Clinical Study Protocol: ICP-3718-202-P-03

Final Version, 27 July 2016

Study Title:	A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Trial of IW-3718 Administered Orally for 8 Weeks to Patients with Symptomatic Gastroesophageal Reflux Disease Not Completely Responsive to Proton Pump Inhibitors
Study Number:	ICP-3718-202
Study Phase:	2b
Product Name:	IW-3718
Indication:	Gastroesophageal reflux disease (GERD) not completely responsive to proton pump inhibitor (PPI) therapy
Sponsor:	Ironwood Pharmaceuticals, Inc. 301 Binney Street Cambridge, MA 02142, USA
Sponsor Contact:	Lara Lane, Clinical Study Manager
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	Date
Original Protocol:	09 November 2015 (v1.0)
Amendment 1	05 April 2016 (v2.0)
Amendment 2	27 July 2016 (v3.0)

SYNOPSIS

Study Number: ICP-3718-202

Study Title: A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Trial of IW-3718 Administered Orally for 8 Weeks to Patients with Symptomatic Gastroesophageal Reflux Disease Not Completely Responsive to Proton Pump Inhibitors

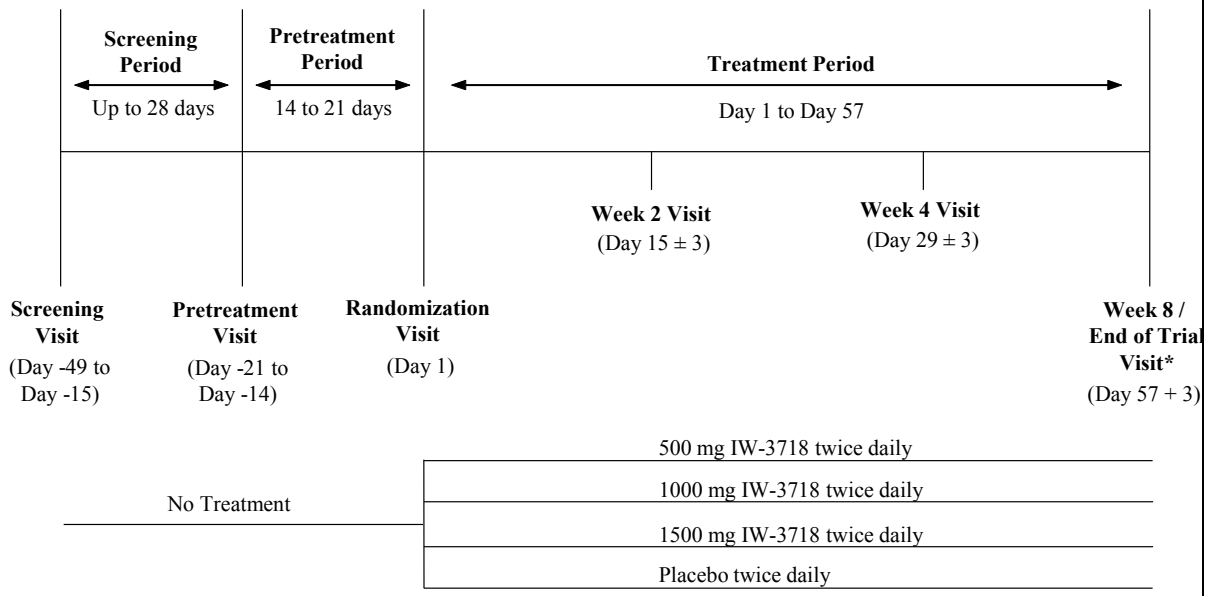
Study Centers: Approximately 60-80 centers in the United States

Development Phase: 2b

Objectives: The objectives of this study are to evaluate the safety, efficacy, and dose-response relationship of IW-3718 administered orally to patients who have GERD and continue to experience GERD symptoms while receiving once-daily (QD), optimized, standard-dose PPIs.

Methodology: This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-week study, consisting of 3 distinct periods as illustrated in the figure below. The study will enroll patients who have GERD and continue to experience GERD symptoms while receiving QD, standard-dose PPI therapy that in the investigator's opinion has been optimized. Eligible patients will continue to take their PPI and will be randomized to placebo or to 500 mg IW-3718 twice daily (BID), 1000 mg IW-3718 BID, or 1500 mg IW-3718 BID.

Overview of Study Design



Note: There is no Day 0

* This visit represents the end of the study

Screening Period: The Screening Period starts with the signature of the informed consent form (ICF) and may last for up to 28 days. During this period, patient eligibility for entry into the Pretreatment Period will be determined. Two procedures will be required during the Screening

Period in all patients; a third procedure (Bilitec® testing) will be optional for all patients at selected sites (all will be done while patients continue to take their PPI):

- An esophagogastroduodenoscopy (EGD)
- Approximately 48 to 96 hours of pH testing with the Bravo® device. If for some reason 96 hours of testing is not possible, then approximately 48 hours of testing is acceptable (Please refer to section 3.5.1.10 for further instruction)
- Approximately 24 hours of bilirubin detection using the Bilitec® monitoring system (optional at selected sites)

Histamine-2 receptor antagonists (H2RAs) should be stopped at least 5 calendar days prior to the EGD and Bravo pH monitoring; antacids should be stopped at least 1 calendar day prior to the EGD and Bravo pH monitoring. The EGD must be performed during the Screening Period and at least 7 days before the start of the Pretreatment Period to allow time for pH collection and allow the patient to stabilize following these procedures. Upon completion of the Bravo testing, patients will continue to refrain from using H2RAs, but may continue to use antacids if needed until 1 day prior to entering the Pretreatment Period. During the Pretreatment Period, patients may use protocol-defined rescue medication per protocol requirements. Patients will continue to use their current PPI throughout the entire Screening Period. The end of the Screening Period coincides with the start of the Pretreatment Period.

At selected sites, patients who are screened for the study with EGD and Bravo testing will also be given the option of having a Bilitec monitor inserted at that time. The Bilitec procedure is being completed in a subset of patients to collect information about whether bilirubin is present in the duodenogastric refluxate. Previous Bilitec 2000 studies have shown associations between total bile acid concentrations and Bilitec 2000 absorbance. Patients participating in the Bilitec procedure will agree to comply with a "white diet" (see Appendix 8 for example "white diet") and return approximately 24 hours later for removal of the probe. The results of the Bilitec monitoring will not affect qualification for enrollment and during participation in the study, patients will be blinded of their Bilitec testing results.

Pretreatment Period: The Pretreatment Period is defined as the 14 to 21 calendar days immediately before the Randomization Visit. During this period, patients will continue to use their PPI and will refrain from using other anti-reflux medications, including antacids and H2RAs, except for the antacid that is dispensed as rescue medicine. They will also provide the following information in a handheld electronic diary (eDiary); they will perform at least 2 weeks of symptom assessments during which they will be required to complete daily assessments for at least 5 days each week during the last 14 calendar days before the Randomization Visit and weekly assessments at least once during the last 7 calendar days before the Randomization Visit in order to be eligible for randomization:

- GERD symptoms assessed once daily in the evening in the modified Reflux Symptom Questionnaire Electronic Diary (mRESQ-eD; Appendix 1) (Note: any patient who completed the Pretreatment Visit under the original RESQ-eD, protocol version ICP-3718-202-P-01 dated November 9, 2015 will continue completing daily e-diary assessments for the remainder of the study under the original RESQ-eD; patients completing the

Pretreatment Visit under subsequent versions of the protocol will complete the mRESQ-eD for the duration of the study.)

- Dyspepsia symptoms assessed once daily in the evening using Daily Dyspepsia Symptoms (Appendix 2)
- Assessment of sleep assessed once daily in the morning using Daily Assessment of Sleep (Appendix 3)
- Use of per-protocol rescue medicine assessed twice daily.
- Symptom relief and bothersomeness assessed once a week in the evening

Patients will be instructed to take their PPI approximately 30-60 minutes before breakfast each day, even on study visit days. Patients who satisfy all of the entry criteria will enter the Treatment Period.

Treatment Period: The Treatment Period begins with treatment assignment and lasts for 8 weeks. Patients will be stratified by whether they have, or do not have, erosive esophagitis on the screening EGD and randomly assigned to 1 of 4 treatments (1:1:1:1) within each stratum: placebo or 500 mg IW-3718 BID, 1000 mg IW-3718 BID, or 1500 mg IW-3718 BID. The treatment schedule will be managed by a central vendor. Enrollment will be monitored to ensure that no single center contributes > 15% of the targeted study enrollment, unless otherwise approved by the Medical Monitor. Study drug will be taken immediately after the morning and evening meals. Patients will continue to take their PPI approximately 30-60 minutes before breakfast each day and to use the eDiary to provide their daily assessments (GERD symptoms, dyspepsia symptoms, assessment of sleep), weekly assessments (weekly symptom bothersomeness and degree of relief questions; Appendix 6), and use of per-protocol rescue medicine.

Study Population: The study population will consist of adult patients with GERD who are not completely responsive to QD PPI therapy. Patients must be receiving optimized PPI therapy for 8 weeks or longer, for which no further adjustments to the patient's PPI therapy would be beneficial to the patient, per the investigator's opinion. PPI dosing must be consistent with current labeling (Appendix 11). Approximately 260 patients (65 patients per treatment arm) will be randomized into the Treatment Period. Patients will be randomized through central randomization in a 1:1:1:1 ratio to receive either 500 mg IW-3718 BID, 1000 mg IW-3718 BID, 1500 mg IW-3718 BID, or placebo BID. Patients will be stratified by whether they have or do not have erosive esophagitis on the screening EGD.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

1. Patient has signed an ICF before any study-specific procedures are performed.
2. Patient is an ambulatory, community-dwelling male or nonpregnant female and is at least 18 years old at the Screening Visit. Lactating females must agree not to breastfeed.

3. Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on ≥ 4 days per week during the 8 weeks before the Screening Visit while taking standard QD PPI therapy.
4. Patient has been receiving individually optimized, standard-labeled dose, QD, PPI therapy (treatment that, according to the Investigator's judgment, could not be further improved by changing the brand or timing of PPI administration) for a minimum of 8 weeks before the Screening Visit. Patients should be on a PPI dose and schedule that is consistent with the approved labeling (Appendix 11). Patients who have their PPI modified during the Screening Period may be re-screened after 8 weeks of optimized, standard-labeled dose, QD, PPI therapy provided they have not previously entered the Pretreatment Period.
5. An EGD with approximately 48 to 96 hours of pH monitoring (with a Bravo® device) during the Screening Period (while the patient continues taking their PPI) demonstrates 1 or more of the following:
   a. Erosive esophagitis (Grade A or greater based on the Los Angeles classification of esophagitis; Appendix 5) on EGD
   b. Evidence of pathological acid reflux (pH is < 4 for ≥ 4.2% of the recording time) during at least 1 of the 24-hour time intervals of pH testing with the Bravo device
6. Patient reports heartburn severity (HS, Item #1 on mRESQ-eD) ≥ 3 (moderate) on at least 2 days and has an average HS of ≥ 2 (mild) during the last 7 days before randomization.
7. Sexually active female patients of childbearing potential (i.e., women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) must agree to use 1 of the following methods of birth control from the date they sign the ICF until 24 hours after their final dose of study drug:
   a. Hormonal contraception (i.e., contraceptive implant or injectable hormonal contraceptive)
   b. Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide, etc.); Patients may continue taking oral contraceptives while using one or more barrier methods.
   c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
8. Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing.
9. Patient agrees not to make any changes to their usual diet during the study, except those patients participating in Bilitec testing, who must agree to a "white diet" during Bilitec testing only.

10. Patient is compliant with eDiary completion; that is, they have adequately completed the eDiary questions on at least 5 days each week during the 14 calendar days before the start of the Treatment Period.
11. Patient is compliant with QD PPI dosing during the 14 calendar days before the start of the Treatment Period. Patients are considered compliant if, as reported in the eDiary, they take their PPI on at least 5 days each week.
12. Patient is fluent and literate in English or Spanish.
13. Patient is able to operate the eDiary adequately and agrees to adhere to the study requirements.
14. For patients who are receiving supplementation of a fat-soluble vitamin in order to correct or avoid a fat-soluble vitamin deficiency, the patient is willing to take the vitamin supplement at least 4 hours before taking study medication.

Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient has a history of complete lack of GERD symptom response to PPIs in the past.
2. Patient reports epigastric pain or burning as his or her predominant symptom at the Screening Visit.
3. Patient has a history of gastroparesis, bowel obstruction, or is at risk for a bowel obstruction (e.g., patient has an organic gastrointestinal [GI] motility disorders or a history of major GI surgery).
4. Patient has a history of serum triglycerides concentrations > 500 mg/dL on a fasting specimen, or has serum triglycerides concentrations > 500 mg/dL on a fasting specimen at Screening or any time during the Pretreatment Period.
5. Patient has a history of hypertriglyceridemia-induced pancreatitis.
6. In the Investigator's opinion, patient is susceptible to a deficiency of fat-soluble vitamins (especially vitamin D deficiency; e.g., the patient is African American or Hispanic or has osteoporosis, osteomalacia, etc.) and will be put at risk by receiving colesevelam for 8 weeks.
7. Patient has an active swallowing disorder that would prevent them from being able to swallow the study medication.
8. Patient has any alarm symptoms including but not limited to GI bleeding, anemia, vomiting, or unexpected weight loss any time during the Screening or Pretreatment Periods
9. Patient has undergone surgery that meets any of the following criteria:
    a. Surgery of the GI tract (including gastric banding) other than an appendectomy, cholecystectomy, minor oral or rectal surgery (e.g., tonsillectomy, hemorrhoidectomy, rectocele repair) at any time before the Screening Visit

b. An appendectomy during the 3 months before the Screening Visit or a cholecystectomy during the 6 months before the Screening Visit or minor oral or rectal surgery during the 30 days before the Screening Visit
c. Non-GI surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
d. Thoracic surgery during the 6 months before the Screening Visit
e. Other major non-GI surgery during the 30 days before the Screening Visit

10. Patient has previously undergone thoracic or abdominal radiotherapy
11. EGD, conducted during the Screening Period, reveals that the patient has long-segment Barrett's esophagus (greater than 3 centimeters) or definite dysplastic changes in the esophagus, peptic ulcer disease, active GI bleeding, presence of symptomatic esophageal strictures, presence of esophageal or fundic varices, erosive gastritis, or eosinophilic, herpetic or Candida esophagitis.
12. Patient has Gilbert's disease, Crohn's disease, diabetes mellitus, Zollinger-Ellison syndrome, pancreatitis, cholecystitis, or systemic sclerosis.
13. Patient has elevated (defined as > 1.5 times the upper limit of normal by the laboratory) levels of serum bilirubin at Screening or any time during the Pretreatment Period.
14. Patient has a history of clinically significant hypersensitivity or allergies to any of the excipients contained in the study medication (active or placebo).
15. Patient has a history of cancer (resected basal cell or squamous cell carcinoma is acceptable). Note: patients with a history of cancer are allowed provided that the malignancy has been in complete remission for at least 5 years before the Screening Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment.
16. Patient has history of active alcoholism, drug addiction, or illicit drug use (including marijuana) during the 12 months before the Screening Visit.
17. Patient has any clinically significant finding on a physical exam, 12-lead electrocardiogram (ECG), or clinical laboratory test after signing the ICF but before receiving the first dose of study medication. (Note: The Investigator will determine if a particular finding is clinically significant. In making this determination, the Investigator will consider whether the particular finding could prevent the patient from performing any of the protocol-specified assessments, could represent a condition that would exclude the patient from the study, could represent a safety concern if the patient participates in the study, or could confound the study-specified assessments of safety or efficacy.)

18. Patient reports using a prohibited medication during the Screening or Pretreatment Periods, or is not willing or able to abide by the restrictions regarding use of prohibited medications as defined in Appendix 4.
19. Patient has received an investigational drug during the 30 days before the Screening Visit, or is planning to receive another investigational drug or use an investigational device at any time during the study.
20. Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.
21. Patient has previously entered the Treatment Period of a study in which IW-3718 is a treatment.
22. Patient has previously entered the Pretreatment Period of this study.
23. Patient is enrolled in this study at another clinical study site; is an employee of the Institution or Ironwood Pharmaceuticals; or is a first-degree family member, significant other, or relative residing with an employee of the Institution or Ironwood Pharmaceuticals.

Test Product, Dose and Mode of Administration:

Test product will be administered as follows:

- 500 mg IW-3718 BID: One 500 mg IW-3718 oral tablet plus 2 placebo oral tablets (3 tablets total) administered BID, immediately after the morning and evening meals
- 1000 mg IW-3718 BID: Two 500 mg IW-3718 oral tablets plus 1 placebo oral tablet (3 tablets total) administered BID, immediately after the morning and evening meals
- 1500 mg IW-3718 BID: Three 500 mg IW-3718 oral tablets administered BID, immediately after the morning and evening meals

Reference Therapy, Dosage, and Mode of Administration:

Matching placebo: Three oral placebo tablets administered BID immediately after the morning and evening meals

Duration of Treatment:

Study medication will be administered orally BID for 8 weeks; total patient participation is expected to last up to 109 days, including the Screening Period.

Total participation for patients who qualify for a one-week screening extension could last up to 116 days.

Criteria for Evaluation:

Key Efficacy Assessments

The daily patient assessments used to determine the key efficacy parameters are the once-daily assessment of heartburn symptoms and regurgitation symptoms obtained from the mRESQ-eD.

The items in the mRESQ-eD used to score heartburn severity will be the 3 items in the Heartburn Domain assessed on a 0-to-5 ordinal severity scale:

- Heartburn
- A burning feeling behind the breastbone or in the center of the upper stomach
- Pain behind the breastbone or in the center of the upper stomach

The items in the mRESQ-eD used to score regurgitation frequency will be the 2 items in the Regurgitation Domain assessed on a 0-to-4 ordinal frequency scale:

- Regurgitation (liquid or food moving upwards towards your throat or mouth)
- An acid or bitter taste in the mouth

Other Efficacy Assessments

The daily patient assessments used to determine the other efficacy parameters are as follows:

- Once-daily assessment of hoarseness, cough, and difficulty swallowing, all assessed on a 0-to-5 ordinal severity scale
- Once-daily assessment of burping, assessed on a 0-4 frequency scale
- Once-daily assessment of sleep: number of awakenings, sleep time, overall sleep quality assessed on a 5 point verbal rating scale
- Once-daily assessment of dyspepsia: nausea, stomach fullness after eating, difficulty finishing meals, abdominal pain; all assessed at their worst on a 0-to-10 numerical rating scale

Safety Assessments:

Adverse event (AE) recording, clinical laboratory measures (clinical chemistry, hematology, and urinalysis), vital sign measurements, ECGs, physical examinations, and EGDs.

Statistical Methods:

Sample Size Determination

The sample size per arm was determined by estimating the overall power of a trend test in a one-way design that included placebo and all the active treatment arms (500 mg BID, 1000 mg BID, and 1500 mg BID of IW-3718 BID). The efficacy parameter of interest in the previous Phase 2a study (ICP-3718-201) was change from baseline in daytime heartburn defined as the presence of heartburn since the patient awoke that morning (assessed in the evening) and assessed with an 11-point (0 to 10) NRS, where 0=none and 10=very severe. In that study, IW-3718 demonstrated treatment differences near 0.70 points for change over the treatment period (e.g., -0.73 vs. -1.38 for placebo and IW-3718, respectively), and standard deviations near 1.35 for the least-squares means (LSMs). Employing these historical values, it is expected that a study with 58 patients per arm (the expected number of patients at Week 8 given an enrollment of 260 patients) will have statistical power of at least 80% for the overall trend test (i.e., linear contrast) for the mRESQ-eD parameter of weekly heartburn severity score (WHSS), defined as the average of DHSS in a particular week, where the highest active

treatment arm reflects 110% of the previously observed treatment difference and the lowest 2 active treatment arms reflect 55% of the same (two-sided, α=0.05). At the proposed sample size, a subsequent pairwise comparison between placebo and an active treatment arm reflecting the previously observed treatment difference will have 80% statistical power (two-sided, α=0.05).

Analysis Populations

The Screened Population consists of all patients who consented to participate in the study. The modified Intent-to-treat (mITT) Population consists of all randomized patients who received at least 1 dose of study treatment. The Per-Protocol Population (PP) is defined as those patients in the mITT Population who have a minimum of 6 weeks of eDiary data for the heartburn and regurgitation severity scores and > 80% compliance with study treatment for the available Treatment Period days. The Safety Population is defined identically to the mITT Population.

General Methods

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, and range). Categorical variables will be summarized using the count and proportion of patients in each category. Unless otherwise specified, all confidence intervals will be two-sided and with a confidence level of 95%. No adjustments will be made for multiplicity. Details of the data handling methods will be specified in the Statistical Analysis Plan. If not otherwise specified, the baseline value is defined as the last non-missing value measured before administration of study treatment on Day 1. All statistical analyses will be performed using SAS® Version 9.3 (or later) for Windows.

Primary Efficacy Parameter

Percent change from baseline in WHSS at Week 8

Secondary Efficacy Parameters

1. Percent change from baseline in WHSS at Week 4.
2. Change from baseline in WHSS at (a) Week 4 and (b) Week 8.
3. Proportion of patients who are overall heartburn responders
   a. Weekly heartburn responder: patient with a decrease from baseline of ≥ 30% in WHSS
   b. Overall heartburn responder: patient who is a weekly heartburn responder for at least 1 of the final 2 weeks and for ≥ 50% of the treatment weeks
4. Proportion of patients with a daily heartburn severity score (DHSS) of no more than very mild (≤ 1) on any day during (a) Week 4 and (b) Week 8.
5. The number of days per week where DHSS was no more than very mild (≤ 1) at (a) Week 4 and (b) Week 8.
6. Change from baseline in each mRESQ-eD item by week.
7. Proportion of heartburn free days in Week 4 and Week 8.

Note: DHSS is defined as the maximum of the 3 items in the heartburn assessments of a particular day, collected with the mRESQ-eD instrument. Further, WHSS is defined as the average of DHSS in a particular week.

Heartburn-free days will be calculated by 2 approaches. The first will employ the single heartburn item in the heartburn domain (Item #1 from mRESQ-eD: Heartburn) which is similar to the heartburn rating scale(s) used in the PPI literature. The second will employ all 3 items in the heartburn domain (Items #1 through #3 from mRESQ-eD: Heartburn; Burning feeling behind the breastbone or in the center of the upper stomach; Pain behind the breastbone or in the center of the upper stomach. In the first approach, the heartburn item needs to be assessed at 0 (Did not have) while in the second approach all 3 heartburn domain items need to be assessed at 0 (Did not have).

Efficacy Analyses for the Primary and Secondary Efficacy Parameters

For the analysis of continuous parameters (e.g., absolute change from baseline and percent change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. Each IW-3718 group will be compared with the placebo group using an analysis of covariance (ANCOVA) model with treatment group and esophagitis stratum as fixed effect terms and the corresponding baseline efficacy value as a covariate. Least-squares means for each treatment group, a linear contrast among the LSMs to test the overall ordinal dose response, LSMs differences between each IW-3718 group and the placebo group and their corresponding confidence intervals, and p-values for the pairwise comparisons versus placebo will be presented. The treatment by esophagitis stratum interaction term will be explored to evaluate whether quantitative or qualitative interaction(s) are present, and treatment comparisons within each stratum will be conducted, as warranted.

The cumulative distribution function (CDF) of change from baseline for key efficacy parameters will be plotted by treatment group. To aid in the interpretation of the graphical representation of the CDF across treatments, a two-sample Kolmogorov-Smirnov test will be conducted (22). A p-value ≤ 0.05 indicates that the 2 treatment samples are unlikely to have been drawn from the same continuous distribution by chance alone.

For the analysis of responder parameters (i.e., responder vs. non-responder), the counts and proportions of responders will be calculated for each treatment group. The proportions of responders between each IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling esophagitis stratum. The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between each IW-3718 group and the placebo group as well as the CMH estimates of the odds ratio (IW-3718 over placebo) and the corresponding 95% confidence intervals will also be presented.

Safety Analysis

All safety parameters will be analyzed with descriptive statistics. Safety analyses will be performed on the Safety Population. The safety parameters will include AEs, treatment-emergent AEs (TEAEs), clinical laboratory evaluations, vital signs, ECG, and physical examination. For each safety parameter, the last non-missing assessment made before randomization will be used as the baseline for all analyses of that safety parameter.

Schedule of Events

	Screening Period (Up to 4 weeks)[w]	**Pretreatment Period (2 weeks)**	**Treatment Period (8 weeks)**				**Follow-up**
Visit Days →	Screening Visit (Day -49 to Day -15)	Pretreatment Visit (Day -21 to Day -1)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ± 3)	Week 4 Visit (Day 29 ± 3)	Week 8 / End-of-treatment Visit (Day 57 + 3)	EOT + 7 days
Visit Numbers →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Study Procedure ↓							
Inclusion and Exclusion Criteria Verification	X	X	X				
Signing of ICF	X						
IWRS Registration (a)	X	X	X	X	X	X	
Demographics	X						
Medical History	X						
Physical Examination (b)	X					X	
Body Weight and Height (c)	X	X	X	X	X	X	
H2RA/Antacid Washout (d)	X						
Bilitec Monitoring (e)	X						
EGD (f)	X					X	
48 to 96 Hours of pH Testing with Bravo Device (g)	X						
Seated Vital Signs (h)	X	X	X	X	X	X	
12-Lead ECG (i)	X		X			X	
Prior and Concomitant Medications (j)	X	X	X	X	X	X	
Clinical Laboratory Tests (k)	X		X		X	X	
Serum Pregnancy Test (l)	X					X	

Schedule of Events

	Screening Period (Up to 4 weeks)[w]	**Pretreatment Period (2 weeks)**	**Treatment Period (8 weeks)**				**Follow-up**
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Visit Numbers →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Study Procedure ↓							
Urine Pregnancy Test (l)			X		X		
Drug and Alcohol Screen (m)	X						
AE Evaluations (n)	X	X	X	X	X	X	
Rescue Medicine Dispensed (o)		X	X	X	X		
PDA Training and Dispensation		X					
Saliva Collection (p)	X	X	X		X	X	
eDiary (q)		X	X	X	X	X	
Weekly Symptom and Treatment Assessments (r)		X	X	X	X	X	
GSRS-Self			X		X	X	
QIDS-SR-16			X				
SF-12V2			X		X	X	
EQ-5D-3L			X		X	X	
Randomization			X				
Study Medication Dispensed (s)			X	X	X		
Study Medication Return (t)				X	X	X	
PDA Return						X	
mRESQ-eD Debrief Interview (x)		X (x)			X (x)		
End of Treatment Question (u)						X	

Schedule of Events

	Screening Period (Up to 4 weeks)[w]	Pretreatment Period (2 weeks)	Treatment Period (8 weeks)				Follow-up
Visit Days →	Screening Visit (Day -49 to Day -15)	Pretreatment Visit (Day -21 to Day -1)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ± 3)	Week 4 Visit (Day 29 ± 3)	Week 8 / End-of-treatment Visit (Day 57 + 3)	EOT + 7 days
Visit Numbers →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Study Procedure ↓							
Safety Follow-up Call (v)							X

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; EGD = esophagogastroduodenoscopy; EOT = End-of-treatment; EQ = EuroQol; GSRS = Gastrointestinal Symptoms Rating Scale; H2RA = histamine-2 receptor antagonist; HEENT = head, eyes, ears, nose, and throat; ICF = informed consent form; IWRS = interactive web response system; PDA = personal digital assistant; PPI = proton pump inhibitor; QID = Quick Inventory of Depressive Symptomology; mRESQ-eD = modified Reflux Symptom Questionnaire Electronic Diary; SAE = serious adverse event; SF = short form

a. Site personnel will interact with IWRS to register the patient visit and transition the patient to the next appropriate study period.
b. A physical examination should include the following assessments: general appearance; HEENT; neck; cardiovascular; respiratory; abdomen/liver/spleen; musculoskeletal; lymph nodes; skin; neurologic; nervous system, and mental status. Breast, genitourinary, and rectal examinations are optional and may be performed at the discretion of the Investigator.
c. Height will be measured only at the Screening Visit.
d. During the Screening Period, patients will begin to washout H2RAs and antacids. H2RAs should be stopped 5 calendar days prior to the EGD and Bravo pH monitoring and antacids should be stopped 1 calendar day prior to the EGD and Bravo pH monitoring. Patients may resume antacid use upon completion of the Bravo testing, but must refrain from H2RA use for the remainder of the study. During the Pretreatment Period, patients will refrain from using any anti-reflux medications, antacids, and H2RAs, except for the antacids that are provided as rescue medicine). Patients will continue to use their current PPI during the Pretreatment Period.
e. At selected sites, selected patients who are screened for the study with EGD and Bravo testing will also be given the option of having a Bilitec monitor inserted during the same procedure. These patients will return 24 hours later for removal of the probe. The results of the Bilitec test will not affect qualification for enrollment. The Bilitec device and Bravo recorder internal clocks must be synchronized, and both devices should be activated concurrently; however, if it is not possible to simultaneously activate both devices, the Bravo recorder should be activated first, with the Bilitec device activation immediately (within 5 minutes) after the Bravo pH recorder activation.
f. All patients will be required to undergo an EGD during the Screening Period. There must be a minimum of 7 days between the EGD and the start of the Pretreatment Period to allow for pH testing and patient stabilization. An EGD will be performed at the Week 8 / EOT Visit in all patients who have Grade C or D esophagitis (based on the Los Angeles classification of esophagitis, see Appendix 5) on the EGD obtained during the Screening Period.

g. Approximately 48 to 96 hours of pH testing with the Bravo device. If for some reason 96 hours of testing is not possible, then approximately 48 hours of testing is acceptable. During the entire period of Bravo pH monitoring (approximately 48-96 hours), patients will record ingestion of anything other than water by depressing the 'meal' button on the Bravo recorder upon the beginning and completion of the meal, snack, or drink. Patients will also record any periods during which they are lying down by depressing the 'supine' button on the Bravo recorder at the beginning and upon completion of the supine period. In addition, for the entire 48-96 hour Bravo pH monitoring period, patients will complete a paper diary (see Appendix 9), recording at a minimum all instances of meals, snacks, drinks, and/or resting in the supine position.
h. Vital sign measurements include oral temperature (°C), respiratory rate, systolic and diastolic BP, and pulse. Respiratory rate, BP, and pulse measurements must be obtained after the patient has been seated for at least 5 minutes.
i. 12-Lead ECGs should be obtained after the patient has been supine for at least 5 minutes.
j. Prior medications will be collected at the Screening Visit as follows: all medicines taken by the patient during the 30 days before the Screening Visit, most recent use of an H2RA, and most recent use of an antacid.
k. Clinical laboratory tests include clinical chemistry, hematology (CBC), coagulation, and urinalysis. If the triglyceride value exceeds the protocol-specified criteria and the patient was not under fasted conditions, the patient may return to complete a fasted lipid panel.
l. For all female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit, and a negative urine pregnancy test must be documented at the Randomization Visit (before dosing) in order for the patient to be randomized into the study. A urine pregnancy test will be obtained at the Week 4 Visit; a serum pregnancy test will be conducted at the EOT Visit.
m. Patients must undergo a urine drug screen for selected drugs of abuse (cocaine, barbiturates, amphetamines, opiates, benzodiazepines, and cannabinoids) and a serum alcohol screen at the Screening Visit.
n. All AEs will be captured from the time the patient signs the ICF through the EOT Visit.
o. Rescue medicine will be supplied to patients at the Pretreatment Visit, and if needed, at subsequent visits.
p. At each of the indicated visits, patients will provide approximately 1 mL of saliva for future use (bile acids will be quantified in the saliva, and the quantity of bile acid may be used to define potential responders to IW-3718). At the time of saliva collection, study site staff will collect the following information: time of day, time of patient's last meal, and time of last study medication administration. During the Randomization Visit, study site staff will collect the saliva sample immediately following the light snack but prior to study drug administration.
q. The eDiary will be dispensed at the Pretreatment Visit and patients must complete at least 5 days each week during the 14 days before the Treatment Period in order to be eligible for randomization. Patients should bring their eDiary to each visit. The eDiary will collect daily PPI administration, rescue medication use, mRESQ-eD (Appendix 1; daily), Daily Assessment of Sleep (Appendix 3; daily), Daily Dyspepsia Symptoms (Appendix 2; daily).
r. Symptom bothersomeness and symptom relief items (Appendix 6; weekly); Treatment satisfaction (Appendix 6; weekly).
s. The first dose of study medication will be administered in the clinic with liquid and a snack at the Randomization Visit. At all other visits, patients will take their study medication prior to arriving at the clinic, but will be dispensed additional doses needed until the next study visit.
t. Treatment compliance with study drug will be assessed based on return of unused tablets.
u. All patients will be asked an EOT question regarding the difficulty of swallowing the IW-3718 or placebo tablets (Appendix 6).
v. Study site will contact each patient via telephone 7 days after the EOT Visit to collect information pertaining to ongoing AEs/SAEs and information concerning any new AEs/SAEs since the EOT Visit.
w. Ironwood may grant a one-week extension of the screening period window if needed for logistical delays (e.g., subject travel, scheduling issues, delays in test results, equipment malfunction, etc.). Approval should be requested from Ironwood prior to each extension.
x. Patients participating in the optional mRESQ-eD Cognitive Debriefing interviews will be assigned to one of three interview groups. Interviews will take place at different timepoints depending on the patient's group assignment. (see Appendix 10)

STUDY IDENTIFICATION

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ANCOVA	analysis of covariance
BAS	bile acid sequestrant
BID	twice daily
BP	blood pressure
CBC	complete blood count
CDF	cumulative distribution function
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
DGER	duodenogastroesophageal reflux
DHSS	daily heartburn severity score
DRFS	daily regurgitation frequency score
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EGD	esophagogastroduodenoscopy
EOT	End-of-treatment
EQ	EuroQol
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	Gastrointestinal
GSRS	Gastrointestinal Symptoms Rating Scale
H2RA	histamine-2 receptor antagonist
HCl	Hydrochloride
HS	heartburn severity
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board

IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
LSM	least-square mean
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
mRESQ-eD	modified Reflux Symptom Questionnaire Electronic Diary
NRS	numerical rating scale
PDA	personal digital assistant
PID	patient identification
PP	Per-Protocol
PPI	proton pump inhibitor
QD	once daily
QIDS-SR-16	Quick Inventory of Depressive Symptomatology (16 Item) Self Report
SAE	serious adverse event
SAP	statistical analysis plan
SF	short form
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States
WHSS	weekly heartburn severity score
WRFS	weekly regurgitation frequency score

1. INTRODUCTION

1.1 BILE ACIDS AND GERD

Bile acids play an important role in the digestive process; however, data from nonclinical and mechanistic studies suggest that the prolonged presence or excess of bile acids in the stomach and esophagus can result in toxic effects on regional tissues (1,2,3,4). Duodenogastroesophageal reflux (DGER), which contains bile acids, is thought to produce symptoms such as retrosternal pain, heartburn, nausea, and vomiting (5,6), and is associated with more severe esophageal pathology in patients with gastroesophageal reflux disease (GERD) and Barrett's esophagus, a precancerous change in the esophagus (4,7).

Gastroesophageal reflux disease is a chronic and common medical disorder with a prevalence estimated at approximately 20% to 40% in Western countries (8), and is associated with rising healthcare utilization and cost (9). Currently, proton pump inhibitors (PPIs) are the standard of care for GERD; however, it is estimated that approximately 10% to 40% of GERD patients remain symptomatic on standard-dose PPI therapy (10). DGER is hypothesized to be a potential cause of incomplete symptom response in patients who continue to experience bothersome GERD symptoms despite treatment with PPIs (11).

There is significant evidence to support DGER as a putative mechanism for persistent GERD symptoms. Pathological bile acid reflux occurs in approximately 65% of patients who continue to experience bothersome GERD symptoms despite treatment with PPIs and is hypothesized to be a cause of their incomplete symptom response (11). There is considerable clinical and nonclinical evidence that bile acid can cause esophageal damage both in conjunction with stomach acid as well as independently (1,2,5).

There is currently no widely used diagnostic technique for evaluating the role of bile acid salts in the presence of GERD that is refractory to standard dose PPIs. In this study we require patients to have esophageal erosions demonstrated by EGD or to have acid reflux confirmed by the use of the Bravo device inserted at the time of the EGD.

The Bilitec® device can be placed in the esophagus and uses the spectrophotometric analysis of the presence of bilirubin as a marker for the presence of bile acid salts that might be contributing

to reflux. It was demonstrated that bilirubin content detected by this device correlates with the concentrations of pancreatic enzymes in aspirated refluxate, suggesting that bilirubin is a good tracer for DGER (12). Therefore it is reasonable to correlate the results of Bilitec testing with the response to IW-3718 in a subgroup of patients selected to have this testing, along with the other procedures outlined in this protocol.

1.2 IW-3718

Ironwood is developing IW-3718 for the treatment of symptomatic GERD not completely responsive to PPIs and for and other gastrointestinal (GI) disorders. IW-3718 is colesevelam hydrochloride (HCl), a bile acid sequestrant (BAS).

Colesevelam HCl (hereafter referred to as colesevelam) is an orally administered, nonabsorbed, nondigestible polymer that binds bile acids in the GI tract. Colesevelam was approved in 2000 in the United States (US) as the active ingredient in Welchol™, and is indicated as an adjunct to diet and exercise for reduction of elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia. Colesevelam is currently available as an immediate-release formulation only.

IW-3718 tablets are formulated as a controlled-release, solid oral dosage form intended to extend the release of the drug substance, colesevelam, into the stomach. The released colesevelam is expected to bind bile acids that are refluxed into the stomach and upper duodenum, forming a bile acid-colesevelam complex and preventing the free bile acids from entering the esophagus. The bile acid-colesevelam complex will travel down the GI tract and be excreted without being absorbed.

The controlled-release formulation in IW-3718 tablets is based on Depomed's Acuform® technology which utilizes swelling polymers to allow the tablet to be retained in the stomach for approximately 9 hours when dosed in the fed state, during which time the tablet slowly releases the active ingredient in the stomach and upper GI tract. The tablet's active ingredient is steadily delivered to the stomach and upper GI tract in a near zero-order manner. The technology is used in the formulation of 5 Food and Drug Administration (FDA)-approved drugs: Glumetza® (metformin HCl, extended release), Janumet® XR (sitagliptin and metformin HCl extended-

release), Proquin® XR (ciprofloxacin HCl monohydrate, extended release), NUCYNTA® ER (tapentadol extended-release tablets), and once-daily Gralise™ (gabapentin) tablets.

Colesevelam is not systemically absorbed and does not interfere with systemic drug metabolizing enzymes. Distribution of colesevelam is limited to the GI tract and elimination occurs through fecal excretion.

Colesevelam reduces serum LDL-C concentrations by binding bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-α-hydroxylase, is upregulated, which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effect of increasing transcription and activity of the cholesterol biosynthetic enzyme, HMG-CoA reductase, and increasing the number of hepatic LDL receptors. These compensatory effects result in increased clearance of LDL-C from the blood, resulting in decreased serum LDL-C concentrations. Serum triglyceride concentrations may increase or remain unchanged. The mechanism by which colesevelam improves glycemic control is unknown. However, increasing evidence suggests that colesevelam, as a BAS, may function by signaling molecules in the liver and GI tract for lipid and glucose metabolism (13,14,15,16). The mechanism by which colesevelam is expected to reduce symptoms in GERD is by binding bile acids that are refluxed into the stomach and preventing the free bile acids from entering the esophagus and reacting with the esophageal mucosa.

There are no reported clinical efficacy studies with colesevelam in patients with GERD, or other upper GI disorders.

Colesevelam (as Welchol) has been evaluated for safety in clinical studies and via post-marketing pharmacovigilance. In general, colesevelam was safe and well-tolerated in adults with hyperlipidemia or type 2 diabetes mellitus, and in adolescents with familial hypercholesterolemia. Due to the large doses required for lipid lowering, and its local effects in the GI tract, most of the adverse events (AEs) related to colesevelam are GI in nature (constipation, flatulence, and dyspepsia). Most of these AEs were of mild or moderate intensity. In clinical lipid-lowering studies, the incidence of dyspepsia was greater at the higher doses (3.8 and 4.5 g/day).

IW-3718 has been evaluated in a Phase 2a study. This study was a 4-week, randomized, double-blind, placebo-controlled, proof-of-concept study in patients with GERD not completely responsive to QD PPI therapy. In this study patients were randomized in a 1:1 fashion to either IW-3718 1000 mg bid or placebo. A Bilitec procedure was performed as an optional procedure. Esophageal duodenogastroscopy and pH monitoring were not required, but results were collected if these procedures were performed prior to randomization or in the recent past. Symptoms were assessed over the four week period to determine severity of heartburn-related symptoms.

Safety and efficacy data are available for 93 patients, 46 of whom received 1000 mg IW-3718 BID. IW-3718 was well tolerated among patients with GERD. There were no deaths or study medication-related serious adverse events (SAEs). Common TEAEs (>5% of patients) among patients who received IW 3718 or placebo included constipation (13% vs 0%) and abdominal pain (7% vs 2%).

In this study, among all patients (Intent-to-treat [ITT] Population), severity of daytime heartburn showed a trend toward being numerically reduced in IW-3718 patients compared to placebo (p=0.124). The largest differences between IW-3718 and placebo for this parameter were seen in patients who underwent Bilitec monitoring. Improvements were also observed for nighttime heartburn severity at Week 4. A greater percentage of IW-3718-treated patients (9 patients, 19.6%) reported an absence of heartburn during Week 4 compared with those receiving placebo (5 patients, 10.6%).

2. STUDY OBJECTIVES

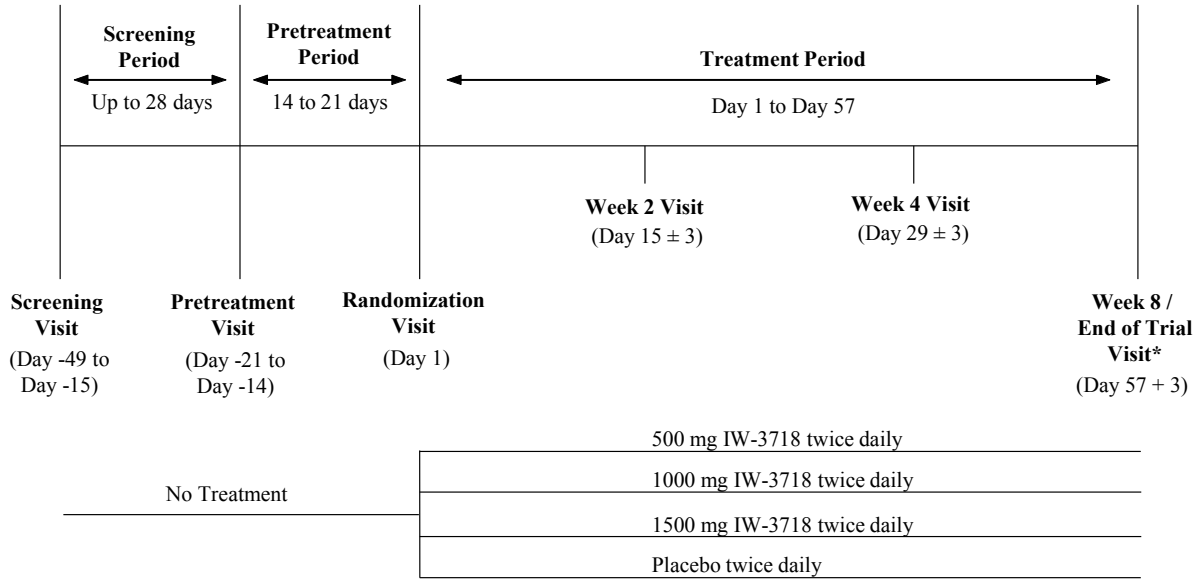
The objectives of this study are to evaluate the safety, efficacy, and dose-response relationship of IW-3718 administered orally to patients who have GERD and continue to experience GERD symptoms while receiving once-daily (QD), standard-dose PPIs.

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-week study, consisting of 3 distinct periods as illustrated in Figure 1. The study will enroll patients who have GERD and continue to experience GERD symptoms while receiving QD, standard-dose PPI therapy. Eligible patients will continue to take their PPI and will be randomized to placebo or to 500 mg IW-3718 twice daily (BID), 1000 mg IW-3718 BID, or 1500 mg IW-3718 BID. Randomization will be stratified by whether they have, or do not have, erosive esophagitis on the screening esophagogastroduodenoscopy (EGD).

Figure 1. Overview of Study Design



Note: There is no Day 0

* This visit represents the end of the study

All patients will take their current PPI approximately 30-60 minutes before breakfast each day during the Screening, Pretreatment, and Treatment Periods. During the Treatment Period, all patients will take IW-3718 or matching placebo immediately upon completion of the morning and evening meal each day.

Screening Period: The Screening Period starts with the signature of the informed consent form (ICF) and is expected to last for up to 28 days. During this period, patient eligibility for entry into the Pretreatment Period will be determined. Two procedures will be required during the

Screening Period in all patients; a third procedure Bilitec® testing will be optional for all patients at selected sites (all will be done while patients continue to take their PPI):

- An EGD
- Approximately 48 to 96 hours of pH testing with the Bravo® device. If for some reason 96 hours of testing is not possible, then approximately 48 hours of testing is acceptable (Please refer to section 3.5.1.10 for further instruction)
- Approximately 24 hours of bilirubin detection using the Bilitec monitoring system (optional at selected sites)

Histamine-2 receptor antagonists (H2RAs) should be stopped 5 calendar days prior to the EGD and Bravo pH monitoring and antacids should be stopped 1 calendar day prior to the EGD and Bravo pH monitoring. The EGD must be performed during the Screening Period and at least 7 days before the start of the Pretreatment Period to allow time for pH collection and allow the patient to stabilize following these procedures. Upon completion of the Bravo testing, patients will refrain from using H2RAs, but may continue to use antacids if needed. Patients will continue to use their current PPI throughout the Screening Period. The end of the Screening Period coincides with the start of the Pretreatment Period

At selected sites, patients who are screened for the study with EGD and Bravo testing will also be given the option of having a Bilitec monitor inserted at that time. The Bilitec procedure is being completed in a subset of patients to collect information about whether bilirubin is present in the duodenogastric refluxate. Previous Bilitec 2000 studies have shown associations between total bile acid concentrations and Bilitec 2000 absorbance. Patients participating in the Bilitec procedure will agree to comply with a "white diet" (see Appendix 8 for example "white diet") and return approximately 24 hours later for removal of the probe. The results of the Bilitec monitoring will not affect qualification for enrollment and during participation in the study, patients will be blinded of their Bilitec testing results.

Ironwood may grant a one-week extension of the screening period window if needed for logistical delays, as described in Section 3.6.1.2.

Pretreatment Period: The Pretreatment Period is defined as the 14 to 21 calendar days immediately before the Randomization Visit. During this period, patients will continue to use their PPI and will refrain from using other anti-reflux medications, including antacids and H2RAs, except for the antacid that is dispensed as rescue medicine. They will also provide the following information in a handheld eDiary; they will perform at least 2 weeks of symptom assessments during which they will be required to complete daily assessments for at least 5 days each week during the 14 calendar days before the start of the Treatment Period and weekly assessments at least once during the 7 calendar days before the start of the Treatment Period in order to be eligible for randomization**:**

- GERD symptoms assessed once daily in the evening in the modified Reflux Symptom Questionnaire eDiary (mRESQ-eD; Appendix 1)
- Dyspepsia symptoms assessed once daily in the evening using Daily Dyspepsia Symptoms (Appendix 2)
- Assessment of sleep assessed once daily in the morning using Daily Assessment of Sleep (Appendix 3)
- Use of per-protocol rescue medicine assessed twice daily
- Symptom relief and bothersomeness assessed once a week in the evening

Patients will be instructed to take their PPI at least approximately 30-60 minutes before breakfast each day, even on study visit days. Patients who satisfy all of the entry criteria will enter the Treatment Period.

Treatment Period: The Treatment Period begins with treatment assignment and lasts for 8 weeks. Patients will be stratified by whether they have, or do not have, erosive esophagitis on the screening EGD and randomly assigned to 1 of 4 treatments (1:1:1:1) within each stratum: placebo or 500 mg IW-3718 BID, 1000 mg IW-3718 BID, or 1500 mg IW-3718 BID. The treatment schedule will be managed by a central vendor. Enrollment will be monitored to ensure that no single center contributes > 15% of the targeted study enrollment, unless otherwise approved by the Medical Monitor. Study drug will be taken immediately after the morning and evening meals. Patients will continue to take their PPI approximately 30-60 minutes before breakfast each day and to use the eDiary to provide their daily assessments (GERD symptoms, dyspepsia symptoms, assessment of sleep), weekly assessments (weekly symptom

bothersomeness and degree of relief questions; Appendix 6), PPI compliance, and use of per-protocol rescue medicine.

For details regarding the assessments during each study period, see the Schedule of Events (Table 2).

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

A double-blind, placebo-controlled, parallel-group study design was chosen in accordance with the concepts in International Conference on Harmonisation (ICH) E10, Choice of Control Groups and Related Issues in Clinical Trials (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2001), in order to provide comparable treatment groups and minimal chance of selection or Investigator bias.

This study has a 14- to 21-day Pretreatment Period to establish a baseline without therapy and to familiarize patients with data collection methodology (i.e., personal digital assistants [PDAs]), and an 8-week Treatment Period to compare the test treatment with a placebo control.

3.3 SELECTION OF STUDY POPULATION

This study will be conducted in patients with GERD not completely responsive to QD PPI therapy. Approximately 260 patients will be randomized (approximately 65 patients per treatment group). The study will be conducted at approximately 60-80 study centers in the US. Optional Bilitec testing will be done at a selected number of sites participating in the protocol. The goal at these sites will be to enroll a minimum of 60 patients with Bilitec testing who are randomized to treatment with IW-3718 or placebo.

Study medication will be administered orally BID for 8 weeks; total patient participation is expected to last up to 109 days, including the Screening Period.

3.3.1 Eligibility Criteria

3.3.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be eligible for enrollment in this study:

1. Patient has signed an ICF before any study-specific procedures are performed.

2. Patient is an ambulatory, community-dwelling male or nonpregnant female and is at least 18 years old at the Screening Visit. Lactating females must agree not to breastfeed.
3. Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on ≥ 4 days per week during the 8 weeks before the Screening Visit while taking standard QD PPI therapy.
4. Patient has been receiving individually optimized, standard-labeled dose, QD, PPI therapy (treatment that, according to the Investigator's judgment, could not be further improved by changing the brand or timing of PPI administration) for a minimum of 8 weeks before the Screening Visit. Patients should be on a PPI dose and schedule that is consistent with the approved labeling (Appendix 11). Patients who have their PPI modified during the Screening Period may be re-screened after 8 weeks of optimized, standard-labeled dose, QD, PPI therapy provided they have not previously entered the Pretreatment Period.
5. An EGD with approximately 48 to 96 hours of pH monitoring (with a Bravo device) during the Screening Period (while the patient continues taking their PPIs) demonstrates 1 or more of the following:
   a. Erosive esophagitis (Grade A or greater based on the Los Angeles classification of esophagitis; Appendix 5) on EGD
   b. Evidence of pathological acid reflux (pH is < 4 for ≥ 4.2% of the recording time) during at least 1 of the 24-hour time intervals of pH testing with the Bravo device
6. Patient reports heartburn severity (HS, Item #1 on mRESQ-eD) ≥ 3 (moderate) on at least 2 days and has an average HS of ≥ 2 (mild) during the last 7 days before randomization.
7. Sexually active female patients of childbearing potential (i.e., women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) must agree to use 1 of the following methods of birth control from the date they sign the ICF until 24 hours after their final dose of study drug:
   a. Hormonal contraception (i.e., contraceptive implant or injectable hormonal contraceptive)
   b. Double-barrier birth control (e.g., condom plus intrauterine device, diaphragm plus spermicide, etc.) Patients may continue taking oral contraceptives while using one or more barrier methods.
   c. Maintenance of a monogamous relationship with a male partner who has been surgically sterilized by vasectomy
8. Females of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit prior to dosing.

9. Patient agrees not to make any changes to their usual diet during the study, except those patients participating in Bilitec testing, who must agree to a "white diet" during Bilitec testing only.
10. Patient is compliant with eDiary completion; that is, they have adequately completed the eDiary questions on at least 5 days each week during the 14 calendar days before the start of the Treatment Period.
11. Patient is compliant with QD PPI dosing during the 14 calendar days before the start of the Treatment Period. Patients are considered compliant if, as reported in the eDiary, they take their PPI on at least 5 days each week.
12. Patient is fluent and literate in English or Spanish.
13. Patient is able to operate the eDiary adequately and agrees to adhere to the study requirements.
14. For patients who are receiving supplementation of a fat-soluble vitamin in order to correct or avoid a fat-soluble vitamin deficiency, the patient is willing to take the vitamin supplement at least 4 hours before taking study medication.

3.3.1.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient has a history of complete lack of GERD symptom response to PPIs in the past.
2. Patient reports epigastric pain or burning as his or her predominant symptom at the Screening Visit.
3. Patient has a history of gastroparesis, bowel obstruction, or is at risk for a bowel obstruction (e.g., patient has an organic GI motility disorder or a history of major GI surgery).
4. Patient has a history of serum triglycerides concentrations > 500 mg/dL on a fasting specimen, or has serum triglycerides concentrations > 500 mg/dL on a fasting specimen at Screening or any time during the Pretreatment Period.
5. Patient has a history of hypertriglyceridemia-induced pancreatitis.
6. In the Investigator's opinion, patient is susceptible to a deficiency of fat-soluble vitamins (especially vitamin D deficiency; e.g., the patient is African American or Hispanic or has osteoporosis, osteomalacia, etc.) and will be put at risk by receiving colesevelam for 8 weeks.
7. Patient has an active swallowing disorder that would prevent them from being able to swallow the study medication.
8. Patient has any alarm symptoms including but not limited to GI bleeding, anemia, vomiting, or unexpected weight loss any time during the Screening or Pretreatment Periods.
9. Patient has undergone surgery that meets any of the following criteria:

a. Surgery of the GI tract (including gastric banding) other than an appendectomy, holecystectomy, minor oral or rectal surgery (e.g., tonsillectomy, hemorrhoidectomy, rectocele repair) at any time before the Screening Visit
b. An appendectomy during the 3 months before the Screening Visit or a cholecystectomy during the 6 months before the Screening Visit or minor oral or rectal surgery during the 30 days before the Screening Visit
c. Non-GI surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit
d. Thoracic surgery during the 6 months before the Screening Visit
e. Other major non-GI surgery during the 30 days before the Screening Visit

10. Patient has previously undergone thoracic or abdominal radiotherapy.
11. EGD, conducted during the Screening Period, reveals that the patient has long-segment Barrett's esophagus (greater than 3 centimeters) or definite dysplastic changes in the esophagus, peptic ulcer disease**,** active GI bleeding, presence of symptomatic esophageal strictures, presence of esophageal or fundic varices, erosive gastritis, or eosinophilic, herpetic or candida esophagitis.
12. Patient has Gilbert's disease, Crohn's disease, diabetes mellitus, Zollinger-Ellison syndrome, pancreatitis, cholecystitis, **or** systemic sclerosis**.**
13. Patient has elevated (defined as > 1.5 times the upper limit of normal by the laboratory) levels of serum bilirubin at Screening or anytime during the Pretreatment Period.
14. Patient has a history of clinically significant hypersensitivity or allergies to any of the excipients contained in the study medication (active or placebo).
15. Patient has a history of cancer (resected basal cell or squamous cell carcinoma is acceptable). Note: patients with a history of cancer are allowed provided that the malignancy has been in complete remission for at least 5 years before the Screening Visit. A complete remission is defined as the disappearance of all signs of cancer in response to treatment**.**
16. Patient has history of active alcoholism, drug addiction, or illicit drug use (including marijuana) during the 12 months before the Screening Visit.
17. Patient has any clinically significant finding on a physical exam, 12-lead electrocardiogram (ECG), or clinical laboratory test after signing the ICF but before receiving the first dose of study medication. (Note: The Investigator will determine if a particular finding is clinically significant. In making this determination, the Investigator will consider whether the particular finding could prevent the patient from performing any of the protocol-specified assessments, could represent a condition that would exclude the patient from the study, could represent a safety concern if the patient participates in the study, or could confound the study-specified assessments of safety or efficacy.)

18. Patient reports using a prohibited medication during the Screening or Pretreatment Periods, or is not willing or able to abide by the restrictions regarding use of prohibited medications as defined in Appendix 4.
19. Patient has received an investigational drug during the 30 days before the Screening Visit, or is planning to receive another investigational drug or use an investigational device at any time during the study.
20. Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.
21. Patient has previously entered the Treatment Period of study in which IW-3718 is a treatment.
22. Patient has previously entered the Pretreatment Period of this study.
23. Patient is enrolled in this study at another clinical study site; is an employee of the Institution or Ironwood Pharmaceuticals; or is a first-degree family member, significant other, or relative residing with an employee of the Institution or Ironwood Pharmaceuticals.

3.3.2 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who has signed the ICF ceases participation in the study, regardless of circumstances, before completion of the Treatment Period.

A patient will be considered to have completed the study after receiving 8 weeks of treatment and completing the End-of-treatment (EOT) Visit at Day 57. A window of +3 days will be allowed for the EOT visit; if a patient completes the EOT Visit prior to Day 57, this will be considered a protocol deviation.

Patients will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator may remove a patient from the study if, in the Investigator’s opinion, it is not in the best interest of the patient to continue the study. Patients may also be discontinued from the study by the Investigator or the Sponsor at any time for any reason, including the following:

- Failure to meet an inclusion/exclusion criterion that is clinically relevant and affects patient safety
- Adverse event(s)

- Protocol violation, including lack of compliance
- Insufficient therapeutic response (lack of efficacy)
- Lost to follow-up (every effort must be made to contact the patient; a certified letter must be sent)
- Withdrawal of consent (attempts should be made to determine the reason for the patient withdrawing consent if possible)
- Study termination by the Sponsor
- Other reasons (e.g., administrative reasons or pregnancy)

The date the patient is withdrawn from the study and the reason for discontinuation will be recorded on the study termination form of the electronic case report form (eCRF). Patients who discontinue from the study for any reason should complete the assessments required at the EOT Visit at the time of their discontinuation. Patients who discontinue from the study will be followed until resolution of all of their AEs or until the unresolved AEs are judged by the Investigator to have stabilized. Study centers should make a reasonable effort to follow any pregnant patients until delivery or end of the pregnancy.

If a patient does not return for a scheduled visit, the study center should contact the patient. An effort must be made to contact the patient, including sending a certified letter. In every case, the patient outcome, including lost to follow-up information, will be documented.

3.3.3 Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

3.4 STUDY TREATMENTS

3.4.1 Investigational Product

3.4.1.1 IW-3718

Study medication will be provided as 500 mg IW-3718 tablets which are white to off-white, oval shaped, film-coated tablets intended for oral administration. In addition to the active drug substance, colesevelam, 500 mg IW-3718 tablets contain the following inactive ingredients: microcrystalline cellulose, polyethylene oxide, colloidal silicon oxide, butylated hydroxyl

toluene, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc. Tablets should be taken whole and never broken, crushed, or chewed.

Patients randomized to receive IW-3718 will administer the test product as follows:

- 500 mg IW-3718 BID: One 500 mg IW-3718 oral tablet plus 2 placebo oral tablets (3 tablets total) administered BID, immediately after the morning and evening meals
- 1000 mg IW-3718 BID: Two 500 mg IW-3718 oral tablets plus 1 placebo oral tablet (3 tablets total) administered BID, immediately after the morning and evening meals
- 1500 mg IW-3718 BID: Three 500 mg IW-3718 oral tablets administered BID, immediately after the morning and evening meals

3.4.1.2 Placebo

Placebo to match 500 mg IW-3718 tablets will be provided as white to off-white, oval shaped, film-coated, oral tablets containing microcrystalline cellulose, polyethylene oxide, colloidal silicon oxide, butylated hydroxyl toluene, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, and talc. Tablets should be taken whole and never broken, crushed, or chewed.

Patients randomized to receive placebo will administer the test product as follows:

- Three oral placebo tablets will be administered BID immediately after the morning and evening meals.

3.4.1.3 Rescue Medicine

Antacid rescue medicine will be provided to the clinical site as a bottled liquid (magnesium hydroxide 200 mg/aluminum hydroxide 200 mg per 5 mL).

During completion of the PDA daytime and nighttime diary questions, patients will be asked about their rescue medicine use by responding to the following questions:

- “How many times did you use your rescue medicine (liquid antacid) from the time you got out of bed this morning until now?” (Daytime assessment, completed at night before going to bed)

- "How many times did you use your rescue medicine (liquid antacid) last night?" (Nighttime assessment, completed in the morning)

3.4.1.4 Treatment Compliance

Patients will be dispensed the appropriate number of Sponsor-packaged, labeled blister wallets needed until the next study visit (see Section 3.6). Patients will be asked to return all blister wallets (including unused tablets) at each study visit for assessment of compliance with the dosing regimen.

Patients will record their PPI administration each day (once daily) in their eDiary.

3.4.2 Packaging and Labeling

Study medication (IW-3718 and placebo tablets) will be provided by Ironwood as 60 count blisters in wallets, indicating morning and evening doses. Study medication will be uniquely numbered and labeled in a double-blind fashion that conforms to regulatory requirements.

3.4.3 Storage and Stability

Study medication (IW-3718 and placebo tablets) will be shipped at refrigerated temperatures between 2°C and 8°C (36°F and 46°F) and must be stored at refrigerated temperatures between 2°C and 8°C (36°F and 46°F). Antacid rescue medicine will be shipped at room temperature between 20°C and 25°C (68°F and 77°F) and must be stored at room temperature between 20°C and 25°C (68°F and 77°F). Any deviation from these storage conditions must be reported to Ironwood and use of the study medication suspended until authorization for its continued use has been provided by Ironwood.

The Investigator must ensure that the receipt and use of all study medication supplied is recorded and must supervise the storage and allocation of these supplies. All study medication supplies must be retained in a locked room that may only be accessed by the Investigator, or other duly designated persons. Study medication must not be used outside the context of this protocol, and under no circumstances should the Investigator or study center personnel allow the supplies to be used other than as directed by this protocol without prior authorization from Ironwood.

3.4.4 Method of Assigning Patients to Treatment Groups

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized into the study on Day 1. Patients will be stratified by whether they have or do not have erosive esophagitis on the screening EGD then randomized through central randomization in a 1:1:1:1 ratio to receive either 500 mg IW-3718 BID, 1000 mg IW-3718 BID, 1500 mg IW-3718 BID, or placebo BID.

The computer-generated randomization schedule will be prepared by an independent statistician not otherwise associated with the study.

3.4.5 Selection of Dosage in the Study

During this study, oral doses of IW-3718 at 500 mg BID (total daily dose of 1000 mg/day), 1000 mg BID (total daily dose of 2000 mg/day), and 1500 mg BID (total daily dose of 3000 mg/day) given as an adjunct to QD PPI for 56 days will be studied in order to evaluate the dose-response relationship for IW-3718 in a placebo-controlled study. The 1000 mg BID dose was used in a previous Phase 2a study (Study ICP-3718-201) and provided a reasonable level of efficacy with an acceptable safety and tolerability profile. The highest dose level (1500 mg BID) was chosen to determine whether it can provide a higher level of efficacy with an acceptable safety profile. The lowest dose level (500 mg BID) will be included since it may demonstrate efficacy, and will allow for a more accurate assessment of the dose-response relationship for IW-3718. This could support the proof-of-concept for efficacy and support further evaluation of IW-3718 in Phase 3 studies with any of the 3 dose levels. In addition to assessing efficacy for each dose group, the safety profile at all 3 doses will also be evaluated.

3.4.6 Selection and Timing of Dose for Each Patient

Patients will be randomized to receive 500 mg IW-3718 BID, 1000 mg IW-3718 BID, 1500 mg IW-3718 BID, or placebo BID. The first dose of study medication will be taken with liquid and a snack in clinic at the Randomization Visit (on Day 1). Patients should take their second dose that evening immediately upon completion of dinner, ensuring that at least 8 hours have elapsed since the first dose in clinic.

During the Treatment Period, patients will take study medication BID at home, in the morning (immediately upon completion of breakfast) and in the evening (immediately upon completion of dinner), even on study visit days. The last dose of study medication will be taken the morning of the EOT Visit.

Additionally, all patients will take their current PPI during the Pretreatment, Randomization, and Treatment Periods (i.e., Day -21 through Day 57 [+ 3 days]). The PPI will be taken each day, approximately 30-60 minutes before breakfast.

During completion of the PDA daily diary questions, patients will be asked to confirm daily dosing of their PPI by responding to the following question:

- "Did you take your PPI this morning?"

3.4.7 Blinding

This study is double-blind and placebo-controlled. The Sponsor, Investigator, and study center staff will be blinded to treatment assignments.

Unblinding of a patient's treatment assignment is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper handling of the patient. Except in a medical emergency, the Investigator and blinded study center staff will remain blinded during the conduct of the study and until such time that all discrepancies in the clinical database are resolved (i.e., at the time of the database lock). Individual patient treatment assignment unblinding is available to the Investigator through the interactive web response system (IWRS) in the event of an emergency. The Investigator should make all reasonable efforts to notify and discuss the circumstances requiring unblinding with the Medical Monitor or designee in advance of breaking the blind. If the treatment blind is broken, the reason and the date should be recorded and signed by the Investigator and information regarding the unblinding should be submitted as soon as possible to the Sponsor. The patient will be immediately withdrawn from the study if the code is broken.

The Sponsor may also break the blind in circumstances where unblinding is necessary for the safety of the patients.

3.4.8 Prior and Concomitant Medications

At the Screening Visit, the following information will be recorded for each patient:

- All medications the patient is taking (ongoing)
- All prior medications taken during the 30 days before the Screening Visit
- Most recent use of an H2RA
- Most recent use of an antacid

Any medication taken by a patient during the course of the study (beginning at the Screening Visit), including any new medications added or changes in medications previously reported, and the reason for its use will be documented in the source documents and the eCRF.

3.4.8.1 Rescue Medication

During the Pretreatment and Treatment Periods, patients may use dispensed, protocol-permitted antacid (magnesium hydroxide 200 mg/aluminum hydroxide 200 mg per 5 mL; 15 mL up to 4 times/day) as rescue medicine when their heartburn becomes intolerable. Each day, patients will record in their eDiary the number of times that rescue medication was used.

3.4.8.2 Prohibited Medicines

Medicines that are not permitted during the Pretreatment and Treatment Periods are provided in Appendix 4.

3.4.9 Dietary Requirements

Per the inclusion criteria, patients must agree not to make any changes to their usual diet during the study, except as required for study-specific procedures (e.g., Bilitec).

3.5 SAFETY AND EFFICACY ASSESSMENTS

The timing of safety and efficacy assessments is presented in Section 3.6.

3.5.1 Safety Assessments

3.5.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to, the following:

- Any unfavorable changes in general condition
- Any clinically significant worsening of a pre-existing condition
- Any intercurrent diseases and accidents

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

3.5.1.1.1 Causality Assessment

For all AEs, the Investigator must provide an assessment of causal relationship to study medication. The causality assessment must be recorded in the patient's source documentation and on the AE page of the patient's eCRF. Causal relationship must be assessed according to the following:

- Related: An AE where there is a reasonable possibility of a causal relationship between the event and the study medication
- Unrelated: Any other AE

3.5.1.1.2 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating in the patient's source documentation and on the AE page of the patient's eCRF. Severity will be assessed according to the following scale:

- Mild: The AE was an annoyance to the patient but did not further hinder baseline functioning

- Moderate: The AE caused the patient to experience some discomfort or some interference with normal activities but was not hazardous to health; prescription drug therapy may have been employed to treat the AE
- Severe: The AE caused the patient to experience severe discomfort or severely limited or prevented normal activities and represented a definite hazard to health; prescription drug therapy and/or hospitalization may have been employed to treat the AE

3.5.1.2 Serious Adverse Events

A serious AE (SAE) is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening: the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form)
- Hospitalization or prolongation of an existing hospitalization
- Persistent or significant disability or incapacity: a substantial disruption of a person's ability to conduct normal daily functions
- Congenital anomaly or birth defect
- Important medical events: events that may not result in death, be life-threatening, or require hospitalization. Such an event may be considered serious when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Emergency room visits that do not result in admission to the hospital should be evaluated for 1 of the other serious outcomes (e.g., life-threatening, other serious [medically important] event).

3.5.1.3 Reporting Adverse Events and Serious Adverse Events and Pregnancy

SPECIAL SITUATION: EXPOSURE TO STUDY DRUG DURING PREGNANCY

1. A patient who reports pregnancy prior to study drug randomization must be withdrawn from the study. The pregnancy is recorded as a reason for screen failure. Since there has been no exposure to study drug, there is no need to notify Ironwood Drug Safety of the pregnancy.
2. A patient who reports pregnancy after randomization, must discontinue study drug at once. The site must notify Ironwood Drug Safety via PPD PVG email: Wilsafety@ppdi.com; fax: 1-888-488-9697 of the pregnancy (within 24 hours), using the standard Pregnancy Notification Form. The site makes reasonable efforts to follow the pregnancy to term and notifies PPD PVG email: Wilsafety@ppdi.com; fax: 1-888-488-9697 of the pregnancy outcome (within 24 hours of being informed), using the standard Pregnancy Outcome Form.

General Reporting Requirements

Adverse events will be collected and recorded from the time the patient signs the ICF at the Screening Visit until 7 days after the EOT Visit. The study site will make contact with the patient via telephone 7 days following the EOT visit to collect information pertaining to ongoing AEs and information concerning new AEs. All AEs, regardless of the assumption of a causal relationship with study procedures or study medication, must be recorded in the patient's source documentation and subsequently on the appropriate AE page of the patient's eCRF. This record includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during the study, such as "Have you had any health problems since your last visit?"

For every AE, the Investigator must

- Provide an assessment of the severity, causal relationship to the study medication, and seriousness of the event;
- Document all actions taken with regard to the study medication (i.e., no action taken, treatment temporarily interrupted, or treatment discontinued); and
- Detail any other treatment measures taken for the AE, including concomitant medications and/or procedures.

Pretreatment AEs will be collected from the time the patient signs the ICF until the patient receives study medication. Pretreatment AEs will be captured in the patient's source documentation, but will only be entered for randomized patients on the AE page of the patient's eCRF.

Laboratory abnormalities and changes in vital signs, physical examination findings, and 12-lead ECG parameters should be considered AEs and reported on the AE page of the patient's eCRF if the Investigator considers them clinically significant and/or they necessitate intervention.

Any medical condition that is present when a patient is screened and does not worsen in severity and/or frequency should be reported as Medical History and not as an AE. However, if the condition does deteriorate in severity and/or frequency at any time during the study, it should be reported as an AE.

Serious Adverse Event Reporting Requirements

An AE that meets any of the serious criteria as described in Section 3.5.1.2 must be reported to Ironwood within 24 hours from the time that site personnel first learn of the event, using the SAE Report Form provided for the study. Regardless of causality, all SAEs must be reported and will be collected and recorded from the time the patient signs the ICF at the Screening Visit until 7 days after the EOT Visit. The study site will make contact with the patient via telephone 7 days following the EOT visit to collect information pertaining to ongoing SAEs and information concerning new SAEs. Any SAE that occurs at any time after that 7-day time period, and which the Investigator considers to be related to study medication, should be reported to Ironwood immediately. All SAEs must also be recorded in the patient's source documentation and on the AE page of the patient's eCRF.

The initial report should include at least the following information:

- Patient identification number
- Description and onset of the event
- Serious criteria
- Causality assessment to study medication

All SAE Report Forms should be faxed or emailed to:

PPD PVG

Fax: 1-888-488-9697

Email: Wilsafety@ppdi.com

If follow-up is obtained, or requested by Ironwood, the additional information should be faxed or emailed on an SAE Report Form to Ironwood in a timely manner according to the procedures outlined above. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the SAE. These measures and the patient's response to these measures should be recorded. All SAEs regardless of relationship to study medication, will be followed by the Investigator until satisfactory resolution, the Investigator deems the SAE to be chronic or stable, or until the patient is lost to follow-up. Clinical, laboratory, and diagnostic measures should be employed by the Investigator as needed to adequately determine the etiology of the event.

The Investigator will be responsible for reporting all SAEs to the Institutional Review Board (IRB). Ironwood will be responsible for reporting to the regulatory authorities.

All SAEs will be followed until resolution, until the event has stabilized, or until the patient is lost to follow-up.

3.5.1.4 Medical History

A complete medical history will be performed as defined in the Schedule of Events (Table 2).

3.5.1.5 Physical Examination, Body Weight, and Height

A complete physical examination will be performed as defined in the Schedule of Events (Table 2). The physical examination of each patient should include examination and assessment of the following:

General appearance	Head, eyes, ears, nose, and throat
Cardiovascular system	Neck
Respiratory system	Musculoskeletal system
Abdomen/liver/spleen	Nervous system
Lymph nodes	Skin
Neurologic status	Mental status

Breast, genitourinary, and rectal examinations are optional and may be performed at the discretion of the Investigator. Any new, clinically significant abnormal findings from the physical examination will be reported as an AE.

Each patient's weight will be recorded at every study visit; height will only be recorded at the Screening Visit.

3.5.1.6 Electrocardiograms

A 12-lead ECG will be performed as defined in the Schedule of Events (Table 2) and documented on the eCRF. Electrocardiograms should be obtained after the patient has been supine for at least 5 minutes.

3.5.1.7 Vital Signs

Vital sign measurements will be performed as defined in the Schedule of Events (Table 2) and documented on the eCRF. Vital sign measurements include oral temperature (°C), respiratory rate, systolic and diastolic blood pressure (BP), and pulse. Respiratory rate, pulse, and BP readings will be taken after the patient has been seated for at least 5 minutes.

3.5.1.8 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits defined in the Schedule of Events (Table 2). The clinical laboratory evaluations will include the clinical chemistry, hematology, coagulation, and urinalysis parameters presented in Table 1.

Table 1. Clinical Laboratory Tests

Clinical Chemistry	Hematology (CBC)	Complete Urinalysis
A1C	Hematocrit	pH and specific gravity
Albumin	Hemoglobin	Bilirubin
Alkaline phosphatase	Platelet count	Glucose
ALT	MPV	Ketones
AST	RBC count	Leukocytes
Bicarbonate	WBC count	Nitrites
BUN	WBC differential	Occult blood
Calcium	(% and absolute)	Protein
Chloride	Basophils	Urobilinogen
Total cholesterol	Eosinophils	
HDL cholesterol	Lymphocytes	
LDL cholesterol	Monocytes	
Creatinine	Neutrophils	
GGT	RBC indices	
Glucose	MCH	
Iron	MCHC	
LDH	MCV	
Magnesium	RDW	
Phosphorus	Coagulation	
Potassium	aPTT	
Sodium	PT	
Total bilirubin		
Total protein		
Triglycerides		
Uric acid		

Abbreviations: A1C = glycated hemoglobin; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; PT = prothrombin time; RBC = red blood cell; RDW = red cell distribution width; WBC = white blood cell

A blood sample for serum pregnancy testing will be collected from all female patients of childbearing potential (i.e., women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) at the Screening and EOT Visits, and a urine sample will be collected at the Randomization Visit (prior to dosing) and the Week 4 Visit.

These pregnancy test results must be negative for patient eligibility. Ironwood may perform non-genetic analyses on existing plasma or serum samples for research purposes (e.g., bile in serum).

A urine screen for selected drugs of abuse (cocaine, barbiturates, amphetamines, opiates, benzodiazepines, and cannabinoids) and a serum alcohol screen will be performed at the Screening Visit.

3.5.1.9 Esophagogastroduodenoscopy

At all sites, an EGD will be performed on all patients at the screening visit. An additional EGD will be performed at the Week 8/EOT Visit in all patients who had an EGD during the Screening Period that demonstrated Grade C or D esophagitis (based on the Los Angeles classification of esophagitis; Appendix 5).

3.5.1.10 Bravo

At all sites, all patients will undergo 48 to 96 hours of pH testing with the Bravo device. If for some reason 96 hours of testing is not possible, then approximately 48 hours of testing is acceptable. During the entire period of Bravo pH monitoring (approximately 48-96 hours), patients will record ingestion of anything other than water by depressing the 'meal' button on the Bravo device upon the beginning and completion of the event. Patients will also record any periods during which they are lying down by depressing the 'supine' button on the Bravo device at the beginning and upon completion of the supine period. In addition, for the entire 48-96 hour Bravo pH monitoring period, patients will also complete a paper diary (see Appendix 9), recording at a minimum all instances of meals, snacks, drinks, and/or resting in the supine position. All patients will return to the site with their Bravo pH monitor and patient diary after approximately 96 hours (or 48 hours where applicable) to return the recording device. Please refer to the Bravo Site Manual for specific instructions.

3.5.1.11 Bilitec

At certain participating sites, selected patients who are screened with EGD and Bravo testing will also receive insertion of a Bilitec device during the same procedure. The patient selection will be dependent on Investigator selection and patient consent. All such patients will return to the site approximately 24 hours after the procedure for removal of the device. All patients

participating in the Bilitec testing will also have to follow very specific procedures including a "white diet" (see Appendix 8 for a sample "white diet") during this 24 hour period. Please refer to the Bilitec Site Manual for specific instructions. Notes for patients who are participating in Bilitec testing: the internal clocks for the Bravo pH recorder and Bilitec device should be synchronized, and both devices should be activated and begin recording simultaneously; if it is not possible to simultaneously activate both devices, the Bravo recorder should be activated first, with the Bilitec device activated immediately (within 5 minutes) after the Bravo pH recorder activation.

3.5.2 Efficacy Assessments

The daily patient assessments used to determine the key efficacy parameters are the daily assessment of heartburn symptoms (assessed on a 0-to-5 ordinal severity scale) and regurgitation symptoms (assessed on a 0-to-4 ordinal frequency scale) obtained from the mRESQ-eD. Additional assessments will also be used to determine the other efficacy parameters, as described in the sections that follow.

3.5.2.1 Symptom Severity Assessment

3.5.2.1.1 Daily Assessments

During the Pretreatment and Treatment Periods, patients will enter information into their eDiary at approximately the same time each day.

- GERD symptoms (mRESQ-eD, Appendix 1) completed once daily before going to bed each night.

  Note: The following items are assessed on a 0-5 severity scale: 0=Did not have, 1=Very mild, 2=Mild, 3=Moderate, 4=Moderately severe, 5=Severe

  - Heartburn
  - Burning feeling behind breastbone or in the center of the upper stomach
  - Pain behind the breastbone or in the center of the upper stomach
  - Difficulty swallowing
  - Hoarseness
  - Cough

Note: The following items are assessed on a 0-4 frequency scale: 0=Never, 1= Rarely, 2=Sometimes, 3=Often, 4=Very often

- Regurgitation (liquid or food) moving upwards toward your throat or mouth
- An acid or bitter taste in the mouth
- Burping
- Coughing

- Dyspepsia symptoms (Daily Dyspepsia Symptoms, Appendix 2) completed once daily before going to bed each night.

Note: All items are assessed on a 0-to-10 numerical rating scale (NRS) with 0=not having the symptom and 10=having the worst possible level of the symptom

- Worst nausea (feeling like you might throw up)
- Worst stomach fullness after you finished eating
- Difficulty you had finishing your meals because you felt full too quickly
- Worst abdominal pain

- Assessment of sleep (Daily Assessment of Sleep, Appendix 3) completed once daily upon getting up each morning (5:00 a.m. to 12:00 p.m.)

- Last night, did you wake up during the night after falling asleep? Y/N
- [If yes], how many times did you wake up last night after falling asleep?
- How long did you sleep last night? Do not count any time you lay in bed, but did not sleep.
- Please rate the overall quality of your sleep last night. 1=very poor, 2=poor, 3=fair, 4=good, 5=very good

- Use of per-protocol rescue medicine (antacids)

3.5.2.1.2 Weekly Assessments

The following information will be entered into the eDiary each week at about the same time as the evening daily assessment (see Appendix 6):

- Degree of relief questions

  Note: all items are assessed on a 7-point balanced ordinal scale: 1=Significantly relieved, 2=Moderately relieved, 3=Somewhat relieved, 4=Unchanged, 5=Somewhat worse, 6=Moderately worse, 7=Significantly worse

  - How would you rate your heartburn (a burning sensation in your chest, behind the breastbone) over the past 7 days?
  - How would you rate your regurgitation (the feeling of stomach contents, either liquid or food, moving upwards to your throat or mouth) over the past 7 days?
  - Compared to before you started this study, how would you rate your overall GERD symptoms over the past 7 days?

- Global Treatment Satisfaction Assessment

  Note: the following items will be assessed on a 5-point ordinal scale: 1=Very dissatisfied, 2=Dissatisfied, 3=Neither satisfied nor dissatisfied, 4=Satisfied, 5=Very satisfied

  - How would you rate your satisfaction with the study treatment?

- Bothersomeness Assessment.

  Note: the following items will be assessed on a 5-point ordinal scale: 1=Not at all, 2=A little bit, 3=A moderate amount, 4=A great deal, 5=An extreme amount

  - How much were you bothered by heartburn (a burning sensation in your chest, behind the breastbone) over the past week?
  - How much were you bothered by regurgitation (the feeling of stomach contents, either liquid or food, moving upwards to your throat or mouth) over the past week?

Weekly items assessing symptom bothersomeness and symptom relief will be used to explore responder definitions and treatment benefit analysis.

3.5.2.2 GSRS-Self

The Gastrointestinal Symptoms Rating Scale (GSRS)-Self is a self-administered 15-item questionnaire that uses a 7-point Likert scale for discomfort:

1 = None
2 = Minor
3 = Mild
4 = Moderate
5 = Moderately severe
6 = Severe
7 = Very severe

The items can then be grouped into 5 domains: abdominal pain (3 items), reflux syndrome (2 items), indigestion (4 items), diarrhea (3 items), and constipation (3 items) (17). Patients will complete the GSRS-Self at the Randomization Visit, the Week 4 Visit, and at the EOT Visit; responses will be recorded in an electronic diary via a portable PDA device.

3.5.2.3 QIDS-SR-16

The Quick Inventory of Depressive Symptomatology (QIDS)-SR-16 is a self completed questionnaire designed to assess the severity of 9 clinically defined symptoms of depression on a scale from 0 (no symptom impact) to 3 (severe impact) (18). The tool can be used to screen for depression or as a measure of symptom severity. Patients will complete the QIDS-SR-16 at the Randomization Visit. Responses will be recorded in an electronic diary via a portable PDA device.

3.5.2.4 SF-12V2 Health Survey

The SF-12V2 is a widely used generic measure of health status and measures 8 concepts of health: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being). These 8 scales are aggregated into 2 summary measures: the physical component and mental component summary scores (19). Patients will complete the SF-12V2 at the Randomization Visit, the Week 4 Visit, and at the EOT Visit; responses will be recorded in an electronic diary via a portable PDA device.

3.5.2.5 EQ-5D-3L

The EuroQol (EQ)-5D-3L is a generic measure of health widely used in Europe (20). The first component consists of 5 questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the 5 questions define a health state for which a utility index can be derived from published algorithms (21). The second component of the EQ-5D is a visual analogue scale, asking patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health state). Patients will complete the EQ-5D-3L at the Randomization Visit, the Week 4 Visit, and at the EOT Visit; responses will be recorded in an electronic diary via a portable PDA device.

3.5.2.6 End-of-treatment Question

Patients will be asked a single item at their final visit (EOT), asking about the difficulty of swallowing the treatment medication (see Appendix 6). The item will ask "How difficult were the tablets to swallow?" and be rated on a 4 point ordinal scale:

1 = Not at all difficult
2 = A little difficult
3 = Moderately difficult
4 = Extremely difficult

3.5.2.7 mRESQ Cognitive Debriefing Interviews

Cognitive debriefing interviews will be conducted to support the modified mRESQ as fit for purpose in the context of a clinical trial. The original RESQ-eD was modified including instructions, removal of redundant items, and inclusion of alternate response scales for selected symptoms. Guidance on instrument development emphasizes the need for adequate empirical evidence in the patient population targeted for enrollment in the clinical trials to support content validity for the desired claim. To that end, a sample of patients at selected sites will be asked to participate in an optional symptom diary interview, either via phone or face to face. Approximately 30 subjects will be interviewed from participating sites; 5 screen failures, 5 pre-treatment and 20 active treatment subjects will be interviewed. During the one time interview, patients will be asked to respond to open-ended questions intended to assess content validity of the mRESQ-eD instrument. See Appendix 10 for further details.

3.6 SCHEDULE OF EVENTS

The schedule of study procedures and assessments is presented by visit in the Schedule of Events in Table 2.

Table 2. Schedule of Events

	Screening Period (Up to 4 weeks)[w]	**Pretreatment Period (2 weeks)**	**Treatment Period (8 weeks)**				**Follow-up**
Visit Days →	Screening Visit (Day -49 to Day -15)	Pretreatment Visit (Day -21 to Day -1)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ± 3)	Week 4 Visit (Day 29 ± 3)	Week 8 / End-of-treatment Visit (Day 57 +3)	EOT + 7 days
Visit Numbers →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Study Procedure ↓							
Inclusion and Exclusion Criteria Verification	X	X	X				
Signing of ICF	X						
IWRS Registration (a)	X	X	X	X	X	X	
Medical History	X						
Demographics	X						
Physical Examination (b)	X					X	
Body Weight and Height (c)	X	X	X	X	X	X	
H2RA/Antacid Washout (d)	X						
Bilitec Monitoring (e)	X						
EGD (f)	X					X	
48 to 96 Hours of pH Testing with Bravo Device (g)	X						
Seated Vital Signs (h)	X	X	X	X	X	X	
12-Lead ECG (i)	X		X			X	
Prior and Concomitant Medications (j)	X	X	X	X	X	X	
Clinical Laboratory Tests(k)	X		X		X	X	
Serum Pregnancy Test (l)	X					X	
Urine Pregnancy Test (l)			X		X		

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	Screening Period (Up to 4 weeks)[w]	**Pretreatment Period (2 weeks)**	**Treatment Period (8 weeks)**				**Follow-up**
Visit Days →	Screening Visit (Day -49 to Day -15)	Pretreatment Visit (Day -21 to Day -1)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ± 3)	Week 4 Visit (Day 29 ± 3)	Week 8 / End-of-treatment Visit (Day 57 +3)	EOT + 7 days
Visit Numbers →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	
Study Procedure ↓							
Drug and Alcohol Screen (m)	X						
AE Evaluations (n)	X	X	X	X	X	X	
Rescue Medicine Dispensed (o)		X	X	X	X		
PDA Training and Dispensation		X					
Saliva Collection (p)	X	X	X		X	X	
eDiary (q)		X	X	X	X	X	
Weekly Symptom and Treatment Assessments (r)		X	X	X	X	X	
GSRS-Self			X		X	X	
QIDS-SR-16			X				
SF-12V2			X		X	X	
EQ-5D-3L			X		X	X	
Randomization			X				
Study Medication Dispensed (s)			X	X	X		
Study Medication Return (t)				X	X	X	
PDA Return						X	
mRESQ Debrief Interview (x)		X (x)			X (x)		
End-of-treatment Question (u)						X	
Safety Follow-up Call (v)							X

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; EGD = esophagogastroduodenoscopy; EOT = End-of-treatment; EQ = EuroQol; GSRS = Gastrointestinal Symptoms Rating Scale; H2RA = histamine-2 receptor antagonist; HEENT = head, eyes, ears, nose, and throat; ICF = informed consent form; IWRS = interactive web response system; PDA = personal digital assistant; PPI = proton pump inhibitor; QID = Quick Inventory of Depressive Symptomology; mRESQ-eD = modified Reflux Symptom Questionnaire Electronic Diary; SAE = serious adverse event; SF = short form

a. Site personnel will interact with IWRS to register the patient visit and transition the patient to the next appropriate study period.
b. A physical examination should include the following assessments: general appearance; HEENT; neck; cardiovascular; respiratory; abdomen/liver/spleen; musculoskeletal; lymph nodes; skin; neurologic; nervous system, and mental status. Breast, genitourinary, and rectal examinations are optional and may be performed at the discretion of the Investigator.
c. Height will be measured only at the Screening Visit.
d. During the Screening Period, patients will begin to washout H2RAs and antacids. H2RAs should be stopped 5 calendar days prior to the EGD and Bravo pH monitoring and antacids should be stopped 1 calendar day prior to the EGD and Bravo pH monitoring. Patients may resume antacid use upon completion of the Bravo testing, but must refrain from H2RA use for the remainder of the study. During the Pretreatment Period, patients will refrain from using any anti-reflux medications, antacids, and H2RAs, except for the antacids that are provided as rescue medicine). Patients will continue to use their current PPI during the Pretreatment Period.
e. At selected sites, selected patients who are screened for the study with EGD and Bravo testing will also be given the option of having a Bilitec monitor inserted during the same procedure. These patients will return 24 hours later for removal of the probe. The results of the Bilitec test will not affect qualification for enrollment. The Bilitec device and Bravo recorder internal clocks must be synchronized, and both devices should be activated concurrently; however, if it is not possible to simultaneously activate both devices, the Bravo recorder should be activated first, with the Bilitec device activated immediately (within 5 minutes) after the Bravo pH recorder activation.
f. All patients will be required to undergo an EGD during the Screening Period. There must be a minimum of 7 days between the EGD and the start of the Pretreatment Period. An EGD will be performed at the Week 8/EOT Visit in all patients who have Grade C or D esophagitis (based on the Los Angeles classification of esophagitis; see Appendix 5) on the EGD obtained during the Screening Period.
g. Approximately 48 to 96 hours of pH testing with the Bravo device. If for some reason 96 hours of testing is not possible, then approximately 48 hours of testing is acceptable. During the entire period of Bravo pH monitoring (approximately 48-96 hours), patients will record ingestion of all meals, snacks, and drinks by depressing the 'meal' button on the Bravo recorder upon the beginning and completion of the meal, snack, or drink. Patients will also record any periods during which they are lying down by depressing the 'supine' button on the Bravo recorder at the beginning and upon completion of the supine period. In addition, for the entire 48-96 hour Bravo pH monitoring period, patients will also complete a paper diary (see Appendix 9), recording at a minimum, all instances of meals, snacks, drinks, and/or resting in the supine position.
h. Vital sign measurements include oral temperature (°C), respiratory rate, systolic and diastolic BP, and pulse. Respiratory rate, BP, and pulse measurements must be obtained after the patient has been seated for at least 5 minutes.
i. 12-lead ECGs should be obtained after the patient has been supine for at least 5 minutes.
j. Prior medications will be collected at the Screening Visit as follows: all medicines taken by the patient during the 30 days before the Screening Visit, most recent use of an H2RA, and most recent use of an antacid.
k. Clinical laboratory tests include clinical chemistry, hematology (CBC), coagulation, and urinalysis. If the triglyceride value exceeds the protocol-specified criteria and the patient was not under fasted conditions, the patient may return to completed a fasted lipid panel.
l. For all female patients of childbearing potential, a negative serum pregnancy test must be documented at the Screening Visit, and a negative urine pregnancy test must be documented at the Randomization Visit (before dosing) in order for the patient to be randomized into the study. A urine pregnancy test will be obtained at the Week 4 Visit; serum pregnancy test will be conducted at the EOT Visit.

m. Patients must undergo a urine drug screen for selected drugs of abuse (cocaine, barbiturates, amphetamines, opiates, benzodiazepines, and cannabinoids) and a serum alcohol screen at the Screening Visit.
n. All AEs will be captured from the time the patient signs the ICF through the EOT Visit.
o. Rescue medicine will be supplied to patients at the Pretreatment Visit, and if needed, at subsequent visits.
p. At each of the indicated visits, patients will provide approximately 1 mL of saliva for future use (bile acids will be quantified in the saliva, and the quantity of bile acid may be used to define potential responders to IW-3718). At the time of saliva collection, study site staff will collect the following information: time of day, time of patient's last meal, and time of last study medication administration. During the Randomization Visit, study site staff will collect the saliva sample immediately following the light snack but prior to study drug administration.
q. The eDiary will be dispensed at the Pretreatment Visit and patients must complete 5 days each week during the 14 calendar days before the Treatment Period in order to be eligible for randomization. Patients should bring their eDiary to each visit. The eDiary will collect daily PPI administration, rescue medication use, mRESQ-eD (Appendix 1; daily), Daily Assessment of Sleep (Appendix 3; daily), Daily Dyspepsia Symptoms (Appendix 2; daily).
r. Symptom bothersomeness and relief items (Appendix 6; weekly); Treatment satisfaction item (Appendix 6; weekly).
s. The first dose of study medication will be administered in the clinic with liquid and a snack at the Randomization Visit. At all other visits, patients will take their study medication prior to arriving at the clinic, but will be dispensed additional doses needed until the next study visit.
t. Treatment compliance with study drug will be assessed based on return of unused tablets.
u. All patients will be asked an EOT question regarding the difficulty of swallowing the IW-3718 or placebo tablets (Appendix 6).
v. Study site will contact each patient via telephone 7 days after the EOT Visit to collect information pertaining to ongoing AEs/SAEs and information concerning any new AEs/SAEs since the EOT Visit
w. Ironwood may grant a one-week extension of the screening period window if needed for logistical delays (e.g., subject travel, scheduling issues, delays in test results, equipment malfunction, etc.). Approval should be requested from Ironwood prior to each extension.
x. Patients participating in the optional mRESQ-eD Cognitive Debriefing interviews will be assigned to one of three interview groups. Interviews will take place at different timepoints depending on the patient's group assignment. (see Appendix 10)

3.6.1 Screening Period (Day –49 to Day -15)

3.6.1.1 Screening Visit (Visit 1) Procedures

- Signing of ICF
- Register visit in IWRS
- Review of inclusion and exclusion criteria
- Demographics
- Medical history
- Physical examination
- Body weight and height
- Begin H2RA and antacid washout (for 5 calendar days before the EGD and Bravo pH monitoring [H2RA] and 1 calendar day before the EGD and Bravo pH monitoring [antacids])
- EGD
- Approximately 48 to 96 hours of pH testing with a Bravo device (if 96 hours of testing is not possible, then approximately 48 hours of testing is acceptable)
- Optional 24 hours of measurements of bilirubin using the Bilitec device (for patients undergoing the Bilitec procedure – device removed after 24 hours)
- Seated vital signs
- 12-lead ECG
- Prior medications (all medicines taken during the 30 days before the Screening Visit, most recent use of an H2RA, and most recent use of an antacid)
- Collection of blood and urine samples for clinical laboratory test, including:
  - Clinical chemistry
  - Hematology (complete blood count [CBC])
  - Coagulation
  - Urinalysis
- Serum pregnancy test for all female patients of childbearing potential (must be confirmed negative)
- AE evaluation (throughout the Screening Period)
- Saliva collection

3.6.1.2 Extension of Screening Period

Ironwood may grant a one-week extension of the screening period window if needed for logistical delays (e.g., subject travel, scheduling issues, delays in test results, equipment malfunction, etc.). Approval should be requested from Ironwood prior to each extension.

If an extension of greater than one week is needed for logistical delays, subjects will be considered screen failures and will need to re-screen. If these subjects had already completed the EGD/Bravo (and Bilitec, if applicable) assessments during the original screening period, they will not need to repeat these tests as long as they enter Pre-Treatment within 35 days of the assessments. All other study assessments should be repeated during re-screening. Pretreatment Period (Day –21 to Day -1).

3.6.1.3 Pretreatment Visit (Visit 2) Procedures

- Register visit in IWRS
- Review of inclusion and exclusion criteria
- Body weight
- Seated vital signs
- Prior and concomitant medications
- AE evaluation (throughout the Pretreatment Period)
- Antacid rescue medicine dispensation
- PDA training
- PDA is dispensed (for recording daily and weekly evaluations throughout the Pretreatment and Treatment Periods in the eDiary)
- Saliva collection
- A subset of patients participating in the optional Cognitive Debriefing Interview at selected sites will undergo the interview at this visit.

3.6.2 Treatment Period (Day 1 to Day 57)

For all visits during the Treatment Period, patients will take their PPI and study medication (except for the Randomization Visit) prior to reporting to the study site.

3.6.2.1 Randomization Visit (Visit 3) Procedures

- Register visit in IWRS
- Review of inclusion and exclusion criteria
- Body weight
- Seated vital signs
- 12-lead ECG
- Concomitant medications
- Collection of blood and urine samples for clinical laboratory tests, including:
  - Clinical chemistry
  - Hematology (CBC)
  - Coagulation
  - Urinalysis
- Urine pregnancy test for all females of childbearing potential (must be confirmed negative prior to dosing)
- AE evaluation (throughout the Treatment Period)
- Antacid rescue medicine dispensation (if needed)
- Saliva collection
- Collect PDA and review eDiary
- GSRS-Self
- QIDS-SR-16
- SF-12V2
- EQ-5D-3L
- Randomization
- Study medication dispensed
- Study medication administration (first dose of study medication taken in clinic with liquid and a snack. Patients should take their second dose that evening, with liquid, immediately upon completion of dinner and ensure that at least 8 hours have elapsed since the first dose in clinic).

3.6.2.2 Week 2 Visit (Visit 4) Procedures

- Register visit in IWRS
- Body weight
- Seated vital signs
- Concomitant medications
- AE evaluation (throughout the Treatment Period)
- Antacid rescue medicine dispensation (if needed)
- Collect PDA and review eDiary
- Return of all unused study medication
- Additional study medication dispensed

3.6.2.3 Week 4 (Visit 5) Procedures

- Register visit in IWRS
- Body weight
- Seated vital signs
- Concomitant medications
- Collection of blood and urine samples for clinical laboratory tests, including:
  - Clinical chemistry
  - Hematology (CBC)
  - Coagulation
  - Urinalysis
- Urine pregnancy test for all females of childbearing potential
- AE evaluation (throughout the Treatment Period)
- Antacid rescue medicine dispensation (if needed)
- Saliva collection
- Collect PDA and review eDiary
- GSRS-Self
- SF-12V2

- EQ-5D-3L
- Study medication dispensed
- Return of all unused study medication
- A subset of patients participating in the optional Cognitive Debriefing Interview at selected sites will undergo the interview at this visit.

3.6.2.4 Week 8/End-of-treatment (Visit 6) Procedures

- Register visit in IWRS
- Physical examination
- Body weight
- EGD
- Seated vital signs
- 12-lead ECG
- Concomitant medications
- Collection of blood and urine samples for clinical laboratory tests, including:
  - Clinical chemistry
  - Hematology (CBC)
  - Coagulation
  - Urinalysis
- Serum pregnancy test for all female patients of childbearing potential
- AE evaluation (throughout the Treatment Period)
- Saliva collection
- Review eDiary
- GSRS-Self
- SF-12V2
- EQ-5D-3L
- Return of all unused study medication
- Return PDA device
- End of treatment question

3.6.3 Follow-up

The study site will contact all patients via telephone 7 days following the EOT Visit in order to collect information regarding ongoing AEs and/or SAEs and any new AEs and/or SAEs since the EOT Visit (Section 3.5.1.3).

3.6.4 Early Termination Procedures

Patients who discontinue from the study for any reason should complete the assessments required at the EOT Visit (Section 3.6.2.4) at the time of their discontinuation.

3.7 STATISTICAL METHODS

Additional details regarding the statistical methods will be provided in the Statistical Analysis Plan (SAP), to be finalized prior to unblinding of the study.

3.7.1 Analysis Populations

- The Screened Population consists of all patients who consented to participate in the study.
- The modified Intent-to-Treat (mITT) Population consists of all randomized patients who received at least 1 dose of study treatment.
- The Per-Protocol Population (PP) is defined as those patients in the mITT Population who have a minimum of 6 weeks of eDiary data for the heartburn severity and regurgitation frequency scores and > 80% compliance with study treatment for the available Treatment Period days.
- The Safety Population is defined as all randomized patients who received at least 1 dose of study treatment.

3.7.2 General Methods

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, and range). Categorical variables will be summarized using the subject count and proportions of patients in each category. Unless otherwise specified, all confidence intervals will be two-sided and with a confidence level of 95%. Due to the exploratory nature of the trial, no adjustments will be made for multiplicity. Details of the data handling methods will be specified in the SAP. If not otherwise specified, the baseline value is defined as the last non-

missing value measured before administration of study treatment on Day 1. All statistical analyses will be performed using SAS® Version 9.3 (or later) for Windows.

3.7.3 Patient Disposition, Demographics, and Baseline Characteristics

The count and proportion of patients included in the mITT, PP, and Safety Populations will be presented overall and by treatment group. The number of patients in the Screened Population will be presented overall.

The count and proportion of screen failures (i.e., patients who enter the Screening Period but not the Pretreatment Period) and patients ineligible for randomization (i.e., patients who enter the Pretreatment Period but are not randomized), along with the associated reasons for failure or ineligibility, will be tabulated overall for the Screened Population.

The count and proportion of patients who complete treatment, who complete the study, and who prematurely discontinue will be presented for each treatment group and overall for the mITT Population. The reason for premature discontinuation as recorded on the study completion forms of the eCRFs will be summarized by treatment group and overall for the mITT Population.

Demographic parameters (e.g., age, sex, race, weight, height, and body mass index) and other baseline characteristics (including heartburn severity, regurgitation frequency, and weekly assessments) will be summarized by treatment group.

3.7.4 Efficacy Analyses

Table 3 provides the analysis time windows allowed for the efficacy analyses in the Pretreatment and Treatment Periods.

Table 3. Analysis Time Windows for Efficacy Analysis

Period	Analysis Week	Begins[a]	Ends[a]
Pretreatment (Baseline[b])	Week -2	Day -14	Day -8
	Week -1	Day -7	Day -1 (Day before first dose)
Treatment	Week 1	Day 1 (Day of first dose)	Day 7
	Week 2	Day 8	Day 14
	Week 3	Day 15	Day 21
	Week 4	Day 22	Day 28
	Week 5	Day 29	Day 35
	Week 6	Day 36	Day 42
	Week 7	Day 43	Day 49
	Week 8	Day 50	Day 56

a. Relative to the date of first dose (Day 1).
b. Baseline values for efficacy parameters will be derived from the daily eDiary and eCRF data collected in the Pretreatment Period Week -2 and Week -1.

3.7.4.1 Primary and Secondary Efficacy Parameters

The primary efficacy parameter is the percent change from baseline (i.e., Pretreatment) in weekly heartburn severity score (WHSS) at Week 8.

Daily heartburn severity score (DHSS) is defined as the maximum of the 3 items measuring heartburn from a particular day collected with the mRESQ-eD instrument; WHSS is defined as the average of available DHSS in a particular week.

The secondary efficacy parameters include the following:

1. Percent change from baseline in WHSS at Week 4
2. Change from baseline in WHSS at (a) Week 4 and (b) Week 8
3. Proportion of patients who are overall heartburn responders
   a. Weekly Heartburn Responder: patient with a decrease from baseline of ≥ 30% in WHSS
   b. Overall heartburn responder: patient who is a weekly heartburn responder for at least 1 of the final 2 weeks and for ≥ 50% of the treatment weeks
4. Proportion of patients with a DHSS of no more than very mild (≤ 1) on any day during (a) Week 4 and (b) Week 8

5. The number of days per week where DHSS was no more than very mild (≤ 1) at (a) Week 4 and (b) Week 8.
6. Change from baseline in each mRESQ-eD item by week.
7. Proportion of heartburn free days in Week 4 and Week 8

Note: DHSS is defined as the maximum of the 3 items in the heartburn assessments of a particular day, collected with the mRESQ-eD instrument. Further, WHSS is defined as the average of DHSS in a particular week.

Heartburn-free days will be calculated by 2 approaches. The first will employ the single heartburn item in the heartburn domain (Item #1 from mRESQ-eD: Heartburn) which is similar to the heartburn rating scale(s) used in the PPI literature. The second will employ all 3 items in the heartburn domain (Items #1 through #3 from mRESQ-eD: Heartburn; Burning feeling behind the breastbone or in the center of the upper stomach; Pain behind the breastbone or in the center of the upper stomach. In the first approach, the heartburn item needs to be assessed at 0 (Did not have) while in the second approach all 3 heartburn domain items need to be assessed at 0 (Did not have).

For the analysis of continuous parameters (e.g., absolute change from baseline and percent change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. Each IW-3718 group will be compared with the placebo group using an analysis of covariance (ANCOVA) model with treatment group, and esophagitis stratum as fixed effect terms and the corresponding baseline efficacy parameter value as a covariate. Least-squares means (LSMs) for each treatment group, a linear contrast among the LSMs to test the overall ordinal dose response, LSMs differences between each IW-3718 group and the placebo group and their corresponding confidence intervals, and p-values for the pairwise comparisons versus placebo will be presented. The treatment by esophagitis stratum interaction term will be explored to evaluate whether quantitative or qualitative interaction(s) are present, and treatment comparisons within each stratum will be conducted, as warranted.

The cumulative distribution function (CDF) of change from baseline for key efficacy parameters will be plotted by treatment group. To aid in the interpretation of the graphical representation of the CDF across treatments, a two-sample Kolmogorov-Smirnov test will be conducted (22). A

p-value ≤ 0.05 indicates that the 2 treatment samples are unlikely to have been drawn from the same continuous distribution by chance alone.

For the analysis of responder parameters (i.e., responder vs. non-responder), the counts and proportion of responders will be calculated for each treatment group. The proportions of responders between each IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for esophagitis stratum. The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between each IW-3718 group and the placebo group as well as the CMH estimates of the odds ratio (IW-3718 over placebo) and the corresponding 95% confidence intervals will also be presented.

3.7.4.2 Other Efficacy Parameters

Other efficacy parameters include the following:

1. Percent change from baseline in weekly regurgitation frequency scores (WRFS) to (a) Week 4 and (b) Week 8 in patients with a mean baseline regurgitation frequency of ≥ 2 (sometimes).
2. Change from baseline in WRFS to (a) Week 4 and (b) Week 8
3. Proportion of patients who are overall regurgitation responders (of patients with a baseline regurgitation frequency of ≥ 2 [sometimes])
   a. Weekly regurgitation responder: patient with a decrease from baseline of ≥ 30% in WRFS
   b. Overall regurgitation responder: patient who is a weekly responder for at least 1 of the final 2 weeks and for ≥ 50% of the treatment weeks
4. Proportion of patients with regurgitation frequency of no more than rarely (daily regurgitation frequence score [DRFS] ≤ 1) on any day during (a) Week 4 and (b) Week 8
5. Change from baseline to (a) Week 4 and (b) Week 8 in the number of days per week where DRFS was no more than rarely (≤ 1)
6. Change from baseline to Week 8 in weekly means for each of the daily symptom assessments

Note: DRFS is the maximum of the 2 items in the regurgitation domain scores of a particular day, collected with the mRESQ-eD instrument. Similarly, WRFS is defined as the average of DRFS in a particular week. A DRFS of zero is considered Regurgitation Free for a particular day.

7. Weekly means for daily sleep assessments (number of awakenings, hours of sleep, sleep quality)
8. Weekly means for weekly symptom bothersomeness assessments, symptom relief assessments, and treatment satisfaction assessment
9. Exploratory non-efficacy parameters and analysis:
    a. Summarize patient baseline disease characteristics and key efficacy differences for patients with or without Bilitec monitoring performed during the Screening Period
    b. Compare patient baseline disease characteristics and key efficacy parameters between bile acid positive versus bile acid negative patients (on the subgroup of patients with Bilitec monitoring during the Screening Period).
    c. Assess sensitivity and specificity (i.e., receiver operating characteristic [ROC] curve) of bile acid levels measured in saliva as a test for bile acid pathophysiology with Bilitec test findings as the reference standard (on the subgroup of patients with Bilitec monitoring during the Screening Period)
    d. Utilize bile acid levels in saliva as a predictor of response to treatment

For analysis of continuous parameters, descriptive statistics (n, mean, standard deviation, median, and range) will be presented for each treatment group. Each IW-3718 group will be compared with the placebo group using an ANCOVA model with treatment group and esophagitis stratum as fixed effect terms and corresponding baseline efficacy parameter value as a covariate.

3.7.5 Safety Analyses

All safety parameters will be analyzed with descriptive statistics. Safety analyses will be performed on the Safety Population. The safety parameters will include AEs, treatment-emergent AEs (TEAEs), clinical laboratory evaluations, vital signs, ECGs, and physical examination. For each safety parameter, the last non-missing assessment made before randomization will be used as the baseline for all analyses of that safety parameter.

3.7.5.1 Adverse Events

Adverse event verbatim terms will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) available at the start of the study. An AE (classified by preferred term) will be considered a TEAE if the AE onset date was after initial study medication administration and within 1 day of the last dose of study medication. The

number and percentage of patients reporting TEAEs will be tabulated by system organ class (SOC), preferred term, and treatment group. The number and percentage of patients reporting TEAEs will also be tabulated by SOC, preferred term, severity, and treatment group. Listings will be provided for deaths (if any), severe AEs, drug-related AEs, SAEs, and AEs leading to study discontinuation.

If a patient has more than 1 TEAE coded to the same preferred term, the patient will be counted only once for that preferred term. For the analysis of TEAEs by severity, the patient's highest severity TEAE within a preferred term will be used.

3.7.5.2 ECGs, Vital Signs, and Clinical Laboratory Tests

Descriptive statistics will be calculated on ECGs, vital signs, and clinical laboratory test results at each assessment time point, by treatment group. The change from baseline at each post-baseline time point also will be summarized by treatment group.

3.7.6 Interim Analysis

An interim analysis is not planned for this study.

3.7.7 Determination of Sample Size

The sample size per arm was determined by estimating the overall power of a linear trend test in a one-way design that included placebo and all the active treatment arms (500 mg BID, 1000 mg BID, and1500 mg BID of IW-3718). The efficacy endpoint of interest in the previous Phase 2a study (ICP-3718-201) was change from baseline in daytime heartburn defined as the presence of heartburn since the patient awoke that morning (assessed in the evening) and assessed with an 11-point [0 to 10] NRS, where 0=none and 10=very severe. In that study, IW-3718 demonstrated treatment differences near 0.70 points for change over the treatment period (e.g., -0.73 vs. -1.38 for placebo and IW-3718, respectively), and standard deviations near 1.35 for the LSMs. Employing these historical values, a study with 58 patients per arm (the expected number of patients at Week 8 given an enrollment of 260 patients) will have statistical power of at least 80% for the overall trend test (i.e., linear contrast) where the highest active treatment arm reflects 110% of the previously observed treatment difference and the lowest 2 active treatment arms reflect 55% of the same (two-sided, α=0.05). At the proposed sample size, a subsequent pairwise

comparison between placebo and an active treatment arm reflecting the previously observed treatment difference will have 80% statistical power (two-sided, α=0.05).

3.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by Ironwood or its designee. Prior to implementation, any protocol amendment regarding reportable deviations (as defined by the IRB) must be approved by the IRB and the signature page must be signed by the Investigator and received by Ironwood or its designee, with the following exception: If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Deviating from the protocol is permitted only if absolutely necessary for the safety of the patients and must immediately be reported to Ironwood or its designee.

4. ETHICAL CONSIDERATIONS

This study will be performed in accordance with the Declaration of Helsinki (i.e., the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and later revisions), ICH E6 Good Clinical Practice (GCP) guidelines, and applicable regulatory documents.

4.1 INSTITUTIONAL REVIEW BOARD

Prior to the study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB.

All IRB approvals must be dated and signed by the IRB Chairman or his or her designee and must identify the IRB by name and address, the clinical protocol by title and/or protocol number, and the date upon which approval or favorable opinion was granted for the clinical research. Copies of IRB approvals should be forwarded to Ironwood. All correspondence with the IRB should be maintained in the Investigator File.

No drug will be released to the site to dose a patient until written IRB authorization has been received by Ironwood.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB. The Investigator must supply Ironwood with written documentation of the approval of the continued clinical research.

The IRB must be constituted in accordance with Federal and ICH GCP guidelines and any relevant and applicable local regulations.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by Ironwood and by the IRB that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB for approval prior to patients being enrolled into the amended protocol.

4.2 PATIENT INFORMATION AND INFORMED CONSENT

Informed consent procedures will comply with the Code of Federal Regulations (CFR) 21 CFR, Parts 50 and 312.

The written ICF must be approved by the IRB for the purposes of obtaining and documenting consent.

Before entry into the study, each patient will be provided with a written explanation of the study. It is the responsibility of the Investigator or appropriately trained health professional to give each patient full and adequate information regarding the objectives and procedures of the study and the possible risks involved. Patients will then be given the opportunity to ask questions and the Investigator will be available to answer questions as needed. Patients will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before entering the study, the patient will voluntarily sign an ICF. The patient should receive a copy of the signed and dated ICF. The Investigator must retain each patient's original signed ICF.

If new information becomes available that may be relevant to the patient's consent and willingness to participate in the study, the ICF will be revised. The revised ICF must be submitted to the IRB for review and approval prior to its use.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at approximately 60-80 study centers in the US. The Investigator at each study center will be responsible for ensuring that the study is conducted according to the signed Clinical Trial Agreement, the protocol, IRB requirements, and GCP guidelines.

The Investigator will be responsible for the oversight of the site's conduct of the study, which will consist of completing all protocol assessments, maintaining the study file and the patient records, drug accountability, corresponding with the IRB, and completing the eCRFs.

5.1 GENERATION OF STUDY RECORDS

Ironwood or its designated representative will conduct a study center visit to verify the qualifications of each Investigator, inspect study center facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. All information recorded in the eCRFs for this study must be consistent with the patient's source documentation.

During the course of the study, the Clinical Site Monitor will make study center visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability (in a blinded manner), and ensure that the study is being conducted according to pertinent regulatory requirements. All eCRFs will be verified with source documentation. The review of medical records will be performed in a manner that ensures patient confidentiality is maintained.

The Clinical Site Monitor will discuss instances of missing or uninterpretable data with the Investigator for resolution. Any changes to the study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

5.2 DATA QUALITY ASSURANCE

Ironwood performs quality control and assurance checks on all of its clinical studies. Section 5.4 provides details regarding study monitoring procedures.

The study may be subject to audit by Ironwood, its representatives, or regulatory authorities. In the event of an audit, the Investigator must agree to allow Ironwood, representatives of Ironwood, or the FDA or other regulatory agencies access to all study records.

5.3 ELECTRONIC CASE REPORT FORMS AND DATA MANAGEMENT

All data relating to the study will be recorded in the patient's source documentation and eCRF to be provided by Ironwood or designee via the electronic data capture (EDC) system. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, all observations, and patient status. The Investigator is responsible for verifying that all data entries on the eCRFs are accurate and correct and ensuring that all data are entered in a timely manner, as soon as possible after the information is collected. An explanation should be provided for any missing data. The Investigator must provide through the EDC system his or her formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for each patient.

Ironwood will retain the final eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the Investigator's study file.

A record of screen failures and pretreatment failures will be maintained for patients who do not qualify for randomization, including the reason for the failure.

5.4 STUDY MONITORING

Ironwood performs quality control and assurance checks on all of its clinical studies. Before any patients are enrolled in the study, a representative of Ironwood or its authorized designee will meet with the Investigator and his/her staff to review relevant and important study-related information including, but not limited to, the protocol, the Investigator's Brochure, the eCRFs

and instructions for their completion using the EDC system, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs.

An Ironwood representative, the Clinical Site Monitor, will monitor the progress and conduct of the study by periodically conducting monitoring visits and by frequent communications (telephone, e-mail, letter, and fax) with the study centers. The site monitor will ensure that the study is conducted according to the protocol and regulatory requirements. During monitoring visits, the information recorded on the eCRFs will be verified against source documents. Upon request of the monitor, auditor, IRB, or regulatory authority, the Investigator should make all requested study-related records available for direct access.

All aspects of the study will be carefully monitored by Ironwood or its designee for compliance with applicable government regulations with respect to GCP and current standard operating procedures.

6. STUDY SPONSORSHIP

6.1 INVESTIGATOR AND STUDY TERMINATION

Ironwood may terminate Investigator participation at any institution for any reason. If participation is ended at the site by either Ironwood or the Investigator, the Investigator must

- Return all study medications and any study materials to Ironwood;
- In cases where the Investigator opts to self-terminate, provide a written statement describing why the study was terminated prematurely.

Ironwood may terminate the study in its entirety or at a specific center at any time for any reason, including but not limited to the following:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practice
- Questionable safety of the study medication
- Suspected lack of efficacy of the study medication
- Administrative decision

6.2 REPORTING AND PUBLICATION

All data generated in this study will be the property of Ironwood. An integrated clinical and statistical report will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Ironwood.

7. INVESTIGATOR OBLIGATIONS

7.1 DOCUMENTATION

The Investigator must provide the Sponsor with the following documents BEFORE the enrollment of any subjects, in accordance with ICH E6 (Note: Ironwood must be notified if there are any changes to these documents):

1. Completed and signed Form FDA 1572 (Statement of Investigator) including all sub-investigators involved in the study
2. Financial disclosure form(s) for the Investigator and all sub-investigators listed on Form FDA 1572
3. Current, signed curricula vitae of the Investigator and all sub-investigators
4. Current medical license of the Investigator and all sub-investigators (as applicable)
5. IRB approval letter for the protocol and ICF
6. IRB-approved ICF to be used
7. IRB approval of recruitment advertising (if applicable)
8. A list of IRB members and their qualifications, and a description of the committee's working procedures
9. Protocol Approval Page signed by the Investigator
10. Fully executed Clinical Trial Agreement
11. Written document containing the name, location, certification number, and date of certification of the local laboratory to be used for laboratory assays and those of other facilities conducting tests
12. List of normal laboratory values and units of measurements for all laboratory tests required by the protocol. This list is required for each local laboratory to be used during the study.

During the study, the Investigator must maintain the following essential/administrative documents related to the study:

1. Signed Protocol Signature Page
2. Financial disclosure form(s) for the Investigator and all sub-investigators (as applicable) if updated
3. Curricula vitae of any new Investigator(s) and/or sub-investigators involved in the study
4. Current medical license of the Investigator and all sub-investigators (as applicable) if updated
5. Signed Form FDA 1572

6. IRB Approval Notification for the following:
    a. Protocol
    b. Informed consent document
    c. Recruitment advertising (if applicable)
    d. Amendment(s) (if applicable)
    e. Annual review of the protocol and the informed consent document
    f. SAEs
    g. Study closure
7. SAE Reports
8. Drug Inventory Forms (drug receipts, drug dispensing, and inventory forms)
9. Name and address of local or central laboratory, list of normal laboratory values and units of measurement, as well as laboratory certification or hospital accreditation
10. Updates of medical/laboratory/technical procedures/tests:
    a. Normal value(s)/ranges(s)
    b. Certification
    c. Accreditation
    d. Established quality control and/or external quality assessment
    e. Other validation (where required)
11. Record of retained body fluids/tissue samples (if any)
12. Correspondence with Sponsor
13. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB must also be provided to the Sponsor. Any changes in this study or unanticipated problems involving risks to the patients must be reported promptly to the IRB. An Investigator must not make any changes in a study without IRB and Sponsor approval, except when necessary to eliminate apparent immediate hazards to the subjects. All protocol amendments must be submitted to the IRB and approved.
14. Responsibility Log
15. Other logs (e.g., screening, enrollment)
16. Signed ICFs
17. Patient source documentation
18. eCRFs
19. Audit certificate(s), if applicable

7.2 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study. The Sponsor may terminate the study with any Investigator for any reason, including, but not limited to, Investigator nonperformance or Investigator noncompliance.

7.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or sub-investigators. Study medication must be stored in a safe and secure temperature-monitored location. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The study center must record the date the study medication was received and maintain a dispensing record in which to record each patient's use. Study medication will be dispensed to patients at the Randomization Visit on Day 1, at the Week 2 Visit on Day 15 (± 3 days) and at the Week 4 Visit on Day 29 (± 3 days). A complete reconciliation of study medication will be performed at the site close out visit with a final accountability report provided to Ironwood as part of the site close out report. Written instructions for return of all unused and reconciled study medication to an appropriate waste handler will be provided prior to the end of the study. No study medication may be destroyed by study centers without prior written permission of Ironwood.

7.4 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator in accordance with locally applicable regulatory requirements; and, in any event, for a minimum period of 5 years.

No study records shall be destroyed without notifying Sponsor and giving Sponsor the opportunity to take such study records or authorizing in writing the destruction of records after the required retention period.

If the Investigator retires, relocates, or otherwise withdraws from the responsibility of keeping the study records, custody must be transferred to another person (Ironwood, IRB, or other

Investigator) who will accept the responsibility. Ironwood must be notified of and agree to the change.

7.5 PATIENT CONFIDENTIALITY

All data collected in the context of this study will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. All patient records will be identified only by initials and patient identification (PID) number. Patient names are not to be transmitted to Ironwood or its authorized designee. The Investigator will keep a Master Patient List on which the PID number and the full name, address, and telephone number of each patient is listed.

8. REFERENCE LIST

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9. SPONSOR SIGNATURES

Study Title:	A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Trial of IW-3718 Administered Orally for 8 Weeks to Patients with Symptomatic Gastroesophageal Reflux Disease Not Completely Responsive to Proton Pump Inhibitors
Study Number:	ICP-3718-202
Final Date:	27 July 2016

This clinical study protocol was subject to critical review and has been approved by the sponsor.

Signed: _____ Date: 8 AUG 2016

Robert Mittleman, MD, MS, FACC
Senior Director, Clinical Research
Ironwood Pharmaceuticals, Inc.

10. INVESTIGATOR'S STATEMENT

Study Title:	A Phase 2b, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose-range-finding Trial of IW-3718 Administered Orally for 8 Weeks to Patients with Symptomatic Gastroesophageal Reflux Disease Not Completely Responsive to Proton Pump Inhibitors
Study Number:	ICP-3718-202
Final Date:	27 July 2016

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed: _____ Date: _____

Investigator Name: _____

11. APPENDICES

APPENDIX 1 mRESQ-eD

Please answer the following questions to help us understand the symptoms you experienced since waking today because of your reflux disease. For each question, please choose the answer most appropriate for you.

Over the past 24 hours, how would you rate the severity of your [insert symptom]?
0=Did Not Have, 1=Very Mild, 2=Mild, 3=Moderate, 4=Moderately Severe, 5=Severe

1. Heartburn
2. Burning feeling behind the breastbone or in the center of the upper stomach
3. Pain behind the breastbone or in the center of the upper stomach
4. Difficulty swallowing
5. Hoarseness
6. Coughing

Over the past 24 hours, how often did you experience [insert symptom]
0=Never, 1= Rarely, 2=Sometimes, 3=Often, 4=Very often

1. Regurgitation (liquid or food moving upwards towards your throat or mouth)
2. An acid or bitter taste in the mouth
3. Burping
4. Cough

APPENDIX 2 DAILY DYSPEPSIA SYMPTOMS

Completed before going to bed each night. Note: all items are assessed on a 0-to-10 numerical rating scale [NRS] with anchors of 0=not having the symptom and 10= having the worst possible symptom

1. Over the past 24 hours, rate your worst nausea (feeling like you might throw up).
   NRS anchors: 0= No nausea, 10= Worst possible nausea

2. Over the past 24 hours, rate your worst stomach fullness after you finished eating.
   NRS anchors: 0= No stomach fullness, 10= Worst possible stomach fullness

3. Over the past 24 hours, how would you rate the difficulty you had finishing your meals because you felt full too quickly
   NRS anchors: 0= No difficulty, 10= Worst possible difficulty

4. Over the past 24 hours, how would you rate your worst abdominal pain?
   NRS anchors: 0= No pain, 10= Worst possible pain

APPENDIX 3 DAILY ASSESSMENT OF SLEEP

Completed each morning upon waking.

Awakenings

Last night, did you wake up during the night after falling asleep?
[Yes, No]

[If yes], how many times did you wake up last night after falling asleep?
[Enter number of times]

Sleep Time

How long did you sleep last night? Do not count any time you lay in bed, but did not sleep.
[Enter hours, enter minutes]

Overall Sleep Quality

Please rate the overall quality of your sleep last night.

1=Very poor
2=Poor
3=Fair
4=Good
5=Very good

APPENDIX 4 PROHIBITED MEDICATIONS

All medicine listed in the sections below are excluded during the Screening, Pretreatment, Randomization, and Treatment Periods. A 1-day washout means the that the particular medicine is not allowed during the calendar day before the EGD and Bravo pH monitoring; a 5-day washout means that the particular medicine is not allowed during the 5 calendar days before the EGD and Bravo pH monitoring; a 14-day washout means that the particular medicine is not allowed during the 14 calendar days before the Pretreatment Visit.

Patients should be on a stable dose of all concomitant medications at the time of the Screening Visit and should intend to maintain their usual medication regimen throughout the study. Changes in concomitant medication regimens or use of a new concomitant medication other than as described below is not allowed during the study unless required to treat an AE or is prescribed by a physician to treat another emergent medical issue.

1-DAY WASHOUT

- Antacids
- Sucralfate

5-DAY WASHOUT

- H_2 Receptor Antagonists (prescribed or over-the-counter [OTC]) (e.g. cimetidine, ranitidine, famotidine, and nizatidine).

14-DAY WASHOUT

- Bile acid sequestrants (e.g., Welchol (colesevelam), cholestyramine, and colestipol)
- Drugs with a known drug-drug interaction or a potential for a drug-drug interaction with colesevelam (cyclosporine, levothyroxine [and other thyroid replacement therapies], olmesartan medoxomil, phenytoin, warfarin)
- Drugs with a narrow therapeutic index (e.g. warfarin, digoxin, theophylline)
- Prokinetic agents (e.g. metoclopramide, tegaserod, erythromycin); anti-cholinergic and anti-muscarinic agents (e.g. dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solifenacin, darifenacin, and trospium)
  [Note: inhaled ipratropium and tiotropium are permitted]

- Antipsychotic agents (e.g., risperidone, haloperidol, droperidol, chlorpromazine, perphenazine, all phenothiazines, quetiapine, olanzapine, clozapine)
- GABAergics (e.g., baclofen, valproic acid, gabapentin, pregabalin, benzodiazepine)
- Calcium channel blockers (e.g., verapamil, nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine)
- Beta blockers (e.g., metoprolol, timolol, atenolol, betaxolol)
- All narcotics either alone or in combination (e.g., tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate)
  [Note: narcotics used as anesthesia for an EGD require a 7 calendar day wash-out prior to the patient entering into the Pretreatment Period.]
- Tricyclic antidepressants (e.g. amitriptyline, imipramine, and nortriptyline)
  [Note: Patients may take another single antidepressant (such as a selective serotonin reuptake inhibitor {SSRI}, or serotonin-norepinephrine reuptake inhibitor {SNRI} medication) as long as the dose has been stable for at least 30 days prior to the Screening Visit and the patient plans to continue a stable dose of the medications throughout the study. Use of more than 1 antidepressant medication is exclusionary.]
- Other gastric-retentive drugs (e.g., Glumetza, Gralise)

Notes Regarding Concomitant Medications:

Patients must have been on once-daily (QD) PPI therapy for at least 8 weeks before the Screening Visit.

Daily use of estrogens and/or low-dose aspirin (up to 162 mg/day) is permitted if, after an appropriate evaluation (e.g., history and physical exam), the Investigator believes these medications are not contributing to the patient's symptoms.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are permitted for occasional use. Chronic use is not permitted.

Oral contraceptives containing ethinyl estradiol and norethindrone have a known drug-drug interaction with colesevelam. All female patients of childbearing potential using oral contraceptives with the ingredients listed above as birth control must agree to use another additional form of contraception from the date they sign the ICF until 24 hours after their final dose of study drug (e.g. condom).

APPENDIX 5 LOS ANGELES CLASSIFICATION OF ESOPHAGITIS

Classification	Definition
Not Present	No breaks (erosions) in the esophageal mucosa. (However, edema, erythema, or friability may be present.)
Grade A	One or more mucosal breaks not more than 5 mm in maximum length.
Grade B	One or more mucosal breaks more than 5 mm in maximum length, but not continuous between the tops of 2 mucosal folds.
Grade C	Mucosal breaks that are continuous between the tops of 2 or more mucosal folds, but involve less than 75% of the esophageal circumference.
Grade D	Mucosal breaks that involve at least 75% of the esophageal circumference.

APPENDIX 6 WEEKLY AND END OF TREATMENT ASSESSMENTS

Degree of Relief Assessments

***Administered weekly starting during Pretreatment Period*:**

How would you rate your heartburn (a burning sensation in your chest, behind the breastbone) over the past 7 days?

How would you rate your regurgitation (the feeling of stomach contents, either liquid or food, moving upwards to your throat or mouth) over the past 7 days?

Administered weekly during Treatment Period:

Compared to before you started this study, how would you rate your overall GERD symptoms over the past 7 days?

Response Scale for all Degree of Relief Assessments:

1=Significantly relieved
2=Moderately relieved
3=Somewhat relieved
4=Unchanged
5=Somewhat worse
6=Moderately worse
7=Significantly worse

Global Treatment Satisfaction Assessment

Administered weekly during Treatment Period:

How would you rate your satisfaction with the study treatment?

1=Very dissatisfied
2=Dissatisfied
3=Neither satisfied nor dissatisfied
4=Satisfied
5=Very satisfied

Bothersomeness Assessments

***Administered weekly starting during Pretreatment Period*:**

How much were you bothered by heartburn (a burning sensation in your chest, behind the breastbone) over the past week?

How much were you bothered by regurgitation (the feeling of stomach contents, either liquid or food, moving upwards to your throat or mouth) over the past week?

1=Not at all
2=A little bit
3=A moderate amount
4=A great deal
5=An extreme amount

Swallow Item Question

Administered End of Treatment Visit only:

How difficult were the tablets to swallow?

1=Not at all difficult
2=A little difficult
3=Moderately difficult
4=Extremely difficult

APPENDIX 7 IN-CLINIC ASSESSMENTS

EQ-5D-3L

Health Questionnaire

English version for the USA

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

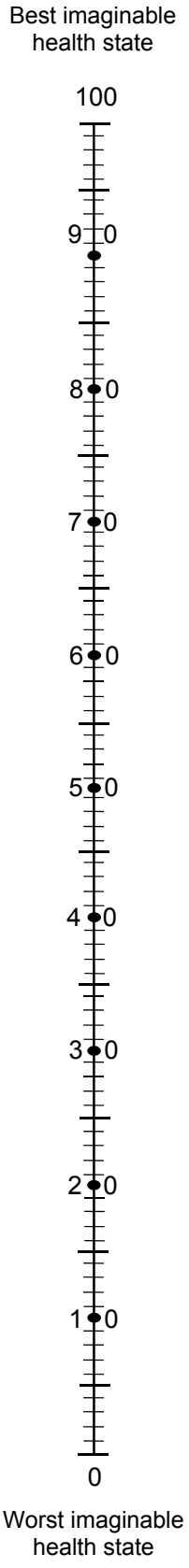
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



GSRS-Self

THE GASTROINTESTINAL SYMPTOM RATING SCALE (GSRS)

Please read this first:

This survey contains questions about how you have been feeling and what it has been like DURING THE PAST WEEK. Mark the choice that best applies to you and your situation with an "X" in the box.

1. Have you been bothered by PAIN OR DISCOMFORT IN YOUR UPPER ABDOMEN OR THE PIT OF YOUR STOMACH during the past week?

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

2. Have you been bothered by HEARTBURN during the past week? (By heartburn we mean an unpleasant stinging or burning sensation in the chest.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

3. Have you been bothered by ACID REFLUX during the past week? (By acid reflux we mean the sensation of regurgitating small quantities of acid or flow of sour or bitter fluid from the stomach up to the throat.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

4. Have you been bothered by HUNGER PAINS in the stomach during the past week? (This hollow feeling in the stomach is associated with the need to eat between meals.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

5. Have you been bothered by NAUSEA during the past week? (By nausea we mean a feeling of wanting to throw up or vomit.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

6. Have you been bothered by RUMBLING in your stomach during the past week? (Rumbling refers to vibrations or noise in the stomach.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

7. Has your stomach felt BLOATED during the past week? (Feeling bloated refers to swelling often associated with a sensation of gas or air in the stomach.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

8. Have you been bothered by BURPING during the past week? (Burping refers to bringing up air or gas from the stomach via the mouth, often associated with easing a bloated feeling.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

9. Have you been bothered by PASSING GAS OR FLATUS during the past week? (Passing gas or flatus refers to the need to release air or gas from the bowel, often associated with easing a bloated feeling.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

10. Have you been bothered by CONSTIPATION during the past week? (Constipation refers to a reduced ability to empty the bowels.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

11. Have you been bothered by DIARRHEA during the past week? (Diarrhea refers to a too frequent emptying of the bowels.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

12. Have you been bothered by LOOSE STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being loose.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

13. Have you been bothered by HARD STOOLS during the past week? (If your stools (motions) have been alternately hard and loose, this question only refers to the extent you have been bothered by the stools being hard.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

14. Have you been bothered by an URGENT NEED TO HAVE A BOWEL MOVEMENT during the past week? (This urgent need to go to the toilet is often associated with a feeling that you are not in full control.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

15. When going to the toilet during the past week, have you had the SENSATION OF NOT COMPLETELY EMPTYING THE BOWELS? (This feeling of incomplete emptying means that you still feel a need to pass more stool despite having exerted yourself to do so.)

- ☐ No discomfort at all
- ☐ Minor discomfort
- ☐ Mild discomfort
- ☐ Moderate discomfort
- ☐ Moderately severe discomfort
- ☐ Severe discomfort
- ☐ Very severe discomfort

PLEASE CHECK THAT ALL QUESTIONS HAVE BEEN ANSWERED!

THANK YOU FOR YOUR CO-OPERATION.

QIDS-SR

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

Name or ID: _____ Date: _____

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:

☐ 0 I never take longer than 30 minutes to fall asleep.

☐ 1 I take at least 30 minutes to fall asleep, less than half the time.

☐ 2 I take at least 30 minutes to fall asleep, more than half the time.

☐ 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night

☐ 0 I do not wake up at night.

☐ 1 I have a restless, light sleep with a few brief awakenings each night.

☐ 2 I wake up at least once a night, but I go back to sleep easily.

☐ 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

☐ 0 Most of the time, I awaken no more than 30 minutes before I need to get up.

☐ 1 More than half the time, I awaken more than 30 minutes before I need to get up.

☐ 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.

☐ 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

☐ 0 I sleep no longer than 7-8 hours/night, without napping during the day.

☐ 1 I sleep no longer than 10 hours in a 24-hour period including naps.

☐ 2 I sleep no longer than 12 hours in a 24-hour period including naps.

☐ 3 I sleep longer than 12 hours in a 24-hour period including naps.

During the past seven days...

5. Feeling Sad:

☐ 0 I do not feel sad.

☐ 1 I feel sad less than half the time.

☐ 2 I feel sad more than half the time.

☐ 3 I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

☐ 0 There is no change in my usual appetite.

☐ 1 I eat somewhat less often or lesser amounts of food than usual.

☐ 2 I eat much less than usual and only with personal effort.

☐ 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:

☐ 0 There is no change from my usual appetite.

☐ 1 I feel a need to eat more frequently than usual.

☐ 2 I regularly eat more often and/or greater amounts of food than usual.

☐ 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight loss.

☐ 2 I have lost 2 pounds or more.

☐ 3 I have lost 5 pounds or more.

- OR -

9. Increased Weight (Within the Last Two Weeks):

☐ 0 I have not had a change in my weight.

☐ 1 I feel as if I have had a slight weight gain.

☐ 2 I have gained 2 pounds or more.

☐ 3 I have gained 5 pounds or more.

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

During the past seven days...

10. Concentration / Decision Making:

☐ 0 There is no change in my usual capacity to concentrate or make decisions.

☐ 1 I occasionally feel indecisive or find that my attention wanders.

☐ 2 Most of the time, I struggle to focus my attention or to make decisions.

☐ 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

☐ 0 I see myself as equally worthwhile and deserving as other people.

☐ 1 I am more self-blaming than usual.

☐ 2 I largely believe that I cause problems for others.

☐ 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

☐ 0 I do not think of suicide or death.

☐ 1 I feel that life is empty or wonder if it's worth living.

☐ 2 I think of suicide or death several times a week for several minutes.

☐ 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest

☐ 0 There is no change from usual in how interested I am in other people or activities.

☐ 1 I notice that I am less interested in people or activities.

☐ 2 I find I have interest in only one or two of my formerly pursued activities.

☐ 3 I have virtually no interest in formerly pursued activities.

During the past seven days...

14. Energy Level:

☐ 0 There is no change in my usual level of energy.

☐ 1 I get tired more easily than usual.

☐ 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).

☐ 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

☐ 0 I think, speak, and move at my usual rate of speed.

☐ 1 I find that my thinking is slowed down or my voice sounds dull or flat.

☐ 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

☐ 3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

☐ 0 I do not feel restless.

☐ 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

☐ 2 I have impulses to move about and am quite restless.

☐ 3 At times, I am unable to stay seated and need to pace around.

SF-12v2

SF-12v2® Health Survey Single-Item Acute Recall for Handheld Device

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
	Your Health and Well-Being						
	This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one box that best describes your answer.						
SF36v2_GH1	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor	
	The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?						
SF36v2_PF02	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF04	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?						
SF36v2_RP2	During the past week, how much of the time have you accomplished less than you would like as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	

SF-12v2® Health Survey Single-Item Acute Recall for Handheld Device

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_RP3	During the past week, how much of the time were you limited in the kind of work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?						
SF36v2_RE2	During the past week, how much of the time have you accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE3	During the past week, how much of the time have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_BP2	During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely	
	These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling.						
SF36v2_MH3	How much of the time during the past week have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	

SF-12v2® Health Survey Single-Item Acute Recall for Handheld Device

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_VT2	How much of the time during the past week did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH4	How much of the time during the past week have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF2	During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	SF-12v2® Health Survey © 1994, 2002, 2010, 2012 Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved. SF-12® is a registered trademark of Medical Outcomes Trust. (SF-12v2® Health Survey Acute, United States (English))						

Swallow Item Question

Administered End of Treatment Visit only:

How difficult were the tablets to swallow?

1=Not at all difficult
2=A little difficult
3=Moderately difficult
4=Extremely difficult

APPENDIX 8 EXAMPLE "WHITE DIET"

Acceptable foods:

- Water
- Milk
- Chicken
- Fish
- Potatoes

APPENDIX 9 BRAVO PH RECORDER INSTRUCTIONS AND PATIENT DIARY

GIVEN® IMAGING

Expanding the scope of GI

Bravo® pH
Patient Diary

Patient Instructions

The purpose of this pH study is to monitor the frequency and duration of gastric reflux during a normal day. To get the most accurate results, you must eat, drink, work, and exercise as you normally would.

DO NOT take any antacid or anti-reflux drugs during your study unless instructed to do so by your physician. If in doubt, contact your physician.

Recording Events

Events include meals, sleep and "other" types of activities with duration. Record an event in the Patient Diary sheet by marking the type of the event and writing down the event starting and stopping times, using the time displayed on the Bravo pH recorder. You can record a meal or a sleep event automatically also by pressing the appropriate event button on the Bravo pH Recorder.

	Meals	includes snacks
	Sleep	includes lying down
	Other	includes sports and other activities

To record "other" type events use the Patient Diary (next page).

Recording Symptoms

Symptoms include heartburn, regurgitation, and chest pain.

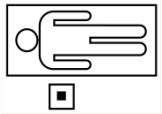
Record a symptom in the Patient Diary by marking the type of the symptom and writing down the symptom appearance time using the time displayed on the Bravo pH Recorder. You can record a symptom automatically also by pressing the appropriate symptom button on the Bravo pH Recorder.

Symptom Button	Symptom Icon
	
	
	

The green indicator light turns on for 3 seconds and a beep is heard (if the audio alert feature is turned on). This tells you that the symptom was recorded.

Recorder Placement when lying down

You may remove the Bravo pH recorder when lying down or you may leave it on you. If you choose to remove it, place it on a stable surface within arm's length of your chest with the display facing up and the symptom buttons facing towards you.



Recorder Out of Range

If the Bravo pH recorder is too distant from the Bravo pH capsule and reception is weak, it beeps for 30 seconds and the icon 1 (for 48-hour procedure) or 2 (for 96-hour procedure) disappears from the screen to indicate loss of communication. ***Move the recorder closer to you until the beep stops and the 1 or 2 icon reappears on the screen.***

If you have any questions or encounter technical issues during your study, call

_____

at _____

At the completion of your pH study, return the Bravo pH recorder and your Patient Diary to the Endoscopy/GI Lab at:

Manufactured by:

GIVEN® IMAGING

Given Imaging
3950 Shackleford Road
Duluth, GA 30096, United States
www.givenimaging.com

DOC-2124-01

GIVEN IMAGING

Bravo® pH Patient Diary

Start Time ____:____ **End Time** ____:____

Patient _____

Recorder _____

Capsule ID _____

Time of Event	Circle am or pm	Meal Start	Meal End	Supine Start	Supine End	Chest Pain	Regurgitation	Heartburn	Other	Comments
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									
:	am|pm									

Always refer to the time displayed on the recorder to write down the Time of Event above.

Recording event on the Bravo pH recorder

	Press any of the three *Symptom Buttons (chest pain, regurgitation, heartburn)* once for each individual event.
	Press the *Meal Button* once at the start of the meal and once at the end of the meal. In between the two presses, the button LED will blink until the button is pressed to mark the end the event.
	Press the *Supine Button* once when lying down for bed and once at the end of the lying period. In between the two presses, the button LED will blink until the button is pressed to mark the end the event.

Notes:

All button functions are active only when backlight is ON. If OFF, pressing any of the enabled recorder buttons will first turn backlight ON and no function will be activated. Pressing the desired button when the backlight is ON will activate the desired function.

DOC-2124-01

APPENDIX 10 COGNITIVE DEBRIEFING INTERVIEWS TO EVALUATE THE CONTENT VALIDITY OF THE MODIFIED REFLUX SYMPTOM QUESTIONNAIRE (mRESQ-eD) STUDY MANUAL

Cognitive Debriefing Interviews to Evaluate the Content Validity of the Modified Reflux Symptom Questionnaire (mRESQ-eD)

Study Manual

Version 6.0
July 27, 2016

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LIST OF ATTACHMENTS

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Attachment C Site-Completed Screening Form: Cohort 3

Attachment D Cognitive Debriefing Interview Guide: Evaluating the Modified Reflux Symptoms Questionnaire Electronic Diary (mRESQ-eD)

ABBREVIATIONS

AE	Adverse Event
EGD	Esophagogastroduodenoscopy
FDA	US Food and Drug Administration
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Independent Review Board
mRESQ-eD	Modified Reflux Symptoms Questionnaire Electronic Diary
PPI	Proton Pump Inhibitors
PRO	Patient-Reported Outcome
RESQ	Reflux Symptom Questionnaire
rGERD	Refractory Gastroesophageal Reflux Disease
SAE	Serious Adverse Event

1. INTRODUCTION

The measurement properties of a modified version of the Reflux Symptom Questionnaire (RESQ) are being examined in the ICP-3718-202 protocol. The ICP-3718-202 trial is evaluating the safety, efficacy, and dose-response relationship of IW-3718 administered orally to patients who continue to experience GERD symptoms while receiving once-daily, optimized, standard-dose PPIs. In keeping with the FDA's guidance for instrument modification, Ironwood would like to document the content validity of the modified RESQ electronic diary (mRESQ-eD) through cognitive debriefing interviews. Endpoint Outcomes personnel will conduct cognitive debriefing interviews with participants recruited for the ICP-3718-202 protocol. This study manual outlines the procedures specific to the cognitive debriefing interviews.

2. OBJECTIVES

The primary objective of the cognitive debriefing interviews is to evaluate the content validity of the mRESQ-eD and qualitatively examine how rGERD patients think about and define a meaningful change in symptom improvement. To achieve the primary objective, cognitive debriefing interviews of the mRESQ-eD with 30 ICP-3718-202 study participants will be conducted.

3. METHODOLOGY

3.1 STUDY DESIGN

A subset of ICP-3718-202 clinical trial participants will be invited to participate in cognitive debriefing interviews. A total of 30 eligible patients will be scheduled for interviews. The interview sample will be divided into three cohorts:

- **Cohort 1:** Patients in Cohort 1 will meet all ICP-3718-202 study eligibility criteria and will complete the mRESQ-eD daily for the duration of the Pretreatment Period and at least four weeks of the Treatment Period (n=20). Patients in Cohort 1 must have completed the mRESQ-eD rather than the RESQ in order to be eligible to participate in the cognitive interviews.
- **Cohort 2:** Patients in Cohort 2 will meet select ICP-3718-202 study eligibility criteria (see section 3.3.2 below), including the ICP-3718-202 study eligibility criterion for erosive esophagitis (evaluated by EGD) and/or evidence of pathological acid reflux (evaluated with the Bravo® device), and be mRESQ-eD naïve (n=5). Screen failures are not eligible for Cohort 2.
- **Cohort 3:** Patients in Cohort 3 will meet select ICP-3718-202 study eligibility criteria (see section 3.3.2 below), excluding the ICP-3718-202 study eligibility criterion for erosive esophagitis (evaluated by EGD) and/or evidence of pathological acid reflux (evaluated with the Bravo® device), and be mRESQ-eD naïve (n=5). Cohort 3 will be comprised of screen failures for ICP-3718-202.

Cohorts will be scheduled for interviews during the clinical trial visits outlined in Table 1 below. All patients will be consented prior to the interview occurring.

Table 1. Cognitive interview schedule by cohort

Cohort	Schedule Interview to Occur During:
Cohort 1	Week 4 or Week 8 Visit
Cohort 2	Pretreatment Visit
Cohort 3	Any time after screen fail. Interviews will be scheduled to coincide with other Cohort 1 or 2 interviews as scheduled for the same day.

Regardless of cohort or interview timing, all interview participants will be cognitively debriefed on the mRESQ-eD and asked to provide input on what constitutes a meaningful change in symptom improvement on the mRESQ-eD.

3.2 INTERVIEW MATERIALS

In addition to this Study Manual, the following materials have been developed for consenting, screening and conducting the cognitive debriefing interviews:

- Patient-Completed Screening Questions (Attachment A);
- Site-Completed Screening Form: Cohort 2 (Attachment B);
- Site-Completed Screening Form: Cohort 3 (Attachment C); and
- Cognitive Debriefing Interview Guide (Attachment D).

3.3 INTERVIEW SAMPLE

3.3.1 Number of patients and sites

A total of 30 clinical trial participants will be enrolled from a subset of sites participating in the ICP-3718-202 study. The interview sample will be divided into the three cohorts outlined in section 3.1.

3.3.2 Interview eligibility criteria

The interview eligibility criteria for Cohort 1 is the same as the ICP-3718-202 study eligibility criteria. Patients in Cohort 1 must have completed the mRESQ-eD rather than the RESQ in order to be eligible for the cognitive interviews. Patients are eligible for Cohort 2 if they meet all of the interview inclusion and exclusion criteria outlined below. Patients are eligible for Cohort 3 if they meet inclusion criteria 1 through 7 and all of the exclusion criteria outlined below.

Inclusion criteria

1. Patient has signed the optional ICF (specific to the interview) before the interview is conducted.
2. Patient is able to speak, read, write, and comprehend US English.
3. In the judgement of the investigator, the patient has adequate communication skills to reflect on his/her experience with GERD during the qualitative interview.
4. Patient is willing and able to participate in a 60-minute interview.

5. According to the Patient-Completed Screening Questions 1a and/or 2, the patient reports heartburn and/or regurgitation on ≥ 4 days during the past 7 days.[1]
6. According to the Patient-Completed Screening Question 1b, the patient reports heartburn severity of ≥ "mild" on average over the past 7 days.
7. According to the Patient-Completed Screening Question 1c, the patient reports heartburn severity of ≥ "moderate" at its worst over the past 7 days.
8. ***(Cohort 2 only)*** Patient has an EGD with approximately 48 to 96 hours of pH monitoring (with a Bravo® device) during the Screening Period (while the patient continues taking their PPI) that demonstrates 1 or more of the following:
   a. Erosive esophagitis (Grade A or greater based on the Los Angeles classification of esophagitis) on EGD; and/or
   b. Evidence of pathological acid reflux (pH is < 4 for ≥ 4.2% of the recording time) during at least 1 of the 24-hour time intervals of pH testing with the Bravo® device.

Exclusion criteria

1. Patient is unable to understand the nature, scope, and possible consequences of the interview, and/or presents evidence of an uncooperative attitude.
2. Patient does not meet any of the following ICP-3718-202 inclusion criteria:
   a. Patient is an ambulatory, community-dwelling male or nonpregnant female and is at least 18 years old at the Screening Visit. Lactating females must agree not to breastfeed (for the interview study, pregnant and breastfeeding females are not disqualified).
   b. Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on ≥ 4 days per week during the 8 weeks before the Screening Visit while taking standard daily PPI therapy.
3. Patient meets any of the following ICP-3718-202 exclusion criteria:
   a. Patient has a history of complete lack of GERD symptom response to PPIs in the past.
   b. Patient reports epigastric pain or burning as his/her predominant symptom at the Screening Visit.
   c. Patient has a history of gastroparesis, bowel obstruction, or is at risk for a bowel obstruction (e.g., patient has an organic gastrointestinal [GI] motility disorders or a history of major GI surgery).

[1] This criterion is met when patients respond in the following manner on the Patient-Completed Screening Questions: Question 1a response ≥ 4 days; Question 2 response ≥ 4 days; or the sum of the responses to Question 1a and Question 2 is ≥ 4 days.

d. Patient has any alarm symptoms including but not limited to GI bleeding, anemia, vomiting, or unexpected weight loss any time during the Screening or Pretreatment Periods.
e. Patient has undergone surgery that meets any of the following criteria:
    - Surgery of the GI tract (including gastric banding) other than an appendectomy, cholecystectomy, minor oral or rectal surgery (e.g., tonsillectomy, hemorrhoidectomy, rectocele repair) at any time before the Screening Visit;
    - An appendectomy during the 3 months before the Screening Visit or a cholecystectomy during the 6 months before the Screening Visit or minor oral or rectal surgery during the 30 days before the Screening Visit;
    - Non-GI surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit;
    - Thoracic surgery during the 6 months before the Screening Visit; and/or
    - Other major non-GI surgery during the 30 days before the Screening Visit.
f. Patient has previously undergone thoracic or abdominal radiotherapy.
g. Patient has Gilbert's disease, Crohn's disease, diabetes mellitus, Zollinger-Ellison syndrome, pancreatitis, cholecystitis, or systemic sclerosis.
h. Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.
i. ***(Cohort 2 only)*** EGD, conducted during the Screening Period, reveals that the patient has long-segment Barrett's esophagus (greater than 3 centimeters) or definite dysplastic changes in the esophagus, peptic ulcer disease, active GI bleeding, presence of esophageal strictures, presence of esophageal or fundic varices, erosive gastritis, or eosinophilic, herpetic or Candida esophagitis.

If a patient screened for Cohort 2 does not meet the exclusion criterion 3i above due to the EGD or pH monitoring results, the patient may still be eligible to participate in Cohort 3.

3.4 INTERVIEW RECRUITMENT

3.4.1 Site onboarding and training

Sites will be trained prior to screening and enrolling interview participants. During the training, sites will be informed about the process to determine eligibility and schedule interviews.

3.4.2 Process

The majority of the recruitment and interview scheduling responsibilities will be completed by the participating sites. Sites will contact Endpoint Outcomes to schedule interviews in accordance with Table 1. Endpoint Outcomes will work with the sites to determine a mutually acceptable time to interview the participants. The specific recruitment process for each cohort is outlined below.

Cohort 1 patients will be invited to participate in the cognitive debriefing interview and will sign a separate optional consent. No screening is required to determine interview eligibility. Prior to each interview, site staff will email Endpoint Outcomes to confirm receipt of written informed consent. The 60-minute interview will be conducted in-person by an Endpoint Outcomes interviewer during the Week 4 or Week 8 Visit. Every effort will be made to accommodate in-person interviews; however, allowances may be made for telephone interviews if scheduling prohibits in-person interviews.

Cohorts 2 and 3 patients will be invited to participate in the cognitive debriefing interview and will sign a separate optional consent. In order to determine interview eligibility, potential participants will need to complete the Patient-Completed Screening Questions and site staff will need to complete the Site-Completed Screening Form: Cohort 2 or Site-Completed Screening Form: Cohort 3. Site staff will transmit copies of these redacted documents to Endpoint Outcomes, and will email Endpoint Outcomes to confirm receipt of written informed consent prior to the interview. The 60-minute interview will be conducted in-person by an Endpoint Outcomes interviewer during the Pretreatment Visit for Cohort 2 participants and any time after the Screening Visit for Cohort 3. Interviews for Cohort 3 participants should be scheduled to coincide with other Cohort 1 or 2 interviews at the site. Every effort will be made to accommodate in-person interviews; however, allowances may be made for telephone interviews if scheduling prohibits in-person interviews.

3.5 COGNITIVE DEBRIEFING INTERVIEWS

The Cognitive Debriefing Interview Guide (Attachment D) was prepared to facilitate the evaluation of the face and content validity of the mRESQ-eD. The Cognitive Debriefing Interview Guide includes questions targeting specific information related to patient perceptions of how well the mRESQ-eD captures the overall experience of symptoms related to rGERD. The Cognitive Debriefing Interview Guide will also facilitate a discussion regarding what constitutes a meaningful change in symptom improvement on the mRESQ-eD from the patient's perspective.

3.5.1 Conduct

The cognitive debriefing interviews will be conducted in-person by trained and experienced Endpoint Outcomes interviewers. Interviewers have completed National Institutes of Health Human Participant Protection Training, as well as internal data protection and interview training.

The interviews will be conducted in-person at the site; however, allowances may be made for telephone interviews. If telephone interviews are used, patients will still be required to be in the clinic during the interview. Interviews will be conducted while the participant has the electronic diary in hand to most closely simulate the conditions during the ICP-3718-202 study. The diary used during the interview will be set to training mode. Data entered by the participant during the interview will be used only for purposes of this cognitive interview sub-study, and will not be part of the analysis for the main ICP-3718-202 protocol. For in-person interviews, Endpoint Outcomes will provide an electronic diary for the participant to use during the interview. In the case of telephone interviews, the site will provide an electronic diary in training mode for use during the interview.

3.5.2 Procedures

During each cognitive debriefing interview, patients will be asked to complete the mRESQ-eD using a "think-aloud" method whereby the patients are encouraged to verbalize their thoughts while completing the questions. Under this methodology, the interviewer simply reminds participants to verbalize their thought process (e.g., "what were you considering when you selected that answer?").[i] However, the think-aloud process does not always yield the data needed to answer all of the research questions (e.g., if the patient does not spontaneously think-

aloud about a point of interest to the interviewers). For this reason, more specific verbal probing (e.g., "what does this question mean to you?") is incorporated into the interviews as well to ensure the objectives of the research are accomplished.

Each interview will be audio-recorded, with the patient's consent, and last approximately 60-minutes. Patients will be compensated by the site for their participation in an interview.

3.5.3 Adverse event reporting

Definitions for adverse events (AEs) and serious adverse events (SAEs) and the procedures for reporting AEs are outlined in section 3.5.1 of the ICP-3718-202 protocol. While soliciting AEs/SAEs is not part of the cognitive debriefing interview, patients may spontaneously report potential AEs/SAEs during the course of the interview. If a potential AE/SAE is reported, the interviewer will notify the site investigator and study coordinator via email following the interview. Each email will use the following format: "During the course of the interview [Patient ID number] reported experiencing [event(s) as described by patient] during the course of the study. Please follow-up with the patient as appropriate regarding the event(s) per the study protocol."

3.5.4 Qualitative data analysis

Audio-recordings of the interviews will be transcribed verbatim and de-identified by removing identifying information such as names and places. An initial coding scheme will be developed based on the interview guide and research objectives, and applied and operationalized using ATLAS.ti version 7.5.11 or higher (ATLAS.ti GmbH, Berlin). The coding scheme will clearly define types of item interpretation issues so that they can be consistently applied across coders.

The cognitive debriefing coding process will be guided by established qualitative research methods, including grounded theory and constant comparative method.[i,ii] Each transcript will be considered a unit of analysis, and data from all transcripts will be aggregated following coding. Once the cognitive debriefing interview data are aggregated, researchers will review all of the codes in order to ensure that the coding scheme has been used consistently by all coders and to ensure all relevant themes (e.g., unanticipated issues with items) have been captured during the

coding process. Ultimately, frequencies of codes will be reported, with accompanying exemplary quotes.

In addition to the qualitative analyses described above, mRESQ-eD scores and Degree of Relief Assessment scores at baseline and Week 4 and Week 8 for Cohort 1 will be analyzed to inform what constitutes a meaningful change. Further, responses to "How much would you need to improve on the answer scale for the change to be meaningful" for each item will be summarized as well.

4. DATA PROTECTION AND STORAGE

The interview audio-recordings and de-identified transcripts will be labeled by Patient ID number only and will be stored on a secure server only accessible to Endpoint Outcomes. Following completion of the interviews, Endpoint Outcomes will provide each site with a complete and accurate copy of the original audio-recording(s) for the site's patient(s). Sites are expected to maintain the audio-recording(s) with other study documents according to applicable clinical trial regulations.

5. REFERENCES

i Beatty P, Willis G. Research synthesis: the practice of cognitive debriefing interviews. Public Opinion Quarterly 2007;71(2):287-311.

ii Glaser BG, Strauss AL. The discovery of grounded theory: Strategies for qualitative research. New York: Aldine de Gruyter, 1967:1-18.

iii Charmaz K. Grounded theory. In: Smith JA, Harré R, Van Langenhove L. Rethinking methods in psychology. London: Sage Publications, 1995: 27-49.

ATTACHMENT A: mRESQ-eD COGNITIVE DEBRIEFING INTERVIEWS: PATIENT-COMPLETED SCREENING QUESTIONS

Patient ID

Patient-Completed Screening Questions

The information included in this form is for the patient to complete in order to confirm the eligibility of a patient in Cohorts 2 or 3 for interviews. Patients in Cohort 1 are automatically eligible and do not need to be screened.

This form should be maintained with other ICP-3718-202 study documents. A copy should be transmitted to:

Endpoint Outcomes
Attn: Siobhan McDonold
Fax: 617-507-5654
E-mail: siobhan.mcdonold@endpointoutcomes.com

Screening Questions

1a. Over the past 7 days, how many days did you have heartburn (including pain or burning feeling behind the breastbone or in the center of the upper stomach)?

- ☐ 0 days
- ☐ 1 day
- ☐ 2 days
- ☐ 3 days
- ☐ 4 days
- ☐ 5 days
- ☐ 6 days
- ☐ 7 days

If you answered 1 or more days to Question 1a above, answer Questions 1b and 1c below.
If you answered "0 days" to Question 1a above, skip to Question 2.

1b. Over the past 7 days, how would you rate the severity of your heartburn **on average** (including pain or burning feeling behind the breastbone or in the center of the upper stomach)?

- ☐ Very Mild
- ☐ Mild
- ☐ Moderate
- ☐ Moderately Severe
- ☐ Severe

1c. Over the past 7 days, how would you rate the severity of your heartburn **at its worst** (including pain or burning feeling behind the breastbone or in the center of the upper stomach)?

- ☐ Very Mild
- ☐ Mild
- ☐ Moderate
- ☐ Moderately Severe
- ☐ Severe

2. Over the past 7 days, how many days did you have regurgitation (liquid or food moving upwards towards your throat or mouth) and/or reflux (acid or bitter taste in the mouth)?

- ☐ 0 days
- ☐ 1 day
- ☐ 2 days
- ☐ 3 days
- ☐ 4 days
- ☐ 5 days
- ☐ 6 days
- ☐ 7 days

ATTACHMENT B: mRESQ-eD COGNITIVE DEBRIEFING INTERVIEWS: SITE-COMPLETED SCREENING QUESTIONS – COHORT 2

Patient ID

Site-Completed Screening Form: Cohort 2

The information included in this form is for the investigator or a designated representative (e.g., study coordinator) to complete in order to confirm the eligibility of a patient in Cohort 2. To confirm the eligibility of a patient in Cohort 3, please refer to the Site-Completed Screening Form: Cohort 3. Patients in Cohort 1 are automatically eligible and do not need to be screened.

This form should be maintained with other ICP-3718-202 study documents. A copy should be transmitted to:

Endpoint Outcomes
Attn: Siobhan McDonold
Fax: 617-507-5654
E-mail: siobhan.mcdonold@endpointoutcomes.com

#	INTERVIEW INCLUSION CRITERIA	YES	NO
1	Has the patient voluntarily provided written informed consent?	☐1	☐0
2	Is the patient able to speak, read, write, and comprehend US English?	☐1	☐0
3	In the judgment of the investigator, does the patient have adequate communication skills to reflect on his/her experience with Gastrointestinal Reflux Disease (GERD) during a qualitative interview?	☐1	☐0
4	Is the patient willing and able to participate in a 60-minute interview?	☐1	☐0
5	According to the Patient-Completed Screening Questions 1a and/or 2, does the patient report heartburn and/or regurgitation on ≥ 4 days during the past 7 days?[2]	☐1	☐0
6	According to the Patient-Completed Screening Question 1b, does the patient report heartburn severity of ≥ mild on average over the past 7 days?	☐1	☐0
7	According to the Patient-Completed Screening Question 1c, does the patient report heartburn severity of ≥ moderate at its worst over the past 7 days?	☐1	☐0
8	**Does the patient have an esophagogastroduodenoscopy (EGD) with approximately 48 to 96 hours of pH monitoring (with a Bravo® device) demonstrating 1 or more of the following:** a. **Erosive esophagitis (Grade A or greater based on the Los Angeles classification of esophagitis) on EGD; and/or** b. **Evidence of pathological acid reflux (pH is < 4 for ≥ 4.2% of the recording time) during at least 1 of the 24-hour time intervals of pH testing with the Bravo device?**	☐1	☐0

Please review the following carefully before proceeding to the next section:

- **If the answers to any inclusion criterion questions 1 through 7 above is "NO", please stop. This patient is not eligible to participate in the interview. You do not need to complete any further sections of this form.**
    - **If the answer to inclusion criterion question 8 above is "NO", patient may still be eligible to participate in Cohort 3. Please refer to the Site-Completed Screening Form: Cohort 3.**
- **If the answer to every inclusion criterion questions 1 through 8 above is "YES", please proceed to evaluating the exclusion criteria below. This patient may be eligible to participate in the interview in Cohort 2.**

[2] This criterion is met when patients respond in the following manner on the Patient-Completed Screening Questions: Question 1a response ≥ 4 days; Question 2 response ≥ 4 days; or the sum of the responses to Question 1a and Question 2 is ≥ 4 days.

#	INTERVIEW EXCLUSION CRITERIA	YES	NO
1.	Is the patient unable to understand the nature, scope, and possible consequences of the interview, and/or presents evidence of an uncooperative attitude?	☐$_1$	☐$_0$
2.	Did the patient screen fail on any of the following ICP-3718-202 inclusion criteria? Check all that apply: ☐ Patient is an ambulatory, community-dwelling male or nonpregnant female and is at least 18 years old at the Screening Visit. Lactating females must agree not to breastfeed (for the interview study, pregnant and breastfeeding females are not disqualified). ☐ Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on ≥ 4 days per week during the 8 weeks before the Screening Visit while taking standard daily PPI therapy.	☐$_1$	☐$_0$
3.	**Did the patient screen fail on any of the following ICP-3718-202 exclusion criteria? Check all that apply:** ☐ **Patient has a history of complete lack of GERD symptom response to PPIs in the past.** ☐ **Patient reports epigastric pain or burning as his/her predominant symptom at the Screening Visit.** ☐ **Patient has a history of gastroparesis, bowel obstruction, or is at risk for a bowel obstruction (e.g., patient has an organic gastrointestinal [GI] motility disorders or a history of major GI surgery).** ☐ **Patient has any alarm symptoms including but not limited to GI bleeding, anemia, vomiting, or unexpected weight loss any time during the Screening or Pretreatment Periods.** ☐ **Patient has undergone surgery that meets any of the following criteria:** b. **Surgery of the GI tract (including gastric banding) other than an appendectomy, cholecystectomy, minor oral or rectal surgery (e.g., tonsillectomy, hemorrhoidectomy, rectocele repair) at any time before the Screening Visit;** c. **An appendectomy during the 3 months before the Screening Visit or a cholecystectomy during the 6 months before the Screening Visit or minor oral or rectal surgery during the 30 days before the Screening Visit;** d. **Non-GI surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit;** e. **Thoracic surgery during the 6 months before the Screening Visit; and/or** f. **Other major non-GI surgery during the 30 days before the Screening Visit.** ☐ **Patient has previously undergone thoracic or abdominal radiotherapy.** ☐ **Patient has Gilbert's disease, Crohn's disease, diabetes mellitus, Zollinger-Ellison syndrome, pancreatitis, cholecystitis, or systemic sclerosis.**	☐$_1$	☐$_0$

#	INTERVIEW EXCLUSION CRITERIA	YES	NO
	☐ **Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.** ☐ **EGD, conducted during the Screening Period, reveals that the patient has long-segment Barrett's esophagus (greater than 3 centimeters) or definite dysplastic changes in the esophagus, peptic ulcer disease, active GI bleeding, presence of esophageal strictures, presence of esophageal or fundic varices, erosive gastritis, or eosinophilic, herpetic or Candida esophagitis.**		

Please review the following carefully before proceeding to the next section:

- **If the answer to any exclusion criterion question above is "YES", this patient is not eligible to participate in the interview as part of Cohort 2.**
  - **If the answer to exclusion criterion question 3 above is "YES" due to the EGD results, the patient may still be eligible to participate in Cohort 3. Please refer to the Site-Completed Screening Form: Cohort 3.**
- **If the answer to every exclusion criterion question above is "NO" *and* the answer to every inclusion criterion question 1 through 8 above is "YES", this patient is eligible to participate the interview in Cohort 2.**

Investigator Signature Required:

Investigator signature: _____

Date: _____

ATTACHMENT C: mRESQ-eD COGNITIVE DEBRIEFING INTERVIEWS: SITE-COMPLETED SCREENING QUESTIONS – COHORT 3

Patient ID

Site-Completed Screening Form: Cohort 3

The information included in this form is for the investigator or a designated representative (e.g., study coordinator) to complete in order to confirm the eligibility of a patient in Cohort 3. To confirm the eligibility of a patient in Cohort 2, please refer to the Site-Completed Screening Form: Cohort 2. Patients in Cohort 1 are automatically eligible and do not need to be screened.

This form should be maintained with other ICP-3718-202 study documents. A copy should be transmitted to:

Endpoint Outcomes

Attn: Siobhan McDonold

Fax: 617-507-5654

E-mail: siobhan.mcdonold@endpointoutcomes.com

AAPX-C

Patient ID

#	INTERVIEW INCLUSION CRITERIA	YES	NO
1.	Has the patient voluntarily provided written informed consent?	☐1	☐0
2.	Is the patient able to speak, read, write, and comprehend US English?	☐1	☐0
3.	In the judgment of the investigator, does the patient have adequate communication skills to reflect on his/her experience with Gastrointestinal Reflux Disease (GERD) during a qualitative interview?	☐1	☐0
4.	Is the patient willing and able to participate in a 60-minute interview?	☐1	☐0
5.	According to the Patient-Completed Screening Questions 1a and/or 2, does the patient report heartburn and/or regurgitation on ≥ 4 days during the past 7 days?*	☐1	☐0
6.	According to the Patient-Completed Screening Question 1b, does the patient report heartburn severity of ≥ mild on average over the past 7 days?	☐1	☐0
7.	According to the Patient-Completed Screening Question 1c, does the patient report heartburn severity of ≥ moderate at its worst over the past 7 days?	☐1	☐0

Please review the following carefully before proceeding to the next section:

- If the answers to any inclusion criterion question above is "NO", please stop. This patient is not eligible to participate in the interview. You do not need to complete any further sections of this form.
- If the answer to every inclusion criterion question above is "YES", please proceed to evaluating the exclusion criteria below. This patient may be eligible to participate in the interview.

* This criterion is met when patients respond in the following manner on the Patient-Completed Screening Questions: Question 1a response ≥ 4 days; Question 2 response ≥ 4 days; or the sum of the responses to Question 1a and Question 2 is ≥ 4 days.

Patient ID

#	INTERVIEW EXCLUSION CRITERIA	YES	NO
1.	Is the patient unable to understand the nature, scope, and possible consequences of the interview, and/or presents evidence of an uncooperative attitude?	☐1	☐0
2.	Did the patient screen fail on any of the following ICP-3718-202 inclusion criteria? Check all that apply: ☐ Patient is an ambulatory, community-dwelling male or nonpregnant female and is at least 18 years old at the Screening Visit. Lactating females must agree not to breastfeed (for the interview study, pregnant and breastfeeding females are not disqualified). ☐ Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on ≥ 4 days per week during the 8 weeks before the Screening Visit while taking standard daily PPI therapy.	☐1	☐0
3.	Did the patient screen fail on any of the following ICP-3718-202 exclusion criteria? Check all that apply: ☐ Patient has a history of complete lack of GERD symptom response to PPIs in the past. ☐ Patient reports epigastric pain or burning as his/her predominant symptom at the Screening Visit. ☐ Patient has a history of gastroparesis, bowel obstruction, or is at risk for a bowel obstruction (e.g., patient has an organic gastrointestinal [GI] motility disorders or a history of major GI surgery). ☐ Patient has any alarm symptoms including but not limited to GI bleeding, anemia, vomiting, or unexpected weight loss any time during the Screening or Pretreatment Periods. ☐ Patient has undergone surgery that meets any of the following criteria: a. Surgery of the GI tract (including gastric banding) other than an appendectomy, cholecystectomy, minor oral or rectal surgery (e.g., tonsillectomy, hemorrhoidectomy, rectocele repair) at any time before the Screening Visit; b. An appendectomy during the 3 months before the Screening Visit or a cholecystectomy during the 6 months before the Screening Visit or minor oral or rectal surgery during the 30 days before the Screening Visit; c. Non-GI surgery of the abdomen, pelvis, or retroperitoneal structures during the 6 months before the Screening Visit;	☐1	☐0

Patient ID

#	INTERVIEW EXCLUSION CRITERIA	YES	NO
	d. Thoracic surgery during the 6 months before the Screening Visit; and/or e. Other major non-GI surgery during the 30 days before the Screening Visit. ☐ Patient has previously undergone thoracic or abdominal radiotherapy. ☐ Patient has Gilbert's disease, Crohn's disease, diabetes mellitus, Zollinger-Ellison syndrome, pancreatitis, cholecystitis, or systemic sclerosis. ☐ Patient has an acute or chronic condition that, in the Investigator's opinion, would limit the patient's ability to complete or participate in this clinical study.		

Please review the following carefully before proceeding to the next section:

- If the answer to any exclusion criterion question above is "YES", this patient is not eligible to participate in the interview.
- If the answer to every exclusion criterion question above is "NO" *and* the answer to every inclusion criterion question above is "YES", this patient is eligible to participate the interview.

Investigator Signature Required:

Investigator signature: _____

Date: _____

ATTACHMENT D: mRESQ-eD COGNITIVE DEBRIEFING INTERVIEW GUIDE

Patient ID

Cognitive Debriefing Interview Guide: Evaluating the Modified Reflux Symptoms Questionnaire Electronic Diary (mRESQ-eD)

Site ID:	Patient ID:
Date of interview:	Time of interview:
Type of interview: ☐ In person ☐ Telephone	Cohort: ☐ 1 ☐ 2 ☐ 3
Name of interviewer:	

Patient ID

Part 1:
Interviewer Instructions

Prior to the interview

- Verify receipt of written informed consent
- Verify confirmation of eligibility

During the interview

- This interview guide is semi-structured in nature and meant to serve as a basis for the discussion. Actively listen, probe as necessary and take note of nonverbal communication during in-person interviews (e.g., long pauses, facial expressions, gestures).

After the interview

- Thank the patient for his/her time.
- Write down brief overall impressions of the interview immediately after it is completed, making sure to note any issues encountered during the interview (e.g., time issues, patient's understanding issues, etc.) that may explain the quality or quantity of the data. Overall impressions can be extremely useful and informative for the subsequent interviews, and therefore, you should be prepared to discuss preliminary interview findings with the research team based on your written notes and recollection.

Patient ID

Part 2:
Study Introduction

[Duration: 5/60 minutes]

Introduction

- Thank you for your interest and willingness to be a part of the interview.
- My name is [first name] and I work with Endpoint Outcomes, a company that works with pharmaceutical companies to develop and modify questionnaires used by doctors when they treat patients like you. I will be interviewing you today.

What to expect

- During the interview I will ask you to complete a questionnaire and provide your feedback on it. Please understand that there are no right or wrong answers. We welcome you to speak freely; your opinions and perspectives are appreciated. If you need to take a break, or would like to stop the interview at any time, you are free to do so. You also do not have to answer any of the interview questions if you don't want to.
- Our interview is scheduled to last about 60 minutes.
- I, as well as other researchers involved in this study, have been trained to maintain participant confidentiality. Personally identifying information, such as your name, will remain with Endpoint Outcomes and will only be accessible to research staff.
- Our conversation today will be audio-recorded so that we have an accurate record of the discussion. Please speak clearly and loudly so that you can be heard on the audio-recording.
- Do I have your permission to audio-record this session?
  - *If yes:* Thank you. I will ask you again for the record once I have the audio-recorder turned on.
  - *If no:* Do not proceed with the interview.
- Do you have any questions at this point?

Once the audio-recorder is turned on

- This is interviewer, [*state your name*], here with patient [*state patient's ID*].
- Do I have your permission to audio-record this interview?

Patient ID

Part 3:
Think-Aloud and Cognitive Debriefing for the mRESQ-eD

[Duration: 55/60 minutes]

Think-aloud

- ***[Cohort 1]:*** Now I will ask you to complete the modified Reflux Symptoms Questionnaire (mRESQ-eD) using the electronic device. I know you have been completing the questionnaire for the last several weeks or so and you are already familiar with the questionnaire.
- ***[Cohorts 2 and 3]:*** Now I will ask you to complete a questionnaire called the modified Reflux Symptoms Questionnaire on an electronic device (mRESQ-eD).
- Please read the instructions and items, basically everything written on the screen, out loud. And as you're choosing answers, please tell me verbally which answer you chose and why you chose that particular answer. You're basically "thinking out loud" and telling me your thought process as you're completing the questionnaire.
- For example, if I asked you how much fruit you ate this week, rather than just saying "three" you might say, "On Monday I ate a banana with breakfast, on Tuesday I had an apple at lunch, and on Thursday I ate an orange after lunch. So, I ate three pieces of fruit this week."
- I understand that this is not the way people usually complete questionnaires, so I might have to remind you to "think out loud." I may also interrupt occasionally and ask you questions as you are completing the questionnaire.

[Ensure participant has the mRESQ-eD in front of him/her]

- Please start completing the questionnaire in the manner we discussed.

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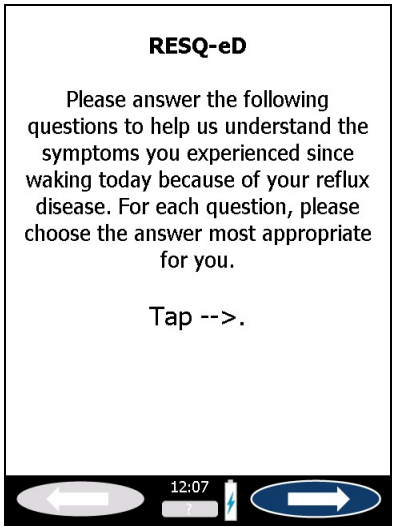
Cognitive interviewing: Instructions

Screen 1



- What do you think these **instructions** are asking you to do? Can you put them into your own words?
  - What does **"reflux disease"** mean to you?
  - What time period are you being asked to consider when answering the questions?
  - Was it **clear or unclear** to you what to do from reading these instructions? If unclear, why was it unclear?
- Would you **reword** it in any way? Please explain.

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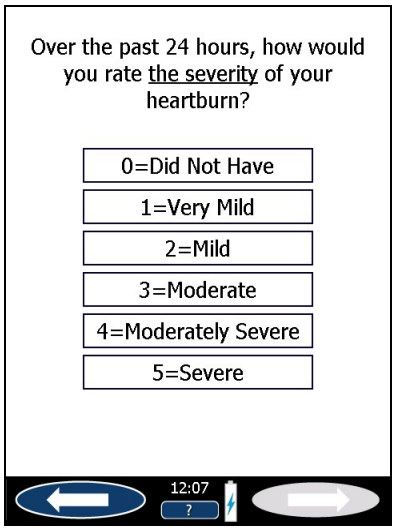
Cognitive Interviewing: Items 1-10

Screen 2



- What does this question mean to you? Can you put the question into your own words?
  - What does **heartburn** mean to you?
    - What does the **severity** of your heartburn mean to you?
  - What does **over the past 24 hours** mean to you?
- I see you selected *[patient's response]*. What made you choose that answer?
  - What does *[response selected]* mean to you?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Did Not Have" ask]:* Have you ever had heartburn?
  - *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Thinking about improvement in your heartburn, what would need to improve for it to be meaningful to you?
    - How often you have heartburn?

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- How long the heartburn lasts?
- How bad the heartburn is?

- *[If the participant selected "5=Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate, moderately severe) for the change to be meaningful to you? Please explain.
- *[If the participant selected "4=Moderately Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Moderate" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2= Mild" ask]:* How much would you need to improve on the answer scale (did not have, very mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Very Mild" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Did Not Have" ask]:* What is more important to you: that your heartburn is less severe or happens less often?

- What do the other responses *[run through each unchecked response]* mean for you?
- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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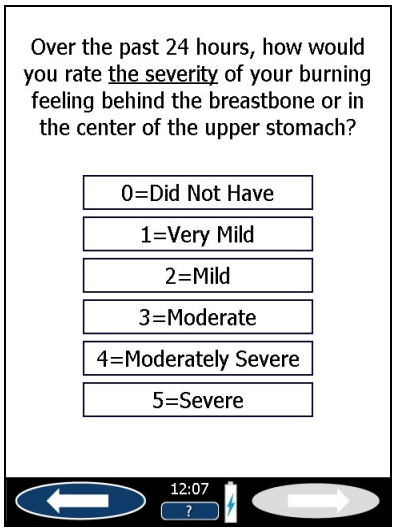
Screen 3



- What does this question mean to you? Can you put the question into your own words?
  - What does **burning feeling behind the breastbone or in the center of the upper stomach** mean to you?
    - What does the **severity** of your burning feeling behind the breastbone or in the center of the upper stomach mean to you?

Note to interviewer: *If the patient interprets the item on screen 3 similar to the item on screen 2, establish if they are in fact the exact same or if they are at all different.*

- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Did Not Have" ask]:* Have you ever had a burning feeling behind the breastbone or in the center of the upper stomach?
  - *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Thinking about improvement in your burning feeling behind the breastbone or in the center of the upper stomach, what would need to improve for it to be meaningful to you?

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- How often you have a burning feeling behind the breastbone or in the center of the upper stomach?
- How long the burning feeling behind the breastbone or in the center of the upper stomach lasts?
- How bad the burning feeling behind the breastbone or in the center of the upper stomach is?

- *[If the participant selected "5=Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate, moderately severe) for the change to be meaningful to you? Please explain.
- *[If the participant selected "4=Moderately Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Moderate" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2= Mild" ask]:* How much would you need to improve on the answer scale (did not have, very mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Very Mild" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Did Not Have" ask]:* What is more important to you: that your burning feeling behind the breastbone or in the center of the upper stomach is less severe or happens less often?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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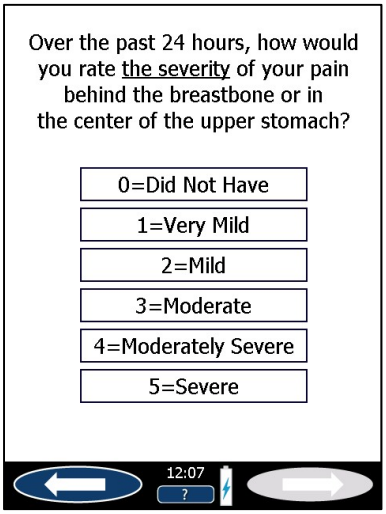
Screen 4



- What does this question mean to you? Can you put the question into your own words?
  - What does **pain behind the breastbone or in the center of the upper stomach** mean to you?
    - What does the **severity** of your pain behind the breastbone or in the center of the upper stomach mean to you?

Note to interviewer: *If the patient interprets the item on screen 4 similar to the item on screens 2 or 3, establish if they are in fact the exact same or if they are at all different.*

- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Did Not Have" ask]:* Have you ever had pain behind the breastbone or in the center of the upper stomach?
  - *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Thinking about improvement in your pain behind the breastbone or in the center of the upper stomach, what would need to improve for it to be meaningful to you?
    - How often you have pain behind the breastbone or in the center of the upper stomach?

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- How long the pain behind the breastbone or in the center of the upper stomach lasts?
- How bad the pain behind the breastbone or in the center of the upper stomach is?

- *[If the participant selected "5=Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate, moderately severe) for the change to be meaningful to you? Please explain.
- *[If the participant selected "4=Moderately Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Moderate" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2= Mild" ask]:* How much would you need to improve on the answer scale (did not have, very mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Very Mild" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Did Not Have" ask]:* What is more important to you: that your pain behind the breastbone or in the center of the upper stomach is less severe or happens less often?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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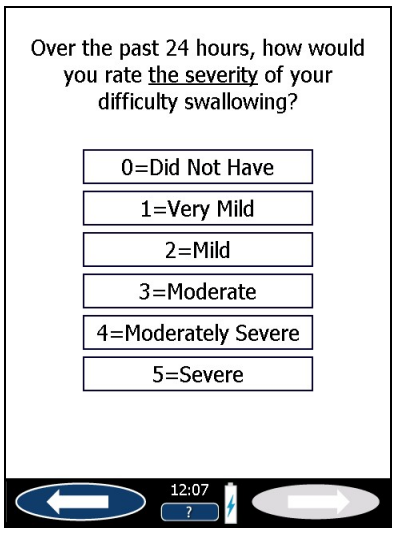
Screen 5



- What does this question mean to you? Can you put the question into your own words?
  - What does **difficulty swallowing** mean to you?
    - What does the **severity** of your difficulty swallowing mean to you?

Note to interviewer: *We want to understand if difficulty swallowing means having difficulty with the physical act of swallowing or if it means experiencing a sensation (e.g., pain, discomfort) while swallowing. If this is unclear based on the interpretation provided by the patient, probe further:*

- What makes swallowing difficult?
  - Is it actually trying to swallow that is difficult?
- What does it feel like when swallowing is difficult?
  - *[If the subject reports pain when swallowing, ask]:* Is difficulty swallowing the same as or different than pain when swallowing? Were you thinking about how it feels when answering the question?

- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?

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- How far back were you thinking when you answered the question?
- *[If the participant selected "0=Did Not Have" ask]:* Have you ever had difficulty swallowing?
- *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Thinking about improvement in your difficulty swallowing, what would need to improve for it to be meaningful to you?
  - How often you have difficulty swallowing?
  - How long the difficulty swallowing lasts?
  - How bad the difficulty swallowing is?
- *[If the participant selected "5=Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate, moderately severe) for the change to be meaningful to you? Please explain.
- *[If the participant selected "4=Moderately Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Moderate" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2= Mild" ask]:* How much would you need to improve on the answer scale (did not have, very mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Very Mild" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Did Not Have" ask]:* What is more important to you: that your difficulty swallowing is less severe or happens less often?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please expl

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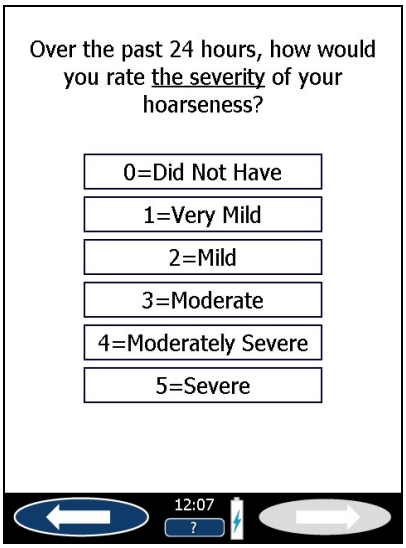
Screen 6



- What does this question mean to you? Can you put the question into your own words?
  - What does **hoarseness** mean to you?
    - What does the **severity** of your hoarseness mean to you?
- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Did Not Have" ask]:* Have you ever had hoarseness?
  - *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Thinking about improvement in your hoarseness, what would need to improve for it to be meaningful to you?
    - How often you have hoarseness?
    - How long the hoarseness lasts?
    - How bad the hoarseness is?

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- *[If the participant selected "5=Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate, moderately severe) for the change to be meaningful to you? Please explain.
- *[If the participant selected "4=Moderately Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Moderate" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2= Mild" ask]:* How much would you need to improve on the answer scale (did not have, very mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Very Mild" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Did Not Have" ask]:* What is more important to you: that your hoarseness is less severe or happens less often?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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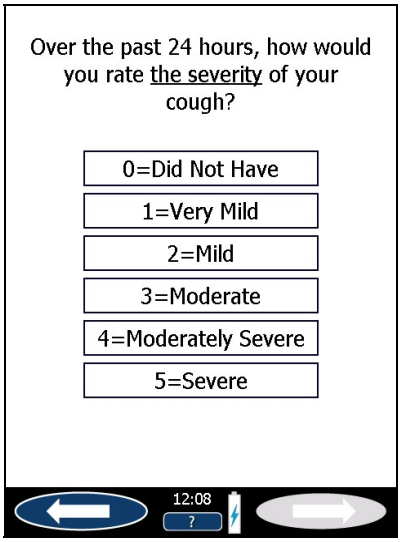
Screen 7



- What does this question mean to you? Can you put the question into your own words?
  - What does **cough** mean to you?
    - What does the **severity** of your cough mean to you?
- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Do you think your cough is because of your GERD or something else?
  - *[If the participant selected "0=Did Not Have" ask]:* Have you ever had coughing due to your GERD?
  - *[If the participant selected "1=Very Mild," "2=Mild," "3=Moderate," "4=Moderately Severe" or "5=Severe," ask]:* Thinking about improvement in your cough, what would need to improve for it to be meaningful to you?
    - How often you have coughing?
    - How long the coughing lasts?

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- How bad the coughing is?

- *[If the participant selected "5=Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate, moderately severe) for the change to be meaningful to you? Please explain.
- *[If the participant selected "4=Moderately Severe" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild, moderate) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Moderate" ask]:* How much would you need to improve on the answer scale (did not have, very mild, mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2= Mild" ask]:* How much would you need to improve on the answer scale (did not have, very mild) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Very Mild" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Did Not Have" ask]:* What is more important to you: that your coughing is less severe or happens less often?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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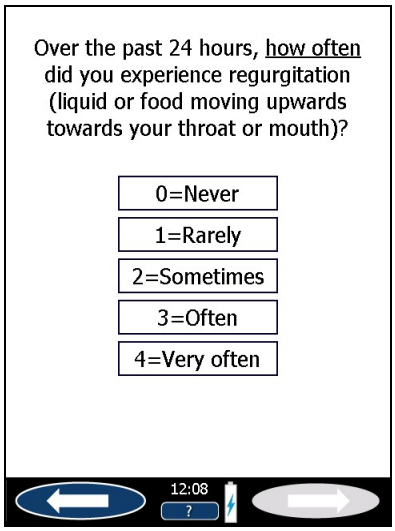
Screen 8



- What does this question mean to you? Can you put the question into your own words?
  - What does **regurgitation (liquid or food moving upwards towards your throat or mouth)** mean to you?
    - What does **how often** did you experience regurgitation (liquid or food moving upwards towards your throat or mouth) mean to you?
- I see you selected *[patient's response]*. What made you choose that answer?
  - What does *[response selected]* mean to you?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Never" ask]:* Have you ever had regurgitation?
  - *[If the participant selected "1=Rarely," "2=Sometimes," "3=Often," or "4=Very Often," ask]:* Thinking about improvement in your regurgitation, what would need to improve for it to be meaningful to you?
    - How often you have regurgitation?

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- How long the regurgitation lasts?
- How bad the regurgitation is?

- *[If the participant selected "4=Very Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes, often) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2=Sometimes" ask]:* How much would you need to improve on the answer scale (never, rarely) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Rarely" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Never" ask]:* What is more important to you: that your regurgitation happens less often or is less severe?

- What do the other responses *[run through each unchecked response]* mean for you?
- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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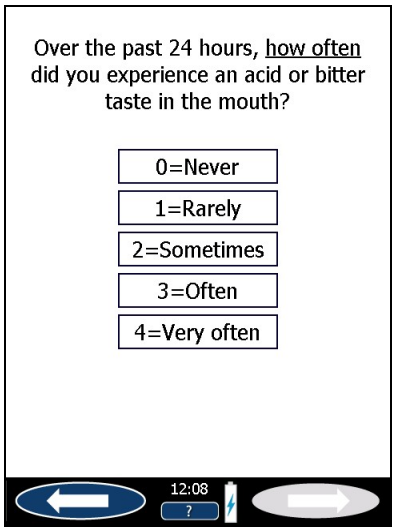
Screen 9



- What does this question mean to you? Can you put the question into your own words?
  - What does **acid or bitter taste in the mouth** mean to you?
    - What does **how often** did you experience an acid or bitter taste in the month mean to you?
- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Never" ask]:* Have you ever had an acid or bitter taste in the mouth?
  - *[If the participant selected "1=Rarely," "2=Sometimes," "3=Often," or "4=Very Often," ask]:* Thinking about improvement in the acid or bitter taste in your mouth, what would need to improve for it to be meaningful to you?
    - How often you have the acid or bitter taste in your mouth?
    - How long the acid or bitter taste in your mouth lasts?
    - How bad the acid or bitter taste in your mouth is?

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- *[If the participant selected "4=Very Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes, often) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2=Sometimes" ask]:* How much would you need to improve on the answer scale (never, rarely) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Rarely" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Never" ask]:* What is more important to you: that your acid or bitter taste in the mouth happens less often or is less severe?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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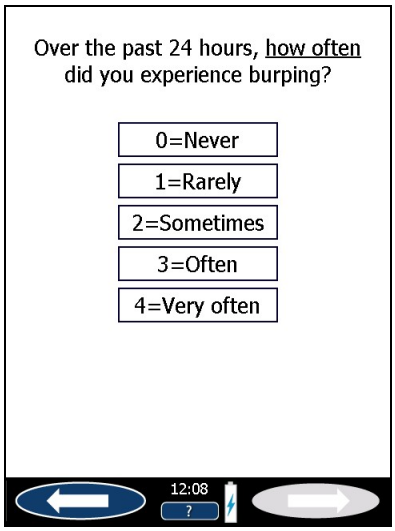
Screen 10



- What does this question mean to you? Can you put the question into your own words?
  - What does **burping** mean to you?
    - What does **how often** did you experience burping mean to you?
- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Never" ask]:* Have you ever had burping?
  - *[If the participant selected "1=Rarely," "2=Sometimes," "3=Often," or "4=Very Often," ask]:* Thinking about improvement in your burping, what would need to improve for it to be meaningful to you?
    - How often you have burping?
    - How long the burping lasts?
    - How bad the burping is?

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ENDPOINT OUTCOMES

- *[If the participant selected "4=Very Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes, often) for the change to be meaningful to you? Please explain.
- *[If the participant selected "3=Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2=Sometimes" ask]:* How much would you need to improve on the answer scale (never, rarely) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Rarely" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.
- *[If the participant selected anything other than "0=Never" ask]:* What is more important to you: that your burping happens less often or is less severe?

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

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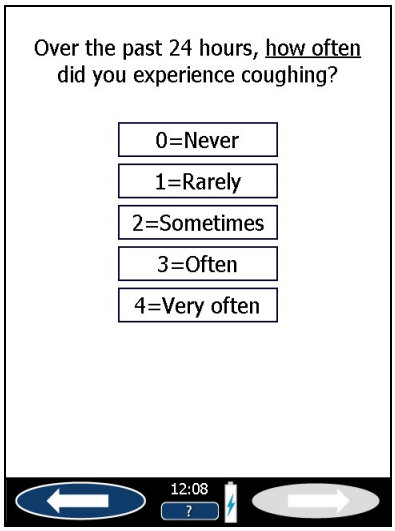
Screen 11



- What does this question mean to you? Can you put the question into your own words?
  - What does **coughing** mean to you?
    - What does **how often** did you experience coughing mean to you?
  - How is this question different than the previous question on coughing?
    - Which is more meaningful to you, the severity of your coughing or how often you cough?
    - Do you think both are important to ask? Please explain.
- I see you selected *[patient's response]*. What made you choose that answer?
  - What were you considering when you answered the question?
  - How far back were you thinking when you answered the question?
  - *[If the participant selected "0=Never" ask]:* Have you ever had coughing?
  - *[If the participant selected "4=Very Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes, often) for the change to be meaningful to you? Please explain.TEST-

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- *[If the participant selected "3=Often" ask]:* How much would you need to improve on the answer scale (never, rarely, sometimes) for the change to be meaningful to you? Please explain.
- *[If the participant selected "2=Sometimes" ask]:* How much would you need to improve on the answer scale (never, rarely) for the change to be meaningful to you? Please explain.
- *[If the participant selected "1=Rarely" ask]:* How much would you need to improve on the answer scale for the change to be meaningful to you? Please explain.

- Do the response choices seem to match the question? Why or why not?
- Would you reword or change anything about this item, including the response options? Please explain.

General impressions of mRESQ-eD

- I'd like to ask you some questions about your overall opinion of the questionnaire.
- How easy or difficult was it for you to think about your symptoms over 24 hours when answering the questions?
- Is the time of day that you answer the questions important?
  - Would you answer the same or differently in the morning versus at night?
- Was it easy or difficult for you to transition from one set of response options used for the questions on screens 2-7 and another set of response options used for questions on screens 8-11? Please explain.
- Were there any words that may be difficult or hard for someone to understand when completing the questionnaire? If so, which ones and why?
- Is there anything important related to your experience with GERD that is missing in the questionnaire? If so, do you think we should add it?
- Are any of the questions redundant, in other words, asking you about the same thing? If so, which ones and why?
- What is your opinion on how the questionnaire looks on the device?

Thank you!

- Thank you for your time. We appreciate you sharing your experiences and providing feedback.

APPENDIX 11 PPI DOSE LEVELS DURING STUDY PARTICIPATION

Acceptable Dose Levels of the Various PPIs for Participation in the Trial[1]

PPI Generic Name	Common Brand Name(s)	Acceptable Dose Levels for Non-Erosive Esophagitis[2]	Acceptable Dose Level for Erosive Esophagitis
dexlansoprazole	Dexilant®, Kapidex®	30-60 mg QD	60 mg QD
esomeprazole	Nexium®	20-40 mg QD	40 mg QD
lansoprazole	Prevacid®	15-30 mg QD	30 mg QD
omeprazole	Prilosec®	20 mg QD	20 mg QD
pantoprazole	Protonix®	No indication	40 mg QD
rabeprazole	AcipHex®	20 mg QD	20 mg QD

1. The dose levels are acceptable provided that the PPI treatment has been optimized. (Optimized means treatment that, according to the Investigator's judgment, could not be further improved by changing the brand or timing of PPI administration.)

2. For dexlansoprazole, esomeprazole, and lansoprazole, the approved dose level for non-erosive esophagitis is the first one that is listed. However, either dose is acceptable for enrollment in the study.