03 to 0.12 mcg/mL while the MIC range of clarithromycin was 0.03 to 0.12 mcg/mL. The addition of vonoprazan did not change the MIC of amoxicillin, clarithromycin, or metronidazole when incubated with strains of *H. pylori* (ATCC 43504, ATCC 43526, ATCC, 43579, ATCC 43629, ATCC 49503, and ATCC 700392). The MIC range for amoxicillin was 0.03 to 0.06 μg/mL while the MIC range for clarithromycin was 0.03 to 0.25 mcg/mL. No in vitro nor in vivo studies testing the antimicrobial activity of amoxicillin or clarithromycin were submitted in these NDAs nor in the reference abbreviated new drug applications (ANDAs). No in vivo studies testing the antimicrobial activity of amoxicillin or clarithromycin in the presence of vonoprazan were submitted in these NDAs. The reference ANDAs indicate activity of both amoxicillin and clarithromycin against *H. pylori*. Additionally, published literature reveals evidence of antimicrobial activity for both amoxicillin and clarithromycin. The antimicrobial activity of amoxicillin was assessed against *H. pylori* Pylo 112, Institut Pasteur Collection (CIP) 101260, Culture Collection University of Gothenburg (CCUG) 19104, CCUG 19107, and CCUG 19110 strains attached to Hep-2 epithelial cells. A bactericidal effect was observed in a dose-dependent manner. Both amoxicillin and clarithromycin demonstrated antimicrobial activity in an assay measuring intracellular killing of *H. pylori* UdA203 in Hep-2 cells. These data support the antimicrobial activity of amoxicillin and clarithromycin against *H. pylori*.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

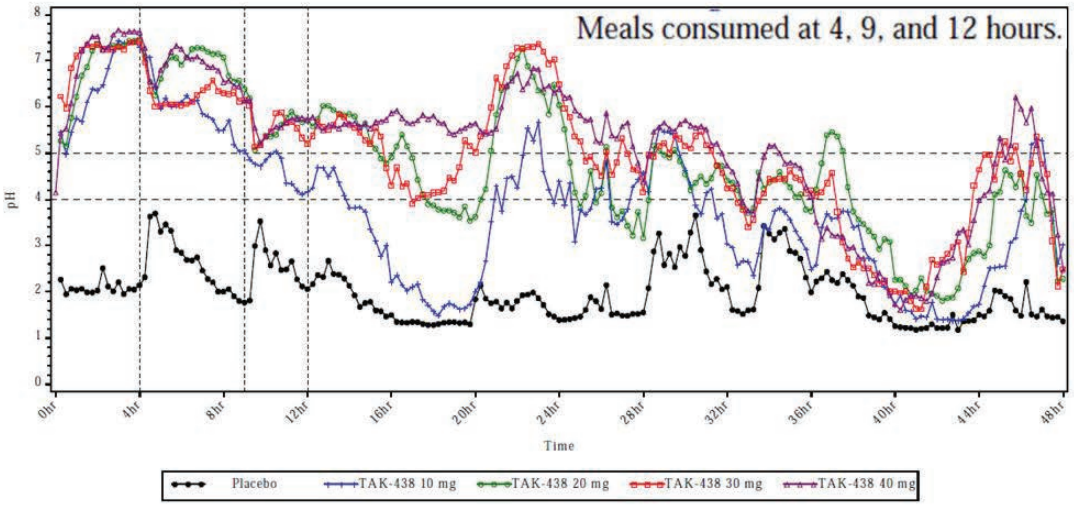
The Applicant’s proposed dosages for vonoprazan triple and dual therapies were same as the dosages evaluated in the pivotal trial HP-301 and the proposed dosages are acceptable for approval.

For triple and dual therapies, the proposed dosages for amoxicillin and clarithromycin are the same as the dosages recommended within the respective FDA-approved prescribing information as part of the triple and dual therapies for *H. pylori* infection (in adults).

The proposed vonoprazan dosages in triple and dual therapies are primarily supported by the safety and efficacy data from the pivotal trial HP-301. See Section 6.2.1.4 for efficacy results of the HP-301 trial.

The dosage selection for the HP-301 trial was based on the safety and efficacy findings from the TAK-438/CCT-401 trial, in which the evaluated vonoprazan dosage was the same as the dosage being proposed. However, the TAK-438/CCT-401 trial evaluated a lower amoxicillin and clarithromycin dosage than the dosage being proposed for triple and dual therapies. In addition, the dose-response findings from a multiple ascending dose study (Study TAK-438_107) supports the proposed dosage regimen of 20 mg twice daily (BID) because the inhibitory effect of vonoprazan on acid secretion increases with repeated daily dosing in a dose-dependent manner and reaches a maximum at the 40 mg daily dose on Day 7. Vonoprazan at doses ≥20 mg shows a clear elevation in pH levels compared with placebo (Figure 1).

Figure 1. Mean Intragastric pH Versus Time Profiles on Day 7 After Multiple Daily Doses Ranging From 0 to 40 mg



Source: Adapted from Figure 11.k, Study TAK438-107 Clinical Study Report

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. HP-301

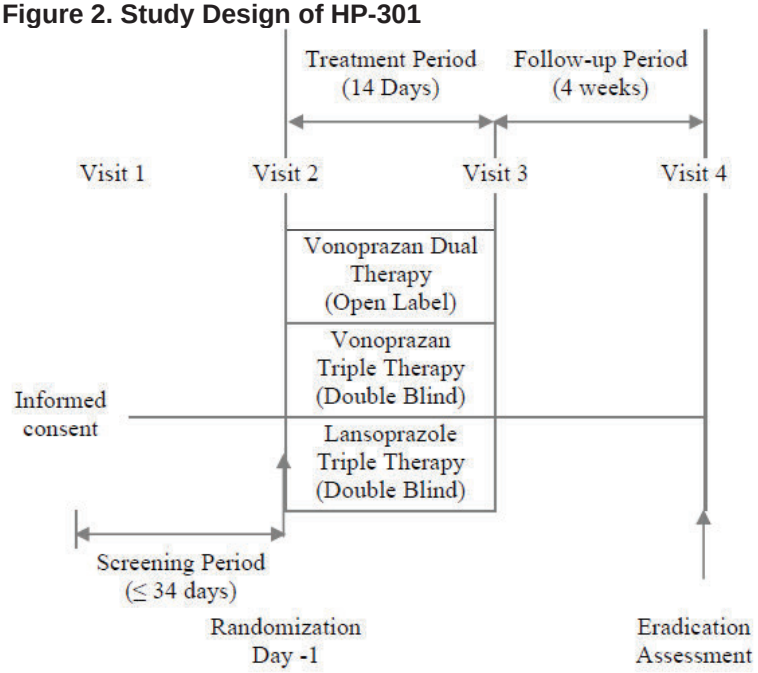
6.2.1.1. Design, HP-301

Refer to Section 15 for the protocol synopsis.

Study HP-301 was the phase 3 pivotal study conducted in the United States and Europe. Approximately 975 subjects with confirmed *H. pylori* infection were randomized 1:1:1 to receive the test triple regimen (vonoprazan 40 mg, amoxicillin 2 g, and clarithromycin 1 g daily), test dual regimen (vonoprazan 40 mg and amoxicillin 3 g daily) or active control regimen (lansoprazole 60 mg, amoxicillin 2 g, and clarithromycin 1 g daily) for 14 days. After the last

dose of the study drug, subjects proceeded to the follow-up period of 4 weeks. The vonoprazan triple therapy arm and the lansoprazole triple therapy arm were blinded, while the vonoprazan dual therapy arm was open-label. The study schematic is summarized in Figure 2.

Figure 2. Study Design of HP-301



Source: Clinical Study Report, Figure 9.a

The Applicant proposed a non-inferiority margin of 10% for both investigational regimens compared to the active control. The Division agreed to this margin. See Section 6.2.2 for detailed discussion on non-inferiority margin justification.

6.2.1.2. Eligibility Criteria, HP-301

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.

Inclusion criteria

(1) The subject is ≥ 18 years of age at the time of informed consent signing.
(2) The subject has at least one of the following clinical conditions with confirmed *H. pylori* infection demonstrated by a positive ^{13}C-UBT during the Screening Period.

- Dyspepsia (i.e., pain or discomfort centered in the upper abdomen) lasting at least 2 weeks
- A confirmed diagnosis of functional dyspepsia
- A recent / new diagnosis of (non-bleeding) peptic ulcer
- A history of peptic ulcer not previously treated for *H. pylori* infection
- A requirement for long-term non-steroidal anti-inflammatory drug (NSAID) treatment at a stable dose of the NSAID

Exclusion criteria

(3) The subject has gastric or duodenal ulcer with endoscopic evidence of current or recent bleeding.
(4) The subject is receiving colchicine.
(5) The subject has cutaneous lupus erythematosus or systemic lupus erythematosus.
(6) The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to randomization.
(7) The subject has Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.
(8) The subject has a history or clinical manifestations of significant central nervous system, cardiovascular, pulmonary, hepatic, renal, metabolic, other gastrointestinal, urological, endocrine or hematological disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.
(9) The subject has a history of malignancy (including mucosa-associated lymphoid tissue lymphoma) or has been treated for malignancy within 5 years prior to the start of the Screening Period (Visit 1) (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
(10) The subject has acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, or tests positive for the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or HCV RNA. However, subjects who test positive for HCV antibody, but negative for HCV RNA are permitted to participate.
(11) The subject has any of the following abnormal laboratory test values at the start of the Screening Period:

- Creatinine levels: >2 mg/dL (>177 μmol/L).
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN.

6.2.1.3. Statistical Analysis Plan, HP-301

The following analysis populations were included in the study. The Applicant and the review division agreed on the statistical analysis plan prior to the trial's completion.

- Modified intent-to-treat (mITT) Analysis Set: all randomized subjects with *H. pylori* infection documented by ^{13}C-UBT and biopsy (i.e., culture or histology) at baseline.
- Modified Intent-to-Treat primary (mITTp) Set: the subset of subjects in the mITT Set who did not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline.
- Per-Protocol (PP) Analysis Set: mITT subjects with all of the following:
    - Visit 4 occurs between 28 and 56 days after the end of treatment with documented diagnostic testing by ^{13}C-UBT, unless the subject has documented persistence of *H. pylori* infection at any time after the end of treatment
    - At least 75% of each study drug was taken, unless caused by treatment failure.
    - An antimicrobial known to be effective against *H. pylori* was not taken within 7 days of Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure

– A proton pump inhibitor or high dose (as per below) H2-receptor antagonist was not taken within 14 days of Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure.

- Per Protocol primary (PPp) Analysis Set: mITTp subjects meeting all of above 4 criteria listed for PP analysis set.
- Safety (SAF) Analysis Set: all subjects who received at least 1 dose of study drug.
- Pharmacokinetic (PK) Analysis Set: all subjects who have received at least one dose of study drug and who have at least 1 evaluable post-dose PK concentration value.

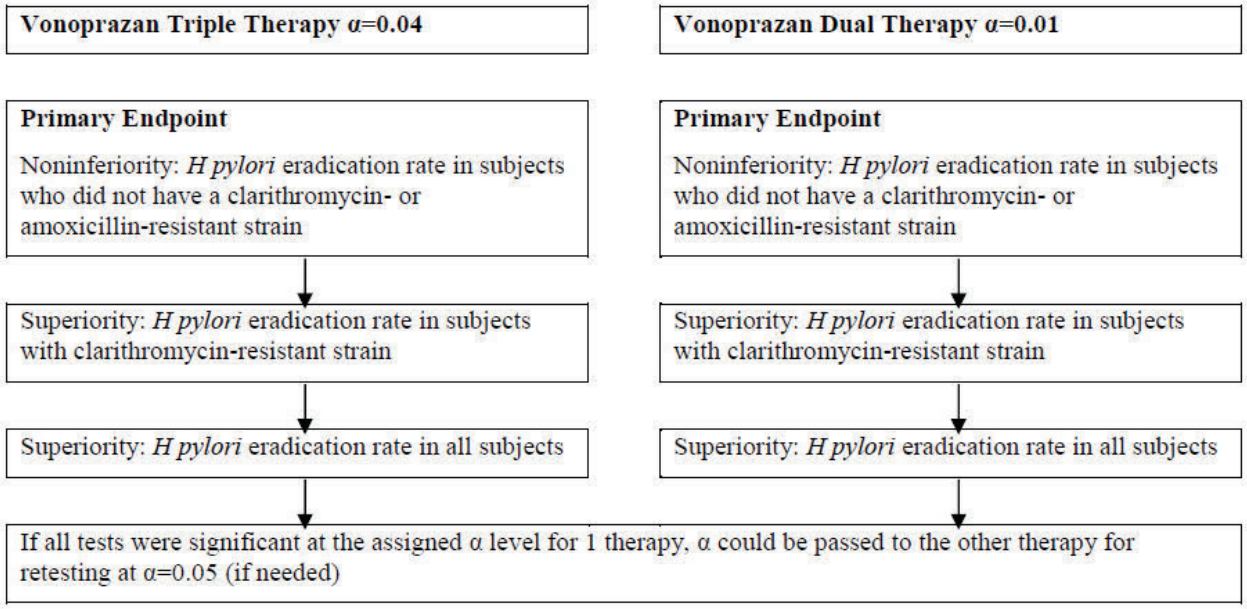
Reviewer comment: In the review, we define a Modified Intent-to-Treat Clarithromycin-Resistant (mITTc) set, which is the subset of subjects in the mITT Set who had a clarithromycin resistant strain of H. pylori at baseline.

The primary analysis was conducted using the mITTp population.

The primary efficacy endpoint was the proportion of subjects with successful *H. pylori* eradication after the treatment period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, in the mITTp (subjects who do not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline). The secondary efficacy endpoints were the proportion of subjects with successful *H. pylori* eradication after the treatment period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, in the mITTc (subjects who had a clarithromycin resistant strain of *H. pylori* at baseline) and the proportion of subjects with successful *H. pylori* eradication after the treatment period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug among all mITT subjects. Subjects who did not have a postbaseline ^{13}C-UBT would be considered treatment failures, i.e., “not eradicated.”

To control the overall family-wise type-I error rate at a level of two-sided $\alpha = 0.05$, an α level of 0.04 was initially assigned to the vonoprazan triple therapy, and an α level of 0.01 was initially assigned to the vonoprazan dual therapy. For each therapy, the 1-sided p-value for the respective non-inferiority or superiority test must be less than the assigned $\alpha/2$ to be significant. The p-value reported for a superiority test corresponds to a traditional p-value with a null hypothesis of no treatment effect. A p-value reported for a non-inferiority test signifies the probability of the observed results or those more extreme with a null hypothesis that the treatment effect equals the non-inferiority margin. If non-inferiority is declared from the primary efficacy analysis of a therapy, testing for that therapy will continue to the next endpoint following the testing hierarchy in Figure 3. If all endpoints are significant for a therapy, the α can be passed to the other therapy, if needed. Therefore, endpoints for the other therapy can be retested at the 0.05 level in hierarchical order until a 1-sided p-value is > 0.025.

Figure 3. Testing Hierarchy of HP-301



Source: Summary of Clinical Efficacy, Figure 2.a

The non-inferiority of vonoprazan triple therapy to lansoprazole triple therapy, and vonoprazan dual therapy to lansoprazole triple therapy, was evaluated with a Farrington and Manning test with a non-inferiority margin of 10% for the difference in *H. pylori* eradication rates between treatments. The noninferiority test was 1-sided with an overall significance level of α/2 for each pair of treatments. The point estimate and 2-sided (1- α)% confidence interval (CI) of the difference in *H. pylori* eradication rates between each of the pairs of treatments were calculated via the Miettinen and Nurminen method.

To account for the COVID-19 impact, the visit window was modified to allow late (>56 days post-treatment) ^{13}C-UBT results as well as those obtained 1 day early (day 27 posttreatment) to be included in the analyses for the primary and secondary endpoints. Sensitivity analyses were added to assess the impact of this change. See Section 6.2.1 for detailed discussion.

6.2.1.4. Results of Analyses, HP-301

Of the 3385 subjects screened for the study, 1046 subjects from 103 sites were randomized to treatment.

Table 7. Subject Disposition, Trial HP-301

Disposition Outcome	Vonoprazan Dual Therapy N=349	Vonoprazan Triple Therapy N=349	Lansoprazole Triple Therapy N=348
Subjects randomized, n	349	349	348
mITT population	324	338	330
mITTp population	265	262	255
mITTc population	56	73	72
PP population	265	280	277
PPp population	218	219	212
Safety population	348	346	345

Disposition Outcome	Vonoprazan Dual Therapy N=349	Vonoprazan Triple Therapy N=349	Lansoprazole Triple Therapy N=348
Discontinued study drug[a], n (%)	11 (3.2)	14 (4)	11 (3.2)
Pre-treatment event (PTE) or adverse event (AE) or serious adverse event (SAE)[a]	3 (0.9)	8 (2.3)	5 (1.4)
Significant protocol deviation[a]	2 (0.6)	0	0
Lost to follow-up[a]	0	2 (0.6)	1 (0.3)
Voluntary withdrawal[a]	0	1 (0.3)	1 (0.3)
Withdrawal of consent[a]	1 (0.3)	0	0
Lack of efficacy[a]	1 (0.3)	0	0
Other[a]	4 (1.1)	3 (0.9)	4 (1.2)
Discontinued study[b], n (%)	15 (4.3)	18 (5.2)	14 (4.0)
Pre-treatment event (PTE) or adverse event (AE) or serious adverse event (SAE)[b]	1 (0.3)	7 (2.0)	4 (1.1)
Significant protocol deviation[b]	3 (0.9)	1 (0.3)	0
Lost to follow-up[b]	0	3 (0.9)	3 (0.9)
Voluntary withdrawal[b]	0	1 (0.3)	1 (0.3)
Withdrawal of consent[b]	4 (1.1)	1 (0.3)	3 (0.9)
Other[b]	7 (2.0)	5 (1.4)	3 (0.9)

Source: Reviewer's analysis
[a] Percentages are based on number of treated subjects
[b] Percentages are based on number of randomized subjects
Abbreviations: AE, adverse event; mITT, modified intent-to-treat; n, number of patients in specified population or group; N, number of patients in treatment arm; PP, per-protocol; PTE, pre-treatment event; SAE, serious adverse event

Demographic characteristics are listed in Table 8. The three groups had similar distributions in these characteristics. All subjects were between 20 and 87 years of age. Approximately 62% of subjects were female, 43% of subjects were from the United States, and 41% of subjects were from Poland.

Table 8. Baseline Demographic and Clinical Characteristics, All Randomized Subjects, Trial HP-301

Characteristic	Vonoprazan Dual Therapy N=349	Vonoprazan Triple Therapy N=349	Lansoprazole Triple Therapy N=348
Sex, n (%)			
Female	210 (60.2)	226 (64.8)	216 (62.1)
Male	139 (39.8)	123 (35.2)	132 (37.9)
Age, years			
Mean (SD)	51.9 (13.5)	50.7 (13.9)	51.6 (13.6)
Median (min, max)	52 (20, 80)	51 (20, 81)	52 (21, 87)
Age group, years, n (%)			
<45	101 (28.9)	128 (36.7)	109 (31.3)
≥45 to <65	171 (49.0)	145 (41.5)	174 (50.0)
≥65 to <75	68 (19.5)	67 (19.2)	53 (15.2)
≥75	9 (2.6)	9 (2.6)	12 (3.4)
Race, n (%)			
American Indian or Alaska Native	0 (0)	1 (0.3)	1 (0.3)
Asian	4 (1.1)	6 (1.7)	6 (1.7)
Black or African American	22 (6.3)	30 (8.6)	25 (7.2)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0)	0 (0)
White	316 (90.5)	307 (88.0)	312 (89.7)
Other	4 (1.1)	1 (0.3)	3 (0.9)
Unknown or Not Reported	2 (0.6)	4 (1.1)	1 (0.3)

Characteristic	Vonoprazan Dual Therapy N=349	Vonoprazan Triple Therapy N=349	Lansoprazole Triple Therapy N=348
Ethnicity, n (%)			
Hispanic or Latino	95 (27.2)	99 (28.4)	89 (25.6)
Not Hispanic or Latino	251 (71.9)	249 (71.3)	259 (74.4)
Unknown or Not Reported	3 (0.9)	1 (0.3)	0 (0)
Country of participation, n (%)			
Bulgaria	42 (12.0)	42 (12.0)	38 (10.9)
Czechia	7 (2.0)	7 (2.0)	4 (1.1)
United Kingdom	5 (1.4)	1 (0.3)	2 (0.6)
Hungary	9 (2.6)	8 (2.3)	8 (2.3)
Poland	136 (39.0)	141 (40.4)	149 (42.8)
United States	150 (43.0)	150 (43.0)	147 (42.2)

Source: Reviewer's Analysis
Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Table 9 displays results for the primary and secondary efficacy analyses.

Table 9. *H. pylori* Eradication Rate (%) 4 Weeks After Treatment Completion, HP-301

mITTp Population (all mITT subjects who did not have a clarithromycin- or amoxicillin-resistant strain at baseline)

Parameter	Vonoprazan Dual Therapy	Vonoprazan Triple Therapy	Lansoprazole Triple Therapy
N	265	262	255
Success, n (%)	208 (78.5)	222 (84.7)	201 (78.8)
Difference vonoprazan-lansoprazole (adjusted CI)[a]	-0.3% (-9.6%, 9.0%)	5.9% (-1.1%, 12.9%)	
Two-sided p-value for non-inferiority	0.007	<0.0001	

mITTc Population (all mITT subjects with clarithromycin-resistant strain at baseline)			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	56	73	72
Success, n (%)	39 (69.6)	48 (65.8)	23 (31.9)
Difference vonoprazan-lansoprazole (95% CI)	37.7% (20.5%, 52.6%)	33.8% (17.7%, 48.1%)	
Two-sided p-value for superiority	<0.0001	<0.0001	
mITT Population			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	324	338	330
Success, n (%)	250 (77.2)	273 (80.8)	226 (68.5)
Difference vonoprazan-lansoprazole (95% CI)	8.6% (1.9%, 15.4%)	12.3% (5.7%, 18.8%)	
Two-sided p-value for superiority	0.013	0.0003	

Source: Reviewer's analysis. Confidence intervals are calculated with pre-specified Miettinen and Nurminen method.
[a] Adjusted based on 1% and 4% two-sided type-I error rates for comparing vonoprazan dual therapy and triple therapy to lansoprazole triple therapy. The corresponding vonoprazan-lansoprazole 95% CI's for dual and triple therapies are (-7.4%, 6.8%) and (-0.8%, 12.6%), respectively.
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; N, number of patients in treatment group; n, number of patients with given characteristic

The vonoprazan triple therapy was non-inferior to the active control in the mITTp population with a two-sided type I error rate of 0.04. The vonoprazan triple therapy was also superior to the active control in the mITTc and mITT populations with a two-sided type I error rate of 0.04.

The vonoprazan dual therapy was non-inferior to the active control in mITTp with a two-sided type I error rate of 0.01. The vonoprazan dual therapy was also superior to the active control in mITTc with a two-sided type I error rate of 0.01. After using α passed from tests of the triple therapy (as described in the statistical analysis plan), the vonoprazan dual therapy was superior to the active control in mITT with a two-sided type I error rate of 0.05.

Hence, with control of the overall type I error rate across comparisons defined for different regimens and populations, both vonoprazan triple therapy and vonoprazan dual therapy were non-inferior to the active control in the mITTp population, superior to the active control in the mITTc population, and superior to the active control in the mITT population.

Additional subgroup analyses are available in Section 16.

Comparison between Two Vonoprazan Therapies

The table below summarizes the comparison of *H. pylori* eradication rates between two vonoprazan treatment regimens in trial HP-301. The vonoprazan triple therapy had numerically higher eradication rates compared to vonoprazan dual therapy in mITTp and mITT populations, with p-values of 0.063 and 0.255, respectively. The vonoprazan dual therapy had a numerically higher eradication rate compared to vonoprazan triple therapy in the mITTc population with p-value of 0.639. These analyses were post hoc, and no statistical significance was met. The vonoprazan dual therapy was open-label while the vonoprazan triple therapy was blinded.

Table 10. *H. pylori* Eradication Rate (%) 4 Weeks After Treatment Completion, HP-301

Analysis Population	Vonoprazan Dual Therapy	Vonoprazan Triple Therapy	Two-sided t-test p-value
mITTp	208/265 (78.5)	222/262 (84.7)	0.063
mITTc	39/56 (69.6)	48/73 (65.8)	0.255
mITT	250/324 (77.2)	273/338 (80.8)	0.639

Source: Reviewer's Analysis
Abbreviations: mITT, modified intent-to-treat

6.2.2. CCT-401

6.2.2.1. Design, CCT-401

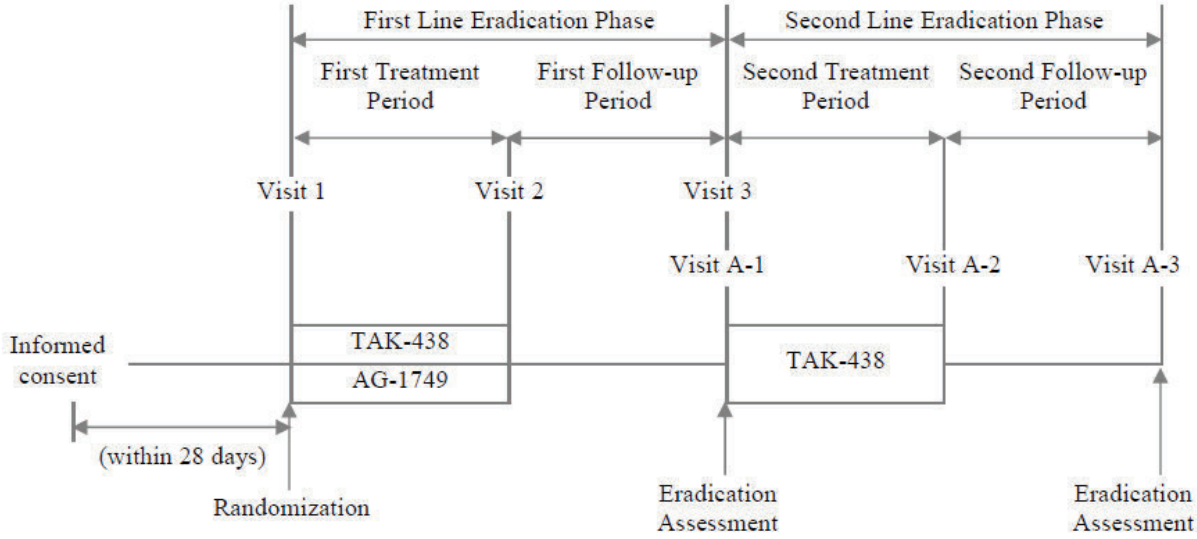
Refer to Section 15 for the protocol synopsis.

Study CCT-401 was a phase 3 study conducted in Japan. Subjects with confirmed *H. pylori* infection and cicatrized GU or DU were randomized 1:1:1:1 to receive one of the following 4 regimens for 7 days as the first line eradication phase treatment.

- Vonoprazan (TAK-438) 40 mg, amoxicillin 1.5 g, clarithromycin 400 mg daily
- Vonoprazan (TAK-438) 40 mg, amoxicillin 1.5 g, clarithromycin 800 mg daily
- Lansoprazole (AG-1749) 60 mg, amoxicillin 1.5 g, clarithromycin 400 mg daily
- Lansoprazole (AG-1749) 60 mg, amoxicillin 1.5 g, clarithromycin 800 mg daily

After the completion of first line eradication treatment, subjects were followed in an observation phase for four weeks. Subjects considered unsuccessful after first line eradication proceeded to the second line eradication phase (treated with vonoprazan 40 mg, amoxicillin 1.5 g, metronidazole 500 mg daily for 7 days). After the completion of second line eradication treatment, subjects were followed in another observation phase for four weeks. The study schematic is summarized in Figure 4.

Figure 4. Study Design of CCT-401



Source: Clinical Study Report, Figure 9.a

The originally planned sample size was (b) (4) subjects. After a pre-planned blinded sample size re-estimation, the total sample size was increased to 648 subjects.

The study was planned to use a non-inferiority margin of 10% for comparing the primary efficacy endpoint between the two arms, but the test arm was declared superior to control in a post hoc analysis.

Though the doses of amoxicillin and clarithromycin were lower, and treatment was given for fewer days compared to the proposed doses and duration, this study can support the efficacy of a higher dose and longer duration regimen.

6.2.2.2. Eligibility Criteria, CCT-401

Key eligibility criteria are summarized in this section and the full criteria are available in Section 15.

Inclusion criteria

(1) The subject was *H. pylori*-positive (confirmed by a rapid urease test, culture, ^{13}C-urea breath test, or stool *H. pylori* antigen test before the start of the study drug administration) at the start of the study (Visit 1).
(2) The subject had endoscopically cicatrized GU or DU. Subjects with a history of ulcer, confirmed by an interview or a medical record, were allowed to participate, even if their cicatrized ulcer had disappeared.
(3) The subject was a male or female outpatient (including inpatient for examination) ≥ 20 years of age at the time of informed consent signing.

Exclusion criteria

(1) The subject had donated at least 400 mL of blood within the 90 days prior to the start of the study (Visit 1).
(2) The subject had any of the following conditions at the start of the study (Visit 1): acute upper gastrointestinal bleeding, GU or DU characterized by defective mucosa with white coating (with or without adherent blood clots) 3 mm or more in size, acute gastric mucosal lesion, or acute duodenal mucosal lesion. However, subjects with gastric or duodenal erosion were permitted to participate.
(3) The subject had undergone any surgery which might affect gastric acid secretion (e.g., upper gastrointestinal tract resection, vagotomy), or such surgery was scheduled for the subject.
(4) Medicinal therapy was not indicated because the subject's condition accompanied perforation, pyloric stenosis, or severe bleeding, or for other reasons.
(5) The subject had, or had a history of, Zollinger-Ellison syndrome or other gastric acid hypersecretion disorders.
(6) The subject was receiving colchicine for his/her hepatic or renal disorder.
(7) The subject had any serious neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrinological, or hematologic disorders.
(8) The subject had a history of malignancy or was treated for malignancy within 5 years prior to the start of the study (Visit 1). However, subjects who had recovered completely from cutaneous basal cell carcinoma or from cervical carcinoma in situ were permitted to participate.
(9) The subject had acquired immunodeficiency syndrome (AIDS) or hepatitis, was a human immunodeficiency virus (HIV) carrier, or tested positive for the hepatitis B surface

antigen (HBsAg) or the hepatitis C virus (HCV) antibody. However, subjects who tested negative for HCV antigen or HCV-RNA were permitted to participate.

(10) The subject had infectious mononucleosis.

(11) The subject had any organic disease of the brain or spinal cord.

(12) The subject had any of the following abnormal laboratory test values at the start of the study (Visit 1):

- Creatinine > 2 mg/dL
- ALT or AST > 2.5 × ULN
- Total bilirubin > 2 × ULN

6.2.2.3. Statistical Analysis Plan, CCT-401

The following analysis populations were included in the study.

- Full Analysis Set (FAS): subjects who were randomized to the study treatments and received at least one dose of the study drugs
- Per-Protocol Set (PPS), first line eradication phase: among the subjects in the FAS, those who, had no major protocol violation, satisfied the minimum protocol requirements, and were evaluable for the primary endpoint
- Per-Protocol Set (PPS), second line eradication phase: among the subjects in the FAS, those who had no major protocol deviation, satisfied the minimum protocol requirements, and were evaluable for the secondary endpoint
- Safety Data Analysis Set (SAF): Subjects who received at least one dose of the study drug

The primary analysis was conducted using the FAS population.

The primary efficacy endpoint was *H. pylori* eradication four weeks after the completion of first line eradication treatment (confirmed by ^{13}C-urea breath test). The secondary efficacy endpoint was *H. pylori* eradication four weeks after the completion of second line eradication treatment (confirmed by ^{13}C-urea breath test). Comparison between vonoprazan triple therapy and lansoprazole triple therapy was conducted using a Farrington and Manning non-inferiority test, with a non-inferiority margin of 10% and a two-sided type I error rate of 0.05. The vonoprazan triple therapy group included subjects who were randomized to receive clarithromycin 400 mg daily or 800 mg daily together with vonoprazan and amoxicillin. The lansoprazole triple therapy group included subjects who were randomized to receive clarithromycin 400 mg daily or 800 mg daily together with lansoprazole and amoxicillin.

A blinded sample size re-estimation was planned after approximately 200 subjects pooled from all arms were evaluable for the primary efficacy endpoint. The total number of subjects needed for the primary efficacy endpoint of 80%, 85%, and 90% power were to be calculated. If the number needed was between 400 (b) (4) and 760, the sample size would be adjusted based on the sample size re-calculation. If the number was larger than 760, then 760 would be used.

Reviewer comment: The interim analysis was completed after 190 subjects were evaluable for the primary efficacy endpoint, with a pooled eradication rate of 155/190 (81.6%). The sample size needed per group for 80%, 85% and 90% power was calculated to be 238, 272 and 318. The total sample size was changed to 648.

6.2.2.4. Results of Analyses, CCT-401

A total of 826 subjects were enrolled in the study and 650 were randomized in the first line eradication phase (from 65 sites). All randomized subjects were treated with at least one dose of study drug. Approximately 99% of randomized subjects completed the first line eradication phase and the first follow-up period of the study.

Table 11. Patient Disposition, CCT-401

Disposition Category	Vonoprazan Triple Therapy N=329 n (%)	Lansoprazole Triple Therapy N=321 n (%)
Patients randomized	329 (100)	321 (100)
FAS population	329 (100)	321 (100)
SAF population	329 (100)	321 (100)
PPS population first line eradication phase	315 (95.7)	308 (96.0)
Discontinued first line eradication treatment	6 (1.8)	3 (0.9)
Pretreatment Event/AE	3 (0.9)	2 (0.6)
Major Protocol Deviation	2 (0.6)	1 (0.3)
Abnormal Laboratory Test Value	1 (0.3)	0
Discontinued first follow-up period	5 (1.5)	2 (0.6)
Pretreatment Event/AE	2 (0.6)	1 (0.3)
Major Protocol Deviation	2 (0.6)	1 (0.3)
Abnormal Laboratory Test Value	1 (0.3)	0
Number of Subjects Who Moved on to Second Line Eradication Phase	14 (4.3)	36 (11.2)
PPS population second line eradication phase	14 (4.3)	34 (10.6)

Source: Reviewer's analysis
Abbreviation: AE, adverse event; FAS, full analysis set; PPS, per protocol set; SAF, safety analysis set; N, number of patients in treatment arm; n, number of patients in specified population or group

Demographic characteristics are listed in the following table. The two groups had similar distributions in these characteristics. All subjects were between 20 and 88 years of age. 40% of subjects were female. All subjects were from Japan.

Table 12. Baseline Demographic and Clinical Characteristics, Safety Population, CCT-401

Characteristic	Vonoprazan Triple Therapy N=329	Lansoprazole Triple Therapy N=321
Sex, n (%)		
Female	133 (40.4)	127 (39.6)
Male	196 (59.6)	194 (60.4)
Age, years		
Mean (SD)	55.2 (12.3)	53.9 (12.9)
Median (min, max)	56 (20, 82)	55 (20, 88)
Age group, years, n (%)		
<65	247 (75.1%)	250 (77.9%)
≥65	82 (24.9%)	71 (22.1%)
Race, n (%)		
Asian	329 (100)	321 (100)
Ethnicity, n (%)		
N/A		

Characteristic	Vonoprazan Triple Therapy N=329	Lansoprazole Triple Therapy N=321
Country of participation, n (%)		
Japan	329 (100)	321 (100)

Source: adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Primary Efficacy Analysis

The table below displays results for the primary endpoint analysis. The eradication rate of vonoprazan triple therapy was significantly higher than the active control. Note that the Applicant's planned non-inferiority analysis as displayed in the table below did not exclude subjects who had clarithromycin- or amoxicillin- resistant strains at baseline.

Table 13. *H. pylori* Eradication Rate (%) 4 Weeks After Completion of First Line Eradication Treatment, FAS, CCT-401

Parameter	Vonoprazan Triple Therapy	Lansoprazole Triple Therapy
N	329	321
Success, n (%)	300 (91.2)	243 (75.7)
Difference vonoprazan-lansoprazole (95% CI)	15.5% (9.9%, 21.1%)	
p-value for non-inferiority		<0.0001
p-value for superiority		<0.0001

Source: Reviewer's analysis
Abbreviations: CI, confidence interval; N, number of patients in treatment group; n, number of patients with given characteristic

Reviewer comment: Although the Applicant's primary non-inferiority analysis did not exclude subjects who had clarithromycin- or amoxicillin-resistant strains at baseline, the result still supports the efficacy of vonoprazan with a significantly higher eradication rate compared to the active control.

Additional Analysis on Two Clarithromycin Dosings

In CCT-401, all subjects were randomized 1:1 to receive clarithromycin 200 mg or 400 mg BID. Table 14 summarizes trial CCT-401 *H. pylori* eradication rates four weeks after completion of first line treatment, with different clarithromycin dosings. Vonoprazan was superior to lansoprazole for both clarithromycin dosings, with both two-sided p-values less than 0.05.

Table 14. *H. pylori* Eradication Rate (%) 4 Weeks After Completion of First Line Eradication Treatment by Baseline Clarithromycin Dosing (FAS population), CCT-401

Dose of Clarithromycin	Vonoprazan Triple Therapy (N=329) n (%)	Lansoprazole Triple Therapy (N=321) n (%)	Two-sided t-test p-value
200 mg BID	152/168 (90.5)	129/164 (78.7)	0.0028
400 mg BID	148/161 (91.9)	114/157 (72.6)	<0.0001

Source: Reviewer's Analysis
Abbreviations: BID, twice daily; N, number of patients in treatment group; n, number of patients with given characteristic

Secondary Efficacy Analysis

The *H. pylori* eradication rate 4 weeks after the completion of the second line eradication was 49/50 (98.0%) in the subjects who were treated in the second line eradication phase. The one subject who failed the second line eradication treatment was originally assigned to lansoprazole triple therapy in the first line eradication phase.

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. COVID-19 Impact on Visit 4 Evaluations in HP-301

Issue

Shortly after this study began enrolling subjects, the SARS-COV-2 virus, which causes COVID-19, was declared a global pandemic by the World Health Organization. Study data collection was amended for subjects to capture visits missed/delayed and assessments completed via alternative methods due to COVID-19 related reasons.

To account for the COVID-19 impact, the visit window for Visit 4 was modified to allow late (>56 days post-treatment) ^{13}C-UBT results as well as those obtained 1 day early (day 27 post-treatment) to be included in the analyses for the primary and secondary endpoints.

Assessment

Table 15 below summarizes all post screening ^{13}C-UBT results in study HP-301. All negative results collected between Day 28 and Day 56 post-treatment completion are considered successful eradications in the mITT population. Following statistical analysis plan (SAP) version 3, all negative results collected on Day 27 and after Day 56 post-treatment completion are also considered successful eradications in the primary and secondary efficacy analyses.

Table 15. ^{13}C-UBT Test Results 4 Weeks After Treatment Completion, mITT set, HP-301

Test Results	Vonoprazan Dual Therapy N=324	Vonoprazan Triple Therapy N=338	Lansoprazole Triple Therapy N=330
Negative, n (%)	255 (78.7)	278 (82.2)	226 (68.5)
Success in primary and secondary analyses	250 (77.2)	273 (80.8)	226 (68.5)
Day 28 – Day 56, inclusive	237 (73.1)	259 (76.6)	214 (64.8)
=Day 27	2 (0.6)	5 (1.5)	3 (0.9)
>Day 56 [a]	11 (3.4)	9 (2.7)	9 (2.7)
<Day 27, considered as Failure in all analyses	5 (1.5)	5 (1.5)	0
Positive, n (%)	58 (17.9)	48 (14.2)	94 (28.5)
Missing, n (%)	11 (3.4)	12 (3.6)	10 (3.0)
Eradication Success under COVID impact, n (%)	13 (4.0)	14 (4.1)	12 (3.6)

Source: Reviewer's analysis
[a] Subject (b) (6) had tests on Day 26 and Day 77 post-treatment, both negative (success). Only Day 77 result is used in the analyses. Subject (b) (6) had tests on Day 36 and Day 88 post-treatment, both negative (success). Only Day 36 result is used in the analyses.
Abbreviations: mITT, modified intent-to-treat; N, number of patients in treatment group; n, number of patients with given characteristic

The three groups were comparable in terms of percentage of successful eradications affected by COVID-19 due to earlier (by 1 day) and delayed (any day after Day 56) study visits 4 weeks after treatment completion (all being approximately 4%). The three groups were also comparable in terms of missing eradication status four weeks after treatment completion.

Table 16 shows the sensitivity analyses on the primary and secondary efficacy endpoints where only negative results obtained between Day 28 and Day 56 (inclusive) were considered successful.

Table 16. *H. pylori* Eradication Rate (%) 4 Weeks (Day 28-56) After Treatment Completion, HP-301

mITTp Population (all mITT subjects who did not have a clarithromycin- or amoxicillin-resistant strain at baseline)			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	265	262	255
Success, n (%)	197 (74.3)	214 (81.7)	190 (74.5)
Difference vonoprazan-lansoprazole	-0.2%	7.2%	
Two-sided p-value for non-inferiority	0.0101	<0.0001	
mITTc Population (all mITT subjects with clarithromycin-resistant strain at baseline)			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	56	73	72
Success, n (%)	37 (66.1)	42 (57.5)	22 (30.6)
Difference vonoprazan-lansoprazole	35.5%	27.0%	
Two-sided p-value for superiority	<0.0001	0.001	
mITT Population			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	324	338	330
Success, n (%)	237 (73.1)	259 (76.6)	214 (64.8)
Difference vonoprazan-lansoprazole	8.3%	11.8%	
Two-sided p-value for superiority	0.022	0.0008	

Source: Reviewer's analysis
Abbreviations: mITT, modified intent-to-treat; N, number of patients in treatment group; n, number of patients with given characteristic

In the sensitivity analyses, the vonoprazan triple therapy was non-inferior to the active control in the mITTp with a two-sided type I error rate of 0.04. The vonoprazan triple therapy was also superior to the active control in the mITTc and mITT with a two-sided type I error rate of 0.04.

After using α passed from tests of the triple therapy, the vonoprazan dual therapy was non-inferior to the active control in the mITTp with a two-sided type I error rate of 0.05. The vonoprazan dual therapy was superior to the active control in the mITTc and mITT with a two-sided type I error rate of 0.05.

Conclusion

Expanding the visit 4 window in order to address more missed/delayed visits due to the COVID-19 pandemic did not overly impact the results. The sensitivity analyses using the original visit window for visit 4 supported the efficacy conclusions for vonoprazan from study HP-301.

6.3.2. Non-inferiority Margin Determination for HP-301

Issue

The following three treatment regimens were investigated in Study HP-301.

- vonoprazan 40 mg, amoxicillin 2 g, and clarithromycin 1 g daily for 14 days
- vonoprazan 40 mg and amoxicillin 3 g daily for 14 days
- lansoprazole 60 mg, amoxicillin 2 g, and clarithromycin 1 g daily for 14 days

The Applicant set the NI margins at 10% for Study HP-301 according to the following study results (these historical eradication rates are from studies in which the clarithromycin and amoxicillin resistance rate was low, approximately 5% or less):

- A pooled estimate of the eradication rate for lansoprazole triple therapy for 14 days of 83%.
- A pooled estimate of the eradication rate for a regimen of amoxicillin 2 g and clarithromycin 1 g of 42%.
- An eradication rate for amoxicillin 3 g of 0% (0/66) from a double-blind, multicenter study evaluating lansoprazole and amoxicillin dual therapy (Harford et al. 1996).

Detailed historical *H. pylori* eradication rates for amoxicillin/clarithromycin and lansoprazole triple therapy are listed in the following table.

Table 17. Historical *H. pylori* Eradication Rate (%)

Amoxicillin/Clarithromycin Dual 14-Day Therapy	
Study	**Eradication Rate (%)**
Prevacid Study M95-392	64% (51/80)
Lansoprazole/Amoxicillin/Clarithromycin 14-Day Triple Therapy	
Study	**Eradication Rate (%)**
Prevacid Study M95-392	83% (58/70)
Prevacid Study M93-131	85% (47/55)
Prevacid Study M93-399	82% (103/126)
Amoxicillin/Clarithromycin Dual 10-Day Therapy	
Study	**Eradication Rate (%)**
Prilosec Study 1	37% (31/84)
Prilosec Study 2	36% (30/83)
Prilosec Study 3	32% (32/99)

Source: HP-301 Clinical Study Report, Table 9.e

Assessment

For a comparison between a vonoprazan + additional therapy regimen and the lansoprazole triple therapy regimen, a non-inferiority margin M1 is considered justified if the eradication rate of lansoprazole triple therapy would exceed the eradication rate of a placebo + additional therapy regimen by at least M1.

For the comparison of vonoprazan dual therapy to lansoprazole triple therapy, the difference in the *H. pylori* eradication rate for triple therapy with lansoprazole (83%, pooled data) versus treatment with 3 g amoxicillin alone (0%, 0/66) is 83%, with a lower limit 95% CI of 75%. A

non-inferiority margin of 10% retains 87% of the lansoprazole triple regimen treatment effect compared to amoxicillin alone.

Since the treatment duration of Prilosec studies (10 days) was shorter than that of Study M95-392 (14 days), the difference in *H. pylori* eradication rates for the amoxicillin/clarithromycin treatment between M95-392 and Prilosec studies might be reflecting the effect of longer treatment duration. Since the duration of triple therapies in trial HP-301 is 14 days, pooling data from Prilosec studies in calculation of the non-inferiority margin may not be appropriate. Comparing the amoxicillin/clarithromycin 14-day therapy (Study M95-392) and lansoprazole 14-day triple therapy (pooled lansoprazole triple therapy data from the table above), M1 is calculated to be 7.6%. The M1 of 7.6% is smaller than the proposed margin of 10%.

Considering the results of the current NI trial HP-301, given that the *H. pylori* eradication rates of the vonoprazan triple therapy and lansoprazole triple therapy in the mITTp population are 84.7% (222/262) and 78.8% (201/255), respectively, the difference in eradication rates with the adjusted 96% CI is 5.9% (-1.1%, 12.9%). The vonoprazan triple therapy is non-inferior to the lansoprazole triple therapy even using a non-inferiority margin of 7.6%.

Conclusion

For efficacy conclusions for vonoprazan in the comparison of vonoprazan dual therapy to lansoprazole triple therapy, the 10% non-inferiority margin is well-justified. The efficacy conclusions for vonoprazan in vonoprazan triple therapy remain unchanged if using a non-inferiority margin of 7.6%.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical safety studies submitted to support the safety evaluation of vonoprazan and its metabolites included pharmacology studies (primary, secondary, and safety pharmacology), pharmacokinetics studies (absorption, distribution, metabolism, and excretion), toxicology studies (repeat-dose studies in rats (up to 26 weeks) and dogs (up to 39 weeks)), genotoxicity (in vitro and in vivo), carcinogenicity (2-year studies in rats and mice), and reproductive and developmental toxicity in rats and rabbits.

Amoxicillin and clarithromycin have been previously reviewed and the safe use of these component drugs relies on the nonclinical safety data described in the prior FDA findings of safety and efficacy for the listed drugs (Amoxil (amoxicillin) NDA 050760 and Biaxin (clarithromycin) NDA 050698).

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 (more than 100-fold higher than the mean maximum plasma concentration (C_{max}) for vonoprazan 20 mg in human PK). A single dose of vonoprazan had no significant effect on blood pressure, heart rate, and electrocardiogram (ECG) in conscious dogs tested up to 20 mg/kg. A single dose of 600 mg/kg vonoprazan in male rats caused an increase in

bronchoconstriction and death in 4 of 8 animals as well as decreased tidal volume and minute volume, which recovered in surviving animals. No effects were seen in the next dose group of 100 mg/kg. In a functional observational battery in rats, mydriasis was reported at 100 mg/kg and had returned to normal by 22 hours post-dosing. Clinical signs in the rats, including decreased muscle resistance, decreased locomotor activity, partially closed eye lids, difficulty in hopping, and decrease in body temperature, were reported at 600 mg/kg. The no-effect level in this study was 30 mg/kg. In rats and dogs, vonoprazan exposure increased with greater than dose-proportionality and accumulated up to 2-fold with repeated dosing. In rats and dogs, the $t_{1/2}$ is 1.3 and 1.1 hours, respectively. In rats and dogs, absorption following a single oral dose of [^{14}C]vonoprazan was as high as 92.2% and 86.3%, respectively. Bioavailability in rats and dogs was 10.3% and 52.4%, respectively. In rats vonoprazan or its metabolites were widely distributed and were at higher concentrations in liver, kidney, intestine, lung, and stomach than in the plasma. Human metabolism of vonoprazan is predominately by CYP3A4, CYP2D6 and CYP 2C19, and SULT2A1, based on data from in vitro assays with human enzymes. Vonoprazan is metabolized in vivo to M-I, M-II, M-II, M-IV-Sul and/or N-demethylated TAK-438 in species tested. Major human metabolites (>10% of the active pharmaceutical ingredient [API]) 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 [^{14}C]vonoprazan. In both rats and dogs, the M-IV-Sul metabolite accounted for <1% of the dose in excreted urine and plasma. Vonoprazan and its metabolites do not significantly induce or inhibit CYPs.

Target Organs of Toxicity

Stomach

Increased stomach weights with histopathology including atrophy of the parietal cells, eosinophilic changes in chief cells, hyperplasia of mucus neck cells, increased inflammatory cell infiltration, squamous epithelial hyperplasia in the limiting ridge, and vacuolation of parietal cells were reported in 4-, 13-, and 26-week rat studies. Thickening of the glandular stomach wall was reported in 13- and 26-week rat studies and muscular fibrosis in the 26-week rat study. In dogs, single cell parietal cell necrosis, parietal cell atrophy, and inflammatory cell infiltration in the fundus mucosa were reported in the 4-week study, degeneration of the tunica muscularis, single cell necrosis of the fundic gland, inflammatory cell infiltration of the fundus mucosa and hyperplasia of the fundus mucosa in the 13-week study, and single cell necrosis, inflammatory cell infiltration in fundic mucosa, stomach thickening, degeneration of the muscular layer, hyperplasia of the fundic mucosa, in the fundic gland, and vacuolation of parietal cells in the 26-week study.

Liver

Vacuolation of midlobular hepatocytes were reported in 100 mg/kg rats in the 4-week study, 13-week study, and 30 mg/kg males in the 26-week study.

Adrenal Gland

Hypertrophy in the zona glomerulosa of the adrenal gland was reported in 100 and 300 mg/kg males and 300 mg/kg females in the 13-week rat study and in 30 mg/kg females in the 26-week rat study.

No toxicities were associated with the metabolite M-IV-Sul in separate 13-week toxicology studies in rats up to 20 mg/kg subcutaneous (SC) dose under the conditions tested.

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. Based on the lack of genotoxicity and the short duration of use for the treatment of *H. pylori,* the clinical significance of the positive findings in the carcinogenicity studies with vonoprazan is uncertain.

Reproduction and Developmental Toxicology

Reproductive toxicology studies with vonoprazan included a fertility study in rats, an embryo-fetal development study in rats, an embryo-fetal development study in rabbits, and peri- and postnatal development (PPND) studies in rats.

In the fertility study, no changes in fertility parameters measured were reported up to the highest dose tested (300 mg/kg/day).

In embryo-fetal developmental studies 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 incidence 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 diminished 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 PPND study, changes in the F_1 animals in the 100 mg/kg dose group included liver discoloration in postnatal day (PND) 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 studies in which dams were dosed during gestation and through lactation up to doses of 100 mg/kg from gestation day (GD) 6 to lactation day (LD) 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.

Exposure Multiples

Animal exposure multiples to the human AUC for vonoprazan based on a human dose of 40 mg oral dose at steady state are presented in Table 18. Exposure multiples for vonoprazan may be slightly lower with use of the triple pack based on the higher vonoprazan clinical exposures measured with concomitant dosing with clarithromycin (see Section 14.)

Table 18. Nonclinical Studies Exposure Multiples for Vonoprazan

Study	NOAEL (mg/kg/day)	Nonclinical AUC (mcg*hr/mL)[a] [Exposure Multiple[b]]	Adverse Effects (Doses Found (mg/kg/day))
General toxicology			
4-week rat	10	0.570 [1-fold]	Increase in stomach weights (≥30) Histopathology: 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, atrophy of the parietal cells (≥30)
13-week rat	10	1.17 [2-fold]	Increased stomach weights (≥100) Inflammatory cell infiltration in the stomach (≥100) Thickening of the glandular stomach in males with mucous metaplasia (300) Vacuolation of midlobular hepatocytes (≥100 males; 300 females) Adrenal gland: hypertrophy in the zona glomerulosa (≥100 males; 300 females)
26-week rat	5 (males) 10 (females)	0.210 [0.4-fold] 1.62 [3-fold]	Thickening of the glandular stomach wall (≥10 in males) Red patch in the stomach (≥30) Increased stomach weights (≥5) Atrophy of parietal cells (≥10) Stomach mucosal fibrosis (≥10 in males and 30 in females) Stomach mucosal angiectasis (30) Inflammatory cell infiltration (30) Adrenal gland hypertrophy of the zona glomerulosa (30 females) Vacuolation of hepatocytes (30 in males)
4-week dog	0.6	0.49 [1-fold]	Parietal cell necrosis (≥2) Parietal cell atrophy (≥2) Inflammatory cell infiltration in the fundus mucosa (≥2)
13-week dog	<1	<0.92 [<1.9-fold]	Degeneration of the tunica muscularis (≥1) Hyperplasia of the fundus mucosa (≥1) Inflammatory cell infiltration of the fundic mucosa (≥1) Single cell necrosis of the fundic gland (≥1)
39-week dog	0.6	0.38 [0.8-fold]	Stomach thickening (≥2) Hyperplasia of the fundic mucosa (≥2) Single cell necrosis in the fundic gland (≥2) Inflammatory cell infiltration in the fundic mucosa (≥2)

Study	NOAEL (mg/kg/day)	Nonclinical AUC (mcg*hr/mL)[a] [Exposure Multiple[b]]	Adverse Effects (Doses Found (mg/kg/day))
			Degeneration of the stomach muscular layer (≥2)
Fertility and early embryonic development			
Rat	300[d]	64.9[e] [133-fold]	No adverse effects observed
Embryo-fetal development			
Rat	100	13.4[c] [25-fold]	External and visceral malformations (300)
Rabbit	10 (maternal)	0.74 [1.5-fold]	Clinical signs, decrease in body weights and body weight gains (30)
	30 (fetal)	4.71[f] [9.6-fold]	No adverse effects observed
Pre- and postnatal development			
Rat	10	0.56 [1-fold]	Reduced F1 pup weights (100) Hepatic discoloration in F1 pups at PND 4 (100) Increased copulatory intervals for F1 pups (100)

Source: Reviewer table from data in Applicant provided nonclinical studies
[a] Nonclinical AUC is an average of male and female AUC in the nonclinical study unless otherwise indicated.
[b] Based on mean steady state exposures in Study #TAK-438-107 (steady state AUC= 0.488 mcg*h/mL).
[c] Values for AUC from female animals in the 4-week rat repeat dose study (#TAK-438-00085)
[d] NOAEL for reproductive and developmental parameters. Clinical signs were seen at the 100 and 300 mg/kg/day doses.
[e] Values for AUC from average of male and female animals in the 13-week rat repeat dose study (#TAK-438-00143)
[f] Maternal AUC
Abbreviations: AUC, area under the curve; NOAEL, no observed adverse effect level

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

Long-term use of proton pump inhibitors is associated with safety concerns such as risk of bone fracture, C. *difficile* infection, hypergastrinemia, magnesium, vitamin B12 malabsorption, among others. Short-term use may be associated with increased risk and recurrence of C. *difficile* colitis. Risk of intestinal colonization with multidrug resistant organisms and acute interstitial nephritis are issues which may not be dose or duration dependent. It might be expected that vonoprazan and the PPIs would have a similar effect on micronutrient absorption and gastrin/parathyroid hormone (PTH)-mediated bone homeostasis. However, it is unclear if the difference in structure and the nature of the interaction with the proton pump between vonoprazan and PPIs would lead to similar interaction like PPIs. Adverse events noted in the clinical trials with vonoprazan which may be a drug class effect are summarized in section 7.6.3.

The treatment-emergent adverse events (TEAEs) of special interest identified for this submission are events associated with *C. difficile* enteric infection, bone fracture, severe cutaneous adverse reactions, hepatotoxicity, gastric cancer, hypersensitivity, and QT prolongation.

Hepatotoxicity

A drug-induced liver injury (DILI) assessment showed that none of the subjects in any of the treatment groups met biochemical Hy's Law criteria. One (0.3%) subject in the vonoprazan triple therapy group and 1 (0.3%) subject in the lansoprazole triple therapy group had a post-baseline ALT value >3 × ULN; none of the other abnormal liver function test criteria were met by any subject. There was a Temple's Corollary case, which is described under laboratory findings section below.

Table 19. Adverse Events of Special Interest Assessment, Drug-Induced Liver Injury (DILI), Safety Population, Trial HP-301

DILI Assessment	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
AE grouping related to AESI	0	1 (0.3)	1 (0.3)	-0.3 (-0.9, 0.3)	-0.0 (-0.8, 0.8)
Alanine aminotransferase increased	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Aspartate aminotransferase increased	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)

DILI Assessment	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Maximum severity					
Death	0	0	0	0 (0, 0)	0 (0, 0)
Life-threatening	0	0	0	0 (0, 0)	0 (0, 0)
Severe	0	0	0	0 (0, 0)	0 (0, 0)
Moderate	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Mild	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Serious	0	0	0	0 (0, 0)	0 (0, 0)
Deaths	0	0	0	0 (0, 0)	0 (0, 0)
Resulting in discontinuation	0	0	0	0 (0, 0)	0 (0, 0)
Relatedness	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Duration for treatment defined as 14 days.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; DILI, drug-induced liver injury; N, number of patients in treatment arm; n, number of patients with adverse event

C. *difficile* Infection

C. difficile-associated diarrhea (CDAD) has been associated with PPIs and antibacterials used in convenience packs for eradication of *H. pylori*. CDAD is included in the warnings and precautions section of the labels. Although there were no subjects with *C. difficile* infection in trial HP-301, one subject was identified in the CCT-401 study. Subject (b) (6), a 64-year-old male, completed first-line *H. pylori* eradication therapy with lansoprazole 20 mg, amoxicillin 750 mg, and clarithromycin 400 mg BID for 7 days. The subject began second-line therapy with vonoprazan 20 mg, amoxicillin 750 mg, and metronidazole 250 mg BID for 7 days approximately 2 months after completing first-line therapy. The subject was hospitalized for an appendectomy 12 days after the completion of the second-line therapy, developed diarrhea 9 days after the surgery, and was diagnosed with pseudomembranous enterocolitis.

Bone Fracture

See Section 7.7 for discussion of this review issue.

Hypersensitivity and Severe Cutaneous Adverse Reactions

The overall incidence of subjects who experienced TEAEs associated with hypersensitivity was comparable among the vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups (1.1%, 1.2%, and 1.4%).

Two subjects in each of the treatment groups had hypersensitivity TEAEs that were considered related to the study drug. Subject (b) (6) had a moderate pruritic rash and subject (b) (6) had a mild generalized rash on the vonoprazan dual therapy (VDUAL) that led to treatment

interruption. In the vonoprazan triple therapy (VTRI) group, subject (b) (6) had moderate drug hypersensitivity that led to treatment discontinuation and another subject had allergic dermatitis. Subject (b) (6), a 52-year-old female, had swelling around the eyes and mouth with itching which developed at day 1 and continued for 5 days. In the lansoprazole triple therapy (LTRI) group, subject (b) (6) had a mild rash and subject (b) (6) had mild allergic dermatitis. The hypersensitivity TEAEs were mild to moderate, ranging from mild erythematous rash to macular rash, and all were resolved. The reactions were treated with antihistamines, topical steroids, and petroleum jelly.

Table 20. Treatment-Emergent Adverse Events Associated With Hypersensitivity, Safety Population, HP-301

Preferred terms	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)
Subjects with any TEAE	4 (1.1)	4 (1.2)	5 (1.4)
Dermatitis allergic	1 (0.3)	3 (0.9)	1 (0.3)
Drug hypersensitivity	0	1 (0.3)	0
Rash	1 (0.3)	0	2 (0.6)
Rash erythematous	0	0	1 (0.3)
Rash generalized	1 (0.3)	0	0
Rash macular	0	0	1 (0.3)
Rash pruritic	1 (0.3)	0	0

Source: Clinical data scientist and clinical reviewer analysis
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; TEAE, treatment-emergent adverse events

Gastric Cancer

No TEAEs associated with gastric cancer were reported in any treatment group.

QT Prolongation

The percentages of subjects who met the most extreme criteria for abnormal QTcF results (>500 msec or >60 msec increase) was 2.3% in the vonoprazan dual therapy group, 1.4% in the vonoprazan triple therapy group, and 1.2% in the lansoprazole triple therapy group. The overall incidence of subjects with a post-baseline QTcF value >450 msec that was higher than the baseline value was 7.5% in the vonoprazan dual therapy group, 6.6% in the vonoprazan triple therapy group, both higher than in the lansoprazole triple therapy (5.5%) group. However, subjects with QTcF intervals >480 ms or >500 ms or increase of >30ms were comparable between the 3 groups. Most significant was QTcF interval >450 with increase from baseline >30 ms was noted in VDUAL (5.2%) and VTRI (3.5%) compared with the LTRI (2.3%) group. The subjects were asymptomatic except for one subject (subject (b) (6)) in the VTRI group of the HP-301 study, who died of cardiac arrest and had an increase of QTcF to 449 msec on Day 19. Of note, this subject had multiple risk factors for cardiovascular disease (see section 7.6.2.2 of this review for additional details). Although QT prolongation and arrhythmias like torsades de pointes have been noted with clarithromycin, the increased frequency of QTcF in the VDUAL (containing no clarithromycin) in comparison to the triple therapy groups with clarithromycin is to be noted. However, some of the subjects had positive risk factors for drug-induced QT prolongation (underlying conditions and concomitant medications), therefore, causality cannot be determined. In addition, the small increase in frequency of VDUAL in the > 450 msec group

and no increase compared to other comparators in >480 msec group, with no prolongation seen in the thorough QT study with vonoprazan, does not suggest a specific safety signal. Routine pharmacovigilance will be recommended.

Table 21. Abnormal QTc Results, Safety Population, HP-301

QTcF in msec	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)
QTcF			
>450	26 (7.5)	23 (6.6)	19 (5.5)
>480	5 (1.4)	6 (1.7)	4 (1.2)
>500	2 (0.6)	2 (0.6)	0
Change in QTcF interval (msec)			
Increase from baseline >30	25 (7.2)	24 (6.9)	24 (7.0)
Increase from baseline >60	8 (2.3)	5 (1.4)	4 (1.2)
QTcF interval >450 with increase from baseline >30	18 (5.2)	12 (3.5)	8 (2.3)

Source: Clinical data scientist and clinical reviewer analysis
Abbreviations: N, number of subjects; n, number of subjects who met the most extreme criteria for abnormal QTcF results; QTcF, the corrected QT interval by Fridericia

7.3. Potential Safety Concerns Identified Through Postmarket Experience

In Japan, vonoprazan is marketed in combination packs as an adjunct treatment for *H. pylori* eradication. The combination packs for primary eradication of *H. pylori* contain vonoprazan 20 mg × 2 tablets, amoxicillin hydrate 250 mg × 6 capsules, and clarithromycin 200 mg × 2 tablets/sheet/day (Vonosap Pack 400) for 7 days or vonoprazan 20 mg × 2 tablets, amoxicillin hydrate 250 mg × 6 capsules and clarithromycin 200 mg × 4 tablets/sheet/day (Vonosap Pack 800) for 7 days. As of December 25, 2020, exposure to Vonosap Pack is estimated to be approximately (b) (4) patients. Adverse drug reactions reported in ≥30 patients from spontaneous individual case study reports in the Applicant's postmarketing database, as reported from various health authorities and literature, show 1847 reports of skin and subcutaneous disorders (erythema, drug eruption, erythema multiforme, etc.), 928 reports of gastrointestinal disorders (diarrhea, abdominal pain, constipation, nausea, etc.) and 300 reports of nervous system disorders (dysgeusia, taste disorder, headache, dizziness, etc.). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among the postmarketing bone fracture cases reported with vonoprazan monotherapy, there were 4 spinal compression fractures, 2 femoral neck fractures, 1 neck fracture, 1 rib fracture, and 7 were unspecified.

Safety of vonoprazan in other acid-related gastrointestinal disorders ex-US: In short-term studies involving 5 to 40 mg/day administered for 2 to 8 weeks, the most common adverse drug reaction reported (≥5%) in vonoprazan-treated subjects was nasopharyngitis. In the short-term studies, one subject died of a severe subarachnoid hemorrhage after one dose of the study drug. This subject was a 49-year-old man with hypertension who developed headache and high blood pressure prior to administration of study drug, therefore unlikely related to the study drug. In

long-term studies with 10 to 20 mg per day for 24 to 80 weeks, subjects most commonly reported diarrhea and nasopharyngitis.

The treatment-related TEAEs in ≥1.0% of subjects in either the vonoprazan or lansoprazole groups (quadruple therapy) were pepsinogen test positive (1.3% and 0.6%, respectively), dysgeusia (1.3% and 0.6%, respectively), and dizziness (1.0% versus 1.3%). The quadruple therapy included vonoprazan 20 mg, bismuth 220 mg/clarithromycin 500 mg/amoxicillin 1000 mg or lansoprazole 30 mg/bismuth 220 mg/clarithromycin 500 mg/amoxicillin 1000 mg BID × 14 days followed by vonoprazan 20 mg or lansoprazole 30 mg once daily (QD) for up to 6 weeks (i.e., up to a total of 8 weeks of treatment).

7.4. FDA Approach to the Safety Review

Data from the HP-301 trial are the focus of the safety review. Although the CCT-401 trial included subjects with *H. pylori*, the data were not pooled for safety assessments given differences in study design, treatment duration, and drug dosages. Since vonoprazan is approved outside the United States, the postmarketing data and the safety assessments from short-term and long-term studies, including non *H. pylori* indications, submitted in the NDA were summarized.

7.5. Adequacy of Clinical Safety Database

The dosing, duration, and number of subjects in the safety database are sufficient to conduct a safety review for the treatment of *H. pylori* indication. The safety of vonoprazan triple therapy was evaluated in 675 adult patients (aged 20 to 82 years) in clinical trials in the United States, Europe, and Japan and vonoprazan dual therapy was evaluated in 348 adult patients (aged 20 to 80 years) in a clinical trial in the United States and Europe. The same dose of vonoprazan was used in both the HP-301 and CCT-401 studies but only for seven days in CCT-401. Additional subjects in the non-*H. pylori* indications treated with vonoprazan long term (outside the United States) provided supportive safety data.

In Study HP-301, the majority of the subjects in the vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups received ≥14 days of treatment (97.1%, 96.0%, and 96.5%, respectively).

In Study TAK-438/CCT-401, the majority of the subjects in the vonoprazan triple therapy and lansoprazole triple therapy groups received ≥7 days of treatment (98.2% and 98.8%, respectively).

Table 22. Duration of Exposure, Safety Population, Trial HP-301

Parameter	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)
Duration of treatment, days			
Mean (SD)	14.2 (1.8)	14 (1.4)	14.1 (2.3)
Median (Q1, Q3)	14 (14, 14)	14 (14, 14)	14 (14, 14)
Min, Max	1, 36	1, 17	1, 49
Total exposure (person weeks)	704	690	694

Parameter	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)
Patients treated, by duration, n (%)			
<7 days	2 (0.6)	4 (1.2)	3 (0.9)
≥7 to <14 days	8 (2.3)	9 (2.6)	6 (1.7)
≥14 to <21 days	336 (96.6)	333 (96.2)	335 (97.1)
≥21 days	2 (0.6)	0	1 (0.3)

Source: adex.xpt and adsl.xpt; Software: R
Duration for treatment defined as 14 days.
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

Table 23. Duration of Exposure (First Line Eradication Phase), Safety Population, Trial TAK-438/CCT-401

Parameter	Vonoprazan Triple Therapy N=329 n (%)	Lansoprazole Triple Therapy N=321 n (%)
Duration of treatment, days		
Mean (SD)	6.9 (0.6)	7 (0.4)
Median (Q1, Q3)	7 (7, 7)	7 (7, 7)
Min, Max	1, 7	1, 7
Total exposure (person weeks)	325.6	319.3
Patients treated, by duration, n (%)		
<7 days	6 (1.8)	4 (1.2)
7 days	323 (98.2)	317 (98.8)
>7 days	0	0

Source: adsl.xpt; Software: R
Duration is 7 days.
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. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns- Overall

Vonoprazan is an oral potassium competitive acid blocker, copackaged with amoxicillin and clarithromycin as a triple pack and with amoxicillin as a dual pack for treatment of *H. pylori* infection. The safety data are from the pivotal trial HP-301 in the United States, conducted in comparison to lansoprazole, amoxicillin, and clarithromycin triple therapy for 14 days. Supportive data are obtained from another trial, CCT-401 in Japan, in which vonoprazan was used in combination with low dose amoxicillin and clarithromycin for seven days. Postmarketing safety data from short-term and long-term studies in non-*H. pylori* indications were also considered. In HP-301 study, the overall incidence of TEAEs was 34.1% in the vonoprazan triple therapy group, 29.9% in the vonoprazan dual therapy group, and 34.5% in the lansoprazole triple therapy group. All groups experienced similar incidences of serious TEAEs. There were three deaths which were unrelated to the study drug. In the vonoprazan and lansoprazole triple therapy groups, gastrointestinal disorders (diarrhea, upper abdominal pain, vomiting) were the most common types of TEAEs that led to treatment discontinuation (1.7% and 1.2%, respectively). In

the vonoprazan dual therapy group, skin and subcutaneous tissue disorders were the most common types of TEAEs that led to treatment discontinuation (0.6%). The most commonly reported TEAEs, occurring at >1% in any study arm, included diarrhea, dysgeusia, and vulvovaginal mycotic infection. Laboratory findings showed risk differences among subjects with glucose >200 mg/dl but less than 250 mg/dl, neutrophils <2000 cells/ul between VDUAL versus LTRI and VTRI versus LTRI. In trial CCT-401, there were no deaths. The SAEs were not related to the study drug. The TEAEs leading to study drug discontinuation in the VTRI group were vertigo in one subject and diarrhea in two subjects. The TEAEs leading to study drug discontinuation in the LTRI group were enterocolitis hemorrhagic and eczema. The overall incidence of drug-related TEAEs was 20.4% in the VTRI group and 24.6% in the LTRI group. The most common adverse reactions in >2% of VTRI therapy treated subjects were diarrhea, dysgeusia and nasopharyngitis. The incidence of elevated transaminases was low and not more than >3x ULN. Two subjects who appeared to have predisposing risk factors developed bone fractures. There were no cases of gastric cancer or neuroendocrine tumors. Hypersensitivity reactions and a case of *C. difficile* were seen consistent with ex-US postmarketing findings. The concomitant use of amoxicillin and clarithromycin may have led to AEs more specific to the amoxicillin or clarithromycin component of the drug. No safety signals were identified in subgroup analyses.

7.6.2. Safety Findings and Concerns, Trial HP-301

7.6.2.1. Overall Treatment-Emergent Adverse Event Summary, Trial HP-301

The overall incidence of TEAEs was 34.1% in the vonoprazan triple therapy group, 29.9% in the vonoprazan dual therapy group, and 34.5% in the lansoprazole triple therapy group. All groups experienced similar incidences of serious TEAEs (1.7%, 1.4%, and 0.9%, respectively). The overall incidence of subjects who experienced TEAEs that led to treatment discontinuation was low and comparable among the vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups (0.9%, 2.3%, and 1.2%, respectively). The VTRI group had the highest number of TEAEs leading to treatment discontinuation at 9 (2.6%). In the vonoprazan and lansoprazole triple therapy groups, gastrointestinal disorders (diarrhea, upper abdominal pain, vomiting) were the most common types of TEAEs that led to treatment discontinuation (1.7% and 1.2%, respectively). In the vonoprazan dual therapy group, skin and subcutaneous tissue disorders were the most common types of TEAEs that led to treatment discontinuation (0.6%). TEAEs that led to discontinuation from study were higher in the VTRI group (2%) compared to VDUAL group (0.6%). Most of the TEAEs were mild in severity and comparable in the treatment arms (20%) and comparator (22%).

Table 24. Overview of Adverse Events, Safety Population, Trial HP-301

Event Category	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
SAE	5 (1.4)	6 (1.7)	3 (0.9)	0.6 (-1.0, 2.2)	0.9 (-0.8, 2.6)
SAEs with fatal outcome	0	2 (0.6)	1 (0.3)	-0.3 (-0.9, 0.3)	0.3 (-0.7, 1.3)
Life-threatening SAEs	0	0	0	0 (0, 0)	0 (0, 0)
AE leading to permanent discontinuation of study drug	3 (0.9)	8 (2.3)	4 (1.2)	-0.3 (-1.8, 1.2)	1.2 (-0.8, 3.1)
AE leading to dose modification of study drug	1 (0.3)	3 (0.9)	2 (0.6)	-0.3 (-1.3, 0.7)	0.3 (-1.0, 1.6)
AE leading to interruption of study drug	1 (0.3)	3 (0.9)	2 (0.6)	-0.3 (-1.3, 0.7)	0.3 (-1.0, 1.6)
AE	104 (29.9)	118 (34.1)	119 (34.5)	-4.6 (-11.6, 2.3)	-0.4 (-7.5, 6.7)
Death	0	2 (0.6)	1 (0.3)	-0.3 (-0.9, 0.3)	0.3 (-0.7, 1.3)
Life-threatening	0	0	0	0 (0, 0)	0 (0, 0)
Severe	2 (0.6)	3 (0.9)	1 (0.3)	0.3 (-0.7, 1.3)	0.6 (-0.6, 1.7)
Moderate	34 (9.8)	44 (12.7)	41 (11.9)	-2.1 (-6.7, 2.5)	0.8 (-4.1, 5.7)
Mild	68 (19.5)	69 (19.9)	76 (22.0)	-2.5 (-8.5, 3.6)	-2.1 (-8.2, 4.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Duration for treatment defined as 14 days.
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

7.6.2.2. Deaths, Trial HP-301

Three subjects (two in VTRI and one in LTRI) died during the post-treatment follow-up period of the study.

- Subject (b) (6) (Poland) was a 67-year-old male, a current smoker with obesity, atherosclerosis, dyspepsia, hypertension, and gastroesophageal reflux disease who completed a 14-day course of VTRI then experienced a cardiac arrest and died on Day 56. He was on candesartan. The immediate cause of death was unknown, and an autopsy was not performed. The investigator considered the event not related to the study drug.

MO comment: The subject appears to have had risk factors for cardiac causes of death, e.g., hypertension, obesity and smoking; therefore, it is possible that the sudden death was unrelated to the use of VTRI. A thorough QT/QTc study was conducted as part of the vonoprazan clinical program and vonoprazan was not known to cause an increase in QT interval. The VTRI contains clarithromycin, which has been associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and torsades de pointes; however, a sudden cardiac death associated with study drug would be expected to occur sooner than day 56.

- Subject (b) (6) (Hungary) was a 54-year-old male, an ex-smoker with history of arteriosclerosis, diabetes mellitus, alcoholic liver disease, hypertension, diabetic nephropathy, and gastroesophageal reflux disease. He completed 14 days of VTRI. On Day 45, the subject was admitted to the hospital with fevers, positive results for COVID-19 antigen test and developed acute respiratory insufficiency and cardiogenic shock. The subject died the same day. The investigator considered the event not related to study drug and attributed the event to COVID-19. No other AEs were recorded within a +/- 3-day window around the onset of the event.
- The third subject who died received 14 days of LTRI. Subject (b) (6) (United States) was a 56-year-old female who had history of diabetes mellitus type 2, asthma, and gastroesophageal reflux disease. She developed COVID-19 pneumonia on day 58, and died on day 94 after a prolonged hospitalization post COVID. The investigator considered the event not related to study drug and attributed the event to COVID-19.

MO comment: Subjects (b) (6) likely died of COVID-19 and the deaths were unrelated to study drugs.

Table 25. Deaths, Safety Population, Trial HP-301

Preferred Term	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Any AE leading to death	0	2 (0.6)	1 (0.3)	-0.3 (-0.9, 0.3)	0.3 (-0.7, 1.3)
Cardiac arrest	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Coronavirus infection	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Pneumonia viral	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Duration for treatment defined as 14 days.
For patient-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.2.3. Serious Adverse Events, Trial HP-301

The overall incidence of subjects with at least one serious TEAE (including the three deaths) were comparable among the vonoprazan dual therapy and vonoprazan triple therapy groups (1.7% each) and slightly lower incidence in the lansoprazole triple therapy group (0.9%). None of the serious TEAEs were considered related to the study drug and most of the serious TEAEs were outside the treatment window. Three serious TEAEs were fatal, three not recovered, and the rest recovered. About 50% of the serious TEAEs were moderate in intensity.

Table 26. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial HP-301

System Organ Class Preferred Term	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Cardiac disorders (SOC)	1 (0.3)	2 (0.6)	0	0.3 (-0.3, 0.8)	0.6 (-0.2, 1.4)
Atrial fibrillation	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Cardiac arrest	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Coronary artery occlusion	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Gastrointestinal disorders (SOC)	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 0.8)	0.3 (-0.3, 0.9)
Abdominal pain upper	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Duodenal polyp	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Hepatobiliary disorders (SOC)	1 (0.3)	0	1 (0.3)	-0.0 (-0.8, 0.8)	-0.3 (-0.9, 0.3)
Cholecystitis	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Cholecystitis acute	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Infections and infestations (SOC)	1 (0.3)	1 (0.3)	1 (0.3)	-0.0 (-0.8, 0.8)	-0.0 (-0.8, 0.8)
Corona virus infection	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 0.8)	0.3 (-0.3, 0.9)
Pneumonia viral	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Injury, poisoning and procedural complications (SOC)	1 (0.3)	1 (0.3)	0	0.3 (-0.3, 0.8)	0.3 (-0.3, 0.9)
Lower limb fracture	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Jaw fracture	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Spinal pain	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Lung cancer metastatic	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)

System Organ Class Preferred Term	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Vascular disorders (SOC)	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Peripheral ischaemia	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Serious adverse events defined as any untoward medical occurrence that, at any dose 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.
Duration for treatment defined as 14 days.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

MO comment: Section 12.3.1.2 of the clinical study report states a total of 14 serious TEAEs but a calculation by the above analysis shows a total of 16 serious TEAEs, which does not affect assessment of the safety data. The subject with abdominal pain was a 26-year-old female who developed abdominal pain, diarrhea (moderate), leukocytosis (mild), nausea (mild), and vomiting (mild). Concomitant medications taken at the onset of the SAE included: aluminum magnesium silicate, ranitidine, bismuth, ibuprofen, and pantoprazole. Pain lasted 1 day at day 33 of VDUAL, which resolved. There was a 75-year-old man with atrial fibrillation at day 40 of VDUAL, which was unrelated to study treatment, and he recovered. A 57-year-old female with cardiac risk factors of hypercholesterolemia, gastroesophageal reflux disease, hypertension, and type 2 diabetes mellitus had coronary artery occlusion at day 38 of VTRI which resolved. Troponin levels were not reported and the subject was not reported to have had chest pain, which is unusual. Subject (b) (6) *with a fatal TEAE of cardiac arrest was already described in the section above. The two subjects who died from COVID infection were also described in the death section (7.6.2.2.). A 34-year-old white male with erosive esophagitis and gastroesophageal reflux disease developed acute cholecystitis on day 1 of LTRI, was treated with antibacterials and required hospitalization. The event resolved in 5 days, but trial medication was stopped at the onset of the event. There was another subject on VDUAL who developed cholecystitis but off treatment at day 40 which resolved. A 69-year-old female with history of osteoarthritis developed lower limb fracture off treatment at day 40 of VDUAL which did not resolve. A 70-year-old female on VDUAL was diagnosed with a lung tumor at day 21 which was metastatic lung cancer. She did not follow-up at day 68. A 33-year-old on VTRI with jaw fracture was reported at day 86 but this was secondary to an assault. A 53-year-old female with spinal pain did not recover. She had osteoarthritis on VTRI. There were also cases of duodenal polyp unrelated to study drug treatment and a case of upper limb peripheral ischemia on LTRI at day 18, which recovered. No lines or ultrasound findings were reported, but the subject was noted to be a vasculopath.*

Table 27 shows the incidence of SAEs by demographic subgroups of sex, age, ethnicity and race. No specific trend of safety signal was noted in any of the subgroups. The incidence of SAEs in the VTRI arm was higher in age group >45 through <65 years compared to VDUAL and LTRI, but the number of SAEs were too small to draw any meaningful conclusions.

Table 27. Overview of Serious Adverse Events by Demographic Subgroup, Safety Population, Trial HP-301

Characteristic	Vonoprazan Dual Therapy N=348 [n/N_S (%)]	Vonoprazan Triple Therapy N=346 [n/N_S (%)]	Lansoprazole Triple Therapy N=345 [n/N_S (%)]	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Sex, n (%)					
Female	3/209 (1.4)	3/224 (1.3)	2/213 (0.9)	0.5 (-1.6, 2.6)	0.4 (-1.6, 2.4)
Male	2/139 (1.4)	3/122 (2.5)	1/132 (0.8)	0.7 (-1.8, 3.2)	1.7 (-1.4, 4.8)

Characteristic	Vonoprazan Dual Therapy N=348 [n/N_s (%)]	Vonoprazan Triple Therapy N=346 [n/N_s (%)]	Lansoprazole Triple Therapy N=345 [n/N_s (%)]	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Age group, years, n (%)					
<45	2/101 (2.0)	1/126 (0.8)	1/109 (0.9)	1.1 (-2.2, 4.3)	-0.1 (-2.5, 2.2)
≥45 to <65	0/170 (0)	4/144 (2.8)	2/171 (1.2)	-1.2 (-2.8, 0.4)	1.6 (-1.5, 4.7)
≥65 to <75	2/68 (2.9)	1/67 (1.5)	0/53 (0)	2.9 (-1.1, 7.0)	1.5 (-1.4, 4.4)
≥75	1/9 (11.1)	0/9 (0)	0/12 (0)	11.1 (-9.4, 31.6)	0 (0, 0)
Race, n (%)					
American Indian or Alaska Native	0/0 (NA)	0/1 (0)	0/1 (0)	NA	0 (0, 0)
Asian	0/4 (0)	0/6 (0)	0/6 (0)	0 (0, 0)	0 (0, 0)
Black or African American	0/22 (0)	0/30 (0)	0/25 (0)	0 (0, 0)	0 (0, 0)
Native Hawaiian or Other Pacific Islander	0/1 (0)	0/0 (NA)	0/0 (NA)	NA	NA
Not Reported	0/1 (0)	0/3 (0)	0/0 (NA)	NA	NA
Other	0/4 (0)	0/1 (0)	0/3 (0)	0 (0, 0)	0 (0, 0)
Unknown	0/1 (0)	0/1 (0)	0/1 (0)	0 (0, 0)	0 (0, 0)
White	5/315 (1.6)	6/304 (2.0)	3/309 (1.0)	0.6 (-1.1, 2.4)	1.0 (-0.9, 2.9)
Ethnicity, n (%)					
Hispanic or Latino	0/95 (0)	0/98 (0)	2/89 (2.2)	-2.2 (-5.3, 0.8)	-2.2 (-5.3, 0.8)
Not Hispanic or Latino	5/250 (2.0)	6/247 (2.4)	1/256 (0.4)	1.6 (-0.3, 3.5)	2.0 (-0.0, 4.1)
Not Reported	0/1 (0)	0/1 (0)	0/0 (NA)	NA	NA
Unknown	0/2 (0)	0/0 (NA)	0/0 (NA)	NA	NA

Source: adae.xpt; Software: R
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

7.6.2.4. Dropouts and/or Discontinuations Due to Adverse Events, Trial HP-301

The overall incidence of subjects who experienced TEAEs that led to treatment discontinuation (see Table 28 below) was low and comparable among the vonoprazan dual therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups (0.9%, 2.3%, and 1.2%, respectively). The VTRI group had the highest number of TEAEs leading to treatment discontinuation at 9 (2.6%). In the vonoprazan and lansoprazole triple therapy groups, gastrointestinal disorders (diarrhea, upper abdominal pain, vomiting) were the most common types of TEAEs that led to treatment discontinuation (1.7% and 1.2%, respectively). In the vonoprazan dual therapy group, skin and subcutaneous tissue disorders were the most common types of TEAEs that led to treatment discontinuation (0.6%).

The TEAEs leading to drug withdrawal and withdrawal from the study included dyspepsia and tongue discomfort in the VTRI group, which were deemed related to the drug. There were also subjects with hematochezia, mouth hemorrhage, and hypertension in this group leading to drug withdrawal, but were deemed unrelated to the study drug. The LTRI group had AEs of vomiting, upper abdominal pain, mild, transient diarrhea, and dizziness which were related to the study

drug and led to drug withdrawal and withdrawal from the study. There were two related TEAEs of pruritic rash and nausea in the VDUAL group leading to drug withdrawal and withdrawal from study. There was a case of papular rash on the VDUAL group and a case of mild stomatitis on the LTRI group leading to drug withdrawal but not withdrawal from the study. There were AEs of diarrhea, hypertension and drug hypersensitivity in the VTRI arm leading to drug withdrawal but not withdrawal from the study.

MO comment: The case of hypertension (mild) on VTRI was likely not related to the study therapy given the history of hypertension in the subject, even though the investigator felt it may have been related to the study therapy.

All of the TEAEs that led to treatment discontinuation were noted as recovered/resolved, except for the dyspepsia event in the vonoprazan triple therapy group that was noted as recovering/resolving.

Subject (b) (6) with diarrhea and drug hypersensitivity, subject (b) (6) with diarrhea and hypertension in the VTRI arm, subject (b) (6) with a papular rash on the VDUAL arm and subject (b) (6) with stomatitis in LTRI arm had treatment discontinuations due to these related TEAEs, but were not discontinued from the study.

An additional subject, (b) (6) developed abdominal pain (drug-related) leading to drug interruption in the VTRI arm, but not withdrawal from the therapy or study.
The following are selected narratives of subjects whose treatment was withdrawn:

- (b) (6) on VDUAL, experienced a pruritic cutaneous rash on bilateral lower extremities, bilateral upper extremities and back area of torso (moderate) which was considered a significant adverse event (AE) on day 10. The rash resolved on day 22 after treatment given for the rash.
- (b) (6) on VTRI, experienced drug hypersensitivity (moderate swelling around the eyes and mouth, itching) on day one, which was considered a significant adverse event. No therapeutic measures were administered to treat the event. Adverse events that occurred within a +/- 3-day window of the onset of the AE included abdominal pain (moderate). The investigator considered the AE to be related to study medication. The event resolved on day 5.
- (b) (6) on LTRI, participant experienced a mild mouth hemorrhage (unknown etiology). The investigator considered the AE to be not related to study medication. The event resolved on day 3.
- (b) (6) on VDUAL, experienced a moderate papular rash on the face which resolved on day 20 after drug withdrawal.
- (b) (6) on VTRI with hiatal hernia experienced a dyspepsia exacerbation on day 1. The investigator thought it was treatment related.
- (b) (6) on VTRI, experienced moderate tongue discomfort [burning of the tongue on day 10. The investigator considered the AE to be related to study medication. The event resolved on Day 40.

MO comment: In the vonoprazan and lansoprazole triple therapy groups, gastrointestinal disorders (diarrhea, upper abdominal pain, vomiting) were the most common types of TEAEs that led to treatment discontinuation. Rash was noted in the VDUAL group with one case of

hypersensitivity in the VTRI arm. The LTRI group had a case of stomatitis as noted above and perhaps the case of mild mouth hemorrhage was also related to VTRI. The case of dyspepsia with a history of hiatal hernia and an active H. pylori infection seem unlikely to be related to study therapy.

Table 28. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial HP-301

System Organ Class Preferred Term	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)	1 (0.3)	6 (1.7)	4 (1.2)	-0.9 (-2.1, 0.4)	0.6 (-1.2, 2.4)
Nausea	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Dyspepsia	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Haematochezia	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Mouth haemorrhage	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Tongue discomfort	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Abdominal pain upper	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Diarrhoea	0	2 (0.6)	1 (0.3)	-0.3 (-0.9, 0.3)	0.3 (-0.7, 1.3)
Stomatitis	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Vomiting	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Immune system disorders (SOC)	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Drug hypersensitivity	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Nervous system disorders (SOC)	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Dizziness	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Skin and subcutaneous tissue disorders (SOC)	2 (0.6)	0	0	0.6 (-0.2, 1.4)	0 (0, 0)
Rash papular	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Rash pruritic	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Vascular disorders (SOC)	0	2 (0.6)	0	0 (0, 0)	0.6 (-0.2, 1.4)
Hypertension	0	2 (0.6)	0	0 (0, 0)	0.6 (-0.2, 1.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Duration for treatment defined as 14 days.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Trial HP-301

The majority of the TEAEs reported in each of the treatment groups were mild or moderate in intensity, not related to the study therapy, and most recovered or resolved. The overall incidence of subjects with at least one severe TEAE was low and comparable among the vonoprazan dual

therapy, vonoprazan triple therapy, and lansoprazole triple therapy groups (0.6%, 1.4%, and 0.6%, respectively). The number of mild and moderate events were also comparable among the groups.

All of the severe TEAEs were considered not related to the study therapy, except for an event of neutropenia in the vonoprazan dual therapy group. Subject (b) (6) had a severe event of neutropenia reported on Day 15. The subject had normal values for neutrophils at baseline that had decreased below the normal range on Day 15 (0.97 × 109/L). The event was resolved on Day 21 without any treatment.

Table 29. Treatment Emergent Adverse Events by Severity, Causality and Outcome in the Safety Population

			Actual Treatment		
Analysis Severity/Intensity	**Analysis Causality**	**Outcome of Adverse Event**	**LTRI30 N=345**	**VDUAL20 N=348**	**VTRI20 N=346**
Mild	Not related	Not recovered/not resolved	13	12	15
		Recovered/resolved	46	54	50
		Recovering/resolving	0	4	5
		Unknown	0	0	3
	Related	Not recovered/not resolved	3	2	0
		Recovered/resolved	61	33	37
		Recovered/resolved with sequelae	0	0	1
Total number of events			123	105	111
Moderate	Not related	Not recovered/not resolved	4	14	7
		Recovered/resolved	21	16	23
		Recovered/resolved with sequelae	0	1	1
		Recovering/resolving	2	1	4
	Related	Not recovered/not resolved	5	2	2
		Recovered/resolved	21	13	17
		Recovering/resolving	0	0	3
Total number of events			53	47	57
Severe	Not related	Fatal	1	0	2
		Not recovered/not resolved	0	1	2
		Recovered/resolved	1	0	0
		Recovering/resolving	0	0	1
	Related	Recovered/resolved	0	1	0
Total number of events			2	2	5

Source: Clinical reviewer analysis
Abbreviations: LTRI, lansoprazole triple therapy; N, number of patients in treatment arm; n, number of patients with adverse event; VDUAL, vonoprazan dual therapy; VTRI, vonoprazan triple therapy

For the following three tables (Table 30, Table 31, and Table 32), the following preferred terms of the common AEs were combined into the following groups:

- Diabetes mellitus: diabetes mellitus and hyperglycemia
- Hypertension: hypertension and blood pressure increased
- Headache: headache
- Rash: rash erythematous, rash generalized, rash macular, rash popular, rash pruritic
- Pruritus: pruritus and pruritus generalized

- Vulvovaginal candidiasis: pruritus genital, vulvovaginal pruritus, urogenital infection fungal, vulvovaginal candidiasis, vulvovaginal mycotic infection, genital infection fungal
- Abdominal pain: abdominal discomfort, abdominal pain upper, abdominal pain lower, abdominal pain
- Dysgeusia: dysgeusia and taste disorder
- Conduction abnormalities: bundle branch block right and trifascicular block
- Back pain: spinal pain and back pain
- Oral candidiasis: oral fungal infection, tongue fungal infection and oral candidiasis
- Cholecystitis: cholecystitis acute and cholecystitis

Table 30. Treatment-Emergent Adverse Events Occurring at >1% Higher Frequency in Treatment Arm Than Comparator Arm, Phase 3 Safety Population, HP-301

	VDUAL20		VTRI20		LTRI30	
	N=348		N=346		N=345	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Vulvovaginal candidiasis	7	2.0	11	3.2	5	1.4
Nasopharyngitis	7	2.0	1	0.3	3	0.9
Hypertension	4	1.1	8	2.3	3	0.9
Headache	5	1.4	9	2.6	5	1.4

Source: Clinical data scientist and Clinical reviewer analysis
Abbreviations: LTRI, lansoprazole triple therapy; N, number of patients in treatment arm; n, number of patients with adverse event; VDUAL, vonoprazan dual therapy; VTRI, vonoprazan triple therapy

The most commonly reported TEAEs occurring at >1% higher frequency in vonoprazan dual or triple therapy arm than comparator included vulvovaginal mycotic infection, hypertension, headache, and nasopharyngitis.

Table 31. Treatment-Emergent Adverse Events Occurring at >0.5% Higher Frequency in Treatment Arm Than Comparator Arm, Phase 3 Safety Population, HP-301

	VDUAL20		VTRI20		LTRI30	
	N=348		N=346		N=345	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Vulvovaginal candidiasis	7	2.0	11	3.2	5	1.4
Nasopharyngitis	7	2.0	1	0.3	3	0.9
Hypertension	4	1.1	8	2.3	3	0.9
Headache	5	1.4	9	2.6	5	1.4
Oral candidiasis	1	0.3	3	0.9	1	0.3
Dizziness	2	0.6	3	0.9	1	0.3
Diabetes mellitus	3	0.9	2	0.6	0	0.0
Dermatitis allergic	1	0.3	3	0.9	1	0.3
Constipation	2	0.6	3	0.9	1	0.3

Source: Clinical data scientist and Clinical reviewer analysis
Abbreviations: LTRI, lansoprazole triple therapy; N, number of patients in treatment arm; n, number of patients with adverse event; DUAL, vonoprazan dual therapy; VTRI, vonoprazan triple therapy

The most commonly reported TEAEs occurring at >0.5% higher frequency in vonoprazan dual or triple therapy arm than comparator included vulvovaginal mycotic infection, hypertension, headache, nasopharyngitis, oral candidiasis, dizziness, diabetes mellitus, allergic dermatitis**,** and constipation.

Table 32.Treatment-Emergent Adverse Events Occurring at >1% Frequency in Any Arm (Treatment or Comparator) Phase 3 Safety Population, HP-301

	VDUAL20		VTRI20		LTRI30	
	N=348		N=346		N=345	
Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Diarrhoea	18	5.2	14	4.0	33	9.6
Dysgeusia	2	0.6	16	4.6	21	6.1
Vulvovaginal candidiasis	7	2.0	11	3.2	5	1.4
Nasopharyngitis	7	2.0	1	0.3	3	0.9
Hypertension	4	1.1	8	2.3	3	0.9
Headache	5	1.4	9	2.6	5	1.4
Abdominal pain	9	2.6	8	2.3	10	2.9
Nausea	6	1.7	6	1.7	9	2.6
Dyspepsia	5	1.4	4	1.2	6	1.7
Rash	4	1.1	0	0.0	5	1.4

Source: Clinical data scientist and Clinical reviewer analysis
Abbreviations: LTRI, lansoprazole triple therapy; N, number of patients in treatment arm; n, number of patients with adverse event; DUAL, vonoprazan dual therapy; VTRI, vonoprazan triple therapy

The most commonly reported TEAEs occurring at >1% in any study arm, included diarrhea, dysgeusia, and vulvovaginal mycotic infection. Diarrhea was more commonly experienced in the lansoprazole triple therapy group (9.6%) compared with the vonoprazan dual and triple therapy groups (5.2% and 4.0%, respectively). Dysgeusia was reported more commonly in both the vonoprazan and lansoprazole triple therapy groups (4.6% and 6.1%, respectively) compared with the vonoprazan dual therapy group (0.6%), which would be expected as this event is frequently associated with clarithromycin use. Vulvovaginal mycotic infection was more commonly reported in the vonoprazan triple therapy group (3.2%) compared with the lansoprazole triple therapy group (1.4%); the incidence in the vonoprazan dual therapy group was 2%. There were cases of coronavirus infection which were deemed unrelated to the study drugs.

Among the less frequent adverse events, there was one subject (b) (6)) in the VTRI arm with mild orbital edema which developed on treatment on day 4. The study therapy was stopped, and the AE resolved on day 17. The subject, a 69-year-old female, was on bisphosphonates for osteoporosis, but the orbital edema was likely a drug-related AE.

An analysis of patients with adverse events by system organ class and FDA medical query (broad and narrow), occurring at higher frequency in treatment arm than comparator arm was performed. Arrhythmias, systemic hypertension and headache were identified as having notable risk differences between the VTRI and LTRI. A review of cases identified three subjects with arrhythmia ((b) (6)) as having dizziness. The other three subjects on VTRI had mild (b) (6) and moderate (b) (6) tachycardia and mild bradycardia (b) (6) which resolved. The subject with moderate tachycardia was a 27-year-old female with dyspepsia, who developed intermittent tachycardia during treatment; the dose was not changed, and she completed treatment. The AE was considered likely related to the study drug by the investigator. A review of subjects with hypertension showed most of the cases were not related to the study drug, were mild to moderate in intensity, mostly resolved, occurred any time between days 3 to 10, and did not require additional treatment. There were two subjects for whom drug was withdrawn (which could have been due to the AE or because the subject did

not have *H. pylori* on the biopsy). In the subjects with headaches, the headaches were mostly mild in nature and resolved. Most did not require additional treatment.

An evaluation of the AEs by demographic subgroups (age, sex, race and ethnicity) is presented in Table 33. Overall, males had a higher incidence of AEs in the VTRI group than the VDUAL or LTRI groups. This likely is a reflection that overall AEs were slightly higher in VTRI. The small number of subjects precludes meaningful comparisons across subgroups.

Table 33. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial HP-301

Characteristic	Vonoprazan Dual Therapy N=348 [n/N_s (%)]	Vonoprazan Triple Therapy N=346 [n/N_s (%)]	Lansoprazole Triple Therapy N=345 [n/N_s (%)]	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Sex, n (%)					
Female	70/209 (33.5)	78/224 (34.8)	82/213 (38.5)	-5.0 (-14.2, 4.1)	-3.7 (-12.7, 5.4)
Male	34/139 (24.5)	40/122 (32.8)	37/132 (28.0)	-3.6 (-14.0, 6.9)	4.8 (-6.6, 16.1)
Age group, years, n (%)					
<45	28/101 (27.7)	38/126 (30.2)	37/109 (33.9)	-6.2 (-18.7, 6.2)	-3.8 (-15.8, 8.2)
≥45 to <65	48/170 (28.2)	50/144 (34.7)	57/171 (33.3)	-5.1 (-14.9, 4.7)	1.4 (-9.1, 11.9)
≥65 to <75	24/68 (35.3)	28/67 (41.8)	21/53 (39.6)	-4.3 (-21.7, 13.1)	2.2 (-15.5, 19.9)
≥75	4/9 (44.4)	2/9 (22.2)	4/12 (33.3)	11.1 (-30.9, 53.1)	-11.1 (-49.2, 27.0)
Race, n (%)					
American Indian or Alaska Native	0/0 (NA)	1/1 (100)	1/1 (100)	NA	0 (0, 0)
Asian	1/4 (25.0)	0/6 (0)	2/6 (33.3)	-8.3 (-65.1, 48.4)	-33.3 (-71.1, 4.4)
Black or African American	4/22 (18.2)	7/30 (23.3)	6/25 (24.0)	-5.8 (-29.1, 17.4)	-0.7 (-23.2, 21.9)
Native Hawaiian or Other Pacific Islander	1/1 (100)	0/0 (NA)	0/0 (NA)	NA	NA
Not Reported	0/1 (0)	1/3 (33.3)	0/0 (NA)	NA	NA
Other	0/4 (0)	0/1 (0)	1/3 (33.3)	-33.3 (-86.7, 20.0)	-33.3 (-86.7, 20.0)
Unknown	1/1 (100)	1/1 (100)	0/1 (0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
White	97/315 (30.8)	108/304 (35.5)	109/309 (35.3)	-4.5 (-11.9, 2.9)	0.3 (-7.3, 7.8)
Ethnicity, n (%)					
Hispanic or Latino	26/95 (27.4)	29/98 (29.6)	25/89 (28.1)	-0.7 (-13.7, 12.2)	1.5 (-11.5, 14.5)
Not Hispanic or Latino	77/250 (30.8)	89/247 (36.0)	94/256 (36.7)	-5.9 (-14.1, 2.3)	-0.7 (-9.1, 7.7)
Not Reported	0/1 (0)	0/1 (0)	0/0 (NA)	NA	NA
Unknown	1/2 (50.0)	0/0 (NA)	0/0 (NA)	NA	NA

Source: Clinical data scientist and Clinical reviewer analysis
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

7.6.2.6. Laboratory Findings, Trial HP-301

Mean changes from baseline to the end of treatment in hematology, serum chemistry values were small, with no clinically important differences observed among the treatment groups. In the table below, subjects with glucose>200 mg/dl but less than 250 mg/dl, neutrophils <2000 cells/ul were noted to have a risk difference between VDUAL versus LTRI and VTRI versus LTRI. There was also a risk difference for leucopenia <3500 cells/ul for VTRI versus LTRI.

Table 34. Patients Meeting Laboratory Abnormality Criteria, Elevated or Low Values Meeting Specified Levels, Safety Population, HP-301

Laboratory Parameter	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Sodium, low (mEq/L)					
Level 1 (<132)	2/340 (0.6)	2/340 (0.6)	1/337 (0.3)	0.3 (0.7, 1.3)	0.3 (0.7, 1.3)
Potassium, low (mEq/L)					
Level 1 (<3.6)	6/339 (1.8)	9/340 (2.6)	6/337 (1.8)	0.0 (2.0, 2.0)	0.9 (1.3, 3.1)
Level 2 (<3.4)	2/339 (0.6)	3/340 (0.9)	2/337 (0.6)	0.0 (1.2, 1.2)	0.3 (1.0, 1.6)
Glucose, random, high (mg/dL)					
Level 2 (≥200)	12/341 (3.5)	10/339 (2.9)	6/335 (1.8)	1.7 (0.7, 4.1)	1.2 (1.1, 3.5)
Level 3 (>250)	8/341 (2.3)	4/339 (1.2)	5/335 (1.5)	0.9 (1.2, 2.9)	0.3 (2.0, 1.4)
Calcium, high (mg/dL)					
Level 1 (>10.5)	0/340 (0)	4/340 (1.2)	1/335 (0.3)	0.3 (0.9, 0.3)	0.9 (0.4, 2.2)
Level 2 (>11)	0/340 (0)	2/340 (0.6)	0/335 (0)	0 (0, 0)	0.6 (0.2, 1.4)
Level 3 (>12)	0/340 (0)	0/340 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Creatinine, high (mg/dL)					
Level 1 (≥1.5X baseline)	1/341 (0.3)	2/340 (0.6)	0/335 (0)	0.3 (0.3, 0.9)	0.6 (0.2, 1.4)
Level 2 (≥2X baseline)	0/341 (0)	1/340 (0.3)	0/335 (0)	0 (0, 0)	0.3 (0.3, 0.9)
Level 3 (≥3X baseline)	0/341 (0)	0/340 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
eGFR, low (ml/min/1.73 m2)					
Level 1 (≥25% decrease)	6/341 (1.8)	2/340 (0.6)	5/335 (1.5)	0.3 (-1.6, 2.2)	-0.9 (-2.4, 0.6)
Level 2 (≥50% decrease)	0/341 (0)	1/340 (0.3)	0/335 (0)	0 (0, 0)	0.3 (-0.3, 0.9)
Level 3 (≥75% decrease)	0/341 (0)	0/340 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Complete Blood Count					
WBC, low (cells/uL)					
Level 1 (<3500)	12/340 (3.5)	3/335 (0.9)	10/335 (3.0)	0.5 (2.1, 3.2)	2.1 (4.2, 0.0)
Level 2 (<3000)	3/340 (0.9)	1/335 (0.3)	2/335 (0.6)	0.3 (1.0, 1.6)	0.3 (1.3, 0.7)
Level 3 (<1000)	0/340 (0)	0/335 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
WBC, high (cells/uL)					
Level 1 (>10800)	12/340 (3.5)	7/335 (2.1)	10/335 (3.0)	0.5 (2.1, 3.2)	0.9 (3.3, 1.5)
Level 2 (>13000)	2/340 (0.6)	3/335 (0.9)	2/335 (0.6)	0.0 (1.2, 1.1)	0.3 (1.0, 1.6)
Level 3 (>15000)	0/340 (0)	2/335 (0.6)	0/335 (0)	0 (0, 0)	0.6 (0.2, 1.4)

Laboratory Parameter	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Neutrophils, low (cells/uL)					
Level 1 (<2000)	26/339 (7.7)	20/335 (6.0)	33/335 (9.9)	2.2 (6.4, 2.1)	3.9 (8.0, 0.2)
Level 2 (<1000)	2/339 (0.6)	0/335 (0)	1/335 (0.3)	0.3 (0.7, 1.3)	0.3 (0.9, 0.3)
Level 3 (<500)	0/339 (0)	0/335 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Eosinophils, high (cells/uL)					
Level 1 (>650)	6/339 (1.8)	3/335 (0.9)	4/335 (1.2)	0.6 (1.2, 2.4)	0.3 (1.8, 1.2)
Level 2 (>1500)	1/339 (0.3)	1/335 (0.3)	0/335 (0)	0.3 (0.3, 0.9)	0.3 (0.3, 0.9)
Level 3 (>5000)	0/339 (0)	0/335 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)

Source: Clinical data scientist and clinical reviewer analysis
Duration for treatment defined as 14 days.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm

None of the subjects in any of the treatment groups met biochemical Hy's Law criteria. One (0.3%) subject in the vonoprazan triple therapy group and one (0.3%) subject in the lansoprazole triple therapy group had a post-baseline ALT value >3 × ULN; none of the other abnormal liver function test criteria were met by any subject.

There was one subject ([redacted] (b) (6)) in the VTRI arm who had ALT> 3x ULN but not elevated Total bilirubin and fell in the right lower quadrant of the eDISH plot (Temple's Corollary case). This subject, a 23-year-old male, received general anesthesia but no other concomitant medication, had high baseline ALT of 56 U/L, which increased to 75 U/L and an AST normal at baseline that increased to 53 U/L at 2 weeks of treatment. Similarly, another subject, a 55-year-old female [redacted] (b) (6)) in the LTRI arm was a Temple's Corollary case, who had an elevated ALT 4 weeks post-treatment to 75U/L. None of these subjects were noted to have an SAE. Of note, clarithromycin is known to cause elevation of liver function tests, which confounded the findings.

Table 35. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial HP-301

Laboratory Parameter	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Alkaline phosphatase, high (U/L)					
Level 1 (>1.5X ULN)	0/340 (0)	0/340 (0)	1/335 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Level 2 (>2X ULN)	0/340 (0)	0/340 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Level 3 (>3X ULN)	0/340 (0)	0/340 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Alanine aminotransferase, high (U/L)					
Level 1 (>3X ULN)	0/341 (0)	1/339 (0.3)	1/335 (0.3)	-0.3 (-0.9, 0.3)	-0.0 (-0.8, 0.8)
Level 2 (>5X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Level 3 (>10X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Aspartate aminotransferase, high (U/L)					
Level 1 (>3X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Level 2 (>5X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Level 3 (>10X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Bilirubin, total, high (mg/dL)					
Level 1 (>1.5X ULN)	1/341 (0.3)	1/339 (0.3)	0/335 (0)	0.3 (-0.3, 0.9)	0.3 (-0.3, 0.9)
Level 2 (>2X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)
Level 3 (>3X ULN)	0/341 (0)	0/339 (0)	0/335 (0)	0 (0, 0)	0 (0, 0)

Source: Clinical data scientist and Clinical reviewer analysis
Duration for treatment defined as 14 days.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; ULN, upper limit of normal

Mean changes from baseline to the end of treatment and to the end of post-treatment in vital sign values were small, with no clinically important differences observed among the treatment groups. Among the subjects who met the prespecified abnormal vital sign criteria for diastolic blood pressure, three subjects (all vonoprazan triple therapy) had an associated TEAE reported.

Subject (b) (6) with history of hypertension was started on antihypertensive medication on day 7 (blood pressure [BP] baseline was 154/98 mm Hg). Subsequently, the BP was elevated to 168/109 mm Hg on day 26. Subject (b) (6), with history of hypertension on amlodipine, had elevated BP to 180/115 mm Hg on day 17, requiring captopril. The event resolved. Subject (b) (6) had mild blood pressure increase reported on Day 18 and moderate hypertension on Day 59 that were both considered not related to the study drug. The subject had no prior history of hypertension and recovered from the event.

Table 36. Percentage of Subjects With Hypotension or Hypertension by Category of Blood Pressure Post-Baseline, Safety Population, Trial HP-301

Blood Pressure Parameters	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Systolic Blood Pressure (mm Hg)					
<90	0/346 (0)	0/344 (0)	0/342 (0)	0 (0, 0)	0 (0, 0)
≥160	10/346 (2.9)	6/344 (1.7)	6/342 (1.8)	1.1 (-1.1, 3.4)	-0.0 (-2.0, 2.0)
≥180	0/346 (0)	1/344 (0.3)	0/342 (0)	0 (0, 0)	0.3 | (-0.3, 0.9)
Diastolic Blood Pressure (mm Hg)					
<60	0/346 (0)	0/344 (0)	0/342 (0)	0 (0, 0)	0 (0, 0)
≥60	346/346 (100)	344/344 (100)	342/342 (100)	0 (0, 0)	0 (0, 0)
≥90	72/346 (20.8)	77/344 (22.4)	69/342 (20.2)	0.6 (-5.4, 6.7)	2.2 (-3.9, 8.3)
≥110	0/346 (0)	1/344 (0.3)	0/342 (0)	0 (0, 0)	0.3 (-0.3, 0.9)

Source: Clinical data scientist and Clinical reviewer analysis
Abbreviations: CI, confidence interval; Hg, mercury; N, number of patients in treatment arm

7.6.3. Safety Findings and Concerns, CCT-401

7.6.3.1. Overall Adverse Event Summary, CCT-401

No subjects died during the study. The percentages of subjects in the vonoprazan triple therapy and lansoprazole triple therapy groups who experienced serious TEAEs were 1.2% and 0.6%, respectively, and TEAEs that led to discontinuation of treatment were 0.9% and 0.6%, respectively.

Table 37. Overview of Adverse Events, Safety Population, Trial TAK-438/CCT-401

Event Category	Vonoprazan Triple Therapy N=329 n (%)	Lansoprazole Triple Therapy N=321 n (%)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
SAE	4 (1.2)	2 (0.6)	0.6 (-0.9, 2.1)
SAEs with fatal outcome	0	0	0 (0, 0)
Life-threatening SAEs	0	0	0 (0, 0)
AE leading to permanent discontinuation of study drug	3 (0.9)	2 (0.6)	0.3 (-1.1, 1.6)
AE leading to dose modification of study drug	0	0	0 (0, 0)
AE leading to interruption of study drug	0	0	0 (0, 0)
AE leading to reduction of study drug	0	0	0 (0, 0)
AE leading to dose delay of study drug	0	0	0 (0, 0)
Other	0	0	0 (0, 0)
AE	112 (34.0)	132 (41.1)	-7.1 (-14.5, 0.4)
Death	0	0	0 (0, 0)
Life-threatening	0	0	0 (0, 0)
Severe	1 (0.3)	2 (0.6)	-0.3 (-1.4, 0.7)
Moderate	7 (2.1)	6 (1.9)	0.3 (-1.9, 2.4)
Mild	104 (31.6)	124 (38.6)	-7.0 (-14.3, 0.3)

Source: adae.xpt (ISS); Software: R
Treatment-emergent adverse events defined as an adverse event occurring after receiving the study medication in the first line eradication phase, but before the receiving the second line eradication, or an aggravation of an existing condition.
Duration is 7 days.
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

7.6.3.2. Deaths, Trial CCT-401

None.

7.6.3.3. Serious Adverse Events, CCT-401

The percentages of subjects in the vonoprazan triple therapy and lansoprazole triple therapy groups who experienced serious TEAEs were 1.2% and 0.6%, respectively. One severe TEAE (cholangitis suppurative) was reported in the VTRI group, and two severe TEAEs (femoral neck fracture and pancreatic carcinoma) were reported in the LTRI group. Four subjects in the VTRI group (infectious enteritis, gastric ulcer hemorrhage, cholangitis, acute myocardial infarction) and two subjects in the LTRI group (femoral neck fracture, pancreatic cancer) experienced an SAE. One SAE (acute myocardial infarction) reported in the VTRI group was considered to be related to the study drug.

MO comment: The subject with acute myocardial infarction was a 69-year-old male with alcohol consumption and smoking, who was treated with 7 days of VTRI. On day 8, he developed myocardial ischemia on EKG and a month later developed coronary artery occlusion. He was treated and recovered. Since he had cardiac risk factors and the clarithromycin dosage was low, it is less likely that the event was related to the study therapy. A review of the rest of the SAEs showed that they were unlikely to be related to the study therapy.

Table 38. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial TAK-438/CCT-401

System Organ Class Preferred Term	Vonoprazan Triple Therapy N=329 n (%)	Lansoprazole Triple Therapy N=321 n (%)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Cardiac disorders (SOC)	1 (0.3)	0	0.3 (-0.3, 0.9)
Acute myocardial infarction	1 (0.3)	0	0.3 (-0.3, 0.9)
Gastrointestinal disorders (SOC)	1 (0.3)	0	0.3 (-0.3, 0.9)
Gastric ulcer haemorrhage	1 (0.3)	0	0.3 (-0.3, 0.9)
Infections and infestations (SOC)	2 (0.6)	0	0.6 (-0.2, 1.4)
Cholangitis infective	1 (0.3)	0	0.3 (-0.3, 0.9)
Enteritis infectious	1 (0.3)	0	0.3 (-0.3, 0.9)
Injury, poisoning and procedural complications (SOC)	0	1 (0.3)	-0.3 (-0.9, 0.3)
Femoral neck fracture	0	1 (0.3)	-0.3 (-0.9, 0.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps) (SOC)	0	1 (0.3)	-0.3 (-0.9, 0.3)
Pancreatic carcinoma	0	1 (0.3)	-0.3 (-0.9, 0.3)

Source: adae.xpt (ISS); Software: R
Treatment-emergent adverse events defined as an adverse event occurring after receiving the study medication in the first line eradication phase, but before the receiving the second line eradication, or an aggravation of an existing condition.
Duration is 7 days.
Serious adverse events defined as any untoward medical occurrence that, at any dose 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.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

7.6.3.4. Dropouts and/or Discontinuations Due to Adverse Events, CCT-401

TEAEs that led to discontinuation of treatment were 0.9% in the VTRI group and 0.6% in the LTRI group. The TEAEs leading to study drug discontinuation in the VTRI group were vertigo in one subject and diarrhea in two subjects. The TEAEs leading to study drug discontinuation in the LTRI group were enterocolitis hemorrhagic and eczema. The reactions were not serious, resolved after discontinuation of study drug. The onset of AEs ranged from day 1 to 6.

Table 39. Adverse Reactions Which Led to Treatment Discontinuations, Safety Population, CCT-401

Study Arm	Patient ID	Dosage	MedDRA Preferred Term	Verbatim Term	SAE	AE Study Day of Onset/Stop	Study Day of Last Dose of Study Drug	Study Day of Discontinuation	Investigator's Assessment of Relatedness
Vonoprazan 20 mg	(b) (6)	20 mg	Vertigo	Vertigo	N	2, 2	1	1	RELATED
Vonoprazan 20 mg		20 mg	Diarrhoea	Diarrhea	N	3, 13	6	6	RELATED
Vonoprazan 20 mg		20 mg	Diarrhoea	Diarrhea	N	1, 4	3	3	RELATED
Lansoprazole 30 mg		30 mg	Enterocolitis haemorrhagic	Hemorrhagic colitis	N	5, 10	5	5	RELATED
Lansoprazole 30 mg		30 mg	Eczema	Eczema	N	3, 6	4	4	RELATED

Source: adae.xpt (ISS); Software: R
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, severe adverse event

7.6.3.5. Treatment-Emergent Adverse Events, Trial CCT-401

In Study CCT-401, the overall incidence of TEAEs was 34.0% in the vonoprazan triple therapy group and 41.1% in the lansoprazole triple therapy group. In both treatment groups, the majority of subjects who experienced TEAEs had events that were mild or moderate in intensity. The overall incidence of drug-related TEAEs was 20.4% in the VTRI group and 24.6% in the LTRI group.

Table 40. Common Adverse Events Occurring at >1% Frequency in Treatment Arm Safety Population, Trial CCT-401

Preferred Term	Vonoprazan Triple Therapy N=329 n (%)	Lansoprazole Triple Therapy N=321 n (%)
Diarrhoea	41(12.5)	49(15.3)
Dysgeusia/taste disorder	14 (4.2)	10 (3.1)
Nasopharyngitis	18 (5.5)	15 (4.7)
Urticaria	4 (1.2)	2 (0.6)

Source: Clinical data scientist and Clinical reviewer analysis
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event

The incidences of “gastrointestinal disorders,” “infections and infestations,” and “nervous system disorders” were relatively high (≥ 5%) in both treatment groups. No other remarkable differences between the treatment groups were observed in the incidences of TEAEs by system organ class (SOC). The incidences of diarrhea, nasopharyngitis, and dysgeusia were relatively high (> 2%) in both treatment groups, while those of other preferred terms were less than 2%. No remarkable differences between the treatment groups were observed in the incidences of TEAEs by preferred term.

Table 41. Subjects With Treatment Emergent Adverse Events, Occurring at >0.5% Frequency in Any Treatment Arm Safety Population, Trial CCT-401

Preferred Term	Vonoprazan Triple Therapy N=329 n (%)	Lansoprazole Triple Therapy N=321 n (%)
Any AE	112 (34.0)	132 (41.1)
Diarrhoea	41 (12.5)	49 (15.3)
Nasopharyngitis	18 (5.5)	15 (4.7)
Dysgeusia/Taste disorder	14 (4.2)	10 (3.1)
Gastroenteritis/enterocolitis	4 (1.2)	2(0.6)
Abdominal pain	4 (1.2)	11 (3.4)
Liver function test increased	4(1.2)	4 (1.2)
Drug-induced liver injury	0	2 (0.6)
Jaundice	1 (0.3)	0
Myocardial infarction	2 (0.6)	0
Drug hypersensitivity	4(1.2)	5 (1.5)
Rash	4 (1.2)	3 (0.9)
Arthralgia	2 (0.6)	0
Insomnia	2 (0.6)	0
Gastrooesophageal reflux disease	3 (0.9)	5 (1.5)
Dermatitis	0	4 (1.2)
Eczema	3 (0.9)	2 (0.6)
Hot flush	2 (0.6)	0
Paraesthesia/hypoaesthesia	2 (0.6)	0
Headache	3 (0.9)	3 (0.9)
Constipation	3 (0.9)	2 (0.6)
Upper respiratory tract inflammation	2 (0.6)	2 (0.6)
Fall	1 (0.3)	2 (0.6)
Femoral neck fracture	0	1 (0.3)
Nausea	1 (0.3)	2 (0.6)
Rhinitis	0	2 (0.6)
Pharyngitis	0	3 (0.9)

Source: Clinical data scientist and Clinical reviewer analysis
The following terms were combined in the table above:
Paresthesia and Hypoaesthesia
Dermatitis: Allergic dermatitis and dermatitis
Drug hypersensitivity: facial edema, urticaria, drug eruption, glossitis, drug hypersensitivity
Erythema: erythema and rash
Headache: headache and migraine
Hot flush: heat illness and hot flush
Dysgeusia: dysgeusia, hypergeusia and taste disorder
Abdominal pain: upper abdominal pain, abdominal pain, abdominal discomfort
Liver function test increased: Liver function test increased, elevated aspartate aminotransferase, elevated alanine transferase, elevated gamma glutamyl transferase.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

7.6.3.6. Laboratory Findings, Trial CCT-401

The Applicant reported that no clinically significant changes were observed in the mean values of hematology or chemistry parameters during the study. The Applicant did not provide grading information in the laboratory dataset.

Mean levels of serum gastrin, pepsinogen I, and pepsinogen II increased after the administration of VTRI and LTRI in the first line eradication phase. In both treatment groups, the mean serum

gastrin level decreased to the level below baseline at the follow-up examinations scheduled four weeks after the completion of the first line eradication.

Subject (b) (6), a 29-year-old male with alcohol abuse, on LTRI, was drinking while on treatment and found to have elevated transaminases. His ALT and AST levels were elevated to 1110 IU/L and 803 IU/L, respectively, on day 7, exceeding 3 times the ULN. His total bilirubin level was within normal range. His γ-GTP and lactate dehydrogenase (LDH) levels were also elevated to 312 IU/L and 429 IU/L, respectively. He had mild fatigue which resolved. His liver function tests (LFTs) returned to normal a month later. Another subject (b) (6) was noted to have mild abnormal liver function tests which occurred within one week of treatment and persisted for one month. The investigator thought this was an unrelated event.

MO comment: Although subject (b) (6) had a transaminase elevation pattern not typical of alcoholic hepatitis, clarithromycin in the LTRI can cause such elevation of LFTs.

Subject (b) (6), a 77-year-old man on VTRI, developed infectious enteritis with elevated transaminases 1 month after completion of treatment, which was likely unrelated to the study drug.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Liver Lesions and Increased Stomach Weights in Neonatal Rats With Gestational and/or Lactational Exposure to Vonoprazan (TAK-438)

Issue

Liver lesions and increased stomach weights in neonatal rats with gestational and/or lactational exposure to vonoprazan (TAK-438).

Background

Vonoprazan and its metabolites are present in rat milk. In nonclinical studies, liver discoloration associated with necrosis, hemorrhage and fibrosis and increased stomach weights were noted in rat offspring from pregnant and lactating dams. Although, there is no human data regarding the presence of vonoprazan in human milk or the effects on the breastfed infant, when a drug is present in animal milk, it is expected that the drug will generally be present in human milk. Therefore, there is a concern regarding development of hepatic lesions and increased stomach weights in the fetus and newborn from pregnant and lactating mothers.

Assessment

In a dose range-finding study, pregnant rats were orally administered TAK-438 at doses up to 300 mg/kg, from GD 6 to LD 13. A statistically significant increase in liver discoloration associated with necrosis, hemorrhage, and fibrosis was noted in pups from dams in the 30 and 100 mg/kg dose groups (16.7% and 12.5%, respectively). In pups culled on LD 4, up to 34% had liver discoloration in the 100 mg/kg dose group. No discolored livers were seen in pups from the

300 mg/kg dose group and no histopathological examinations of the pup livers in that group were performed. In a second dose range-finding study, pregnant rats were orally administered TAK-438 from GD 6 to LD 13 at doses of 0, 3, 10, 30 or 100 mg/kg. In this study, pups culled on LD 4 showed liver discoloration in 2% in the controls (1 pup), 6.1% in the 3 mg/kg group (2 pups), 20.6% in the 10 mg/kg group (7 pups), and 33.9% in the 100 mg/kg group (17 pups). In the pups euthanized on LD 14, 7.2% and 14.1% had liver discolorations in the 10 and 100 mg/kg dose groups, respectively. Upon histopathological examination, necrosis was found in 3/18 and 7/25 of the examined livers in the 10 and 100 mg/kg dose groups, respectively. In this second dose range-finding study, stomach weights in the 100 mg/kg pups were found to be increased in those culled on LD 4 or LD 14 with reported evidence of solidified milk present in the stomachs.

In a GLP pre-and postnatal development study in pregnant rats orally administered vonoprazan at doses of 1, 3, 10, and 100 mg/kg, (0.01-, 0.18-, 1.1-, and 22-times the maximum recommended human dosage (MRHD) based on AUC, respectively) between GD 6 and LD 21, hepatic discoloration in 4 culled pups in the 100 mg/kg dose group were noted at 4 days post birth, but no histopathological examination was performed. There were no gross liver findings in the lower dose groups and no liver findings were reported in animals examined at or after weaning. In a separate study to determine the sensitive period for oral TAK-438-induced hepatic lesions in neonatal rats from pregnant/lactating dams, group 1 rats were orally administered vehicle during GD 6 to LD 13, group 2 rats were orally administered 100 mg/kg TAK-438 during GD 6 to LD 13, group 3 rats were orally administered 100 mg/kg TAK-438 during GD 6 to 21, and group 4 rats were orally administered 100 mg/kg TAK-438 during LD 0 to 13. In dams administered TAK-438 during lactation (groups 2 and 4), several pups in both groups showed liver discoloration noted on LD 4 and LD 14, associated histologically with hepatic necrosis and hemorrhage.

The Applicant proposed that the liver discoloration and necrosis resulted from delayed stomach emptying leading to impingement on the portal vein and ischemia from reduced blood flow. However, the follow-up mechanistic data does not definitively support this hypothesis as the causal mechanism for these adverse effects seen in the pup livers. Similarly, because much of the nonclinical tests included both gestational and lactational exposure of TAK-438 to pups, and hepatic injury in pups was associated with fibrosis (in addition to necrosis and hemorrhage), the potential for an adverse gestational effect on developing livers in rats could not be ruled out.

In the clinical trials, none of the adult subjects in any of the treatment groups met biochemical Hy's Law criteria. One (0.3%) subject in the vonoprazan triple therapy group and 1 (0.3%) subject in the lansoprazole triple therapy group had a post-baseline ALT value >3 × ULN; none of the other abnormal liver function test criteria were met by any adult subject. There were no hepatic necrosis or hepatic tumors identified in the follow-up period.

There were no pregnancies in the pivotal trial, HP-301, or in the supportive trial, CCT-401. There are no adequate and well-controlled studies of vonoprazan or amoxicillin or clarithromycin (used separately or together) in pregnant women to inform about the drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

There are no data regarding the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. No combination of vonoprazan and amoxicillin and/or clarithromycin were conducted that examined the effects on animals to determine the effect of lactational exposure on offspring.

Therefore, a postmarketing requirement (PMR) clinical trial in pregnancy and lactation will be necessary to further characterize the risks associated with VTRI and VDUAL. The risks of hepatic necrosis/discoloration will be included in the labeling. The Division of Pediatric and Maternal Health (DPMH) was consulted for input regarding the design of the PMR studies and to inform labeling.

Conclusion

Increased stomach weights and liver discoloration associated with necrosis, hemorrhage, and fibrosis were noted in rat offspring from pregnant and lactating dams administered oral vonoprazan. Vonoprazan and its metabolites are present in rat milk. As a postmarketing requirement, a trial in pregnant and lactating women will be necessary to further characterize the risks associated with VTRI and VDUAL.

7.7.2. Risk of Bone Fracture

Issue

Risk of bone fracture**.**

Background

The warnings and precautions section of the PPI drug labels note several published observational studies which suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose (defined as multiple daily doses) and long-term (a year or longer) PPI therapy. The proposed warnings and precautions section of the vonoprazan labeling does not contain the risk of bone fractures.

The mechanism of action of vonoprazan differs somewhat from the PPIs, but both suppress acid secretion. Vonoprazan inhibits acid release into the gastric lumen through reversible potassium competitive binding at the luminal portion of the H+/K+-ATPase (“proton pump”), while PPIs act to suppress acid secretion through irreversible inactivation of the gastric H+/K+ ATPase. The established pharmacological class of vonoprazan is a potassium-competitive acid blocker (PCAB), although vonoprazan has been characterized as a type of gastric proton-pump inhibitor, in that it blocks the final step of gastric acid production. (refer to Division of Gastroenterology (DG) consult note dated January 26, 2022, DG consult addendum on March 11, 2022, and final package insert).

Clarithromycin and amoxicillin are not known to increase the risk of bone demineralization or bone fractures. The coadministration of clarithromycin with vonoprazan increases exposure of vonoprazan approximately 1.9-fold which may increase risks associated with vonoprazan.

Given the similarities between vonoprazan and PPIs and the identification of two cases (serious adverse events) of bone fracture noted in the pivotal phase 3 trial HP-301, a risk assessment with potential mechanism of bone fracture, in depth analysis of the cases and the overall short term and long term risk of bone fractures with use of vonoprazan in clinical trials and the postmarketing database was conducted.

Assessment

Thong et al. (2019) proposed two mechanisms underlying bone fractures induced by PPIs, i.e., hypergastrinemia and hypochlorhydria. Hypochlorhydria caused by PPIs is hypothesized to decrease the absorption of minerals essential for bone health. Hypergastrinemia causes hyperplasia of enterochromaffin-like cells, histamine secretion, and stimulation of osteoclastic precursors along with hyperparathyroidism, which causes bone resorption, decreased bone mineral density and increased risk of fracture. It is anticipated that potassium competitive PPIs would exert similar effects on bone homeostasis.

There were two cases (serious adverse events) of bone fracture noted in the pivotal phase 3 trial HP-301 with vonoprazan dual therapy and triple therapy (1 each). Subject (b) (6) in the vonoprazan dual therapy group was a 69-year-old female with history of osteopenia who slipped and fell and suffered a lower limb fracture on Day 42. Subject (b) (6), a 33-year-old female in the vonoprazan triple therapy group, experienced bilateral mandibular fracture following a physical assault on Day 86. Both these subjects appeared to have the AE due to mechanical reasons. However, it is unknown if vonoprazan could have predisposed them to have the fractures.

The Applicant also summarized the risk of bone fracture in short-term (2-8 weeks) and long-term studies (>8 weeks) of vonoprazan use in non-*H. pylori* indications. In the placebo-controlled short-term studies pool, the incidence of TEAEs associated with bone fracture was 0.4% in the overall vonoprazan group compared with no reports in the placebo group. In the PPI-controlled short-term studies pool, the overall vonoprazan and PPI groups were comparable with respect to the incidence of TEAEs associated with bone fracture (0.2% in each group). Most fractures were of the hand, wrist, spinal compression, and humerus.

In the long-term studies pool, TEAEs associated with bone fracture were experienced in 1.7% of the overall vonoprazan group. In the lansoprazole-controlled long-term studies pool, the overall vonoprazan and lansoprazole groups were comparable with respect to the incidence of TEAEs associated with bone fracture (2.0% and 1.4%, respectively).

Spinal compression fracture was experienced in 14 (0.8%) subjects in the overall vonoprazan group compared with no reports in the lansoprazole group.

In Study TAK-438/CCT-401, a 75-year-old female subject in the lansoprazole triple therapy group (b) (6)) experienced a serious TEAE of femoral neck fracture on Study Day 7 after falling off a chair while putting on her socks. Postmarketing reports of use of vonoprazan monotherapy ex-US noted four spinal compression fractures, two femoral neck fractures, one neck fracture, one rib fracture, and seven cases of fracture were unspecified.

Since the treatment duration is 14 days, the overall risk of bone fractures with VDUAL and VTRI appears low.

This risk can be mitigated by labeling under adverse reactions. Bone fractures appear to be low-frequency adverse events and there is a plausible mechanism to suggest causality. Therefore, inclusion under less common adverse events in the labeling is appropriate. Given the low frequency of events and short-term use of the drug, this adverse reaction does not merit escalation to the warnings and precautions section of the labeling. A consultation with the Division of Gastroenterology (see consult note dated February 18, 2022) stated that evidence does not support an association between short-term use of PPIs and fracture risk. It might be expected that vonoprazan and the PPIs would have similar effects on micronutrient absorption

and gastrin/PTH-mediated bone homeostasis. However, it is unclear if the difference in structure and the nature of the interaction with the proton-pump between vonoprazan and PPIs would lead to similar interactions as observed with PPIs.

Conclusion

There appears to be a plausible mechanism by which vonoprazan can increase the risk of bone fractures. The risk is low with short-term use of 14 days of therapy. Bone fracture will be listed under the musculoskeletal system in the "other adverse reactions" section 6.1 of the labeling. Routine pharmacovigilance will be conducted postapproval.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Sex

There were no clinically significant differences in the pharmacokinetics of vonoprazan based on sex.

In a phase 1 food effect study (Study TAK-438_109), vonoprazan exposures were approximately 20% lower in female subjects (16%↓ in AUC, 22%↓ in C_{max}) compared to male subjects. The Reviewer's independent analyses using PK data from 4 additional phase 1 studies (TAK-438_114, TAK-438_113, and TAK-438_112) showed an inconsistent trend of vonoprazan exposures based on sex. Population PK analysis (N=1179) also did not identify a relationship between sex and vonoprazan exposure. However, the analysis findings suggest an approximately 25% lower drug absorption rate (Ka) in females compared to males. See Section 14.3 for additional details. Further, results from the phase 3 trial (Study HP-301) did not reveal any clinically significant difference in response rates of vonoprazan triple/dual therapy versus lansoprazole triple therapy based on sex. In the combined results for mITT population, response rates in females were 12.2% (95% CI= 4.78, 19.70) and 7.6% in males (-1.98, 17.25). In the same study, the difference in response rates compared to vonoprazan triple therapy versus lansoprazole triple therapy in females were 13.1% (4.87, 21.34) and 10.9% in males (0.13, 21.68). Therefore, the review team concludes that the observed differences in vonoprazan exposures in males and females do not appear to be of clinical relevance for vonoprazan dual and triple therapy in the treatment of *H. pylori* infection.

Renal Impairment

The Applicant proposes that use of vonoprazan triple and dual therapy should be avoided in patients with severe renal impairment (glomerular filtration rate [GFR] < 30 mL/min). The Applicant's proposal is reasonable.

Results of the human mass balance study showed that out of 67% of administered radioactivity that was recovered in urine, 12% was unchanged vonoprazan (8% of the total recovered radioactivity), suggesting that vonoprazan is not substantially renally eliminated. In a dedicated renal impairment study (Study TAK-438_113), following a single 20 mg oral dose, vonoprazan AUC was 1.7-, 1.3-, and 2.4-times greater in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. In subjects requiring

dialysis, vonoprazan AUC was 1.3-fold greater compared to subjects with normal renal function. Protein binding of vonoprazan was not affected by impaired renal function. The maximally tolerated vonoprazan dose is unknown. The highest evaluated multiple dose in humans is 40 mg per day (20 mg BID and 40 mg QD). Safety and tolerability information above the proposed vonoprazan dosage, i.e., 20 mg BID, is not available. In addition, both amoxicillin and clarithromycin prescribing information recommends dosage reduction for patients with severe renal impairment (GFR <30 mL/min). Given the limitation of the proposed copackaged drug products, dosage adjustment for all three drugs is not feasible. Taken together, the review team agreed that use of vonoprazan triple and dual therapy should be avoided in patients with severe renal impairment.

Hepatic Impairment

The Applicant proposes that use of vonoprazan triple and dual therapy should be avoided in patients with moderate (Child-Pugh Class [CP] B) and severe (CP C) hepatic impairment. The Applicant's proposal is reasonable.

The effect of hepatic impairment on vonoprazan PK was evaluated in a dedicated PK study (Study TAK-438_112). The study findings showed that vonoprazan AUC estimates after a single 20 mg oral dose were 1.2-, 2.4-, and 2.6- times greater in subjects with mild (CP A), moderate (CP B), and severe (CP C) hepatic impairment, respectively, compared to subjects with normal hepatic function. Protein binding of vonoprazan was not affected by impaired hepatic function.

For amoxicillin, a primarily renally eliminated drug, no specific dosage adjustment recommendations based on CP classification is included in the currently approved labeling. For clarithromycin, its use is contraindicated in patients with a history of cholestatic jaundice or hepatic dysfunction associated with prior use of clarithromycin. However, no specific dosage adjustment recommendations based on CP classification are included in the currently approved labeling.

Overall, given the unknown safety/tolerability above the proposed dosage, i.e., 20 mg BID and the limitation with the copackaged products, the review team agreed that use of vonoprazan triple and dual therapy should be avoided in patients with moderate and severe hepatic impairment.

CYP2C19 Metabolizer Status

Genetic polymorphisms and metabolizer status did not appear to significantly impact the AUC or C_{max} of vonoprazan. In a phase 1 study (TAK-438-CPH-002), the Applicant investigated the *2 and *3 polymorphisms in CYP2C19 and their impact on PK parameters of AUC and C_{max} at day 7. All subjects had a blood sample taken on day 1 for CYP2C19 genotyping and all subjects had CYP2C19 genotyping data available (N=60). Of the subjects on vonoprazan (N=45), there were 19 extensive metabolizers (EM) or normal metabolizers (NM), 21 intermediate metabolizers (IM), and 5 poor metabolizers (PM). Mean AUC values at day 7 were approximately 10% higher in IMs and 50% higher in PMs, while C_{max} values at day 7 were approximately 5% higher in IMs and 20% higher in PMs. These differences in PK are not expected to be clinically significant.

8.2. Extrinsic Factors

8.2.1. Food Effect

The review team agreed with the Applicant's proposal that the proposed drug products can be taken with or without food based on the following available information:

- In a food effect study (TAK-438 109), the impact of a high-fat meal (884 kcal, 62% fat, 23% carbohydrates, and 14% protein) on the vonoprazan exposures was low (≤ 15%↑ in AUC or C_{max}).
- Clarithromycin immediate release tablets are recommended to be administered with or without food.
- The amoxicillin labeling does not include specific recommendations whether amoxicillin should be administered with or without food.

8.2.2. Drug Interactions

Vonoprazan triple therapy includes clarithromycin, whereas the dual therapy does not. Considering clarithromycin is a strong CYP3A inhibitor as well as an inhibitor of P-gp, OATP1B1, and OATP1B3, DDI potential with the triple therapy is significantly different and wide-ranging compared to the dual therapy. For amoxicillin and clarithromycin specific DDI information, refer to the respective prescribing information. The summary of DDI information for vonoprazan-based triple and dual therapy is provided in this section.

Effects of Other Drugs on Vonoprazan Dual and Triple Therapy

Vonoprazan is metabolized via multiple pathways by a combination of (CYP isoforms (CYP3A4/5, CYP2B6, CYP2C19, CYP2C9, and CYP2D6) along with sulfo- and glucuronosyl-transferases. Vonoprazan is not a substrate of P-gp, breast cancer resistance protein (BCRP), OATP1B1, or OATP1B3. Based on the available drug metabolism and DDI information from in vitro studies, clinical DDI studies, and modeling based DDI assessments (See Section 14), this review focused on the potential effects of CYP3A, CYP2D6, and CYP2C19 inhibitors as well as CYP3A inducers on the proposed vonoprazan dual and triple therapy.

CYP3A Inhibitors

The Applicant has not proposed any mitigation strategy for concomitant use of vonoprazan triple and dual therapy with CYP3A inhibitors for its effect on vonoprazan. Vonoprazan is a substrate and a weak inhibitor of CYP3A (see below); whereas clarithromycin is a substrate and a strong inhibitor of CYP3A. When a single 40 mg dose of vonoprazan was co-administrated with multiple doses (500 twice daily for 7 days) of clarithromycin, vonoprazan C_{max} and $AUC_{0\text{-}inf}$ increased approximately 1.3- and 1.6-fold, respectively. In healthy subjects receiving twice daily vonoprazan (20 mg), amoxicillin (750 mg), and clarithromycin (400 mg) for 7 days, amoxicillin exposure was unchanged; however, vonoprazan C_{max} and $AUC_{0\text{-}12}$ increased by 1.9-fold and 1.8-fold, clarithromycin C_{max} and $AUC_{0\text{-}12}$ increased by 1.6-fold and 1.5-fold, respectively. Despite the increase in vonoprazan and clarithromycin exposure when administered together as proposed for the triple therapy, the phase 3 trial (Study HP-301) demonstrated an acceptable safety profile for vonoprazan triple therapy. Given that clarithromycin is a strong CYP3A inhibitor and there are multiple pathways involved in vonoprazan metabolism, co-administration of additional

CYP3A inhibitors with the triple therapy is unlikely to further increase vonoprazan exposure to a clinically significant extent. For vonoprazan dual therapy, the safety findings from the triple therapy treatment arm in Study HP-301 supports the use of dual therapy with CYP3A inhibitors.

Therefore, the review team agreed with the concomitant use of vonoprazan triple and dual therapy with CYP3A inhibitors for the treatment of *H. pylori* provided that the DDI mitigation strategies are followed as recommended in the clarithromycin labeling. Of note, clarithromycin has been associated with prolongation of the QT interval and infrequent cases of arrhythmia. Consistent with recommendations in the clarithromycin labeling, caution should be exercised when coadministration of vonoprazan-based triple therapy containing clarithromycin with strong CYP3A inhibitors, e.g., itraconazole. Refer to clarithromycin prescribing information for the DDI information with strong CYP3A inhibitors. Given that vonoprazan is a weak CYP3A inhibitor, concomitant use of triple therapy with a strong CYP3A inhibitor is unlikely to further increase clarithromycin exposure to a clinically significant extent compared to when clarithromycin alone is co-administered with a strong CYP3A inhibitor. Therefore, mitigation strategies for concomitant use of vonoprazan triple therapy with strong CYP3A inhibitors will align with those from the clarithromycin labeling with modifications as appropriate due to the limitation of the copackaged combination products.

CYP2D6 Inhibitors

The Applicant stated that vonoprazan is mainly metabolized by CYP3A4/5, and to a lesser extent by CYP2D6 and CYP2C19; therefore, they did not propose any DDI mitigation strategies for coadministration of vonoprazan triple or dual therapy with CYP2D6 inhibitors. This is acceptable based on the limited information; however, the review team recommends a postmarketing study for conducting an in vitro reaction phenotyping study with a selective chemical inhibitor to further determine the role of CYP2D6 in vonoprazan metabolism.

The Applicant's assertion that CYP2D6's contribution in vonoprazan metabolism is not significant is based on the following rationale:

- Findings from an in vitro study (TAK-438-00096) using human liver microsomes showed that vonoprazan elimination rate was not highly correlated (r=0.17-0.25) with CYP2D6 specific activity, based on the comparison with dextromethorphan O-demethylation rate. In contrast, the correlation coefficient is highest between vonoprazan elimination rate and CYP3A4 activity (using midazolam as a probe substrate). See Section 14.1 for additional details on Study TAK-438-00096 findings.
- A separate in vitro study (TAK- 438-00097) using recombinant human CYP isoforms showed the highest vonoprazan elimination rate with CYP2D6 followed by CYP3A and 2C19. Both CYP2D6 and 2C19 are primarily responsible for the formation of the N-demethylated vonoprazan metabolite. However, this metabolite is unique to in vitro incubations and has not been detected in plasma or excreta samples from animals or humans. See Section 14.1 for additional details on Study TAK-438-00097 findings.
- Since CYP2D6 is highly polymorphic, a bimodal distribution of drug exposure is expected when CYP2D6 is the major contributor to the metabolism of a drug. However, no discernable bimodality was observed in the vonoprazan AUC across the clinical program.

Based on the review of this information, the review team does not agree that there is adequate information provided from in vitro and in vivo studies to ascertain the extent of CYP2D6 contribution in vonoprazan metabolism for the following reasons:

- In vitro approaches for reaction phenotyping usually include correlation analysis, chemical inhibition, and metabolism by recombinant human CYP enzymes. Collectively, these approaches allow for identifying CYP enzyme(s) and ascertaining the extent of each enzyme's contribution in drug metabolism.
- Findings from correlation analysis itself are not adequate to rule out the role of CYP2D6 in vonoprazan metabolism. While the metabolism rate for vonoprazan could be lower than a reference compound (dextromethorphan in Study TAK-438-00096), it does not inform to what extent CYP2D6 contributes to vonoprazan metabolism.
- Although the N-demethylated metabolite was not detected in vivo, the possibility that this metabolite is formed in vivo and gets further metabolized cannot be ruled out.
- The Applicant has not specifically evaluated the effect of CYP2D6 status on vonoprazan PK in a population PK analysis or in a clinical study. The absence of any discernable bimodality in the observed vonoprazan exposure is based on a limited sample size (N=116). It is not clear there is adequate representation of various CYP2D6 statuses in subjects enrolled across the clinical development program. In addition, vonoprazan is eliminated by multiple pathways. The existence of compensatory mechanisms may also be the potential reason for no evident bimodal distribution of vonoprazan PK.

Overall, based on the available in vitro and clinical PK data, the role of CYP2D6 in vonoprazan metabolism is inconclusive. Vonoprazan is metabolized by multiple CYP enzymes, and it is important to assess the extent of CYP2D6's contribution in vonoprazan metabolism considering potential DDIs via multiple mechanisms. Therefore, the review team recommends a postmarketing in vitro study to further determine the role of CYP2D6 in vonoprazan metabolism. Depending on the results of the in vitro study, additional studies may be needed.

CYP2C19 Inhibitors

For vonoprazan triple or dual therapy, the Applicant is not proposing any clinical mitigation strategies for coadministration with CYP2C19 inhibitors. The Applicant's proposal is acceptable based on the available clinical PK information summarized below.

The Applicant's proposal is mainly supported by an analysis of clinical PK data from 45 subjects with various CYP2C19 metabolizer status. Specifically, the relationship between vonoprazan exposures (dose normalized C_{max} and AUC values) and CYP2C19 genotype was evaluated as part of a phase 1 study and the findings showed no clear association between vonoprazan exposures and CYP2C19 genotypes (see Section 8.1). In addition, a population PK analysis evaluated the effect of CYP2C19 genotype status using data from 1179 subjects, of which 651 were CYP2C19 extensive metabolizers (EMs), 37 were CYP2C19 intermediate metabolizers (IM), and 109 were CYP2C19 poor metabolizers (PMs). The population PK analysis did not identify CYP2C19 metabolizer status as a significant covariate affecting vonoprazan exposures.

Given the lack of effect of CYP2C19 metabolizer status on vonoprazan exposures, coadministration of CYP2C19 inhibitors is unlikely to affect vonoprazan exposure.

CYP3A Inducers

In the original submission, the Applicant had proposed [redacted] (b) (4) The review team did not agree and requested a rationale in support of the proposed [redacted] (b) (4) The Applicant subsequently proposed to avoid the use of triple or dual therapy with both moderate and strong CYP3A4 inducers. The Applicant's revised proposal is reasonable based on the information summarized below.

The Applicant has not conducted any clinical DDI study to evaluate the effect of CYP3A4 inducers on vonoprazan exposures. Instead, the Applicant conducted physiologically based pharmacokinetic (PBPK) analysis. The PBPK model predicted that coadministration of 20 mg BID vonoprazan with a strong CYP3A inducer (rifampin, 600 mg QD for 16 days) and a moderate CYP3A inducer (efavirenz, 600 mg QD for 16 days) may reduce vonoprazan exposures by 72 to 78% and 44 to 54%, respectively, compared to when vonoprazan is administered alone. Given that for the proposed indication the effectiveness of vonoprazan at exposures below the recommended 20 mg BID dosing regimen is unknown, the Applicant's proposal is acceptable. In addition, it is noteworthy that for clarithromycin, it is recommended to consider an alternative antibacterial treatment when treating patients receiving inducers of CYP3A.

Effects of Vonoprazan Dual and Triple Therapy on Other Drugs

In vitro study findings showed that vonoprazan inhibits CYP2B6, CYP2C19, and CYP3A4/5 in a time- and concentration-dependent manner. Vonoprazan had little or no inhibitory effect on P-gp, BCRP, OATPB1, OATP1B3, organic anion transporter (OAT)1, or OAT3, organic cation transporter (OCT)2 (IC_{50}>30 µmol/L). See Section 14 for details. This review focuses on the potential effects of vonoprazan dual and triple therapy on CYP3A4/5, CYP2C19, and CYP2B6 substrates.

CYP3A4/5 Substrates

In the original submission, the Applicant had not proposed any vonoprazan-specific clinical mitigation strategies for its coadministration with drugs that are metabolized by CYP3A4/5. Instead, the proposed language noted the DDI prevention and mitigations strategies were attributed to the clarithromycin component.

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 (Study TAK-438/CPH-401), compared with the use of clarithromycin (CYP3A4 substrate and inhibitor) alone, clarithromycin exposures increased approximately 1.6-fold when co-administered with vonoprazan.

For triple therapy, given vonoprazan is to be administered with clarithromycin (a strong CYP3A4 inhibitor), the mitigation strategies for concomitant use of vonoprazan triple therapy with CYP3A substrates will be recommended such that it aligns with the recommendations in the clarithromycin prescribing information.

For dual therapy, considering a near 2-fold increase in midazolam systemic exposure by vonoprazan, the review team recommends frequent monitoring for concentrations and/or adverse reactions for certain concomitantly administered CYP3A substrate drugs where minimal concentration changes may lead to serious toxicities.

CYP2C19 Substrates

The Applicant is not proposing any vonoprazan-specific clinical mitigation strategies for its coadministration with drugs that are metabolized by CYP2C19. The review team recommends monitoring for effectiveness and adverse effects related to CYP2C19 substrate drugs when triple or dual therapy is co-administered with CYP2C19 substrate drugs. The rationale for these recommendations is discussed below.

In vitro study findings (Study TAK-438-12124) suggested that vonoprazan is a time-dependent inhibitor of CYP2C19. Moreover, mechanistic static model-based predictions suggested that vonoprazan with or without clarithromycin may increase proguanil (CYP2C19 substrate) AUC by 1.5-fold. See Section 14.4 for PBPK analysis that estimated the effects of vonoprazan on CYP2C19 substrates omeprazole and lansoprazole. A published clinical study by Funakoshi et al. (2019) that investigated the effects of vonoprazan on the proguanil PK reported that vonoprazan increased the AUC of proguanil by approximately 42% and decreased the AUC of cycloguanil (proguanil's metabolite mediated by CYP2C19) by approximately 28%. The published study had limitations with respect to the dosing regimen evaluated and the PK assessment plans, which do not allow an extrapolation of these findings to inform prescribing information. In addition, publications with clinical data show that vonoprazan, when administered at doses lower than the recommended dose for *H. pylori* treatment, attenuates anti-platelet functions of clopidogrel (a prodrug of which the efficacy depends on conversion to the active metabolite primarily mediated by CYP2C19) (Kagami et al. 2018; Higuchi et al. 2022). Collectively, the available information suggests that vonoprazan is a CYP2C19 inhibitor.

CYP2B6 Substrates

In vitro study findings (Study TAK-438-11315) suggested that vonoprazan is a time-dependent inhibitor of CYP2B6 and mechanistic static model-based predictions suggested that vonoprazan with or without clarithromycin may increase bupropion (CYP2B6 substrate) AUC by 1.5-fold. An information request was sent to the Applicant requesting a summary on CYP2B6 substrates that were used concomitantly with triple or dual therapy in subjects enrolled in Study HP-301, along with safety findings. The review of the Applicant's response suggests that very limited information is available for the concomitant use of triple or dual therapy with CYP2B6 substrate (< 5 subjects in Study HP-301). Considering the lack of sensitive index substrates for CYP2B6 and the weak inhibition potential from model predictions, the review team agreed with the Applicant that no DDI mitigation strategy is needed for concomitant use of vonoprazan triple and dual therapy with CYP2B6 substrates.

Drug Interaction Potential of Vonoprazan Metabolite

Findings from a clinical radiolabeled mass balance study showed that of the total radioactivity in plasma over 24 hours following dosing with [^{14}C]-vonoprazan, glucuronic acid conjugate of vonoprazan metabolite M-I (M-I-G) accounts for 19.2%, compared to 13.9% for vonoprazan suggesting M-I-G may have higher AUC than vonoprazan. The Applicant has not provided

information on the inhibition potential of M-I-G on CYP450 isoforms or drug transporters. Therefore, the review team recommends postmarketing in vitro DDI studies to determine the need for clinical DDI studies with vonoprazan and concomitant drugs, as well as labeling revisions related to the appropriate use of vonoprazan dual and triple therapies.

8.3. Plans for Pediatric Drug Development

The Applicant submitted the agreed initial pediatric study plan along with a request for a full waiver from the requirement to perform pediatric studies. The prevalence of *H. pylori* infection that requires treatment is low in the pediatric population, and studies are impossible or highly impracticable. The Applicant's request was discussed with the Pediatric Review Committee (PeRC) on April 5, 2022, and PeRC concurred with the Division's plan to grant a full waiver for the pediatric population.

8.4. Pregnancy and Lactation

The use of vonoprazan in pregnant or lactating women has not been evaluated in adequate and well-controlled clinical studies to inform about the drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Pregnancy

Based on animal reproduction studies with clarithromycin, the triple therapy regimen is not recommended for use in pregnant women except in clinical circumstances where no alternative therapy is appropriate. If VTRI is used during pregnancy, pregnant women should be apprised of the potential risk to a fetus.

There were no pregnancies in the pivotal trial, HP-301 or in the supportive trial, CCT-401. There were four cases of pregnancy noted on vonoprazan, with one spontaneous and one elective abortion.

- Trial TAK438-109 (single dose PK/pharmacodynamic [PD])/N=24: one case of spontaneous abortion 1 month after 2 single doses of 20 mg, 5 days apart.
- Trial CCT-304 (quadruple therapy for *H. pylori*), N=226: one subject was pregnant after 14 days of therapy and underwent an elective abortion.
- Trial CCT-102 (short term treatment for DU): one subject received 12 days of 20 mg vonoprazan, tested negative for pregnancy at end of study, then had normal pregnancy 6 months later.
- Trial OCT-301 (NSAID induced ulcer recurrence prevention): one subject received 344 days of vonoprazan and conceived on day 321 with normal pregnancy.

There were 3 cases of pregnancy on lansoprazole in trial CCT-301 (quadruple therapy for *H. pylori*, N=230), with 2 subjects becoming pregnant 2 months after 14 days of therapy, 1 with a normal pregnancy and the other with a spontaneous abortion. The remaining case had a normal pregnancy, with a positive test 3 weeks after a 28-day course (conceived on day 26).

Lactation

There are no data regarding the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. Vonoprazan and its metabolites are present in rat milk. Based on limited human data, clarithromycin and its active metabolite 14-OH clarithromycin are present in human milk at less than 2% of the maternal weight-adjusted dose. Reported adverse effects on breastfed children are rash, diarrhea, loss of appetite, and somnolence, comparable to amoxicillin. A recently published study provided new data on clarithromycin human milk concentrations from a female subject given a 500 mg (8.9 mg/kg) dose of clarithromycin orally. The study did not report serum concentrations, therefore, the reported dose of 500 mg for this single subject cannot be confirmed by maternal serum concentrations. Assuming milk consumption of 150 mL/kg/day, the reviewer estimated that an exclusively human milk fed infant would receive < 7% of the maternal weigh-adjusted dose and < 3.5% of the pediatric dose recommended in the clarithromycin label. Considering: (1) the new data are from a single female subject, (2) the serum concentrations were not reported to allow an estimation of the plasma/serum: milk concentration ratio, and (3) the estimated daily infant dose is not notably higher than that included in the clarithromycin label (7% versus 2%), the review team does not recommend any revisions to the human lactation data included in the clarithromycin label.

DPMH was consulted to review the risks of VDUAL and VTRI. As per their consult dated March 25, 2022, given the lack of information on use during pregnancy and the potential use in an at-risk population, DPMH recommended gathering additional pregnancy exposure data to assess the safety of vonoprazan-containing product use during pregnancy. A PMR for a pregnancy exposure registry and a postmarketing pregnancy study of a different design should be issued for vonoprazan-containing products. DPMH also recommended a PMR for a “milk only” clinical lactation study to assess whether vonoprazan is present in clinically relevant quantities in human milk, to determine if further lactation studies may be needed to assess vonoprazan levels in infants exposed to the product via lactation.

Animal Data

See Table 42 for the nonclinical information used in support of the drug’s labeling. The reproductive and developmental toxicology studies with vonoprazan are summarized in Section 7.1. Additional details are available in Section 13.

Table 42. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1. Pregnancy	Vonoprazan 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 at lower dose groups in the GLP rat PPND

Labeling Section	Nonclinical Data
	study, liver discoloration was seen in lower doses (3, 10 and 30 mg/kg) in non-GLP rat dose-range finding studies, dosed from GD 6 to LD 13. Amoxicillin Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin. Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions. In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 1.6 times the human dose in mg/m^2). Clarithromycin In pregnant mice administered clarithromycin during organogenesis, at 100 mg/kg/day reduced survival and body weight of fetuses was observed, at 500 mg/kg/day there were increases in the incidence of post-implantation loss and cleft palate, and the NOAEL in this study was 250 mg/kg. In pregnant rats orally administered clarithromycin during organogenesis at 150 mg/kg dam body weights and feed consumption were reduced, increased resorptions and body weights were observed in the fetuses, as was a low incidence of cardiovascular abnormalities. The NOAEL in this study was 50 mg/kg. In a study of pregnant Sprague Dawley rats administered clarithromycin by IV during organogenesis up to 160 mg/kg/day was associated with maternal toxicity but not adverse developmental effects on the fetuses. In pregnant Wistar rats, clarithromycin was orally administered during organogenesis with doses up to 160 mg/kg/day. Reduced body weight and food consumption were observed in dams at 160 mg/kg/day but there was no evidence of adverse developmental effects at any dose. In pregnant rabbits, clarithromycin orally administered during organogenesis (GD 6 to 18) at doses of up to 125 mg/kg/day resulted in reduced maternal food consumption and decreased body weight at the highest dose, with no evidence of any adverse developmental effects at any dose. Clarithromycin administered by IV to pregnant rabbits during organogenesis (GD 6 to 18) at 20, 40, 80, or 160 mg/kg/day resulted in maternal toxicity and implantation losses at all doses. In pregnant monkeys, clarithromycin was administered (GD 20 to 50) at oral doses of 35 or 70 mg/kg/day. Dose-dependent emesis, poor appetite, fecal changes, and reduced body weight were observed in dams at all doses. There was no evidence of primary drug-related adverse developmental effects at any dose tested. In a reproductive toxicology study in rats administered oral clarithromycin late in gestation through lactation (GD 17 to PND 21) at doses up to 160 mg/kg/day, reductions in maternal body weight and food consumption were observed at 160 mg/kg/day. Reduced body-weight gain observed in offspring at 160 mg/kg/day was considered secondary to maternal toxicity. No adverse developmental effects were observed with clarithromycin at any dose tested.
8.2. Lactation	Vonoprazan Vonoprazan and its metabolites are present in rat milk. 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 at lower dose groups in the GLP rat PPND study, liver discoloration was seen in lower doses (3, 10 and 30 mg/kg) in non-

Labeling Section	Nonclinical Data
	GLP rat dose-range finding studies, dosed from GD 6 to LD 13. In follow-up rat mechanistic studies, increased stomach weights and liver discoloration similarly associated with necrosis, hemorrhage and fibrosis were found with lactational only dosing at 100 mg/kg.
13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility	Vonoprazan 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. Amoxicillin In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg. Clarithromycin Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring.

Source: Reviewer generated table based on data and information from Sponsor provided reports for vonoprazan and FDA approved labeling for amoxicillin and clarithromycin.
*Doses in the animal studies were calculated based on the free vonoprazan molecule
Abbreviations: GD, gestation day; GLP, good laboratory practice; 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

Information in Table 42 is derived from a list of fertility and reproductive toxicology studies provided below. All safety factors shown are based on systemic exposures compared between animals and humans. Further details are available in Section 13.1.

Table 43. Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical exposure (ng*h/mL)	Safety Margins[a] (multiples)
Vonoprazan			
Fertility rat	300	64,910[b]	133
EFD rat	100	12,016[c]	25
EFD rabbit	30	4,710	10
PPND rat	10	5,590	1
Amoxicillin[d]			
Mouse reproduction			3[e,f]
Rat reproduction			6[e,f]
Rat multi-generation	500		1.6[e,f]

Study	NOAEL (mg/kg)	Nonclinical exposure (ng*h/mL)	Safety Margins[a] (multiples)
Clarithromycin[d]			
Fertility rat	160		2[g]
EFD mouse	250		1[e]
EFD rat (oral)	50		0.3[e]
EFD rat (IV)	160		1[e]
EFD rat (oral)	160		1[e]
EFD rabbit (oral)	125		2[e]
EFD rabbit (IV)	20		0.3[e]
Monkey (GD 20-50)	70[h]		
PPND rat	160		1[e]

Source: Reviewer created table based on Sponsor provided reports for vonoprazan and FDA approved labeling for amoxicillin and clarithromycin.
[a] Exposure multiples were based on population pharmacokinetics analysis where a 40 mg QD clinical dose resulted in systemic exposures of $AUC_{0\text{-}24h}$r = 488 µM•hr. (Study #TAK-438-107)
[b] Exposure from 13-week repeat dose rat study in nonpregnant animals
[c] Exposure from 4-week repeat dose rat study in nonpregnant animals
[d] Studies references from labeling from listed drug
[e] BSA comparison
[f] Margin for the 3 g amoxicillin dose in the Dual Pak
[g] From the RLD label: "Plasma levels in rats after 150 mg/kg/day were twice the human serum levels."
[h] Maternal toxicity noted; no developmental effects
Abbreviations: EFD, embryo-fetal development; GD, gestation day; IV, intravenous; NOAEL, no observed adverse effect level; PPND, peri- and postnatal development

9. Product Quality

The proposed commercial drug product under NDA 215152 (triple therapy pack) is a combination of three co-packaged drug components: vonoprazan tablets, 20 mg, and previously approved amoxicillin capsules, 500 mg, and clarithromycin tablets, 500 mg. The proposed commercial triple therapy blister cards contain 2 vonoprazan tablets 20 mg, 4 amoxicillin capsules 500 mg, and 2 clarithromycin tablets 500 mg. Each card contains the dosing regimen for one day. The proposed commercial packaging presentation includes 14 blister cards packaged in a carton and creates a convenience pack to cover the entire course of treatment (14 days).

The proposed commercial drug product under NDA 215153 (dual therapy pack) is a combination of two co-packaged drug components: vonoprazan tablets, 20 mg, and previously approved amoxicillin capsules, 500 mg. The proposed commercial dual therapy blister cards contain 2 vonoprazan tablets, 20 mg, and 4 amoxicillin capsules, 500 mg. Each card contains the dosing regimen for one day. The proposed commercial packaging presentation includes 14 blister cards packaged in a carton and creates a convenience pack to cover the entire course of treatment (14 days).

The comprehensive chemistry, manufacturing and controls (CMC) information for vonoprazan and vonoprazan tablets has been submitted in NDA 215152. For CMC information regarding the approved amoxicillin capsules and clarithromycin tablets used in the dual and triple therapy packs, the Applicant provided letters of authorization (LoAs) to ANDAs 64076 and 65136, respectively, held by Sandoz. In addition, NDA 215153 includes a letter of cross-reference to NDA 215152.

NDA 215152: Voquezna Triple Pak (vonoprazan/clarithromycin/amoxicillin)
NDA 215153: Voquezna Dual Pak (vonoprazan/amoxicillin)

Both NDAs, as amended, have provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug products, triple and dual packs. That includes stability information to support the 24 months expiry dating for both drug products, to be stored under controlled room temperature conditions. In addition, manufacturing and testing facilities listed in both NDAs for commercial use have been found acceptable. Therefore, these NDAs are recommended for approval by the Office of Pharmaceutical Quality (OPQ).

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) performed clinical investigator inspections at three study sites that participated in Study HP-301. OSI's assessment was that the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of this indication. Please refer to the review by Cheryl Grandinetti, PharmD, for additional information. The Applicant certified that there were no investigators with disclosable financial interests or arrangements. Please refer to the financial disclosure form in Section 23.

11. Advisory Committee Summary

An advisory committee was not convened for these NDAs. There were no controversial issues that would benefit from advisory committee discussion.

III. Appendices

12. Summary of Regulatory History

Pre-investigational new drug (PIND) application 143190 was submitted by Takeda Pharmaceuticals International, Inc. (initial Sponsor) on April 24, 2019, for vonoprazan/amoxicillin/clarithromycin (b) (4) indicated for eradication of *H. pylori*. A guidance meeting was held on July 9, 2019, to discuss the phase 3 development program to support an indication for eradication of *H. pylori*. The Division of Anti-Infectives (DAI) recommended to have two separate PINDs for the eradication of *H. pylori* infection: one IND for vonoprazan triple therapy (vonoprazan/amoxicillin/clarithromycin tablets) and another IND for vonoprazan dual therapy (vonoprazan/amoxicillin).

On May 13, 2019, the change in ownership of PIND 143190 and PIND 144399 was submitted. Takeda Pharmaceuticals International, Inc. was replaced by Phathom Pharmaceuticals, Inc.

On June 18, 2019, Phathom Pharmaceuticals, Inc., (the current Applicant) submitted two requests for Qualified Infectious Disease Product (QIDP) designation, one for vonoprazan/amoxicillin/clarithromycin (b) (4) (under PIND 143190) and one for vonoprazan/amoxicillin (b) (4) (under PIND 144399), both for the indication of eradication of *H. pylori* infection. On August 15, 2019, in response to DAI's recommendations, the Applicant amended their requests for QIDP for both combinations, to a new indication of treatment of *H. pylori* infection. Both PINDs received QIDP designation for the same indication on August 17, 2019.

On August 23, 2019, Investigation New Drug (IND) 143190 for vonoprazan, amoxicillin and clarithromycin (b) (4) and IND 144399 for vonoprazan, amoxicillin (b) (4) were submitted by the Applicant to the Division for 30-Day IND safety review; both INDs were indicated for the treatment of *H. pylori* infection. DAI determined both INDs were safe to proceed.

On October 21, 2019, the Applicant was granted fast track designation for IND 143190, for the development of vonoprazan and amoxicillin/clarithromycin tablets for the treatment of *H. pylori* infection. The Applicant was also granted fast track designation for IND 144399 for vonoprazan/amoxicillin (b) (4) for the treatment of *H. pylori* on the same date.

DAI has jurisdiction for IND 143190 for vonoprazan/amoxicillin/clarithromycin and IND 144399 for vonoprazan/amoxicillin (b) (4) On February 13, 2020, the Applicant submitted Type C meeting requests to all (b) (4) INDs, to discuss their planned in vitro and in vivo drug-drug interaction (DDI) studies as a follow-up to Food and Drug Administration (FDA) recommendations provided by both Divisions. (b) (4) the comments indicated that both Divisions agreed with the overall design of the proposed DDI studies with further comments to be provided upon submission of the full protocol to the INDs.

On March 6, 2020, the Applicant submitted their proposed Initial Pediatric Study Plan (iPSP) to both IND 143190, and IND 144399, for both triple and dual combinations and requesting a waiver for the indication of treatment of *H. pylori* infection across all pediatric age groups (Full Waiver) because the required studies are impossible or highly impracticable given the pediatric prevalence in this indication. On June 2, 2020, DAI issued the Sponsor Agreed Initial Pediatric Study Plan letters for both IND 143190, vonoprazan/amoxicillin/clarithromycin for the treatment of *H. pylori* infection and IND 144399 for vonoprazan/amoxicillin for the treatment of *H. pylori* infection.

On August 28, 2020, the Applicant submitted a request for proprietary name review for the tradename (b) (4) Triple Pak for vonoprazan, amoxicillin and clarithromycin tablets and (b) (4) Dual Pak for vonoprazan and amoxicillin (b) (4) Both names were found conditionally acceptable by the Division of Medication Error Prevention Analysis (DMEPA) on February 23, 2021, and December 13, 2021.

On November 10, 2020, a Pre-New Drug Application (NDA) teleconference was held to discuss the content of the nonclinical and clinical sections required to support the submission of NDAs for vonoprazan used in combination with amoxicillin and clarithromycin and vonoprazan used in combination with amoxicillin, both for the treatment of *Helicobacter pylori* infection. DAI and the Applicant discussed different aspects of the Applicant's plan to submit NDAs.

A Chemistry, Manufacturing and Controls (CMC) Pre-NDA teleconference was subsequently held on January 7, 2021, wherein feedback was provided on drug substance, drug product, and stability batch requirements in support of the submission of NDAs.

On January 22, 2021, the Applicant was granted fast track designation under IND 143190 for the development of vonoprazan tablets, amoxicillin capsules and clarithromycin tablets (copackaged) to be used in combination for the treatment of *H. pylori* infection. Additionally, on January 22, 2021, the Applicant was granted fast track designation under IND 144399 for vonoprazan tablets and amoxicillin capsules (copackaged) to be used in combination for the same indication.

On April 14, 2021, a follow-up Pre-NDA teleconference was held to further discuss drug substance, drug product, and stability batch requirements in support of NDA submissions, and the regulatory impact on the June 2, 2020, agreed iPSPs. The Division confirmed that the agreed iPSPs from June 2, 2020, can be used to fulfill the NDA requirements for their planned NDAs with (b) (4) amoxicillin capsules (formulations).

On April 30, 2021, the Office of New Drug Policy (ONDP) provided an official Memorandum to File describing ONDP's rationale for granting QIDP designation under section 505E of the Federal Food, Drug and Cosmetic Act (the FD&C Act) for the following proposed, copackaged drugs:

- IND 143190: vonoprazan tablets, amoxicillin capsules, and clarithromycin tablets, to be copackaged for use in combination for the treatment of *H. pylori* infection and
- IND 144399: vonoprazan tablets and amoxicillin capsules, to be copackaged for use in combination for the treatment of *H. pylori* infection.

Following extensive internal discussions between DAI, ONDP group, and the Applicant, on May 5, 2021, IND 143190 was granted QIDP designation for vonoprazan tablets, amoxicillin

capsules, and clarithromycin tablets (copackaged) and for IND 144399 for vonoprazan tablets and amoxicillin capsules (copackaged), both for the treatment of *H. pylori* infection.

Phathom Pharmaceuticals, Inc. submitted NDA 215152 for vonoprazan tablets 20 mg, amoxicillin capsules 500 mg, (b) (4) clarithromycin tablets, 500 mg, (b) (4) and NDA 215153 for vonoprazan tablets 20 mg, amoxicillin capsules 500 mg, (b) (4) on September 3, 2021. Both NDAs are indicated for the treatment of *H. pylori* infection and the Applicant requested Priority NDA Reviews. The NDAs were filed on November 2, 2021, as new molecular entity (NME) 505(b)(2) NDAs to be reviewed under 'the Program.' These NDAs have a Prescription Drug User Fee Act (PDUFA) goal date of May 3, 2022.

On January 11, 2022, the Applicant requested the conditionally acceptable proprietary name for (b) (4) Triple Pak and (b) (4) Dual Pak tradenames to be withdrawn due to potential confusion with (b) (4). On January 11, 2022, the Applicant requested a new proprietary name review by DMEPA for the tradenames (b) (4) Triple Pak for vonoprazan fumarate, amoxicillin and clarithromycin, and (b) (4) Dual Pak for vonoprazan fumarate and amoxicillin. On March 11, 2022, both (b) (4) Triple Pak and (b) (4) Dual Pak were found unacceptable by DMEPA, because as proposed, the names created a misleading impression regarding the efficacy of the drug. On March 11, 2022, an additional request for a proprietary name review was submitted for the tradenames Voquezna Triple Pak and Voquezna Dual Pak. On April 26, 2022, DMEPA concluded that the proposed proprietary name Voquezna Dual Pak and Voquezna Triple Pak are acceptable.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

Voquezna Dual Pak contains vonoprazan as well as amoxicillin. Voquezna Triple Pak contains vonoprazan, amoxicillin, and clarithromycin. Amoxicillin and clarithromycin have been previously reviewed and found to be safe and effective in other FDA-approved products. Vonoprazan has not previously been reviewed and approved by FDA.

No combination nonclinical studies with vonoprazan and amoxicillin and/or clarithromycin were submitted to FDA for review under this NDA. Data evaluated on vonoprazan is in Section 13.2.1. Data from FDA's previous review of amoxicillin is included in Section 13.2.2 and of clarithromycin is included in Section 13.2.3.

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Vonoprazan

Vonoprazan was reviewed under several INDs for the indication of treatment of *H. pylori* infection in combination with amoxicillin under IND 144399, for use to treat *H. pylori* in combination with amoxicillin and clarithromycin under IND 143190, (b) (6)

(b) (6). All nonclinical safety studies conducted to support the safety of vonoprazan were also submitted to these NDAs.

Dr. Dinesh Gautam in the Division of Pharmacology and Toxicology for Immunology and Inflammation reviewed the primary and secondary pharmacology studies, safety pharmacology studies, absorption, distribution, metabolism, and excretion (ADME) studies, single dose toxicology studies (Study Nos. TAK-438-0053, TAK-438-00141, TAK-438-00141, TAK-438-00215, TAK-438-00066), repeat dose toxicology studies (Study Nos. TAK-438-00143, TAK-438-00212, TAK-438-10742, TAK-438-00217), genetic toxicology studies (Study Nos. TAK-438-00052, TAK-438-00051, TAK-438-00083), reproductive and development studies (Study Nos. TAK-438-00172 and TAK-438-00135, TAK-438-11215), and carcinogenicity (Study Nos. TAK-438-10883, TAK-438-10882). All other nonclinical studies were reviewed completely in these NDAs.

Studies are reviewed or summarized from previous reviews in the following sections. Vonoprazan fumarate is referred to with the code TAK-438 in several of the studies, and the freebase of vonoprazan is referred to as TAK-438F. Doses in the provided nonclinical studies are based on the exposure to the free base TAK-438F.

13.2.1.1. Pharmacology

The pharmacology of vonoprazan was studied in in vitro and in vivo assays. Additional studies including the use of antibiotic combinations in the treatment of *H. pylori* are described in Section 15.1.

- In vitro, TAK-438 is a potent inhibitor of forskolin-induced acid formation in isolated rabbit gastric glands (half maximal inhibitory concentration [IC_{50}]=0.3 micromolar/L) (Study #TAK-438-00067-001R).
- TAK-438 is an inhibitor of K+-stimulated porcine gastric H+, K+-ATPase activity at pH 6.5 (IC_{50}= 19.3 to 29.9 nmol/L), the metabolite M-IV-Sul is a weak inhibitor of this enzyme (IC_{50} =4120 nmol/L) and the metabolites M-I, M-II and M-III do not inhibit the enzyme up to the highest dose tested (Studies #TAK-438-00115, #TAK-438-11415, #TAK-438-11416).
- TAK-438 inhibition of H+, K+-ATPase activity is reversible as shown by changes in percent inhibition by TAK-438 with dilution on the enzyme-inhibitor mix resulting in decreased inhibition (Study #TAK-438-00139). Enzyme kinetics were consistent with competitive inhibition (Study #TAK-438-00117). TAK-438 inhibited forskolin-stimulated gastric acid formation in isolated rabbit gastric glands, though the metabolites TAK 438-M-III and TAK-438-M-VI did not (Studies # TAK-438-00067-001R, #TAK-438-10130)
- TAK-438 and metabolites M-I and M-II did not inhibit Na+, K+-ATPase activity in vitro (Study #TAK-43811415).
- In rats, vonoprazan was administered at 0.5, 1, 2, and 4 mg/kg by oral gavage followed by ligation of the pylorus closed one hour later. Three hours post ligation the stomachs were removed, and acid output was measured. The 2 and 4 mg/kg doses significantly reduced the acid compared to controls, with complete inhibition at 4 mg/kg (Study #TAK-438-00071). Similar effects were seen with histamine stimulated acid secretion in pylorus ligated rats and 2-deoxy-D-glucose-stimulated acid secretion, though significant reduction in acid secretion started at 1 mg/kg in the latter (Studies #TAK-438-00072, #TAK-438-00073).
- In dogs with cannulated Heidenhain pouches, dogs were administered vonoprazan at 0.1, 0.3, or 1 mg/kg by oral gavage or vehicle or lansoprazole in a crossover design. Gastric secretion

was stimulated using subcutaneous (SC) injected histamine and acid output was measured. Dogs administered 1 mg/kg vonoprazan had complete inhibition of acid secretion at 1, 3, and 6 hours post dosing (Study #TAK-438-00074).

- In radioligand binding assays in vitro, TAK-438 at 10 micromolar inhibited L-type calcium channel phenylalkylamine, muscarinic M_1, muscarinic M_3, and non-selective serotonin 5-HT_2 receptors 90%, 80%, 84% and 81%, respectively, with IC_{50} values of 2.27, 1.49, 0.80, and 1.43 micromolar, respectively. TAK-438 also had greater than 50% inhibition at 10 micromolar of muscarinic M^2 receptors, nonselective sigma receptors, and sodium channels (Study #TAK-438-0005).

13.2.1.2. Safety Pharmacology

Table 44. Safety Pharmacology Studies

Study/ Study No.	Findings
Study No.: TAK-438-00063 Study Title: Safety Pharmacology Studies of TAK-438: Effects on hERG Current	TAK-438 was tested at concentrations of 0.5, 5, and 50 mcg/mL (maximum dose based on solubility) for potential effects of the hERG current in HEK293 cells. Inhibition at the doses was 8.0%, 50.8% and 94.7%, respectively and the IC_{50} was 4.8 mcg/mL. C_{max} in clinical trials for 20 mg vonoprazan was 23.5 ng/mL, which is >100-times less that the IC_{50}.
Study No.: TAK-438-00081 Study Title: Safety Pharmacology Studies of TAK-438: Effects on the Cardiovascular System in Conscious Dogs Dog/beagle 4/male/group Dose: 2, 6, 20 mg/kg/day Oral administration in a 0.5% methylcellulose solution Frequency: Cross-over design with single dose per week	Blood pressure, heart rate and ECG were assessed in 4 conscious telemetered male dogs in a crossover-design study. Two dogs in the highest dosing condition vomited. No effect on measured cardiovascular parameters was reported up to the highest dose tested 20 mg/kg. This dose is >100-fold higher compared to expected clinical exposures on an AUC basis from exposures seen at this dose in dogs in Study #TAK-438-00084.
Study No.: TAK-438-00082 Study Title: Safety Pharmacology Studies of TAK-438: Effects on the Respiratory System in Rats Rats/Crl:CD(Sprague Dawley) 8/males/group Dose: 0, 30, 100, 600 mg/kg/day Oral gavage dosing in a 0.5% methylcellulose suspension. Frequency: single dose	Groups of 8 male rats were assessed for respiratory parameters, including the respiratory rate (frequency), tidal volume (TV), minute volume (MV), and Penh (enhanced pause, which is an index of airway constriction) pretreatment and at 1, 2, 4, 8, and 22 hours after a single oral dose. In the 600 mg/kg group 4 animals died and an increase in bronchoconstriction was reported in one of these animals prior to death. Decreased TV and MV at 4 and 8 hours after dosing was reported in the 600 mg/kg dose group. These values returned to normal by 22 hours after dosing. NOEL: 100 mg/kg, 46-fold higher than expected clinical exposure based on AUC measured at this dose in rats in study no. TAK-438-00085
Study No.: TAK-438-00080 Study Title: Safety Pharmacology Studies of TAK-438: Effects on the Central Nervous System in Rats Rats/Crl:CD(Sprague Dawley) 6 males/group Dose: 0, 30, 100, 600 mg/kg/day Single oral dose in 0.5% methylcellulose solution	Free moving male rats were assessed using a functional observational battery (FOB). Observations were made before dosing, and at 1, 2, 4, 8, and 22 hours after dosing. Mydriasis was reported in 100 mg/kg dose group animals from 1-8 hours post-dosing and returned to normal by 22 hours. There was one death in 600 mg/kg animals 2-4 hour after dosing. In 600 mg/kg animals, clinical signs 1-4 hours post dosing including decreased muscle resistance, decreased locomotor activity, partially closed eye lids, difficulty in hopping and decrease in body temperature were reported. No treatment-related findings were reported in the 30 mg/kg dose group. NOEL=30 mg/kg.

Source: Evaluation of reviewer and Dr. Dinesh Gautam under IND applications.
Abbreviations: AUC, area under the curve; IC_{50}, concentration inhibiting 50% activity; NOEL, no observed effect level

13.2.1.3. ADME/PK

The ADME profile of TAK-438 and related compounds have been studied in vitro and in vivo in rats and dogs. There is one major human metabolite, TAK438 M-IV-Sul, that was

disproportionately higher in humans than found in vitro or in vivo in rats and dogs (16.9% in humans versus >1% in rats and dogs). The Applicant therefore conducted additional toxicology testing specifically on this metabolite.

Absorption

Following oral and IV administration of [^{14}C]-TAK-438, serum levels of TAK-438F (free base of TAK-438) were measured to determine the oral bioavailability in rats and dogs. The oral bioavailability of TAK-438 was 52.4% in dogs and 10.3% in rats. After oral administration of TAK-438 to rats (2 to 18 mg/kg) and dogs (0.1 to 1.0 mg/kg), the plasma concentration of TAK-438F increased more than dose proportionally. The oral absorption of [^{14}C]-TAK-438 was as high as 92.2% in rats and 86.3% in dogs. The apparent lower bioavailability compared to absorption is likely due to metabolism related to the first pass effect.

Distribution

In rats orally administered [^{14}C]-TAK-438, radioactivity was widely distributed into tissues, indicating wide distribution of TAK-438 or metabolites. The total radioactivity reached the maximum level at one hour in most tissues. The total radioactivity concentration was higher in the liver, kidney, intestine, lung, and stomach wall than in the plasma, and lower in the brain and the spinal cord.

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.

Metabolism

Metabolism of TAK-438 was assessed in vitro and in vivo studies. In liver microsomes from mouse, rat, dog, monkey, and human, TAK-438 was metabolized to metabolites identified as M-1, M-II, N-demethylated TAK-438F, and up to 6 other unidentified metabolites. When TAK-438 was incubated with hepatocytes from rats, dogs, monkeys, and humans for 6 hours, metabolites M-I, M-II, M-III, M-IV-Sul, and N-demethylated TAK-438 were identified. M-IV-Sul was a greater proportion of the human metabolites than in rats, dogs, or monkeys. Consistent with the in vitro metabolism data, in vivo data from clinical trials support that M-IV-Sul is a major human metabolite, and the other metabolites are adequately assessed in the general toxicology studies. Therefore, additional in vivo studies with TAK-438 M-IV-Sul administered directly to rats were performed to separately evaluate its potential toxicity.

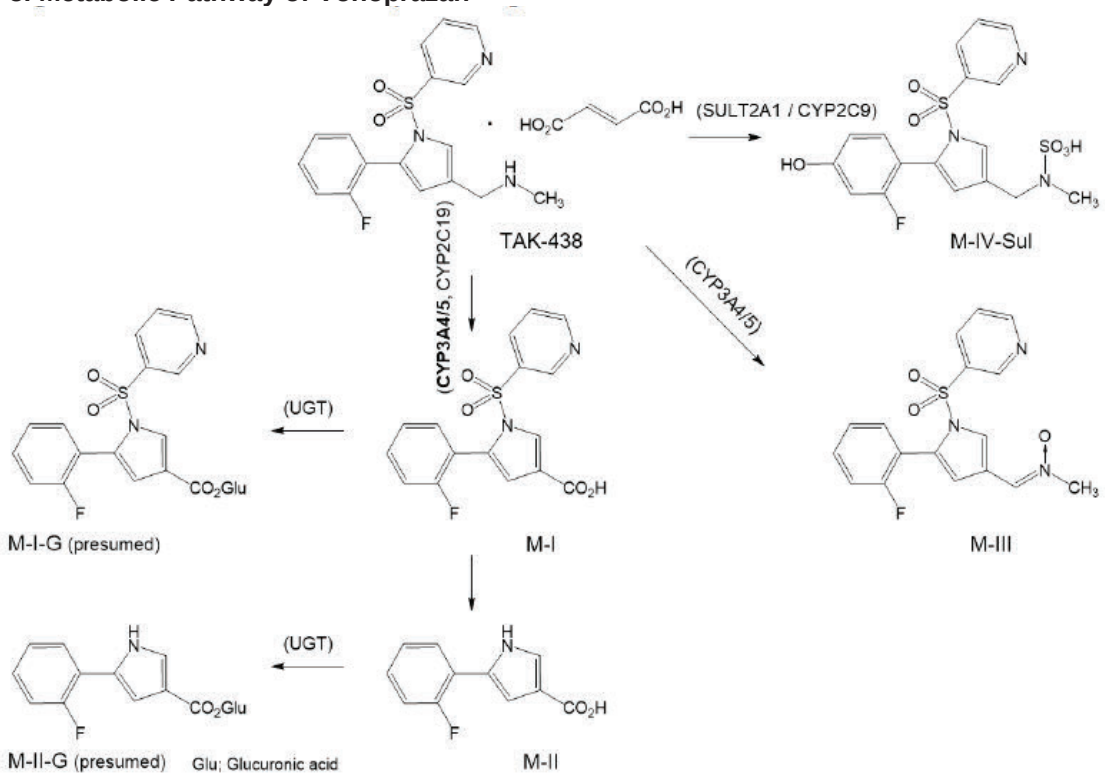
Metabolism in humans was identified to be mainly by cytochrome P450 (CYP) 2D6, 2C19 and 3A4 based on in vitro metabolism with microsomes expressing human CYP isoforms (Study #TAK-438-00097) and correlation with metabolic rates using CYP isoform specific substrates. Vonoprazan is also sulfated by SULT2A1 to TAK-N-sulfate which is further metabolized by CYP2C9 or CYP 3A4 to M-IV-Sul (Study #TAK-438-11251).

Table 45. In Vitro Metabolism of Vonoprazan by Hepatocytes

Study/ Study No. TAK-438-00131						
	Elimination amount (nmol/L)	Formation amount (nmol/L)				
Animal Species	Vonoprazan	M-I	M-II	M-III	M-IV-Sul	N-demethylated TAK-438
Rat	3180	996	8	45	71	961
Dog	1324	241	2	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: Applicant's table from NDA file Module 2, Section 2.6.4 Pharmacokinetics Written Summary

Figure 5. Metabolic Pathway of Vonoprazan



Source: Applicant's figure from NDA file Module 2, Section 2.6.4 Pharmacokinetics Written Summary

Analysis of plasma collected from rat and dog studies indicated that vonoprazan was present, as were the metabolites M-I, M-II, M-II-G, M-II, M-IV-Sul and other metabolites. Percentages of vonoprazan and the metabolites in rats and dogs are shown in Table 46.

Table 46. In Vivo Metabolism of Vonoprazan in Rats and Dogs

Animal Species	Vonoprazan	M-I	M-I-G	M-II	M-II-G	M-III	M-IV-Sul	Others	Study No.
Rat	0.9	51.9	11.8	7.4	4.5	NE	NE	23.5	TAK-438-00109
Rat	NE	NE	NE	NE	NE	0.5	0.0	99.5	TAK-438-11243
Dog	1.9	8.8	14.0	5.2	39.4	NE	NE	30.7	TAK-438-00093
Dog	NE	NE	NE	NE	NE	1.1	0.3	98.6	TAK-438-11245

Source: Reviewer table from Applicant data based in indicated studies
Rat Studies: 3 male rats administered 2 mg/kg [^{14}C]-TAK-438F in 0.5% methylcellulose by oral gavage
Dog Studies: 3 male dogs administered 0.3 mg/kg [^{14}C]-TAK-438F in 0.5% methylcellulose by oral gavage
% total reactivity in plasma (as %AUC of total radioactivity of AUC_{0-24})
Sampling period 0-24h
Abbreviations: NE, not examined

Excretion

Following oral administration of [^{14}C]-TAK-438 to thoracic duct cannulated rats, the radioactivity was recovered 0.6% in the lymph, 17.1% in the urine and 79% in the feces. In rats orally administered [^{14}C]-TAK-438, radioactivity was almost completely eliminated from all tissues within 168 hours after dosing. In separate studies, proportion of administered [^{14}C]-TAK-438 as parent compound or metabolites in urine and feces were measured. Through 24 hours, in the urine, the parent compound, M-I, M-I-G, M-II, M-II-G, and others (not identified) made up 2.1, 0.1, 1.3, 0.7, 1.4 and 10.2% of the total dose respectively. In the feces, the parent compound, M-I, M-I-G, M-II, M-II-G, and others (not identified) made up 0.8, 1.6, 8.5, 0.4, 0.6 and 65%, respectively.

Following oral administration of [^{14}C]-TAK-438 to dogs, the radioactivity was recovered 62.5% in the urine and 31.4% in the feces within 48 hours following administration. In dogs orally administered [^{14}C]-TAK-438, radioactivity was almost completely eliminated from all tissues within 120 hours after dosing. The proportion of administered [^{14}C]-TAK-438 (administered orally to male dogs at a dose of 0.3 mg/kg measured as free base TAK-438F) as parent compound or metabolites in urine and feces were measured. Through 24 hours, in the urine, the parent compound, M-I, M-I-G, M-II, M-II-G, and others (not identified) made up 0.5, 0.6, 0.8, 1.0, 42.6, 22.6% and 13.3% of the total dose, respectively. In the feces, through 48 hours, the parent compound, M-I, M-I-G, M-II, M-II-G, and others (not identified) made up 0.5, 0.7, 0.6, 0.5, 0.1 and 28.9%, respectively. M-III and M-IV-Sul were <1% of the dose in urine and feces.

Toxicokinetics

Toxicokinetics were measured in single and repeat-dose studies and the parameters are included with the study summaries in section 13.2.1.4. A study examining pharmacokinetics (PK) in pregnant rats is summarized in Table 47.

Table 47. Toxicokinetic Summaries Not Found Elsewhere

Reproductive Toxicology Studies	Data
The Plasma Concentrations of TAK-438 in Pregnant Rats (Study #TAK-438-10005)	Table 5 Toxicokinetic parameters for TAK-438F, M-I, M-II, M-III and M-IV-Sul in pregnant rats

Dose*1 (mg/kg/day)	Analyte	Day of pregnancy	Female (N=3) Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng·h/mL)
100	TAK-438F	6	0.8 (0.3)	2266.6 (173.5)	18170 (3072)
		17	2.0 (1.7)	1410.3 (188.7)	12943 (1011)
	M-I	6	2.0 (1.7)	1340.8 (133.4)	15711 (2476)
		17	2.3 (1.5)	1750.4 (133.8)	20484 (1808)
	M-II	6	8.0 (0.0)	96.7 (24.2)	1738 (544)
		17	8.0 (0.0)	185.7 (91.6)	3451 (1269)
	M-III	6	1.7 (0.6)	19.9 (2.3)	175 (2)
		17	1.2 (0.8)	7.1 (1.4)	64 (3)
	M-IV-Sul	6	1.0 (0.0)	30.1 (2.0)	187 (48)
		17	1.0 (0.0)	6.5 (2.0)	51 (12)

Mean (S.D.)
*1: As TAK-438F

Source: Sponsor Study Report page 17
Note this is a non-GLP PK study. The GLP embryo-fetal developmental toxicity study used doses of 30, 100, and 300 mg/kg.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; SD, standard deviation; T_{max}, time to maximum concentration

13.2.1.4. Toxicology

In the toxicology studies, doses administered were calculated as the free base TAK-438F.

13.2.1.4.1. General Toxicology

Single-Dose and Acute Toxicology/Toxicokinetic Studies

- Single dose toxicology studies have been conducted in rats and dogs.
- In a study in rats (Study #TAK-438-00053) the median lethal dose (LD_{50}) for TAK-438 was between 600 and 2000 mg/kg/day.
- In an acute preliminary dose-escalating study in dogs (Study #TAK-438-00141), doses were administered by oral gavage for 3 days to beagle dogs at a dose of 10 and 60 mg/kg (N=2/sex/dose). There were no mortalities. Effects were vomiting at 60 mg/kg and elevated alanine aminotransferase (ALT) in one male animal at 10 mg/kg and all animals at 60 mg/kg, all of which were reversed by 7 days after the dose.
- In acute oral gavage dose-escalation study in beagle dogs, (Study #TAK-438-00066), TAK-438 was administered in an escalating manner at a weekly interval at doses of 0, 2, 10, and 60 mg/kg (N=2/sex/dose). One male and one female animal in the high dose group displayed clinical signs including convulsions, tachypnea, cyanosis, and mydriasis, and died about 2 hours following dosing. In the surviving animals, vomiting and salivation was observed, as was a decrease in body temperature. Surviving animals had a transitory increase in plasma ALT, aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). Vomiting was also observed at 10 mg/kg.

Repeat-Dose Toxicology/Toxicokinetic Studies on Vonoprazan

Study #TAK-438-00085/ Four-Week Oral Gavage Toxicity Study In Rats With A 4-Week Recovery Period:

Key Study Findings

- Primary target organs of toxicity were the stomach, thyroid gland, and liver.
- At the mid (30 mg/kg) and high (100 mg/kg) doses, TAK-438 produced an increase in stomach weights in both sexes and histopathology 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. In the high-dose males, there was minimal vacuolation of the midlobular hepatocytes and follicular cell hypertrophy in the thyroid. Although these effects were likely related to the pharmacological effects of the drug, they should be considered adverse due to the adverse effect on the animal at that dose.
- The no observed adverse effect level (NOAEL) was 10 mg/kg dose, associated with an area under concentration-time curve (AUC) of 0.482 and 0.658 mcg*h/mL for males and females, respectively, at 4 weeks, and with safety margins of approximately 1.0 and 1.3, respectively, on an AUC basis.

Table 48. Study Information (#TAK-438-00085)

Study Features and Methods	Details
GLP compliance	Yes (Japan)
Dose and frequency of dosing	0, 10, 30, 100 mg/kg/day (as calculated free base TAK-438F); Once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% (w/v) methylcellulose solution
Species/strain	Rats/Crl: CD (Sprague Dawley)
Number/sex/group	10/sex/group
Age	6 weeks
Satellite groups/unique design	Toxicokinetics: 4/sex/group
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: GLP, good laboratory practices

Table 49. Observations and Results (#TAK-438-00085)

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined 3 times daily. No drug-related findings.
Body weights	Measured 3-times the first week and weekly after. No treatment-related changes.
Feed consumption	Measured 2-3 times per week. No treatment-related findings.
Ophthalmoscopy	Prior to dosing and at week 4. No treatment-related findings.
Hematology	Collected at necropsy from the abdominal aorta. In males, decreased hemoglobin, MCV, MCH and MCHC values; increased WBC, and decreased fibrinogen levels at 100 mg/kg/day. At the end of the recovery period, only the decrease in hemoglobin was reversed.
Clinical chemistry	Collected at necropsy.

Parameters	Major Findings
	100 mg/kg: Increased AST (males: 7%), Increased ALT (males: 27%), creatinine kinase (males: 18%), ALP (Males 29%, females 22%) and decrease creatinine (females: 17%), AST (females 10%). 30 mg/kg: Increased AST (males 13%, ALT (males 12%)
Urinalysis	Collected in Week 4 and end of recovery period. A decrease in urine pH was reported in 30 and 100 mg/kg animals. A decrease in sodium and potassium excretion was observed in 100 mg/kg males and 30 and 100 mg/kg females. A decrease in potassium excretion was still observed in recovery group females.
Gross pathology	Assessed at termination. No treatment-related abnormalities.
Organ weights	Assessed at termination. 100 mg/kg: increased stomach weights, liver weights, decreased adrenal weight, increase thyroid weight in males 30 mg/kg: Increased stomach weights 10 mg/kg: Increased stomach weights In recovery animals, 100 mg/kg females stomach weights were increased compared to controls.
Histopathology Adequate battery: Yes	Evaluated after necropsy. Stomach: 30 and100 mg/kg/day dose groups: atrophy of the parietal cells vacuolation of the parietal cells (minimal to moderate), hyperplasia of the mucous neck cells, increased globule leucocytes, increased eosinophils (minimal or mild) in the mucosa/ submucosa squamous epithelial hyperplasia (minimal or mild) in the limiting ridge Eosinophilic changes (minimal or mild) in the chief cells (females only) 100 mg/kg only: Eosinophilic changes (minimal or mild) in the chief cells (males) Liver: 30 and 100 mg/kg dose groups: Centrilobular hypertrophy of the hepatocytes in males (considered adaptive) 100 mg/kg dose groups: Vacuolation of the midlobular hepatocytes in males. Thyroid: 100 mg/kg dose groups: Follicular cell hypertrophy in males
Plasma gastrin	At the end of the dosing plasma gastrin increased in 100 mg/kg group animals (1081% in males, 843% in females) and 30 mg/kg animals (168% in males, 323% in females). At the end of recovery, plasma gastrin concentrations were similar between treated and control animals.

Source: Reviewer table using data from the Applicant's submitted study report. Abbreviations: ACT, activated clotting time; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; pH, potential hydrogen; WBC, white blood cells

Toxicokinetics

- Sample collection times: 0.5, 1, 2, 4, 8, and 24 hours after dosing on day 1 and week 4.

- Accumulation: At the low dose, greater exposure was seen at week 4 compared to week 1. However, at the mid-dose the exposure was not consistently higher and in the high dose group the exposure was reduced at week 4.

Table 50. Toxicokinetics (#TAK-438-00085)

		Dose of TAK-438 (mg/kg/day)					
		10		30		100	
Parameter	Sex	Day 1	Week 4 (27th dose)	Day 1	Week 4 (27th dose)	Day 1	Week 4 (27th dose)
$AUC_{0\text{-}24h}$ (ng*h/mL)	Male	227	482	4065	2239	22,730	10,656
	Female	419	658	2722	3319	22,590	13,375
C_{max} (ng/mL)	Male	103.7	241.1	884.5	498.8	1705.3	906.4
	Female	126.2	355.3	772.6	583.7	2159.5	392.6
T_{max} (h)	Male	1.0	0.5	1.0	0.8	3.7	2.3
	Female	1.0	0.5	0.7	0.8	0.7	0.8

Source: Applicant study report
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Study #TAK-438-00143/ Thirteen-Week Oral Gavage Toxicity Study in Rats:

Key Study Findings

- Primary target organs of toxicity were stomach, adrenal gland, and liver.
- At the high dose (300 mg/kg/day) TAK-438 produced an increase in stomach weights in both sexes and thickening of the glandular stomach in males with mucous metaplasia and inflammatory cell infiltration in both sexes. Increased stomach weights and inflammatory cell infiltration were considered adverse and observed at the mid-dose (100 mg/kg). In the liver vacuolation of midlobular hepatocytes was observed in males at and above the mid-dose and at the high dose in females. The adrenal gland had hypertrophy in the zona glomerulosa from the mid-dose and above in males and in the high dose females.
- The NOAEL was designated at the 10 mg/kg dose group, associated with AUC of 0.989 and 1.343 mcg*h/mL for males and females respectively, at 13 weeks, with margins of approximately 2.0 and 2.7-times the clinical exposure on an AUC basis.

Table 51. Study Information (#TAK-438-00143)

Study Features and Methods	Details
GLP compliance	Yes (Japan)
Dose and frequency of dosing	0, 1, 10, 100, 300 mg/kg/day (as calculated free base TAK-438F); Once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% (w/v) methylcellulose solution
Species/strain	Rats/Crl:CD(Sprague Dawley) SPF
Number/sex/group	Main study: 10/sex/group
Age	6 weeks
Satellite groups/unique design	Toxicokinetics: 4/sex/group
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: GLP, good laboratory practices

Table 52. Observations and Results (#TAK-438-00143)

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Examined 3 times daily. No drug-related findings.
Body weights	Measured 2-3 times/week. Decreased body weight at the 300 mg/kg/day dose (males: 14%, females: 10%).
Ophthalmoscopy	Prior to dosing and at week 13. No treatment-related findings.
Hematology	Collected at necropsy. Decreased fibrinogen (18%), MCV (4%) and MCH (5%) in males.
Clinical chemistry	Collected at necropsy. 300 mg/kg: Increased ALP (males: up to 102%), total cholesterol (females: up to 55%), Decreased triglycerides (males: up to 92%) and glucose (males: up to 34%; females: up to 14%). Increased ALT (males: 79%), BUN (males: 23%) and creatinine (males: 15%). Decreased phospholipids (males: 21%) 100 mg/kg: Increased ALP in males (36%), cholesterol in females (23%). Decreased glucose in males (14%) and creatinine in females (15%).
Urinalysis	Collected in Week 13. 300 mg/kg: Increased urine volume (males: 89%; females: 167%) and decreased osmotic pressure (males:52%; females: 56%) in both sexes. 100 mg/kg: Increased urine volume in females (82%)
Gross pathology	Assessed at termination. 300 mg/kg: Thickening of glandular stomach wall in 2/10 males and enlargement of liver in males (10/10) and females (8/10).
Organ weights	Assessed at termination. 300 mg/kg: Increased stomach weights (males and females: 26%) and liver weights (male: 91%; females: 71%). 100 mg/kg: Increased stomach weights (males: 14%; females: 27%) and liver weights (males: 30%; females: 25%).

Parameters	Major Findings
Histopathology Adequate battery: Yes	Evaluated at necropsy. Stomach: 10 mg/kg/day and above dose groups: • Atrophy and vacuolation of the parietal cells, eosinophilic change of the chief cells, squamous epithelial hyperplasia and increased globule leukocyte in both sexes. 100 and 300 mg/kg/day dose groups: • Hyperplasia of the chief cells, widening of the proliferative zone in the pylorus and inflammatory cell infiltration in both sexes. 300 mg/kg/day dose groups: • Mucous metaplasia Inflammatory cell infiltration and mucous gland metaplasia were considered to be adverse. Liver: 100 and 300 mg/kg dose groups: • Vacuolation of the midlobular hepatocytes in males. • Centrilobular hypertrophy of the hepatocytes in both sexes (considered adaptive) 300 mg/kg dose groups: • Vacuolation of the midlobular hepatocytes in females. Thyroid: • 300 mg/kg dose groups: • Follicular cell hypertrophy in females. Adrenal: 100 and 300 mg/kg dose groups: • Hypertrophy of the zona glomerulosa in males. 300 mg/kg dose group: • Hypertrophy of the zona glomerulosa in females.

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: ACT, activated clotting time; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; pH, potential hydrogen; WBC, white blood cells

Toxicokinetics

- Sample collection times: prior to dosing (week 13 only), 0.5, 1, 2, 4, 8, and 24 hours after dosing on day 1 and week 13.
- Accumulation: Exposures increased dose-dependently, greater than dose-proportionally between the 1 mg/kg and 100 mg/kg doses and approximately dose-proportionally between 100 and 300 mg/kg. Increased exposure was reported from day 1 to week 13 for the 10 mg/kg dose and in females in the 1 mg/kg dose.

Table 53. Toxicokinetics (#TAK-438-00143)

		Dose of TAK-438 (mg/kg/day)							
		1		10		100		300	
Parameter	Sex	Day 1	Week 13	Day 1	Week 13	Day 1	Week 13	Day 1	Week 13
AUC_{0-24h} (mcg*h/mL)	Male	0.004	0.004	0.218	0.989	28.681	26.071	85.475	66.567
	Female	0.005	0.017	0.376	1.343	20.139	20.190	55.290	63.253
C_{max} (mcg/mL)	Male	0.001	0.001	0.085	0.328	2.312	1.980	6.858	4.170
	Female	0.001	0.011	0.117	0.495	2.016	3.776	4.114	4.273
T_{max} (h)	Male	0.7	0.5	0.8	1.2	1.8	5.7	2.3	4.0
	Female	0.5	0.5	0.8	05	2.2	3.0	1.8	5.5

Source: Applicant study report
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Week 13 data were following the 91st dose. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Study #TAK-438-00212/ Twenty-Six-Week Oral Gavage Toxicity Study of TAK-438 in Rats with 13-Week Recovery Period

Study Summary and Key Findings

- Six-week-old Crl:CD (Sprague Dawley) specific-pathogen free (SPF) rats were administered TAK-438 at 0, 1, 5, 10, 30 mg/kg/day by oral gavage once daily for 26 weeks (N=15/sex/group main necropsy, 10/sex/group control and high dose for recovery necropsy, and 5/sex/group for toxicokinetics).
- Primary target organs of toxicity were stomach and liver.
- Histopathological findings in the stomach included thickening of the glandular stomach wall in males starting at 10 mg/kg, red patch in the stomach in the high dose group, increased stomach weights for the 5, 10, and 30 mg/kg dose groups (males (19%, 19%, and 20%); females (26%, 33%, 30%), respectively), atrophy of parietal cells (10 mg/kg and above), mucosal fibrosis (10 and 30 mg/kg males and 30 mg/kg females), mucosal angiectasis and inflammatory cell infiltration (30 mg/kg animals)), adrenal gland (hypertrophy of the zona glomerulosa in 30 mg/kg females).
- Histopathological changes in the liver included increased weights (16% and 12% in the 30 mg/kg group, males and females, respectively), vacuolation of hepatocytes (30 mg/kg males)).
- Plasma gastrin levels was reported increased in animals 10 mg/kg dose and above.
- Decreased urinary pH (up to 7) and urinary sodium (27%) were reported in males at 10 and 30 mg/kg dose groups; increased urine volume (43%) and decreased osmotic pressure (22%) were reported in males at 30 mg/kg dose group.
- The NOAEL at 26 weeks was 5 mg/kg in males and 10 mg/kg in females, associated with a mean AUC_{0-24h} of 0.210 and 1.615 mcg*h/mL for males and females, respectively (approximately 0.4 and 3.3-fold margins above the expected clinical exposure at the maximum recommended human dosage [MRHD], respectively).

Toxicokinetics

- Sample collection times: Prior to dosing (week 13 and 26 only), 0.5, 1, 2, 4, 8, and 24 hours after dosing on day 1, week 13, and week 26

- Exposures increased with increasing dose with greater than dose-proportionality for $AUC_{0\text{-}24h}$. Exposures ($AUC_{0\text{-}24h}$ and maximum plasma concentration [C_{max}]) increased between day 1 and week 13 and were similar between week 13 and week 26.

Table 54. Toxicokinetics (#TAK-438-00212)

		Dose of TAK-438 (mg/kg/day)											
		1			5			10			30		
Parameter	Sex	Day 1	Week 13	Week 26	Day 1	Week 13	Week 26	Day 1	Week 13	Week 26	Day 1	Week 13	Week 26
AUC_{0-24h} (mcg*h/mL)	Male	0.003	0.003	0.005	0.038	0.243	0.210	0.239	0.814	1.054	4.031	6.067	8.536
	Female	0.004	0.012	0.020	0.149	0.434	0.424	0.532	1.303	1.615	2.633	5.496	6.364
C_{max} (mcg/mL)	Male	0.0007	0.0009	0.002	0.016	0.1066	0.0727	0.0893	0.2845	0.2814	0.7695	1.062	1.028
	Female	0.0016	0.0053	.0088	.0932	0.1255	0.1815	0.2651	0.5378	0.5848	1.0178	1.102	1.593
T_{max} (h)	Male	0.5	0.5	1.0	0.5	0.5	0.5	1.0	1.0	1.0	1.0	2.0	2.0
	Female	0.5	1.0	0.5	1.0	1.0	1.0	1.0	0.5	0.5	0.5	0.5	0.5

Source: Applicant study report.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Week 13 data were following the 85th dose and week 26 data were following 180th dose. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Study #TAK-438-00084/ Four-Week Oral Gavage Toxicity Study of TAK-438 in Dogs:

Summary of Key Study Findings

- Toxicity findings were vomiting, decrease in plasma chloride and histopathological stomach findings (minimal single cell parietal cell necrosis, minimal parietal cell atrophy and minimal inflammatory cell infiltration in the fundus mucosa) at 2 mg/kg/day and above, increased salivation (6 and 20 mg/kg), and repeated, transient loose stool (one female at 20 mg/kg).
- The NOAEL for this study 0.6 mg/kg/day which corresponded to a C_{max} averaging 115-117 ng/mL and AUC_{0-24h} averaging 492 ng*h/mL on day 29, corresponding to 1-fold margin between the clinical exposure to the NOAELs, respectively, based on the week 4 AUC_{0-24h}).

Table 55. Study Information (#TAK-438-00084)

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0.6, 2, 6, 20 mg/kg/day of the drug as free base (TAK-438F); once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose solution
Species/strain	Dog/beagle
Number/sex/group	3/sex/group
Age	12 months
Satellite groups/unique design	None
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report. Abbreviations: GLP, good laboratory practices

Table 56. Observations and Results (#TAK-438-00084)

Parameters	Major Findings
Mortality	Monitored three times a day during the treatment period. There were no unscheduled deaths.
Clinical signs	Monitored two-three times a day during the treatment period (before dosing, and 1 and 6 hours after dosing; 6-hour observation not on weekends or holidays). Vomiting was reported in animals at 2 mg/kg and above. An increase in salivation was reported
Body weights	Measured twice during pretreatment and once a week during treatment. No treatment related changes.
Feed Consumption	Feed consumption was measured 3 times in the first week of administration and twice weekly for the remainder of the treatment period. Feed consumption was measured twice a week in the first week of the recovery period and once weekly for the remaining treatment period. No treatment related changes.
Ophthalmoscopy	Examined once during pretreatment and on day 24 of treatment. No treatment-related changes.
ECG	Measured once during pretreatment and before dosing and 1-hour after dosing on Day 22 (males) or Day 23 (females) of the treatment period. No treatment-related changes.

Hematology	Blood samples for hematology and blood coagulation analysis were collected at necropsy from abdominal aorta. No treatment related changes.
Clinical chemistry	Blood samples for clinical chemistry were collected at necropsy from abdominal aorta. A decrease in chloride was reported in animals in the 6 and 20 mg/kg dose groups.
Urinalysis	Uranalysis was performed on Day 22 or 23 of treatment and Day 22 or 23 of the recovery period. No changes were reported.
Gross pathology	Examined at necropsy. No treatment-related changes.
Organ weights	Absolute liver weights were increased 21% and 16% in males in the 6 and 20 mg/kg dose groups, respectively.
Histopathology Adequate battery: Yes	Stomach: In the 2 mg/kg dose group and above: 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.
Hepatic drug metabolizing enzymes	Liver tissue was harvested at necropsy and evaluated for drug metabolism enzyme activity. Increases in aniline hydroxylase in males at ≥ 0.6 mg/kg, p-nitrophenol UDP-glucuronosyltransferase activity in females at ≥ 0.6 mg/kg and in males at 20 mg/kg, and aminopyrine N-demethylase activity in both sexes at ≥ 6 and 20 mg/kg.

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: UDP, uridine 5'-diphosphate

Toxicokinetics

- Sample collection times: prior to dosing (day 29 only), 0.5, 1, 2, 6, and 24 hours after dosing on day 1 and day 29
- Exposures increased with increasing doses in a dose-proportional manner between 2 and 20 mg/kg. There was no apparent accumulation between day 1 and day 29.

Table 57. Toxicokinetics (#TAK-438-00084)

		Dose of TAK-438 (mg/kg/day)							
		0.6		2		6		20	
Parameter	**Sex**	**Day 1**	**Day 29**	**Day 1**	**Day 29**	**Day 1**	**Day 29**	**Day 1**	**Day 29**
$AUC_{0\text{-}24h}$ (mcg*h/mL)	Male	0.479	0.491	4.15	4.473	12.566	12.725	43.23	55.471
	Female	0.421	0.493	3.566	3.993	13.151	14.268	33.162	65.81
C_{max} (mcg/mL)	Male	0.1263	0.124	0.5952	0.716	1.5627	1.8551	3.4261	6.591
	Female	0.1076	0.1063	0.617.4	0.7265	1.3296	2.0129	2.8762	6.7371
T_{max} (h)	Male	0.5	0.7	1.0	1.2	1.3	1.3	2.7	1.0
	Female	0.8	0.8	1.0	1.0	1.7	1.0	3.0	1.7

Source: Applicant study report.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group. Values copied from study report.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Study #TAK-438-10742/ Thirteen-Week Oral Gavage Toxicity Study of TAK-438 in Dogs with a 4-Week Recovery period

Key Study Findings

- Stomach histopathology included single cell necrosis of the fundic gland, degeneration of the tunica muscularis, hyperplasia of the fundus mucosa, inflammatory cell infiltration of the fundus mucosa in all treatment groups.
- Most findings reversed by the end of the recovery period except the degeneration of the tunica muscularis, which was found in one male and one female animal.
- There was no NOAEL established in the study. The lowest-adverse-effect level (LOAEL) was 1 mg/kg/day, which was the lowest dose tested (with an exposure margin of approximately 1.5-fold on an AUC basis).

Table 58. Study Information (#TAK-438-10742)

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 1, 1.3, 1.6, or 2 mg/kg/day Once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% methylcellulose solution
Species/strain	Dog/beagle
Number/sex/group	3/sex/group
Age	7 or 10 months old
Satellite groups/unique design	Additional 3 animals in high dose and control as recovery groups
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: GLP, good laboratory practices

Table 59. Observations and Results (#TAK-438-10742)

Parameters	Major Findings
Mortality	Mortality was assessed once a day during pretreatment and recovery periods and twice a day during treatment. No unscheduled deaths.
Clinical signs	Clinical signs were assessed once a day during pretreatment and recovery periods and twice a day during treatment. Vomiting was observed in several animals transiently, and generally increased with higher dosing, though the trend was unclear. Vomiting was reported in one male and one female at 1.6 mg/kg and one male and 3 females at 2 mg/kg.
Body weights	Body weights were assessed once during the pretreatment period, once on the day before dosing and once a week during treatment and recovery. No treatment-related changes in body weight.
Feed Consumption	Daily feed consumption was measured daily during the treatment period. No treatment-related changes in feed consumption.
Hematology	Blood was collected from the cephalic vein once during the pretreatment period, once before dosing on day 86 of treatment and once on recovery day 23.

Parameters	Major Findings
Clinical chemistry	Blood was collected from the cephalic vein once during the pretreatment period, once before dosing on day 86 of treatment and once on recovery day 23. ALT was increased (31-105%) in all treated dose groups at the end of the dosing period compared to controls.
Urinalysis	Not done.
Gross pathology	Necropsy limited to stomach only for 3/sex/group for all groups at the end of the treatment period and the recovery animals at the end of the recovery period.
Organ weights	Not done.
Histopathology Adequate battery: No	Histopathology limited to the stomach. In treated animals, minimal fundic gland single cell necrosis, minimal hyperplasia of the mucosa fundus, minimal degeneration of the tunica muscularis, minimal to mild inflammatory cell infiltration of the fundus mucosa, minimal to mild vacuolization of parietal cells, were observed. At the end of the recovery period, only minimal degeneration of the tunica muscularis remained in 1 male and 1 female in the 2 mg/kg dose group.

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: ALT, alanine transaminase

Toxicokinetics

Sample collection times: prior to dosing (day 28 and 90 only), 0.5, 1, 2, 6, and 24 hours after dosing on day 1, day 28, and day 90

Table 60. Toxicokinetics (#TAK-438-10742)

		Dose of TAK-438 (mg/kg/day)											
		1			1.3			1.6			2		
Parameter	**Sex**	**Day 1**	**Day 28**	**Day 90**	**Day 1**	**Day 28**	**Day 90**	**Day 1**	**Day 28**	**Day 90**	**Day 1**	**Day 28**	**Day 90**
$AUC_{0\text{-}24h}$ (mcg*h/mL)	Male	0.787	0.996	0.981	1.986	1.854	2.394	2.064	1.989	2.094	1.660	1.703	1.765
	Female	0.654	0.903	0.853	1.212	1.117	1.055	1.345	1.125	1.233	2.412	2.184	2.494
C_{max} (mcg/mL)	Male	0.1895	0.1954	0.2023	0.3599	0.3329	0.3658	0.3382	0.3416	0.3486	0.2953	0.2805	0.3402
	Female	0.1163	0.1483	0.1284	0.2169	0.23	0.1762	0.2687	0.2098	0.2431	0.4054	0.3635	0.4856
T_{max} (h)	Male	0.8	1.2	0.8	1.0	0.7	0.8	1.0	0.8	1.0	1.2	1.3	0.9
	Female	1.3	1.3	1.0	1.0	0.7	1.0	1.0	0.7	1.0	1.2	1.1	1.0

Source: Applicant study report.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Study # TAK-438-00217/ Thirty-Nine-Week Oral Gavage Toxicity Study of TAK-438 in Dogs

Study Summary and Key Findings

- Seven-month-old beagle dogs were administered TAK-438 once daily by oral gavage at doses of 0, 0.3, 0.6, and 2 mg/kg/day (N=3/sex/group).
- Treated animals exhibited transient vomiting following dosing, in a non-dose dependent manner.
- Primary target organ was the stomach (in 2 mg/kg animals: degeneration of the muscular layer, single cell necrosis in the fundic gland, stomach thickening, hyperplasia of the fundic mucosa, inflammatory cell infiltration in fundic mucosa; in all vonoprazan treated groups: vacuolation of parietal cells.).
- Plasma gastrin levels were higher in 2 mg/kg females at 26 weeks compared to controls.
- The NOAEL was 0.6 mg/kg/day ($AUC_{0\text{-}24h}$ means equal to 0.253-0.426 mcg*h/mL, margins to clinical exposures of 0.5-0.8-times.)

Toxicokinetics

- Sample collection times: prior to dosing (all doses except first), 0.5, 1, 2, 6, and 24 hours after dosing on day
- Exposures increased with increasing dose in a greater than dose proportional manner and were similar between males and females. Exposures increased between day 1 and day 273 indicating accumulation.

Table 61. Toxicokinetics (#TAK-438-00217)

		Dose of TAK-438 (mg/kg/day)											
		0.3				0.6				2			
Parameter	Sex	Day 1	Day 91	Day 182	Day 273	Day 1	Day 91	Day 182	Day 273	Day 1	Day 91	Day 182	Day 273
$AUC_{0\text{-}24h}$ (mcg*h/mL)	Male	0.097	0.074	0.162	0.191	0.263	0.286	0.426	0.415	2.762	2.673	3.69	4.481
	Female	0.08	0.08	0.113	0.134	0.275	0.253	0.347	0.346	2.865	3.925	4.199	4.026
C_{max} (mcg/mL)	Male	0.0403	0.0223	0.046	0.0458	0.0923	0.0741	0.1053	0.0889	0.4966	0.5377	0.6368	0.8231
	Female	0.0299	0.275	0.372	0.394	0.0834	0.0746	0.0911	0.0805	0.4929	0.5688	0.5794	0.4805
T_{max} (h)	Male	0.7	1.0	0.7	1.2	0.8	0.8	1.0	1.2	0.8	1.0	1.5	0.8
	Female	0.8	0.8	0.8	0.8	0.7	0.8	0.8	0.8	1.0	1.0	1.0	1.3

Source: Applicant study report.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Repeat-Dose Toxicology Studies of Metabolites of Vonoprazan

Study #TAK-438-10049/ Thirteen-week Subcutaneous Toxicity Study of TAK-438-Sul in Rats

Study Summary and Key Findings

- Four-week-old Crl:CD (Sprague Dawley) SPF rats were administered 0, 6, or 20 mg/kg/day TAK438 M-IV-Sul (disproportionate human metabolite) by SC injection once daily for 13 weeks
- No adverse treatment-related findings in this study.
- NOAEL of 20 mg/kg, the highest dose tested, with AUC on week 13 of 11.278 mcg*hr/mL (with a safety margin of at least 23-times the expected human exposure).

Toxicokinetics

- Sample collection times: 0.5, 1, 2, 4, 8, and 24 hours after dosing on day 1 and week 13.
- Exposure is higher in males and increases between day 1 and week 13.

Table 62. Toxicokinetics (#TAK-438-10049)

		Dose of TAK-438 M-IV-Sul (mg/kg/day)			
		6		20	
Parameter	**Sex**	**Day 1**	**Week 13**	**Day 1**	**Week 13**
$AUC_{0\text{-}24h}$ (mcg*h/mL)	Male	1.553	3.547	5.233	11.278
	Female	1.108	2.216	4.366	8.183
C_{max} (mcg/mL)	Male	3.27	4.86	10.83	16.57
	Female	2.28	3.58	9.76	16.66
T_{max} (h)	Male	0.25	0.25	0.25	0.25
	Female	0.25	0.25	0.25	0.25

Data source: Applicant study report.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

13.2.1.4.2. Genetic Toxicology

Table 63. Genetic Toxicology of Vonoprazan

Study No./Study Title	Key Study Findings
Study No. TAK-438-00052 In Vitro Reverse Mutation Assay in Bacterial Cells with TAK-438 GLP compliance: Yes Study is valid: Yes	Salmonella typhimurium (TA98, TA100, TA1535, and TA1537) and E. coli (WP2 uvrA) were pre-incubated at 37ºC for 20 minutes with up to 5000 mcg/plate TAK-438, followed a 48-hour incubation on agar plates for 48 hours in the presence and absence of S9. Vehicle (DMSO) and positive controls (2-(2-furyl)-3-(5-nitro -2-furyl) acrylamide (AF-2), sodium azide, 9-aminoacridine hydrochloride, and 2-aminoanthracene) produced appropriate responses. No drug-related increases in the number of revertant colonies were observed in either the presence or absence of S9. TAK-438 was considered negative under the conditions of this study.
Study No. TAK-438-00051 Cytogenic Assay with TAK-438 in Chinese	CHL/IU cells were initially tested in a growth inhibition test in a 6-hours treatment and 18-hour recovery with and without S9 metabolic activation and a continuous treatment for 24 hours without metabolic activation. A preliminary test was performed at 33, 333, and 3,333 mcg/mL in which the relative cell density was reduced 50% compared to the control plate in the 333 mcg/mL condition. In the definitive assay the cells were treated

Study No./Study Title	Key Study Findings
Hamster Lung (CHL) Cells GLP compliance: Yes Study is valid: Yes	with 50, 100, 150, 200, 250, 300, 350, 400 mcg/mL for a 6-hour exposure with and without metabolic activation and 6.25, 12.5, 25, 50, 75, 100, 200 mcg/mL in a 24-hour exposure without metabolic activation. The concentrations selected for analysis are bolded, based on the concentrations where the cell growth index was reduced by greater than 50%. Because there were not 200 mitoses available for analysis in the 24-hour exposure, an additional concentration (25 mcg/mL) was analyzed. Positive controls were mitomycin C (0.1 mcg/mL or 0.05 mcg/mL) and benzo[a]pyrene. An increase was reported with all the positive controls and the tested concentrations were not statistically different from the vehicle treated control. TAK-438 was considered negative under the conditions of this study.
Study No. TAK-438-00083 Micronucleus Assay with TAK-438 in Rats GLP compliance: Yes Study is valid: Yes	Sprague-Dawley rats (6 males/group) were treated by oral gavage with either TAK-438 (250, 125, 62.5 mg/kg/dose) or vehicle (0.5% methylcellulose solution) on days 1 and 2, or positive control (10 mg/kg cyclophosphamide, i.p.) on day 2 only, and were euthanized on day 3. Doses were selected based on a dose range finding test. Vehicle and positive controls produced appropriate responses. No drug-related increases in polychromatic erythrocytes or micronucleated cells from the bone marrow were observed. TAK-438 was considered negative under the conditions of this study.

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: CHL/IU, Chinese hamster lung cells; DMSO, dimethylsulfoxide; GLP, good laboratory practices

Table 64. Genetic Toxicology of M-IV-Sul Metabolite

Study No./Study Title	Key Study Findings
Study No. TAK-438-00203 In Vitro Reverse Mutation Assay in Bacterial Cells with TAK-438 M-IV-Sul GLP compliance: Yes Study is valid: Yes	Salmonella typhimurium (TA98, TA100, TA1535, and TA1537) and E. coli (WP2 uvrA) were preincubated with TAK-438-IV-Sul at 37ºC for 20 minutes followed by a 48-hour incubation with up to up to 5000 mcg/plate of TAK-438 in the presence and absence of S9. Cytotoxicity was observed at 5000 mcg/plate. Vehicle (DMSO) and positive controls (2-(2-furyl)-3-(5-nitro -2-furyl) acrylamide (AF-2), sodium azide, 2-methoxy-6-chloro-9-[3-(2-chloroethyl) aminopropylamino]acridine·2HCl) (ICR-191), and 2-aminoanthracene) produced appropriate responses. No drug-related increases in the number of revertant colonies were observed in either the presence or absence of S9. TAK-438-IV-Sul was considered negative under the conditions of this study.
Study No. TAK-438-0000211 Cytogenic Assay with TAK-438 M-IV-Sul in Chinese Hamster Lung (CHL) Cells GLP compliance: Yes Study is valid: Yes	CHL/IU cells were initially tested in a growth inhibition test in a 6-hours treatment and 18-hour recovery with and without S9 metabolic activation and a continuous treatment for 24 hours without metabolic activation. Doses selected for the analysis were 1560, 2210, and 3120 mcg/mL for the 6-hour exposure without metabolic activation, 1100, 2210 and 4410 mcg/mL for the 6-hour exposure with S9 metabolic activation, and 551, 780, and 1100 mcg/mL for the 24-hour exposure. The relative number of cells and % mitotic index did not reach 50% in the concentrations tested with S9 but exceeded it in the other conditions. Positive controls were mitomycin C (0.1 mcg/mL or 0.05 mcg/mL) and cyclophosphamide monohydrate (6 mcg/mL). An increase was reported with all the positive controls and the tested concentrations were not statistically different from the vehicle treated control. TAK-438 M-IV-Sul was considered negative under the conditions of this study.

Study No./Study Title	Key Study Findings
Study No. TAK-438-00202 Micronucleus Assay with TAK-438 M-IV-Sul in Rats GLP compliance: Yes Study is valid: Yes	Sprague-Dawley rats (6 males/group) were treated by SC injection with either TAK-438 M-IV-Sul (25, 50, 100 mg/kg/dose) or vehicle (saline) on days 1 and 2, or positive control (10 mg/kg cyclophosphamide i.p.) on day 2 only and were euthanized on day 3. High dose was set based on the maximum solubility and method of administration. Vehicle and positive controls produced appropriate responses. No drug-related increases in polychromatic erythrocytes or micronucleated cells from the bone marrow were observed. TAK-438 M-IV-Sul was considered negative under the conditions of this study.

Source: Reviewer table using data from the Applicant's submitted study reports.
Abbreviations: CHL/IU, Chinese hamster lung cells; DMSO, dimethylsulfoxide; GLP, good laboratory practices; SC, subcutaneous

13.2.1.4.3. Reproductive Toxicology

Effects of TAK-438 on Fertility and Early Embryonic Development to Implantation in Rats (Study #TAK-438-00172)

Key Study Findings

- Findings included mortality at the 300 mg/kg dose group, changes in body weight in the 300 mg/kg dose group, and clinical signs seen in the 100 and 300 mg/kg dose groups
- The NOAEL for general toxicity was 30 mg/kg (calculated to be a 7.3-fold margin to the proposed human dose of 40 mg/day on a body surface area (BSA) basis; calculated as 5.7-fold margin on an AUC basis when using the AUC from study TAK-438-00085 and the 40 mg/day dose in the clinical trial #TAK-438-017).
- No adverse effects were seen on reproductive or developmental parameters and the reproductive function NOAEL was 300 mg/kg (calculated to be a 73-fold margin to the proposed human dose of 40 mg/day on a BSA basis; and 133-fold margin on an AUC basis when using the AUC from study #TAK-438-00143 and the 40 mg/day dose in the clinical trial #TAK-438-017).

Table 65. Methods (#TAK-438-00172)

Parameter	Method Details
Dose, frequency of dosing	0, 30, 100, 300 mg/kg/day, once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% w/v methylcellulose
Species/strain	Rat/Crl:CD (Sprague Dawley)
Number/sex/group	20
Study design	Males were treated starting from 14 days prior to cohabiting through the mating period and ending the day prior to necropsy (approximately day 55). Females were treated starting from 14 days prior to cohabitation, through the mating period up to GD 6 and were euthanized on GD 15. The females paired with the males that died during the premating period were paired with males that had already copulated once.
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report. Abbreviations: GD, gestational day

Table 66. Observations and Results (#TAK-438-00172)

Parameters	Major Findings
Mortality	Four high dose males died during days 2-4 of the treatment.
Clinical signs	Clinical signs were assessed twice daily during the dosing period, and once daily during non-dosing periods. Males: Clinical signs before death in 4 male animals that died in the 300 mg/kg dose group included mydriasis (4 animals), soiled perineal region by urine (3 animals), tremor (3 animals), trace reddish rhinorrhea (2 animals), prone position (2 animals), decrease in spontaneous activity (2 animals), and reddish eye mucus (1 animal). In the animals that survived, the following clinical signs were observed for some or all of treatment days: 1-5: mydriasis in 16 animals, tremor in 5 animals, decrease in spontaneous activity in 4 animals, and soiled perineal region by urine in 1 animal. In the 100 mg/kg dose group, mydriasis was observed in 3 animals on the first day of treatment. Females: In the high-dose group, mydriasis was observed in 19 animals for 1-5 days soon after the start of dosing. One animal on dosing day 0 exhibited prone position and tremor. Soiled perineal region by urine was reported in 2 animals at the end of the dosing period. In the 100 mg/kg dose group, 2 animals were observed with mydriasis on day 0 or day 1 of dosing.
Body weights	Body weights were measured approximately twice a week. Males Decreased body weight was seen in the 300 mg/kg dose group males for days 0-3 (-34.8 +/- 11.0 g) compared to a gain in controls (6.2 +/- 4.5 g) and lower body weight compared to control from day 3 to necropsy. Females Lower weight gain was seen in the females for days 0-3 during the premating period. Lower body weight gain was noted in this dose for GDs 0-6.

Parameters	Major Findings
Feed consumption	Feed consumption was measured on days 0,3,7,10 and 13 for males and on days 0, 3, 7, 10, and 13 prior to confirmation of copulation and days 0, 3, 6, 10, 12, and 14 of gestation for pregnant animals. For both males and females, a decrease in feed consumption was reported for animals in the 300 mg/kg dose group for days 0-1 and 3-4 of treatment during the premating period compared to controls.
Fertility parameters	No treatment related effects were reported on estrus frequency or interval for any treatment group, copulatory index, fertility index or the mean copulatory interval between the control and any treated group.
Cesarean section data	No significant differences were noted in the number of post-implantation losses, number of live embryos, embryo viability rate or post-implantation loss rate between the control and any treated groups. In the 300 mg/kg group, a statistically significant decrease in the number of implantations was reported when compared with the control group; however, no significant differences were reported in the number of corpora lutea, preimplantation loss rate or implantation rate above the control group and historical control ranges.
Necropsy findings	Males: In the 300 mg/kg dose group, a red focus in the stomach was observed in one of the animals that died prematurely. Three animals that died had urine soiled thoracoabdominal region and three had reddish rhinorrhea. No differences in reproductive organ weights were found between treated and control animals. Females: No gross pathological findings were reported. No adverse effects were seen on reproductive parameters and the reproductive function NOAEL was 300 mg/kg.

Source: Reviewer table using data from the Applicant's submitted study report. Abbreviations: GD, gestational day; NOAEL, no-observed-adverse-effect level

Effects of TAK-438 on Embryo-Fetal Development in Rats (Study #TAK-438-00135)

Key Study Findings

- Maternal toxicity was seen at the 300 mg/kg/day dose (one death and other clinical signs)
- Fetal malformations of the tail as well as visceral malformations (membranous ventral septal defect and malpositioned subclavian branch) were seen in the 300 mg/kg/day dose 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, approximately a 25-fold AUC exposure margin in the dams extrapolated from exposures from a 4-week repeat dose rat study in nonpregnant rats.

Table 67. Methods (#TAK-438-00135)

Parameter	Method Details
Dose and frequency of dosing	0, 30, 100, 300 mg/kg/day Once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% w/v methylcellulose solution
Species/strain	Rat/Crl:CD (Sprague Dawley)
Number/sex/group	19-20 dams
Study design	Dams were dosed from GD 6-19 and euthanized and necropsied on day 20
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: GD, gestational day

Table 68. Observations and Results (#TAK-438-00135)

Parameters	Major Findings
Mortality	One dam in the high dose group died on day 15 of gestation. At death the animal had mydriasis and a decrease in feces, but no abnormal clinical findings were reported before death and no findings were seen at necropsy.
Clinical signs	Animals were observed for clinical signs before and approximately 1 hour after dosing and once on non-dosing days. In the 300 mg/kg animals, reported clinical signs include prone position (2 dams, day 7), head tremor (2 dams), mydriasis (19 dams), increased salivation (2 dams), and decrease in feces (8 dams).
Body weights	Body weights were measured on gestational days 0, 6, 8, 10, 12, 14, 16, 18, and 20. No toxicologically important changes in maternal body weights were reported.
Feed consumption	Feed consumption was measured for 24-hour periods on gestation days 0, 6, 8, 10, 12, 14, 16, 18 and 19. Feed consumption was decreased on days 6, 8, 10, 12 by 41%, 32%, 28%, 21%, and 10%, respectively, and increased on days 18 and 19, by 15%, in dams in the 300 mg/kg/day group. Feed consumption was decreased 10-11% on days 6, 8, and 10 in dams in the 100 mg/kg/day group.
Necropsy findings	No gross pathology was reported at necropsy.
Cesarean section data	Placental weights were reported to be low (average of -8.8%) for the male fetuses in the 300 mg/kg group. No treatment-related changes in post-implantation loss rate, number of live fetuses, or dead implants.

Parameters	Major Findings
Necropsy findings Offspring	Three litters had 1 fetus each (3/19 litter incidence) with external malformations in the 300 mg/kg dose group, with each having a tail malformation, sometimes in conjunction with a small anus. The incidence of visceral malformations on a per litter basis was increased in the 300 mg/kg dose group compared to controls (16/19, versus 0/19 litter incidence). Membranous ventricular septal defect was the most commonly reported malformation (15/19 litters, 38 fetuses), followed by malpositioned subclavian branch (4/19 litters, 6 fetuses). Absent adrenal, fused kidney, diaphragmatic hernia, and microphthalmia were present in a single fetus. It was unclear from the way the data were presented if these defects were in separate fetuses in the same litter or in the same fetus.

Source: Reviewer table using data from the Applicant's submitted study report.

Table 69. Visceral Findings in Fetuses (Litter Data) - Abnormalities

Test article	Dose (mg/kg/day)	Animal number	No. of fetuses examined	Visceral findings			
				No. of fetuses	(%)	Types	Number
TAK-438	300	4F01	8	1	12.5	Membranous ventricular septal defect	1
		4F02	7	0	0.0		
		4F03	7	4	57.1	Membranous ventricular septal defect	4
		4F04	8	3	37.5	Diaphragmatic hernia	1
						Membranous ventricular septal defect	3
						Absent adrenal	1
						Fused kidney	1
						Malpositioned ovary	1
		4F05	8	1	12.5	Malpositioned subclavian branch	1
		4F06	8	3	37.5	Membranous ventricular septal defect	3
		4F07	7	3	42.9	Membranous ventricular septal defect	2
						Malpositioned subclavian branch	1
		4F08	7	4	57.1	Membranous ventricular septal defect	4
		4F09	7	3	42.9	Membranous ventricular septal defect	1
						Malpositioned subclavian branch	2
		4F10	5	0	0.0		
		4F12	7	2	28.6	Membranous ventricular septal defect	2
		4F13	7	1	14.3	Membranous ventricular septal defect	1
		4F14	9	0	0.0		
		4F15	7	1	14.3	Membranous ventricular septal defect	1
		4F16	7	5	71.4	Membranous ventricular septal defect	5
		4F17	7	3	42.9	Membranous ventricular septal defect	3
		4F18	6	3	50.0	Membranous ventricular septal defect	3
		4F19	7	4	57.1	Membranous ventricular septal defect	4
						Malpositioned subclavian branch	1
		4F20	8	1	12.5	Microphthalmia	1
						Membranous ventricular septal defect	1
		Total	137	42			
		Mean	7.2	2.2	31.1		
		S.D.	0.9	1.5	22.4		

Source: Study report Appendix 9
Abbreviations: SD, standard deviation

There was one visceral malformation in the 100 mg/kg dose group, interrupted aortic arch. This was considered not test-article related. Visceral malformation data were not examined in the 30 mg/kg dose group.

Table 70. Fetal Malformations/Variations (External and Visceral)

Fetal Parameters	0 mg/kg	30 mg/kg	100 mg/kg	300 mg/kg
No. litters examined	19	20	20	19
External Fetal Malformations: number of fetuses (number of litters with at least one affected fetus)				
No. fetuses examined	264	273	269	257
Small anus	0	0	0	2 (2)
Bent tail	0	0	1 (1)	1 (1)
Thread like tail	0	0	0	1 (1)
Absent tail	0	0	0	1 (1)
Multiple malformations	0	0	0	1 (1)
Visceral Fetal Malformations: number of fetuses (number of litters with a least one affected fetus)				
No. fetuses examined	143	ND	144	137
Interrupted aortic arch	0	ND	1 (1)	0
Membranous ventral septal defect	0	ND	0	38 (15)
Diaphragmatic hernia[1]	0	ND	0	1 (1)
Absent adrenal[1]	0	ND	0	1 (1)
Fused kidney[1]	0	ND	0	1 (1)
Malpositioned subclavian branch	0	ND	0	6 (4)
Malpositioned ovary	0	ND	0	1 (1)
Microphthalmia	0	ND	0	1 (1)

Source: Review table based on data in the study report.
[1]Unclear if present in same or different fetuses in the same litter.
Abbreviations: ND, not done

Effects of TAK-438 on Embryo-Fetal Development in Rabbits (Study #TAK-438-00137)

Good laboratory practice (GLP) Compliance: Yes

Key Study Findings

- No embryo-fetal developmental toxicity or malformations were observed in any treatment group.
- The maternal NOAEL was 10 mg/kg/day corresponding to C_{max} of 65-394 ng/mL and AUC_{0-24h} of 143-737 ng*hr/mL (margin of 0.3-1.5 based on AUC_{0-24h}).
- The fetal NOAEL was the highest dose tested 30 mg/kg/day, corresponding to C_{max} of 900 to 1540 ng/mL and AUC_{0-24h} of 3370 to 4710 ng*hr/mL (margin of 7 to 10 based on AUC_{0-24h}).

Table 71. Methods (#TAK-438-00137)

Parameter	Method Details
Dose and frequency of dosing	0, 3, 10, 30 mg/kg/day once daily
Route of administration	Oral gavage
Formulation/vehicle	0.5% w/v methylcellulose solution
Species/strain	Rabbit/Kbl:JW
Number/sex/group	20 females were mated for each group. Pregnancies were found in 18-20 dams per group
Study design	Dams were administered test article from gestational day 6-18 and euthanized and necropsied on GD 28. Dams that aborted their litter or accidently injured were euthanized and necropsied on the day of abortion
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report
Abbreviations: GD, gestational day

Table 72. Observations and Results (#TAK-438-00137)

Parameters	Major Findings
Mortality	One 3 mg/kg dam died because of an accidental injury during blood collection. One control dam and 2 dams in the 30 mg/kg group aborted their litters on days 22, 21, and 27, respectively. For one high dose dam, the whole litter died.
Clinical signs	Clinical signs were assessed prior to dosing and approximately one-hour post-dosing during the dosing period and once a day during the non-dosing periods. A slight-to-severe decrease in fecal pellets was noticed in 10/20 dams (10 during treatment and 5 in the post-treatment period) in the 30 mg/kg dose group and 4/20 dams (3 during treatment and 3 post-treatment) in the 10 mg/kg dose group. Three dams in the control (one during treatment and 2 post-treatment) and one in the 3 mg/kg (during treatment) also had slight decrease in pellets on individual days. One dam that aborted her litter showed emaciation, loss of fur and hemorrhage (interpreted from a vaginal sanguineous discharge from the vagina) on several days before aborting. Another dam, which did not abort, also had a vaginal sanguineous discharge.
Body weights	Body weights were measured on gestational days 0, 6, 8, 10, 12, 14, 16, 18, 19, 22, 25 and 28. No adverse changes in body weights or body weight gains were reported, though small reductions (~5%) were statistically significant.
Feed consumption	Feed consumption was assessed the day after feed was supplied on gestational days 0, 6, 8, 10, 12, 14, 16, 18, 19, 22, 25, and 27. Feed consumption was decreased 16%-31% in the 10 mg/kg dose group and 33%-48% 30 mg/kg dose groups during GDs 8-18 and 6-18, respectively.
Necropsy findings Cesarean section data	Hydrothorax was reported in one dam that aborted her litter and hemorrhage was reported in the dam in which the whole litter died, both in the 30 mg/kg dose group.

Parameters	Major Findings
	One control animal and two 30 mg/kg dose animals aborted the entire litter (days 22, 21, and 27, respectively). In one dam in the 30 mg/kg dose group, the whole litter died.
Necropsy findings offspring	No test-article related changes were reported for external or visceral abnormalities or variations. The number of litters with fetuses with skeletal variation was increased but this was not adverse.

Source: Reviewer table using data from the Applicant's submitted study report Abbreviations: GD, gestational days

Toxicokinetics

Sample collection times: (prior to dosing gestation day [GD] 18 only), 0.5, 1, 2, 4, 8 and 24 hours after dosing on GD6 and GD18

Exposures increased in the 10 mg/kg from GD 6 to GD 18 and increased with increasing dose in a greater than dose-proportional manner.

Table 73.Toxicokinetics (#TAK-438-00137)

	Dose of TAK-438 (mg/kg/day)					
	3		10		30	
Parameter	GD6	GD18	GD6	GD18	GD6	GD18
$AUC_{0\text{-}24h}$ (mcg*h/mL)	0.02	0.021	0.143	0.737	3.370	4.71
C_{max} (mcg/mL)	0.0123	0.0146	0.0652	0.3939	1.5393	0.8999
T_{max} (h)	0.5	0.5	0.7	0.5	0.5	0.5

Data source: Applicant study report.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=4)/timepoint/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; GD, gestational day; T_{max}, time to maximum plasma concentration

Study for Effects of TAK-438 on Pre- and Postnatal Development, Including Maternal Function, in Rats (Study # TAK-438-11215)

Key Study Findings

The NOAEL for this study in the F_0 and F_1 generations was 10 mg/kg based on the following findings in the 100 mg/kg dose group:

- Reduced body weight for F_0 during lactation days (0 to 7), (14 to 22), (0 to 22)
- Lower F_1 pup body weights, males and females, days 11 to 22
- Hepatic discoloration in pups culled at 4 days post birth
- Continued reduced body weights compared to controls for animals retained past weaning
- Increase in copulatory interval for F_1 animals
- There were no malformations reported in the F_2 pups.
- Exposure at the NOAEL: AUC559 ng*hr/mL, C_{max} 150.3 ng/mL (margin of approximately 1).

Table 74. Methods (#TAK-438-11215)

Parameter	Method Details
Dose and frequency of dosing	0, 1, 3, 10, 100 mg/kg/day Once daily dosing.

Parameter	Method Details
Route of administration	Oral gavage
Formulation/vehicle	0.5% w/v methylcellulose solution
Species/strain	Rat/Crl:CD (Sprague Dawley)
Number/sex/group	20 mated females per group
Satellite groups	4 mated females per group for toxicokinetic measurement
Study design	F_0 females were treated once daily from gestational day 6 to post-delivery day 21. F_0 females that delivered were euthanized on postnatal day (PD) 22 or 23. TK was conducted before dosing, and 1, 2, 4, 8, and 24 hours after dosing on day 14 after delivery. The number of pups per dam were standardized on PD4. If there were adequate pups in F_1, then the pups were culled to 4 males and 4 females on PD4, selected randomly, if there were at least 8 pups they were culled to 8, if there were less than 8 pups, pups were not culled. One or two F_1 males and females from each dam were retained for behavior, learning and evaluation of reproductive function. The rest were culled and evaluated by necropsy at weaning. All the F_1 pups necropsied at weaning in the control and high dose groups were examined by soft x-rays for skeletal abnormalities and variations. When the F_1 animals reached 11 or 12 weeks of age, 1 male and 1 female from each litter in the same dose group were caged together to evaluate reproductive function. The retained F_1 animals were euthanized following the end of the reproductive performance test and F_2 necropsy on day 7 after birth.
Deviation from study protocol affecting interpretation of results	No

Source: Reviewer table using data from the Applicant's submitted study report
Abbreviations: GD, gestational day; PD, postnatal day

Table 75. Study Findings (F_0 Generation) (#TAK-438-11215)

Parameters	Major Findings
Mortality	No unexpected deaths
Clinical signs	Clinical signs were monitored for prior to dosing and 1-2 hours after dosing during the dosing period and once daily during non-dosing periods. No test-article related clinical signs were reported during pregnancy.
Body weights	Dams were weighed on GD 0 and every 2 days of gestation and on days 0, 4, 7, 11, 14, 18, and 22 after delivery. No adverse changes in body weight were reported during gestation. Body weight gain during lactation was statistically significantly reduced in test-article administered animals for the time periods for days 0-7, 14-22, and 0-22, with less gain in the high dose animals. Overall body weight during lactation was not significantly different between treated animal groups and the control group.
Feed consumption	Feed consumption was weighed on GDs 5, 6, 10, 12, 14, 16, and 18 of gestation and days 4, 7, 14, and 19 after delivery. Small non-adverse decreases in feed consumption were reported.
Pregnancy status	No drug-related findings. One dam in each the 3 mg/kg and 100 mg/kg dose groups were found to be not pregnant.
Necropsy findings	No drug-related findings.

Source: Reviewer table using data from the Applicant's submitted study report.
Abbreviations: GD, gestational day

Table 76. Study Findings (F_1 Generation) (#TAK-438-11215)

Parameters	Major Findings
Mortality	One control group litter died one day following delivery. No unscheduled deaths.
Clinical signs	Clinical signs were monitored for once daily. No test article related clinical signs.
Body weights	Up to weaning Body weights were measured on days 0, 4, 7, 11, 14, 18, 22, 28, 42, 56, and 70 and on the day of necropsy. Animals in the high dose group were lower on days 11, 14, 18, and 22 after birth. After weaning Body weights in the 100 mg/kg group F_1 male animals retained for behavioral testing were reduced at day 28, 42, and 56 and in male animals retained for reproduction on days 28 and 42. Body weights in F_1 female animals retained for behavioral testing were reduced at day 28, 42, and 70, and in female animals retained for reproduction on day.
Sexual maturation	In the 10 and 100 mg/kg dose group females there was a statistically significant delay in vaginal opening; however, the values were comparable to historical controls.
Behavior and activity	No adverse test-article related changes were reported for reflexes, behavior, and learning.
Fertility parameters	In the 100 mg/kg dose group there was a statistically significant increase in copulatory interval (7.1 +/- 5.8 days compared to 3.2 +/- 2.9 days in controls).
Pregnancy parameters	No test-article related changes in pregnancy parameters were reported.
Necropsy findings (cull)	High dose: Three pups had a white discoloration of the hepatic caudate lobe, and one had a black color discoloration of the caudate lobe. No histopathology examination was performed on these livers.
Necropsy findings (weaning)	No test article related findings were reported.

Source: Reviewer table using data from the Applicant's submitted study reportTable 77. Study Findings (F_2 Generation) (#TAK-438-11215)

Parameters	Major Findings
Mortality	No test article related changes.
Body weights	No test article related differences in body weight.
Necropsy findings Cesarean section data	No test article related abnormalities or variations were reported.

Source: Reviewer table using data from the Applicant's submitted study report

Toxicokinetics

Sample collection times: Prior to dosing at 1-, 2-, 4-, 8-, and 24-hours post-dosing.

Table 78. Toxicokinetics (#TAK-438-11215)

TAK-438F:

Dosage (mg/kg/day)	Day 14 after delivery (n=3)		
	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
1	1.0	3.0	5
3	1.0	44.8	89
10	1.0	150.3	559
100	3.3	841.8	10687

Source: Applicant study report.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Metabolites

Effects of TAK-438 M-IV-Sul on Embryo-Fetal Development in Rats (Study # TAK-438-10069))

Key Study Findings

The maternal NOAEL was 60 mg/kg/day, the highest dose tested corresponding to C_{max} of 53,840 ng/mL and AUC_{0-24h} of 24,901 ng*hr/mL on GD 17 (safety margin >100 to the expected human exposure).

Table 79. Methods (#TAK-438-10069)

Parameter	Method Details
Dose and frequency of dosing	0, 6, 20 and 60 mg/kg/day Once daily from gestational days 6-17
Route of administration	Subcutaneous injection
Formulation/vehicle	Test article was dissolved in 1 mol/L NaOH and then diluted to final formulation with saline. Control was dosed with saline.
Species/strain	Rat/Crl:CD(Sprague Dawley)
Number/sex/group	19-20 dams/group
Satellite groups	TK group: 4/treatment group
Study design	Dams were administered test article from gestational day 6-17 and euthanized on day 20 of gestation. TK measurements were on first and last day of dosing at times pre-dosing (last day only), 0.25-, 0.5-, 1-, 2-, 6-, and 24-hours post-dosing.
Deviation from study protocol affecting interpretation of results	None

Source: Reviewer table using data from the Applicant's submitted study report
Abbreviations: TK, Toxicokinetics

Table 80. Observations and Results (#TAK-438-10069)

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Cage-side observations were made prior to dosing and one-hour post-dosing. No abnormal clinical signs.
Body weights	Gestational days 0, 6, 8, 10, 12, 14, 16, 18, and 20. No treatment-related differences.
Feed consumption	Difference between provided and residual feed on GD 0-1, 6-7, 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, and 19-20, with provided measured on the first day and remainder on the second. A statistically significant decrease in food consumption was reported in 60 mg/kg dams on day 16 of gestation but was not considered adverse as there was no change in body weights or body weight gains.
Necropsy findings Cesarean section data	No treatment-related gross pathology in the dams.
Necropsy findings Offspring	No difference between control and treated groups in number of corpora lutea, implantations, live fetuses, pre- or post-implantation loss, sex ratio, body weights or placental weights of live fetuses.

Source: Reviewer table using data from the Applicant's submitted study report
Abbreviations: GD, gestational day

Toxicokinetics

Sample collection times: Prior to dosing (GD 17 only) and 0.25, 0.5, 1-, 2-, 6-, and 24-hours post-dosing.

Exposures increased approximately dose-proportionately.

Table 81. Toxicokinetics (#TAK-438-10069)

Table 1 Toxicokinetic parameters for TAK-438 M-IV-Sul in pregnant rats

		Female (N=3)		
Dose (mg/kg/day)	Day of pregnancy	Tmax (h)	Cmax (ng/mL)	AUC_{0-24h} (ng·h/mL)
6	6	0.25 (0.00)	2642.2 (189.6)	1672 (141)
	17	0.25 (0.00)	3394.3 (721.8)	2329 (190)
20	6	0.25 (0.00)	10717.1 (193.6)	5392 (846)
	17	0.25 (0.00)	15035.3 (3256.3)	7794 (1512)
60	6	0.25 (0.00)	45556.8 (5237.3)	24976 (4924)
	17	0.25 (0.00)	53840.6 (14601.6)	27901 (6277)

Mean (S.D.)

Source: Applicant study report page 206
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; N, number of patients in treatment arm; T_{max}, time to maximum plasma concentration

Range-Finding Study for the Effects of TAK-438 on Pre- and Postnatal Development, Including Maternal Function, in Rats (Study #TAK-438-10760)

In a non-GLP dose-range finding study, TAK-438 was administered by oral gavage to Crl:CD (Sprague Dawley) dams at a dose of 0, 30, 100, or 300 mg/kg/day from GD 6 to lactation day

(LD) 13 (N=7 to 8 dams/group. Litters were standardized to 8 pups/litter on LD 4. Clinical signs of mydriasis (in eight animals), prone position, tremors, and salivation (each in one animal) were reported following administration to the dams. In 300 mg/kg dams there was a significant decrease in body weight gain and feed consumption. No changes were reported in number of implants, duration of gestation or gestational index. At necropsy red discoloration in the stomach was reported in one 100 mg/kg dam, and one 300 mg/kg dam. In the pups, birth index, number of newborns, live pups on day 0, and viability index on day 4 were all significantly lower in the 300 mg/kg dose group compared to controls. Body weights were reduced in 30 mg/kg male and female pups on day 14, in 100 mg/kg male pups on day 11 and 14, and female pups on day 14, and on days 0, 4, 7, 11, and 14 in 300 mg/kg male and female pups. There was a statistically significant increase in liver discoloration in 30 and 100 mg/kg pups (16.7% and 12.5%, respectively); 2 pups in the 100 mg/kg group had black discoloration in the caudate lobe of the liver. In the dead F_1 pup, one had a membranous ventricular septal defect in the 300 mg/kg dose group. In livers in the 30 and 100 mg/kg dose groups examined, necrosis of hepatocytes was noted in the 30 and 100 mg/kg dose groups in pups with liver discoloration (5/5 in each dose group compared to 0/2 in control animals examined).

Range-Finding Study for the Effects of TAK-438 on Pre- and Postnatal Development, Including Maternal Function, in Rats -Supplemental Study- (Study #TAK-438-10763)

In a supplemental non-GLP dose-range finding study, TAK-438 was administered by oral gavage to Crl:CD(Sprague Dawley) dams at a dose of 0, 3, 10, 30 or 100 mg/kg/day from GD 6 to LD 13 (N=8 dams/group). Litters were standardized to 8 pups/litter on LD 4. Body weight gain was reduced in 10 and 100 mg/kg group animals, though feed consumption was increased in all TAK-438 treated animals. No changes were reported in number of implants, duration of gestation, or gestational index. No necropsy findings in the dams. No change in birth index, number of newborns, number of live pups on day 0, sex ratio, no decrease in viability index, or pup body weights. Stomach weights including contents were increased in 100 mg/kg group pups culled on day 4 and those euthanized on day 14 in males and females. Maternal milk appeared to have solidified in the stomach. In the LD 4 culled pups, 2% in the controls had discolored liver (white) as did 6.1% in the 3 mg/kg group (3.3% black, 2.8% white), 20.6% in the 10 mg/kg group (white), and 33.9% in the 100 mg/kg group (white). The number in the TAK-438 treated group animals were statistically significantly higher than the controls. In the examined livers, 2/2 and 2/7 had necrosis of hepatocytes in the 3 and 10 mg/kg groups, respectively, which was not seen in the 1 examined control liver or the 17 livers examined from the 100 mg/kg group. In the pups euthanized on day 14, in the 10 and 100 m/kg dose groups 7.2% and 14.1% had discolored liver, respectively, and 3/18 and 7/25 of the examined livers in these groups had necrosis, respectively. Other hepatic findings included hemorrhage, inflammatory cell infiltration, mineralization with giant cells and fibrosis in the TAK-438 treated animal groups. The caudate lobe was the main location of hepatic changes.

Toxicology reviewer comment: To evaluate the incidence of increased stomach size and formation of discolored lesions on the liver in the pups, a study was performed in which metoclopramide was administered to the pups of dams orally administered vonoprazan. Metoclopramide is a dopamine D_2 antagonist but also acts as an agonist on serotonin 5-HT_4 receptors, causes weak inhibition of 5-HT_3 receptors, and is used as a gastric prokinetic drug that increases motility and stimulates gastric emptying. The study authors hypothesized that the

liver lesions are induced by impaction of the larger stomach on the liver, and therefore increased stomach emptying should decrease stomach size and the occurance of liver lesions. While the results of the two following studies is consistent with this hypothesis, the effect in decreasing liver lesions may not be directly related to the change in stomach size and may be related to a different activity of metoclopramide on the pups in these studies. The Sponsor also did not show both stomach size reduction and a change in liver lesion development in the same study.

Effects of Concurrent Treatment with TAK-438 and Metoclopramide on Hepatic White Discoloration in Neonatal Rats (Study #TAK-438-10852)

In a non-GLP study, TAK-438 was administered by oral gavage to Crl:CD(Sprague Dawley) dams at a dose of 0 or 100 mg/kg/day and administered to the pups of dams admistered vonoprazan, at a dose of 0 or 50 mg/kg SC, twice per day, from LD 0 to LD 13 (N=12 dams/group). The pups were euthanized more than 15 hours after the last dose on postnatal day (PND) 14. Pups per litter were standardized to 8 on LD 4 by culling. In the dams, mydriasis was reported in 1 dam in the TAK-438/0 MET group and 3 in the TAK-438/50 MET group. In those 2 groups, body weight gain was reduced on LD 11. One dam in the TAK-438/50 MET group had no retrieving pups and pups with insufficient suckling and lost the litter on LD 5. The number of live pups on LD 0 was similar between groups; the TAK-438/50 MET group had fewer live pups on day 4. Clinical signs in the TAK-438/50 MET group pups included emaciation, decrease in locomotor activity and hypothermia and the viability index was reduced for day 0 to 4. The body weights of pups from dams treated with TAK-438 was reduced compared to controls. Relative stomach weights were increased in the TAK-438/50 MET group males and females and that TAK-438/0 MET group females though absolute weights were only increased in TAK-438/50 MET group females. There was a significant increase in discolored livers in TAK-438/0 MET group pups (5 pups) compared to controls (1 pup) that was not seen in the TAK-438/50 MET group pups (0 pups). No histopathology data were collected.

Effects of Metoclopramide Treatment to Pups on Increased Pup Stomach Weights Induced by Maternal Treatment with TAK-438 in Rats (Study # TAK-438-10943)

In a non-GLP study, TAK-438 was administered by oral gavage to Crl:CD(Sprague Dawley) dams at a dose of 0 or 100 mg/kg/day and metoclopramide, a gastric prokinetic drug that increases motility and stimulates gastric emptying, administered to the pups at a dose of 0 or 50 mg/kg SC, twice per day, from day 0 to day 3 of lactation (N=5 dams/group). Half the pups from each dam were treated with metoclopramide. The pup stomach weights were measured 8 or 10 hours after the last dosing on PND 3. In pups treated with saline, those in the TAK-438 administered dams had higher stomach weights than those treated with vehicle. The absolute and relative stomach weights in the metoclopramide-treated pups were statistically significantly lower or tended to be lower than those of the saline-treated pups except for the relative weights eight hours after metoclopramide treatment with vehicle-treated dams. The body weights of metoclopramide-treated pups were lower than the vehicle-administered pups. Pups from TAK-438-treated dams who were administered metoclopramide had lower stomach weights than those pups administered saline, but higher than pups from control-treated dams.

Study of Sensitive Period for TAK-438-Induced Hepatic Lesions in Neonatal Rats Oral Administration to Pregnant/Lactating Dams (Study # TAK-438-10873))

In a non-GLP study, 15-week-old female Crl:CD (Sprague Dawley) rats were administered vehicle (GD 6-PND 13, group 1) or 100 mg/kg TK-438 (GD 6-PND 13 (group 2), GD 6 to 21 (group 3), or PND 0 to 13 (group 4)) (N=8 dams/group). Pups in groups 4 had significantly lower average body weights on PND 11 and 14 compared to control, as did pups in group 2 on PND 14. Pups in groups 2 and 4 had significantly higher stomach weights for pups euthanized on PND 4 (except group 4 females), and PND 14. In pups culled on day 4, in groups 2 and 4, there was one pup in each group with a white focus in the liver, but not in the other groups. In pups euthanized on PND 14, in group 2, one pup had a small lobe of liver and three had a white focus in the liver, with histopathology of hepatic infarction and diffuse hepatocyte vacuolation. In group 4, 2 pups had a black discolored liver, 9 had a small caudate lobe of liver and 7 had a white focus in liver, with histopathology of hepatic infarction and diffuse hepatocyte vacuolation.

13.2.1.5. Carcinogenicity

2-year Oral Carcinogenicity Study in Mice (Study #TAK-438-10883)

- The carcinogenic potential of TAK-438 was evaluated in a study of B6C3F1/Crlj mice administered TAK-438 by a once daily oral gavage in a 0.5% w/v methylcellulose solution at dose levels of 0 (vehicle), 6, 20, 60, and 200 mg/kg/day (n=55/sex/group) for up to 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 0 (vehicle), 6, 20, 60, and 200 mg/kg/day dose groups in male mice, respectively, and 42 (76.4%), 34 (61.8%), 42 (76.4%), 41(74.5%), and 19 (34.5%), in female mice, respectively. There were statistically significant increases in mortality across the vehicle control group and the four treated groups for both males and females. Pairwise comparison using log-rank showed a statistically significant increase in mortality in male and female mice between the highest dose group (200 mg/kg/day) and the vehicle control group.
- There was a drug-related increase in the incidence of hepatocellular adenomas and hepatocellular carcinomas at ≥60 mg/kg/day, and combined incidences of hepatocellular adenomas and carcinomas in male mice at doses ≥20 mg/kg/day. There was a drug-related increase in the incidence of hepatocellular adenomas at ≥60 mg/kg/day, hepatocellular carcinomas at 200 mg/kg/day, and combined incidences of hepatocellular adenomas and carcinomas in female mice at doses ≥60 mg/kg/day.
- There was a drug-related increased incidence of benign neuroendocrine cell tumors at ≥60 mg/kg, and combined incidences of benign + malignant neuroendocrine cell tumors in the stomach of male mice at doses ≥20 mg/kg/day. There was a drug-related increased incidence of benign and malignant neuroendocrine cell tumors at 200 mg/kg/day and combined incidences of benign + malignant neuroendocrine cell tumors in the stomach of female mice at doses ≥60 mg/kg/day.

Table 82. Tumor Types With P-Values ≤0.05 for Dose Response Relationship or the Pairwise Comparisons

Sex	Organ Name	Tumor Name	0 mg Cont (N=55) P - Trend	6 mg Low (N=55) P - VC vs. L	20 mg Med (N=55) P - VC vs. M	60 mg High (N=55) P - VC vs. H	200 mg Posi (N=55) P - VC vs. HH
Male	Liver	Adenoma, Hepatocellular	20/55 (48) 0.0002*	29/55 (51) 0.0949	31/55 (50) 0.0347@	36/55 (47) 0.0005*	33/55 (41) 0.0002*
		Carcinoma, Hepatocellular	6/55 (48) 0.0016*	8/55 (48) 0.3867	15/55 (48) 0.0233@	20/55 (46) 0.0008*	13/55 (30) 0.0026*
		Adenoma, Hepatocellular / Carcinoma, Hepatocellular	21/55 (49) <0.0001*	32/55 (52) 0.0463@	38/55 (52) 0.0019*	43/55 (49) <0.0001*	36/55 (42) <0.0001*
	Stomach	Adenoma	0/54 (46) 0.0154*	0/55 (46) NC	0/55 (45) NC	0/55 (43) NC	2/55 (26) 0.1272
		Neuroendocrine Tumor, Benign	0/54 (46) <0.0001*	0/55 (46) NC	3/55 (45) 0.1168	27/55 (45) <0.0001*	35/55 (42) <0.0001*
		Neuroendocrine Tumor, Malignant	0/54 (46) 0.4843	2/55 (46) 0.2473	7/55 (46) 0.0061*	4/55 (43) 0.0505	1/55 (25) 0.3521
		Neuroendocrine Tumor, Benign / Neuroendocrine Tumor, Malignant	0/54 (46) <0.0001*	2/55 (46) 0.2473	9/55 (46) 0.0013*	28/55 (45) <0.0001*	35/55 (42) <0.0001*
Female	Liver	Adenoma, Hepatocellular	16/55 (50) <0.0001*	15/55 (50) 0.6671	18/55 (49) 0.3881	40/55 (52) <0.0001*	38/55 (49) <0.0001*
		Carcinoma, Hepatocellular	4/55 (50) <0.0001*	3/55 (48) 0.7649	4/55 (49) 0.6311	7/55 (50) 0.2623	42/55 (49) <0.0001*
		Adenoma, Hepatocellular / Carcinoma, Hepatocellular	19/55 (50) <0.0001*	18/55 (50) 0.6605	22/55 (49) 0.3113	41/55 (52) <0.0001*	49/55 (51) <0.0001*
	Stomach	Neuroendocrine Tumor, Benign	0/55 (49) <0.0001*	0/55 (48) NC	0/55 (49) NC	4/55 (50) 0.0612	33/55 (46) <0.0001*
		Neuroendocrine Tumor, Malignant	0/55 (49) <0.0001*	0/55 (48) NC	0/55 (49) NC	1/55 (51) 0.5100	7/55 (44) 0.0040*
		Neuroendocrine Tumor, Benign / Neuroendocrine Tumor, Malignant	0/55 (49) <0.0001*	0/55 (48) NC	0/55 (49) NC	5/55 (51) 0.0312*	35/55 (47) <0.0001*

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
@ = Not statistically significant in rare tumor at 0.025 level for test of dose response relationship and at 0.05 level for test of pairwise comparisons, or in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons

Source: Statistician's memo (Dr. Malick Mbodj) dated 6/16/2021

Toxicokinetics

Sample collection times: prior to dosing (week 54 only), 0.5, 1, 2, 4, 8 and 24 hours after dosing on day 1 and week 52.

There was no accumulation between day 1 and week 52 exposures. Males and females had similar exposures. Exposures increased with increasing dose, greater than dose-proportionately.

Table 83. Toxicokinetics (#TAK-438-100883)

		Dose of TAK-438 (mg/kg/day)							
		6		20		60		200	
Parameter	Sex	Day 1	Week 52	Day 1	Week 52	Day 1	Week 52	Day 1	Week 52
AUC_{0-24h} (mcg*h/mL)	Male	0.258	0.225	2.168	1.969	12.086	8.772	47.771	45.664
	Female	0.191	0.161	1.901	1.539	11.738	9.538	46.835	45.238
C_{max} (mcg/mL)	Male	0.1731	0.1549	1.1365	1.092	4.0504	3.257	12.652.2	7486.4
	Female	0.1541	0.1311	0.9129	0.8365	3.2639	3.0871	8.2964	6.2757
T_{max} (h)	Male	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Female	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Source: Applicant study report.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

2-year Oral Carcinogenicity Study in Rats (Study #TAK-438-10882)

- The carcinogenic potential of TAK-438 was evaluated in a study of Sprague Dawley rats administered TAK-438 by a once daily oral gavage in a 0.5% w/v methylcellulose solution at dose levels of 0 (vehicle), 5, 15, 50, and 150 mg/kg/day (n=60/sex/group) for up to 104 weeks.
- 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 0 (vehicle), 5, 15, 50, and 150 mg/kg/day dose groups, in male rats, respectively, and 24 (40%), 29 (48.3%), 23 (38.3%), 25 (41.7%), and 19 (31.7%) in the 0 (vehicle), 5, 15, 50, and 150 mg/kg/day dose groups, in female rats, respectively. There was no statistically significant difference in mortality between the vehicle control groups and treated groups.
- There was a drug-related increase in hepatocellular adenomas in male rats at doses ≥50 mg/kg/day, hepatocellular carcinoma in males at 150 mg/kg and combined incidences of hepatocellular adenomas and carcinomas in males at ≥50 mg/kg. There was a drug-related increase in the incidence of hepatocellular adenomas and combined incidences of hepatocellular adenomas and carcinomas in female rats at doses ≥50 mg/kg/day.
- There was a drug-related increase in the incidence of benign neuroendocrine cell tumors and the combined incidences of benign and malignant neuroendocrine cell tumors in the stomach of male rats at 150 mg/kg. There was a drug-related increase in the incidence of benign neuroendocrine cell tumors, malignant neuroendocrine cell tumors and combined benign and malignant neuroendocrine cell tumors in the stomach of female rats at all dose levels (≥5 mg/kg/day).
- The full table of tumors analyzed by FDA's statistician is shown in Table 84.

Table 84. Tumor Types With P-Values ≤0.05 for Dose Response Relationship or the Pairwise Comparison

Sex	Organ Name	Tumor Name	0 mg Cont (N=60) P - Trend	5 mg Low (N=60) P - VC vs. L	15 mg Med (N=60) P - VC vs. M	50 mg High (N=60) P - VC vs. H	150 mg Posi (N=60) P - VC vs. HH
Male	Hemolympho reticular	Leukemia, Granulocytic	0/60 (47) 0.0338@	0/60 (51) NC	0/60 (48) NC	1/60 (47) 0.5000	2/60 (51) 0.2683
	Liver	Adenoma, Hepatocellular	3/60 (47) <0.0001*	3/60 (51) 0.6994	7/60 (49) 0.1760	15/60 (47) 0.0015*	31/60 (52) <0.0001*
		Carcinoma, Hepatocellular	0/60 (47) <0.0001*	0/60 (51) NC	0/60 (48) NC	1/60 (46) 0.4946	7/60 (51) 0.0084*
		Adenoma / Carcinoma, Hepatocellular	3/60 (47) <0.0001*	3/60 (51) 0.6994	7/60 (49) 0.1760	16/60 (47) 0.0008*	31/60 (52) <0.0001*
		Carcinoma, Hepatocholangiocellular	0/60 (47) 0.0088*	0/60 (51) NC	0/60 (48) NC	0/60 (46) NC	3/60 (51) 0.1369
	Pancreas	Adenoma, Acinar Cell	0/60 (47) 0.4476	6/60 (51) 0.0171*	2/60 (49) 0.2579	0/60 (46) NC	3/60 (51) 0.1369
	Skin + Subcutaneous	Fibrosarcoma	1/60 (47) 0.0313@	0/60 (51) 1.0000	0/60 (48) 1.0000	1/60 (46) 0.7473	3/60 (51) 0.3401
	Stomach	Neuroendocrine Cell Tumor, B	1/60 (47) <0.0001*	7/60 (51) 0.0386@	7/60 (49) 0.0338@	8/60 (47) 0.0152@	21/60 (53) <0.0001*
		Nec.Cell Tumor, B., With Eosinophilic Cell Change	0/60 (47) 0.0018*	0/60 (51) NC	0/60 (48) NC	0/60 (46) NC	4/60 (51) 0.0692
		Total NEC Tumor, Benign	1/60 (47) <0.0001*	7/60 (51) 0.0386@	7/60 (49) 0.0338@	8/60 (47) 0.0152@	23/60 (53) <0.0001*
		Neuroendocrine Cell Tumor, M	0/60 (47) 0.0231*	1/60 (51) 0.5204	0/60 (48) NC	0/60 (46) NC	3/60 (51) 0.1369
		Total NEC Tumor, Malignent	0/60 (47) 0.0422@	1/60 (51) 0.5204	1/60 (48) 0.5053	0/60 (46) NC	3/60 (51) 0.1369
		Total with NEC Tumors	1/60 (47) <0.0001*	8/60 (51) 0.0210@	7/60 (49) 0.0338@	8/60 (47) 0.0152@	23/60 (53) <0.0001*
Female	Liver	Adenoma, Hepatocellular	2/60 (42) <0.0001*	2/60 (46) 0.7255	5/60 (42) 0.2163	14/60 (49) 0.0025*	20/60 (43) <0.0001*
	Stomach	Neuroendocrine Cell Tumor, B	0/60 (42) <0.0001*	18/60 (47) <0.0001*	31/60 (46) <0.0001*	33/60 (53) <0.0001*	37/60 (48) <0.0001*
		Neuroendocrine Cell Tumor, M	0/60 (42) 0.1131	7/60 (46) 0.0084*	22/60 (44) <0.0001*	18/60 (49) <0.0001*	11/60 (41) 0.0002*
		Total NEC Tumor, Benign	0/60 (42) <0.0001*	18/60 (47) <0.0001*	31/60 (46) <0.0001*	33/60 (53) <0.0001*	37/60 (48) <0.0001*
		Total NEC Tumor, Malignent	0/60 (42) 0.1295	7/60 (46) 0.0084*	23/60 (44) <0.0001*	18/60 (49) <0.0001*	11/60 (41) 0.0002*
		Total with NEC Tumors	0/60 (42) <0.0001*	21/60 (47) <0.0001*	33/60 (47) <0.0001*	35/60 (53) <0.0001*	37/60 (48) <0.0001*
	Vagina	Granular Cell Tumor	0/60 (42) 0.0493@	0/60 (46) NC	1/60 (41) 0.4940	0/60 (47) NC	2/60 (41) 0.2410
	Whole Body	Hemangioma	0/60 (42) 0.0350@	0/60 (46) NC	0/60 (41) NC	0/60 (47) NC	2/60 (41) 0.2410

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable
*: Statistically significant at 0.005 and 0.025 level for common and rare tumor or 0.01 and 0.05 level for common and rare tumors for tests of dose response relationship and pairwise comparison, respectively.
@ = Not statistically significant in rare tumor at 0.025 level for test of dose response relationship and at 0.05 level for test of pairwise comparisons, or in common tumor at 0.005 level for test of dose response relationship and at 0.01 level for test of pairwise comparisons

Source: Statistician's memo (Dr. Malick Mbodj) dated 6/16/2021

Toxicokinetics

Sample collection times: prior to dosing (week 54 only), 0.5, 1, 2, 4, 8 and 24 hours after dosing on day 1 and week 52.

Exposures increased with increasing dose. Between 5 and 50 mg/kg, exposure increases with a greater than dose proportionally. Between 50 and 150 mg/kg the increase is dose proportional.

Table 85. Toxicokinetics (#TAK-438-100882)

		Dose of TAK-438 (mg/kg/day)							
		5		15		50		150	
Parameter	Sex	Day 1	Week 52	Day 1	Week 52	Day 1	Week 52	Day 1	Week 52
$AUC_{0\text{-}24h}$ (mcg*h/mL)	Male	0.06	0.26	0.81	1.66	13.73	9.71	43.81	29.09
	Female	0.11	0.32	0.99	2.39	9.52	8.72	38.05	34.14
C_{max} (mcg/mL)	Male	0.02	0.07	0.24	0.26	1.50	0.90	2.96	2.61
	Female	0.05	0.12	0.26	0.43	1.30	0.82	3.72	2.57
T_{max} (h)	Male	0.5	1.0	1.0	1.0	2.0	2.0	2.0	4.0
	Female	1.0	0.5	1.0	1.0	0.5	2.0	0.5	2.0

Source: Reviewer table derived from reported study data.
All dose levels and toxicokinetic parameters are in terms of TAK-438F. Toxicokinetic parameters were derived from mean plasma concentration data (N=3)/timepoint/sex/group.
Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

13.2.1.6. Other Studies

3T3 NRU Phototoxicity Test of T-1823718 (Study #TAK-438-00179)

The sodium salt of TAK438 (8.81 to 1000 mcg/mL) was tested for the potential to cause phototoxicity in BALB/3T3 clone A31 cells. Hexachlorophene (0.188 to 24 mcg/mL) was the negative control and chlorpromazine (0.313 to 40 mcg/mL without light and 0.016 mcg/mL with light) the positive control. Cells were exposed to the test article, and some were exposed to 5J/cm2 UVA light over the course of 1 hour. Cell viability, IC_{50}, and Photo-Irritation-Factor (PIF) were calculated for the test substance and positive and negative controls, and a Mean Photo Effect (MPE) when PIF could not be determined. The IC_{50} for the TAK-438 sodium salt was 400.252 mcg/mL with irradiation, but the viability was not below 50% at any concentration so the PIF was not calculated and the MPE was determined to be 0.116, which indicates a probable phototoxic response. No change in IC_{50} was found for the negative control with irradiation and the IC_{50} for the positive control was 16.065 without irradiation and 0.902 with irradiation leading to a PIF of 17.81, indicating that the study was valid.

Single-Dosage Phototoxicity Study to Determine the Effects of Oral (Gavage) Administration of TAK-438 on Skin in Hairless Mice (Study # TAK-438-00197)

In a study on the potential for vonoprazan to cause a phototoxic effect in vivo, Crl:SKH1-*hr* mice were administered a single oral gavage dose of vehicle 200 mg/kg, lomefloxacin hydrochloride (positive control) 20, mg/kg TAK-438, 60 mg/kg TAK-438, or 200 mg/kg TAK-438 and then exposed to ultraviolet (UV) radiation 0.5 hours later (n=10 males/group). Mice were examined 0.5, 4 hours, 1, 2, and 3 days following the UV exposure for skin response. The positive control elicited erythema, edema and flaking at the exposure site. TAK-438 did not induce a response and was not considered phototoxic under these study conditions.

Single-Dosage Phototoxicity Study to Determine the Effects of Subcutaneous Administration of TAK-438 M-IV-Sul on Skin in Hairless Mice (Study # TAK-438-10089)

In a study on the potential TAK-438 M-IV-Sul to cause a phototoxic effect in vivo,Crl:SKH1-*hr* mice were tested under the following conditions: (group 1) the mice were administered a single

oral gavage dose of 200 mg/kg lomefloxacin hydrochloride (positive control) then exposed to UV radiation 0.5 hours later; mice in the following groups were administered the indicated concentrations of TAK-438 M-IV-Sul by SC injection and then exposed to UV radiation 18 minutes later: group 2 (0 mg/kg (vehicle)), group 3 (40 mg/kg), group 4 (200 mg/kg), and group 5 (1000 mg/kg); the mice in the last group (group 6) were administered 1000 mg/kg TAK-438 M-IV-Sul by SC injection with no UV exposure (n=10 females/group). Mice were examined 0.5, 4 hours, 1, 2, and 3 days following the UV exposure for skin response.

Group 5 and group 6 each had one mouse found dead and one mouse euthanized moribund. The positive control elicited erythema, edema, and flaking at the exposure site. No phototoxicity was noted in animals treated with 40 or 200 mg/kg of TAK-438 M-IV-Sul. Five animals in the TAK-438 M-IV-Sul 1000 mg/kg and UV radiation group had grade 1 erythema and one of those had grade 1 edema. It occurred 30 minutes after exposure and lasted up to 4 hours in one mouse. Therefore, administration of TAK-438 M-IV-Sul elicited a phototoxic response at the highest dose of 1000 mg/kg TAK-438 M-IV-Sul.

13.2.2. Amoxicillin

13.2.2.1. Overview

No new safety toxicology studies on amoxicillin were submitted with this NDA. The Applicant relied on FDA's prior findings of safety and effectiveness for amoxicillin (NDA 050459 for Amoxil capsules). The approvals of the relied-upon listed drug, NDA 050459 Amoxil, has been withdrawn FR effective (Federal Register determination that both products were not discontinued or withdrawn for safety or efficacy reasons).

Summaries of the data included in labeling from the Reference Listed Drug are included below.

13.2.2.2. Reproductive Toxicology

Reproduction studies have been performed in mice and rats at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to amoxicillin.

Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pigs showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions but moderately increased the height and duration of contractions.

In a multi-generation reproduction study in rats, no impairment of fertility or other adverse reproductive effects were seen at doses up to 500 mg/kg (approximately 1.6 times the human dose in mg/m^2).

13.2.2.3. Genetic Toxicology

Studies to detect the mutagenic potential of amoxicillin alone have not been conducted; however, the following information is available from tests on a 4:1 mixture of amoxicillin and potassium clavulanate (Augmentin). Augmentin was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Augmentin was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Augmentin was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays.

13.2.2.4. Carcinogenicity

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

13.2.3. Clarithromycin

13.2.3.1. Overview

No new safety toxicology studies on clarithromycin were submitted with this NDA. The Applicant relied on FDA's prior findings of safety and effectiveness for clarithromycin (NDA 050662 for Biaxin tablets). The approvals of the relied-upon listed drug, NDA 050459 Biaxin has been withdrawn FR effective (Federal Register determination that both products were not discontinued or withdrawn for safety or efficacy reasons).

Summaries of the data included in labeling from the Reference Listed Drug are included below.

13.2.3.2. Reproductive Toxicology

Animal reproduction studies were conducted in mice, rats, rabbits, and monkeys with oral and intravenously administered clarithromycin. In pregnant mice, clarithromycin was administered during organogenesis (GD 6 to 15) at oral doses of 15, 60, 250, 500, or 1000 mg/kg/day. Reduced body weight observed in dams at 1000 mg/kg/day (3 times the MRHD based on BSA comparison) resulted in reduced survival and body weight of the fetuses. At 500 mg/kg/day, increases in the incidence of postimplantation loss and cleft palate in the fetuses were observed. No adverse developmental effects were observed in mice at ≤ 250 mg/kg/day (≤ 1 times MRHD based on BSA comparison).

In pregnant Sprague Dawley rats, clarithromycin was administered during organogenesis (GD 6 to 15) at oral doses of 15, 50, or 150 mg/kg/day. Reductions in body weight and food consumption was observed in dams at 150 mg/kg/day. Increased resorptions and reduced body weight of the fetuses at this dose were considered secondary to maternal toxicity. Additionally, at 150 mg/kg/day (1 times MRHD based on BSA comparison), a low incidence of cardiovascular anomalies (complete situs inversus, undivided truncus, IV septal defect) was observed in the fetuses. Clarithromycin did not cause adverse developmental effects in rats at 50 mg/kg/day (0.3 times MRHD based on BSA comparison). Intravenous dosing of clarithromycin during organogenesis in rats (GD 6 to 15) at 15, 50, or 160 mg/kg/day was associated with maternal toxicity (reduced body weight, body-weight gain, and food consumption) at 160 mg/kg/day but no evidence of adverse developmental effects at any dose (≤1 times MRHD based on BSA comparison).

In pregnant Wistar rats, clarithromycin was administered during organogenesis (GD 7 to 17) at oral doses of 10, 40, or 160 mg/kg/day. Reduced body weight and food consumption were observed in dams at 160 mg/kg/day but there was no evidence of adverse developmental effects at any dose (≤ 1 times MRHD based on BSA comparison).

In pregnant rabbits, clarithromycin administered during organogenesis (GD 6 to 18) at oral doses of 10, 35, or 125 mg/kg/day resulted in reduced maternal food consumption and decreased body weight at the highest dose, with no evidence of any adverse developmental effects at any dose (≤2 times MRHD based on BSA comparison). Intravenously administered clarithromycin to pregnant rabbits during organogenesis (GD 6 to 18) in rabbits at 20, 40, 80, or 160 mg/kg/day (≤

0.3 times MRHD based on BSA comparison) resulted in maternal toxicity and implantation losses at all doses.

In pregnant monkeys, clarithromycin was administered (GD 20 to 50) at oral doses of 35 or 70 mg/kg/day. Dose-dependent emesis, poor appetite, fecal changes, and reduced body weight were observed in dams at all doses (≤ 0.5 times MRHD based on BSA comparison). Growth retardation in 1 fetus at 70 mg/kg/day was considered secondary to maternal toxicity. There was no evidence of primary drug-related adverse developmental effects at any dose tested.

In a reproductive toxicology study in rats administered oral clarithromycin late in gestation through lactation (GD 17 to PND 21) at doses of 10, 40, or 160 mg/kg/day (≤ 1 times MRHD based on BSA comparison), reductions in maternal body weight and food consumption were observed at 160 mg/kg/day. Reduced body-weight gain observed in offspring at 160 mg/kg/day was considered secondary to maternal toxicity. No adverse developmental effects were observed with clarithromycin at any dose tested.

Fertility and reproduction studies have shown that daily doses of up to 160 mg/kg/day to male and female rats caused no adverse effects on the estrous cycle, fertility, parturition, or number and viability of offspring. Plasma levels in rats after 150 mg/kg/day were twice the human serum levels.

Testicular atrophy occurred in rats at doses 7 times, in dogs at doses 3 times, and in monkeys at doses 8 times greater than the maximum human daily dose (on a BSA basis).

13.2.3.3. Genetic Toxicology

Mutagenesis

The following in vitro mutagenicity tests have been conducted with clarithromycin:

- Salmonella/Mammalian Microsomes Test
- Bacterial Induced Mutation Frequency Test
- In Vitro Chromosome Aberration Test
- Rat Hepatocyte DNA Synthesis Assay
- Mouse Lymphoma Assay
- Mouse Dominant Lethal Study
- Mouse Micronucleus Test

All tests had negative results except the in vitro chromosome aberration test which was positive in one test and negative in another. In addition, a bacterial reverse-mutation test (Ames test) has been performed on clarithromycin metabolites with negative results.

13.2.3.4. Carcinogenicity

There were no studies available.

13.2.4. Other Studies

Corneal opacity occurred in dogs at doses 12 times greater and in monkeys at doses 8 times greater than the maximum human daily dose (on a BSA basis). Lymphoid depletion occurred in dogs at doses 3 times greater than and in monkeys at doses 2 times greater than the maximum human daily dose (on a BSA basis).

13.2.5. Impurities/Degradants

13.2.5.1. Impurities/Degradants in Vonoprazan

The qualification of specified and unspecified impurities within the vonoprazan drug substances, and degradants in the vonoprazan drug product are described below. Overall, the proposed specifications, or lack of specifications, are considered acceptable from a pharmacology/toxicology perspective. This conclusion is based on the general toxicology studies, Ames tests, and/or quantitative structure–activity relationship analysis.

13.2.5.2. Specified Organic Impurities

The Applicant identified nine specified impurities. Five were determined to be in the final drug substance and were evaluated for potential genotoxicity using DEREK Nexus and CASE Ultra in 2016. One positive alert was found in Case Ultra; however, the structure was also present in the drug substance TAK-438 (b) (4) l). Read-across was used to extrapolate from the impurity to the drug substance, as the drug substance was negative in the Ames assay. One intermediate, (b) (4) is potentially mutagenic as it was positive in an Ames test. (b) (4) and structurally related impurities (b) (4) were controlled at (b) (4) ppm, below the threshold of toxicological concern (TTC).

The impurities found to be above the International Conference on Harmonisation (ICH) threshold for qualification (b) (4) were adequately qualified for safety in a 4-week repeat dose rat toxicology study with a 4-week recovery period (Study No TAK-438-00085). The mid dose of the study was considered the LOAEL dose, however the toxicities were considered to be related to the exaggerated pharmacological action of the drug based on the common target. As these impurities are structurally related to the drug substance, they are unlikely to have a significantly stronger pharmacological activity or toxicity and the proposed drug substance and drug product specification levels are considered qualified by this study.

(b) (4)

13.2.5.3. Residual Solvents

Solvents that were identified as possible impurities were (b) (4) The residual solvent concentrations were found acceptable and within limits of the ICH Guidance Q3(R8) based on the CMC review findings. See the CMC review for more details.

(b) (4)

13.2.5.4. Elemental Impurities

TAK-438 is produced using (b) (4). The Applicant evaluated the (b) (4) content in (b) (4). The content was less than the quantitative limit (b) (4)

Tests for total heavy metal were below (b) (4) ppm, addressing theoretical risk for (b) (4), which are present in manufacturing equipment.

Following CMC review, these impurities were found to be within acceptable limits. See CMC review for more details.

14. Clinical Pharmacology: Additional Information and Assessment

Vonoprazan fumarate was referred to as TAK-438 and the free base form of vonoprazan was referred to as TAK-438F. The Applicant used vonoprazan throughout the clinical pharmacology summary documents, however, the study reports appear to use TAK-438 for vonoprazan as well.

14.1. In Vitro Studies

Vonoprazan is postulated to inhibit gastric acid secretion by inhibiting H^+, K^+-ATPase (IC_{50}=19.3 to 29.9 nmol/L) and is reported to have no direct antibacterial activity against *H pylori*. The metabolites of vonoprazan identified are M-I (and glucuronic acid conjugate of M-I: M-I-G), M-II, M-III, and M-IV-Sul. M-I, M-II, and M-III are reported to be inactive against H^+, K^+-ATPase. M-IV-Sul is reported to weakly inhibited gastric H^+, K^+-ATPase activity (IC_{50}= 4120 nmol/L). Clinical pharmacology-related in vitro studies are summarized in Table 88.

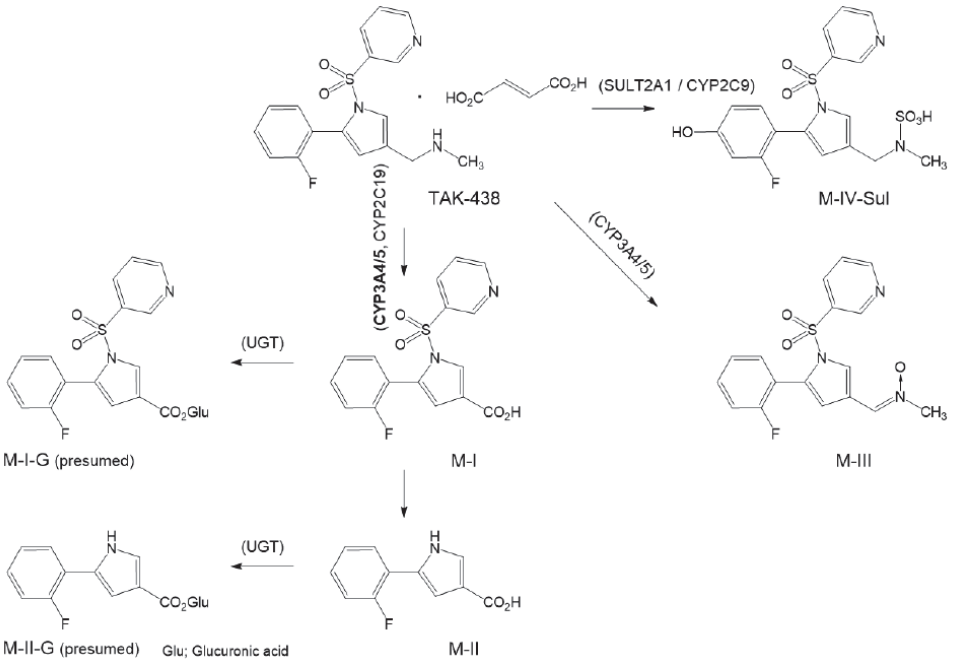
Table 88. Summary of In Vitro Evaluations

Objective	Test System	Summary Findings and Key Conclusions	Report
		Absorption	
Characterization of TAK-438 as P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate	[^{14}C] TAK-438 permeation evaluated across Caco-2 cell monolayers and compared against P-gp substrate [^{3}H] digoxin, BCRP substrate [^{3}H] Estrone 3-sulfate (E3S), high permeability marker [^{14}C] antipyrine, and the low permeability marker [^{14}C] mannitol as reference compounds.	P_{app} ratios for [^{14}C] TAK-438, [^{3}H] Digoxin, [^{3}H] E3S, [^{14}C] Antipyrine, and [^{14}C] Mannitol were 1.2, 4.7, 6.4, 1, and 0.9, respectively. P_{app} value of [^{14}C] TAK-438 from the apical to basal side was approximately 40% of that of [^{14}C] antipyrine, which was noted to be comparable to the previously noted values for high permeability markers, metoprolol, propranolol, theophylline and verapamil. *TAK-438 is not a substrate for P-gp and BCRP. It did not affect permeation of mannitol, i.e., did not affect the paracellular site. TAK-438 has high permeability.*	TAK-438-10811
Evaluation of permeability of TAL-438F across Caco-2 cell monolayers against model drugs	Permeation across Caco-2 cell monolayers for [^{14}C] TAK-438F, [^{3}H] digoxin (a substrate for P-gp), and [^{3}H] E3S (a substrate for BCRP) as well as for high, moderate and low permeability markers was measured and compared.	For TAK-438F P_{app} ratio was 1.6. TAK-438F permeation from the apical to the basal side was noted to be lower than all high permeability markers except for minoxidil, for which it was ~3-fold higher. TAK-438F permeation from the apical to the basal side was higher than moderate and low permeability markers. *TAK-438F has high permeability and is not a substrate for P-gp and BCRP.*	PRE-DDA-438-004

Objective	Test System	Summary Findings and Key Conclusions	Report
		Distribution	
In vitro plasma protein binding evaluation	Protein binding was evaluated for [^{14}C] TAK-438 in human plasma spiked with TAK-438F equivalent concentrations of 100, 1000, and 10000 ng/mL in triplicates using ultrafiltration Method.	The protein binding of [^{14}C] TAK-438 at the TAK-438F equivalent concentrations of 100, 1000, and 10000 ng/mL were 87%, 85%, and 88% in human plasma, respectively. *The protein binding of [^{14}C] TAK-438 in human plasma was mostly constant ranging from 85% to 88%.*	TAK-438-00087
Determining distribution ratio into the human blood cells	Distribution ratio for [^{14}C] TAK-438 in human blood cell was evaluated at TAK-438F equivalent concentration of 10, 100, and 1000 ng/mL in triplicate by comparing radioactivity in plasma and blood after adjusting for hematocrit value.	The distribution ratios of [^{14}C] TAK-438 into the blood cells at the TAK-438F equivalent concentrations of 10, 100 and 1000 ng/mL were 46%, 44%, and 46% in humans, respectively. *The distribution ratios of TAK-438 into the human blood cells was mostly constant ranging from 44% to 46%.*	TAK-438-00090

Objective	Test System	Summary Findings and Key Conclusions	Report
		Metabolism	
Metabolism characterization in human CYP-expressing microsomes	[^{14}C]TAK-438 solution (10 µmol/L) was incubated in the panel of human hepatic microsomes with NADPH-generating system.	TAK-438 was metabolized to M-I, M-II, T-1641510 (*N*-demethylated TAK-438), and the unidentified metabolites, UK-A, UK-B, UK-C (Identified later as M-IV-Sul), UK-D (Identified as M-III later), UK-E, UK-F, and UK-G. The elimination rate of TAK-438 most strongly correlated with CYP3A4/5 activity (r =0.9). The formation rate of M-I most strongly correlated with CYP3A4/5 activity (r = 0.9), and also correlated with CYP2C19 (r = 0.5). The formation rate of T-1641510 most strongly correlated with CYP3A4/5 activity (r =0.9), and also correlated with CYP2C19 (r = 0.6) and CYP2C8 (r = 0.5) activities. The formation rates of unidentified metabolites were correlated with CYP3A4, CYP2C19, CYP2D6, and CYP2C8 activity. *TAK-438 was metabolized to aforementioned metabolites. The elimination rates of TAK-438 and formation rates of identified and unidentified metabolites were correlated with CYP3A4/5, CYP2C19, CYP2C8, and CYP2D6 activity.*	TAK-438-00096
CYP reaction phenotyping of [^{14}C]TAK-438 metabolism in individual human CYP isoform expressing microsomes	[^{14}C]TAK-438 solution (10 µmol/L) was incubated with each of the CYP-expressing microsomes with the NADPH-generating system in duplicate.	TAK-438 was metabolized to M-I, M-II, T-1641510, and the unidentified metabolites, UK-A, UK-B, UK-C, UK-D, UK-E, UK-F, and UK-G. The TAK-438 elimination rate was the highest with CYP2D6 followed by CYP2C19, CYP3A4, CYP2B6, and the other CYP isoforms. CYP2D6 mainly formed T-1641510, and also formed UK-D and UK-E. CYP2C19 mainly formed T-1641510, and also formed M-I and UK-E. CYP3A4 mainly formed M-I, T-1641510, UK-B, and UK-D, and also formed UK-E and UK-G. CYP2B6 mainly formed M-I and T-1641510, and also formed UK-D. *TAK-438 elimination rate was the highest with CYP2D6. The formation of identified and unidentified metabolites was observed in presence of CYP3A4/5, CYP2C19, CYP2B6, and CYP2D6.*	TAK-438-00097
Evaluation of [^{14}C]TAK-438's sulfation	[^{14}C]TAK-438 solution (10 µmol/L) was incubated in mixtures prepared with liver cytosol from humans, rats, and dogs.	The percentage to the total radioactivity attributed to TAK-438 and T-1767002 (TAK-438 *N*-sulfate) were 90% and 3% in human cytosol mixture, 93% and 0.2% in rat cytosol mixtures. T-1767002 levels were not detected in dog cytosol mixture. *Study findings showed that T-1767002 (TAK-438 N-sulfate) was formed in presence of cytosols from humans and rats. T-1767002 was not detected in in vivo studies.*	TAK-438-11250

Objective	Test System	Summary Findings and Key Conclusions	Report
Identification of sulfotransferase isoforms involved in [^{14}C]TAK-438 sulfation	[^{14}C]TAK-438 solution (10 µmol/L) was incubated in mixtures prepared with recombinant human SULTs (SULT1A1, SULT1A3, SULT1B1, SULT1E1, and SULT2A1).	TAK-438 was metabolized to T-1767002 (TAK-438 *N*-sulfate) in presence of SULT2A1 only with formation rate of 13508 pmol/h/mg. *Study findings showed that T-1767002 (TAK-438 N-sulfate) was formed in the presence of SULT2A1 only.*	TAK-438-11263
CYP reaction phenotyping of [^{14}C] TAK-438 *N*-sulfate metabolism in individual human CYP isoform expressing microsomes	[^{14}C]TAK-438 *N*-sulfate solution (10 µmol/L) was incubated with each of the CYP-expressing microsomes with the NADPH-generating system in duplicate.	TAK-438 *N*-sulfate was metabolized to M-IV-Sul metabolite and the unidentified metabolites, UK-1, UK-2 UK-3, and UK-4. The TAK-438 *N*-sulfate elimination rate was the highest with CYP2C9 followed by CYP3A4. CYP2C9 mainly formed M-IV-Sul, and also formed unidentified metabolite (UK-2). CYP3A4 mainly formed UK-4 and also formed unidentified metabolites(UK-1 and UK-3). *TAK-438 N-sulfate elimination was the highest with CYP2C9. CYP2C9, and CYP3A4 are responsible for the formation of identified and unidentified metabolites.*	TAK-438-11251
Evaluation of TAK-438's oxidative metabolite profile with human hepatic microsomes	[^{14}C]TAK-438 solution (10 µmol/L) was incubated in the panel of human hepatic microsomes with NADPH-generating system.	*Findings and conclusions in line with Study TAK-438-00096 findings reported above.*	TAK-438-00095
Metabolite profiling of [^{14}C]TAK-438 in human hepatocytes	[^{14}C]TAK-438 solution (10 µmol/L) was incubated in the hepatocytes (from 3 individual donors) in a Dulbecco's Modified Eagle Medium (DMEM, low glucose) culture medium.	Findings and conclusions from this study were in line with Study TAK-438-00095/96 findings reported above, except one additional metabolite M-IV-Sul was identified.	TAK-438-00131

Objective	Test System	Summary Findings and Key Conclusions	Report
Suggested Metabolism Pathway for Vonoprazan Based on Findings from Studies TAK-438-00096, TAK-438-00097, TAK-438-11250, TAK-438-11263, TAK-438-11251			
3			

Objective	Test System	Summary Findings and Key Conclusions	Report
In Vitro Drug-Drug Interaction Studies			
Inhibitory effects of TAK-438 on CYP activities in human liver microsomes	Each CYP substrate (for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was incubated with human liver microsomes in the absence or presence of TAK-438 (1, 3, 10, and 30 µmol/L) in the presence of an NADPH-generating system. In addition, time-dependent inhibitory (TDI) effects of TAK-438 on the CYP activities were examined in human liver microsomes pre-incubated for up to 30 min with TAK-438 (1, 3, 10, and 30 µmol/L) in the presence of an NADPH-generating system.	Without pre-incubation: TAK-438 inhibited the CYP2B6 (Substrate: bupropion) and CYP3A4/5 (midazolam) activities with the IC_{50} values of 16 and 29 µmol/L, respectively. TAK-438 also inhibited the CYP2C19 ((S)-Mephenytoin), CYP2D6 (bufuralol), and CYP3A4/5 (testosterone) activities to 64.3%, 61.3%, and 61.3% of the control activity at 30 µmol/L, respectively, resulting in the IC_{50} values of >30 µmol/L for CYP2C19, CYP2D6, and CYP3A4/5. TAK-438 did not show substantial inhibition of the CYP1A2 (phenacetin), CYP2C8 (paclitaxel), or CYP2C9 (diclofenac) With pre-incubation: TAK-438 inhibited the CYP2B6, CYP2C19, CYP3A4/5 (midazolam), and CYP3A4/5 (testosterone) activities with the IC_{50} values of 2.6, 13, 10, and 9.8 µmol/L, respectively TAK-438 also inhibited the CYP2D6 64.3% of the control activity at 30 µmol/L resulting in the IC_{50} values of >30 µmol/L. TAK-438 did not show substantial inhibition of the CYP1A2, CYP2C8, or CYP2C9 *TAK-438 had direct inhibitory effects on the CYP2B6 and CYP3A4/5 activities as well as time-dependent inhibitory effects on the CYP2B6, CYP2C19, and CYP3A4/5 activities.*	TAK-438-11256
Examination of time- and concentration-dependent inactivation of CYP2B6 and CYP3A4/5 in human liver microsomes	Inactivation of CYP2B6 (Substrate: bupropion) and CYP3A4/5 (midazolam) activities (hydroxylation and 1'-hydroxylation) by TAK-438 (0, 2, 5, 10, 20, and 50 µmol/L) was evaluated in incubation (Pre-incubation duration range 0-30 mins) with human liver microsomes in the presence of NADPH-generating system. Ticlopidine and verapamil were used as the positive control substances.	In CYP2B6, k_{inact}, K_I, and k_{inact}/K_I ratio for TAK-438 were 0.0115 min-1, 3.50 µmol/L, and 0.00329 L/min/µmol, respectively. In CYP3A4/5, k_{inact}, K_I, and k_{inact}/K_I ratio for TAK-438 were 0.0161 min-1, 1.22 µmol/L, and 0.0132 L/min/µmol, respectively. *TAK-438 inhibited CYP2B6 and CYP3A4/5 in time- and concentration-dependent manner.*	TAK-438-11315

Objective	Test System	Summary Findings and Key Conclusions	Report
Examination of time- and concentration-dependent inactivation of CYP2C19 in human liver microsomes	Inactivation of CYP2C19 (Substrate: (S)-mephenytoin) by TAK-438 (0,0.3, 1, 3, 10, and 30 µmol/L) was evaluated in incubation (Pre-incubation duration range 0-30 mins) with human liver microsomes in the presence of NADPH-generating system. S-Fluoxetine, omeprazole, and esomeprazole were used as the positive control substances.	In CYP2C19, k_{inact}, K_I, and k_{inact}/K_I ratio for TAK-438 were 0.0182 min-1, 3.67 µmol/L, and 0.00496 L/min/µmol, respectively. *TAK-438 inhibited CYP2C19 in time- and concentration-dependent manner.*	TAK-438-12124
Inhibitory effects of TAK-438 metabolites (TAK-438 M-I, TAK-438 M-II, TAK-438 M-III, and TAK-438 M-IV-Sul) on CYP activities in human liver microsomes	Each CYP substrate (for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) was incubated with human liver microsomes in the absence or presence of TAK-438 metabolites (0, 1, 3, 10, and 30 µmol/L) in the presence of an NADPH-generating system. In addition, time-dependent inhibitory (TDI) effects of TAK-438 metabolites on the CYP activities were examined in human liver microsomes pre-incubated for up to 30 min with TAK-438 metabolites (1, 3, 10, and 30 µmol/L) in the presence of an NADPH-generating system.	Without pre-incubation, none of the metabolites shows notable inhibition towards any of the CYPs tested. With pre-incubation, only TAK-438 M-III inhibited the CYP2B6 activity with the IC_{50} value of 7.69 µmol/L. *TAK-438 M-III showed time-dependent inhibition of the CYP2B6.* *Note: The estimated maximal concentration of M-III in human plasma is 0.047 µmol/L.*	TAK-438-11787

Objective	Test System	Summary Findings and Key Conclusions	Report
Evaluating of induction of CYP1A, CYP2B6, and CYP3A activities by TAK-438	Human hepatocytes from 3 donors were incubated with TAK-438 metabolites (1, 3, and 10 µmol/L) for one day and then metabolism of phenacetin (CYP1A), bupropion (CYP2B6), and testosterone (CYP3A) substrates were measured. The induction ratios were calculated by comparing relative metabolism of the CYP substrates in hepatocytes treated with TAK-438 to that of in hepatocytes treated with respective positive control (omeprazole (CYP1A), phenobarbital (CYP2B6), and rifampin (CYP3A)).	The induction ratios after treatment with 1, 3, 10, and 30 µmol/L TAK-438 for day one and two were approximately 4%, 4%, 6%, and 8%, respectively, compared to after treatment with omeprazole. The induction ratios after treatment with 1, 3, 10, and 30 µmol/L TAK-438 for day two and three were approximately 14%, 16%, 17%, and 15%, respectively, compared to after treatment with phenobarbital. The induction ratios after treatment with 1, 3, 10, and 30 µmol/L TAK-438 for up to 4 days was less than 1% compared to after treatment with rifampin. *These results indicate that TAK-438 has little or no potency to induce CYP1A, CYP2B6, and CYP3A activity* in vitro.	TAK-438-10443 TAK-438-11235 TAK-438-00216
Evaluating of induction of CYP1A, CYP2B6, and CYP3A activities by TAK-438 metabolites	Human hepatocytes from 3 donors were incubated with TAK-438 metabolites (M-I, M-II, M-III, and M-IV-Sul) at concentrations of 1, 3, and 10 µmol/L. The gene expression of 3 CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) were examined after 48 hours. The induction ratios were calculated by comparing relative gene expression in hepatocytes treated with TAK-438 metabolites to that of in hepatocytes treated with respective positive control (omeprazole (CYP1A), phenobarbital (CYP2B6), and rifampin (CYP3A)).	The mean of % positive control values in the gene expression of CYP2B6 and CYP3A4 at M-III 30 µmol/L was 77.9% and 49.2%, respectively, and that of CYP1A2 was 1.4%. The means of % positive control value in the gene expression of CYP1A2, CYP2B6, and CYP3A4 after M-I, M-II, and M-IV-Sul exposure were 9.3% or less. *M-III showed no induction potency for CYP1A2, however, demonstrated induction potency for CYP2B6 and CYP3A4. In addition, these results indicated that M-I, M-II, and M-IV-Sul have no induction potency for CYP1A2, CYP2B6, or CYP3A4.* *Note: The estimated maximal concentration of M-III in human plasma is 0.047 µmol/L.*	TAK-438-11788

Objective	Test System	Summary Findings and Key Conclusions	Report
Inhibitory effects of TAK-438 on P-gp transporter	Effect of TAK-438 on [^{3}H]digoxin (3 µmol/L) transport across Caco-2 cell monolayers was examined to assess the inhibitory effect of TAK-438 (0, 1, 3, 10, 30, 100, 300 and 1000 µmol/L) on P-gp function. [^{14}C]Mannitol (10 µmol/L) was used as a paracellular marker and quinidine (1, 3, 10, and 30 µmol/L) was used as a positive control.	TAK-438 affected the paracellular transport of [^{14}C]Mannitol at ≥ 300 µmol/L After incubation of [^{3}H]digoxin at 37°C for 1 and 2 h, in the presence of TAK-438, at concentrations of 0, 1, 3, 10, 30, 100, 300 and 1000 µmol/L, the Papp ratios were 7.3, 7.4, 7.4, 5.5, 4.9, 3.5, 2.1, and 1.3, respectively, and the IC_{50} estimated as 50.3 µmol/L. *These results indicate that TAK-438 inhibits P-gp with an IC_{50} value of 50.3 µmol/L.* *Note: The potential for clinical inhibition of P-gp substrates is excluded based on the Applicant reported Igut/IC_{50} ratio of 4.6 at 20 mg unit dose.*	TAK-438-10807
Inhibitory effects of TAK-438 on BCRP transporter	Effects of TAK-438 on [^{3}H]prazosin (0.01 µmol/L) transport across BCRP-expressing monolayers (LLC-PK1) as well as control cells were examined to assess the inhibitory effect of TAK-438 (0, 1, 3, 10, 30, 100, and 300 µmol/L) on BCRP function. [^{14}C]Mannitol (10 µmol/L) was used as a paracellular marker and Ko143 (1 µmol/L) was used as a positive control.	TAK-438 affected the paracellular transport of [^{14}C]Mannitol at ≥ 300 µmol/L After incubation of [^{3}H]prazosin at 37°C for 1 and 2 h, in the presence of TAK-438, at concentrations of 0, 1, 3, 10, 30, 100, and 300 µmol/L, the Papp ratios were 9.9, 10.5, 10.6, 10.7, 9.0, 8.9, and 5.5 across the BCRP-expressing cells, and 1.2, 1.2, 1.1, 1.1, 1.1, 1.1, and 1.0 across control cells, respectively. The corrected Papp ratios were 8.3, 8.8, 9.6, 9.7, 8.2, 8.1, and 5.5, respectively. The percentages of control were 100.0%, 106.0%, 115.7%, 116.9%, 98.8%, 97.6%, and 66.3% respectively. Note: Percentage of control is defined as the percentage ratio of corrected Papp ratio in the presence and absence of TAK-438 or Ko143. *These results indicate that TAK-438 does not inhibit BCRP at concentrations up to 100 µmol/L.*	TAK-438-11346
Transport Study of [^{14}C]TAK-438 using OATP1B1 and OATP1B3 Expressing Cells	The uptake of [^{14}C]TAK-438 (0.3 µmol/L) after incubation at 37°C for 0.5, 1, 2, and 5 min, was evaluated using OATP1B1, 1B3-expressing HEK293 as well as control cells. Rifampicin (10 µmol/L) was used as an inhibitor and [^{3}H]$E_2$17βG (0.05 µmol/L) was used as a reference substrate.	The cleared volumes of [^{14}C]TAK-438 into OATP1B1- and OATP1B3-expressing cells were similar to those into control cells over the time examined. *These results indicate that TAK-438 is not a substrate of OATP1B1 or OATP1B3.*	TAK-438-1134

Objective	Test System	Summary Findings and Key Conclusions	Report
Inhibitory effects of TAK-438 on OATP1B1/1B3, OAT1/3, and OCT2 transporter	The inhibitory effects of TAK-438 (0, 0.3, 1, 3, 10, and 30 µmol/L) on the uptake of typical substrates, [^{3}H]$E_2$17βG (OATP1B1 and OATP1B3), [^{3}H]PAH (OAT1), [^{3}H]E3S, and [^{14}C]Metformin (OCT2) were evaluated using respective expressing cells and compared against control cells. For inhibitors, rifampicin (OATP1B1 and OATP1B3), probenecid (OAT1 and OAT3), and quinidine (OCT2) were used.	In the presence of TAK-438, at concentrations of 0, 0.3, 1, 3, 10, and 30 µmol/L: for OATP1B1, the percentages of control were 100.0, 95.7, 97.5, 100.1, 96.9, and 95.7%, respectively. for OATP1B3, the percentages of control were 100.0, 89.9, 100.0, 90.9, 100.6, and 81.7%, respectively. for OAT1, the percentages of control were 100.0, 84.7, 101.9, 102.3, 100.3, and 84.2%, respectively. for OAT3, the percentages of control were 100.0, 96.3, 95.0, 83.9, 61.1, and 58.1%, respectively. for OCT2, the percentages of control were 100.0, 96.4, 92.1, 91.9, 93.4, and 76.0%, respectively. Note: Percentage of control is defined as the percentage ratio of differences between cleared volume of transporter expressing and control cells in the presence versus absence of the inhibitor tested. *These results indicate that TAK-438 does not inhibit OATP1B1, OATP1B3, and OAT1at concentrations up to 30 µmol/L. TAK-438 has weak inhibitory potency against OAT3 and OCT2; however, the IC_{50} values could not be calculated.*	TAK-438-11345
Inhibitory effects of TAK-438 on MATE1, MATE2-K, and OCT1 SLC (uptake) transporters	The inhibitory effects of TAK-438 on the uptake of reference substrates Metformin (MATE1 and MATE2K) and sumatriptan (OCT1) were evaluated by determining their relative accumulation and comparing against control cells. Pyrimethamine (MATE1 and MATE2K) and verapamil (OCT1) were used as inhibitors.	TAK-438 is an in vitro inhibitor of the human MATE1 and OCT1 transporters with IC_{50} values of 11.79 µM and 2.196 µM, respectively. TAK-438 is not an in vitro inhibitor of the human MATE2-K transporter up to 20 µM. *These results indicate that TAK-438 shows concentration dependent inhibition of both MATE1 and OCT1.* *Note: The estimated maximal concentration of TAK-438 in human plasma is 0.15 µmol/L.*	Takeda-12-02

Source: Compiled by reviewer based on the in vitro study reports and clinical pharmacology study reports.
Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; DMEM, Dulbecco's Modified Eagle Medium; E3S, Estrone 3-sulfate; Glu, glucuronic acid; K_I, concentration at the 1/2 K_{Inact} ; k_{Inact}, maximum inactivation rate constant; NADPH, nicotinamide adenine dinucleotide phosphate; Papp, pulmonary artery proportional pulse pressure; P-gp, permeability glycoprotein; SULT, sulfotransferase; TAK-438, vonoprazan; TDI, time-dependent inhibitory

14.2. In Vivo Studies

Vonoprazan Single Ascending Dose Study (Study TAK-438_101)

Study Design

Study TAK-438_101 was a phase 1 single ascending dose (SAD) study that evaluated the safety, tolerability, and PK of TAK-438 in healthy male Western subjects. A total of 63 male subjects (Weight range: 58 to 92 kg, Age range: 18 to 39 years) were randomly assigned to Cohorts 1 to 7. Each cohort enrolled 9 subjects with 6 received assigned single does between 1 mg to 40 mg and 3 subjects received placebo. On Day 1 following dosing post 10-hour fast, 18 blood samples were collected for PK analysis between pre-dose and 48 hours post-dose. The collected blood samples were used to measure plasma concentrations of vonoprazan and its inactive metabolites M-I and M-II. In each cohort, the stomach pH was also monitored over a 24-hour period at baseline and over a 96-hour period following the administration of the study drug. Meals were consumed at 4 hours and 9 hours after dose.

Results

PK Results

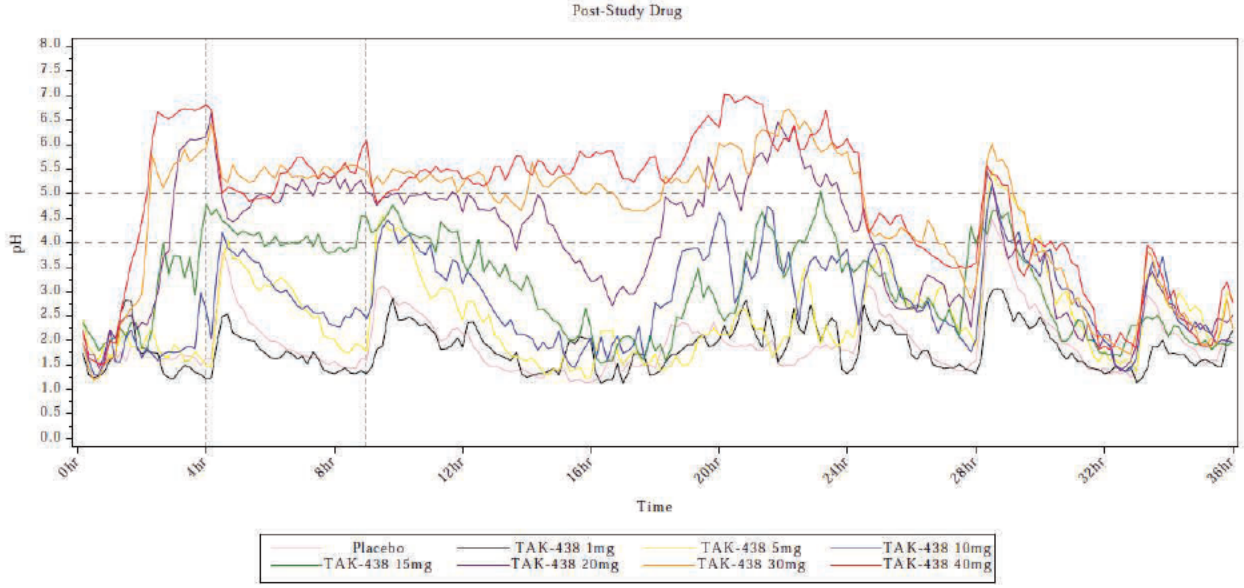
Table 89. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, and M-II

Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
1 mg (N=6)	3 (42)	0.4 (29)	2 (2-3)	7 (44)
5 mg (N=6)	26 (57)	4 (51)	2 (2-2)	8 (62)
10 mg (N=6)	50 (35)	7 (43)	2 (1-4)	8 (21)
15 mg (N=6)	97 (22)	14 (25)	2 (2-2)	7 (15)
20 mg (N=6)	149 (24)	22 (32)	2 (1-3)	8 (14)
30 mg (N=6)	246 (37)	37 (36)	2 (1-2)	8 (13)
40 mg (N=6)	391 (44)	50 (33)	2 (1-3)	8 (10)
M1				
1 mg (N=6)	10 (33)	3 (16)	1 (1-2)	4 (67)
5 mg (N=6)	100 (28)	15 (23)	1 (1-2)	7 (24)
10 mg (N=6)	174 (28)	28 (33)	1 (1-3)	7 (18)
15 mg (N=6)	372 (24)	52 (19)	1 (1-2)	9 (23)
20 mg (N=6)	422 (25)	58 (42)	1 (1-2)	10 (39)
30 mg (N=6)	572 (23)	80 (36)	1 (1-2)	12 (37)
40 mg (N=6)	792 (19)	102 (33)	1 (1-2)	10 (9)
M2				
1 mg (N=6)	BLQ	BLQ	BLQ	BLQ
5 mg (N=6)	10 (136)	1 (39)	8 (4-10)	11 (11)
10 mg (N=6)	15 (68)	2 (24)	5 (3-8)	11 (48)
15 mg (N=6)	32 (55)	3 (30)	5 (2-10)	9 (39)
20 mg (N=6)	45 (65)	3 (45)	4 (3-6)	10 (31)
30 mg (N=6)	73 (26)	5 (30)	5 (3-10)	11 (15)
40 mg (N=6)	102 (49)	6 (42)	4 (3-6)	15 (30)

Source: Study report
[a] Median [Range]
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; BLQ, below the lower limit of quantitation; C_{max}, maximum serum concentration; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

PD Results

Figure 6. Mean pH Time Profiles (0 to 36 Hours) in Single Rising Dose Study (Cohorts 1 to 7)



Note 1: Vertical dashed lines indicate that meals are consumed at 4 hours and 9 hours. Horizontal dashed lines indicate pH=4 and pH=5
Note 2: Due to a technical recording problem, Only pH data from 0 to 24 hours for subject (b)(6) are displayed
Note 3: Due to monitoring problems, pH data have not been fully collected for subject (b)(6)
Source: Figure 11.g, Clinical Study Report
Abbreviations: pH, potential of hydrogen

Conclusions

- The C_{max} and $AUC_{(0\text{-}24hr)}$ values for vonoprazan increased with TAK-438 dose escalation in a greater than dose proportional manner
- The $T_{1/2}$ estimates for vonoprazan were comparable across the single doses evaluated
- The M-I metabolite was present in plasma in greater quantities than the parent or M-II metabolite
- Overall increase in post-dose stomach pH was dose-dependent and the pharmacodynamic effect of vonoprazan started to wane after 24 hours, with all doses of vonoprazan returning to stomach pH profiles that were similar to placebo by the 32-hour time point

Vonoprazan SAD and Food Effect Study (Study TAK-438/CPH-001)

Study Design

Study TAK-438/CPH-001 was a phase 1 SAD study that evaluated the safety, tolerability, and PK of TAK-438 in healthy male Japanese subjects. A total of 108 healthy Japanese male subjects (Weight range: 51 to 85 kg, Age range: 20 to 42 years) were randomly assigned to a dose-escalation part and food-effect part. For the dose-escalation part, each of the 7 cohorts enrolled 12 subjects with 9 randomly assigned single doses between 1 mg to 120 mg and 3 subjects received placebo. In the food-effect part, 24 subjects were enrolled in 2 cohorts, with 8 subjects in each cohort receiving TAK-438 treatment and 4 subjects receiving placebo. TAK-438 treatments were administered as a single dose of 10 mg or 40 mg twice in two different periods (once with meal and once under fasting) with a wash out period of at least 13 days.

In both parts, 18 blood samples were collected for PK analysis between pre-dose and 48 hours post-dose. The collected blood samples were used to measure plasma concentrations of vonoprazan and its inactive metabolites M-I and M-II. In each cohort, the stomach pH was also monitored over a 24-hour period at baseline (once for the food-effect part) pre-dose and over a 24-hour period following the administration of study drug (twice for the food-effect part).

Results

PK Results

PK parameter estimates from the dose-escalation and food effect parts are summarized in Table 90. The AUC_{0-24} and C_{max} estimates from the food-effect part are also reported in Figure 7 that shows comparison of estimates with and without food.

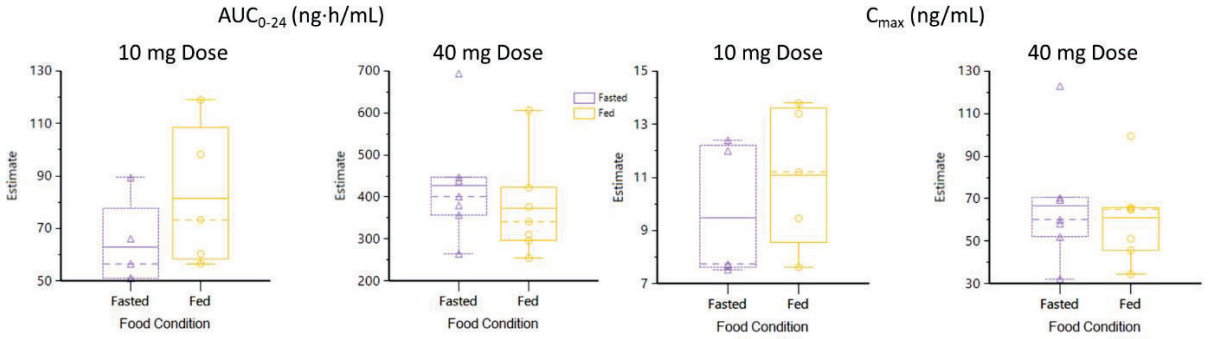
Table 90. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, and M-II

Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
1 mg (N=5)	3 (45)	1 (42)	2 (2-2)	5 (21)
5 mg (N=9)	27 (33)	4 (32)	2 (1-3)	8 (15)
10 mg (N=8)	56 (15)	9 (22)	2 (1-2)	7 (15)
20 mg (N=7)	145 (24)	24 (22)	2 (1-2)	7 (12)
40 mg (N=9)	415 (29)	68 (32)	2 (1-3)	7 (8)
80 mg (N=7)	774 (27)	124 (31)	2 (1-3)	9 (12)
120 mg (N=8)	1801 (19)	298 (21)	1 (1-2)	7 (11)
10 mg Fasted (N=5)[b]	61 (26)	9 (26)	2 (1-2)	9 (15)
10 mg After Meal (N=5)[b]	78 (33)	11 (24)	2 (1-3)	8 (14)
40 mg Fasted (N=7)[b]	359 (31)	58 (34)	2 (1-2)	7 (8)
40 mg After Meal (N=7)[b]	410 (31)	62 (42)	2 (1-4)	7 (14)
M1				
1 mg (N=5)	11 (29)	4 (29)	1 (1-2)	2 (24)
5 mg (N=9)	91 (17)	15 (14)	2 (1-3)	6 (53)
10 mg (N=8)	218 (11)	36 (17)	2 (1-3)	8 (22)
20 mg (N=7)	409 (19)	70 (18)	1 (1-2)	10 (29)
40 mg (N=9)	604 (16)	99 (20)	1 (1-2)	11 (16)
80 mg (N=7)	1085 (22)	167 (32)	1 (1-3)	11 (9)
120 mg (N=8)	1920 (19)	311 (16)	1 (1-2)	11 (23)
10 mg Fasted (N=5)[b]	204 (17)	33 (17)	2 (1-2)	9 (15)
10 mg After Meal (N=5)[b]	176 (20)	23 (10)	2 (2-3)	10 (23)
40 mg Fasted (N=7)[b]	786 (19)	126 (21)	2 (1-2)	9 (27)
40 mg After Meal (N=7)[b]	712 (20)	90 (14)	2 (1-3)	9 (20)

Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
M2				
1 mg (N=5)	BLQ	BLQ	BLQ	BLQ
5 mg (N=9)	BLQ	BLQ	BLQ	BLQ
10 mg (N=8)	21 (40)	2 (17)	3 (3-4)	23 (151)
20 mg (N=7)	63 (35)	5 (26)	4 (3-6)	8 (47)
40 mg (N=9)	88 (42)	6 (30)	4 (4-10)	9 (38)
80 mg (N=7)	182 (24)	11 (28)	4 (4-8)	10 (37)
120 mg (N=8)	276 (30)	17 (26)	4 (4-10)	11 (13)
10 mg Fasted (N=5)[b]	16 (58)	2 (27)	4 (2-10)	10 (27)
10 mg After Meal (N=5)[b]	11 (71)	2 (25)	4 (2-4)	9 (38)
40 mg Fasted (N=7)[b]	100 (24)	7 (14)	4 (3-8)	10 (48)
40 mg After Meal (N=7)[b]	81 (17)	6 (13)	4 (4-8)	10 (31)

Source: Reviewer's calculations from the data provided with the study report. The study report noted that plasma pharmacokinetic analysis excluded data from subject with at least one sample with hemolysis. Therefore, the Reviewer's analysis was performed using the same exclusion conditions.
[a] Median [Range]
[b] the food-effect part with cross-over study design
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; BLQ, below the lower limit of quantitation; C_{max}, maximum serum concentration; h, hours, T_{max}; N, number of subjects; time at which the C_{max} is observed; $T_{1/2}$, half-life

Figure 7. Comparison of Vonoprazan Exposures Following Oral Administration Under Fed and Fasted Conditions

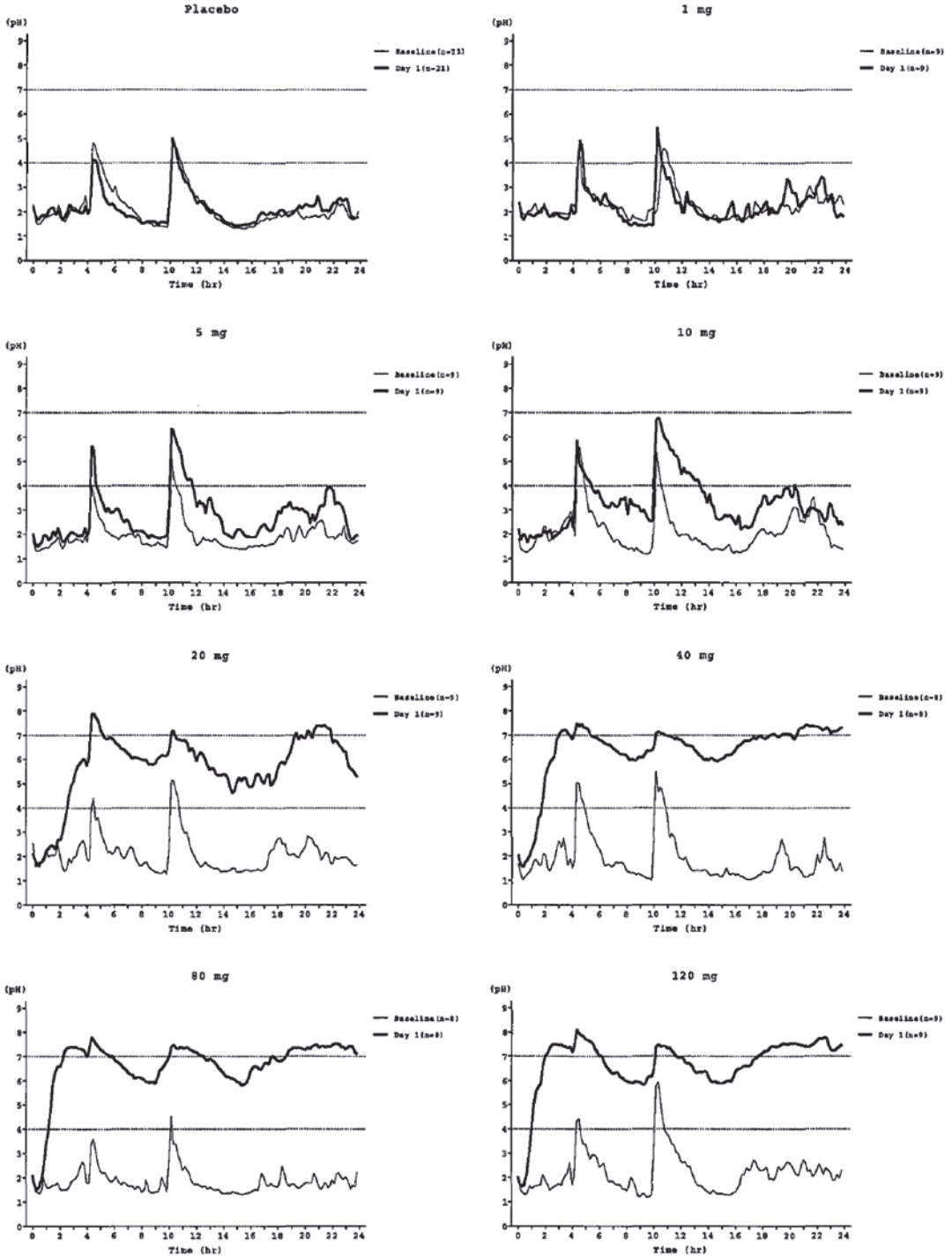


Source: Reviewer's calculations from the data provided with the study report.
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; h, hours

PD Results

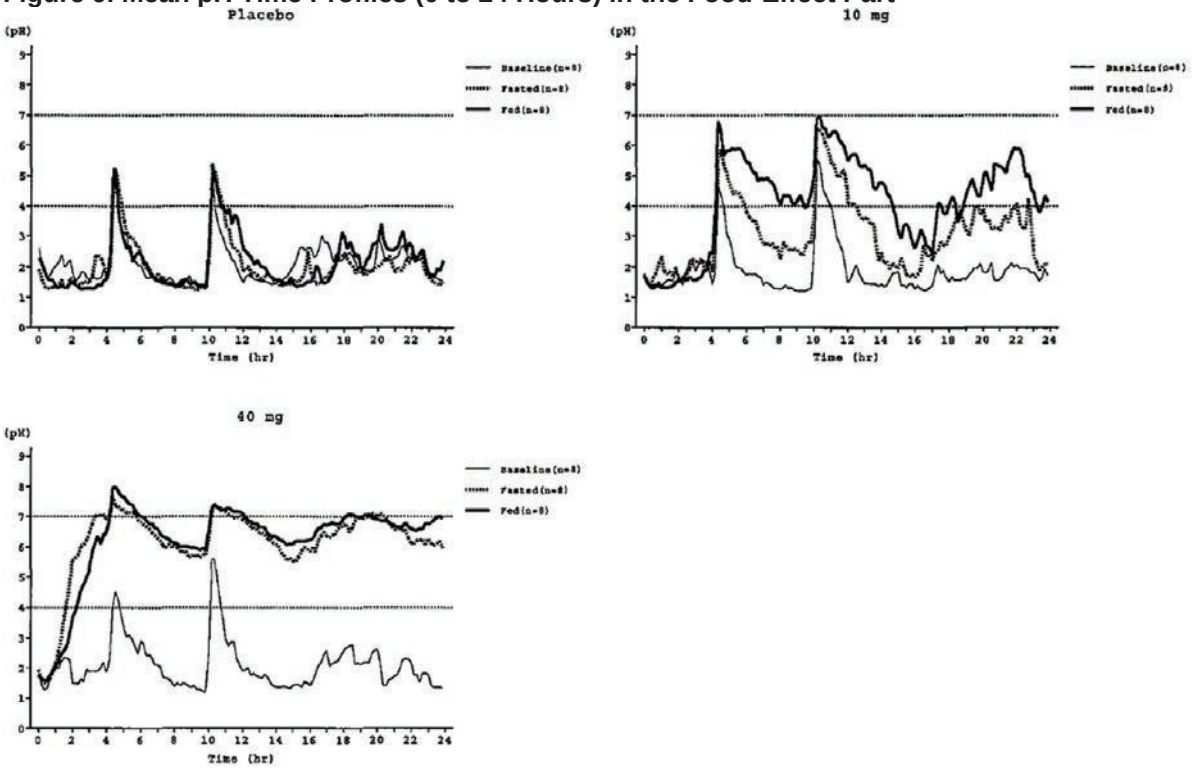
Mean pH time profiles (0 to 24 hours) in the dose-escalation part and the food effect parts are reported in Figure 8 and Figure 9, respectively.

Figure 8. Mean pH Time Profiles (0 to 24 Hours) in the Dose-Escalation Part



Source: Study Report
Abbreviations: pH, potential of hydrogen

Figure 9. Mean pH Time Profiles (0 to 24 Hours) in the Food-Effect Part



Source: Study Report
Abbreviations: pH, potential of hydrogen

Conclusions

- The single oral dose of TAK-438 was well tolerated over the doses ranging from 1 to 120 mg
- The C_{max} and $AUC_{(0\text{-}24hr)}$ values for vonoprazan increased with TAK-438 dose escalation in a greater than dose proportional manner
- The vonoprazan exposures were slightly increased when administered with a meal
- The ratios of M-1 to vonoprazan in AUC were decreased with dose increase, suggesting possible effect of saturated first-pass metabolism
- Overall increase in post-dose stomach pH was dose-dependent and the gastric acid secretion was suppressed resulting in gastric pH up to 7 at the TAK-438 doses from 20 mg to 120 mg

Vonoprazan Single Dose Food Effect Study (Study TAK-438_109)

Study Design

Study TAK438-109 was a single dose food effect study that evaluated the PK of TAK-438 in healthy male and female non-Japanese subjects. A total of 24 healthy male and female subjects (Weight range: 53 to 104 kg, Age range: 18 to 41 years) were randomly assigned to fed or fasted arm in a cross-over manner and two sequence of treatments. TAK-438 treatments were administered as a single dose of 20 mg twice in two different periods, once with meal (30 minutes after a high-fat breakfast) and once under fasting condition with a wash-out period of at least 6 days. The high-fat breakfast provided approximately 884 calories, with 551 calories (62%) from fat, 203 calories (23%) from carbohydrate and 124 calories (14%) from protein.

In both the parts, 18 blood samples were collected for PK analysis between pre-dose and 48 hours post-dose. The collected blood samples were used to measure plasma concentrations of vonoprazan and its metabolites M-I, M-II, M-III, and M-IV-Sul.

Results

PK Results

PK parameter estimates for vonoprazan and its metabolites are summarized in Table 91 by fasting status and in Table 92 by fasting status and sex. The % point estimates (90% confidence interval [CI]) for AUC_{0-24} and C_{max} by fasting status and by fasting status + sex are summarized in Table 93.

Table 91. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, M-II, M-III, and M-IV-Sul

Analyte/Dose/N=24	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
20 mg Fasted	174 (30)	18 (29)	4 (2-6)	7 (17)
20 mg Fed	154 (31)	17 (34)	2 (1-4)	7 (20)
M-I				
20 mg Fasted	324 (22)	32 (27)	4 (1-6)	9 (15)
20 mg Fed	357 (20)	54 (29)	1 (1-2)	9 (16)
M-II				
20 mg Fasted	37 (59)	3 (45)	6 (4-10)	9 (34)
20 mg Fed	43 (60)	4 (43)	4 (2-10)	10 (36)
M-III				
20 mg Fasted	106 (47)	14 (38)	4 (2-6)	7 (19)
20 mg Fed	120 (43)	21 (36)	2 (1-2)	7 (19)
M-IV_Sul				
20 mg Fasted	128 (38)	20 (33)	4 (2-6)	5 (32)
20 mg Fed	170 (36)	40 (28)	2 (1-2)	4 (40)

Source: Study report. The study report noted that plasma pharmacokinetic analysis excluded data from subject with at least one sample with hemolysis. Therefore, the Reviewer's analysis was performed using the same exclusion conditions.
[a] Median [Range]
[b] the food-effect part with cross-over study design
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; h, hours, CV. coefficient of variation; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

Table 92. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, M-II, M-III, and M-IV-Sul

Analyte/Dose/N=12	AUC0-24 (ng·h/mL)	Cmax (ng/mL)	Tmax (h)a	T1/2 (h)
Vonoprazan				
20 mg Fasted Male	165 (24)	18 (25)	2 (1-4)	7 (19)
20 mg Fasted Female	143 (37)	16 (41)	2 (2-4)	6 (15)
20 mg Fed Male	185 (24)	19 (16)	4 (2-4)	7 (16)
20 mg Fed Female	165 (35)	18 (39)	5 (4-6)	6 (15)
M-I				
20 mg Fasted Male	323 (15)	45 (25)	1 (1-2)	9 (18)
20 mg Fasted Female	395 (20)	64 (22)	1 (1-2)	8 (12)
20 mg Fed Male	288 (15)	29 (18)	3 (2-4)	9 (15)
20 mg Fed Female	365 (21)	35 (32)	4 (1-6)	8 (15)
M-II				
20 mg Fasted Male	36 (78)	3 (46)	4 (4-10)	11 (41)
20 mg Fasted Female	50 (33)	4 (29)	4 (2-4)	9 (29)
20 mg Fed Male	33 (63)	2 (47)	6 (4-10)	9 (47)
20 mg Fed Female	40 (58)	3 (39)	7 (4-10)	10 (25)
M-III				
20 mg Fasted Male	125 (45)	20 (39)	2 (1-2)	7 (14)
20 mg Fasted Female	116 (43)	22 (33)	2 (1-2)	6 (16)
20 mg Fed Male	111 (48)	14 (40)	4 (2-4)	7 (20)
20 mg Fed Female	101 (47)	14 (38)	4 (2-6)	6 (16)
M-IV_Sul				
20 mg Fasted Male	165 (31)	38 (21)	2 (1-2)	5 (38)
20 mg Fasted Female	174 (42)	42 (34)	2 (1-2)	4 (28)
20 mg Fed Male	125 (31)	20 (24)	3 (2-4)	5 (30)
20 mg Fed Female	131 (45)	21 (41)	4 (2-6)	4 (28)

Source: Study report. The study report noted that plasma pharmacokinetic analysis excluded data from subject with at least one sample with hemolysis. Therefore, the Reviewer's analysis was performed using the same exclusion conditions.
[a] Median [Range]
[b] the food-effect part with cross-over study design
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

Table 93. Summary of the Effect of Food and Sex on Bioavailability Assessment

	% Point Estimates (90% CI)	
Parameters	**Fed/Fasting**	**Female/Male-Fasting, Female/Male-Fed**
Vonoprazan		
AUC_{0-24}	113 (109-118)	87 (70-108), 89 (72-110)
C_{max}	105 (98-112)	88 (70-111), 95 (77-117)
M-I		
AUC_{0-24}	91 (88-94)	122 (108-138), 126 (111-144)
C_{max}	59 (55-64)	141 (122-162), 119 (100-143)
M-II		
AUC_{0-24}	78 (71-86)	138 (94-203), 118 (77-179)
C_{max}	78 (73-82)	147 (113-192), 130 (97-175)
M-III		
AUC_{0-24}	88 (85-91)	92 (68-125), 91 (66-126)
C_{max}	67 (63-71)	111 (87-143), 101 (78-132)

	% Point Estimates (90% CI)	
Parameters	**Fed/Fasting**	**Female/Male-Fasting, Female/Male-Fed**
M-IV-Sul		
AUC_{0-24}	75 (72-79)	106 (82-136), 105 (81-136)
C_{max}	51 (48-54)	112 (92-135), 107 (85-135)

Source: Reviewer's calculations from the data provided with the study report.
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; CI, confidence interval; C_{max}, maximum serum concentration

Conclusions

- Vonoprazan exposures are not affected by food when administered with a high-fat meal
- No clinically relevant effect of food was observed on the PK of the vonoprazan metabolites M-I, M-II, M-III, and M-IV Sul.
- Vonoprazan AUC estimates were on average 16% lower and C_{max} estimates were 22% lower in female subjects than in male subjects. This decrease in exposure in females is not considered clinically relevant.
- The observed exposure to vonoprazan metabolites in females was qualitatively the same or lower than in male subjects and is not considered to be clinically relevant.

Reviewer's Assessment:

- The Applicant's conclusion related to the observed reduced exposure in females is not considered clinically relevant, the Applicant has not provided any specific PK/pharmacodynamic (PD) data to support this conclusion. However, it is noteworthy that the pivotal efficacy study (Study HP-301) findings do not suggest any differences in efficacy response rate between males and females. Specifically, in the combined results for the modified intent-to-treat (mITT) population of Study HP-301, response rates in females were 12.2% (95% CI= 4.78, 19.70) and in males were 7.6% (-1.98, 17.25). In the same study, the difference in response rates compared to vonoprazan triple therapy versus lansoprazole triple therapy in females were 13.1% (4.87, 21.34) and in males were 10.9% (0.13, 21.68). In addition, the effect of sex on vonoprazan was further evaluated via population PK model. See Section 14.3 for additional details.
- The Applicant's conclusion related that the observed exposure to vonoprazan metabolites in females was qualitatively the same or lower than in male subjects is not accurate. Estimates from the Reviewer's analyses (Table 93) showed that on average, the metabolites' exposures were higher in females than males. However, given that the metabolites are inactive, the conclusion that these findings are clinically irrelevant is reasonable.

Vonoprazan Multiple Ascending Dose Study (Study TAK-438_107)

Study Design

Study TAK-438_107 was a phase 1 multiple ascending dose (MAD) study that evaluated the safety, tolerability, and PK of TAK-438 in healthy male non-Japanese subjects. A total of 48 male subjects (Weight range: 58 to 91 kg, Age range: 18 to 45 years) were randomly assigned to Cohorts 1 to 4. Each cohort enrolled 12 subjects with 9 randomly assigned multiple doses from 10 mg to 40 mg and 3 subjects received placebo once daily (QD) for 7 days. On days 1 and 7 following dosing, 16 blood samples were collected for PK analysis between pre-dose and 48

hours post-dose. On days 4, 5, and 6, pre-dose PK samples were collected. The collected blood samples were used to measure plasma concentrations of vonoprazan and its inactive metabolites M-I, M-II, M-III, and M-IV-Sul. In each cohort, the stomach pH was also monitored over a 24-hour period at baseline, 24 hours postdose on Day 1, 24 hours on Day 4, and 8 hours postdose on Day 7, and over a 96-hour period following the administration of study drug. Meals were consumed at 4, 9, and 12 hours postdose.

Results

PK Results

Table 94. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, and M-II

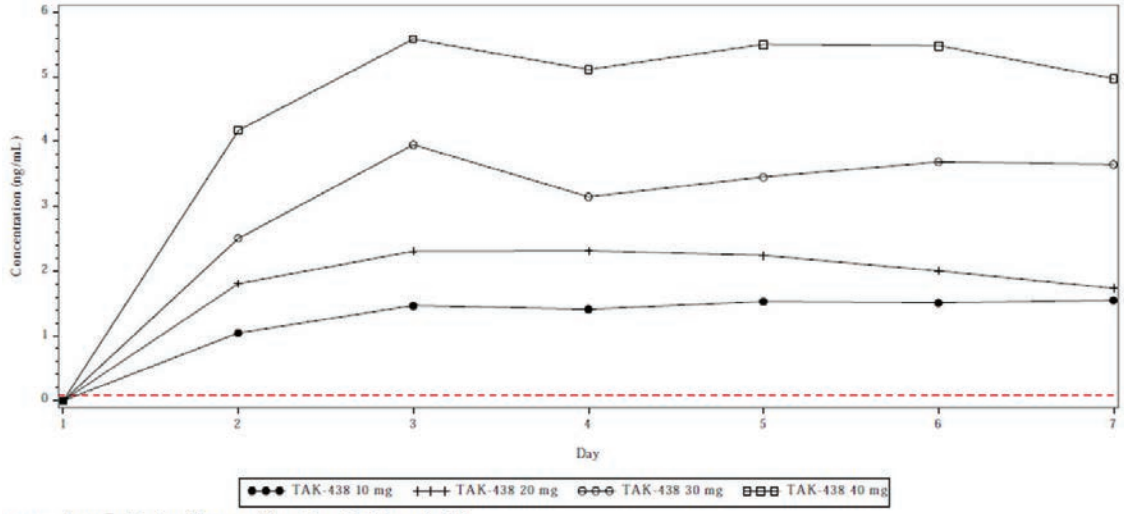
Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
10 mg (N=9) Day 1	76 (44)	10 (54)	2 (1-3)	7 (18)
10 mg (N=9) Day 7	97 (46)	12 (39)	2 (1-2)	8 (38)
20 mg (N=9) Day 1	158 (52)	23 (57)	2 (1-2)	7 (22)
20 mg (N=9) Day 7	186 (35)	24 (44)	1 (1-2)	8 (20)
30 mg (N=9) Day 1	250 (22)	36 (31)	2 (1-4)	6 (6)
30 mg (N=9) Day 7	327 (30)	40 (30)	2 (1-4)	9 (13)
40 mg (N=9) Day 1	408 (28)	58 (20)	2 (1-2)	6 (10)
40 mg (N=9) Day 7	472 (28)	58 (29)	2 (1-4)	8 (9)
M-I				
10 mg (N=9) Day 1	163 (31)	24 (40)	2 (1-2)	10 (33)
10 mg (N=9) Day 7	190 (33)	24 (43)	1 (1-2)	11 (41)
20 mg (N=9) Day 1	321 (25)	51 (23)	1 (1-2)	9 (30)
20 mg (N=9) Day 7	364 (27)	52 (30)	1 (1-2)	9 (25)
30 mg (N=9) Day 1	571 (14)	81 (24)	1 (1-2)	9 (17)
30 mg (N=9) Day 7	641 (14)	81 (23)	1 (1-3)	11 (14)
40 mg (N=9) Day 1	755 (23)	107 (23)	1 (1-2)	9 (12)
40 mg (N=9) Day 7	800 (19)	102 (20)	1 (1-1)	10 (13)
M-II				
10 mg (N=9) Day 1	18 (76)	2 (39)	4 (2-16)	13 (61)
10 mg (N=9) Day 7	22 (94)	2 (47)	4 (3-6)	11 (30)
20 mg (N=9) Day 1	43 (37)	4 (30)	4 (3-8)	10 (27)
20 mg (N=9) Day 7	67 (31)	5 (28)	4 (2-8)	11 (28)
30 mg (N=9) Day 1	70 (32)	5 (29)	4 (3-6)	11 (26)
30 mg (N=9) Day 7	102 (25)	7 (21)	4 (3-10)	12 (19)
40 mg (N=9) Day 1	100 (28)	6 (32)	4 (2-10)	12 (22)
40 mg (N=9) Day 7	146 (32)	9 (26)	4 (3-6)	11 (25)

Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
M-III				
10 mg (N=9) Day 1	58 (37)	11 (39)	2 (1-4)	6 (47)
10 mg (N=9) Day 7	67 (34)	11 (33)	2 (1-2)	7 (30)
20 mg (N=9) Day 1	129 (36)	22 (22)	2 (1-3)	6 (14)
20 mg (N=9) Day 7	149 (22)	24 (21)	2 (1-3)	7 (26)
30 mg (N=9) Day 1	180 (26)	31 (22)	2 (1-2)	5 (14)
30 mg (N=9) Day 7	225 (21)	35 (17)	2 (1-4)	7 (20)
40 mg (N=9) Day 1	319 (21)	48 (11)	2 (1-2)	5 (10)
40 mg (N=9) Day 7	378 (19)	53 (9)	2 (2-3)	6 (25)
M-IV-Sul				
10 mg (N=9) Day 1	70 (40)	18 (39)	2 (2-2)	4 (74)
10 mg (N=9) Day 7	70 (49)	15 (51)	2 (2-2)	5 (65)
20 mg (N=9) Day 1	147 (47)	35 (41)	2 (1-2)	5 (49)
20 mg (N=9) Day 7	146 (41)	30 (35)	2 (2-3)	5 (30)
30 mg (N=9) Day 1	285 (27)	63 (16)	2 (2-2)	6 (10)
30 mg (N=9) Day 7	309 (31)	60 (12)	2 (1-4)	7 (10)
40 mg (N=9) Day 1	477 (51)	98 (43)	2 (2-2)	5 (10)
40 mg (N=9) Day 7	447 (41)	84 (32)	2 (2-2)	6 (24)

Source: Study report
[a] Median [Range]
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

Mean pre-dose vonoprazan concentrations over the treatment duration of 7 days are presented in Figure 10. The $AUC_{(0-24)}$ and C_{max} for vonoprazan were demonstrated to increase with TAK-438 dose escalation in a dose-proportional manner, with slopes of 1.15 and 1.16, respectively on Day 7. The $AUC_{(0-24)}$ and C_{max} for each of the metabolites (M-I, M-II, M-III, and M-IV-Sul) also increased with TAK-438 dose escalation in a dose-proportional manner, with slopes ranging from 1.07 to 1.36 and from 1.05 to 1.25, respectively.

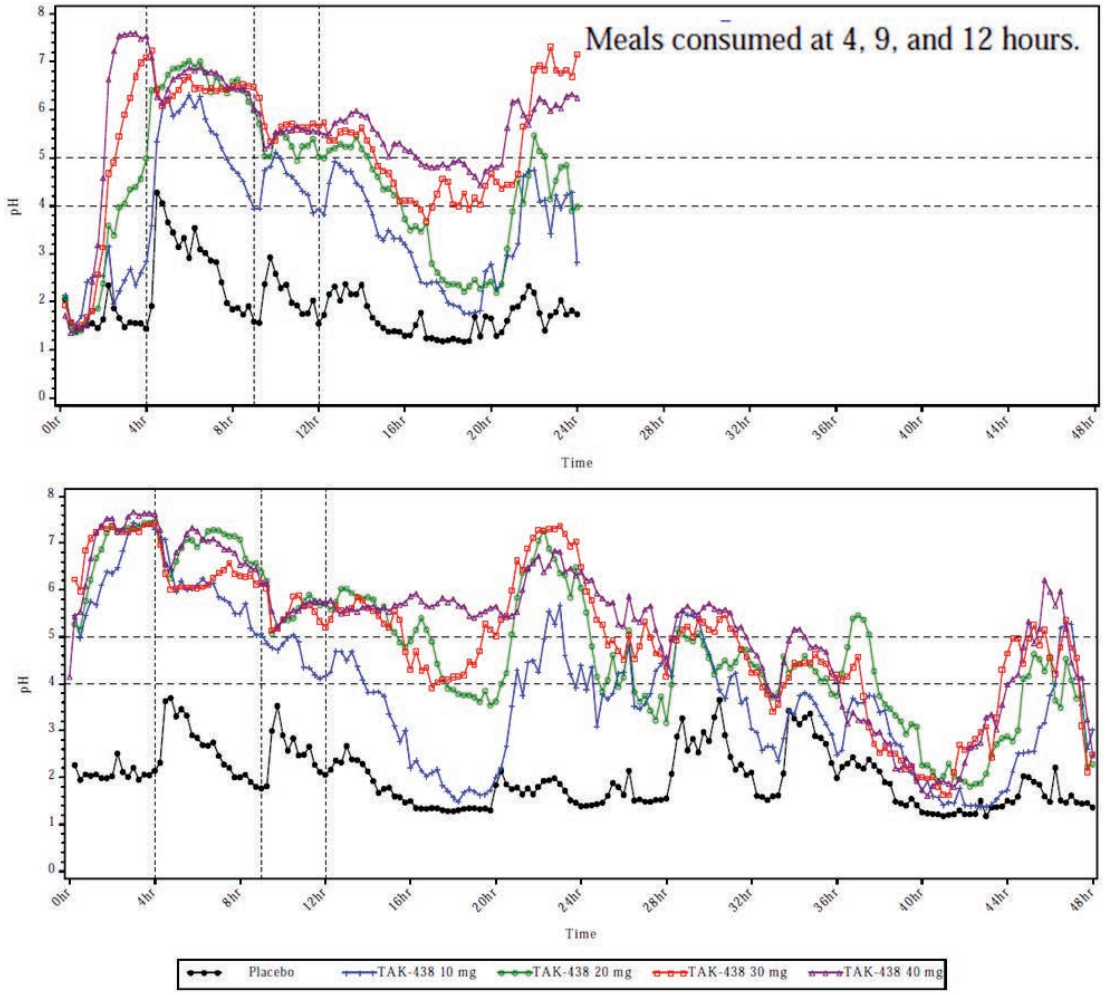
Figure 10. Mean Predose Plasma Concentrations of Vonoprazan on Days 1 Through 7



----- =lower limit of quantification (0.10 ng/mL).
Source: Study report

PD Results

Figure 11. Mean Intragastric pH Versus Time Profiles After Single Dose (Day 1) and Multiple Doses Da 7



Source: Study report

Conclusions

- The $AUC_{(0\text{-}24)}$ and C_{max} estimates for vonoprazan increased in a dose-proportional manner, with slopes of 1.15 and 1.16, respectively on Day 7.
- The $AUC_{(0\text{-}24)}$ and C_{max} estimates of the metabolites (M-I, M-II, M-III, and M-IV-Sul) also increased with vonoprazan in a dose-proportional manner, with slopes ranging from 1.07 to 1.36 and 1.05 to 1.25, respectively.
- The accumulation values indicate that vonoprazan and its metabolites M-I, M-II, M-III, and M-IV-Sul do not accumulate to any clinically relevant degree.
- Steady state was achieved by Day 4 for vonoprazan and its metabolites M-I, M-II, M-III, and M-IV-Sul at doses of TAK-438 ranging from 10 to 40 mg.
- The increase in gastric pH was observed dose-dependently, and reached a maximum at the TAK-438 40-mg dose on Day 7. The higher dose groups, TAK-438 20, 30, and 40 mg, each showed a clear elevation in pH levels compared with placebo.

- The pharmacodynamic effect of TAK-438 started to wane between 24 and 48 hours after multiple dosing on Day 7, but the pH levels did not reach the placebo pH level.

Vonoprazan Multiple Ascending Dose Study (TAK-438/CPH-002)

Study Design

Study TAK-438/CPH-002 was a phase 1 MAD study that evaluated the safety, tolerability, and PK of TAK-438 in healthy male Japanese subjects. A total of 60 male subjects (Wt range: 51 to 79 kg, Age range: 20 to 45 years) were randomly assigned to Cohorts 1 to 5. Each cohort enrolled 12 subjects with 9 received assigned multiple doses from 10 mg to 40 mg and 3 subjects received placebo QD for 7 days. On days 1 and 7 following dosing, up to 15 blood samples were collected for PK analysis between pre-dose and 24 hr post-dose. The collected blood samples were used to measure plasma concentrations of vonoprazan and its inactive metabolites and M-I, M-II, M-III, and M-IV-Sul. In each cohort, the stomach pH was also monitored over a 24-hour period at baseline as well as 24 hours postdose on Day 1 and on Day 7. and over a 96-hour period following the administration of study drug. Meals were consumed at 4, 10, and 13 hours postdose.

Results

PK Results

Table 95. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, and M-II

Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
10 mg (N=9) Day 1	60 (25)	10 (22)	2 (1-3)	7 (25)
10 mg (N=9) Day 7	78 (22)	12 (16)	2 (1-3)	7 (22)
15 mg (N=9) Day 1	92 (36)	15 (33)	2 (1-3)	6 (12)
15 mg (N=9) Day 7	108 (32)	17 (33)	2 (1-2)	6 (14)
20 mg (N=9) Day 1	117 (29)	19 (36)	2 (2-3)	6 (18)
20 mg (N=9) Day 7	147 (27)	22 (31)	2 (1-3)	6 (19)
30 mg (N=9) Day 1	222 (30)	36 (39)	2 (1-3)	6 (13)
30 mg (N=9) Day 7	277 (35)	46 (38)	2 (1-2)	6 (12)
40 mg (N=9) Day 1	358 (48)	57 (44)	2 (1-2)	7 (26)
40 mg (N=9) Day 7	437 (34)	71 (37)	2 (1-3)	6 (18)
M-I				
10 mg (N=9) Day 1	200 (18)	34 (23)	1 (1-2)	11 (56)
10 mg (N=9) Day 7	236 (23)	39 (25)	2 (1-3)	11 (25)
15 mg (N=9) Day 1	316 (17)	50 (22)	2 (1-2)	8 (25)
15 mg (N=9) Day 7	330 (17)	53 (25)	1 (1-3)	10 (34)
20 mg (N=9) Day 1	438 (23)	73 (25)	1 (1-2)	9 (20)
20 mg (N=9) Day 7	472 (17)	72 (21)	2 (1-2)	9 (27)
30 mg (N=9) Day 1	535 (17)	93 (14)	1 (1-3)	9 (39)
30 mg (N=9) Day 7	635 (16)	87 (17)	2 (1-2)	10 (25)
40 mg (N=9) Day 1	721 (26)	121 (28)	1 (1-2)	11 (38)
40 mg (N=9) Day 7	818 (23)	129 (25)	2 (1-3)	12 (20)

Analyte/Dose	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
M-II				
10 mg (N=9) Day 1	19 (55)	3 (31)	3 (2-10)	8 (54)
10 mg (N=9) Day 7	33 (80)	3 (40)	4 (3-12)	10 (56)
15 mg (N=9) Day 1	39 (37)	4 (28)	4 (3-6)	10 (41)
15 mg (N=9) Day 7	57 (33)	5 (26)	4 (2-10)	8 (28)
20 mg (N=9) Day 1	67 (25)	6 (24)	4 (3-4)	8 (29)
20 mg (N=9) Day 7	87 (20)	7 (14)	4 (4-6)	8 (39)
30 mg (N=9) Day 1	92 (40)	7 (32)	4 (3-10)	12 (20)
30 mg (N=9) Day 7	134 (42)	10 (35)	4 (3-8)	10 (24)
40 mg (N=9) Day 1	104 (31)	8 (23)	4 (2-10)	12 (35)
40 mg (N=9) Day 7	153 (25)	10 (24)	4 (4-4)	12 (28)
M-III				
10 mg (N=9) Day 1	68 (30)	14 (34)	2 (1-3)	5 (27)
10 mg (N=9) Day 7	83 (29)	15 (26)	2 (1-3)	5 (20)
15 mg (N=9) Day 1	100 (15)	20 (17)	2 (2-3)	5 (10)
15 mg (N=9) Day 7	110 (16)	20 (17)	2 (1-3)	5 (15)
20 mg (N=9) Day 1	127 (23)	25 (15)	2 (1-3)	5 (14)
20 mg (N=9) Day 7	159 (21)	28 (12)	2 (2-3)	5 (8)
30 mg (N=9) Day 1	240 (22)	41 (13)	2 (2-4)	5 (14)
30 mg (N=9) Day 7	279 (21)	44 (18)	2 (2-3)	5 (15)
40 mg (N=9) Day 1	292 (43)	48 (20)	2 (2-2)	6 (24)
40 mg (N=9) Day 7	372 (33)	56 (17)	2 (2-3)	5 (17)
M-IV-Sul				
10 mg (N=9) Day 1	89 (29)	24 (24)	2 (1-3)	3 (39)
10 mg (N=9) Day 7	92 (33)	23 (27)	2 (1-3)	4 (52)
15 mg (N=9) Day 1	145 (30)	39 (29)	2 (2-2)	3 (44)
15 mg (N=9) Day 7	144 (37)	36 (26)	2 (1-3)	4 (46)
20 mg (N=9) Day 1	182 (19)	47 (19)	2 (2-2)	4 (35)
20 mg (N=9) Day 7	190 (17)	46 (11)	2 (2-2)	5 (23)
30 mg (N=9) Day 1	325 (19)	79 (17)	2 (2-3)	5 (24)
30 mg (N=9) Day 7	300 (20)	65 (24)	2 (2-3)	6 (34)
40 mg (N=9) Day 1	422 (43)	99 (34)	2 (2-3)	5 (34)
40 mg (N=9) Day 7	409 (39)	84 (35)	2 (2-3)	7 (21)

Source: Study report
[a] Median [Range]
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

PD Results

The numerical findings from the study report suggests PD findings are similar to findings in Study TAK-438_107, i.e., intragastric pH values increased dose-dependently following TAK-438 administration at 10 to 40 mg and indicated the highest level at 40-mg dose of TAK-438 on Days 1 and 7.

Conclusions

- The magnitude of the increases in vonoprazan exposures were slightly more than the dose ratio: 2 times of the dose produced approximately 2.4 times of both C_{max} and $AUC_{(0\text{-}inf)}$ on Day 1, and 2.5 times of C_{max} and 2.4 times of $AUC_{(0\text{-}tau)}$ on Day 7.
- The $AUC_{(0\text{-}24)}$ and C_{max} estimates of the metabolites (M-I, M-II, M-III, and M-IV-Sul) increased with vonoprazan in a dose-proportional manner.
- The intragastric pH values increased dose-dependently following TAK-438 administration at 10 to 40 mg and indicated the highest level at the 40-mg dose of TAK-438 on Days 1 and 7.

Vonoprazan Single and Multiple Ascending Dose Study (TAK-438_114)

Study Design

Study TAK-438_114 was a phase 1 single and multiple ascending dose study that evaluated the safety, tolerability, and PK of TAK-438 in healthy Chinese subjects. A total of 33 subjects (Weight range: 50 to 80 kg, Age range: 18 to 33 years) were enrolled in the study and were assigned to 10 mg QD (n=12) or 20 mg QD (n=11), or 20 mg twice daily (BID) (n=10) treatment arm. On Day 1, a single TAK-438 oral dose of 10 mg (n=12) or 20 mg (n=11+10) was administered, and 17 blood samples were collected over 48 hours for PK assessments. On Day 3 through Day 9, subjects received their assigned daily dose(s) of TAK-438 followed by another PK sampling period of 48 hours (17 samples collected from subjects on a QD regimen), or 12 hours (13 samples collected from subjects on the BID regimen) on Day 9. The collected blood samples were used to measure plasma concentrations of vonoprazan and its inactive metabolites and M-I, M-II, M-III, and M-IV-Sul.

Results:

PK Results

Table 96. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, and M-II

Analyte/Dose	$AUC_{0\text{-}12}$ (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
10 mg QD (N=12) Day 1	72 (33)	9 (33)	2 (1-4)	8 (16)
10 mg QD (N=12) Day 9	90 (30)	10 (32)	2 (1-3)	8 (9)
20 mg QD (N=11) Day 1	164 (22)	18 (25)	2 (1-4)	7 (18)
20 mg QD (N=11) Day 9	205 (27)	23 (26)	2 (1-3)	7 (10)
20 mg BID (N=10) Day 1	150 (25)	24 (40)	3 (1-4)	7 (14)
20 mg BID (N=10) Day 9	264 (26)	36 (29)	3 (1-4)	5 (20)
M-I				
10 mg QD (N=12) Day 1	241 (31)	37 (22)	2 (1-2)	10 (38)
10 mg QD (N=12) Day 9	277 (27)	42 (22)	2 (1-2)	9 (17)
20 mg QD (N=11) Day 1	502 (35)	64 (34)	2 (1-3)	9 (31)
20 mg QD (N=11) Day 9	556 (34)	77 (28)	1 (1-2)	8 (9)
20 mg BID (N=10) Day 1	333 (26)	57 (31)	2 (1-4)	8 (16)
20 mg BID (N=10) Day 9	426 (21)	58 (26)	3 (1-10)	13 (82)

Analyte/Dose	AUC_{0-12} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
M-II				
10 mg QD (N=12) Day 1	26 (59)	3 (37)	4 (3-10)	10 (41)
10 mg QD (N=12) Day 9	41 (52)	3 (42)	4 (3-6)	10 (27)
20 mg QD (N=11) Day 1	65 (71)	5 (54)	6 (3-10)	11 (56)
20 mg QD (N=11) Day 9	95 (49)	6 (40)	3 (3-10)	12 (33)
20 mg BID (N=10) Day 1	38 (46)	4 (46)	10 (3-12)	10 (29)
20 mg BID (N=10) Day 9	97 (28)	9 (31)	4 (0-10)	25 (70)
M-III				
10 mg QD (N=12) Day 1	83 (35)	15 (25)	2 (1-2)	7 (21)
10 mg QD (N=12) Day 9	91 (31)	16 (25)	2 (1-3)	7 (16)
20 mg QD (N=11) Day 1	159 (35)	25 (31)	2 (2-3)	7 (16)
20 mg QD (N=11) Day 9	187 (28)	29 (24)	2 (2-3)	7 (13)
20 mg BID (N=10) Day 1	145 (25)	25 (23)	2 (2-4)	6 (19)
20 mg BID (N=10) Day 9	217 (22)	32 (19)	3 (2-4)	4 (25)
M-IV-Sul				
10 mg QD (N=12) Day 1	121 (34)	28 (18)	2 (1-2)	4 (51)
10 mg QD (N=12) Day 9	112 (32)	25 (14)	2 (1-3)	6 (23)
20 mg QD (N=11) Day 1	284 (29)	58 (27)	2 (2-3)	5 (36)
20 mg QD (N=11) Day 9	250 (25)	52 (26)	2 (2-2)	5 (40)
20 mg BID (N=10) Day 1	186 (30)	41 (22)	2 (2-3)	6 (22)
20 mg BID (N=10) Day 9	219 (23)	39 (18)	3 (2-4)	5 (53)

Source: Study report
[a] Median [Range]
Abbreviations: AUC_{0-12}, area under the concentration versus time curve up to 12-hr timepoint; BID, twice daily C_{max}, maximum serum concentration; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life, QD, once daily

Conclusions

- Vonoprazan exposures (C_{max}, and AUC) increased proportionally with increasing doses from 10 mg to 20 mg.
- Steady state was achieved by Day 5 and exhibited time independent PK.
- With QD administration, mean accumulation ratios ranged from 1.25 to 1.32 for C_{max} and 1.28 to 1.29 for AUC.
- With BID administration, mean accumulation ratios were 1.58 for C_{max} and 1.78 for AUC.

Mass Balance and Excretion Study of [14C]TAK-438 (Study TAK-438_103)

Study Design

Study TAK-438_103 was a phase 1 study that evaluated the ADME of TAK-438 and its major metabolites following a single oral 20-mg dose of [^{14}C]TAK-438 in 6 healthy male subjects (weight range: 63 to 83 kg, age range: 30 to 55 years). On Day 1, subjects received a total dose of 20 mg TAK-438 (containing approximately 44 μCi [1.62 MBq] of [^{14}C]TAK-438) orally in the morning, followed by sampling to determine pharmacokinetics and radioactivity in blood, feces, and urine. In total, 22 blood and 10 urine samples were collected for the pharmacokinetic analysis of vonoprazan and its metabolites from dosing to 120 hours post-dose. For metabolite profiling, 7 additional blood and urine samples were collected over 24 hours post-dose. Feces samples were collected for up to 168 hours post-dose. Concentrations of total radioactivity in

plasma, red blood cells, and whole blood were calculated and expressed as ng.Eq/mL or dpm/mL. Amounts of radioactivity in excreta and total recovered radioactivity were expressed as a percentage of the radioactive dose.

Results and Conclusions

- The overall mean recovery of radioactivity in urine+feces was 98.47% (67.38% of the dose excreted in urine and 31.08% excreted in feces).
- Plasma 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 plasma radioactivity.
- Mean plasma to whole blood ratio was approximately 1.6.
- Of the total radioactivity in urine, vonoprazan and its metabolites M-I, M-I-G, M-II, M-III, and M-IV-Sul accounted for 12.0%, 2.8%, 20.6%, 0.1%, 1.1%, and 11.4%, respectively. The remaining 52.0% of the total radioactivity recovered in urine was attributed to other components (not specified).
- Of the total radioactivity in feces, vonoprazan and its metabolites M-I, M-I-G, M-II, M-III, and M-IV-Sul accounted for 4.4%, 1.0%, not detected, 0.2%, 2.4%, and 15.9%, respectively. The remaining 76.1% of the total radioactivity recovered in feces was attributed to other components (not specified).

Vonoprazan PK in Subjects with Renal Impairment Study TAK-438_113

Study Design

Study TAK-438_113 evaluated the effect of renal impairment on the PK of vonoprazan and its metabolites following a single dose of 20 mg TAK-438. A total of 45 subjects (weight range: 50 to 113 kg, age range: 39 to 74 years) were enrolled in five different groups noted in Table 97 below.

Table 97. Renal Impairment Groups for Study Enrollment

Group	Renale Function	eGFR	No. of Subjects
A	Normal renal function	eGFR ≥90 mL/min/1.73 m^2	13
B	Mild renal impairment	eGFR 60-89 mL/min/1.73 m^2	8
C	Moderate renal impairment	eGFR 30-59 mL/min/1.73 m^2	8
D	Severe renal impairment	eGFR 15-29 mL/min/1.73 m^2	8
E	ESRD requiring dialysis	eGFR <15 mL/min/1.73 m^2	8

Source: Study report
Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease

Subjects enrolled in all groups received a single dose on Day 1 after an overnight fast of at least 10 hours. Subjects enrolled in Groupe E received an additional single dose at least 5 days after the first dose and underwent dialysis 2 hours post dose. On both days, 22 PK samples were collected over a period of up to 120 hours post dose. During hemodialysis, five ex vitro blood samples were collected from the blood flowing to the dialyzer (inflow tract) and from the dialyzer to the subject (outflow tract). Both plasma and dialysate samples were analyzed for vonoprazan and its metabolites, M-I, M-II, M-III, and M-IV-Sul. Protein binding of vonoprazan in plasma was assessed for each subject using [^{14}C]TAK-438 and the blood sample collected predose.

Results:

PK Results

Table 98. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, M-II, M-III, and M-IV-Sul

Renal Function	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
Normal (N=13)	104 (29)	13 (37)	2 (1-3)	9 (26)
Mild impairment (N=8)	164 (24)	17 (40)	2 (1-3)	12 (21)
Moderate impairment (N=8)	128 (41)	15 (61)	2 (1-3)	11 (23)
Severe impairment (N=8)	221 (44)	23 (34)	1 (1-4)	13 (21)
ESRD (no dialysis) (N=8)	125 (57)	15 (36)	2 (1-2)	11 (34)
ESRD (dialysis) (N=8)	123 (52)	17 (53)	2 (1-2)	11 (31)
M-I				
Normal (N=13)	309 (26)	49 (33)	1 (1-2)	10 (33)
Mild impairment (N=8)	344 (23)	52 (18)	1 (1-2)	12 (25)
Moderate impairment (N=8)	388 (28)	56 (34)	2 (1-2)	12 (20)
Severe impairment (N=8)	393 (40)	39 (40)	1 (1-2)	14 (19)
ESRD (no dialysis) (N=8)	426 (11)	49 (34)	2 (1-3)	12 (18)
ESRD (dialysis) (N=8)	424 (17)	45 (35)	1 (1-4)	13 (17)
M-II				
Normal (N=13)	40 (41)	3 (44)	4 (2-6)	8 (106)
Mild impairment (N=8)	52 (45)	4 (37)	5 (3-5)	11 (42)
Moderate impairment (N=8)	42 (57)	3 (58)	4 (3-6)	15 (119)
Severe impairment (N=8)	37 (37)	2 (40)	10 (3-16)	25 (50)
ESRD (no dialysis) (N=8)	38 (34)	2 (40)	4 (2-12)	16 (68)
ESRD (dialysis) (N=8)	37 (44)	2 (47)	8 (2-16)	34 (194)
M-III				
Normal (N=13)	111 (31)	20 (27)	2 (1-4)	8 (22)
Mild impairment (N=8)	168 (32)	25 (14)	2 (2-2)	10 (27)
Moderate impairment (N=8)	103 (29)	18 (30)	2 (1-2)	9 (30)
Severe impairment (N=8)	122 (41)	15 (20)	2 (1-3)	11 (22)
ESRD (no dialysis) (N=8)	80 (63)	14 (37)	2 (2-3)	9 (35)
ESRD (dialysis) (N=8)	70 (59)	13 (39)	1 (1-3)	9 (34)
M-IV-Sul				
Normal (N=13)	235 (36)	51 (36)	2 (2-3)	6 (33)
Mild impairment (N=8)	375 (41)	72 (33)	2 (2-2)	9 (50)
Moderate impairment (N=8)	345 (33)	66 (30)	2 (1-2)	8 (50)
Severe impairment (N=8)	409 (55)	59 (39)	2 (2-3)	11 (38)
ESRD (no dialysis) (N=8)	310 (55)	57 (37)	2 (2-3)	9 (74)
ESRD (dialysis) (N=8)	310 (51)	48 (38)	2 (1-2)	8 (38)

Source: Study report
[a] Median [Range]
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; ESRD, end-stage renal disease; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

The mean percentages of unbound vonoprazan were similar in subjects with normal renal function (20.9%) and subjects with mild, moderate, or severe renal impairment, or end-stage renal disease (ESRD) (21.1%, 20.9%, 22.7%, and 19.6%, respectively).

Vonoprazan was present in dialysate and represented 0.94% of the dose administered.

Conclusions

- Based on comparison of mild, moderate, and severe renally impaired groups to the group with normal renal function, with decreasing renal function there was a maximum mean increase in vonoprazan C_{max} and $AUC_{(0\text{-}inf)}$ of 1.8-fold and 2.4-fold, respectively.
- In subjects requiring dialysis (Noted as ESRD Group), vonoprazan AUC was 1.3-fold greater compared to subjects with normal renal function. Dialysis did not remove vonoprazan to an appreciable amount (<1% of the dose administered).
- Comparison of the data from each renally impaired group with data from subjects with normal renal function showed maximum mean AUC(0-inf) increases of 2.4-, 1.6-, 1.6- (for AUC(0-tlqc)), 1.6-, and 2.0-fold and maximum mean C_{max} increases of 1.8-, 1.1-, 1.1-, 1.2-, and 1.4-fold, for vonoprazan, M-I, M-II, M-III, and M-IV-Sul, respectively.
- The mean percentages of unbound vonoprazan were similar across the groups with varying degree of renal function.

Reviewer's Assessment

The PK parameter estimates from subjects with normal renal function were relatively lower compared to PK data from other studies, which evaluated the same 20 mg single dose. The estimates for $AUC_{0\text{-}24hr}$ and C_{max} across different studies at 20-mg dose are compared in Table 99 below. The comparison showed that the mean $AUC_{0\text{-}24}$ and C_{max} estimates were 13 to 67% and 31 to 85% higher in other studies compared to the estimates from this study. Consequently, the reported increase in subjects with renal impairment might be overestimated.

Table 99. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan Following a Single 20-mg Dose

Study	$AUC_{0\text{-}24}$ (ng·h/mL)	C_{max} (ng/mL)
Study TAK-438_113 (renal impairment study)	*104 (29)*	*13 (37)*
Study TAK-438/CPH-002	117 (29)	19 (36)
Study TAK-438_107	158 (52)	23 (57)
Study TAK-438_109_Fed	154 (31)	17 (34)
Study TAK-438_109_Fasted	174 (30)	18 (29)
Study TAK-438/CPH-001	145 (24)	24 (22)

Source: Compiled by the reviewer from respective study reports
Abbreviations: CV, coefficient of variation

Vonoprazan PK in Subjects with Hepatic Impairment Study TAK-438_112

Study Design

Study TAK-438_112 evaluated the effect of hepatic impairment on the PK of vonoprazan and its metabolites following a single dose of 20 mg TAK-438. A total of 34 subjects (weight range: 54 to 116 kg, age range: 43 to 65 years); 8 with Child Pugh Score A, 8 with Child Pugh Score B, 6 with Child Pugh Score C, and 12 subjects with normal hepatic function were to be enrolled. Subjects enrolled in all groups received a single dose on Day 1 after an overnight fast of at least 10 hours. Following dose administration, 20 PK samples were collected over a period of up to 120 hours post-dose. Both plasma samples were analyzed for vonoprazan and its metabolites, M-

I, M-II, M-III, and M-IV-Sul. Protein binding of vonoprazan in plasma was assessed for each subject using [^{14}C]TAK-438, with blood samples collected pre-dose.

Results:

PK Results

Table 100. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, M-II, M-III, and M-IV-Sul

Renal Function	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)[a]	$T_{1/2}$ (h)
Vonoprazan				
Normal (N=13)	143 (28)	17 (32)	2 (1-4)	10 (24)
Child-Pugh A (N=8)	166 (51)	21 (47)	1 (1-2)	10 (18)
Child-Pugh B (N=8)	277 (35)	30 (33)	1 (0-8)	16 (14)
Child-Pugh C (N=8)	286 (21)	30 (44)	1 (1-2)	17 (20)
M-I				
Normal (N=13)	327 (30)	48 (30)	1 (1-4)	11 (21)
Child-Pugh A (N=8)	256 (38)	45 (23)	1 (1-2)	12 (26)
Child-Pugh B (N=8)	246 (22)	35 (43)	1 (1-2)	18 (25)
Child-Pugh C (N=8)	184 (11)	28 (27)	1 (1-1)	20 (22)
M-II				
Normal (N=13)	43 (48)	3 (47)	4 (2-10)	12 (88)
Child-Pugh A (N=8)	39 (53)	3 (42)	4 (2-10)	16 (166)
Child-Pugh B (N=8)	32 (56)	2 (51)	10 (4-30)	43 (193)
Child-Pugh C (N=8)	31 (2)	1 (25)	6 (4-16)	50 (29)
M-III				
Normal (N=13)	135 (34)	21 (27)	2 (1-4)	9 (21)
Child-Pugh A (N=8)	154 (41)	21 (31)	2 (2-2)	10 (28)
Child-Pugh B (N=8)	128 (22)	13 (40)	2 (1-4)	14 (17)
Child-Pugh C (N=8)	124 (12)	11 (15)	2 (1-4)	17 (13)
M-IV-Sul				
Normal (N=13)	237 (29)	46 (33)	2 (2-4)	7 (36)
Child-Pugh A (N=8)	427 (52)	76 (39)	2 (2-2)	7 (46)
Child-Pugh B (N=8)	400 (81)	46 (65)	2 (2-4)	13 (42)
Child-Pugh C (N=8)	419 (39)	41 (39)	3 (2-4)	17 (26)

Source: Study report
[a] Median [Range]
Abbreviations: AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; C_{max}, maximum serum concentration; CV, coefficient of variation; h, hours; N, number of subjects; T_{max}, time at which the C_{max} is observed; $T_{1/2}$, half-life

Plasma protein binding was similar for subjects with normal hepatic function and for subjects with mild, moderate, and severe hepatic impairment with the mean unbound vonoprazan fractions were 21.4%, 18.6%, 23.5%, and 23.3%, respectively.

Conclusions

- For subjects with mild, moderate, and severe hepatic impairment, vonoprazan $AUC_{(0-inf)}$ increased by 1.2-, 2.4-, and 2.6-fold and C_{max} increased by 1.2-, 1.7-, and 1.8-fold, respectively, compared with subjects with normal hepatic function.

- For subjects with mild, moderate, and severe hepatic impairment in comparison to subjects with normal hepatic function, M-I $AUC_{(0\text{-}inf)}$ decreased by 0.8-, 0.9-, and 0.6-fold and C_{max} decreased by 0.9-, 0.7- and 0.6-fold, respectively. M-II $AUC_{(0\text{-}tlqc)}$ decreased by 0.8-, 1.1-, and 0.3-fold and C_{max} decreased by 0.9-, 0.7-, and 0.5-fold, respectively. M-III $AUC_{(0\text{-}inf)}$ increased by 1.2-, 1.2- and 1.2-fold and C_{max} decreased by 1.0-, 0.6- and 0.5-fold, respectively. M-IV Sul $AUC_{(0\text{-}inf)}$ increased by 1.9-, 2.0- and 2.2-fold and C_{max} increased by 1.6-, 1.0-, and 0.9-fold, respectively.

Drug Interactions Between Multiple Doses of Clarithromycin and a Single Dose of Vonoprazan Study TAK-438_110

Study Design

Study TAK-438_110 evaluated the effect of multiple oral doses of clarithromycin on the PK of vonoprazan and its metabolites in healthy male adult subjects following a single oral dose of TAK-438. A total of 16 subjects (weight range: 59 to 100 kg, age range: 19 to 44 years) received a single oral 40-mg dose of TAK-438 on Day 1 and Day 8 and oral 500-mg doses of clarithromycin twice daily on Days 3 to 9. Following dose administration on Day 1 and Day 8, 17 PK samples were collected over a period of up to 48 hours post-dose. Plasma samples were analyzed for vonoprazan and its metabolites, M-I, M-II, M-III, and M-IV-Sul.

Results

PK Results

Table 101. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Vonoprazan, M-I, M-II, M-III, and M-IV-Sul

	$AUC_{0\text{-}24}$ (ng·h/mL)			C_{max} (ng/mL)		
	Day 1	Day 8	Mean Ratio (90% CI) Day 8/Day 1	Day 1	Day 8	Mean Ratio (90% CI) Day 8/Day 1
Vonoprazan	369 (28.1)	549 (23.0)	1.5 (1.4, 1.6)	47.1 (32.5)	63.7 (24.1)	1.3 (1.2, 1.5)
M-I	612 (28.7)	491 (28.6)	0.8 (0.7, 0.9)	68.1 (43.3)	39.3 (34.3)	0.6 (0.5, 0.7)
M-II	67.6 (49.2)	35.9 (26.8)	0.5 (0.5, 0.6)	4.5 (49.0)	2.2 (39.6)	0.5 (0.4, 0.6)
M-III	191 (36.5)	82 (51.0)	0.4 (0.4, 0.5)	28.3 (39.6)	8.6 (34.4)	0.3 (0.3, 0.3)
M-IV-Sul	257 (47.7)	487 (45.3)	1.9 (1.7, 2.1)	45.7 (51.2)	69.2 (36.9)	1.5 (1.3, 1.8)

Source: Study report
Abbreviations: $AUC_{0\text{-}24}$, area under the concentration versus time curve up to 24-hr timepoint; CI; confidence interval; C_{max}, maximum serum concentration; CV, coefficient of variation; h, hours

The mean ratios show that there are approximately 1.5- and 1.3-fold increases in the AUC and C_{max} respectively for vonoprazan when administered following repeated doses of the strong CYP3A4 inhibitor clarithromycin. The AUC and C_{max} ratios for the metabolites M-I, M-II, and M-III decreased whereas there was an approximate 1.9- and 1.5-fold increase in the AUC and C_{max} respectively for M-IV-Sul.

Conclusions

- Co-administration with clarithromycin (a strong CYP3A4 inhibitor) increased C_{max} and AUC values of vonoprazan and its metabolite M-IV-Sul 1.3- to 1.9-fold.

- The C_{max} and AUC values of vonoprazan metabolites M-I, M-II, and M-III decreased in the presence of a strong CYP3A4 inhibitor.

Drug Interactions with Triple Therapy with TAK-438, Amoxicillin, and Clarithromycin
Study TAK-438/CPH-401

Study Design

Study TAK-438/CPH-401 evaluated the influence of triple therapy with TAK-438/amoxicillin/clarithromycin on the pharmacokinetics of each component drug when given as a single agent in *H. pylori*-negative, healthy Japanese adult males. A total of 12 subjects (weight range: 61 to 85 kg, age range: 21 to 35 years) received treatments for 7 days (Table 102.A) in four periods in a cross-over manner (Table 102.B).

Table 102. Dosage and Treatment Assignment Evaluated in Study TAK-438/CPH-401

A

Study Medication	Product Dose Strength and Form	Study Dosage
TAK-438	1 × 20-mg tablet	20 mg BID
Amoxicillin	3 × 250-mg capsule	750 mg BID
Clarithromycin	2 × 200-mg tablet	400 mg BID

B

Sequence	Period 1	Period 2	Period 3	Period 4
Cohort 1				
I	TAK-438	Amoxicillin	Triple therapy	Clarithromycin
II	Amoxicillin	Clarithromycin	TAK-438	Triple therapy
III	Clarithromycin	Triple therapy	Amoxicillin	TAK-438
IV	Triple therapy	TAK-438	Clarithromycin	Amoxicillin

Source: Study report

Between each period, at least 7 days of washout period was scheduled. Following dose administration on Day 7, 12 PK samples were collected over a period of up to 48 hours post-dose. Plasma samples were analyzed for:

- Vonoprazan and its major metabolites (M-I, M-II, M-III, and M-IV-Sul)
- Unchanged amoxicillin
- Unchanged clarithromycin and its metabolite (14-hydroxyclarithromycin)

Results:

PK Results

Table 103. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Clarithromycin, Amoxicillin, Vonoprazan, and Vonoprazan Metabolites

	AUC_{0-12} (ng·h/mL)			C_{max} (ng/mL)		
	Alone	Triple Therapy	Mean Ratio (90% CI) Triple Therapy/Alone	Alone	Triple Therapy	Mean Ratio (90% CI) Triple Therapy/Alone
Vonoprazan and Metabolites						
Vonoprazan	279 (32)	522 (25)	1.8 (1.6-2.1)	36 (34)	68 (25)	1.9 (1.7-2.1)
M-I	381 (22)	287 (21)	-	50 (24)	34 (23)	-
M-II	91 (36)	45 (42)	-	9 (33)	5 (42)	-
M-III	215 (22)	199 (33)	-	30 (19)	22 (29)	-
M-IV-Sul	199 (25)	481 (24)	-	34 (25)	76 (24)	-

	AUC_{0-12} (ng·h/mL)			C_{max} (ng/mL)		
	Alone	Triple Therapy	Mean Ratio (90% CI) Triple Therapy/Alone	Alone	Triple Therapy	Mean Ratio (90% CI) Triple Therapy/Alone
Clarithromycin (CLR)						
CLR	12068 (25)	17643 (27)	1.5 (1.3-1.6)	1655 (32)	2774 (32)	1.6 (1.4-2.0)
14-OH-CLR	3892 (28)	7368 (20)	-	424 (34)	858 (24)	-
Amoxicillin (AMX)						
AMX	35256 (12)	34450 (16)	1.0 (0.9-1.1)	9936 (16)	9858 (23)	1.0 (0.9-1.1)

Source: Study report
Geometric mean and CV% estimates derived from Reviewer's calculations. Mean ratio and 90% CI are reported from study report.
Abbreviations: 14-OH-CLR, 14-hydroxy clarithromycin; AMX, amoxicillin; AUC_{0-24}, area under the concentration versus time curve up to 24-hr timepoint; CI, confidence interval; CLR, clarithromycin; C_{max}, maximum serum concentration; CV, coefficient of variation; h, hours

The mean ratios show that there are approximately 1.8- and 1.9-fold increases in the vonoprazan AUC and C_{max} respectively when administered as triple therapy compared to when administered alone. The AUC and C_{max} estimates for the metabolites M-I, M-II, and M-III decreased and increased for M-IV-Sul when administered as triple therapy compared to when administered alone. Amoxicillin exposures were comparable when administered as triple therapy or alone. The AUC and C_{max} estimates for the clarithromycin increased 1.5-fold and 1.6-fold, respectively, when administered as triple therapy compared to when administered alone.

Conclusions

Vonoprazan and clarithromycin increased the C_{max} and AUC of each other when administered concomitantly.

Drug Interactions Between Multiple Doses of TAK-438 and Midazolam (Study VONO-101)

Study Design

Study VONO-101 evaluated the time-dependent inhibition potential of repeated doses of oral TAK-438 on the PK of a single oral dose of midazolam, a sensitive CYP3A4 substrate, in healthy subjects. A total of 20 subjects (weight range: 54 to 91 kg, age range: 21 to 43 years) received a single oral doses of 2 mg of midazolam syrup on Day 1 and Day 9. The subjects also received BID doses of 20 mg TAK-438 oral tablets on days 2 through 10. Following dose administration on Day 1 and Day 9, 15 and 17 PK samples were collected over period up to 24 and 48 hours post-dose, respectively. Plasma samples were analyzed for midazolam and 1-hydroxy (OH) midazolam. Additional samples were collected near pre-dose time on days 2 through 11 and these samples were analyzed for vonoprazan concentrations.

Results

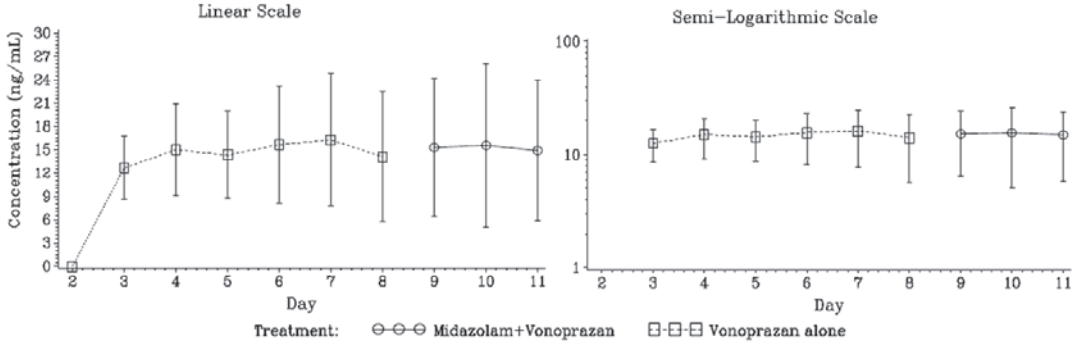
PK Results

Table 104. Geometric Mean (CV%) for Exposure and Pharmacokinetic Parameter Estimates for Midazolam and 1-OH-Midazolam

	$AUC_{0\text{-}inf}$ (ng·h/mL)			C_{max} (ng/mL)		
	Day 1 Alone	Day 9 With TAK-438	Mean Ratio (90% CI) Day 8/Day 1	Day 1 Alone	Day 9 With TAK-438	Mean Ratio (90% CI) Day 9/Day 1
Midazolam	24 (38)	38 (51)	1.9 (1.5, 2.4)	10 (34)	19 (38)	1.9 (1.6, 2.3)
1-OH-Midazolam	10 (43)	13 (43)	1.3 (1.0, 1.7)	4 (55)	5 (40)	1.2 (1.0, 1.6)

Source: Study report
Abbreviations: $AUC_{0\text{-}24}$, area under the concentration versus time curve up to 24-hr timepoint; CI, confidence interval; C_{max}, maximum serum concentration; CV, coefficient of variation; h, hours

Figure 12. Mean Pre-dose Vonoprazan Plasma Concentrations Over Days 2 to 11



Source: Study report

When midazolam was coadministered with vonoprazan, plasma exposure of midazolam as reflected by C_{max} and AUC was approximately 89% to 93% higher compared to administration of midazolam alone. When midazolam was coadministered with vonoprazan, plasma exposure of the 1-hydroxymidazolam metabolite as reflected by C_{max} and AUC was approximately 25% to 37% higher compared to administration of midazolam alone. Steady state plasma concentrations of vonoprazan were achieved after 3 days following daily 20 mg BID doses of vonoprazan.

Conclusions

- Vonoprazan is indicated to be a weak CYP3A4 inhibitor based on the results of this study which used the sensitive CYP3A4 substrate midazolam.
- Steady state plasma concentrations of vonoprazan were achieved after 3 days following daily 20 mg BID doses of vonoprazan.

14.3. Pharmacometrics Review

Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of descriptive labeling and covariate identification. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 105.

Table 105. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	"There were no clinically significant differences in the pharmacokinetics of vonoprazan based on sex or race/ethnicity."	The statement is acceptable. Covariate analysis using the Applicant's final model demonstrates that no clinically meaningful difference exists based on sex, race, or weight (Figure 16 and Figure 17).
	Extrinsic factor	"In a food effect study in healthy subjects (N=24) receiving vonoprazan 20 mg, a high-fat meal resulted in a 5% increase in C_{max}, a 15% increase in AUC, and a delay in median T_{max} of 2 hours. These changes are not considered to be clinically significant."	The numbers in this come from the individual study assessment. Yet the PPK model confirms the influence of food effect is not considered clinically significant (Figure 17).

Source: Reviewer's Analysis
1.2 Introduction
Abbreviations: PK, pharmacokinetics; PPK, population pharmacokinetic

The primary objectives of the Applicant's analysis were to:

- Characterize the structural PK model and quantify the population variability in the PK parameters of vonoprazan.
- Describe the effects of intrinsic and/or extrinsic factors on vonoprazan exposure.

Model development

Data

The analyses were based on PK data from 15 studies. The study design, study population, and timing of blood samples varied among the 15 clinical studies. Brief descriptions of the studies included are presented in Table 106 and PK sampling and doses are presented in Table 107.

The final NONMEM data file for analysis contained 15644 PK observations from 1179 subjects. Table 108 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 106. Summary of Studies Included in the Population PK Analysis

Study	Population	Region	Description
2001	GERD	Europe	A Randomized, Double-Blind, Proof-of-Concept, Phase 2 Study to Evaluate the Efficacy and Safety of Once Daily Oral Vonoprazan 20 mg or Vonoprazan 40 mg Compared to Esomeprazole 40 mg for the Treatment of Subjects with Symptomatic Gastroesophageal Reflux Disease Who Have a Partial Response Following Treatment with a High Dose of Proton Pump Inhibitor
CCT-001	EE	Japan	A Phase 2, Randomized, Double-Blind, Parallel-Group, Multi-Center, Dose-Ranging Study to Evaluate the Efficacy and Safety of TAK-438 (5, 10, 20, and 40 mg Once Daily) and AG-1749 (30 mg Once Daily) in Subjects with Erosive Esophagitis
CPH-001	HV	Japan	A Phase I, Randomized, Double-Blind, Placebo-Controlled, Ascending Multiple Dose Study of the Safety, Tolerability, PK and PD of TAK-438 in Healthy Male Subjects
CPH-002	HV	Japan	A Phase 2, Open-Label, Sequential Design Study to Evaluate the Drug-Drug Interaction between TAK-438 and Low-Dose Aspirin or NSAIDs (Loxoprofen Sodium, Diclofenac Sodium or Meloxicam) in Healthy Male Subjects
CPH-003	HV	Japan	A Phase 3, Open-Label, 2-Way Crossover Study to Evaluate the Food Effect on the PK of Single Oral Dose of TAK-438 with TAK-438 Final Formulation (20 mg) in Healthy Adult Males
CPH-007	HV	Japan	A Phase 3, Open-Label, 2-Way Crossover Study to Evaluate the Food Effect on the PK of Single Oral Dose of TAK-438 with TAK-438 Final Formulation (20 mg) in Healthy Adult Males
CPH-401	HV	Japan	A Phase 3, Open-Label, 4 x 4 Crossover Study to Evaluate the Pharmacokinetic Drug-Drug Interaction of the Triple Therapy with TAK-438, Amoxicillin and Clarithromycin, or with TAK-438, Amoxicillin and Metronidazole in Healthy Japanese Male Subjects
101	HV	Europe	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending Single- and Multiple-Dose Study to Evaluate the Safety, Tolerability, and PK of TAK-438 in Healthy Western Male Subjects, Preliminary Food Effect Analysis, and an Ethnic Comparison with Japanese Subjects
103	HV	Europe	A Phase 1, Open-Label, Mass Balance and Excretion Study of [14C]TAK-438 Following Oral Administration in Healthy Male Subjects
107	HV	Europe	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential, Multiple Repeat Dose Study to Evaluate the Safety, Tolerability, and PK of TAK-438 in Healthy Non-Japanese Male Subjects
109	HV	Europe	A Randomized, Open-Label, 2x2 Cross-Over Study Stratified By Gender To Assess The Safety, Tolerability, PK And PD of a Single Dose of TAK-438 Administered With and Without Food in Healthy Non-Japanese Male and Non-Japanese Female Subjects
110	HV	Europe	A Phase 1, Open-Label, Sequential Design Study to Evaluate the Effect of Multiple Oral Doses of Clarithromycin on the PK of a Single Oral Dose of TAK-438
111	HV	Europe	A Randomized, 4-Period, 4-Sequence, Double Blind, Crossover Design Study to Assess the Effect of Single Doses of TAK-438 40 mg, TAK-438 120 mg, Placebo and Positive Control Moxifloxacin (Open Label) on the QTc Interval in Healthy Adult Subjects
112	HV and Hepatic Impaired	Europe	An Open-Label 4-Group, Parallel Design Study to Assess the Effect of Hepatic Impairment on the PK of TAK-438 and Its Metabolites Following a Single Oral Dose of TAK-438
113	HV and Renally Impaired	Europe	An open label 5-group, parallel design study to assess the effect of renal impairment on the pharmacokinetics of TAK-438 and its metabolites following a single oral dose of TAK-438

HV: healthy volunteers

Source: Applicant's Population PK report, Table 1
Abbreviations: EE, erosive esophagitis; GERD, gastroesophageal reflux disease; HV, healthy volunteer; PK, pharmacokinetics; PD, pharmacodynamics

Table 107. Number of Subjects, Observations, and Doses Per Study in the Population PK Analysis Dataset

		Total			Median by Subj.	
Study	Doses	Num. Subj.	Num. Obs.	Num. Doses	Num. Obs.	Num. Doses
101	1, 5, 10, 15, 20, 30, and 40mg	42	702	42	17.5	1
103	20mg	6	112	6	19.0	1
107	10, 20, 30, and 40mg	36	1254	252	35.0	7
109	20mg	24	766	48	32.5	2
110	40mg	16	272	16	17.0	1
111	40, and 120mg	64	1830	127	29.0	2
112	20mg	34	621	34	18.0	1
113	20mg	37	720	37	19.0	1
CPH-001	1, 5, 10, 20, 40, 80, and 120mg	79	1582	95	18.0	1
CPH-002	10, 15, 20, 30, and 40mg	45	1530	315	34.0	7
CPH-003	40mg	32	447	32	14.0	1
CPH-007	20mg	12	343	24	29.0	2
CPH-401	20mg	6	72	78	12.0	13
CCT-001	5, 10, 20, and 40mg	589	1654	588[a]	3.0	1
2001	20, and 40mg	157	732	627[a]	4.0	4

[a] partially encoded as steady state dosing events

Num. Obs. refers to the number of non-excluded and non-BLQ observations. Num. Doses refers to the NONMEM dosing records (some of which are encoded as steady state dosing events and hence refer to more than one actual treatment).

Source: Applicant's Population PK report, Table 3

Table 108. Summary of Baseline Demographic Covariates for Analysis

Variable	Level	Count	Percent
CYP-2C19 Status	EM	651	55
	IM	37	3
	Not Screened	298	25
	Other	84	7
	PM	109	9
Race	Asian	769	65
	Black	13	1
	Other	4	0
	White	393	33
Gender	F	308	26
	M	871	74
Subject Status	Child-Pugh A	8	1
	Child-Pugh B	8	1
	Child-Pugh C	6	1
	Healthy Volunteer	387	33
	Mild RI	8	1
	Moderate RI	8	1
	Patient	746	63
	Severe RI	8	1

Statistic	Age (years)	Baseline Body Weight (kg)	Baseline Creatinine (umol/L)
Mean	48.1	69.36	73.1376
SD	17.6	12.98	21.5938
Median	49.0	68.20	71.6040
Geom.Mean	44.5	68.21	70.9939
CV%	40.9	18.19	23.1759
Min	18.0	38.00	26.0000
Max	92.0	152.70	339.4560

SD: standard deviation, Geom.Mean: geometric mean, CV: coefficient of variation

Source: Applicant's Population PK report, Table 4 & Table 5
Abbreviations: CV, coefficient of variation; EM, extensive metabolizers; F, female; IM, intermediate metabolizers; M, male; PM, poor metabolizers; SD, standard deviation

Base model

The final base model was a two-compartment PK model with lag time, first-order absorption, dose-dependency on bioavailability, and first-order elimination from the central compartment. The effect of weight was included as a fixed allometric exponent on Vc/F and estimated for CL/F. The effects of food, sex, and Asian ethnicity were included on KA from their previous phase 1 model.

Inter-individual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Additive models on ln-transformed dependent variable were investigated as well. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV), accuracy

of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate analysis

Covariate parameters, including weight, serum creatinine and patient status on CL/F; and weight, age, serum creatinine, and patient status on Vc/F; and disease status on KA were added to the base model using the forward inclusion ($\alpha < 0.01$) procedure. Once all covariates had been included the full model was evaluated with a backward deletion ($a < 0.001$) procedure.

Final Model

The parameter estimates for the final covariate model are listed in Table 109. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 13. The Visual Predictive Check (VPC) plots for the final covariate model with all data are shown in Figure 16 and Figure 17.

Table 109. Parameter Estimates (RSE) and 95% CI for the Final Model

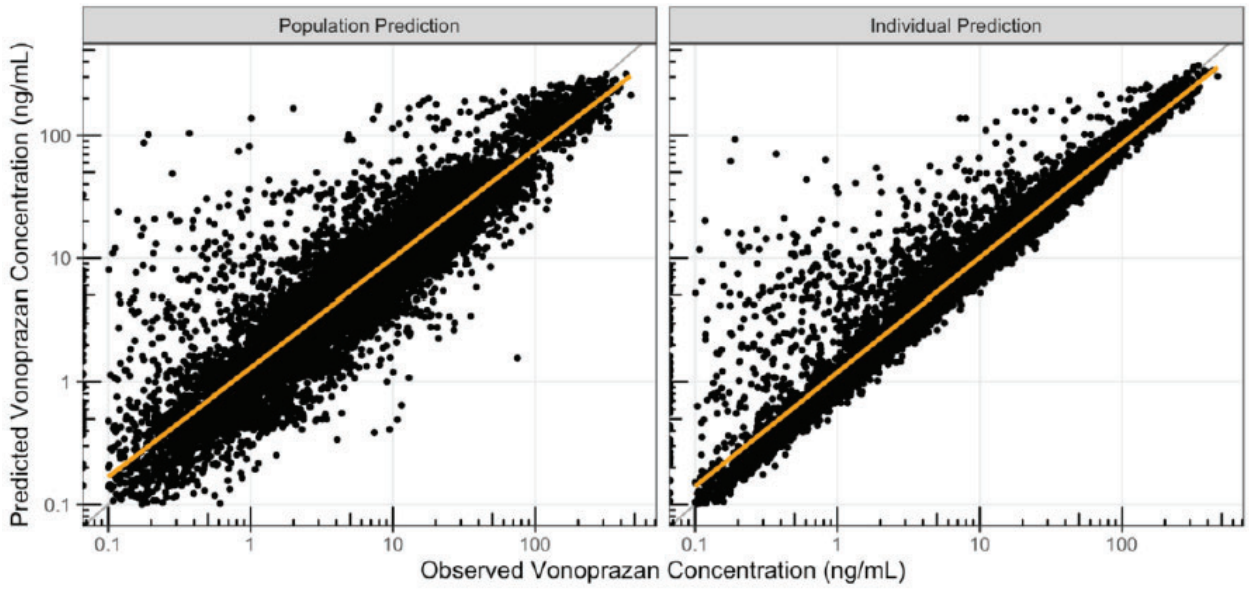
Parameter	Role	Estimate	Rel.Std.Err.	95% CI
F1	Dose effect (exp)	0.387	3.5%	[0.36, 0.414]
ALAG1	TV (h)	0.226	1.3%	[0.22, 0.231]
	Delay (%)	106	2.7%	[100, 111]
KA	TV (1/h)	2.54	8.8%	[2.1, 2.98]
	Food effect (%)	-58.2	9.6%	[-69.1, -47.3]
	non-Asian effect (%)	-30.2	22.0%	[-43.3, -17.2]
	Female effect (%)	-25.3	27.2%	[-38.8, -11.8]
	Patient effect (%)	-55	10.7%	[-66.4, -43.5]
	BSV[a]	0.83	4.9%	[0.75, 0.909]
CL	TV (L/h)	124	1.9%	[119, 128]
	Baseline body weight effect (exp)	0.438	11.0%	[0.343, 0.533]
	Baseline serum creatinine effect (exp)	-0.437	12.3%	[-0.543, -0.332]
	Patient effect (%)	-38.1	5.0%	[-41.8, -34.4]
	BSV(CL,V2)[a]	0.921	1.1%	[0.901, 0.94]
	BSV[a]	0.39	3.3%	[0.364, 0.415]
V2	TV (L)	1075	2.3%	[1027, 1124]
	Baseline serum creatinine effect (exp)	-0.318	18.7%	[-0.434, -0.201]
	Age effect (exp)	0.458	5.6%	[0.408, 0.509]
	Baseline body weight effect (exp)[b]	1	–	–
	Patient effect (%)	-38	10.6%	[-45.9, -30.1]
	BSV[a]	0.372	4.3%	[0.341, 0.404]
Q	TV (L/h)	48.7	5.4%	[43.6, 53.8]
V3	TV (L)	308	3.6%	[286, 330]
	non-Asian effect (%)	-12.9	21.8%	[-18.4, -7.37]
RV	proportional error (%)	29.2	1.5%	[28.4, 30.1]
	additive error (ng/mL)[b]	0.00625	–	–

Rel.Std.Err.: relative standard error, TV: typical value, BSV: between subject variability, exp: exponent of the power model, RV: residual variability

[a] reported on std.dev. scale [b] fixed parameter Goodness of Fit (GOF)

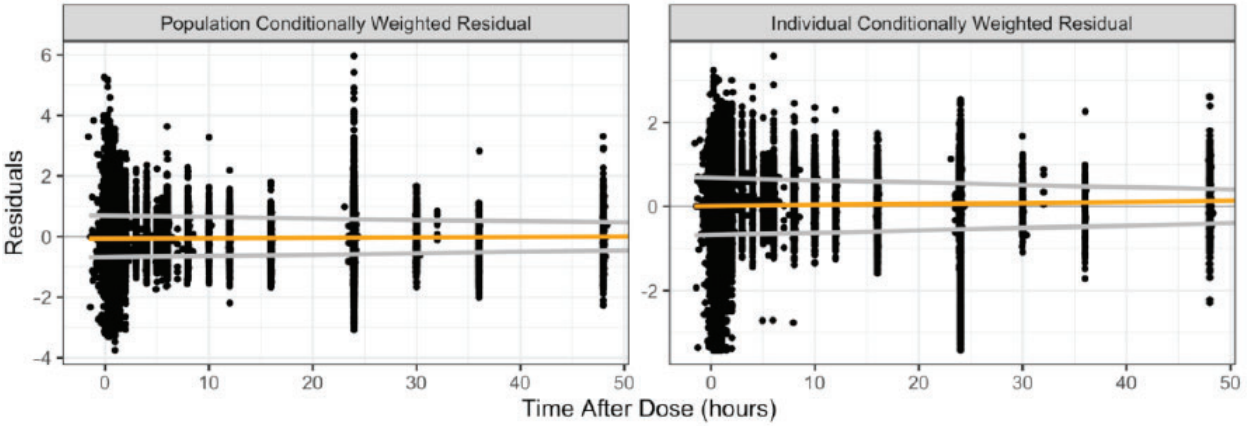
Source: Applicant's Population PK report, Table 8

Figure 13. Goodness-of-fit Plot for Final Covariate Model: Observed Versus Predicted Concentrations



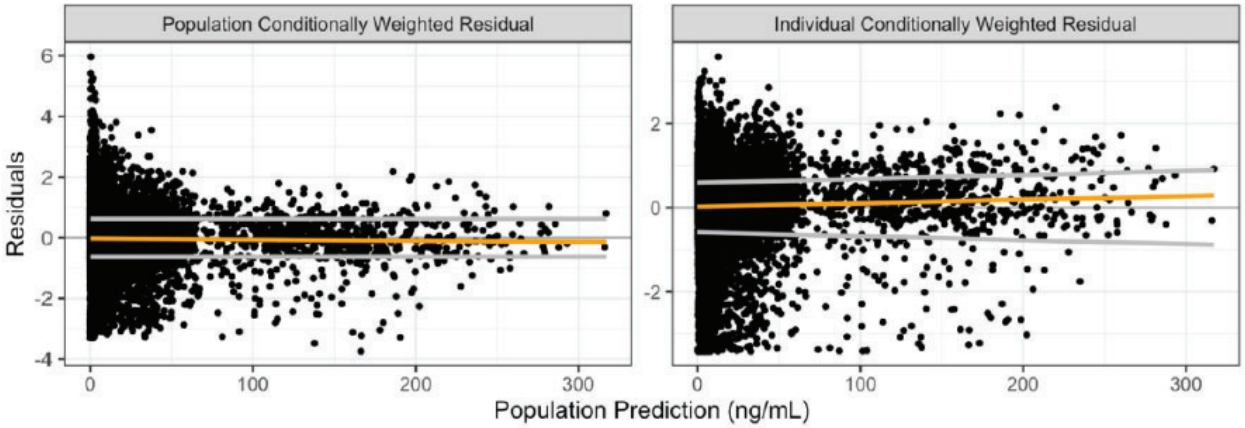
Source: Applicant's Population PK report, Figures 11
Scatterplot of observed versus predicted concentrations. Left panel shows population predictions (PRED), right panel shows individual predictions (IPRED). The orange line represents a linear regression.

Figure 14. Goodness-of-fit Plot for Final Covariate Model: Population and Individual Conditionally Weighted Residuals Versus Time After Dose



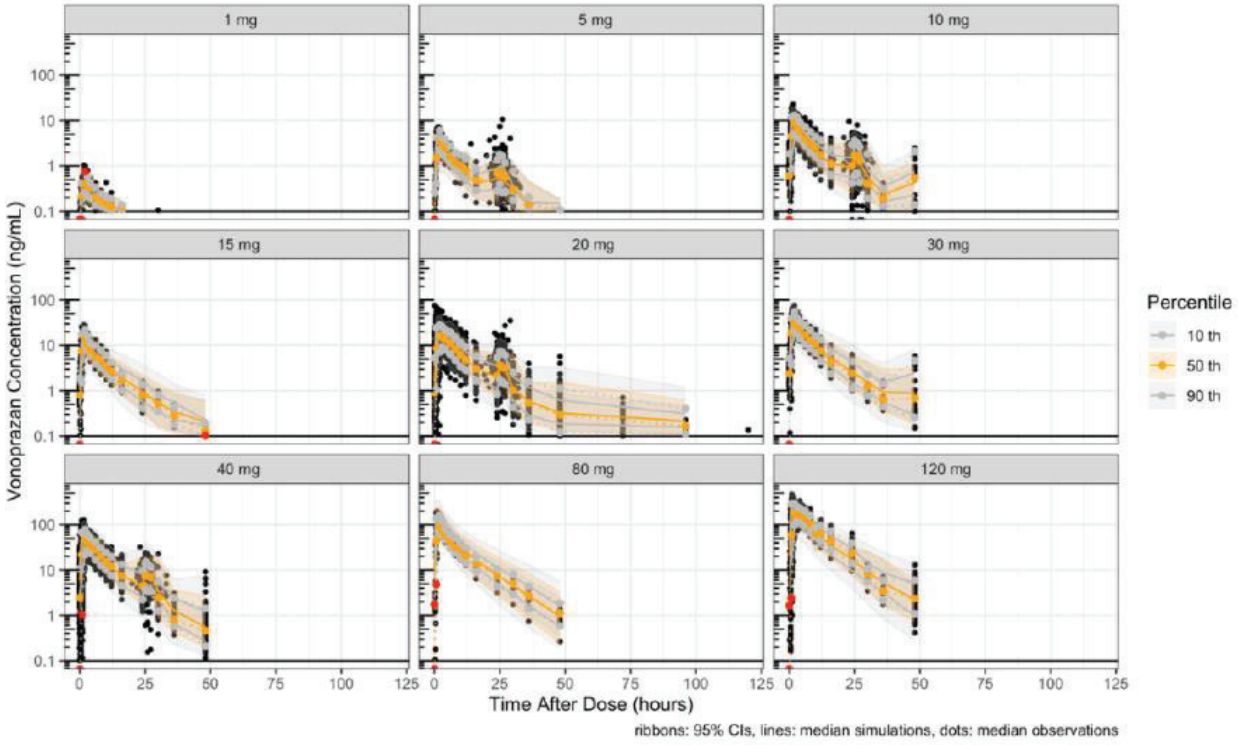
Source: Applicant's Population PK report, Figures 12
Scatterplot of population conditionally weighted residuals (CWRES, left) and individual conditionally weighted residuals (CIWRES, right) versus time after dose. The orange line represents a non-linear smoother on the residuals, while the gray lines represent +/- a non-linear smoother on the absolute residuals. Time-axis was restricted to 48 hours post dose.

Figure 15. Goodness-of-fit Plot for Final Covariate Model: Population and Individual Conditionally Weighted Residuals Versus Population Predictions



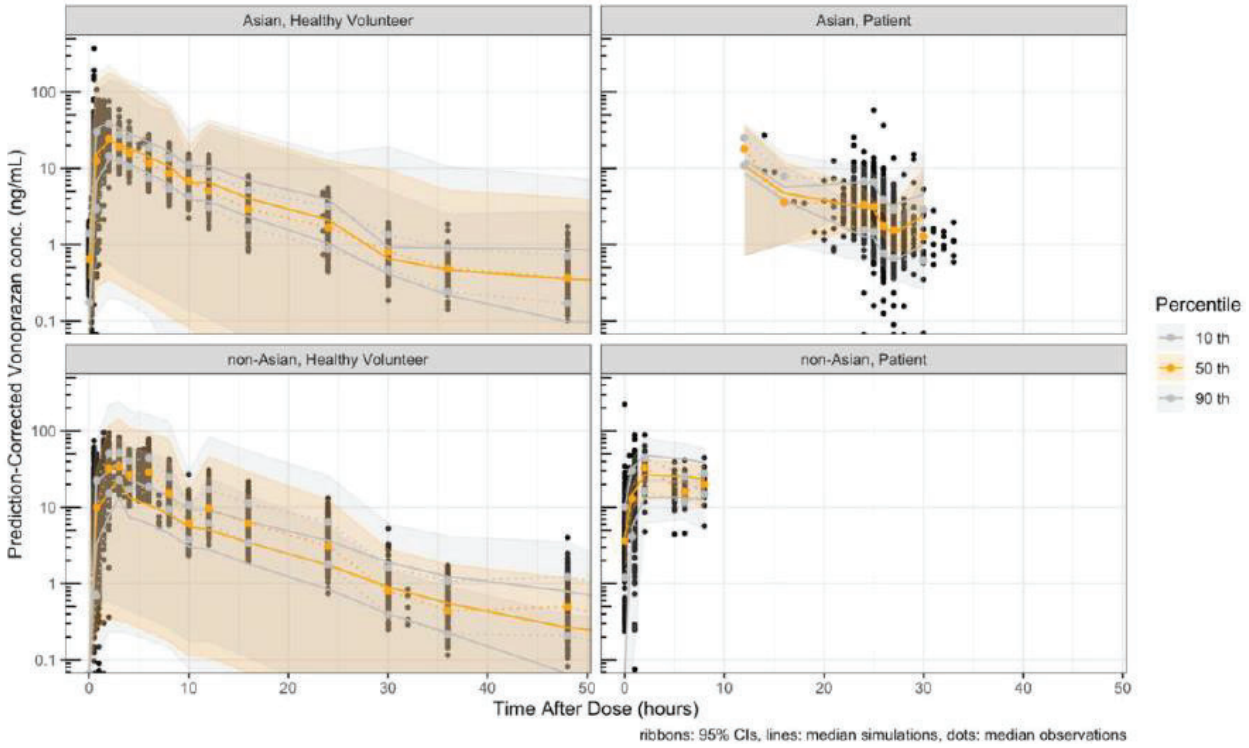
Source: Applicant's Population PK report, Figures 13
Scatterplot of population conditionally weighted residuals (CWRES, left) and individual conditionally weighted residuals (CIWRES, right) versus population predictions. The orange line represents a non-linear smoother on the residuals, while the gray lines represent +/- a non-linear smoother on the absolute residuals. Time-axis was restricted to 48 hours post dose.

Figure 16. Final Population PK Model Visual Predictive Check, Stratified by Dose



Source: Applicant's Population PK report, Figure 17
Black dots: observed data (black dots); orange dots, orange dotted line: median of observed data; grey dots, grey dotted line: 10*th* and 90*th* percentiles of observed data. Solid orange line (shaded orange area): median (95% CI) of simulated data; solid grey lines (shaded grey area): 10*th* and 90*th* percentiles (95% CI) of simulated data. Red dots: respective summary statistic on observed values is outside of simulation-based 95% CI. An LLOQ of 0.1 was applied to the simulated concentrations.
Abbreviations: CI, confidence interval; LLOQ, lower level of quantification; PK, pharmacokinetics

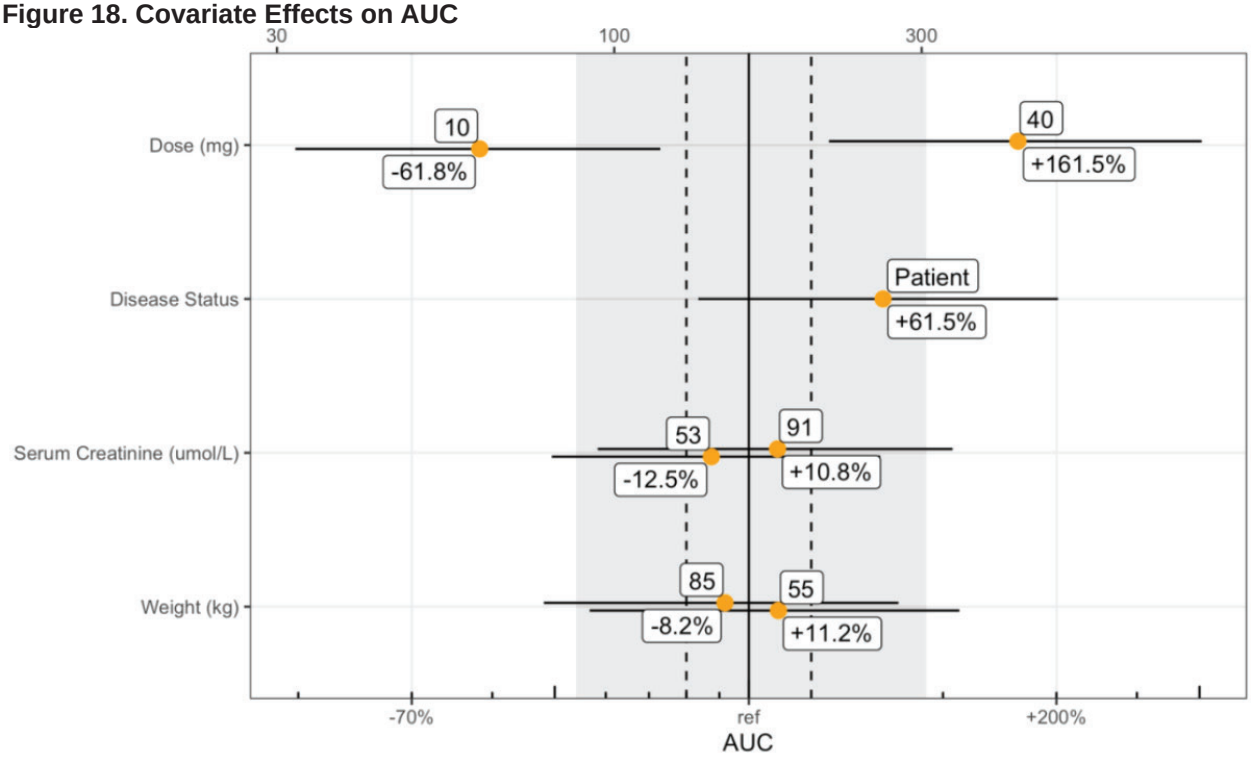
Figure 17. Final Population PK Model Visual Predictive Check, Stratified by Disease Status and Race



Source: Applicant's Population PK report, Figure 18
Black dots: observed data (black dots); orange dots, orange dotted line: median of observed data; grey dots, grey dotted line: 10th and 90th percentiles of observed data. Solid orange line (shaded orange area): median (95% CI) of simulated data; solid grey lines (shaded grey area): 10th and 90th percentiles (95% CI) of simulated data. Red dots: respective summary statistic on observed values is outside of simulation-based 95% CI. An LLOQ of 0.1 was applied to the simulated concentrations.
Abbreviations: CI, confidence interval; LLOQ, lower level of quantification; PK, pharmacokinetics

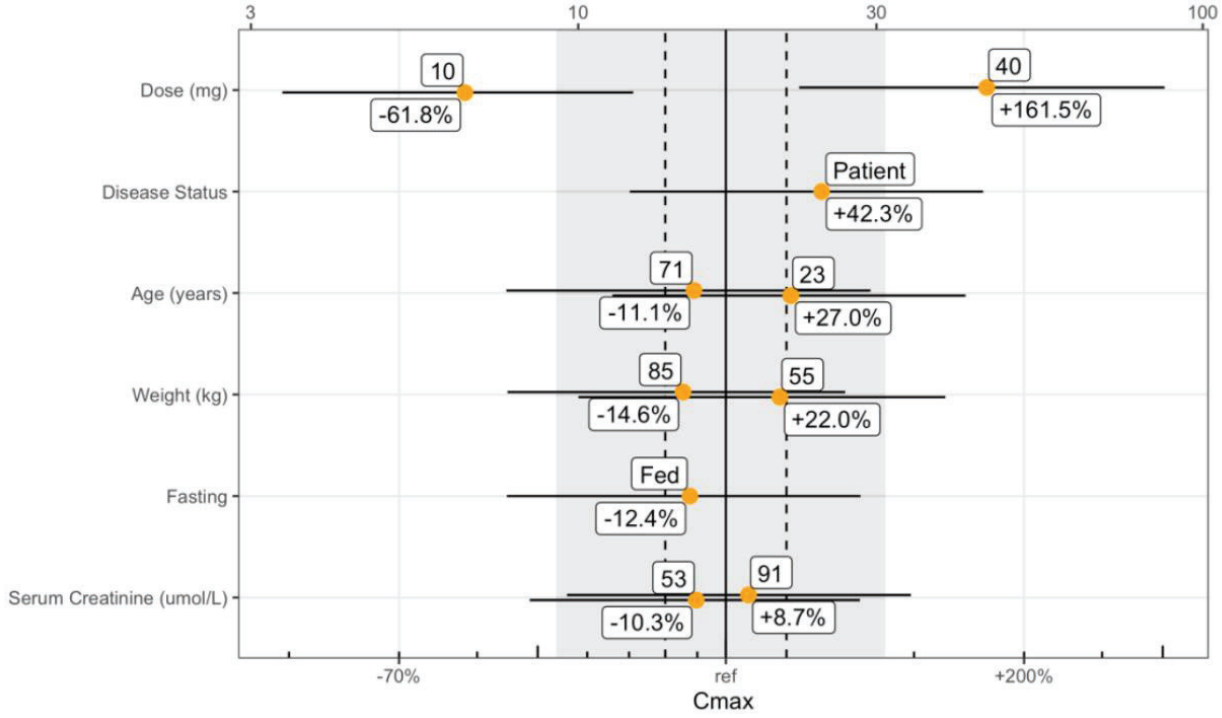
The effects of body weight, age, serum creatinine, sex, race, food and dose on AUC and C_{max} are shown in Figure 18 and Figure 19 relative to the reference subject.

Figure 18. Covariate Effects on AUC



Source: Applicant's Population PK report, Figure 28
The vertical solid black line represents the typical AUC (ng·h/mL) for a reference subject (Healthy Volunteer, serum creatinine at 72µMol/L, 70 kg body weight, male, Asian, 48 years) and the grey shaded area represents its 90% prediction interval. The orange dots represent typical AUC levels for subjects where the respective covariate was altered to the above labelled values and the black error bars represent the respective 90% prediction intervals. The labels below indicate the percent change from the typical reference AUC. For numerical variables, the 10th and 90th percentile was selected for simulations.
Abbreviations: AUC, area under the curve

Figure 19. Covariate Effects on C_{max} (ng/mL)



Source: Applicant's Population PK report, Figure 28
Abbreviations: C_{max}, maximum plasma concentration

14.4. Physiologically Based Pharmacokinetic (PBPK) Model Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) potentials:

- As a victim of strong and moderate CYP3A inducers

The Division of Pharmacometrics has reviewed the PBPK report titled VONOPRAZAN PBPK MODEL DEVELOPMENT AND SUBSEQUENT EVALUATION OF INDUCTION LIABILITY WITH RIFAMPICIN AND EFAVIRENZ, the response to FDA's information request submitted on January 10, 2022, the modeling supporting files, and concluded that:

- The Dual Pak may have a weak inhibitory effect on CYP2C19 substrates, and the Triple Pak may have weak to moderate inhibitory effects on CYP2C19 substrates depending on the contribution of CYP3A4 to its elimination.
- The analyses may underestimate the induction effects of rifampin and efavirenz on vonoprazan PK due to uncharacterized elimination pathways of vonoprazan.
- The contribution of the CYP2D6 pathway in vonoprazan disposition needs to be confirmed.

Background

Vonoprazan is a potassium-competitive acid blocker and is being investigated for treatment of *H. pylori* infection in adults. Vonoprazan is administered as part of a triple (Vonoprazan 20 mg

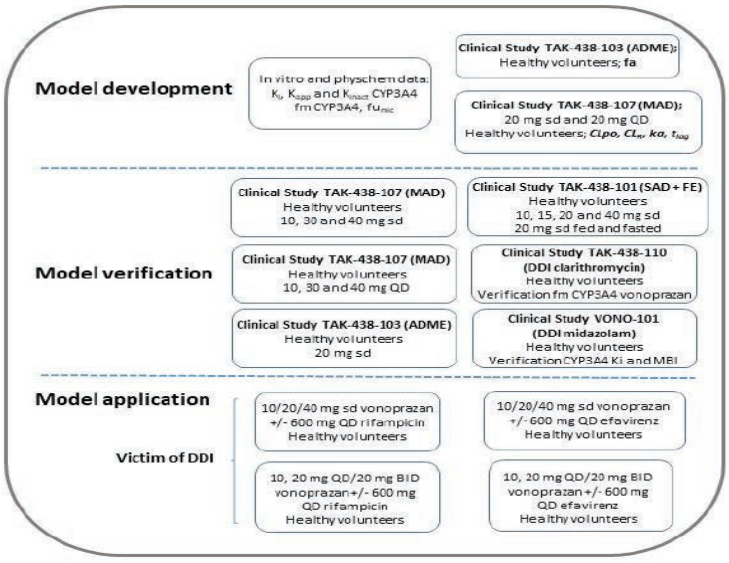
twice daily (BID), amoxicillin 1000 mg BID, and clarithromycin 500 mg BID for 14 days) or dual (Vonoprazan 20 mg BID and amoxicillin 1000 mg 3 times daily (TID) for 14 days) therapy regimen regardless of food. Following oral administration of single doses of vonoprazan in healthy subjects, its AUC and C_{max} increased greater than dose proportional from 1 to 120 mg (TAK438-101 and TAK438/CPH-001). Following oral administration of multiple once daily doses of vonoprazan in healthy subjects, its AUC, C_{max} and C_{min} increased approximately dose proportional from 10 to 40 mg (TAK438-007 and TAK438/CPH-002).

Vonoprazan is well absorbed, and in the human ADME study, approximately 31.1% and 67.4% of radioactivity were recovered in the feces (1.4% unchanged parent) and the urine (8% unchanged parent), respectively. Based on the results from the human ADME (TAK438-103) and reaction phenotyping studies (Report A914-438-036), vonoprazan is eliminated via multiple pathways, with approximately 8% via renal elimination, 13% via sulfation, 35.2% via CYP3A4, 38.1% via CYP2D6 and 4.3% via CYP2C19. Vonoprazan is determined in vitro to be a reversible inhibitor of CYP3A4 with an IC_{50} value of 29 μM, CYP2B6 with an IC_{50} value of 16 μM and CYP2C19 with an IC_{50} value of 13 μM, and a mechanism-based inhibitor of CYP3A4, CYP2B6 and CYP2C19 with the k_{inact} and K_I values of 0.966 h^{-1} and 1.22 μM, 0.69 h^{-1} and 3.5 μM, 1.092 h^{-1} and 3.67 μM, respectively. Vonoprazan has little effect on other CYP enzymes. The Applicant only assessed the effects of vonoprazan on the enzyme activity of CYP1A2, CYP2B6 and CYP3A4 in a hepatocyte induction study, which is insufficient to rule out vonoprazan induction potential because it is also an inhibitor of these enzymes. Vonoprazan has a high permeability and is not a substrate of P-gp, BCRP and OATP1B1/3. The Applicant conducted clinical DDI studies with clarithromycin and midazolam (VONO-101) to evaluate some of the in vitro findings. The Applicant used the PBPK modeling to predict the effects of a strong (rifampicin) and moderate (efavirenz) CYP3A4/5 inducer on the PK of vonoprazan. Refer to the Clinical Pharmacology review section for detail information on vonoprazan regarding ADME properties, in vitro and clinical studies used in PBPK modeling.

Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp Simulator (Version 19 Certara, Sheffield, UK). Schemes of the PBPK simulation strategy are shown in Figure 20**,** which summarizes parameters optimized and the studies used for parameter optimization in model development, studies used in model verification, and model applications in DDI predictions. The vonoprazan PBPK model consists of a first-order absorption model, a full PBPK distribution model and an enzyme kinetics model for elimination (Table 110). Simcyp library files of clarithromycin, rifampin-MD, efavirenz, midazolam, omeprazole, lansoprazole, and sim-Healthy Subject were used for DDI simulations without any modification unless noted in the following review.

Figure 20. Modeling and Simulation Strategy



Source: Figure 2 in the PBPK report

Table 110. Input Parameters for Vonoprazan

PARAMETER	Vonoprazan	Reference
Physchem and Blood Binding		
MW (g/mol)	345.39	Simcyp data checklist
log P	2.74	Simcyp data checklist
Compound type	Monoprotic base	
pKa	9.3	Investigator's Brochure
B:P	0.93	Echizen *et al.* 2016 [1]
fu	0.135	TAK-438-00087
Distribution		Full PBPK
V_{SS} (L/kg)	3.82	Method 2 Predicted
Absorption		First order
fa	0.99	Study TAK-438_103
ka (1/h)	0.5	Optimised
t_{lag} (h)	0.4	Optimised
P_{app} (x10^{-6} cm/s)	17.8	TAK-438-10811
Calibrator P_{app}(x10^{-6} cm/s)	32.8	TAK-438-10811
$P_{eff,man}$ (x10^{-4} cm/s)	2.55	Predicted
Q_{gut} (user) (L/h)	13.5	Retrograde calculator
fu_{gut}	1	Default
Elimination		Enzyme kinetics
CL_R (L/h)	4	Clinical Study TAK-438_107
CYP3A4 CL_{int} (µl/min/pmol)	0.601	Retrograde model CL/F obtained from Clinical Study TAK-438_107 (115 L/h); fa 0.99; F_G 0.86; CL_R 4 L/h; fm_{CYP3A4} 45.4%
Additional HLM CL_{int} (µL/min/mg)	90.9	
Interaction		
CYP3A4 K_i (µM)	3.0	From IC_{50} (10 µM, TAK-438-11256) using Cheng-Prusoff equation
fu_{mic}	0.94	Calculated at 0.2 mg/mL
CYP3A4 K_{app} (µM)	1.22	TAK-438-11315
CYP3A4 K_{inact} (1/h)	0.966	TAK-438-11315
fu_{mic}	0.94	Calculated at 0.2 mg/mL

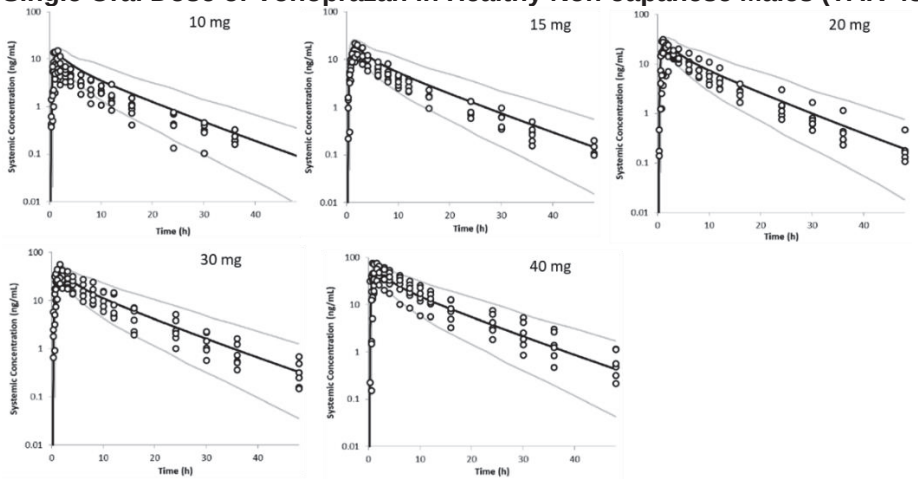
Source: Table 5 in the PBPK report
Abbreviations: MW, molecular weight

Results

1. Can the PBPK model adequately describe the PK profiles of vonoprazan?

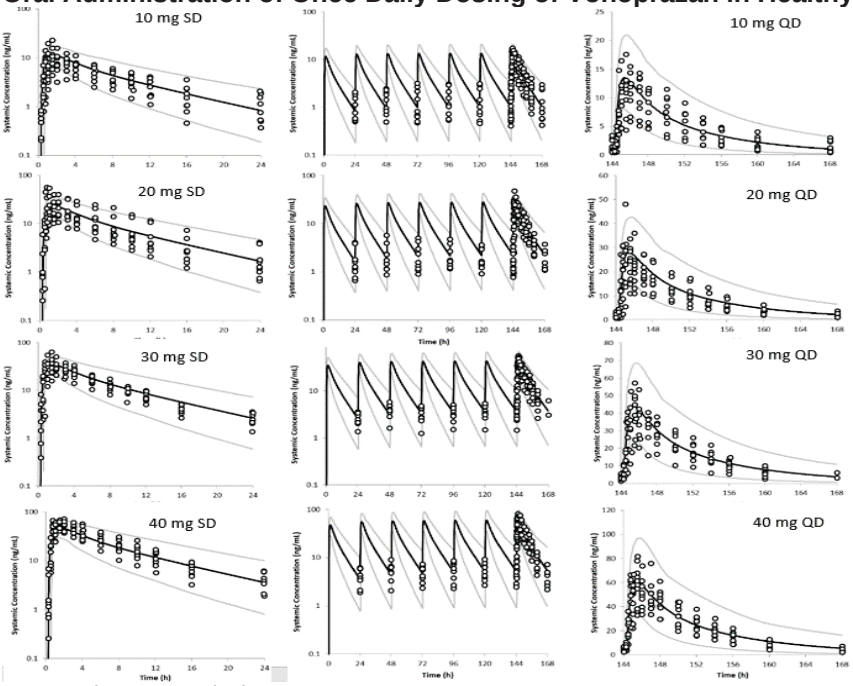
Yes. The vonoprazan PBPK model could describe vonoprazan PK following administration of single doses (Figure 21, Figure 22 and Table 111) and multiple doses of vonoprazan in healthy non-Japanese subjects (Figure 22 and Table 112).

Figure 21. Predicted and Observed Plasma Concentration-time Profiles of Vonoprazan Following a Single Oral Dose of Vonoprazan in Healthy Non-Japanese Males (TAK-438-101)



Source: Figures 14 – 18 in the PBPK report.

Figure 22. Predicted and Observed Plasma Concentration-time Profiles of Vonoprazan Following Oral Administration of Once Daily Dosing of Vonoprazan in Healthy Non-Japanese Subjects



Source: Figures 6- 13 in the PBPK report.
Abbreviations: SD, single dose; QD, once daily

Table 111. Predicted and Observed PK Parameters of Vonoprazan Following a Single Oral Dose of Vonoprazan in Healthy Japanese Males (TAK-438-101)

Dose (mg)	Geometric Mean	T_{max} (h)	C_{max} (ng/mL)	AUC_{inf} (ng.h/mL)
10	Simulated	1.42	11.8	94
	Observed	1.50	7.3	56
	Sim./Obs.	0.94	1.62	1.68
15	Simulated	1.41	17.8	143
	Observed	1.50	13.6	107
	Sim./Obs.	0.94	1.31	1.33
20	Simulated	1.42	23.8	193
	Observed	1.50	23.0	174
	Sim./Obs.	0.95	1.03	1.11
30	Simulated	1.43	36.3	297
	Observed	1.50	35.7	272
	Sim./Obs.	0.95	1.02	1.09
40	Simulated	1.44	48.4	398
	Observed	1.75	49.6	440
	Sim./Obs.	0.82	0.98	0.90

Source: Tables 14 -18 in the PBPK report.
Abbreviations: AUC_{inf}, area under the curve extrapolated to infinity; C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration

Table 112. Predicted and Observed Geometric Mean C_{max} and AUC of Vonoprazan Following Once Daily Dosing of Vonoprazan in Healthy Non-Japanese Males (TAK-438-107)

Dose (mg)	Geometric Mean	Day 1			Day 7			
		T_{max} (h)	C_{max} (ng/mL)	AUC_{0-24h} (ng.h/mL)	T_{max} (h)	C_{max} (ng/mL)	AUC_{tau} (ng.h/mL)	C_{trough} (ng/mL)
10	Simulated	1.40	11.5	84	1.38	13.1	98.3	0.731
	Observed	1.50	9.70	75.6	1.50	11.6	96.8	1.11
	Sim./Obs.	0.93	1.19	1.11	0.92	1.14	1.02	0.66
20	Simulated	1.41	22.9	169	1.41	27.2	206	1.54
	Observed	1.50	23.0	158	1.07	24.2	186	1.67
	Sim./Obs.	0.94	1.00	1.07	1.32	1.12	1.11	0.92
30	Simulated	1.43	34.8	259	1.41	42.5	326	2.50
	Observed	1.50	35.7	250	1.50	40.1	327	3.65
	Sim./Obs.	0.95	0.97	1.03	0.94	1.06	0.99	0.68
40	Simulated	1.45	46.8	351	1.45	58.4	454	3.56
	Observed	1.50	57.6	408	1.50	58.0	472	4.49
	Sim./Obs.	0.97	0.81	0.86	0.97	1.01	0.96	0.79

Source: Tables 6 -13 in the PBPK report.
Abbreviations: AUC_{0-24}, area under the curve during 24 hours; AUC_{tau}, area under the curve during a dosing interval; C_{max}, maximum plasma concentration; C_{trough}, trough concentration; T_{max}, time to maximum plasma concentration

2. Can PBPK analyses predict the effects of CYP perpetrators on the PK of vonoprazan?

The predicted effects of CYP3A inhibitors and inducers are shown in Table 113. The vonoprazan PBPK model could reproduce the observed effects of clarithromycin on vonoprazan PK. However, a potential that the induction effects of strong and moderate CYP3A inducers on vonoprazan PK may be underestimated cannot be ruled out due to unidentified elimination pathways of vonoprazan.

Table 113. Predicted and Observed Effects of CYP3A Perpetrators on Vonoprazan PK Following Co-administration of CYP3A Perpetrators With Single or Multiple Doses of Vonoprazan in Healthy Subjects

CYP3A inhibitors	Vonoprazan Dosing	$C_{max,inh}$ (ng/mL)	$AUC_{0-inf,inh}$ (ng/mL.h)	C_{max} Ratio	AUC_{0-inf} Ratio	
Clarithromycin 500 mg BID 7 d	40 mg SD D6	63.7	648	1.35	1.58	Study TAK-438-110
		72.3	690	1.51	1.78	simulated
		1.14	1.06	1.12	1.13	Sim/obs
Clarithromycin 400 mg BID 7 d	20 mg BID 7d	70.2	538.8*	1.87	1.85*	Study TAK-438/CPH-401
		57.4	403.3*	1.28	1.36*	simulated†
		0.82	0.75	0.67	0.74	Sim/obs
Rifampin 600 mg QD 18d	20 mg SD D16	7.32	38.6	0.28	0.20	predicted
Rifampin 600 mg QD 16d	20 mg BID 16d	11.2	52.6	0.28	0.22	predicted
Efavirenz 600 mg QD 18d	20 mg SD D16	14.9	92.2	0.56	0.46	predicted
Efavirenz 600 mg QD 16d	20 mg BID 16d	21.6	116	0.54	0.46	predicted

Source: Tables 20, 23, 27, 29 and 33 in the PBPK report
Values are geometric mean. Study TAK-438/CPH-401 was conducted in 11 young Japanese males. *AUC0-12 †This simulation was conducted by the reviewer.
Abbreviations: AUC_{0-inf}, area under the curve from time zero to infinity; BID, twice daily; C_{max}, maximum plasma concentration; inh, inh bitor; PK, pharmacokinetics; QD, once daily; SD, single dose

Reviewer's comments: Based on an in vitro recombinant CYP phenotyping study (Report A914-438-036), CYP3A4, CYP2D6, and CYP2C19 accounted for 45.4%, 49.1% and 5.5% of the in vitro CYP-mediated metabolism of vonoprazan, respectively. Based on the human ADME study (TAK438-103) and assuming 100% recovery of radioactivity, 8% of the vonoprazan dose was eliminated via renal excretion, and 13% was eliminated via SULT2A1-mediated sulfation. Assuming the rest of the absorbed radioactivity including those unidentified was all oxidative metabolism-related (77.6%), the f_m of each CYP in vivo was calculated to be 35.2% for CYP3A4, 38.1% for CYP2D6 and 4.3% for CYP2C19, respectively. In the vonoprazan PBPK model, 45.4% of the total clearance was assigned to the CYP3A4-mediated metabolism based on the in vitro phenotyping study. The 10% difference in fraction metabolized in CYP3A will not likely significantly change the results of the clarithromycin-vonoprazan simulations. However, because CYP2D6, CYP2C19 and SULT2A1, and/or any other unidentified pathways, were not explicitly incorporated in the vonoprazan PBPK model (Table 110), and both SULT2A1 and CYP2C19 (and/or any other unidentified pathways) could be induced by PXR ligands (e.g. rifampin and efavirenz)(Fang et al. 2007), there is a potential that the induction effects of rifampin and efavirenz on vonoprazan PK may be underestimated. The confidence in induction prediction is generally low, which is not a major concern in this case because the Applicant recommends avoiding co-administration of vonoprazan with strong or moderate CYP3A inducers in the product labeling.

As mentioned above, the fraction metabolized by CYP2D6 is similar to that by CYP3A4 in the in vitro recombinant CYP phenotyping study. Therefore, there is a concern about an increase in vonoprazan concentration when vonoprazan is co-administered with a strong CYP3A4 inhibitor and a strong CYP2D6 inhibitor. To explore the potential effect of CYP2D6 inhibition on vonoprazan exposure, the reviewer incorporated CYP2D6 into the Applicant's vonoprazan PBPK model. The model-simulated f_m was approximately 38% for CYP2D6, 36% for CYP3A4,

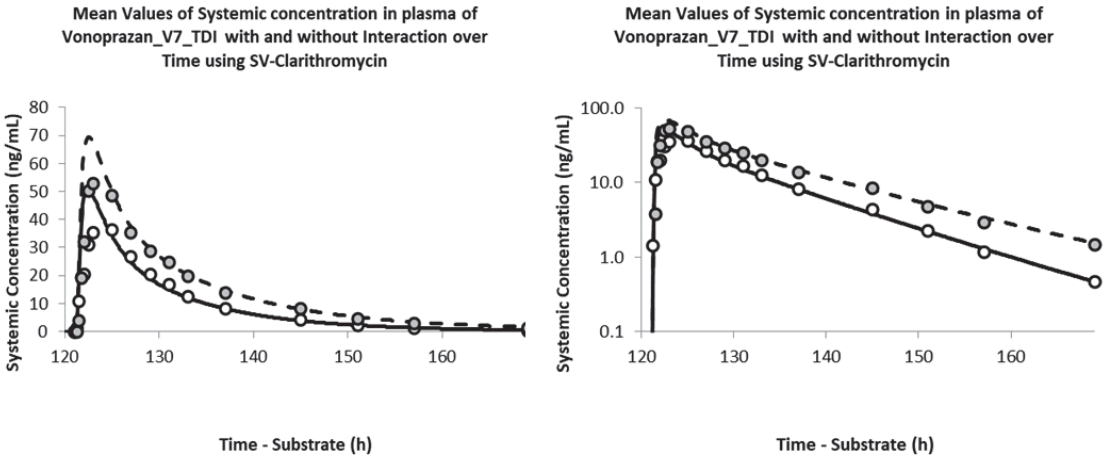
4.4% for CYP2C19, and 12.3% for additional HLM (e.g., SULT2A1). The ability of this model to predict the effect of clarithromycin on vonoprazan exposure was verified with the results from Study TAK-438-110 (Table 114 and Figure 23). The effects of CYP2D6 inhibition alone or in combination with CYP3A4 inhibition on vonoprazan exposure were simulated. For complete CYP2D6 inhibition, simulations were conducted in CYP2D6 poor metabolizers (PMs) and compared with that in extensive metabolizers (EMs). The results are summarized in Table 115. The simulated results showed that a strong CYP3A4 inhibitor had a similar effect on vonoprazan exposure in CYP2D6 PMs compared in CYP2D6 EMs. This is likely because vonoprazan is eliminated by multiple pathways and none of these pathways is the predominant pathway. Inhibition of one or two pathways was compensated by other pathways as shown in Figure 24. However, the overall vonoprazan exposure was significantly increased. Compared to vonoprazan AUC in CYP2D6 EMs in the absence of a CYP3A inhibitor, vonoprazan AUC in dual therapy could increase approximately 2-fold in CYP2D6 PMs and approximately 4-fold in CYP2D6 PMs who also take a strong CYP3A inhibitor. Vonoprazan AUC in triple therapy could increase approximately 2.5-fold in CYP2D6 PMs compared to vonoprazan AUC in CYP2D6 EMs.

Table 114. Predicted Effects of Clarithromycin on Vonoprazan Exposure in Healthy Subjects Following Co-administration of Multiple Doses of Vonoprazan With a Single Dose of Vonoprazan

CYP3A inhibitors	Vonoprazan	C_{max}	$AUC_{0\text{-}inf}$	$C_{max,inh}$	$AUC_{0\text{-}inf,\ inh}$	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	
Clarithromycin 500 mg BID 7d	40 mg SD D6	47.1	411	63.7	648	1.35	1.58	Study TAK-438-110
		48.5	401	67.2	641	1.39	1.6	simulated
		1.03	0.98	1.05	0.99	1.03	1.01	Sim/obs

Source: reviewer's analyses
Simulations were performed by the FDA reviewer using a modified vonoprazan model in which the median f_m of each CYP was 35.6% for CYP3A4, 37.5% for CYP2D6 and 4.4% for CYP2C19, respectively, in the absence of an inhibitor. A single dose of 40 mg vonoprazan was given on Day 6 following oral administration of 500 mg clarithromycin twice daily for 7 days in 10 x10 healthy subjects of equal males and females.
Abbreviations: $AUC_{0\text{-}inf}$, area under the curve from time zero to infinity; BID, twice daily; C_{max}, maximum plasma concentration; inh, inh bitor; PK, pharmacokinetics; SD, single dose

Figure 23. Simulated and Observed Vonoprazan Plasma Concentration-time Profiles in Healthy Subjects Following Co-administration of Multiple Doses of Clarithromycin With a Single Dose of Vonoprazan



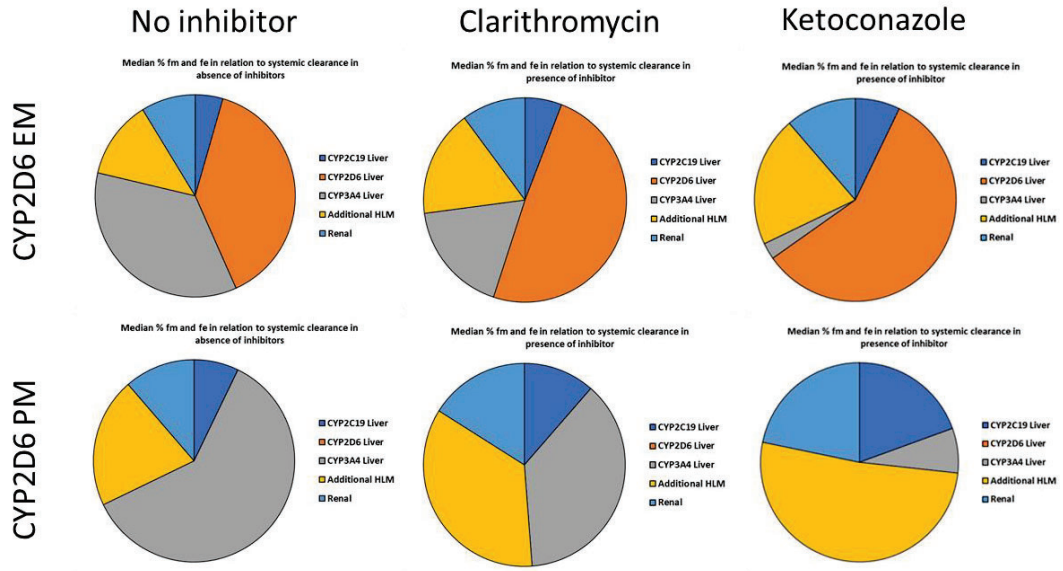
Source: reviewer's analyses
Simulated (lines) and observed (circles) vonoprazan plasma concentration-time profiles in healthy subjects in the presence (filed circle and dash line) or absence (open circle and solid line) of clarithromycin. Simulations were performed by the FDA reviewer using a modified vonoprazan model in which the median f_m of each CYP was 35.6% for CYP3A4, 37.5% for CYP2D6 and 4.4% for CYP2C19, respectively, in the absence of an inh bitor. A single dose of 40 mg vonoprazan was given on Day 6 following oral administration of 500 mg clarithromycin twice daily for 7 days in 10 x10 healthy subjects of equal males and females.

Table 115. Effects of CYP2D6 Polymorphism and Strong CYP3A4 Inhibitors on Vonoprazan Exposure

CYP3A inhibitors	Vonoprazan Dosing	C_{max}	AUC	$C_{max,inh}$	AUC_{inh}	C_{max} Ratio	AUC Ratio	CYP2D6 Phenotype
Clarithromycin 500 mg BID 7d	20 mg SD D6	23.6	189	32.8	302	1.39	1.60	CYP2D6 EM
		33.0	335	50.3	742	1.53	2.22	CYP2D6 PM
	20 mg BID 7d	35.3	226	45.7	313	1.30	1.38	CYP2D6 EM
		64.7	496	96.6	827	1.49	1.67	CYP2D6 PM
Ketoconazole 400 mg qd 7d	20 mg SD D6	23.6	189	34.8	326	1.47	1.73	CYP2D6 EM
		33.0	335	54.7	848	1.66	2.50	CYP2D6 PM
	20 mg BID 7d	35.3	226	47.2	320	1.34	1.42	CYP2D6 EM
		64.7	496	105.8	907	1.64	1.83	CYP2D6 PM

Source: reviewer's analyses
Simulations were performed by the FDA reviewer using a modified vonoprazan model in which the median f_m of each CYP was 35.6% for CYP3A4, 37.5% for CYP2D6 and 4.4% for CYP2C19, respectively, in the absence of an inhibitor. A single or multiple doses of 20 mg vonoprazan were given following oral administration of clarithromycin or ketoconazole in 10 x10 healthy CYP2D6 EMs or CYP2D6 PMs of equal males and females.
Abbreviations: AUC, area under the curve; BID, twice daily; C_{max}, maximum plasma concentration; inh, inhaled; QD, once daily; SD, single dose

Figure 24. Contribution of Various Pathways to Vonoprazan Systemic Clearance in CYP2D6 EMs and PMs in the Presence or Absence of a Strong CYP3A4 Inhibitor



Source: reviewer's analyses

3. Can PBPK analyses be used to estimate the effects of vonoprazan on CYP3A substrate midazolam and CYP2C19 substrates omeprazole and lansoprazole?

Vonoprazan is metabolized by CYP3A and is a time-dependent inhibitor and reversible inhibitor of CYP3A in vitro. Auto-inactivation of CYP3A was incorporated into the vonoprazan PBPK model. The CYP3A inhibition parameters of vonoprazan were verified with the midazolam interaction study (Table 116). Vonoprazan is also an inhibitor of CYP2C19. Vonoprazan was reported to increase the AUC of proguanil, a CYP2C19 substrate, by 1.42-fold following oral administration of vonoprazan 20 mg once daily for 5 days (Funakoshi et al. 2019). In response to FDA's information request dated December 19, 2021, the Applicant incorporated the CYP2C19 inhibition parameters of vonoprazan in its PBPK model and simulate the effects of steady state vonoprazan (20 mg BID for 14 days) alone and in combination with clarithromycin (500 mg BID for 14 days) on the pharmacokinetics of CYP2C19 substrates omeprazole and lansoprazole (Information request dated December 19, 2021). The results are summarized in Table 117.

Table 116. Predicted Geometric Mean C_{max} and AUC Values and Corresponding Geometric Mean Ratios for Midazolam in the Absence and Presence of Vonoprazan

	Control		Plus vonoprazan		Ratio	
	C_{max} (ng/mL)	AUC_{inf} (ng.h/mL)	C_{max} (ng/mL)	AUC_{inf} (ng.h/mL)	C_{max}	AUC_{inf}
Simulated	7.06	21.2	11.7	41.7	1.66	1.97
Trial Range	5.29 - 8.89	16.4 - 25.5	8.34 - 14.7	29.3 - 54.7	1.58 - 1.78	1.78 - 2.15
Observed	9.74	24.0	18.8	45.4	1.93	1.89
90% CI	NA	NA	NA	NA	1.61 - 2.33	1.51 - 2.37
S/O	0.72	0.88	0.62	0.92	0.86	1.04

Source: Table 21 in the PBPK report
Single oral dose of midazolam (2 mg) was given alone or co-administered with vonoprazan on the 8th day of 9 days of dosing (20 mg BID). Observed geometric mean data are from the Study VONO-101.
Abbreviations: AUC_{inf}, area under the curve extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; inh, inhibitor; S/O, simulated/observed

Table 117. Simulated Effects of Vonoprazan on CYP2C19 Substrates Omeprazole and Lansoprazole by Vonoprazan in CYP2C19 EM Subjects Following 14 Days of Co-administration

	Dual PAK or Triple PAK	CYP2C19 substrates	Substrate GMR		Simulation
			Cmax	AUC	
Dual PAK	**vonoprazan** (20 mg BID)	**lansoprazole** (30 mg QD)	1.06	1.16	Sponsor
		omeprazole (20 mg BID)	1.13	1.28	Sponsor
			1.13	1.19	Reviewer
Triple PAK	**vonoprazan** (20 mg BID) + **clarithromycin** (500 mg BID)	**lansoprazole** (30 mg QD)	1.11	1.31	Sponsor
		omeprazole (20 mg BID)	1.47	2.18	Sponsor
			1.22	1.36	Reviewer

Source: Table 2b in Clinical information amendment-2022-01-14 and reviewer's analyses.
A calculated fu_{mic} of 0.94 at 0.2 mg/mL and Ki value of 5.1, calculated using the Cheng-Prusoff equation based on IC_{50} of 13 μM and [S] of 20 μM (report TAK-438-11256) and a K_m of 13 μM,. were incorporated in the PBPK model. Reviewer's analyses were performed using the omeprazole PBPK model without the CYP2C19 time-dependent inhibition parameters of omeprazole.
Abbreviations: AUC_{tau}, area under the curve during a dosing interval; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; QD, once daily

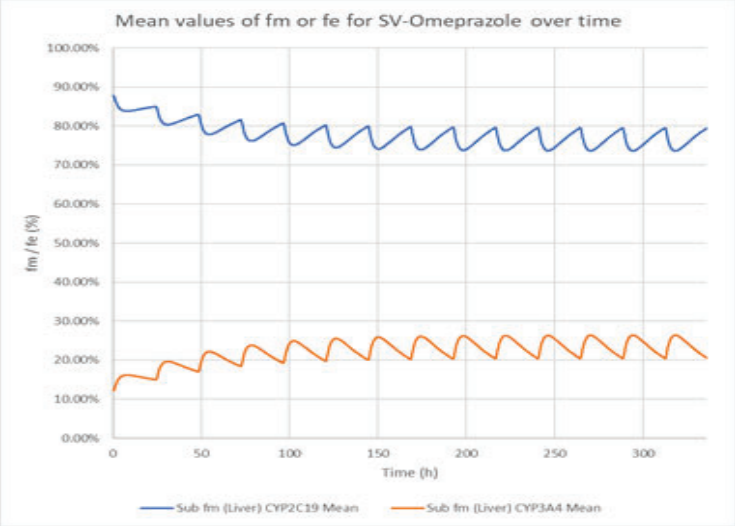
Reviewer's comments: According to the PBPK model summaries of omeprazole and lansoprazole, the contributions of CYP2C19 and CYP3A4 to the elimination of these two drugs are approximately 90% and 10% for omeprazole, and 75% and 12.5% for lansoprazole (12.5% other clearance), respectively. Although the contributions of CYP3A4 to the elimination of these drugs are similar, the predicted effects of triple PAK on their PK were different (Table 117). Omeprazole but not lansoprazole is a time-dependent inhibitor of CYP2C19. To examine the mechanism of the effect of triple PAK on omeprazole PK, simulations of omeprazole multiple-dose PK in the presence or absence of dual PAK or triple PAK were performed by the reviewer. As shown in Figure 25, following oral administration of multiple doses of 20 mg omeprazole once daily, the contribution of CYP3A4 increased to 25%, and the contribution of CYP2C19 decreased to 75%. It is possible that the greater effects of triple PAK on the exposure of omeprazole compared to lansoprazole were due to the increased contribution of CYP3A4 to its elimination as a result of auto-inhibition of omeprazole. To confirm this possibility, simulations were performed using the omeprazole PBPK model without its CYP2C19 time-dependent inhibition parameters, the predicted effects of vonoprazan alone or in combination with clarithromycin on the exposure of omeprazole was similar to that of lansoprazole (Table 117). These results suggest that 20-mg vonoprazan twice a day had little effects on CYP2C19. This conclusion is different from those observed by Funakoshi and his colleagues (Funakoshi et al. 2019).

The data reported by Funakoshi and his colleagues suggested a weak inhibition potential of vonoprazan on proguanil exposure. The clinical study was conducted in Japanese subjects with CYP2C19 EM phenotype. Vonoprazan increased proguanil AUC by 1.42-fold and reduced its metabolic ratio (cycloguanil/proguanil) and apparent formation clearance by 0.507- and 0.433-fold, respectively, following oral administration of vonoprazan with a less frequent dosing regimen (20 mg once daily for 5 days) (Funakoshi et al. 2019). In this study, proguanil was administered as a combination formulation with atovaquone but the later had little effect on proguanil PK (Funakoshi et al. 2019) thus is unlikely to affect the assessment of the interaction between vonoprazan and proguanil. While shorter treatment duration in the control phase (3 days) compared to the treatment phase (5 days) may explain, in part, the greater observed inhibitory effect of vonoprazan on proguanil compared to that predicted, it could not explain the significant reduction in the metabolite formation of cycloguanil. Cycloguanil is the active metabolite of proguanil, and in vitro studies showed that both CYP2C19 and CYP3A4 could be involved in its formation (Birkett et al. 1994; Coller et al. 1999). In CYP2C19 PMs, cycloguanil/proguanil reduced 95% compared to that in CYP2C19 NMs (Watkins et al. 1990), suggesting that cycloguanil is predominantly formed via the CYP2C19 pathway and proguanil is a sensitive substrate of CYP2C19. Therefore, the observed effects of vonoprazan on proguanil and its metabolite could be mainly due to

CYP2C19 inhibition. With the more frequent dosing regimen of vonoprazan in the Dual PAK and Triple PAK, a greater effect on CYP2C19 inhibition may be expected.

One possible explanation for why the inhibitory effects of vonoprazan on CYP2C19 observed in the proguanil study were not predicted by the PBPK modeling could be that the in vitro CYP2C19 time-dependent inhibition parameters of vonoprazan underpredicted its inhibitory effect on CYP2C19 in vivo. It is worth noting that CYP2C19 inhibition parameters in the vonoprazan PBPK model have not been verified with clinical DDI data. In conclusion, the clinical data and PBPK simulation suggested that vonoprazan may be a weak inhibitor of CYP2C19. The in-vivo inhibition potential of Dual PAK or Triple PAK on the PK of a CYP2C19 substrate depends on the contribution of CYP3A4 to its elimination ranging from weak to moderate.

Figure 25. Contribution of CYP3A4 and CYP2C19 to Omeprazole Disposition Following 14 Days of Oral Administration of 20 mg Vonoprazan BID



Source: reviewer's analysis
Abbreviations: BID, twice daily; CYP2C19, cytochrome P450 2C19; CYP3A4, cytochrome P450 3A4; fe, fraction excreted; fm, fraction metabolized; h, hour

Conclusions

The PBPK analyses showed that the Dual Pak may have a weak inhibitory effect on CYP2C19 substrates, and the Triple Pak may have weak to moderate inhibitory effects on CYP2C19 substrates depending on whether the substrates are also a CYP3A4 substrate and the contribution of CYP3A4 to its elimination. The analyses may underestimate the induction effects of rifampin and efavirenz on vonoprazan PK. Confidence in induction prediction is low but is not a major concern in this case because the Applicant recommends avoiding co-administration of vonoprazan with strong or moderate CYP3A inducers in the product labelling. In addition, due to the potential significant effect of CYP2D6 inhibition on vonoprazan exposure, it is prudent to conduct in vitro or/and in vivo studies to confirm the role of CYP2D6 in the metabolism of vonoprazan.

14.5. Summary of Bioanalytical Method Validation and Performance

Multiple bioanalytical methods were utilized for PK assessments from 2007 onwards. The summary of bioanalytical method validation reports is provided in Table 118.

Table 118. Summary of Bioanalytical Methods Validation Report TAK-438-1539-107

Validation report	TAK-438-1539-107 (Studies: TAK-438_109, TAK-438_107, HP-301, TAK-438_114, TAK-438_112, TAK-438_113, TAK-438_110, VONO-101, TAK-438_111)				
Method type	LC-MS/MS (Based on Study number P08-19108)				
Metrix	Plasma				
Analytes	**TAK-438**	**M-I**	**M-II**	**M-III**	**M-IV-Sul**
Calibration range (ng/mL)	0.1-100	1-1000	1-1000	0.1-100	1-1000
LLOQ (ng/mL)	0.1	1	1	0.1	1
QC range (ng/mL)	0.25-80	2.5-800	2.5-800	0.25-80	2.5-800
Inter-assay precision range* (%CV)	3.2-8.6	3.7-10.2	4-9.2	5-8.9	3.9-9.1
Inter-assay accuracy range* (%)	103.8-106	93.9-100	95.1-97.2	97.3-101.6	98.5-100.6
Stability duration at room temperature	24 hours from Report P06-19101				
Long-term stability at temperature	371 days at - 80°C as per Report TAK-438-10631/P08-19110				

Source: Compiled by reviewer
* Inter-assay precision and accuracy values for the QC concentrations are reported as the number of runs for calibration standards appear insufficient. The insufficient number for calibration standard runs is not a concern as the methods used in this report are same as in the Report TAK-438-00195 (Study number P08-19108), which reports values for calibration standards. Findings from Report TAK-438-00195 are summarized below.
Cross-validation findings are also provided in Reports TAK-438-11793 and method transfer information is provided in Report 8445154.
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

Table 119. Summary of Bioanalytical Methods Validation Report TAK-438-1539-094

Validation report	TAK-438-1539-094 (Study: TAK-438_101)				
Method type	LC-MS/MS (Based on Study number P08-19101)				
Metrix	Plasma				
Analytes	**TAK-438**	**M-I**	**M-II**	**M-III**	**M-IV-Sul**
Calibration range (ng/mL)	0.1-100	1-1000	1-1000		
LLOQ (ng/mL)	0.1	1	1		
QC range (ng/mL)	0.25-80	2.5-800	2.5-800	-	
Inter-assay precision range* (%CV)	5.6-6.1	6.2-10.4	3.4-8.6		
Inter-assay accuracy range* (%)	93-108.2	98.4-103.4	97.2-101		
Stability duration at room temperature	24 hours				
Long-term stability at temperature	371 days at - 80°C as per Report TAK-438-10631/P08-19110				

Source: Compiled by reviewer
* Inter-assay precision and accuracy values for the QC concentrations are reported as the number of runs for calibration standards appear insufficient. The insufficient number for calibration standard runs is not a concern as the methods used in this report are same as in the Report TAK-438-00123 (Study number P06-19101), which reports values for calibration standards. Findings from Report TAK-438-00123 are summarized below.
Cross-validation findings are also provided in Reports TAK-438-11793 and method transfer information is provided in Report 8445154.
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

Table 120. Summary of Bioanalytical Methods Validation Report TAK-438-00123

Validation report	TAK-438-00123 (Study: TAK-438/CPH-001)				
Method type	LC-MS/MS (Based on Study number P06-19101)				
Metrix	Plasma				
Analytes	**TAK-438**	**M-I**	**M-II**	**M-III**	**M-IV-Sul**
Calibration range (ng/mL)	0.1-100	1-1000	1-1000		
LLOQ (ng/mL)	0.1	1	1		
QC range (ng/mL)	0.25-80	2.5-800	2.5-800	-	
Inter-assay precision range (%)[#]	1.9-7.2	1.8-8.5	2.6-7		
Inter-assay accuracy range (%CV)[#]	90.2-114	85.5-111	89.7-109.4		
Stability duration at room temperature	24 hours				
Long-term stability at temperature	371 days at - 80°C as per Report TAK-438-10631/P08-19110				

Source: Compiled by reviewer
The study also demonstrated 10-fold dilution integrity.
[#] Based on the Reviewer's calculations
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

Table 121. Summary of Bioanalytical Methods Validation Report TAK-438-00195

Validation report	TAK-438-00195 (Studies: TAK-438/CPH-002, TAK-438/CPH-401)				
Method type	LC-MS/MS				
Metrix	Plasma				
Analytes	**TAK-438**	**M-I**	**M-II**	**M-III**	**M-IV-Sul**
Calibration range (ng/mL)	0.1-100	1-1000	1-1000	0.1-100	1-1000
LLOQ (ng/mL)	0.1	1	1	0.1	1
QC range (ng/mL)	0.25-80	2.5-800	2.5-800	0.25-80	2.5-800
Inter-assay precision range (CV%)[#]	3.5-17.7	3.2-8.2	3.4-9	2.6-5.8	2.8-6.6
Inter-assay accuracy range (%)[#]	82-133	87-111	88.2-115.5	89.6-114.8	87-111.2
Stability duration at room temperature	24 hours				
Long-term stability at temperature	371 days at - 80°C as per Report TAK-438-10631/P08-19110				

Source: Compiled by reviewer
The study also demonstrated 10-fold dilution integrity.
#Based on the Reviewer's calculations
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

For selected clinical studies (with PK assessments), bioanalytical performance reports were reviewed from a clinical pharmacology perspective and the review of these reports are summarized in Table 122.

Table 122. Review of Bioanalytical Performance Reports

Report Type	Criteria	Assessment
	TAK-438 109 (Report 8200767)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided Note: Limited number of chromatograms provided for spiked control matrix.	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438 101 (Report 1539/095)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable Note: ISR analysis was not performed for this study	☐ Yes ☒ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438/CPH-001 (Report P07-19105)	
Performance report(s)	Samples analyzed within the established stability period Note: The report does not discuss sample storage duration, however, a summary document (2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods (Human)) notes that storage duration less than 3 months, which is noted to be within the 371 days of documented stability at -80°C.	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable Note: ISR analysis was not performed for this study	☐ Yes ☒ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438 107 (Report No. 1539-108)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No

Report Type	Criteria	Assessment
	TAK-438/CPH-002 (Report P08-19112)	
Performance report(s)	Samples analyzed within the established stability period Note: The report does not discuss sample storage duration, however, a summary document (2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods (Human)) notes that storage duration of approximately four months, which is noted to be within the 371 days of documented stability at -80°C.	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable Note: ISR analysis was not performed for this study	☐ Yes ☒ No
	Overall performance reasonable	☒ Yes ☐ No
	HP-301 (Report 8447445)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438_112 (Report 8259210)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438_113 (Report 8259212)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No

Report Type	Criteria	Assessment
	TAK-438_114 (Report 8351-626)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438_110 (Report 8229820)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
	TAK-438/CPH-401 (Report P11-19121)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
	VONO-101 (Report 8450577)	
Performance report(s)	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control (QC) samples range acceptable	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No

Source: Compiled by reviewer
Abbreviation: ISR, incurred sample reanalysis; QC, quality control

15. Trial Design: Additional Information and Assessment

15.1. Applicant's Protocol Synopsis for Study HP-301

A synopsis for HP-301 is provided below.

Title

"A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter pylori* Infection."

Study Phase

Phase 3.

Study Sites

Approximately 150 sites in the United States and Europe.

Indication

Helicobacter pylori infection.

Rationale

The purpose of this study is to compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, clarithromycin) administered for 14 days in subjects with *H. pylori* infection.

Objectives

Primary Objective

To compare the efficacy of *H. pylori* eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in *H. pylori* + subjects who do not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline.

Secondary Objectives

- To compare the efficacy of *H. pylori* eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in subjects infected with a clarithromycin resistant strain of *H. pylori.*
- To compare the efficacy of *H. pylori* eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in all subjects.

Safety Objectives

To compare the safety of vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in *H. pylori* + subjects.

Study Population

Subjects ≥18 years of age with confirmed *H. pylori* infection not previously treated with any regimen to attempt to eradicate *H. pylori*.

Study Design

This is a phase 3 randomized study to compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, clarithromycin) administered for 14 days in *H. pylori* + subjects.

Approximately 975 subjects will be randomized in a 1:1:1 ratio to receive:

- Vonoprazan dual therapy arm: vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID for 14 days
- Vonoprazan triple therapy arm: vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days
- Lansoprazole triple therapy arm/control arm: lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.

H. pylori + subjects whose eligibility is confirmed by ^{13}C-urea breath test (^{13}C-UBT) during the Screening Period will have an endoscopy performed to collect gastric mucosal biopsy specimens to document *H. pylori* infection by histology and for culture and susceptibility testing to determine resistance to bacteria to clarithromycin, amoxicillin and metronidazole antibiotics. At Week 6 (4 weeks after the last dose of study drug), *H. pylori* eradication status will be assessed by ^{13}C-UBT. Subjects who remain *H. pylori* + should have a follow-up endoscopy with repeat bacteriological testing for resistant bacteria to the antibiotics used in the study, and the subjects should be treated as per the standard clinical care.

Estimated Study Duration

The study will consist of a ≤34-day screening period, a 14-day treatment period and a 4-week follow-up period.

Efficacy Assessments

The study will evaluate *H. pylori* infection status as determined by a ^{13}C-UBT. If the subject's ^{13}C-UBT test is positive at 4 weeks after the last dose of study drug, an endoscopy will be performed, and gastric mucosal biopsy specimens will be taken for antibiotic susceptibility testing.

Pharmacokinetic or Pharmacodynamic Assessments

For pharmacokinetic analysis of drug concentrations, blood samples will be collected at the Week 2 Visit, unless prohibited by local regulations.

In order to determine the subject's metabolizer status, an optional blood sample will be obtained for CYP2C19 genotype testing, unless prohibited by local regulations.

Safety Assessments

Safety assessments will include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory assessments, physical examinations, electrocardiograms and vital signs.

Study Drug, Dosage, and Route of Administration

- The vonoprazan dual therapy arm will consist of vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID for 14 days.
- The vonoprazan triple therapy arm will consist of vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.
- The lansoprazole triple therapy arm/control arm will consist of lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.
- All study drugs will be administered orally starting on Day 1 (the day after randomization).

Sample Size

325 subjects per arm.

Statistical Methods

The primary endpoint (proportion of subjects with successful *H. pylori* eradication after the treatment period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, in subjects who do not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline) will be calculated as a percentage of subjects in each treatment group.

Noninferiority of vonoprazan triple therapy to lansoprazole triple therapy, and vonoprazan dual therapy to lansoprazole triple therapy, will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in *H. pylori* eradication rates between treatments. For each noninferiority comparison that yields statistical significance, superiority will then be assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

The secondary endpoints will be evaluated in a similar manner as the primary endpoint for superiority of vonoprazan triple therapy to lansoprazole triple therapy and of vonoprazan dual therapy to lansoprazole triple therapy.

HP-301 Full Eligibility Criteria

Inclusion Criteria

Subjects are eligible for enrollment in the study if they meet all of the following inclusion criteria:

(1) The subject is ≥ 18 years of age at the time of informed consent signing.
(2) In the opinion of the investigator or sub-investigators, the subject is capable of understanding and complying with protocol requirements.
(3) The subject signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures. The subject is informed of the full nature and purpose of the study, including possible risks and side

effects. The subject has the ability to cooperate with the investigator. Ample time and opportunity should be given to read and understand verbal and/or written instructions.

(4) The subject has at least one of the following clinical conditions with confirmed *H. pylori* infection demonstrated by a positive ^{13}C-UBT during the Screening Period.

- Dyspepsia (i.e., pain or discomfort centered in the upper abdomen) lasting at least 2 weeks
- A confirmed diagnosis of functional dyspepsia
- A recent / new diagnosis of (non-bleeding) peptic ulcer
- A history of peptic ulcer not previously treated for *H. pylori* infection
- A requirement for long-term non-steroidal anti-inflammatory drug (NSAID) treatment at a stable dose of the NSAID

(5) A female subject of childbearing potential who is or may be routinely sexually active with a nonsterilized male partner agrees to routinely use adequate double barrier contraception from the signing of informed consent until Day -2 and 2 forms of adequate contraception from Day -1 until 4 weeks after the last dose of study drug.

Exclusion Criteria

Subjects are not eligible for study participation if they meet any of the following exclusion criteria:

(1) The subject has previously been treated with any regimen to attempt to eradicate *H. pylori*.
(2) The subject has gastric or duodenal ulcer with endoscopic evidence of current or recent bleeding.
(3) The subject has confirmed diagnosis of gastric cancer by biopsy.
(4) The subject is receiving colchicine.
(5) The subject has received any investigational compound (including those in postmarketing studies) within 30 days prior to the start of the Screening Period. A subject who has screen failed from another clinical study and who has not been dosed may be considered for enrollment in this study.
(6) The subject is a study site employee, an immediate family member, or is in a dependent relationship with a study site employee who is involved in conduct of this study (e.g., spouse, parent, child, sibling) or who may have consented under duress.
(7) The subject has cutaneous lupus erythematosus or systemic lupus erythematosus.
(8) The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to randomization.
(9) The subject has Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.
(10) The subject has a history of hypersensitivity or allergies to vonoprazan (including the formulation excipients: D-mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 8000, titanium oxide, red or yellow ferric oxide), proton pump inhibitors (PPIs), amoxicillin and/or clarithromycin, or any excipients used in the ^{13}C-UBT: mannitol, citric acid or

aspartame. Skin testing may be performed according to local standard practice to confirm hypersensitivity.

(11) The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to screening, or who regularly consume >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine) per week based on self-report. Subjects must have a negative urine drug screen for cannabinoids/tetrahydrocannabinol and non-prescribed medications at screening.

(12) The subject is taking any excluded medications or treatments listed in the protocol.

(13) If female, the subject is pregnant, lactating, or intending to become pregnant before, during, or within 4 weeks after participating in this study; or intending to donate ova during such time period.

(14) The subject has a history or clinical manifestations of significant central nervous system, cardiovascular, pulmonary, hepatic, renal, metabolic, other gastrointestinal, urological, endocrine or hematological disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.

(15) The subject requires hospitalization or has surgery scheduled during the course of the study or has undergone major surgical procedures within 30 days prior to the Screening Visit.

(16) The subject has a history of malignancy (including mucosa-associated lymphoid tissue lymphoma) or has been treated for malignancy within 5 years prior to the start of the Screening Period (Visit 1) (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).

(17) The subject has acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, or tests positive for the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or HCV RNA. However, subjects who test positive for HCV antibody, but negative for HCV RNA are permitted to participate.

(18) The subject has any of the following abnormal laboratory test values at the start of the Screening Period:

- Creatinine levels: >2 mg/dL (>177 μmol/L).
- Alanine aminotransferase (ALT) or AST >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN.

15.2. Applicant's Protocol Synopsis for Study CCT-401

A synopsis for CCT-401 is provided below.

Study Title

"A Phase 3, Randomized, Double-Blind, Double Dummy, Multicenter, Parallel Group Comparison Study to Evaluate Efficacy and Safety of a Triple Therapy with TAK-438, Amoxicillin, and Clarithromycin by Comparison with a Triple Therapy with AG-1749, Amoxicillin, and Clarithromycin for the First Line Eradication of *Helicobacter pylori*."

Phase of Development

Phase 3.

Study Design

This was a phase 3, Randomized, Double-Blind, Multicenter, Parallel Group Comparison Study to evaluate efficacy and safety of a Triple Therapy (twice daily for 1 week by oral administration) with TAK-438 (20 mg/time), amoxicillin (750 mg/time) and clarithromycin (200 mg or 400 mg/time) by Comparison with Triple Therapy (twice daily for 1 week by oral administration) with AG-1749 (30 mg/time), amoxicillin (750 mg/time) and clarithromycin (200 mg or 400 mg/time) in subjects with *H. pylori*-positive gastric ulcer scar or duodenal ulcer scar.

Subjects judged to be eligible were assigned to TAK-438 group (L) (clarithromycin 200 mg/time), TAK-438 group (H) (clarithromycin 400 mg/time), AG-1749 group (L) (clarithromycin 200 mg/time), AG-1749 group (H) (clarithromycin 400 mg/time) at 1:1:1:1 as the first line eradication phase, with the first line eradication phase treatment administered twice daily for 1 week. After the completion of first line eradication treatment, it shifted to the observation phase after first line eradication for 4 weeks and sterilization was evaluated at the end of the observation phase after first line eradication.

Subjects judged unsuccessful by evaluation of sterilization at the end of the observation phase after the first line eradication shifted to the second line eradication phase. Three agents, TAK-438 (20 mg/time), amoxicillin (750 mg/time) and metronidazole (250 mg/time), were orally administered all at the same time, twice daily for 1 week. After the completion of second line eradication treatment, sterilization was evaluated after a four week observation phase.

However, when the number of randomized subjects transitioning to second line eradication phase reaches 50, there may be cases not shifting to second line eradication phase.

Primary Objective:

To confirm the efficacy of a Triple Therapy with TAK-438/amoxicillin/clarithromycin by validating the non-inferiority of a Triple Therapy with TAK-438/amoxicillin/clarithromycin to a Triple Therapy with AG-1749/amoxicillin/clarithromycin in subjects with *H. pylori*-positive gastric ulcer scar or duodenal ulcer scar.

Secondary Objectives

To compare the safety of a Triple Therapy with AG-1749/amoxicillin/clarithromycin with a Triple Therapy with TAK-438/amoxicillin/clarithromycin in subjects with *H. pylori*-positive gastric ulcer scar or duodenal ulcer scar.

Additionally, to evaluate the efficacy and safety of a Triple Therapy with TAK-438/amoxicillin/clarithromycin in subjects with *H. pylori*-positive gastric ulcer scar or duodenal ulcer scar and unsuccessful first line eradication.

Subjects

Subjects with *H. pylori*-positive gastric ulcer scar or duodenal ulcer scar.

Number of Study Sites

Approximately 50 institutions.

Planned Sample Size:

Number of Randomized Subjects (Revised on December 19, 2012)

TAK-438 group: 324 subjects, AG-1749 group: 324, subjects Total: 648 subjects.

Number of Evaluable Subjects for the Primary Endpoints (Revised on December 19, 2012)

TAK-438 group: 318 subjects, AG-1749 group: 318 subjects, Total: 636 subjects.

Target Number of Subjects for the Second Line Eradication Phase

50 subjects.

Route of Administration

Oral.

Dosage and Administration:

See Table 123 and Table 124 for dosage and administration for the first line eradication phase and the second line eradication phase, respectively.

Table 123. First Line Eradication Phase

Treatment group		Treatment description (one time)	Dose regimen
TAK-438 group	TAK-438 group (L) (Clarithromycin 200 mg/time)	TAK-438 20 mg 1 tablet AG-1749 placebo 1 capsule Amoxicillin 250 mg 3 capsules Clarithromycin 200 mg 1 tablet	Twice daily
	TAK-438 group (H) (Clarithromycin 400 mg/time)	TAK-438 20 mg 1 tablet AG-1749 placebo 1 capsule Amoxicillin 250 mg 3 capsules Clarithromycin 200 mg 2 tablets	
AG-1749 group	AG-1749 group (L) (Clarithromycin 200 mg/time)	TAK-438 placebo 1 tablet AG-1749 30 mg 1 capsule Amoxicillin 250 mg 3 capsules Clarithromycin 200 mg 1 tablet	
	AG-1749 group (H) (Clarithromycin 400 mg/time)	TAK-438 placebo 1 tablet AG-1749 30 mg 1 capsule Amoxicillin 250 mg 3 capsules Clarithromycin 200 mg 2 tablets	

Source: CCT-401 Protocol Amendment 3-A Synopsis

Table 124. Second Line Eradication Phase

Treatment group	Treatment description (one time)	Dose regimen
TAK-438 group	TAK-438 20 mg 1 tablet Amoxicillin 250 mg 3 capsules Metronidazole 250 mg 1 tablet	Twice daily

Source: CCT-401 Protocol Amendment 3-A Synopsis

Treatment Period

- One week (First line eradication phase).
- One week (Second line eradication phase).

Evaluation Period

First Line Eradication Phase

- One week (First line eradication treatment phase).
- Four weeks (Observation phase after first line eradication).

Second Line Eradication Phase

- One week (Second line eradication treatment phase).
- Four weeks (Observation phase after second line eradication).

Main Endpoints

Efficacy

Primary endpoint: First *H. pylori* eradication rates 4 weeks after the completion of first line eradication treatment).

Secondary endpoint: Second *H. pylori* eradication rates 4 weeks after the completion of second line eradication treatment).

The rate for both endpoints is for subjects who are diagnosed with *H. pylori* negative by ^{13}C-urea breath test.

Safety

Adverse events, laboratory test data, electrocardiogram, vital signs, serum gastrin, and pepsinogen I/II.

Statistical Methods

Point estimates and two-sided 95% CIs were calculated by treatment group following the frequency tabulation of first *H. pylori* eradication rates 4 weeks after the completion of first line eradication treatment by treatment group in the "full analysis set." Also, the point estimate and two-sided 95% CI of the difference between the first *H. pylori* eradication rates of TAK-438 group and AG-1749 group (TAK-438 group - AG-1749 group) 4 weeks after the completion of first line eradication treatment were calculated.

In addition, comparison between TAK-438 group and AG-1749 group was performed by applying Farrington and Manning non-inferiority test to the population proportions.

Rationale for the Planned Sample Size

From the results of the phase 3 study for *H. pylori* eradication therapy by a Triple Therapy with AG-1749, Amoxicillin, and Clarithromycin, because *H. pylori* eradication rates of the AG-1749 60 mg/day (BID) group, AG-1749 60 mg/day (BID) + amoxicillin 1,500 mg/day (BID) + clarithromycin 400 mg/day (BID) group and AG-1749 60 mg/day (BID) + amoxicillin 1,500 mg/day (BID) + clarithromycin 800 mg/day (BID) group were 0.0%, 87.5% and 89.2% respectively in subjects with *H. pylori* -positive gastric ulcer, and were 4.4%, 91.1% and 83.7% respectively in subjects with *H. pylori* -positive duodenal ulcer, H. *pylori* first eradication rate 4 weeks after end of the first line eradication phase treatment of the AG-1749 group in this study

was assumed to be 90%. Although there is no data of *H. pylori* eradication rate by a Triple Therapy with TAK-438, Amoxicillin, and Clarithromycin, *H. pylori* first eradication rate four weeks after the end of the first line eradication phase treatment of the TAK-438 group was assumed to be 90% based on the decision that it would be possible to expect effectiveness that is comparable to that of AG-1749. When the non-inferiority margin is set at 10%, 200 cases per group would be required as the number of evaluable cases for the primary endpoints to secure 90% power of test. The ratio of dropouts after randomization was assumed to be approximately 10%, and the number of randomized subjects was set to 220 cases per group.

In addition, based on the results of recalculation of the number of subjects conducted on August 23, 2012, the number of randomized subjects was changed to 324 cases per arm, assuming 318 cases per group as the number of cases for which it would be possible to evaluate the primary endpoints and ratio of dropouts after randomization is approximately 2%.

CCT-401 Full Eligibility Criteria

Inclusion Criteria

The eligibility of the subjects shall be assessed based on the following criteria.

(1) Subjects who were judged to have the ability to understand the details of the study and comply with them by the investigators.
(2) Subjects who are able to sign and date the informed consent document by themselves prior to implementation of the study procedures.
(3) Subjects who were confirmed to be *H. pylori*-positive at the start of the study (VISIT 1).
(4) Subjects with stomach or duodenal ulcer scars observed on Endoscopy at the start of the study (VISIT 1). However, subjects with a history of ulcer which was confirmed by an interview or a past medical record were allowed to participate, even if their stomach or duodenal ulcer scars had disappeared.
(5) Outpatient subjects (note that hospitalization for examination is acceptable), regardless of gender, whose age at the time of giving informed consent is at least 20-year-old.
(6) In the case of subjects who may become pregnant, individuals who will consent to use the appropriate contraception on a daily basis throughout the study period starting from the time of the acquisition of informed consent and up to 4 weeks after the final dose.

Exclusion Criteria

Subjects corresponding to any of the following criteria shall not be included in this study.

(1) Subjects administered the study drug (including study drug used in postmarketing clinical study) within 84 days prior to the start of the study (VISIT 1) However, the study drug for phase 3, double-blind study in subjects with gastric ulcer of TAK-438 (TAK-438/CCT-101) or phase 3, double-blind study in subjects with duodenal ulcer of TAK-438 (TAK-438/CCT-102) are excluded.
(2) Subjects who have received TAK-438 with clinical study in the past. However, as for the subjects who participated in phase 3, double-blind study in subjects with gastric ulcer (TAK-438/CCT-101) or duodenal ulcer (TAK-438/CCT-102) and completed the study are allowed to be enrolled. Subjects who have a dependent relationship (e.g., married couple, parents, children, siblings) with employees of study sites, said employees' family

members, or employees of study sites relating to the implementation of this study, or subjects who may be compelled to give consent.

(3) Subjects who donated at least 400 mL of blood within 90 days prior to the start of the study (VISIT 1).
(4) Subjects who have a history of H. pylori eradication therapy
(5) Subjects with any of the following conditions at the start of the study (VISIT 1): acute upper gastrointestinal bleeding, gastric or duodenal ulcer [defective mucosa with white coating (includes adherent blood clots) 3 mm or more in size], acute gastric mucosal lesion (AGML) or acute duodenal mucosal lesion (ADML). However, subjects with gastric or duodenal erosion are permitted to participate.
(6) Subjects who underwent or are going to undergo surgeries that affect gastric acid secretion (upper digestive tract resection, vagotomy, etc.)
(7) Subjects who have conditions, such as perforation, pyloric stenosis, or severe bleeding, for which medicinal therapies are not to be indicated.
(8) Subjects who have a history or complications of Zollinger-Ellison syndrome, or other gastric acid hypersecretion disorders.
(9) Subjects with impaired liver or kidney, receiving colchicine.
(10) Subjects who have a history of hypersensitivity or allergy on TAK-438 (including excipient2), PPI, penicillin-based drug, macrolide-based drug, or antitrichomonal agent.
(11) Subjects who have a history of drug abuse (use of illegal drugs) or alcohol addiction within one year prior to the study (VISIT 1) (including subjects with complications).
(12) Subjects who need a treatment with a prohibited concomitant drug or a prohibited concomitant treatment.
(13) Female subjects who are pregnant or breast-feeding. Female subjects who plan to become pregnant or donate eggs throughout the study period from the time of the acquisition of informed consent and up to 4 weeks after the final dose of the study drug.
(14) Subjects who have serious central nervous system, lung, liver, kidney, metabolic, digestive system, urinary system, endocrine system, or hematologic complications.
(15) Subjects who have a surgery requiring hospitalization scheduled during the trial or is in a condition requiring surgery.
(16) Subjects who have a history of malignancy or of treatment of malignancy within 5 years prior to the start of treatment period (VISIT 1). However, individuals who are completely recovered from cutaneous basal cell carcinoma and cervical intraepithelial carcinoma may be included.
(17) Individuals with complications of acquired immunodeficiency syndrome (AIDS) (including HIV carriers) or hepatitis [including hepatitis virus carriers (HBs antigen-positive or HCV antibody-positive)]. However, individuals who are HCV antigen-negative or HCV-RNA-negative may be included.
(18) Subjects complicated with an infectious mononucleosis.
(19) Subjects who have organic disease in brain, spinal cord.
(20) Subjects who fall under any one of the following categories in laboratory tests at the start of the study (VISIT 1):

- Creatinine level exceeds 2 mg/dL
- ALT or AST level exceeds 2.5 times the upper limit of normal
- Total bilirubin level exceeds 2 times the upper limit of normal

16. Efficacy: Additional Information and Assessment

16.1. Per-Protocol (PP) Analyses for Study HP-301

Table 125 displays eradication rates in PP populations. Results from PP analyses support conclusions obtained from the primary and secondary analyses.

Table 125. *H. pylori* Eradication Rate (%) 4 Weeks After Treatment Completion (PP Population), HP-301

PPp Population (all PP subjects who did not have a clarithromycin- or amoxicillin-resistant strain at baseline)			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	218	219	212
Success, n (%)	177 (81.2)	198 (90.4)	174 (82.1)
Difference vonoprazan-lansoprazole (95% CI)	-0.9% (-8.3%, 6.5%)	8.3% (1.9%, 15.0%)	
all PP subjects with clarithromycin-resistant strain at baseline			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	44	58	62
Success, n (%)	35 (79.5)	39 (67.2)	18 (29.0)
Difference vonoprazan-lansoprazole (95% CI)	50.5% (32.3%, 64.9%)	38.2% (20.6%, 53.4%)	
PP Population			
Parameter	**Vonoprazan Dual Therapy**	**Vonoprazan Triple Therapy**	**Lansoprazole Triple Therapy**
N	265	280	277
Success, n (%)	215 (81.1)	240 (85.7)	194 (70.0)
Difference vonoprazan-lansoprazole (95% CI)	11.1% (3.9%, 18.2%)	15.7% (8.9%, 22.5%)	

Source: Reviewer's analysis. Confidence intervals are calculated with pre-specified Miettinen and Nurminen method.
Abbreviations: CI, confidence interval; PP per protocol; N, number of patients in treatment group; n, number of patients with given characteristic

16.2. Subgroup Analyses for Study HP-301

As shown in Table 125 below in the mITT population, the vonoprazan dual therapy has an eradication rate of 66.7% (14/21) in the Black or African American subgroup, while the lansoprazole triple therapy has a similar eradication rate of 68.2% (15/22). The sample size is small for this subgroup and no conclusion can be made. No other inconsistency in treatment effect of the vonoprazan dual therapy or vonoprazan triple therapy was observed in demographic subgroups of age, gender, race, ethnicity, and geographic region, in Study HP-301.

Table 125. *H. pylori* Eradication Rate 4 Weeks After Treatment Completion by Baseline Demographics (mITT population), HP-301

Demographic Parameters	Vonoprazan Dual Therapy (N=324)	Vonoprazan Triple Therapy (N=338)	Lansoprazole Triple Therapy (N=330)
Sex, n (%)			
Female	155/196 (79.1)	178/220 (80.9)	139/205 (67.8)
Male	95/128 (74.2)	95/118 (80.5)	87/125 (69.6)
Age Group, n (%)			
<65	188/250 (75.2)	206/265 (77.7)	178/268 (66.4)
≥65	62/74 (83.8)	67/73 (91.8)	48/62 (77.4)
Race, n (%)			
White	227/294 (77.2)	242/298 (81.2)	203/297 (68.4)
Black or African American	14/21 (66.7)	21/29 (72.4)	15/22 (68.2)
Other or Unknown	9/9 (100.0)	10/11 (90.9)	8/11 (72.7)
Ethnicity, n (%)			
Hispanic or Latino	61/86 (70.9)	67/94 (71.3)	50/80 (62.5)
Not Hispanic or Latino	187/235 (79.6)	206/243 (84.8)	176/250 (70.4)
Unknown or Not Reported	2/3 (66.7)	0/1 (0)	0/0 (NA)
Region, n (%)			
Europe	151/190 (79.5)	166/194 (85.6)	136/196 (69.4)
USA	99/134 (73.9)	107/144 (74.3)	90/134 (67.2)

Source: Reviewer's Analysis.
Abbreviations: mITT, modified intent-to-treat; N, number of patients in treatment group; n, number of patients with given characteristic

16.3. Subgroup Analyses for Study CCT-401

As shown in Table 126 below, no inconsistency in treatment effect of the vonoprazan triple therapy was observed in demographic subgroups of age and gender in Study CCT-401. Note that this is a study using a shorter treatment duration (10 days). This study was conducted in Japan, and all subjects were Asian.

Table 126. *H. pylori* Eradication Rate 4 Weeks After Completion of First Line Eradication Treatment by Baseline Demographics (FAS population), CCT-401

Demographic Parameters	Vonoprazan Triple Therapy (N=329)	Lansoprazole Triple Therapy (N=321)
Sex, n (%)		
Female	120/133 (90.2)	85/127 (66.9)
Male	180/196 (91.8)	158/194 (81.4)
Age Group, n (%)		
<65	226/247 (91.5)	185/250 (74.0)
≥65	74/82 (90.2)	58/71 (81.7)

Source: Reviewer's Analysis.
Abbreviations: FAS, full analysis set; N, number of patients in treatment group; n, number of patients with given characteristic

17. Clinical Safety: Additional Information and Assessment

Demographic characteristics in trial HP-301 (safety population) are listed in the following table. The three groups had similar distributions in these characteristics. All subjects were between 20 and 87 years of age. Approximately 62% of subjects were female, 43% of subjects were from United States, and 41% of subjects were from Poland. The subjects were predominantly White.

Table 127. Baseline Demographic Characteristics, Safety Population, Trial HP-301

Characteristic	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345
Sex, n (%)			
Female	209 (60.1)	224 (64.7)	213 (61.7)
Male	139 (39.9)	122 (35.3)	132 (38.3)
Age, years			
Mean (SD)	51.9 (13.5)	50.8 (13.9)	51.6 (13.6)
Median (min, max)	52 (20, 80)	51 (20, 81)	52 (21, 87)
Age group, years, n (%)			
<45	101 (29.0)	126 (36.4)	109 (31.6)
≥45 to <65	170 (48.9)	144 (41.6)	171 (49.6)
≥65 to <75	68 (19.5)	67 (19.4)	53 (15.4)
≥75	9 (2.6)	9 (2.6)	12 (3.5)
Race, n (%)			
American Indian or Alaska Native	0 (0)	1 (0.3)	1 (0.3)
Asian	4 (1.1)	6 (1.7)	6 (1.7)
Black or African American	22 (6.3)	30 (8.7)	25 (7.2)
Native Hawaiian or Other Pacific Islander	1 (0.3)	0 (0)	0 (0)
Not Reported	1 (0.3)	3 (0.9)	0 (0)
Other	4 (1.1)	1 (0.3)	3 (0.9)
Unknown	1 (0.3)	1 (0.3)	1 (0.3)
White	315 (90.5)	304 (87.9)	309 (89.6)
Ethnicity, n (%)			
Hispanic or Latino	95 (27.3)	98 (28.3)	89 (25.8)
Not Hispanic or Latino	250 (71.8)	247 (71.4)	256 (74.2)
Not Reported	1 (0.3)	1 (0.3)	0 (0)
Unknown	2 (0.6)	0 (0)	0 (0)

Characteristic	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345
Country of participation, n (%)			
BGR	42 (12.1)	42 (12.1)	38 (11.0)
CZE	7 (2.0)	7 (2.0)	4 (1.2)
GBR	5 (1.4)	1 (0.3)	2 (0.6)
HUN	8 (2.3)	8 (2.3)	7 (2.0)
POL	136 (39.1)	139 (40.2)	147 (42.6)
USA	150 (43.1)	149 (43.1)	147 (42.6)

Source: Clinical data scientist and clinical reviewer analysis
Abbreviations: BGR, Bulgaria; CZE, Czechia; GBR, United Kingdom; HUN, Hungary; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation; POL, Poland; USA, United States of America

The table below summarizes the disposition of subjects in trial HP-301. A total of 1039 subjects received treatment (safety population) in HP-301 trial. The majority of the subjects in the vonoprazan and lansoprazole groups completed study drug (≥96.0% of subjects in each treatment group). A total of 36 subjects (11 vonoprazan dual therapy, 14 vonoprazan triple therapy, 11 lansoprazole triple therapy) discontinued treatment. Reasons for treatment discontinuation reported for at least two subjects included pretreatment event, adverse event (AE), or serious AE, protocol deviation or withdrawal of consent. The percentage of subjects discontinuing treatment was similar across treatment groups.

Table 128. Patient Disposition, Trial HP-301

Disposition Outcome	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345
Patients randomized	348	346	345
mITT population	323	335	328
Per-protocol population	265	280	277
Safety population	348	346	345

Disposition Outcome	Vonoprazan Dual Therapy N=348	Vonoprazan Triple Therapy N=346	Lansoprazole Triple Therapy N=345
Discontinued study drug, n (%)	11 (3.2)	14 (4)	11 (3.2)
Lack of efficacy	1 (0.3)	0	0
Lost to follow-up	0	2 (0.6)	1 (0.3)
Other	4 (1.1)	3 (0.9)	4 (1.2)
Pre-treatment event (PTE) or adverse event (AE) or serious adverse event (SAE)	3 (0.9)	8 (2.3)	5 (1.4)
Significant protocol deviation	2 (0.6)	0	0
Voluntary withdrawal	0	1 (0.3)	1 (0.3)
Withdrawal of consent	1 (0.3)	0	0

Source: Clinical data scientist and clinical reviewer analysis
Abbreviations: AE, adverse event; mITT, modified intent-to-treat; N, number of patients in treatment group; n, number of patients with given characteristic, PTE, pre-treatment event; SAE, serious adverse event

Table 129 shows the adverse events in trial HP-301 by System Organ Class. Gastrointestinal disorders were the most common types of TEAEs experienced in each of the treatment groups, with a higher incidence occurring in the lansoprazole triple therapy group (17.7%) compared with the vonoprazan dual or triple therapy groups (12.1% each).

Table 129. Subjects With Adverse Events by System Organ Class, Safety Population, Trial HP-301

System Organ Class	Vonoprazan Dual Therapy N=348 n (%)	Vonoprazan Triple Therapy N=346 n (%)	Lansoprazole Triple Therapy N=345 n (%)	Vonoprazan Dual Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)	Vonoprazan Triple Therapy vs. Lansoprazole Triple Therapy Risk Difference (%) (95% CI)
Infections and infestations	31 (8.9)	26 (7.5)	22 (6.4)	2.5 (-1.4, 6.5)	1.1 (-2.7, 4.9)
Metabolism and nutrition disorders	6 (1.7)	8 (2.3)	1 (0.3)	1.4 (-0.0, 2.9)	2.0 (0.3, 3.7)
Blood and lymphatic system disorders	5 (1.4)	0	1 (0.3)	1.1 (-0.2, 2.5)	-0.3 (-0.9, 0.3)
Psychiatric disorders	4 (1.1)	4 (1.2)	0	1.1 (0.0, 2.3)	1.2 (0.0, 2.3)
Injury, poisoning and procedural complications	3 (0.9)	5 (1.4)	0	0.9 (-0.1, 1.8)	1.4 (0.2, 2.7)
Renal and urinary disorders	5 (1.4)	1 (0.3)	2 (0.6)	0.9 (-0.6, 2.3)	-0.3 (-1.3, 0.7)
Reproductive system and breast disorders	3 (0.9)	1 (0.3)	1 (0.3)	0.6 (-0.6, 1.7)	-0.0 (-0.8, 0.8)
Cardiac disorders	1 (0.3)	5 (1.4)	0	0.3 (-0.3, 0.8)	1.4 (0.2, 2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0	0	0.3 (-0.3, 0.8)	0 (0, 0)
Respiratory, thoracic and mediastinal disorders	3 (0.9)	3 (0.9)	2 (0.6)	0.3 (-1.0, 1.5)	0.3 (-1.0, 1.6)
Ear and labyrinth disorders	0	3 (0.9)	0	0 (0, 0)	0.9 (-0.1, 1.8)
Immune system disorders	0	1 (0.3)	0	0 (0, 0)	0.3 (-0.3, 0.9)
Congenital, familial and genetic disorders	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Endocrine disorders	0	0	1 (0.3)	-0.3 (-0.9, 0.3)	-0.3 (-0.9, 0.3)
Eye disorders	0	1 (0.3)	1 (0.3)	-0.3 (-0.9, 0.3)	-0.0 (-0.8, 0.8)
Vascular disorders	3 (0.9)	8 (2.3)	4 (1.2)	-0.3 (-1.8, 1.2)	1.2 (-0.8, 3.1)
General disorders and administration site conditions	3 (0.9)	2 (0.6)	5 (1.4)	-0.6 (-2.2, 1.0)	-0.9 (-2.4, 0.6)
Hepatobiliary disorders	1 (0.3)	2 (0.6)	3 (0.9)	-0.6 (-1.7, 0.5)	-0.3 (-1.6, 1.0)
Skin and subcutaneous tissue disorders	7 (2.0)	4 (1.2)	9 (2.6)	-0.6 (-2.8, 1.6)	-1.5 (-3.5, 0.6)
Investigations	1 (0.3)	4 (1.2)	4 (1.2)	-0.9 (-2.1, 0.4)	-0.0 (-1.6, 1.6)
Musculoskeletal and connective tissue disorders	5 (1.4)	7 (2.0)	10 (2.9)	-1.5 (-3.6, 0.7)	-0.9 (-3.2, 1.4)
Nervous system disorders	10 (2.9)	26 (7.5)	28 (8.1)	-5.2 (-8.6, -1.9)	-0.6 (-4.6, 3.4)
Gastrointestinal disorders	41 (11.8)	42 (12.1)	61 (17.7)	-5.9 (-11.2, -0.6)	-5.5 (-10.8, -0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Duration for treatment defined as 14 days.
For specific preferred terms, see the table “Patients With Adverse Events by System Organ Class and Preferred Term…”
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event

Table 130 shows the demographics, treatment received, and cause of death of subjects who died in trial HP-301. Three subjects (two in vonoprazan triple therapy [VTRI] and one in lansoprazole triple therapy [LTRI]) died during the post-treatment follow-up period of the study.

Table 130. Listing of All Individual Patient Deaths, Safety Population, Trial HP-301

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
VTRI20	(b) (6)	54	M	20 mg	14	45	Corona virus infection	Covid-19 infection
VTRI20		67	M	20 mg	14	56	Cardiac arrest	Sudden cardiac arrest
LTRI30		56	F	30 mg	14	94	Pneumonia viral	Covid pneumonia with hypoxia

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any event that occurred after the first dose of study drug or any event at baseline that worsened in either intensity or frequency after the first dose of study drug.
Duration for treatment defined as 14 days.
Abbreviations: F, female; ID, identifier; M, male; NA, not applicable

Demographic characteristics of the safety population in trial CCT-401 are listed in Table 131. The two groups had similar distributions in these characteristics. About 40% of subjects were female. All subjects were from Japan.

Table 131. Baseline Demographic Characteristics, Safety Population, Trial TAK-438/CCT-401

Characteristic	Vonoprazan Triple Therapy N=329	Lansoprazole Triple Therapy N=321
Sex, n (%)		
Female	133 (40.4)	127 (39.6)
Male	196 (59.6)	194 (60.4)
Age, years		
Mean (SD)	55.2 (12.3)	53.9 (12.9)
Median (min, max)	56 (20, 82)	55 (20, 88)
Age group, years, n (%)		
<40	37 (11.2)	50 (15.6)
≥40	292 (88.8)	271 (84.4)
Race, n (%)		
Asian	329 (100)	321 (100)
Ethnicity, n (%)		
N/A		
Country of participation, n (%)		
Japan	329 (100)	321 (100)

Source: adsl.xpt; Software: R
Abbreviations: N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

18. Mechanism of Action / Drug Resistance: Additional Information and Assessment

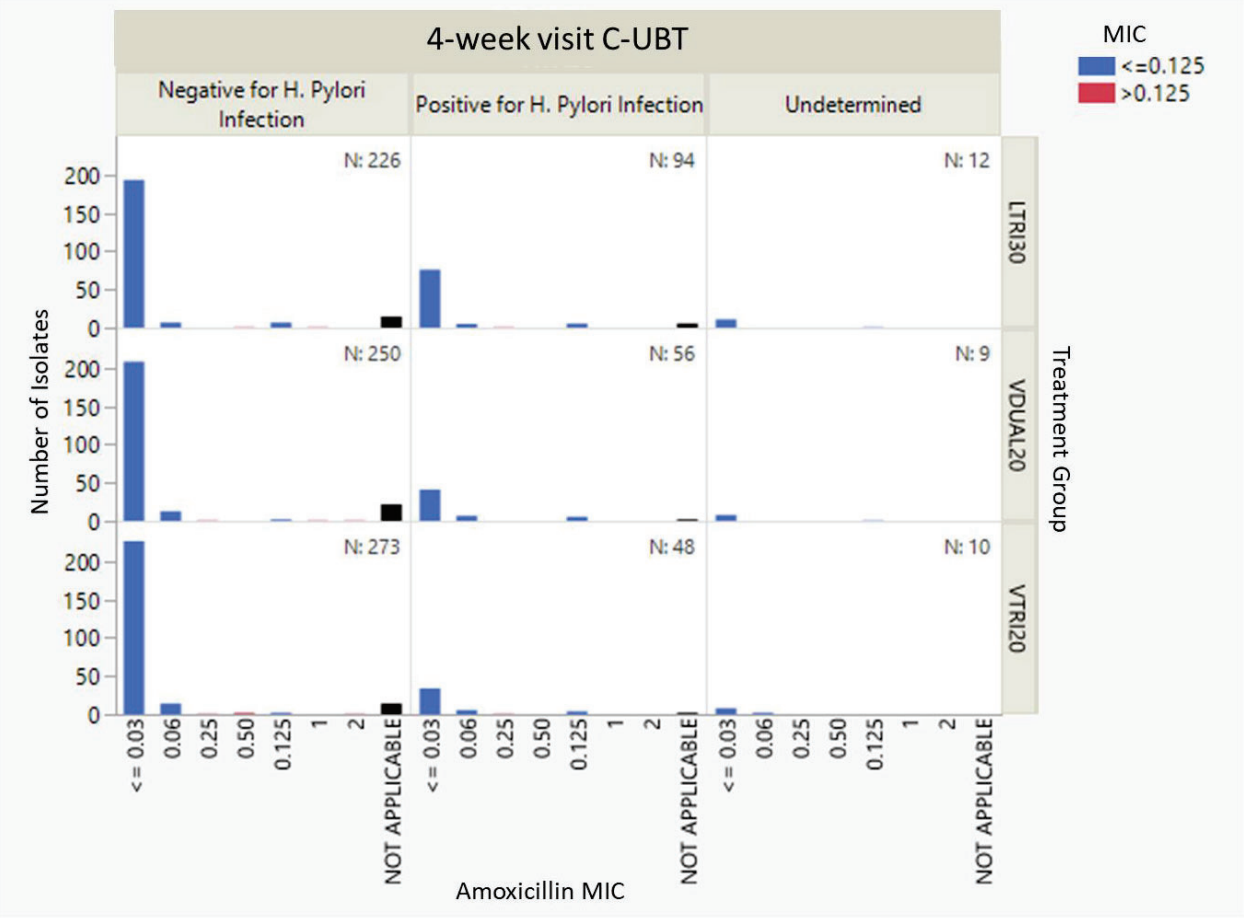
Vonoprazan is a competitive and reversible inhibitor of the hydrolysis of H^+, K^+-ATPase in a dose-dependent manner. Only modest inhibition of a Na^+, K^+-ATPase was observed after treatment with vonoprazan, suggesting the inhibition is ATPase specific. Incubation of vonoprazan with rabbit gastric glands resulted in inhibition of gastric acid formation at concentrations greater than 0.30 mcmol/L.

Amoxicillin is bactericidal against susceptible bacteria during active multiplication by inhibiting cell wall biosynthesis. Resistance to amoxicillin is mediated primarily through enzymes called beta-lactamases. Clarithromycin binds to the 50S ribosomal subunit of susceptible bacteria which results in the inhibition of protein synthesis.

Isolates collected during the pivotal phase three trial, HP-301, were tested to determine their susceptibility to amoxicillin, clarithromycin, and metronidazole using the standard 2-fold dilution method. The study used the resistance breakpoints of > 0.125 mcg/mL for amoxicillin > or equal to 1 mcg/mL for clarithromycin, and 8 mcg/mL for metronidazole. The study followed the FDA-recognized breakpoint for clarithromycin and the EUCAST breakpoints for amoxicillin and metronidazole. Only those subjects with isolates susceptible to amoxicillin and clarithromycin were used in the modified intent-to-treat primary analysis population (MITTp). There was no observable association between treatment failure and high minimum inhibitory concentration (MIC) for either amoxicillin (Figure 26) or clarithromycin (Figure 27). The percent of resistant strains of both amoxicillin and clarithromycin fall within the ranges recently

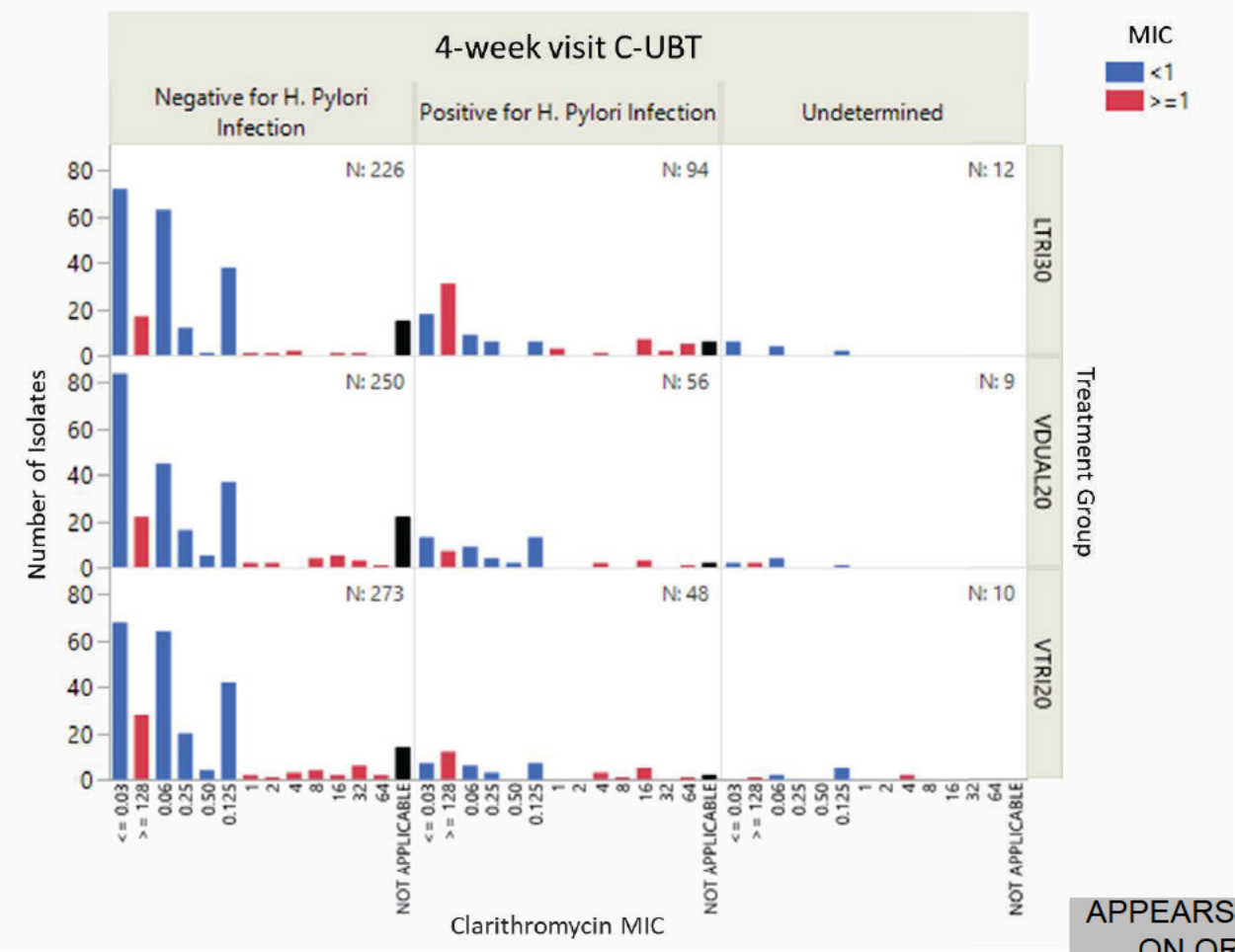
reported by a surveillance study - 0 to 27.7% for amoxicillin (all but one study reporting a resistance rate <10%) and 9 to 73.9% for clarithromycin.

Figure 26. Treatment Outcome by Baseline Amoxicillin MIC



Source: Clinical Study Report HP-301
Abbreviations: C-UBT; C-urea breath test; MIC, minimum inhibitory concentration; N, number of subjects

Figure 27. Treatment Outcome b Baseline Clarithrom cin MIC



APPEARS THIS WAY ON ORIGINAL

Source: Clinical Study Report HP-301
Abbreviations: C-UBT; C-urea breath test; MIC, minimum inhibitory concentration; N, number of subjects

19. Other Drug Development Considerations: Additional Information and Assessment

Vonoprazan is under development for the healing of all grades of erosive esophagitis and relief of heartburn, maintenance of healing of all grades of erosive esophagitis and relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Please refer to Section 10 for OSI's assessment. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of this indication. The Office of Computational Science on September 28, 2021, provided a data quality assessment, adverse event coding report, and overall data fitness assessment for the safety

review. Overall, the data quality for the clinical trials submitted was adequate to perform the review.

21. Labeling Summary of Considerations and Key Additional Information

Prescribing Information

General

This Prescribing Information (PI) review includes a high-level summary of the major changes made to the single PI submitted by the Applicant on September 3, 2021, for VOQUEZNA™ TRIPLE PAK and VOQUEZNA™ DUAL PAK. The following general revisions were made throughout the PI:

- The TRADENAME was changed from (b) (4) TRIPLE PAK and (b) (4) DUAL PAK to VOQUEZNA™ TRIPLE PAK and VOQUEZNA™ DUAL PAK throughout the PI based on the final recommendations of the Division of Medication Error Prevention and Analysis 1 (DMEPA 1). Refer to the DMEPA 1 review dated April 26, 2022, for additional details.
- Extensive revisions (e.g., reformatting and streamlining of the information) were made to the single PI submitted by the Applicant to ensure that the PI clearly identifies which risks belong to which product. Specifically, the important safety/drug interaction information pertaining to VOQUEZNA™ TRIPLE PAK and VOQUEZNA™ DUAL PAK vs. important safety/drug interaction information pertaining only to VOQUEZNA™ TRIPLE PAK due to the clarithromycin component were reformatted with specific headings, subheadings and streamlining of the information as appropriate.

(b) (4) was removed from several sections of the PI because it is not generally available in the U.S.

- *Clostridium difficile* was changed to the new nomenclature *Clostridioides difficile* throughout PI.

HIGHLIGHTS OF PRESCRIBING INFORMATION (HL) AND TABLE OF CONTENTS (TOC)

The **HL** and the **TOC** sections of the PI were revised for consistency with the changes made to the rest of the PI.

FULL PRESCRIBING INFORMATION

2. DOSAGE AND ADMINISTRATION

2.3 Missed Doses

The specific time of 4 hours within which VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK should be administered after a missed dose was added. The Applicant provided supportive PK simulations showing that missing a dose by up to 4 hours will have minimal impact on the exposure of vonoprazan prior to and after the missed dose.

5. WARNINGS AND PRECAUTIONS

5.1 Warnings and Precautions for VOQUEZNA TR IPLE PAK and VOQUEZNA DUAL PAK

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions were removed from the hypersensitivity warning and precaution (W&P) subheading and provided under a separate W&P subheading, to be consistent with the PI for other *H. pylori* combination products (e.g., Talicia and Omeclamox-Pak). Similar revisions were made to the Adverse Reactions section.

Rash with Use in Patients with Mononucleosis

The risk mitigation statement for this warning and precaution was changed from (b) (4) to "Avoid use of VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK in patients with mononucleosis." This revision was per the labeling recommendations in the guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011), that terminology that generally infers a contraindication (e.g., "Do not use" or "Drug X should not be used") should not appear in the WARNINGS AND PRECAUTIONS section.

5.2. Additional Warnings and Precautions for TRADENAME TRIPLE PAK Due to the Clarithromycin Component

Serious Adverse Reactions Due to Concomitant Use of Clarithromycin with Other Drugs
Benzodiazepines: A new risk mitigation statement was added to this warning and precaution as follows: "Closely monitor patients for signs or symptoms of increased or prolonged central nervous system effects when benzodiazepines such as triazolam or midazolam are used concomitantly with VOQUEZNA TRIPLE PAK *[see Drug Interactions (7.2)]*." This revision was per the labeling recommendations in the guidance for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011), to include information on the steps to take to decrease the likelihood, shorten the duration, or minimize the severity of an adverse reaction in the description of the W&P, if known and important to clinical decision making.

6. ADVERSE REACTIONS

6.1. Clinical Trials Experience

- Presentation of the number and incidence of vulvovaginal candidiasis in the table for the most common adverse reactions occurring in ≥2% of patients were modified based on further review of the data. Refer to Section 7 of this review for additional details.

- A disclaimer regarding comparative safety claims was included as a footnote to the table for the most common adverse reactions occurring in ≥2% of patient as follows: "This study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions in the

VOQUEZNA DUAL PAK, VOQUEZNA TRIPLE PAK, and LAC treatment groups." This addition was based on the labeling recommendations in the See page 9 of the *Adverse Reactions Section of Labeling* (January 2006).

- QT prolongation was added to the Cardiac Disorders section and a new section "Musculoskeletal system: bone fracture" was also added to the other adverse drug reactions occurring in <2% of patients with VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK subheading based on further review of the data by the FDA. Refer to Section 7 of this review for additional details.
- Genital infection fungal and taste disorder were removed from the listing of other adverse reactions occurring in <2% of patients treated with VOQUEZNA TRIPLE PAK or VOQUEZNA DUAL PAK listing because they were pooled with vulvovaginal candidiasis and dysgeusia under the most common adverse reactions table.
- Subsection 6.2 entitled "Other Important Adverse Reactions for the Individual Components of VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK was removed because majority of the adverse reactions described in this subsection were already included in subsection 6.1 of the PI .

6.2. Postmarketing Experience with Components of VOQUEZNA TRIPLE PAK and VOQUEZNA DUAL PAK

The information in subsection 6.2 was revised to reconcile redundancies (i.e., duplicated listed adverse reactions) with the information in subsection 6.1. This resulted in several adverse reactions being deleted from this subsection. Severe cutaneous adverse reactions were removed from the hypersensitivity adverse reactions subheading and provided under a separate adverse reactions subheading for the amoxicillin and the clarithromycin components.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

- A statement was added at the end of subsection 8.1 under the Risk Summary heading that will direct prescribers to report any exposed pregnancies to the Applicant's pharmacovigilance call line. The statement was as follows: "Report pregnancies to the Phathom Pharmaceuticals, Inc. Adverse Event reporting line at 1-800-775-PHAT (7428)." Refer to the Division of Pediatrics and Maternal Health (DPMH) review for additional details.

8.3. Females and Males of Reproductive Potential

- The statement under the Infertility subheading was revised to state that "Based on animal fertility study findings for clarithromycin, TRADENAME TRIPLE PAK may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*." Refer to Section 13.2.3.2 of this review and the DPMH review for additional details.

12. Clinical Pharmacology

12.1. Mechanism of Action

- The labeling was updated to include reference to vonoprazan as a proton pump-inhibitor (PPI). Refer to Section 13.2.1.1 of this review, Division of Gastroenterology (DG) consult

note dated January 26, 2022, and DG consult addendum on March 11, 2022 for additional details.

14. CLINICAL STUDIES

- [redacted] (b) (4) were removed from this section because they could be biased due to post-randomization exclusion. Refer to Section 16.1 of this review for additional details.

17. PATIENT COUNSELING INFORMATION

- Added a Severe Cutaneous Adverse Reactions subheading to this section to be consistent with the PI for other *H. pylori* combination products.
- Added the statement "Advise patients who are exposed to TRADENAME TRIPLE PAK or TRADENAME DUAL PAK during pregnancy to contact Phathom Pharmaceuticals, Inc. at 1-800-775-PHAT (7428)" to the Embryo-Fetal Toxicity sub-heading. Refer to the DPMH review for additional details.

Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Carton labeling
- Container label

22. Postmarketing Requirements and Commitments

The following Postmarketing Requirements (PMRs) were agreed to by the Applicant on April 26, 2022.

PMR 4270-1

Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to vonoprazan-containing products during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm births, 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.

PMR Schedule Milestones

- Draft Protocol Submission: November 2022
- Final Protocol Submission: July 2023
- Interim Report Submission: July 2024, July 2025, July 2026, July 2027, July 2028, July 2029, July 2030, July 2031, July 2032, July 2033, July 2034, July 2035
- Study Completion: July 2035

- Final report Submission: April 2036

PMR 4270-2

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

PMR Schedule Milestones

- Draft Protocol Submission: November 2022
- Final Protocol Submission: July 2023
- Interim Report Submission: July 2024, July 2025, July 2026, July 2027, July 2028, July 2029, July 2030
- Study Completion: July 2030
- Final Report Submission: April 2031

PMR 4270-3

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

PMR Schedule Milestones

- Draft Protocol Submission: November 2022
- Final Protocol Submission: June 2023
- Study Completion: August 2024
- Final Report Submission: May 2025

PMR 4270-4

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

PMR Schedule Milestones

- Draft Protocol Submission: July 2022
- Final Protocol Submission: September 2022
- Study Completion: December 2022
- Final Report Submission: March 2023

PMR 4270-5:

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

PMR Schedule Milestones

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

23. Financial Disclosure

Table 132. Covered Clinical Studies: [HP-301]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 155		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

For CCT-401 study: As agreed at the Pre-NDA Meeting on 10 November 2020, Phathom Pharmaceuticals, Inc. agreed to attempt to collect Financial Disclosure Certification for study TAK-438/CCT-401 that was not conducted in the U.S. under an IND. Only 4 sites provided information for all investigators, 9 sites provided partial information, 28 sites received the delivery but did not return information and for 5 sites the delivery was returned unopened. There were total 46 principal investigators in this study.

24. References

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25. Review Team

Table 133. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Eva Zuffova
Nonclinical Reviewer	Leah Rosenfeld
Nonclinical Team Leader	Terry Miller
Office of Clinical Pharmacology (OCP) Reviewer(s)	Abhay Joshi
OCP Team Leader(s)	Zhixia (Grace) Danielsen
OCP/Pharmacometrics Reviewer	Justin Earp
OCP/Pharmacometrics Division Director	Hao Zhu
OCP/PBPK Reviewer	Ying-Hong Wang
OCP/PBPK Team Leader	Yuching Yang
OCP/Pharmacogenomics Reviewer	Jeffrey Kraft
OCP/Pharmacogenomics Division Director	Michael Pacanowski
Division Director (OCP)	Kellie Reynolds
Clinical Reviewer	Mayurika Ghosh
Clinical Team Leader	Thomas Smith
Statistical Reviewer	Jie Cong
Statistical Team Leader	Daniel Rubin
Cross-Disciplinary Team Leader	Thomas Smith
Division Director (pharm/tox)	Hanan Ghantous
Supervisory Mathematical Statistician (OB)	Karen Higgins
Deputy Director (clinical)	Dmitri Iarikov
Division Director (clinical)	Peter Kim
Office Director (or designated signatory authority)	John Farley

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 134. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dorota Matecka, Molly Lee, David Claffey, Karina Zuck, Katherine Windsor, Caryn McNab, Min Kang, Elsbeth Chikhale, Jiao Yang, Anh-Thy Ly, James Laurenson
Clinical Microbiology	Ursula Waack; Avery Goodwin
OPDP	Nima Ossareh
OSI	Cheryl Grandinetti, Philipp Kronstein
OSE/DEPI	Hannah Day, Natasha Pratt
OSE/DMEPA	Damon Birkenmeier, Valerie Vaughan
OSE/DRISK	Brad Moriyama, Naomi Boston
Other	Aleksander Winiarski (OSE); Amy Chung (OSE), Neha Gada(OSE), Jane Liedtka (DMEPA), Tamara Johnson (DMEPA), Dalong Huang (IRT-QT)

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 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Mayurika Ghosh, MD	OND/OID/DAI	I-1, 2, III-3, 4, 7.2-7.7, 8.3, 9.1, 10, 11 III-17, 19-23 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Mayurika Ghosh -S Digitally signed by Mayurika Ghosh -S Date: 2022.05.03 12:16:45 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Thomas Smith, MD	OND/OID/DAI	I-III ☐ Authored ☐ Contributed ☒ Approved
Cross-Disciplinary Team Lead	**Signature:** Thomas D. Smith -S Digitally signed by Thomas D. Smith -S Date: 2022.05.03 10:16:43 -04'00'		

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Leah Rosenfield, PhD	OND/OID/DPT-ID	II-5.1, 7.1, 7.7, 8.4, III-13 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Leah Rosenfeld -S Digitally signed by Leah Rosenfeld -S Date: 2022.05.03 13:00:23 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Terry Miller, PhD	OND/OID/DPT-ID	II-5.1, 7.1, 7.7, 8.4, III-13 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Terry J. Miller -S Digitally signed by Terry J. Miller -S Date: 2022.05.03 14:08:52 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Hanan Ghantous, PhD, DABT	OND/OID/DPT-ID	II-5.1, 7.1, 7.7, 8.4, III-13 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Terry J. Miller -S Digitally signed by Terry J. Miller -S Date: 2022.05.03 16:04:18 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Jie Cong, PhD	OB/DBIV	I-2, II-3, 6.2, 6.3, III-15, III-16 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Jie Cong -S Digitally signed by Jie Cong -S Date: 2022.05.03 10:22:12 -04'00'		

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Daniel Rubin, PhD	OB/DBIV	I-2, II-3, 6.2, 6.3, III-15, III-16 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Daniel Rubin -S Digitally signed by Daniel Rubin -S Date: 2022.05.03 13:07:07 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Statistical	Karen Higgins, ScD	OB/DBIV	I-2, II-3, 6.2, 6.3, III-15, III-16 ☐ Authored ☐ Contributed ☒ Approved
Supervisor	**Signature:** Karen M. Higgins -S Digitally signed by Karen M. Higgins -S Date: 2022.05.03 11:25:51 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Zhixia (Grace) Danielsen, PhD	OTS/OCP/DIDP	II-5, 6.1, 8.1, 8.2, III-14 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Zhixia Y. Danielsen -S Digitally signed by Zhixia Y. Danielsen -S Date: 2022.05.03 11:08:12 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Abhay Joshi, PhD	OTS/OCP/DIDP	II-5, 6.1, 8.1, 8.2, III-14 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Abhay Joshi -S Digitally signed by Abhay Joshi -S Date: 2022.05.03 11:37:49 -04'00'		

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Division of Pharmacometrics (DPM)	Ying-Hong Wang PhD	OTS/OCP/DPM	II-8.2, III-14.4 ☒ Authored ☐ Contributed ☐ Approved
PBPK Reviewer	**Signature:** Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2022.05.03 14:24:53 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Division of Pharmacometrics (DPM)	Yuching Yang, PhD	OTS/OCP/DPM	II-8.2, III-14.4 ☐ Authored ☐ Contributed ☒ Approved
PBPK Team Leader	**Signature:** Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2022.05.03 15:09:31 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Division of Pharmacometrics (DPM)	Justin Earp, PhD	OTS/OCP/DPM	II-5, 8.1, 8.2, III-14.3 ☒ Authored ☐ Contributed ☐ Approved
Pharmacometrics Primary Reviewer	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S Date: 2022.05.03 12:37:42 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Division of Pharmacometrics (DPM)	Hao Zhu, PhD	OTS/OCP/DPM	II-5, 8.1, 8.2, III-14.3 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Hao Zhu -S Digitally signed by Hao Zhu -S Date: 2022.05.03 15:02:30 -04'00'		

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Division of Translational and Precision Medicine (DTPM)	Jeffrey Kraft, PhD	OTS/OCP/DTPM	II-5, 8.2 ☒ Authored ☐ Contributed ☐ Approved
Pharmacogenomics Primary Reviewer	**Signature:** Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S Date: 2022.05.03 11:12:55 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Division of Translational and Precision Medicine (DTPM)	Michael Pacanowski, PharmD, MPH	OTS/OCP/DTPM	II-5, 8.2 ☐ Authored ☐ Contributed ☒ Approved
OCP Pharmacogenomics Division Director	**Signature:** Michael Pacanowski -S Digitally signed by Michael Pacanowski -S Date: 2022.05.03 11:03:00 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Kellie Reynolds, PharmD	OTS/OCP/DIDP	II-5, 6.1, 8.1, 8.2, III-14 ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Kellie S. Reynolds -S Digitally signed by Kellie S. Reynolds -S Date: 2022.05.03 12:24:10 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Microbiology	Ursula Waack, PhD	OND/OID/DAI	II- 5.1, III-18 ☒ Authored ☐ Contributed ☐ Approved
Primary Reviewer	**Signature:** Ursula B. Waack -S (Affiliate) Digitally signed by Ursula B. Waack -S (Affiliate) Date: 2022.05.03 14:33:46 -04'00'		

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Microbiology	Avery Goodwin, PhD	OND/OID/DAI	II- 5.1, III-18 ☐ Authored ☐ Contributed ☒ Approved
Team Leader	**Signature:** Avery C. Goodwin -S Digitally signed by Avery C. Goodwin -S Date: 2022.05.03 12:03:16 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Product Quality	Dorota Matecka, PhD	OPQ	II-9 ☒ Authored ☐ Contributed ☐ Approved
Team Leader	**Signature:** Dorota M. Matecka -S Digitally signed by Dorota M. Matecka -S Date: 2022.05.03 12:48:54 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Regulatory Project Management	Eva Zuffova, PhD	OND/OID/DAI	III-12 ☒ Authored ☐ Contributed ☐ Approved
Project Manager	**Signature:** Eva Zuffova -S Digitally signed by Eva Zuffova -S Date: 2022.05.03 15:24:40 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Regulatory Project Management	Gregory DiBernardo	OND/OID/DAI	III-12 ☐ Authored ☐ Contributed ☒ Approved
Supervisor	**Signature:** Gregory Dibernardo -S Digitally signed by Gregory Dibernardo -S Date: 2022.05.03 15:17:00 -04'00'		

Continued: Table 135. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Dmitri Iarikov, MD, PhD	OND/OID/DAI	I-III ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	**Signature:** Dmitri E. Iarikov -S Digitally signed by Dmitri E. Iarikov -S Date: 2022.05.03 15:50:04 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Peter Kim, MD, MS	OND/OID/DAI	I-III ☐ Authored ☐ Contributed ☒ Approved
Division Director	**Signature:** Peter W. Kim -S Digitally signed by Peter W. Kim -S Date: 2022.05.03 16:10:17 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	John Farley, MD, MPH	OND/OID	I-III ☐ Authored ☐ Contributed ☒ Approved
Office Director	**Signature:** John Farley -S Digitally signed by John Farley -S Date: 2022.05.03 16:24:15 -04'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

EVA ZUFFOVA
05/03/2022 04:32:08 PM

JOHN J FARLEY
05/03/2022 04:36:54 PM