CLINICAL STUDY PROTOCOL

NCT Number: NCT04753437

Study Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With Vonoprazan Versus Quadruple Therapy With Esomeprazole

Study Number: Vonoprazan-1001

Protocol Version and Date:

Version 2: 23-June-2021

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With Vonoprazan Versus Quadruple Therapy With Esomeprazole

Study Identifier: Vonoprazan-1001

Compound: TAK-438 (vonoprazan)

Date: 23 June 2021

Version Number: 2

Date	Amendment Number	Amendment Type	Region
23 June 2021	Amendment 1	Substantial	China
28 October 2020	Initial protocol	Not applicable	China

[redacted]

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Asia Pte Ltd 8 Marina Boulevard #15-01 Marina Bay Financial Centre Singapore 018981.	**Compound:** Vonoprazan (TAK-438)
Study Identifier: Vonoprazan-1001	**Phase:** 1
Protocol Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With Vonoprazan Versus Quadruple Therapy With Esomeprazole.	
Trial Design: A phase 1, double-blind, parallel group study in healthy subjects with *Helicobacter pylori* (*H pylori*–positive) to evaluate the safety, tolerability, and pharmacokinetics (PK) of a quadruple therapy with bismuth, clarithromycin, amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole. Approximately 42 (maximum 46 subjects) *H pylori*–positive healthy subjects aged 18 to 60 years, inclusive, who are considered eligible based on the inclusion and exclusion criteria, will participate in this study. All subjects will be enrolled and randomized to 1 of the 2 treatment groups as indicated in the schematic in Section 2.0. The treatment phase will consist of quadruple therapy twice daily (BID) with bismuth potassium citrate (600 mg [equivalent to 220 mg bismuth]), BID clarithromycin (500 mg), amoxicillin (1000 mg), and vonoprazan (20 mg) (Group B) or quadruple therapy BID with bismuth potassium citrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and esomeprazole (20 mg) (Group A) administered from Days 1 to 14. Subjects will be discharged on Day 15 after all procedures have been performed. The subjects who complete study treatment are to be followed-up at Week 4 post-treatment to provide a ^{13}C urea breath test (^{13}C UBT) for *H pylori*.	
Trial Primary Objective: To evaluate the safety, tolerability, and PK of quadruple therapy with bismuth, clarithromycin, amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole.	
Trial Subject Population: *H pylori* positive, healthy male and female subjects in China, aged 18 to 60 years, inclusive	
Planned Number of Subjects: Approximately 42 (maximum 46, if drop-out rate from PK Analysis Set increases to more than 25%)	**Planned Number of Sites:** 1 site in China
Dose Levels: Vonoprazan (20 mg) Bismuth potassium citrate (600 mg equivalent to bismuth 220 mg) Clarithromycin (500 mg) Amoxicillin (1000 mg) Esomeprazole (20 mg)	**Route of Administration:** Oral
Duration of Treatment: Quadruple therapy BID for 14 days (Days 1 to 14)	**Planned Trial Duration:** Approximately 70 days (including screening, Day -1 through study exit, follow-up call, and follow-up visit)
Main Criteria for Inclusion: To be eligible for study participation, subjects must: 1. Be *H pylori*–positive healthy male or female subjects aged 18 to 60 years. 2. Have a body mass index between >18.0 and ≤30.0 kg/m^2 and weigh ≥50 kg	

Main Criteria for Exclusion:

The subject must be excluded from participating in the study if the subject has:

1. A history of hypersensitivity to clarithromycin, amoxicillin, or any excipients of vonoprazan and esomeprazole.
2. A history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, duodenal ulcer, gastric ulcer, Barrett's esophagus, or Zollinger-Ellison syndrome.
3. Levels of aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels above the upper limit of normal.
4. A history of neurological diseases.
5. Any clinically significant disease or is currently using prescription medications or herbal therapies.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

- Evaluation of bismuth plasma PK parameters when bismuth potassium citrate (600 mg [equivalent to 220 mg bismuth]) BID is coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and vonoprazan (20 mg BID), and when coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and esomeprazole (20 mg BID):
  - Maximum observed plasma concentration (C_{max}) at Day 14.
  - The area under the plasma concentration-time curve during a dosing interval (AUC_{τ}) at Day 14.
  - The amount of drug excreted in urine during a dosing interval (Ae_{τ}) at Day 14.

The secondary endpoints will be assessed through evaluation of the following parameters:

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who discontinue due to an adverse event (AE).

Safety endpoints are as follows:

- Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once post dose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post dose.
- Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once post dose.

Statistical Considerations:

AEs

All TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Data will be summarized using Preferred Term and primary System Organ Class. All TEAEs, drug-related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation will be summarized by treatment group (vonoprazan quadruple therapy and esomeprazole quadruple therapy)

Clinical Laboratory Evaluations, Vital Signs, and 12-Lead Electrocardiograms

Observed values and changes from baseline for continuous variables will be summarized over time by treatment group using descriptive statistics.

For categorical variables, shift tables will be presented by treatment group.

The number and percentage of subjects who meet the markedly abnormal criteria at least once post dose for safety laboratory tests, vital sign measurements, and safety ECG parameters will be summarized by treatment group.

PK

Plasma concentrations of bismuth, freebase of vonoprazan (TAK-438F), and esomeprazole will be summarized at each scheduled sampling point by treatment group using descriptive statistics. The plasma and urine PK parameters of bismuth at Day 14 will be summarized by treatment group using descriptive statistics.

Point estimate and the 2-sided 90% and 95% CIs of the geometric mean ratios between treatment group will be calculated using an analysis of variance with natural log-transformed AUC_{τ} and C_{max} of bismuth. It will be concluded that vonoprazan has no significant effect on bismuth PK compared with esomeprazole if the 90% CIs for AUC_{τ} and

C_{max} completely fall within 0.5 to 2.0. Statistical analyses of other plasma and urine PK parameters will be performed if appropriate.
Sample Size Justification: The study will randomize approximately 42 subjects (maximum 46 subjects, if drop-out rate from PK Analysis Set increases to more than 25%) to provide at least 80% power of showing no significant difference in C_{max} and AUC_{τ} of bismuth potassium citrate between vonoprazan and esomeprazole quadruple therapy.

[redacted]

1.1 Protocol Amendment 1 Summary of Changes

Rationale for Amendment 1

This section describes the changes in reference to the protocol incorporating Amendment 1. The primary reasons for this amendment are to:

- Increase the planned sample size from 34 to 42 subjects (maximum 46 subjects).
- Amend inconsistencies between different sections of the protocol concerning the neurological examination.
- Standardize the interval for continued contraception use (inclusion criteria), anticipated pregnancy (exclusion criteria) and reporting of pregnancy (Appendix D) to 4 weeks.
- Clarify procedures for protocol deviations and add time windows for pharmacokinetic (PK) sample collection.
- Update PK sample storage conditions.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1	Section 1.0 STUDY SUMMARY	Sponsor's address updated	Administrative
2	Section 1.0 STUDY SUMMARY Section 11.3 Determination of Sample Size	The planned sample size was increased from approximately 34 to 42 subjects (maximum of 46 subjects).	This change is being implemented to account for an observed discontinuation rate of approximately 25% compared to the predicted drop out rate of 10%. Increasing the sample size to 42 subjects (maximum 46 if dropout rate increases above 25%) will provide 30 completers and retain the power of the study.
3	Section 1.0 STUDY SUMMARY Section 3.0 Schedule of Study Procedures Section 9.2.8 Laboratory Procedures and Assessments	Clarification that follow up ^{13}C urea breath test was only performed for subjects who completed the study treatment	To clarify end of study procedures
4	Section 3.0 Schedule of Study Procedures Section 9.2 Clinical Procedures and Assessments	Description and timing of neurological exam has been amended.	To correct inconsistencies between Section 3.0 and Section 9.2.1.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5	Section 3.0 Schedule of Study Procedures Section 9.2.5 12-Lead ECG	Time window for electrocardiogram (ECG) assessments added (±15 mins).	Administrative change to standardize the procedure.
6	Section 6.1 Trial Design Section 7.4.1 Diet and Fluid	Text updated to state that subjects only need to fast for a minimum of 8 hours overnight before morning dosing.	To correct a previous inconsistency.
7	Section 7.1 Inclusion Criteria Section 7.2 Exclusion Criteria Appendix D Pregnancy and Contraception	Clarified that contraception use by female subjects of childbearing potential must continue for 4 weeks (not 1 month) after last dose of study medication, that subjects intending or expecting to become pregnant during or within 4 weeks (not 1 month) after participating in the study were excluded and that any pregnancy occurring within 4 weeks (not 30 days) of the last dose should be reported immediately.	To comply with Informed Consent Form
8	Section 9.2.8.1 Clinical Laboratory Tests	Creatinine kinase and creatinine kinase MB, corrected to creatine kinase and creatine kinase MB.	To correct typographical error.
9	Section 9.3 Biomarker, PK, and Pharmacogenomics Samples	Time windows for PK blood samples were added.	To add changes in PK time windows implemented in administrative letter dated 6 January 2021.
10	Section 10.2.8.2 Reporting AEs	Clarified that only start and end date was required for adverse event (AE) recording. Time of day was deleted from the text.	It was not necessary to report the time of day that an AE occurred.

Protocol Amendment 1			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
11	Section 12.2 Protocol Deviations	PK sampling outside of specified time windows were to be regarded as protocol deviations. Procedures for documentation of protocol deviations were clarified.	To add clarity to definitions and procedures for documenting protocol deviations.
12	Section 14.1.1 Study Contact Information	Procedures for reporting serious adverse events and pregnancy have been updated.	To reflect current processes / procedures.
13	Appendix E Collection, Storage, and Shipment of Bioanalytical Samples	Storage conditions for PK samples were updated.	To add changes implemented in administrative letter dated 6 Jan 2021.

[redacted]

2.0 STUDY SCHEMATIC

<table>
<tr><th colspan="2">Pretreatment</th><th colspan="3">Treatment Period</th><th>Follow-Up</th><th colspan="2">Follow-Up</th></tr>
<tr><th>Screening</th><th>Check-in Baseline</th><th colspan="3"><----------Confinement----------></th><th>Check-out</th><th>Follow-up call</th><th>Follow-up visit</th></tr>
<tr><th>Days -28 to -2</th><th>Day -1</th><th>Days 1-11</th><th>Days 12-13</th><th>Day 14</th><th>Day 15</th><th>Day 17 (+2 days)</th><th>Day 42 (+ 6 days)</th></tr>
<tr><td rowspan="4">^{13}C UBT for <i>H pylori</i></td><td rowspan="4"></td><td colspan="3">Group A: clarithromycin [a] + amoxycillin [b] + bismuth [c] + esomeprazole [d]</td><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4">^{13}C UBT for H pylori</td></tr>
<tr><td colspan="3">Group B: clarithromycin [a] + amoxycillin b + bismuth [c] + vonoprazan [e]</td></tr>
<tr><td rowspan="2"></td><td colspan="2">Vonoprazan PK or esomeprazole PK in plasma [f]</td></tr>
<tr><td>Bismuth PK in plasma and urine [g]</td></tr>
</table>

^{13}C: carbon 13 isotope; BID: twice daily; PK: pharmacokinetics; UBT: urea breath test.

[a] Clarithromycin 500 mg BID.

[b] Amoxycillin 1000 mg BID.

[c] Bismuth potassium citrate 600 mg BID.

[d] Esomeprazole 20 mg BID.

[e] Vonoprazan: 20 mg BID.

[f] Blood samples for vonoprazan and esomeprazole PK on Days 12-14 are to be taken predose (morning and evening).

[g] Blood samples for bismuth PK are to be taken on Day 14 predose (0 hours), 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after the morning dose. Urine samples for bismuth PK are to be taken on Day 14 at 0 to 12 hours after the morning dose.

3.0 SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ Vonoprazan or Esomeprazole PK	Quadruple Therapy Dosing / Bismuth PK and Vonoprazan or Esomeprazole PK	Check-out/ Early Termination [a]	Follow-up	
	Days -28 to -2	Day -1	Day 1	Day 2 to 11	Day 12 to 13	Day14	Day 15	Day 17 (+2 Days) [b]	Day 42 (+6 Days) [c]
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria assessment	X	X							
Medical history and demographics [d]	X								
Medication history and concurrent medical conditions	X	X							
Physical examination	X	X					X		
Neurological examination [e]	X	X	X	X	X	X	X		
Vital signs [f]	X	X	X	X	X	X	X		
Body weight and height [g]	X	X				X			
BMI calculation	X	X							
Clinical laboratory tests [h]	X	X		X	X	X	X		
Liver function tests [i]	X	X		X	X	X	X		
Urine drug screen [j]	X	X							
Urine pregnancy test (hCG) [k]	X	X					X		
^{13}C UBT for *H pylori*	X								X
Alcohol breath test	X								
Hepatitis panel and HIV panel	X								
Randomization		X							

[redacted]

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ Vonoprazan or Esomeprazole PK	Quadruple Therapy Dosing / Bismuth PK and Vonoprazan or Esomeprazole PK	Check-out/ Early Termination [a]	Follow-up	
	Days -28 to -2	Day -1	Day 1	Day 2 to 11	Day 12 to 13	Day14	Day 15	Day 17 (+2 Days) [b]	Day 42 (+6 Days) [c]
12-lead ECG [l]	X	X	X	X		X	X		
PTE monitoring	X	X	X						
AE monitoring			X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	
PK sampling [m]					X	X			
CYP2C19 sample collection [n]		X							
Dispense study medication			X	X	X	X			

13C: carbon 13 isotope; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CYP: cytochrome P; ECG: electrocardiogram; hCG: human chorionic gonadotrophin; PK: pharmacokinetic(s); PTE: pretreatment event; UBT: urea breath test.

[a] In the event of early termination, all check-out procedures should be done at the time of withdrawal.

[b] A follow-up phone call will be made approximately 2 days after check-out to update safety information including AEs and concomitant medications. Subjects may be brought back to the unit at the principal investigator's discretion if any laboratory test abnormalities or other abnormalities are deemed clinically significant at the check-out visit.

[c] A follow-up visit will be arranged after 4 weeks for a ^{13}C UBT for *H pylori* for subjects who complete the study treatment.

[d] Demographics are collected at screening only. All medical history updates should include tobacco, alcohol, and caffeine use.

[e] Neurological examination will be performed daily on screening, Day -1, 1, 2, 5, 8, 11, 12, 13, 14, and 15/early termination visit. If the subject has symptoms or signs of neurological deficits, then a full neurological exam is required daily and until symptoms or signs are resolved.

[f] Vital signs will include body temperature (oral or tympanic measurement), sitting blood pressure (after 5 minutes resting), respiration rate, and pulse (bpm) at screening, Day -1, and predose from Days 1 to 15.

[g] Height is only collected at the screening visit and used for BMI calculation.

[h] Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be collected at screening, check-in, and Days 5, 8, 12, 13, 14, and 15. If any results are clinically significant at Day 15, subjects may be requested to return for repeat tests.

[i] Liver function tests comprise AST, ALT, and total and direct bilirubin, and measurements are to be taken at screening, check-in, and Days 5, 8, 12, 13, 14, and 15. If any results are clinically significant at Day 15, subjects may be requested to return for repeat tests.

[redacted]

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ Vonoprazan or Esomeprazole PK	Quadruple Therapy Dosing / Bismuth PK and Vonoprazan or Esomeprazole PK	Check-out/ Early Termination [a]	Follow-up	
	Days -28 to -2	Day -1	Day 1	Day 2 to 11	Day 12 to 13	Day14	Day 15	Day 17 (+2 Days) [b]	Day 42 (+6 Days) [c]

[j] Drug screen includes amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, and opiates.

[k] Urine hCG test to be performed only in female subjects of childbearing potential. Guidance on pregnancy avoidance is provided in Appendix D.

[l] ECGs will be collected at screening and check-in; on dosing Days 1, 3, and 7 before the morning dose; on Day 14 before the morning dose and at 1, 2 and, 4 hours after the morning dose (time window for ECGs: ± 15 minutes) and at check-out or at early termination.

[m] Blood PK samples for vonoprazan or esomeprazole analysis will be collected on Days 12 to 14 at predose (morning and evening). Blood PK samples for bismuth analysis will be collected on Day 14 before the morning dose (0 hours) and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after the morning dose. Urine PK samples for bismuth analysis will be collected on Day 14 at 0 to 12 hours after the morning dose.

[n] Mandatory collection of 1 whole blood sample (3 mL) for DNA CYP2C19 genotyping will be taken at Day -1.

[redacted]

4.0 INTRODUCTION

4.1 Background

Helicobacter pylori (*H pylori*) is a gram-negative, microaerophilic bacteria mainly found in the gastric mucus and mucosa and whose causal relationships to gastrointestinal diseases have been extensively studied [1,2] since it was first isolated from the gastric mucosa of a patient with chronic gastritis in 1983 [3]. Since then, *H pylori* eradication therapy has been shown to be effective in reducing the recurrence of gastric and duodenal ulcer [4,5], and *H pylori* eradication therapy using proton pump inhibitors (PPIs) and antibiotics has been approved in various countries around the world.

In Japan, in September 2000, a triple therapy with lansoprazole/amoxicillin/clarithromycin was the first treatment regimen to gain approval for *H pylori* eradication in patients with gastric or DU, and, in August 2007, a triple therapy with PPI/amoxicillin/metronidazole was approved as second-line eradication therapy for patients who failed first-line eradication therapy. These triple therapies for *H pylori* eradication were approved in June 2010 for gastric mucosa–associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura, and endoscopically treated early gastric cancers.

Developed at Takeda Pharmaceutical Company Ltd, vonoprazan (TAK-438) belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers. Vonoprazan inhibits the hydrogen, potassium adenosine triphosphatase (H^+,K^+-ATPase) enzyme in the final step of acid secretion, as the PPIs do, but it does not require the presence of acid for its activation and it inhibits the H^+,K^+-ATPase enzyme in a potassium-competitive fashion. Vonoprazan is stable in the presence of acid and is water-soluble, requiring no particular pharmacological preparations, such as an enteric coating. Vonoprazan is predominantly metabolized by the cytochrome P-450 (CYP) enzyme CYP3A4, and contribution of polymorphic CYP2C19 is considered to be limited.

The PPIs take 3 to 5 days to produce their maximum acid-inhibitory effects, whereas vonoprazan accumulates rapidly in the gastric parietal cells and has a longer half-life than the PPIs. It is, therefore, expected to produce its maximum acid-inhibitory effects in a much shorter time and have better potential clinical outcomes than the PPIs due to its potent and sustained acid-inhibitory effects.

A 4 × 4 crossover study of pharmacokinetic (PK) drug-drug interactions of triple therapy twice daily (twice daily [BID]) with vonoprazan/amoxicillin/clarithromycin or vonoprazan/amoxicillin/metronidazole was conducted in healthy Japanese male subjects (TAK-438_CPH-401). In Cohort 1 (triple therapy BID with vonoprazan, amoxicillin, and clarithromycin), compared with single-agent use of vonoprazan, the mean area under the plasma concentration-time curve from time 0 to 12 hours (AUC_{0-12}) and mean maximum observed plasma concentration (C_{max}) for freebase of TAK-438 (TAK-438F) increased approximately 1.8- and 1.9-fold, respectively, when vonoprazan was administered as triple therapy. No difference was observed in the PK of plasma amoxicillin when amoxicillin was administered alone or as triple therapy. Compared with single-agent use of clarithromycin, the mean AUC_{0-12} and mean C_{max} for clarithromycin increased approximately 1.5-fold and 1.6-fold, respectively, when clarithromycin

was administered as triple therapy. In Cohort 2 (triple therapy BID with vonoprazan, amoxicillin, and metronidazole), no difference was observed in the PK of plasma metronidazole when metronidazole was administered alone or as triple therapy. Compared with the single-agent therapies, the AUC_{0-12} and C_{max} for TAK-438F and clarithromycin increased during triple therapy with vonoprazan/amoxicillin/clarithromycin. However, no safety concern was identified with the triple therapy. Although further investigation in more subjects is required, the changes during triple therapy with vonoprazan/amoxicillin/clarithromycin or vonoprazan/amoxicillin/metronidazole are not considered to be clinically significant.

In a phase 3 *H pylori* eradication study (TAK-438/CCT-401), 7-day treatment with vonoprazan 20 mg (n = 329) or lansoprazole 30 mg (n = 321) in combination with amoxicillin 750 mg plus clarithromycin 200 or 400 mg, eradication rates were 92.6% and 75.9%, respectively. In this study, the first 50 treatment failures with good compliance received second-line triple-therapy with vonoprazan 20 mg (in combination with amoxicillin 750 mg and metronidazole 250 mg) in an open-label manner, and an eradication rate of 98% was observed. All treatments were well-tolerated.

4.2 Rationale for the Proposed Study

In China, eradication guidelines recommend quadruple therapy for *H pylori* eradication consisting of 2 antibiotics, a PPI and bismuth [6]. As a replacement for PPIs in China, vonoprazan would be expected to be used as part of a quadruple treatment regimen.

As bismuth is minimally absorbed and renally excreted, it is not expected to have an effect on the PK of vonoprazan, esomeprazole, clarithromycin, or amoxicillin, and the combination of clarithromycin and amoxicillin is not expected to have an effect on bismuth concentrations [7]. However, it has been reported that with increasing gastric pH, an increase in bismuth absorption is observed with the exposure to bismuth increasing by 3- to 7-fold when administered with histamine-2 receptor antagonists and PPIs [8]. Increased levels of bismuth may be associated with increased potential for neurotoxicity [9]. As vonoprazan achieves high stomach pH over a full 24-hour period, Study TAK-438_115 in Korea evaluated the drug interaction potential and tolerability when vonoprazan and bismuth are coadministered with lansoprazole as comparator. Mean cumulative fractions of bismuth excreted unchanged in the urine were found to be almost unaffected between the 2 treatment groups, suggesting a lack of a clinically meaningful effect of vonoprazan on the PK of bismuth compared with lansoprazole. Daily neurological examination showed the absence of bismuth-related neurological adverse events (AEs) in the 2 treatment groups, and review of treatment-emergent adverse events (TEAEs) in the vonoprazan and lansoprazole groups did not raise any safety concern that could be related to potential drug-drug interaction between bismuth and vonoprazan.

An ongoing phase 3 study in *H pylori* eradication conducted by the sponsor in China (Vonoprazan-3002) utilizes esomeprazole as the comparator. The China Center for Drug Evaluation (CDE) has indicated that the applicant's combination drug therapy was not approved in China or abroad and that studies on drug interactions should be conducted. They also commented on the potential risk related to the combined use of bismuth and gastric acid inhibitors. The present

phase 1, double-blind, parallel group study was therefore undertaken to evaluate the safety, tolerability, and PK of quadruple therapy with bismuth, clarithromycin, amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole in subjects who were *H pylori* positive. CDE agreement was obtained on the proposed study design.

4.3 Benefit-Risk Profile

In the most recent treatment recommendations, bismuth-based quadruple therapy is now the recommended first-line treatment to eradicate *H pylori* in regions of high dual resistance to clarithromycin and metronidazole. The short-term use of low-dose bismuth for eradication of *H pylori* is not thought to be associated with the high risk of encephalopathy that was reported in the 1970s with chronic intake of large doses of bismuth.

As bismuth is minimally absorbed and renally excreted, it is not expected to have an effect on the PK of vonoprazan, clarithromycin, or amoxicillin, and the combination of clarithromycin and amoxicillin is not expected to have an effect on bismuth concentrations. However, increased bismuth concentration has been observed when administered with PPIs due to increased gastric pH, therefore the coadministration of bismuth and vonoprazan may result in an increase in bismuth exposure. Increased bismuth exposure may be associated with increased potential for neurotoxicity.

The plasma PK parameters of bismuth were evaluated when coadministered with vonoprazan clarithromycin, and amoxicillin, or with lansoprazole, clarithromycin, and amoxicillin for 14 days in Study TAK-438_115 in Korea. There were no obvious differences in plasma PK parameters of bismuth between the 2 treatment groups, with a mean C_{max} of 28 ng/mL in the vonoprazan group and 30 ng/mL in the lansoprazole group.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

This study is being undertaken to evaluate bismuth exposure when vonoprazan or esomeprazole (the comparator in the ongoing phase 3 study Vonoprazan-3002) are administered in quadruple therapy.

5.2 Trial Objectives

To evaluate the safety, tolerability, and PK of quadruple therapy BID with bismuth, clarithromycin, amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole.

5.3 Endpoints

5.3.1 Primary Endpoint

The primary endpoint of the study is:

- To evaluate plasma PK parameters of bismuth potassium citrate (600 mg) when coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and vonoprazan (20 mg BID), and when coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and esomeprazole (20 mg BID):
  - C_{max} at Day 14.
  - The area under the plasma concentration-time curve during a dosing interval (area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval [AUC_{τ}]) at Day 14.
  - The amount of drug excreted in urine during a dosing interval (Ae_{τ}) at Day 14.

5.3.2 Secondary Endpoints

Secondary endpoints include:

1. Percentage of subjects who experience at least 1 TEAE.
2. Percentage of subjects who discontinue due to an AE.

5.3.3 Safety Endpoints

Safety endpoints include:

1. Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once post dose.
2. Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post dose.
3. Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once post dose.

5.3.4 Exploratory Endpoints

Evaluation of plasma drug concentrations at the end of dosing intervals (C_{trough}) of vonoprazan and esomeprazole.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This phase 1, double-blind, parallel group study in *H pylori*–positive subjects is being undertaken to evaluate the safety, tolerability, and PK of quadruple therapy with bismuth, clarithromycin,

amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole.

H pylori–positive male or female subjects aged 18 to 60 years, inclusive, considered eligible based on the inclusion and exclusion criteria, will participate in this study. All subjects will be enrolled and will be randomized to 1 of 2 treatment groups. The study will be conducted at a single center in China.

The treatment phase consists of quadruple therapy BID with bismuth potassium citrate, clarithromycin, amoxicillin, and vonoprazan, or quadruple therapy BID with bismuth potassium citrate, clarithromycin, amoxicillin, and esomeprazole for 14 days (Days 1 to 14). Subjects will be discharged on Day 15 after all procedures have been performed.

Screening for potential subjects will occur between Day -28 and Day -2. Eligibility will be reconfirmed on Day -1, and eligible subjects will be confined at the phase 1 unit. Having fasted overnight for a minimum of 8 hours, subjects will receive treatment with oral doses of bismuth potassium citrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and vonoprazan (20 mg) BID (Group B) or bismuth potassium citrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and esomeprazole (20 mg) BID (Group A) on Days 1 to 14. In both groups, the last dose will be on the evening of Day 14. Blood sampling for vonoprazan and esomeprazole PK measurements will be taken on Days 12 to 14 (predose evening and morning) and for bismuth PK measurements on Day 14 (before the morning dose to 12 hours after the morning dose). Urine sampling for bismuth PK measurements will be taken on Day 14 (before the morning dose to 12 hours after the morning dose).

The subjects will be confined to the phase 1 unit from Day -1 (check-in) through to Day 15 (check-out) and will be contacted by the study site for a follow-up call on Day 17 and a clinic visit on Day 42 for a carbon 13 isotope (^{13}C) urea breath test (UBT) for *H pylori*.

A schematic of the study design is included in Section 2.0, and the Schedule of Study Procedures is provided in Section 3.0.

6.2 Dose Escalation

Not applicable.

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

A parallel group design will be utilized because of the long washout that would be required in a crossover design due to the long half-life of bismuth. The first, second, and third elimination phases for bismuth are: 1 to 4 hours, 5 to 11 days, and 21 to 72 days [8]. The population will comprise healthy subjects who are *H pylori* positive since the target population for bismuth containing quadruple therapy in whom intragastric pH is affected by their *H pylori*–positive status.

6.3.2 Rationale for Dose

The doses selected reflect those used in the ongoing phase 3 study in China (Vonoprazan-3002).

6.3.3 Rationale for Endpoints

6.3.3.1 Efficacy Endpoints

There is no formal efficacy endpoint. However, a ^{13}C UBT for *H pylori* will be conducted at screening and at Day 42 (+6 days) for the assessment of *H pylori* eradication through the detection of urase activity.

6.3.3.2 Safety Endpoints

An increase in bismuth concentration is observed when administered with PPIs, which is associated with increased stomach pH. It is expected that when bismuth is coadministered with either vonoprazan or esomeprazole, there may be an increase in bismuth exposure due to increase solubility of bismuth at higher gastric pH. Increased exposure to bismuth may be associated with increased potential for neurotoxicity.

6.3.3.3 PK Endpoints

Assessing bismuth PK parameters will allow the determination of bismuth exposure on Day 14 following 2 weeks of quadruple therapy and facilitate comparisons of bismuth exposure between the 2 quadruple therapy regimens. Assessing the C_{trough} levels of esomeprazole and vonoprazan will be an exploratory endpoint and will provide an additional measure of exposure.

6.3.3.4 Exploratory Biomarker Research

Esomeprazole is metabolized primarily by CYP2C19. Therefore, CYP2C19 genotyping for metabolized status will be determined.

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this trial, blood sampling and ^{13}C UBT for *H pylori* are critical procedures.

6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

None.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The trial will begin when the first subject enters the screening phase.

6.5.2 Definition of End of the Trial

The end of the trial will occur when the last subject completes the follow-up visit on Day 42 (+ 6 days).

6.5.3 Criteria for Premature Termination or Suspension of the Study or Investigational Sites

6.5.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known benefit-risk profile for the compound, such that the benefit-risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.3.2 Criteria for Premature Termination or Suspension of a Site

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization or first dose.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization before the initiation of any study procedures, including requesting that a subject fast for any laboratory evaluations.

3. The subject is *H pylori* positive at screening.
4. The subject is male or female and aged 18 to 60 years, inclusive, at the time of informed consent and first study medication dose.
5. The subject weighs at least 50 kg and has a body mass index (BMI) >18.0 and ≤30.0 kg/m^2, inclusive, at screening and Day -1 (check-in).
6. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception* from signing of informed consent and throughout the duration of the study and for 4 weeks after last dose of the study medication.

   *Definitions and acceptable methods of contraception together with contraception and pregnancy avoidance procedure and reporting responsibilities are defined in Appendix D.

7. The subject is willing to abstain from strenuous exercise from 72 hours before first dose (Day 1) until the follow-up call on Day 17.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 90 days before providing their informed consent.
2. The subject has received vonoprazan in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member or study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has an uncontrolled, clinically significant cardiovascular condition or other abnormality (other than the disease being studied) that may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a known hypersensitivity to any component of the formulation of vonoprazan, penicillins, macrolides, bismuths, and esomeprazole (eg, D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide).
6. The subject has a positive urine drug result for drugs of abuse at screening or check-in (Day -1).
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 21 units or more units per week) at any time before the screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study (up to Day 17).

8. The subject has taken any prescription medications or herbal remedies or excluded medications, supplements, or food products listed in the table of excluded medications, supplements, and dietary products in Section 7.3 of the protocol.
9. If female, the subject is pregnant or 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.
10. The subject has a history of neurological disease.
11. The subject has evidence of current cardiovascular, central nervous system, hepatic, or hematopoietic disease; renal dysfunction; metabolic or endocrine dysfunction; serious allergy; asthma hypoxemia; hypertension; seizures; or allergic skin rash. Subjects may also be excluded if there is any finding in their medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking vonoprazan, or contraindicate any drug used to reduce acid secretion by the stomach or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
12. The subject has a history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, duodenal or gastric ulcer, Barrett's esophagus, or Zollinger-Ellison syndrome, or has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs.
13. Subjects who have undergone therapeutic upper gastrointestinal endoscopic therapy (eg, endoscopic hemostasis or excision including biopsy) within 30 days before screening.
14. Subjects who have undergone major surgical procedures within the past 1 month or are scheduled to undergo surgical procedures that may affect gastric acid secretion (eg, abdominal surgery, vagotomy, or craniotomy).
15. The subject has any known disease or is taking any medication that is contraindicated with bismuth, clarithromycin, or amoxicillin.
16. The subject has a history of cancer, except basal cell carcinoma or Stage 1 squamous cell carcinoma of the skin that has been in remission for at least 5 years before Day 1.
17. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or HIV antibody/antigen at screening.
18. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 6 weeks before check-in. Cotinine test is positive at screening or check-in.
19. The subject has poor peripheral venous access.
20. The subject has donated or lost ≥450 mL of blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days before Day 1.

21. The subject has a clinically significant abnormality on screening or check-in ECG. Entry of any subject with an abnormality on ECG that is not clinically significant must be approved and documented by signature of both the investigator and the contract research organization (CRO) medical monitor.
22. The subject has abnormal screening or check-in laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin greater than the upper limit of normal (ULN).
23. The subject has reduced renal function assessed by having an estimated glomerular filtration rate <90 mL/min/1.73 m^2 (as estimated by Chronic Kidney Disease-Epidemiology Collaboration) at screening or check-in.

7.3 Excluded Medications, Supplements, Dietary Products

Use of excluded prescription or nonprescription agents or dietary products, outlined in Table 7.a is prohibited from the time points specified until completion of all study activities (Day 17).

Table 7.a Excluded Medications, Supplements, and Dietary Products

6 Weeks Before Check-in (Day -1)	28 Days Before Check-in (Day -1)	7 Days Before Check-in (Day -1)	72 Hours Before Check-in (Day -1)
Nicotine-containing products	Prescription medications	OTC medications including salicylates [a]	Products containing caffeine or xanthine
Immunization/ vaccines	St. John's wort, ginseng, kava, ginkgo biloba, Chinese herbs, melatonin, other herbal or homeopathic preparations or other nutraceuticals	Vitamin supplements CYP3A4 inhibitors/inducers	
		Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	
		Alcohol-containing products	

OTC: over-the-counter.
[a] Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication is allowed. OTC = over-the-counter

Subjects must be instructed not to take any medications including over-the-counter (OTC) products, without first consulting with the investigator. Use of concomitant medications will not be allowed during the study (up to Day 17) except for those approved by CRO/Takeda medical monitor on a case-by-case basis, unless deemed necessary in a medical emergency.

Concomitant medications will include all medications the subject has taken from signing of informed consent to the follow-up call (Day 17). If the subject reports taking any medication or if administration of any medication becomes necessary during the course of this study (up to Day 17), the CRO/Takeda medical monitor must be notified. All medications must be recorded in the source documents as well as on the appropriate electronic case report form (eCRF) along with dosage information, dates of administration, and reasons for use.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

Subjects will be confined to the clinic for the duration of the treatment period (Day -1 until check-out on Day 15).

During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be identical for each treatment group in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor. Subjects should be fasted overnight for a minimum of 8 hours before morning dosing. Breakfast and dinner should be given at approximately the same time each day on Days 1 to 14. Subjects should refrain from drinking for at least 1 hour after the clarithromycin and amoxicillin dose, after which water can be given freely.

7.4.2 Activity

Subjects should refrain from strenuous exercise from 72 hours before the first dose through Day 17 follow-up call.

Blood donation is not allowed for at least 12 weeks after the final examination of this study (Day 17).

If a subject visits another medical institution during the study period, the investigator should be informed of the circumstances and any prescribed therapy and should communicate with the medical institution about the subject's participation in the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
2. Liver function test abnormalities.

   Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests until a subject's laboratory profile has returned to normal/baseline status), if the following circumstances occur at any time during study medication treatment:

   - ALT or AST or total bilirubin >2 times the ULN.
3. Significant protocol deviation. The discovery post randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

5. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Appendix D.

8. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

7.7 Subject Replacement

Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Clinical Study Drug

In this protocol, the term study medication refers to vonoprazan, esomeprazole, bismuth potassium citrate, clarithromycin, and amoxicillin. A description of the investigational drugs is provided in Table 8.a.

Table 8.a Investigational Drugs

Name, Strength, and Dose Form	Description	Manufacturer
Vonoprazan (TAK-438) 20 mg tablets	Overencapsulated TAK-438 20 mg tablets	Takeda Pharmaceutical Company Limited, Hikari Plant, Japan
Esomeprazole 20 mg tablets	Over-encapsulated esomeprazole 20 mg tablets	AstraZeneca
Bismuth potassium citrate 300 mg capsules	Locally sourced	
Clarithromycin 250 mg tablets	Locally sourced	
Amoxicillin 500 mg capsules	Locally sourced	

8.1.1 Clinical Study Drug Labeling

Vonoprazan (TAK-438) and esomeprazole will be foil/foil blister packaged into child-resistant blister cards. Each blister card will contain 32 overencapsulated vonoprazan (TAK-438) 20 mg tablets or 32 over-encapsulated esomeprazole 20 mg tablets. The carton box and each blister card will be labeled in a blinded fashion with a single panel. The labels will include pertinent study information and a country-specific regulatory caution statement.

Amoxicillin (500 mg capsules), clarithromycin (250 mg tablets), and bismuth potassium citrate (300 mg capsules [equivalent to 110 mg bismuth]) will be provided by the sponsor and will be packaged in an open fashion.

8.1.2 Clinical Study Drug Inventory and Storage

Vonoprazan (TAK-438) and esomeprazole overencapsulated tablets will be kept in an appropriate, limited-access, secure place until the supply is used or returned to the sponsor or designee for destruction. Vonoprazan and esomeprazole overencapsulated tablets should be stored at 20°C to 25°C with excursions permitted 15°C to 30°C. Protect from moisture and humidity. Sponsor-supplied drugs are to remain in the white carton box and the blister sheet until time of dosing.

Companion medication will be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Amoxicillin capsules will be stored at 10°C to 30°C. Clarithromycin tablets will be stored at 2°C to 20°C, and bismuth capsules will be stored at 10°C to 30°C. All of these medications will remain in their original containers until dispensed.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All clinical study material must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Temperature excursion must be reported to the sponsor or designee.

[redacted]

8.1.3 Clinical Study Drug Blinding

The investigator will receive the subject's investigational drug blind information in the form of a sealed envelope that will reveal the subject's study treatments if opened. The site-designated study personnel will maintain the investigational drug blind information. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of blinded investigational drug unassigned and assigned treatment packages, sealed envelopes. All treatment packages will be reconciled and returned to the sponsor or a designee before study closure.

8.1.4 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

A blinded randomization schedule will be provided to the site pharmacist or authorized study designee before the start of this study. The medical identification to be dispensed to each subject will be provided in this schedule.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality should be performed, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by opening sealed envelope.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately, and the subject must be withdrawn from the study.

No change should be made to any assessment of the subject after unblinding.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-438 20 mg overencapsulated tablets, esomeprazole 20 mg overencapsulated tablets, bismuth 300 mg, clarithromycin 250 mg, and amoxicillin 500 mg), the

investigator or designee must maintain records of all study drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing the bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs dispensed during his or her entire participation in the study. Proper drug accountability includes but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee (drug label).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization schedule and subject dosing log before Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all study drugs (TAK-438 20 mg overencapsulated tablets, esomeprazole 20 mg overencapsulated tablets, bismuth 300 mg, clarithromycin 250 mg, and amoxicillin 500 mg) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed, initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of supplies already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PROCEDURES

The following sections describe the study procedures and data to be collected. The Schedule of Study Procedures is located in Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Appendix B.

Informed consent must be obtained before the subject enters into the study and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

If the subject is to undergo the ^{13}C UBT for *H pylori* (one of the screening procedures) at a satellite site, the subject must sign the informed consent form before performing this test.

A unique subject identification number (subject number) will be assigned to each subject at the time informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent to participate in this study. The informed consent for the CYP2C19 genotyping analysis is a component of the overall study informed consent.

9.1.2 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.

[redacted]

- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused. If a subject fails screening but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore, the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a standalone subject.

9.1.3 Inclusion and Exclusion

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.1.4 Medical History/Demography

Demographic information to be obtained will include age, sex, alcohol and caffeine consumption, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the condition/disease under study that stopped at or before signing of informed consent.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening examination. The condition (ie, diagnosis) should be described.

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days before signing of informed consent.

9.1.5 Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or OTC medications obtained by the subject. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study [Day 17]), and all medication, including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF.

Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

[redacted]

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Examination

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; (11) genitourinary system; and (12) other.

A neurological examination will be performed per Section 3.0 Schedule of Study Procedures.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. All clinically significant findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.4.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately before the start of the investigational drug (Day 1) must be assessed as not clinically significant or clinically significant by the investigator and recorded in the source document and eCRF. Any clinically significant change or new diagnosis as a result of a clinically significant change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.2.2 Height and Weight

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below.

9.2.3 BMI

Per Takeda standard, height measurements should be collected in centimeters without decimal places and weight should be reported in kilograms with 1 decimal place. BMI should be derived as:

Metric: $BMI = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, a subject whose height is 176 cm (1.76 meters) and weight is 79.2 kg would have a BMI of 25.6 kg/m^2 ($79.2/1.76^2$).

9.2.4 Vital Signs

Vital signs will include body temperature (oral or tympanic measurement), sitting blood pressure (systolic and diastolic, resting more than 5 minutes), respiration rate, and pulse (bpm).

Vital signs may be repeated. All measurements will be recorded on the source documents and in the eCRF.

[redacted]

When vital signs are scheduled at the same time as blood draws, vital signs will be obtained before the scheduled blood draw.

9.2.5 12-Lead ECG

12-lead ECGs printed in standard format will be collected at screening; at check-in; on Days 1, 3, and 7 before the morning dose; on Day 14 before the morning dose, and 1, 2 and 4 hours after the morning dose (time window for ECGs: ± 15 minutes), and at check-out day or the early termination of the study for safety assessment.

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report.

9.2.6 Study Drug Administration

Subjects should be fasted overnight for a minimum of 8 hours before dosing. Breakfast and dinner should be given at approximately the same time each day on Days 1 to 14. Vonoprazan / esomeprazole and bismuth should be administered 0.5 hour before breakfast and dinner. Breakfast and dinner should be completed within 0.5 hour, and then clarithromycin and amoxicillin should be administered 0.5 hour after the start of breakfast and dinner on Days 1 to 14. Subjects should take all doses with 240 mL water (120 mL with bismuth and vonoprazan or esomeprazole dosing and 120 mL with clarithromycin and amoxicillin doses) and refrain from drinking for at least 1 hour post clarithromycin and amoxicillin dose, after which water can be given freely.

For each dose, the subject's actual dose date and time of administration will be recorded, to the nearest minute, in the subject's source documents and transcribed on the eCRF.

9.2.7 AE Monitoring

9.2.7.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen failure. For subjects who discontinue before study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the follow-up telephone call.

9.2.7.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change.

Nonserious PTEs, related or unrelated to the study procedure, do not require follow-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

9.2.7.3 Collection and Reporting of SAEs

When a serious adverse event (SAE) occurs through the AE collection period, it should be reported according to the following procedure:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

[redacted]

Reporting of serious PTEs will follow the procedure described for SAEs.

9.2.8 Laboratory Procedures and Assessments

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit ranges from 20 to 68 mL, and the approximate total volume of blood for the study is 223 mL (may be up to 243 mL if repeat tests are required for laboratory and PK samples. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Section 3.0).

9.2.8.1 Clinical Laboratory Tests

The site's local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis as well as the laboratory screening tests (HIV, hepatitis panel, drug screen, and urine hCG pregnancy tests). The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

Hematology

Hematology will consist of the following tests:

RBCs	Platelets
WBCs (with differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes)	PT/INR
Hemoglobin	aPPT
Hematocrit	Reticulocyte count

aPPT: activated partial thromboplastin time; PT/INR: prothrombin time/international normalized ratio; RBC: red cell count; WBC: white cell count.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

ALT [a b]	Blood urea nitrogen
Albumin	Creatine kinase
Alkaline phosphatase [a]	Creatine kinase MB
Amylase	Potassium
AST [a b]	Sodium
GGT	Glucose
Total bilirubin [a b c]	Chloride
Direct bilirubin [a b]	Magnesium
Uric acid	Calcium
Total protein	Cholesterol (HDL and LDL) [a]
Triglycerides [a]	LDH [d]
Serum creatinine	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; HDL: high density lipoprotein; LDH: lactate dehydrogenase; LDL: low density lipoprotein; MB: myocardial band.
[a] To be measured under fasting conditions.
[b] Included in liver function tests.
[c] Direct bilirubin will be measured if total bilirubin is >1.5 times the ULN.
[d] LDH1/LDH5 (in % and total) will be measured if clinically significant increase in LDH is reported.

If subjects experience an increase in any one of ALT, AST, or total bilirubin >2 times the ULN, then trial medication should be stopped because the criteria for discontinuation has been met (please refer to Section 7.5 for discontinuation criteria). Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and international normalized ratio) to monitor recovery should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Please refer to Section 10.2.8.5 for the appropriate guidance on reporting abnormal liver function test (LFT) as an SAE.

All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified before the first dose will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment/randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

Urinalysis

Urinalysis will consist of the following tests:

pH	Bilirubin
Specific gravity	Hemoglobin
Protein	Ketones
Glucose	Leucocytes
Nitrites	Urobilinogen

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cell/high-power field, white blood cell/high-power field, casts, epithelial cells, crystals, and organisms.

Other

HIV	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, and opiates.
Hepatitis panel: HBsAg and anti-HCV	Female subjects of childbearing potential only: hCG (for pregnancy)
^{13}C UBT for *H pylori* [a] and alcohol breath test	

^{13}C: carbon 13 isotope; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; UBT: urea breath test.

[a] ^{13}C UBT will be performed at screening and must be positive at screening. A follow-up breath test will be performed on Day 42 for subjects who complete the study treatment.

9.3 Biomarker, PK, and Pharmacogenomics Samples

Blood samples for PK analysis of TAK-438F, esomeprazole, and bismuth will be collected into Vacutainers containing anticoagulant sodium heparin according to the schedule in Section 3.0. Instructions for sample processing and shipment are provided in Appendix E.

Serial blood samples for determination of TAK-438F, esomeprazole, and bismuth will be collected according to Table 9.a.

Table 9.a Collection of Blood Samples for PK Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (Hours)
TAK-438F	Plasma	12-14	Predose (morning and evening)
Esomeprazole	Plasma	12-14	Predose (morning and evening)
Bismuth	Plasma	14	Pre–morning dose (0 hours) and 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 hours post morning dose

PK: pharmacokinetic(s); TAK-438F: freebase of TAK-438.

Every attempt will be made to collect each drug concentration (PK) blood sample at the designated timepoint (Table 9.b) and the actual time of each PK blood sample will be recorded accurately on the source document and eCRF (with minute clock time precision).

Table 9.b Time Windows for PK Blood Sample Collection

Nominal PK Blood Sample Time	Actual PK Blood Sample Time Window
0 hours (predose)	No more than 10 minutes predose [a]
Immediately postdose to ≤6 hours postdose	±5 minutes [b]
>6 hours to ≤12 hours postdose	±10 minutes [b]

PK: pharmacokinetic.
[a] For vonoprazan (TAK-438), esomeprazole, and bismuth PK blood samples.
[b] For bismuth PK blood samples only.

The actual time of sample collection will be recorded on the source document and eCRF.

9.3.1 Collection of Urine for PK

Urine samples for PK analysis of bismuth will be collected according to Table 9.c.

Table 9.c Collection of Urine Samples for PK Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Bismuth	Urine	14	0 to 12 hours post morning dose.

PK: pharmacokinetic(s).

Instructions for sample processing and shipment are provided in Appendix E.

9.3.2 PK Measurements

Bismuth PK parameters will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled (nominal) sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated using plasma bismuth concentrations:

[redacted]

Symbol/Term	Definition
Plasma	
AUC_τ	Area under the plasma drug concentration-time curve during a dosing interval, where tau (τ) is the length of the doing interval, calculated using the linear trapezoidal rule.
C_{max}	Maximum observed plasma drug concentration.
CL/F	Apparent clearance after extravascular administration, calculated as dose/AUC_τ after multiple dosing.
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max}.
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.

The following PK parameters will be derived from urine bismuth concentrations:

Urine	
Ae_τ	Amount of drug excreted in urine during a dosing interval (τ).
f_e	Fraction of drug excreted in urine, calculated as $f_e = (Ae_\tau/dose) \times 100$.
CL_R	Renal clearance, calculated as $CL_R = Ae_\tau/AUC_\tau$.

9.3.2.1 Plasma or Serum for PK Measurements

Blood samples for vonoprazan or esomeprazole PK analysis will be collected on Day 12 to Day 14 predose (morning and evening). Blood PK samples for bismuth analysis will be collected on Day 14 before the morning dose (0 hours) and 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after the morning dose.

9.3.2.2 Urine for PK Measurements

Urine samples for bismuth PK analysis will be collected quantitatively on Day 14 at 0 to 12 hours after the morning dose.

9.3.3 Biomarker Measurements

Esomeprazole is metabolized primarily by CYP2C19. Therefore, CYP2C19 genotyping for metabolized status will be determined.

9.3.4 Pharmacogenomics Measurements

9.3.4.1 Blood Sample for DNA Pharmacogenomics Measurements

During the screening period, each subject will provide one 3 mL whole blood sample for DNA isolation and CYP2C19 genotyping that will be collected in a plastic tube that has been spray-coated with potassium ethylenediamine tetraacetic acid.

[redacted]

The genetic material will be sent to a testing laboratory to determine the CYP2C19 metabolic status of each subject. Any remaining sample after pharmacogenomics (PGx) testing will be destroyed.

The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access, and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

9.3.5 Confinement

Confinement will begin once subjects' eligibility is confirmed after study assessments. Randomization will take place on Day -1 after all procedures are completed and the subject will remain confined to the phase 1 unit until Day 15.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator

judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. An abnormal finding during baseline evaluation (eg, laboratory test, ECG, X-ray) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic condition (eg, asthma), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature. Investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

[redacted]

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on an AE CRF(s) according to Section 10.0.
- The SAE of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19 pneumonia COVID-19–related disease	Spontaneous abortion / stillbirth and fetal death

AE: adverse event; COVID-19: coronavirus disease 2019.

Any AE that fulfills 1 or more of the serious criteria above is to be considered an SAE and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

Not applicable.

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications, and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

10.2.5 Pattern of AE (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

[redacted]

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, special interest AEs, and abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call. For subjects who discontinue before the administration of study medication. AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE before the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin before the first exposure to investigational product, related or unrelated to the study procedure, do not require follow-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the

changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date.
- Pattern of AE (frequency).
- Severity/intensity.
- Causality (investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period, it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 14.1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

10.2.8.3.1 SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and

fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting Special Interest AEs

Not applicable.

10.2.8.5 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 times the ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed, providing additional information on relevant recent history, risk factors, clinical signs and symptoms, and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 times the ULN and total bilirubin >2 times the ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

11.1.1 Analysis Sets

The definition of each analysis set will be described in the statistical analysis plan (SAP).

[redacted]

11.1.1.1 Safety Set

The safety analysis set will consist of subjects who received at least 1 dose of the study drug.

11.1.1.2 PK Set

The PK analysis set will consist of subjects who received the study drug, completed the minimum protocol specified procedures with no significant protocol deviations, and were evaluable for the PK.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the safety analysis set and PK analysis set.

11.1.3 PK Analysis

The following analyses will be performed in the PK analysis set.

Plasma concentrations of bismuth, freebase of vonoprazan (TAK-438F) and esomeprazole will be summarized at each scheduled sampling point by treatment group using descriptive statistics. The plasma and urine PK parameters of bismuth at Day 14 will be summarized by treatment group using descriptive statistics.

Point estimates and the 2-sided 90% and 95% CI of the geometric mean ratios between treatment group will be calculated using an analysis of variance with natural log-transformed AUC_{τ} and C_{max} of bismuth. It will be concluded that vonoprazan has no significant effect on bismuth PK compared with esomeprazole if the 90% CIs for AUC_{τ} and C_{max} completely fall within the range 0.5 and 2.0.

Statistical analyses of other plasma and urine PK parameters will be performed if appropriate.

11.1.4 Safety Analysis

All summaries of safety data will be presented based on the safety analysis set. No statistical testing or inferential statistics will be generated.

11.1.4.1 AEs

A TEAE is defined as an AE whose date of onset occurs on or after the start of the study drug. All TEAEs will be coded using the MedDRA dictionary. Data will be summarized using Preferred Term (PT) and primary System Organ Class. All TEAEs, drug-related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation will be summarized by treatment group (vonoprazan quadruple therapy and esomeprazole quadruple therapy).

11.1.4.2 Clinical Laboratory Evaluation, Vital Signs, and ECG

Observed values and changes from baseline for continuous variables will be summarized over time by treatment group using descriptive statistics.

For categorical variables, shift tables will be presented by treatment group.

[redacted]

The number and percentage of subjects who meet the markedly abnormal criteria at least once post dose for safety laboratory tests, vital sign measurements, and safety ECG parameters will be summarized by treatment group.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 Determination of Sample Size

This study will randomize approximately 42 subjects (maximum 46 subjects) to provide at least 80% power of showing no significant difference in C_{max} and AUC_{τ} of bismuth potassium citrate between vonoprazan and esomeprazole quadruple therapy. Assuming the ratio of PK parameter is 0.9 to 1.1, and the SD of the natural log-transformed value in each group is 0.6, based on the results from Study TAK-438_115, a total of 30 subjects (15 subjects per group) is required for the 90% CI of the geometric mean ratio to fall completely within the range of 0.5 to 2.0 with 80% probability. Given the observed discontinuation rate of approximately 25%, and consideration for potential drop-out from the PK analysis set, the plan is to enroll approximately 42 randomized subjects. If the drop-out rate from the PK Analysis Set increases to more than 25%, a maximum of 46 subjects will be enrolled.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A protocol deviation form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (International Conference on Harmonisation [ICH]) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

Institutional review board and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a

central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering

adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date and time of day the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. The sponsor should be notified of consent withdrawal.

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation,

and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

13.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

[redacted]

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type/Role	Contact
SAE reporting	EDC (RAVE) – Primary method of reporting Serious Adverse Events If transmission of an EDC SAE report is not feasible, a completed Takeda paper-based Safety Report Form should be transmitted. The fax number and email address are provided in the Form Completion Guidelines.
Pregnancy reporting	Complete and submit the Takeda paper-based Pregnancy Report Form via fax or email. The fax number and email address are provided in the Form Completion Guidelines.

14.1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the investigator's brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

[redacted]

14.1.3 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the study-related responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the sponsor.

14.1.4 List of Abbreviations

AE	adverse event
Ae_τ	amount of drug excreted in urine during a dosing interval
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_τ	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
$AUC_{0\text{-}12}$	area under the plasma concentration-time curve from time 0 to 12 hours
BID	twice daily
BMI	body mass index
CDE	Center for Drug Evaluation
C_{max}	maximum observed plasma concentration
CRO	contract research organization
C_{trough}	observed plasma concentration at the end of a dosing interval
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
H^+,K^+-ATPase	hydrogen, potassium adenosine triphosphatase
hCG	human chorionic gonadotropin
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PPI	proton pump inhibitors
PT	Preferred Term
PTE	pretreatment event
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reactions
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
UBT	urea breath test
ULN	upper limit of normal

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. Adverse event, medical history, and concurrent conditions will be coded using the MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Relevant medical records should be included in the outpatient or inpatient medical record system. Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRF must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

Electronic case report form will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6

(Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

16.0 REFERENCES

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 4 weeks after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 4 weeks after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

[redacted]

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 4 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an follicle-stimulating hormone (FSH) > 40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:

Barrier Methods (Each Time the Subject Has Intercourse) Where Applicable [a]	**Intrauterine Devices**
Cap (plus spermicidal cream or jelly) PLUS male condom	Copper T
Diaphragm (plus spermicidal cream or jelly) PLUS male condom	

[a] Barrier methods are only applicable in countries where spermicide is available.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Section 3.0). Female subjects must have a negative urine hCG pregnancy test on Day 1 before receiving any dose of study medication.

Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug (vonoprazan 20 mg tablets or esomeprazole 20 mg tablets) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 4 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 14.1.1.

[redacted]

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to outcome using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for PK Analysis of Vonoprazan or Esomeprazole

1. Collect 3 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer at room temperature. All vonoprazan or esomeprazole blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the vacutainer several times to mix the additive with the collected blood before centrifugation and place immediately on ice.
3. Centrifuge the vacutainers for 10 minutes at approximately 1100 to 1300 (relative centrifugal force [RCF]) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (Vonoprazan-1001), sample matrix (ie, plasma), analyte (TAK-438F or esomeprazole), randomization sequence number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C to -70°C or lower until shipment to the selected laboratory in China. No more than 45 to 60 minutes should elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Plasma Samples for PK Analysis of Bismuth

1. Collect 3 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer. All Bismuth blood samples should be collected into vacutainers containing sodium heparin.
2. Gently invert the vacutainer several times to mix the additive with the collected blood before centrifugation and place immediately on ice.
3. Centrifuge the vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (Vonoprazan-1001), sample matrix (ie, plasma), analyte (Bismuth), randomization sequence number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C to -70°C or lower until shipment to the selected laboratory in China. No

more than 45 to 60 minutes should elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Urine Samples for PK Analysis of Bismuth

1. Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 2°C to 8ºC.
2. Stir the urine in the polypropylene container vigorously.
3. Measure the urine volume within 2 hours of the end of the collection period.
4. Transfer approximately 10 mL aliquots of urine in duplicate into appropriate polypropylene containers. Container should be filled to within 60% to 80% of the nominal value. Labeling may include protocol number (Vonoprazan-1001), sample matrix (ie, urine), analyte (bismuth), randomization sequence number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Freeze the urine sample immediately and store frozen at approximately -20°C to -70ºC or lower. Keep samples frozen at approximately -20°C to -70ºC or lower until shipment to the selected laboratory in China.

Shipping of Plasma and Urine Samples

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Plasma samples for vonoprazan, esomeprazole and bismuth will be collected separately and sent to different analytical labs.
2. Biological samples (ie, plasma or urine) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days before a national holiday to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
3. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
    - Separate the duplicate SET 2 samples from the SET 1 samples.
    - Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
    - Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma or urine), number of samples, and "SET 1" on each self-sealing bag.
    - Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat the steps above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

[redacted]

4. An inventory of individual samples should accompany each shipment and should include the sponsor's name (Takeda), study medication (vonoprazan), protocol number (Vonoprazan-1001), investigator's name, sample type (ie, plasma or urine), randomization sequence number, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
5. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
6. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
7. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
8. Follow Central Laboratory Manual for shipping samples.
9. Affix a carbon dioxide label on each carton, specifically:

   Carbon Dioxide Solid UN-1845
   Class 9 PKG GR III
   Quantity _____
   (fill in weight to nearest lb/kg and specify unit of measure used)
10. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark KEEP FROZEN on each carton. Specify a return address and contact person on the carton.
11. Obtain the airway bill number and a receipt of shipment from the carrier.
12. After shipping of the vonoprazan samples, please contact (name) at e-mail to notify her of next day delivery. When calling, provide the following information:

    Name of courier or transport company
    Time and date the shipment left the clinical site
    Airway bill number

[redacted]

Collection of PGx Samples

Sample Collection

1. Mandatory collection for CYP2C19 genotyping:

   During the screening period, each subject will provide one 3 mL whole blood sample for DNA isolation and CYP2C19 genotyping that should be collected in a plastic tube that has been spray-coated with potassium ethylenediamine tetraacetic acid.

Appendix F Protocol History

Date	Amendment Number	Amendment Type	Region
23 June 2021	Amendment 1	Substantial	China
28 October 2020	Initial protocol	Not applicable	China

Amendment 1 to A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With Vonoprazan Versus Quadruple Therapy With Esomeprazole

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	23-Jun-2021 07:16 UTC
[redacted]	Clinical Science Approval	23-Jun-2021 08:04 UTC
[redacted]	Clinical Pharmacology Approval	23-Jun-2021 10:07 UTC