Clinical Study Protocol: C3718-301

Amendment 2, 14 August 2020

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial of Oral IW-3718 Administered to Patients with Gastroesophageal Reflux Disease while receiving Proton Pump Inhibitors
Study Number:	C3718-301
Study Phase:	3
Product Name:	IW-3718
Indication:	IW-3718 is indicated as an adjunct to proton pump inhibitors to treat persistent (also referred to as refractory) gastroesophageal reflux disease symptoms such as heartburn and regurgitation that are not resolved with proton pump inhibitor therapy alone.
Sponsor:	Ironwood Pharmaceuticals, Inc. 100 Summer Street, Suite 2300 Boston, MA 02110 USA
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	15 March 2018
Amendment #1	23 June 2018
Amendment #2	14 August 2020

SYNOPSIS

Study Number: C3718-301

Study Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial of Oral IW-3718 Administered to Patients with Gastroesophageal Reflux Disease while receiving Proton Pump Inhibitors

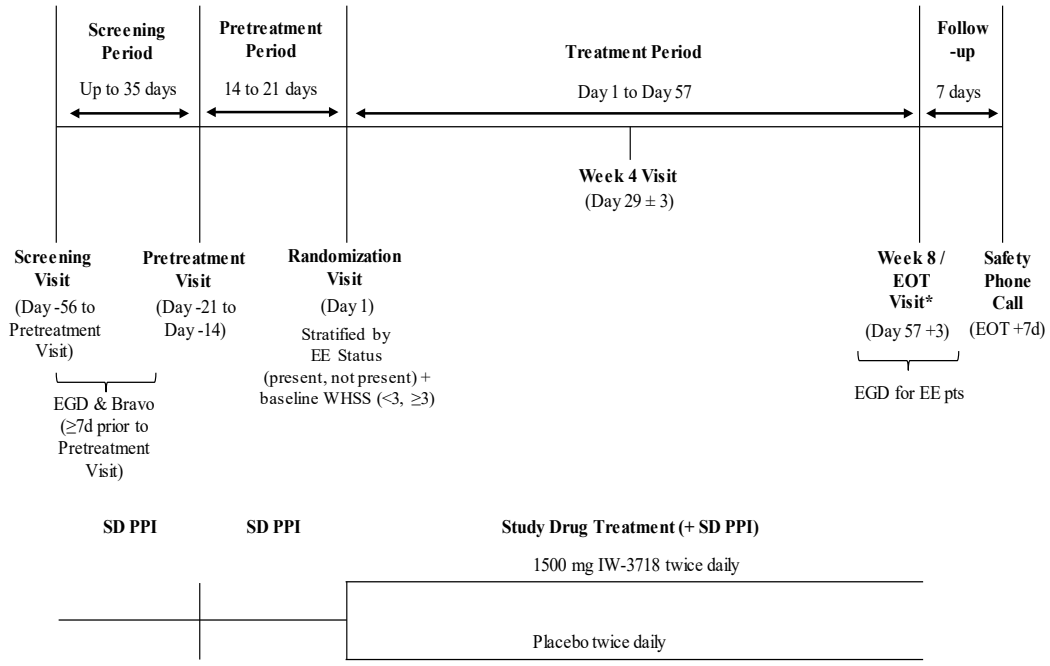
Study Centers: Approximately 100 centers in the United States and Canada

Development Phase: 3

Objectives: The objective of this study is to evaluate the safety and efficacy of IW-3718 administered to patients with GERD who continue to have persistent symptoms, such as heartburn and regurgitation, while receiving once-daily (QD), standard-dose proton pump inhibitors (PPIs).

Methodology: This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-week study, consisting of 4 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. Eligible patients will continue to take their PPI and will be randomized to placebo or to 1500 mg IW-3718 BID.

Overview of Study Design



Note: There is no Day 0

* This visit represents the end of the study
EE = erosive esophagitis; EGD=esophagogastroduodenoscopy; EOT=end of treatment; SD PPI = standard dose proton pump inhibitor; WHSS = Weekly Heartburn Severity Score

Screening Period: The Screening Period starts with the signature of the informed consent form (ICF) and may last for up to 35 days. During this period, patients' eligibility for entry into the Pretreatment Period will be determined. Two procedures will be required during the Screening Period in all patients (all will be done while patients continue to take their PPI):

- An esophagogastroduodenoscopy (EGD)
- Up to 96 hours of pH testing with the Bravo™ device, a capsule-based pH monitor implanted above the lower esophageal sphincter (LES).

The patient must have been adherent to their standard PPI dosage regimen (as per product label) for the 8 weeks prior to the Screening Visit and during the entire Screening Period. Histamine-2 receptor antagonists (H2RAs) should be stopped at least 5 days prior to the EGD and Bravo pH monitoring; antacids should be stopped at least 1 day prior to the EGD and Bravo pH monitoring. The EGD must be performed during the Screening Period and should be performed 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 use antacids if needed until 1 day prior to entering the Pretreatment Period. The end of the Screening Period coincides with the start of the Pretreatment Period.

Pretreatment Period: The Pretreatment Period is defined as the 14 to 21 days immediately before the Randomization Visit. Patients who meet all eligibility criteria, including pH requirements as per the central pH read, will continue into the Pretreatment Period. 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 liquid antacid that is dispensed as rescue medicine (aluminum hydroxide / magnesium hydroxide). Patients will provide the following daily and weekly symptom assessments using a handheld electronic diary (eDiary):

Daily Assessments

- GERD symptoms, recorded in the evening before going to bed, using the modified Reflux Symptom Questionnaire Electronic Diary (mRESQ-eD; Appendix 1)
- Use of per-protocol rescue medicine, recorded in the evening before going to bed
- Sleep disturbance due to GERD symptoms, recorded upon getting up in the morning (Appendix 2)

Weekly Assessments

- Degree of relief of GERD symptoms (Appendix 3)
- GERD symptom bothersomeness (Appendix 3)

Patients will be required to complete the daily assessments for at least 5 days each week during the last 14 days before the Randomization Visit and the weekly assessments at least once during the last 7 days before the Randomization Visit to be eligible for randomization.

Patients will be instructed to take their PPI approximately 30-60 minutes before breakfast each day, even on study visit days. Patients who satisfy 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 their baseline weekly heartburn severity score (WHSS, defined as the average heartburn severity score over the last 7 days prior to randomization of <3 vs. ≥3; see Criteria for Evaluation, below) and randomly assigned within each stratum to placebo or 1500-mg IW-3718 BID (1:1). The treatment randomization schedule will be managed by a central vendor. Enrollment will be monitored to ensure that no single center contributes > 10% 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 and assessment of sleep), weekly assessments (degree of relief of GERD symptoms, symptom bothersomeness, and treatment satisfaction questions). At the end of the treatment period study medication will be discontinued and patients will return for an End-of-Treatment (EOT) Visit. All patients who have erosive esophagitis (LA classification A-D) on EGD at Screening and completed ≥4 weeks of treatment will have a repeat EGD at their EOT Visit. Patients will also complete all End-of-Treatment assessments.

Study Population: The study population will consist of adult patients with diagnosed GERD who continue to have persistent (also referred to as refractory) symptoms, such as heartburn and regurgitation, while receiving QD PPI therapy and have evidence of pathological acid reflux during the Screening Period as determined using the Bravo device. Patients will be stratified for treatment assignment at the time of randomization based on the presence of erosions (erosions, no erosions) and by baseline WHSS (<3 vs. ≥3). The study will aim to enroll up to 50% of patients with esophageal erosions. Patients must be receiving 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 labelling. Approximately 660 patients (330 patients per treatment arm) will be randomized to treatment.

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 male or female (if female, nonpregnant) and is at least 18 years old at the Screening Visit.
3. Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on average ≥ 4 days per week over the last 8 weeks before the Screening Visit.
4. Patient has been receiving 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 (see Appendix 7). Patients who have their PPI modified during the Screening Period may be re-screened after 8 weeks of standard-labeled dose QD PPI therapy provided they have not previously entered the Pretreatment Period.

5. Up to 96 hours of pH monitoring (with a Bravo device) during the Screening Period (while the patient continues taking their PPI) demonstrates 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 as confirmed by centralized review of pH monitoring.
6. During the last 7 days before randomization patient reports an average heartburn severity (HS, maximum of Items #1 and #2 on mRESQ-eD) of ≥ 2 (mild) and has a daily HS ≥ 3 (moderate) for at least 2 of those days.
7. Female patients must be postmenopausal for ≥1 year, surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal ligation); or must agree to completely abstain from heterosexual intercourse; or, if heterosexually active, must agree to use 1 of the following methods of birth control from the date she signs the ICF until 24 hours after her final dose of study drug:
   a. Progesterone implant or an intrauterine device (IUD)
   b. Combination of 2 highly effective birth control methods (eg, diaphragm with spermicide plus a condom, condom with spermicide plus a diaphragm or cervical cap, hormonal contraceptive [eg, oral and transdermal patch] plus a barrier method, partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone or barrier method).
8. Females of childbearing potential must have a negative urine or serum pregnancy test at the Screening Visit and at the Randomization Visit prior to dosing. Positive urine test results will be confirmed by a serum pregnancy test.
9. Patient agrees not to make any changes to their usual diet or exercise regimen during the study.
10. Patient is able to successfully use the eDiary, and has adequately completed the eDiary questions on at least 5 days each week and the weekly questions at least once during the 14 days before the start of the Treatment Period.
11. Patient is compliant with QD PPI dosing during the 14 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 at least one of the languages to be used for patient-reported outcome (PRO) assessments.

13. 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.
2. Patient reports epigastric pain or epigastric burning as his or her predominant symptom at the Screening Visit.
3. Patient has a diagnosis of gastroparesis per gastric emptying study, or a history of bowel obstruction, or is at risk for a bowel obstruction (eg, patient has an organic gastrointestinal [GI] motility disorders or a history of major GI surgery).
4. Patient has a history of serum triglyceride concentrations > 500 mg/dL on a fasting specimen, or has serum triglyceride concentrations > 500 mg/dL on a fasting specimen at Screening.
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; eg, the patient has osteoporosis or osteomalacia) and will be put at risk by receiving colesevelam for 8 weeks.
7. Patient has an active swallowing disorder that would compromise their ability to swallow the study medication.
8. Patient has any alarm symptoms including, but not limited to, GI bleeding, anemia, vomiting, or unexpected weight loss at 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 (eg, 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. Patient has large (>5 cm) hiatal hernia.
12. 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.
13. Patient has Gilbert's disease, Crohn's disease, diabetes mellitus (defined as A1C >6.5%), Zollinger-Ellison syndrome, pancreatitis, cholecystitis, or systemic sclerosis.
14. Patient has elevated (defined as > 1.5 times the upper limit of normal by the laboratory) levels of serum bilirubin at Screening.
15. Patient has a history of clinically significant hypersensitivity or allergies to any of the excipients contained in the study medication (active or placebo).
16. 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.
17. Patient has active substance abuse or history of chronic substance abuse (including alcoholism but not including nicotine) within 12 months before the Screening Visit or is positive for any of the following at the Screening Visit unless legally prescribed for anything but gastrointestinal pain: amphetamines, benzodiazepines, opiates, barbiturates, cocaine, or phencyclidine.

    Note: Marijuana use, whether prescribed or not, is prohibited from 30 days before screening through the duration of the study. Use of illicit drugs is not allowed during the study.
18. 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.)
19. 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.

20. 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.
21. 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.
22. Patient has previously entered the Treatment Period of a IW-3718 study.
23. Patient has previously entered the Pretreatment Period of this study. (Note: patients who failed the Pretreatment Period due to abnormal laboratory findings or timing issues may be re-screened.)
24. 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:

- 1500 mg IW-3718 BID: Three 500 mg IW-3718 oral tablets administered BID, immediately after the morning and evening meals. Dose reductions are not permitted.

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 126 days, including the Screening Period and Follow-up.

Criteria for Evaluation:

Primary and Key Secondary Efficacy Assessments

The once-daily assessment of heartburn symptoms and regurgitation symptoms obtained from the mRESQeD will be used to determine the primary and key secondary efficacy parameters.

The items used to measure heartburn severity will be the 2 items in the Heartburn Domain assessed on a 0-to-5 ordinal severity scale:

- 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 used to measure 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 following GERD symptoms obtained from the mRESQeD will be assessed once-daily:

- Difficulty swallowing, hoarseness, and cough severity, each assessed on a 0-to-5 ordinal severity scale
- Burping frequency, assessed on a 0-4 frequency scale

In addition, Sleep Disturbance due to GERD symptoms - including difficulty falling asleep and the number of nighttime awakenings during the prior evening will be recorded each morning.

Heartburn severity will be assessed once daily in the evening, before bed, on a 0-to-5 ordinal severity scale.

The following patient-reported items will be assessed once weekly:

- Degree of Relief of heartburn, regurgitation, and overall GERD symptoms, each rated on 7-point balanced ordinal scale (1=significantly relieved, 4=unchanged, 7=significantly worse); Degree of Relief of heartburn, regurgitation, and overall GERD symptoms on 7-point patient global impression of change scale (compared to before you started the study; 1=significantly relieved, 4=unchanged, 7=significantly worse)
- Bothersomeness of heartburn, regurgitation, and overall GERD symptoms, each rated 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)
- Global Treatment Satisfaction, rated on a 5-point ordinal scale (1=very dissatisfied, 3=neither satisfied nor dissatisfied, 5=very satisfied)

Other Assessments

The following questionnaires will be administered during the study at the Randomization, Week 4, and EOT Visits:

- EuroQol (EQ)-5D-3L
- Work Productivity and Activity Index (WPAI)-GERD-Sleep

Safety Assessments:

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

Statistical Methods

Analysis Populations:

Screened Population consists of all patients who signed informed consent and received a patient identification (PID) number.

Randomized Population consists of all patients who were assigned to a treatment group (placebo or IW-3718) via randomization.

Safety Population consists of all randomized patients who received at least 1 dose of study drug.

Modified Intent-to-Treat (mITT) Population consists of all randomized patients who received at least 1 dose of study drug and had at least 1 postbaseline primary efficacy assessment.

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 2-sided and with a confidence level of 95%. Details of the data handling methods will be specified in the statistical analysis plan (SAP). Unless otherwise specified, the week prior to randomization will be considered the baseline for efficacy analyses. For safety analyses, the baseline value is defined as the last non-missing value measured before administration of study treatment. All statistical analyses will be performed using SAS® Version 9.4 (or later) for Windows.

Primary Efficacy Parameter

Change from baseline at Week 8 in Weekly Heartburn Severity Score (WHSS).

- The WHSS for a week is the average of the non-missing Daily Heartburn Severity Scores (DHSS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock.
- The DHSS for a day is the greater score of the 2 mRESQ items assessing heartburn severity ("Burning feeling behind the breastbone or in the center of the upper stomach" and "Pain behind the breastbone or in the center of the upper stomach") for that day. Where 1 of the 2 mRESQ heartburn severity items is missing for the day, the maximum will be the score of the remaining item; where both items are missing for the day, the DHSS will be missing.

Key Secondary Efficacy Parameters

1. Change from baseline at Week 8 in Weekly Regurgitation Frequency Score (WRFS)

- The WRFS for a week is the average of the non-missing Daily Regurgitation Frequency Scores (DRFS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock.
- DRFS for a day is the greater score of the 2 mRESQ items assessing regurgitation frequency ("Regurgitation [liquid or food moving upwards toward your throat or mouth]" and "An acid or bitter taste in the mouth") for that day.

2. Overall Heartburn Responder: a patient who is a weekly heartburn responder for at least 4 weeks, including at least 1 of the last 2 weeks (Weeks 7 and 8), during the 8-week Treatment Period.
   - A weekly heartburn responder is a patient with a decrease from baseline of ≥ 45% in Weekly Heartburn Severity Score (WHSS).
   - Rules for missingness of data will be prespecified in the SAP finalized before database lock.
3. Proportion of heartburn-free days during the 8-week Treatment Period.
   - Proportion of heartburn-free days is calculated as the number of heartburn-free (DHSS=0) days divided by the number of diary entry days.

Efficacy Analysis Methods

For analysis of the primary efficacy and first key secondary efficacy parameters, continuous parameters (eg, change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. The IW-3718 group will be compared with the placebo group by employing a linear mixed-effects model for repeated measures (MMRM) framework with week (categorical), treatment group, week-by-treatment group and week-by-baseline value interactions, baseline esophagitis status (present vs. not present), and baseline WHSS (<3 vs. ≥3) as fixed-effect terms and baseline value as a covariate, with patient as a random effect. An unstructured covariance structure will be used. Least-squares mean (LSM) for each treatment group, LSM difference between the IW-3718 group and the placebo group and a 95% confidence interval for the difference at Week 8, as well as the p-value for comparison versus placebo will be presented.

For analysis of responder parameters (ie, responder vs. non-responder), the counts and proportions of responders will be calculated for each treatment group. The proportions of responders between the IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for baseline esophagitis status (erosive esophagitis vs. no erosive esophagitis) and baseline WHSS (<3 vs. ≥3). The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between the IW-3718 group and the placebo group, as well as the CMH estimate of the odds ratio (IW-3718 over placebo) and a 95% confidence interval for the odds ratio, will also be presented.

Time-dependent proportion parameters, defined as days the event of interest occurs, divided by the number of eDiary entry days within the 8-week Treatment Period (eg, proportion of heartburn-free-days), will be analyzed using a Poisson model which is appropriate for count data. The analysis includes the treatment, the baseline esophagitis status (present vs. not present), baseline WHSS (<3 vs. ≥3), covariate of baseline proportion of event-free days, with the eDiary entry days adjusted in the model. In the case of overdispersion, a negative binomial model instead of Poisson regression will be implemented. Model estimates in difference between the rates for IW-3718 and placebo groups will be calculated with corresponding 95% confidence interval and p-value associated with the comparisons to placebo.

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, clinical

laboratory evaluations, vital signs, ECGs, and physical examination. For each safety parameter, the last non-missing assessment made before the first dose of study drug will be used as the baseline for all analyses of that safety parameter.

Sample Size Determination and Controlling for Type-I Error

The sample size calculations for the primary and key secondary efficacy parameters are based on results from patients with evidence of pathological acid reflux (positive baseline Bravo status) in Study ICP-3718-202, which had a similar study population as the current study.

The primary efficacy parameter is Change from Baseline at Week 8 in WHSS, and key secondary efficacy parameters include:

- Change from Baseline at Week 8 in WRFS
- Overall Heartburn Responder
- Proportion of Heartburn-free Days during the 8-week Treatment Period

Using data from patients in Study ICP-3718-202, we derived the estimated results at end of the study as follows:

Order of Hypothesis Testing	**Parameter**	**Placebo (+ PPIs)**	**1500 mg IW-3718 (+ PPIs)**
1	Change from Baseline at Week 8 in WHSS	N = 43 Mean = -1.58 SD = 1.20	N =51 Mean = -2.01 SD = 1.29
2	Change from Baseline at Week 8 in WRFS	N = 43 Mean = -0.81 SD = 1.12	N = 51 Mean = -1.26 SD = 0.91
3	Overall Heartburn Responder	18/49 = 36.7%	31/55 = 56.4%
4	Proportion of Heartburn-free Days during the 8-week Treatment Period	N = 48 Mean = 0.195 SD = 0.2822	N = 55 Mean = 0.268 SD = 0.2928

The efficacy parameters will be tested sequentially according to the above order at a 2-sided significance level of 0.05 so that the overall type-I error rate is maintained at 0.05.

Based on bootstrap simulations, a sample size of 330 patients per group will provide approximately 99% power to detect a treatment difference between 1500-mg IW-3718 (while receiving PPIs) and placebo (while receiving PPIs) for the primary efficacy parameter, assuming the randomized population in this study is consistent with the selected population from Study ICP-3718-202. Power that is based on simulations for all type-I error controlling key efficacy parameters are presented in the table below. The 2-sample t-test was used for continuous parameters and the Chi-square test was used for the responder parameter.

Order of Hypothesis Testing	Parameters	Power for Fixed Sequence Testing
1	Change from Baseline at Week 8 in WHSS	99%
2	Change from Baseline at Week 8 in WRFS	99%
3	Overall Heartburn Responder	99%
4	Proportion of Heartburn-free Days during the 8-week Treatment Period	88%

SCHEDULE OF EVALUATIONS

	Screening Period (Up to 5 weeks)	**Pretreatment Period (2 weeks)**	**Treatment Period (8 weeks)**			**Follow-up**
Visit Days →	Screening Visit (Day -56 to Day -15)	Pretreatment Visit (Day -21 to Day -1)	Randomization Visit (Day 1)	Week 4 Visit (Day 29 ± 3)	Week 8 / End-of-Treatment Visit (Day 57 + 3)	Safety Phone Call (EOT + 7d)
Visit Numbers →	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
Study Procedure ↓						
Inclusion and Exclusion Criteria Verification	X	X	X			
Signing of ICF	X					
IWRS Registration (a)	X	X	X	X	X	
Demographics	X					
Medical & Disease History	X					
Physical Examination (b)	X				X	
Body Weight and Height (c)	X	X	X	X	X	
H2RA/Antacid Washout (d)	X					
EGD (e)	X				X	
Up to 96 Hours of pH Testing with Bravo Device (f)	X					
Seated Vital Signs (g)	X		X	X	X	
12-Lead ECG (h)	X		X		X	
Prior and Concomitant Medications & Procedures (i)	X	X	X	X	X	X
Clinical Laboratory Tests (j)	X		X	X	X	
Pregnancy Test (k)	X		X	X	X	
Drug and Alcohol Screen (l)	X					
AE Evaluations (m)	X	X	X	X	X	X
Rescue Medicine Dispensed (n)		X	X	X		
eDiary Training and Dispensation		X				
eDiary (o)		X	X	X	X	
Weekly Symptom and Treatment Assessments		X	X	X	X	
WPAI-Sleep-GERD			X	X	X	
EQ-5D-3L			X	X	X	
Randomization			X			
Study Medication Dispensed (p)			X	X		
Study Medication Return (q)				X	X	
eDiary Return					X	
Follow-up Phone Call (r)						X

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood count; ECG = electrocardiogram; EGD = esophagogastroduodenoscopy; EOT = End-of-treatment; EQ = EuroQol; H2RA = histamine-2 receptor antagonist; HEENT = head, eyes, ears, nose, and throat; ICF = informed consent form; IWRS = interactive web response system; PPI = proton pump inhibitor; mRESQeD = modified Reflux Symptom Questionnaire Electronic Diary; SAE = serious adverse event

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; 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 washout H2RAs at least 5 days prior, and antacids 1 day prior, to the EGD and Bravo testing. 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 liquid antacid that is provided as rescue medication (aluminum hydroxide / magnesium hydroxide).
e. All patients will be required to undergo an EGD during the Screening Period. There should be a minimum of 7 days between the EGD and the start of the Pretreatment Period to allow for pH testing and patient stabilization. A repeat EGD will be performed at the Week 8 / EOT Visit for all patients who have completed at least 4 weeks of treatment and had erosive esophagitis on the screening EGD (based on the Los Angeles [LA] classification of esophagitis, see Appendix 5) as determined by either the site personnel or the central reader.
f. Up 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.
g. 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.
h. 12-Lead ECGs should be obtained after the patient has been supine for at least 5 minutes.
i. 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 PPIs, H2RAs, and antacids. Concomitant medications and procedures will be collected in the EDC system.
j. 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.
k. For all female patients of childbearing potential, a negative urine or serum pregnancy test must be performed and documented at the Screening Visit, and at the Randomization Visit (before dosing) in order for the patient to be randomized into the study. A urine or serum pregnancy test will also be obtained at the Week 4 and EOT Visits. All positive urine pregnancy test results will be confirmed by a serum pregnancy test.
l. Patients must undergo a urine drug screen for selected drugs of abuse (cocaine, barbiturates, amphetamines, opiates, benzodiazepines, cannabinoids, and phencyclidine) and a serum alcohol screen at the Screening Visit.
m. For randomized patients, all AEs will be captured from the time the patient signs the ICF through the Follow-up Phone call.
n. Rescue medicine (aluminum hydroxide / magnesium hydroxide) will be supplied to patients at the Pretreatment Visit, and if needed, at subsequent visits.
o. The eDiary will be dispensed at the Pretreatment Visit. Patients must complete daily questions at least 5 days each week during the 14 days before the Treatment Period and must complete the weekly questions at least once during the 7 days before the Treatment Period in order to be eligible for randomization. Patients should bring their eDiary to each visit. The eDiary will be used for daily assessments (PPI administration, mRESQ-eD, dyspepsia symptoms, sleep disturbance, and rescue medication use), and weekly assessments (degree of relief, symptom bothersomeness, symptom relief, treatment satisfaction, and questionnaires).
p. 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 study medication prior to arriving at the clinic but will be dispensed additional doses needed until the next study visit.
q. Treatment adherence with study drug will be assessed based on return of unused tablets.
r. Study site will contact each patient via telephone 7 days after the EOT Visit to collect information pertaining to ongoing AEs/SAEs/concomitant medications/concomitant therapies, and information concerning any new AEs/SAEs /concomitant medications/concomitant therapies since the EOT Visit.

STUDY CONTACTS & IDENTIFICATION

Protocol Inquiries and Contract Research Organization (CRO) Medical Monitor	[redacted]
CRO	[redacted]
Clinical Laboratory	[redacted]

SPONSOR CONTACTS & IDENTIFICATION

Sponsor	Ironwood Pharmaceuticals, Inc. 100 Summer Street, Suite 2300 Boston, MA 02110 [redacted]
Medical Monitor	[redacted]
Ironwood Contact	[redacted]
Drug Safety Physician (Serious Adverse Event [SAE] Reporting)	[redacted]
Dedicated SAE Telephone, Facsimile, and Email	[redacted]

TABLE OF CONTENTS

SYNOPSIS....2
SCHEDULE OF EVALUATIONS....14
STUDY CONTACTS & IDENTIFICATION....16
SPONSOR CONTACTS & IDENTIFICATION....17
TABLE OF CONTENTS....18
LIST OF IN-TEXT TABLES....21
LIST OF IN-TEXT FIGURES....22
LIST OF APPENDICES....23
LIST OF ABBREVIATIONS....24
1. INTRODUCTION....26
1.1 BILE ACIDS AND GERD....26
1.2 IW-3718....27
1.3 IW-3718 CLINICAL TRIALS IN GERD PATIENTS....28
2. STUDY OBJECTIVES....33
3. INVESTIGATIONAL PLAN....34
3.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION....34
3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS....37
3.3 SELECTION OF STUDY POPULATION....37
3.3.1 Eligibility Criteria....37
3.3.1.1 Inclusion Criteria....37
3.3.1.2 Exclusion Criteria....39
3.3.2 Screening Failures....41
3.3.3 Removal of Patients from Therapy or Assessment....41
3.3.4 Replacement Procedures....43
3.4 STUDY TREATMENTS....43
3.4.1 Investigational Product....43
3.4.1.1 IW-3718....43
3.4.1.2 Placebo....43
3.4.1.3 Rescue Medicine....43
3.4.1.4 Treatment Adherence....44
3.4.2 Packaging and Labeling....44
3.4.3 Storage and Stability....44
3.4.4 Method of Assigning Patients to Treatment Groups....45
3.4.5 Selection of Dosage in the Study....45
3.4.6 Selection and Timing of Dose for Each Patient....46
3.4.7 Blinding....46

3.4.8 Prior and Concomitant Medications 47
3.4.8.1 Rescue Medication....47
3.4.8.2 Prohibited Medicines 47
3.4.9 Diet and Exercise 48
3.5 SAFETY AND EFFICACY ASSESSMENTS....48
3.5.1 Adverse Events....48
3.5.1.1 Definitions....48
3.5.1.2 Procedures for Recording Adverse Events....49
3.5.1.3 Procedures for Collecting and Reporting Serious Adverse Events 50
3.5.1.4 Recording Requirements....53
3.5.1.5 Termination of Patients from the Study....55
3.5.2 Medical and Disease History 56
3.5.3 Physical Examination, Body Weight, and Height 56
3.5.4 Electrocardiograms 56
3.5.5 Vital Signs....57
3.5.6 Clinical Laboratory Determinations....57
3.5.7 Efficacy Assessments....59
3.5.7.1 Daily Assessments 59
3.5.7.2 Weekly Assessments....60
3.5.7.3 Study Visit Assessments 61
3.5.8 Other Assessments 62
3.5.8.1 Esophagogastroduodenoscopy....62
3.5.8.2 Bravo™....62
3.6 SCHEDULE OF EVENTS 62
3.6.1 Screening Period (Day -49 to Day -15) 63
3.6.1.1 Screening Visit (Visit 1) Procedures....63
3.6.1.2 Pretreatment Visit (Visit 2) Procedures 64
3.6.2 Treatment Period (Day 1 to Day 57)....64
3.6.2.1 Randomization Visit (Visit 3) Procedures 64
3.6.2.2 Week 4 (Visit 4) Procedures 65
3.6.2.3 Week 8/End-of-treatment (Visit 5) Procedures 66
3.6.3 Follow-up Phone Call 66
3.6.4 Early Termination Procedures 67
3.7 STATISTICAL METHODS....67
3.7.1 Analysis Populations....67
3.7.2 General Methods....67
3.7.3 Patient Disposition, Demographics, and Baseline Characteristics 68
3.7.4 Efficacy Analyses 68

3.7.4.1 Primary Efficacy Parameter 70
3.7.4.2 Key Secondary Efficacy Parameters 71
3.7.4.3 Analysis Methods for Primary and Key Secondary Efficacy Parameters 71
3.7.4.4 Controlling Type-I Error 72
3.7.4.5 Sensitivity Analysis of Primary Efficacy Parameter 73
3.7.4.6 Handling of Missing Data 73
3.7.4.7 Exploratory Efficacy Parameters and Analysis Methods 73
3.7.5 Safety Analyses 75
3.7.5.1 Adverse Events 76
3.7.5.2 ECGs, Vital Signs, and Clinical Laboratory Tests 76
3.7.6 Interim Analysis 76
3.7.7 Determination of Sample Size 76
3.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES 78
4. ETHICAL CONSIDERATIONS 79
4.1 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE 79
4.2 PATIENT INFORMATION AND INFORMED CONSENT 80
5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE 81
5.1 GENERATION OF STUDY RECORDS 81
5.2 DATA QUALITY ASSURANCE 81
5.3 ELECTRONIC CASE REPORT FORMS AND DATA MANAGEMENT 82
5.4 STUDY MONITORING 82
6. STUDY SPONSORSHIP 84
6.1 INVESTIGATOR AND STUDY TERMINATION 84
6.2 REPORTING AND PUBLICATION 84
7. INVESTIGATOR OBLIGATIONS 85
7.1 DOCUMENTATION 85
7.2 PERFORMANCE 87
7.3 USE OF INVESTIGATIONAL MATERIALS 87
7.4 RETENTION AND REVIEW OF RECORDS 87
7.5 PATIENT CONFIDENTIALITY 88
8. REFERENCE LIST 89
9. SPONSOR SIGNATURE 90
10. INVESTIGATOR SIGNATURE 91
11. APPENDICES 92

LIST OF IN-TEXT TABLES

Table 1. Overall Heartburn and Regurgitation Responders (Study ICP-3718-202; Modified Intent-to-Treat Population).....31
Table 2. Adverse Event Causality.....54
Table 3. Clinical Laboratory Tests.....58
Table 4. Analysis Time Windows for Efficacy Analysis – Daily Assessments.....69
Table 5. Analysis Time Windows for Efficacy Analysis – Weekly Assessments.....70

LIST OF IN-TEXT FIGURES

Figure 1. Overview of Study Design.....34

LIST OF APPENDICES

Appendix 1 MODIFIED REFLUX SYMPTOM QUESTIONNAIRE ELECTRONIC DIARY (mRESQ-eD) 93
Appendix 2 OTHER DAILY ASSESSMENTS 94
Appendix 3 WEEKLY ASSESSMENTS 95
Appendix 4 PROHIBITED MEDICATIONS 97
Appendix 5 LOS ANGELES CLASSIFICATION OF ESOPHAGITIS 99
Appendix 6 IN-CLINIC ASSESSMENTS 100
Appendix 7 PPI DOSE LEVELS DURING STUDY PARTICIPATION 105

LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BID	twice daily
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRO	contract research organization
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
EE	erosive esophagitis
EGD	esophagogastroduodenoscopy
EOT	End-of-treatment
EQ	EuroQol
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	Gastrointestinal
H2RA	histamine-2 receptor antagonist
HCl	Hydrochloride
HS	heartburn severity
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IRB	Institutional Review Board

IWRS	interactive web response system
LA	Los Angeles
LDL-C	low-density lipoprotein cholesterol
LSM	least-square mean
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MMRM	mixed-effects model for repeated measures
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
PRO	patient-reported outcome
QD	once daily
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
WPAI	Work Productivity and Activity Impairment Questionnaire
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.(1-4) 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) A recent survey using the NIH PROMIS® GERD scale found that half of the North American general population reported heartburn symptoms in the last week, and one-third reported regurgitation symptoms in the last week.(9) GERD is associated with rising healthcare utilization and cost.(10) 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.(11) 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.(12)

There is significant evidence to support DGER as a putative mechanism for persistent GERD (also referred to as refractory 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.(12) There is considerable clinical and nonclinical evidence that bile acid can cause esophageal damage both in conjunction with stomach acid as well as independently.(2, 5)

In this study we require all patients to have acid reflux as confirmed by the Bravo™ reflux testing system, whereby a capsule that measures pH is inserted into the patient's esophagus at the time of the patient's screening esophagogastroduodenoscopy (EGD). Using this criterion will

avoid enrolling patients with functional (non-reflux-evident) forms of GERD, who would be less responsive to IW-3718 treatment.

1.2 IW-3718

Ironwood is developing IW-3718 as an adjunct to PPI therapy for treatment of persistent GERD (also referred to as refractory GERD) in patients whose heartburn and regurgitation symptoms are not resolved with PPI therapy alone. IW-3718 is a sustained-release engineered form of colesevelam hydrochloride (henceforth referred to as colesevelam), a bile acid sequestrant.

IW-3718 tablets are formulated as an extended-release, solid, oral-dosage form intended to extend the release of colesevelam into the stomach. As a result of the sustained release, colesevelam binds to the 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. Subsequently the bile acid-colesevelam complex will travel down the GI tract and be excreted without being absorbed.

The extended-release formulation in IW-3718 tablets is based on Assertio's Acuform® technology which utilizes swelling polymers to allow the tablet to be retained in the stomach for up to 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 released in the stomach and upper GI tract in a near zero-order manner. It's theorized that the resulting sustained levels of colesevelam in the stomach will prevent bile acids from refluxing into the esophagus. The Acuform technology is well-characterized, and currently utilized in several Food and Drug Administration (FDA)-approved drugs such as Glumetza® (metformin HCl, extended release), Proquin® XR (ciprofloxacin HCl monohydrate, extended release), and Gralise™ once-daily (gabapentin) tablets.

Colesevelam is an orally administered, non-absorbed, non-digestible polymer that binds bile acids in the GI tract. Colesevelam was initially approved in 2000 in the United States (US) as the active ingredient in Welchol™ and indicated 1) as an adjunct to diet and exercise for reduction of elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia (as monotherapy or in combination with statin therapy), 2) to reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia as

monotherapy or in combination with a statin after failing an adequate trial of diet therapy, and 3) to improve glycemic control in adults with type 2 diabetes mellitus. Colesevelam is currently available as an immediate-release formulation only for these indications. Colesevelam has also been approved for use in the EU as Cholestagel® (2004) and in Canada as Lodalis™ (2011).

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. 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.

Apart from the IW-3718 development program, 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).

1.3 IW-3718 CLINICAL TRIALS IN GERD PATIENTS

IW-3718 has been evaluated in 2 clinical trials in patients with continuing GERD symptoms despite their PPI treatment.

ICP-3718-201 was a 4-week, randomized, double-blind, placebo-controlled, proof-of-concept, Phase 2a 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. Esophagogastroduodenoscopy 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. A Bilitec™ device was used as an optional procedure for measuring bile reflux.

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%).

ICP-3718-202 was an 8-week, randomized, double-blind, placebo-controlled, dose-ranging, Phase 2b study in patients with continued GERD symptoms despite ongoing per-label QD PPI therapy. Patients were randomized in a 1:1:1:1 fashion to receive either IW-3718 500 mg, 1000 mg, or 1500 mg, or placebo twice daily while continuing their per-label QD PPI therapy. EGD and approximately 48 to 96 hours of pH monitoring (using the Bravo device) were required at Screening. Patients who either had significant acid regurgitation (pH<4 for ≥4.2 % of a 24-hour period) or esophageal erosion noted during the EGD were eligible for randomization. Randomization to double-blind treatment was stratified by whether patients had, or did not have, erosive esophagitis on the screening EGD. Bilitec monitoring of bilirubin levels was optional for all patients at selected sites.

Patients who completed screening entered the 14- to 21-day Pretreatment Period to promote patient familiarity and compliance with study procedures and to establish baseline patient-reported outcomes for the assessment of efficacy following treatment. Patients were instructed to take their PPI approximately 30-60 minutes before breakfast each day, even on study visit days. GERD symptoms were assessed daily using a modified version of the Reflux Symptom

Questionnaire Electronic Diary (mRESQ-eD). Patients who satisfied all of the entry criteria during the Pretreatment Period entered the 8-week Treatment Period. The primary endpoint was percent change from baseline to Week 8 in 6-point heartburn severity score (0=none, 5=severe). Secondary endpoints included percent change from baseline in heartburn severity score and 5-point regurgitation frequency score (0=never, 4=very often) by week, and overall heartburn responders and overall regurgitation responders. Responder criteria required at least a 30% decrease from baseline in weekly heartburn score (or regurgitation score) for at least 4 of 8 treatment weeks, including ≥1 of the 2 final weeks.

A total of 282 patient were randomized. The modified ITT Population included 280 patients (68-71 patients per treatment arm), approximately half (52%) of whom had EGD confirmation of erosive esophagitis (EE) at baseline (52%). Demographics and baseline characteristics were generally similar across the treatment groups. For the primary endpoint, dose-dependent improvements were observed in Week-8 heartburn severity scores; percent changes from baseline were -46.0, -49.0, -55.1, and -58.0 for the placebo, IW-3718 500 mg, 1000 mg, and 1500 mg treatment groups, respectively (dose-response test nominal p-value = 0.02). The treatment difference for the IW-3718 1500 mg group compared with placebo was -11.9 (nominal p-value = 0.04). Week-8 percent change from baseline in regurgitation frequency score was significantly better for the IW-3718 1500 mg group (-55.4) compared with placebo (-37.9) (difference -17.5; nominal p-value = 0.01). Numerical gains were seen at each week of treatment starting at Week 2 for heartburn severity for the IW-3718 1500 mg group versus placebo. Greater weekly improvements were seen at this dose in EE patients. Overall responder rates for heartburn and regurgitation were 52.9% and 46.3% for the IW-3718 1500 mg group compared with 37.1% and 34.3% for the placebo group, respectively; greater improvements compared with placebo were seen in EE patients (Table 1). Note that although a 30% reduction was defined in the protocol as being the criterion for a weekly improvement in WHSS and WRFS, pre- and post-hoc pooled anchor-based analyses suggested that a 45% reduction is better at defining a clinically significant response to treatment.

Table 1. Overall Heartburn and Regurgitation Responders (Study ICP-3718-202; Modified Intent-to-Treat Population)

	% Responders				
		IW-3718			
Parameter	Placebo w/ PPI	500 mg w/PPI	1000 mg w/PPI	1500 mg w/ PPI	Treatment Difference[1]
Heartburn					
≥ 30% Responder					
All patients (N=280)	54.3	52.1	62.0	66.2	11.9
EE patients (N=145)	47.2	50.0	59.5	69.4	22.2
≥ 45% Responder					
All patients (N=280)	37.1	43.7	42.3	52.9	15.8
EE patients (N=145)	30.6	41.7	32.4	50.0	19.4
Regurgitation[2]					
≥ 30% Responder					
All patients (N=277)	42.9	55.7	64.3	64.2	21.3
EE patients (N=142)	36.1	54.3	58.3	62.9	26.7
≥ 45% Responder					
All patients (N=277)	34.3	38.6	37.1	46.3	12.0
EE patients (N=142)	27.8	40,0	27.8	42.9	15.1

EE=erosive esophagitis; PPI=proton pump inhibitor
1. IW-3718 1500 mg compared with placebo
2. Patients with no regurgitation at baseline were excluded.

IW-3718 was well tolerated in patients with persistent GERD at twice-daily doses of 500 mg, 1000 mg, and 1500 mg. The most common TEAEs occurring in >5% of IW-3718 patients overall were constipation (8.1% of IW-3718 patients and 7.1% of placebo patients), nausea (6.2% of IW-3718 patients and 2.9% of placebo patients), and flatulence (5.7% of IW-3718 patients and 4.3% of placebo patients). There were 6 total SAEs (2 patients each in the placebo and 1500 mg IW-3718 groups, and 1 patient each in the IW-3718 500 mg and IW-3718 1000 mg groups) - all SAEs were assessed by the Investigator as unrelated to study treatment. Ten patients discontinued the study due to TEAEs, 3 patients each in the placebo, IW-3718 1000 mg, and IW-3718 1500 mg groups, and 1 patient in the IW-3718 500 mg group. No clinically significant changes were attributable to treatment with any of the IW-3718 treatment groups for any hematology, clinical chemistry, coagulation, urinalysis, vital signs, or ECG parameters, other than reduced total cholesterol and LDL-C, which is consistent with the known pharmacologic effects of colesevelam.

Based on the results of the ICP-3718-202 study, a twice-daily dose of 1500 mg IW-3718 was selected for further investigation in 2 Phase 3 trials.

2. STUDY OBJECTIVES

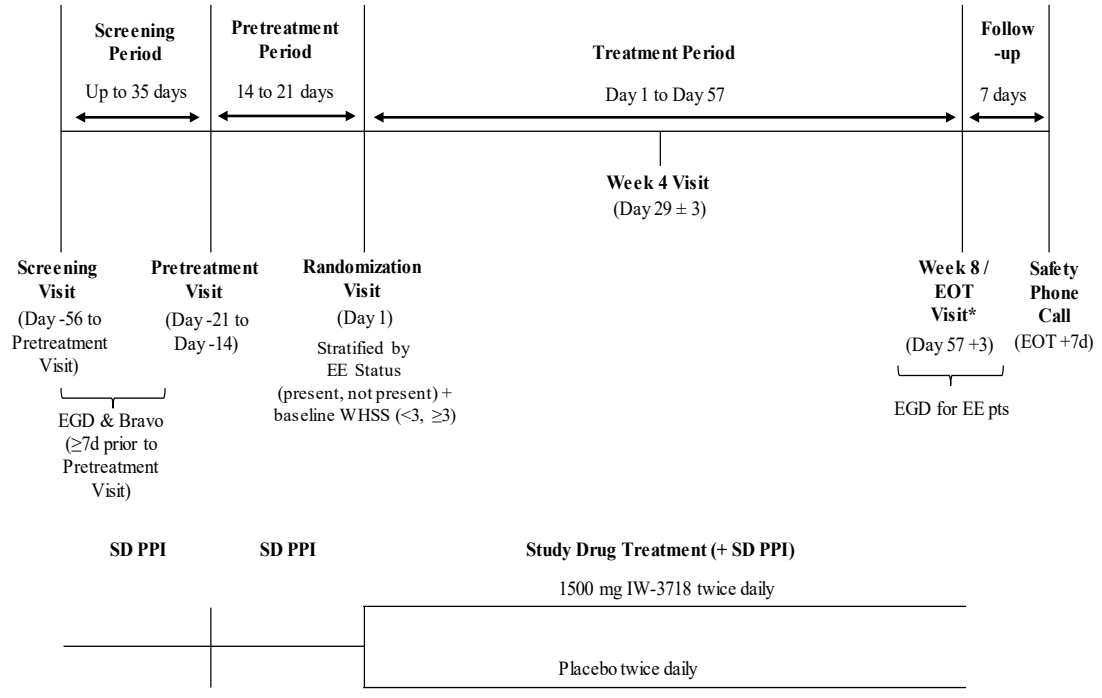
The objective of this study is to evaluate the safety and efficacy of IW-3718 administered to patients with GERD who continue to have persistent symptoms, such as heartburn and regurgitation, while receiving once-daily (QD), standard-dose PPIs.

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

The study consists of three distinct periods as illustrated in the figure below. The study will enroll patients whose heartburn and regurgitation symptoms are not resolved with once-daily (QD) PPI therapy alone. Eligible patients will continue to take their PPI and will be randomized to placebo or to 1500 mg IW-3718 BID.

Figure 1. Overview of Study Design



Note: There is no Day 0

* This visit represents the end of the study
EE = erosive esophagitis; EGD=esophagogastroduodenoscopy; EOT=end of treatment; SD PPI = standard dose proton pump inhibitor; WHSS = Weekly Heartburn Severity Score

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 meals each day.

Screening Period: The Screening Period starts with the signature of the informed consent form (ICF) and may last for up to 35 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 (all will be done while patients continue to take their PPI):

- An esophagogastroduodenoscopy (EGD)
- Up to 96 hours of pH testing with the Bravo device, a capsule-based pH monitor implanted above the lower esophageal sphincter (LES)

The patient must have been adherent to their standard PPI dosage regimen (as per product label) for the 8 weeks prior to the Screening Visit and during the entire Screening Period. Histamine-2 receptor antagonists (H2RAs) should be stopped at least 5 days prior to the EGD and Bravo pH monitoring; antacids should be stopped at least 1 day prior to the EGD and Bravo pH monitoring. The EGD must be performed during the Screening Period and should be performed 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 use antacids if needed until 1 day prior to entering the Pretreatment Period. The end of the Screening Period coincides with the start of the Pretreatment Period.

Pretreatment Period: The Pretreatment Period is defined as the 14 to 21 days immediately before the Randomization Visit. Patients who meet all eligibility criteria, including pH requirements as per the central pH read, will continue into the Pretreatment Period. 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 liquid antacid that is dispensed as rescue medicine (aluminum hydroxide / magnesium hydroxide). Patients will provide the following daily and weekly symptom assessments using a handheld electronic diary (eDiary):

Daily Assessments

- GERD symptoms, recorded in the evening before going to bed, using the modified Reflux Symptom Questionnaire Electronic Diary (mRESQ-eD; Appendix 1)
- Use of per-protocol rescue medicine, recorded in the evening before going to bed
- Sleep disturbance due to GERD symptoms, recorded upon getting up in the morning (Appendix 2)

Weekly Assessments

- Degree of relief of GERD symptoms (Appendix 3)
- GERD symptom bothersomeness (Appendix 3)

Patients will be required to complete the daily assessments for at least 5 days each week during the last 14 days before the Randomization Visit and the weekly assessments at least once during the last 7 days before the Randomization Visit in order to be eligible for randomization.

Patients will be instructed to take their PPI approximately 30-60 minutes before breakfast each day, even on study visit days. Patients who satisfy 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, EE on the screening EGD, and by their baseline weekly heartburn severity score (WHSS, defined as the average heartburn severity score over the last 7 days prior to randomization of <3 vs. ≥3; see Section 3.5.7.1) and randomly assigned within each stratum to placebo or 1500-mg IW-3718 BID (1:1). Dose reductions are not permitted. The treatment randomization schedule will be managed by a central vendor. Enrollment will be monitored to ensure that no single center contributes > 10% 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, assessment of sleep disturbance), weekly assessments (degree of relief of GERD symptoms, symptom bothersomeness, and treatment satisfaction questions). At the end of the treatment period study medication will be discontinued and patients will return for an End-of-Treatment visit. A repeat EGD will be performed at the Week 8/EOT Visit for all patients who have completed at least 4 weeks of treatment and had erosive esophagitis on the screening EGD (based on the Los Angeles [LA] classification of esophagitis, see Appendix 5) as determined by either the site personnel or the central reader. Patients will also complete all End-of-Treatment assessments.

For details regarding the assessments during each study period, see the Schedule of Evaluations in the protocol synopsis.

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

A double-blind, placebo-controlled, parallel-group, multicenter 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), 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 test therapy and to familiarize patients with data collection methodology (ie, 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

The study population will consist of adult patients with diagnosed GERD whose heartburn and regurgitation symptoms are not resolved with once-daily (QD) PPI therapy alone and have evidence of acid reflux during the Screening Period as determined using the Bravo device. Patients will be stratified for treatment assignment at the time of randomization based on the presence of esophageal erosions (erosions, no erosions) and by baseline WHSS (<3 vs. ≥3). The study will aim to enroll up to 50% of patients with esophageal erosions. Patients must be receiving 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 labelling. Approximately 660 patients (330 patients per treatment arm) will be randomized to treatment.

3.3.1 Eligibility Criteria

3.3.1.1 Inclusion Criteria

Each patient must meet all 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 male or female (if female, nonpregnant) and is at least 18 years old at the Screening Visit.

3. Patient has a diagnosis of GERD and reports experiencing GERD symptoms (heartburn or regurgitation) on average ≥ 4 days per week over the last 8 weeks before the Screening Visit.
4. Patient has been receiving 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 (see Appendix 7). Patients who have their PPI modified during the Screening Period may be re-screened after 8 weeks of standard-labeled dose, QD, PPI therapy provided they have not previously entered the Pretreatment Period.
5. Up to 96 hours of pH monitoring (with a Bravo device) during the Screening Period (while the patient continues taking their PPI) demonstrates 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 as confirmed by centralized review of pH monitoring.
6. During the last 7 days before randomization patient reports an average heartburn severity (HS, maximum of Items #1 and #2 on mRESQ-eD) of ≥ 2 (mild) and has a daily HS ≥ 3 (moderate) for at least 2 of those days.
7. Female patients must be postmenopausal for ≥1 year, surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]); or must agree to completely abstain from heterosexual intercourse; or, if heterosexually active, must agree to use 1 of the following methods of birth control from the date she signs the ICF until 24 hours after their final dose of study drug:
    a. Progesterone implant or an intrauterine device (IUD)
    b. Combination of 2 highly effective birth control methods (eg, diaphragm with spermicide plus a condom, condom with spermicide plus a diaphragm or cervical cap, hormonal contraceptive [eg, oral and transdermal patch] plus a barrier method, partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone or barrier method).
8. Females of childbearing potential must have a negative urine or serum pregnancy test at the Screening Visit and at the Randomization Visit prior to dosing. Positive urine test results will be confirmed by a serum pregnancy test.
9. Patient agrees not to make any changes to their usual diet or exercise regimen during the study
10. Patient is able to successfully use the eDiary, and has adequately completed the eDiary questions on at least 5 days each week and the weekly questions at least once during the 14 days before the start of the Treatment Period.

11. Patient is compliant with QD PPI dosing during the 14 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 at least one of the languages to be used for PRO assessments.
13. 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.
2. Patient reports epigastric pain or epigastric burning as his or her predominant symptom at the Screening Visit.
3. Patient has a diagnosis of gastroparesis per gastric emptying study, or a history of bowel obstruction, or is at risk for a bowel obstruction (eg, patient has an organic gastrointestinal [GI] motility disorders or a history of major GI surgery).
4. Patient has a history of serum triglyceride concentrations > 500 mg/dL on a fasting specimen, or has serum triglyceride 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; eg, the patient has osteoporosis or osteomalacia) and will be put at risk by receiving colesevelam for 8 weeks.
7. Patient has an active swallowing disorder that would compromise their ability to swallow the study medication.
8. Patient has any alarm symptoms including, but not limited to, GI bleeding, anemia, vomiting, or unexpected weight loss at 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, or minor oral or rectal surgery (eg, 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. Patient has large (>5 cm) hiatal hernia.
12. 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.
13. Patient has Gilbert's disease, Crohn's disease, diabetes mellitus (defined as A1C >6.5%), Zollinger-Ellison syndrome, pancreatitis, cholecystitis, or systemic sclerosis.
14. Patient has elevated (defined as > 1.5 times the upper limit of normal by the laboratory) levels of serum bilirubin at Screening.
15. Patient has a history of clinically significant hypersensitivity or allergies to any of the excipients contained in the study medication (active or placebo).
16. 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.
17. Patient has active substance abuse or history of chronic substance abuse (including alcoholism but not including nicotine) within 12 months before the Screening Visit or is positive for any of the following at the Screening Visit unless legally prescribed for anything but gastrointestinal pain: amphetamines, benzodiazepines, opiates, barbiturates, cocaine, or phencyclidine.

    Note: Marijuana use, whether prescribed or not, is prohibited from 30 days before screening through the duration of the study. Use of illicit drugs is not allowed during the study.
18. 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.)

19. 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.
20. 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.
21. 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.
22. Patient has previously entered the Treatment Period of an IW-3718 study.
23. Patient has previously entered the Pretreatment Period of this study. (Note: patients who failed the Pretreatment Period due to abnormal laboratory findings or timing issues may be re-screened.)
24. 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 Screening Failures

For all patients who are ineligible to participate in the trial, the reason for their screening failure will be recorded in the eCRF. Reasons for screening failure are as follows:

- Inclusion/Exclusion not met (specify)
- Protocol violation
- Withdrawal of consent
- Adverse event
- Lost to follow up
- Other (specify)

3.3.3 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:

- Adverse event(s)
- Non-compliance with study drug
- Protocol violation
- Withdrawal of consent
- Symptomatic deterioration
- Lost to follow-up
  (Note: every effort must be made to contact the patient; a certified letter must be sent.)
- Study termination by the Sponsor
- Physician decision
- Randomized in error
- Other reasons

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). Randomized patients who discontinue from the study for any reason should complete the assessments required at the EOT Visit at the time of their discontinuation. 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.

3.3.4 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 light blue-green, 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 hydroxytoluene, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C Blue #1, and iron oxide yellow. Tablets should be taken whole and never broken, crushed, or chewed.

Patients randomized to receive IW-3718 will self-administer the three 500 mg IW-3718 tablets 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 light blue-green, oval shaped, film-coated, oral tablets containing microcrystalline cellulose, polyethylene oxide, colloidal silicon oxide, butylated hydroxytoluene, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD&C Blue #1, and iron oxide yellow. Tablets should be taken whole and never broken, crushed, or chewed.

Patients randomized to receive placebo will self-administer the three placebo tablets BID immediately after the morning and evening meals.

3.4.1.3 Rescue Medicine

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

During completion of the nighttime eDiary 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) during the past 24 hours?"

3.4.1.4 Treatment Adherence

Patients will be dispensed the appropriate number of Sponsor-packaged, labeled bottles containing 210 tablets needed until the next study visit (see Section 3.6). Patients will be asked to return all bottles (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 210-count bottles. Study medication will be uniquely numbered and labeled in a double-blind fashion that conforms to regulatory requirements.

3.4.3 Storage and Stability

IW-3718 tablets and matching placebo will be shipped at controlled room temperature between 15°C and 25°C (59°F and 77°F) and must be stored at room temperature between 20°C and 25°C (68°F and 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°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.

Antacid rescue medicine (aluminum hydroxide / magnesium hydroxide liquid) will be supplied by the clinical sites and stored in accordance with the manufacturer's instructions.

3.4.4 Method of Assigning Patients to Treatment Groups

Eligible patients will be stratified by whether they have or do not have erosive esophagitis on the screening EGD, and by their baseline WHSS (<3 vs. ≥3), and then randomized through central randomization in a 1:1 ratio to receive either 1500 mg IW-3718 BID or placebo BID, both administered in addition to the patient's per-label QD PPI therapy.

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, an oral dose of 1500 mg IW-3718 BID (total daily dose of 3000 mg/day) given as an adjunct to QD PPI for 56 days, will be studied to evaluate the safety and efficacy of IW-3718 in a placebo-controlled study. Dose reductions are not permitted. This dose was selected for Phase 3 evaluation based on the results of Phase 2b Study ICP-3718-202. In that dose-ranging study, which evaluated IW-3718 doses of 500 mg, 1000 mg, and 1500 mg BID compared with placebo, dose-dependent improvement compared with placebo was observed for the primary endpoint, percent change from baseline in heartburn severity at Week 8. The 1500 mg dose showed an improvement in heartburn severity from baseline of -58.0 compared with a placebo improvement of -46.0 (nominal p-value = 0.04). Percent change from baseline in regurgitation frequency score at Week 8 was also significantly improved for IW-3718 1500 mg (-55.4) versus placebo (-37.9) (nominal p=0.01). Additional improvement for IW-3718 1500 mg relative to the IW-3718 500 mg and 1000 mg doses when compared with placebo were noted for other endpoints, including the heartburn and regurgitation responder endpoints; greater improvement was also noted for the IW-3718 1500 mg dose group within the EE subpopulation. IW-3718 1500 mg was generally well-tolerated in Study ICP-3718-202. The incidence of TEAEs for the IW-3718 1500 mg group (44.1%) was comparable to the overall IW-3718 incidence (46.2%) and to placebo (41.4%). There was a dose-related trend in the incidence of patients who had nausea (2.9%, 4.2%, 5.6%, and 8.8% of patients in the placebo, 500-mg, 1000-mg, and 1500-mg IW-3718 groups, respectively). Otherwise, no dose-related trends were noted for any TEAEs.

3.4.6 Selection and Timing of Dose for Each Patient

Patients will be randomized to receive 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 (ie, Day -21 through Day 57 [+ 3 days]). The PPI will be taken each day, approximately 30-60 minutes before breakfast.

During completion of the daily eDiary 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 (ie, 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 a PPI
- Most recent use of an H2RA
- Most recent use of an antacid

Any medication/procedure taken/undergone by a patient during the study (beginning at the Screening Visit through the Follow-up Phone Call), including any new medications/procedures added or changes in medications/procedures previously reported, and the reason for its use will be documented in the source documents and collected in the EDC system.

3.4.8.1 Rescue Medication

During the Pretreatment and Treatment Periods, patients may use dispensed, protocol-permitted liquid 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 Diet and Exercise

Per the inclusion criteria, patients must agree not to make any changes to their usual diet or exercise regimen during the study.

3.5 SAFETY AND EFFICACY ASSESSMENTS

Safety will be evaluated by adverse event (AE) reports (discussed herein), standard clinical laboratory assessments, vital signs, physical examinations, medical history, and ECGs. The timing of safety and efficacy assessments is presented in Section 3.6.

3.5.1 Adverse Events

3.5.1.1 Definitions

Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

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.

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

Serious Adverse Event

An AE is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening experience: An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization: AEs requiring hospital admissions that are less than 24 hours in duration do not meet this criterion. A

scheduled hospitalization for a preexisting condition that has not worsened during participation in the study does not meet this criterion. Preplanned hospitalizations for an elective medical/surgical procedure or routine check-ups do not meet this criterion.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly or birth defect
- Is considered an important medical event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Treatment-emergent Adverse Event

A treatment-emergent AE (TEAE) is an event that emerges, or a preexisting event that worsens, any time after administration of the first dose of study drug (Day 1).

3.5.1.2 Procedures for Recording Adverse Events

The Investigator will record all AEs from the time informed consent is obtained until completion of the Follow-up Phone Call. At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit.

The occurrence of an AE or SAE may come to the attention of site personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including SAEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product and to PPI (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All SAEs will be followed to adequate resolution or stabilization for up to a maximum of 30 days after last dose.

Any medical condition that is present when a subject is screened and does not deteriorate (worsen in severity and/or frequency) should be recorded as Medical History and not as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE. AEs characterized as intermittent require documentation of onset and duration of each episode.

Pretreatment AEs will be collected and captured in the subject's source documentation from the time the subject signs the ICF until the subject receives study drug. Pretreatment AEs in randomized patients will additionally be entered 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 subject's eCRF only if the Investigator considers them clinically significant and/or they necessitate intervention.

3.5.1.3 Procedures for Collecting and Reporting Serious Adverse Events

The Investigator or designee is to report any SAE to Ironwood Pharmacovigilance within 24 hours of becoming aware of the event that occurred during the reporting period.

All SAEs will be submitted using the safety reporting tool within the EDC system. The SAE report file will be generated and be available for download once the SAE is submitted by the investigator or designee via the EDC system. The investigator or designee will send by email the SAE report file as an attachment to Ironwood Pharmacovigilance. The system will prompt the Investigator or designee to provide as much information as possible, including the following:

- SAE term
- Serious criteria
- Severity
- Causality assessment to study drug and to PPI
- Action taken with study drug
- Narrative explaining the context of the SAE outcome

If all SAE information is not available at the time of the initial report, follow-up SAE reports will be completed and submitted within the same reporting timelines as initial reports using the EDC system. If the EDC system is not available, the Investigator or designee will complete the hard-copy SAE form, including all of the required information noted above. The completed form should then be provided to the Sponsor using the contact information below:

Ironwood Pharmacovigilance Contact Information

The Investigator or designee should receive confirmation from Ironwood that the SAE information (via EDC or hard-copy form) was received within 24 hours after its submission. In the event this receipt confirmation is not received, the Investigator or designee will alert Ironwood Pharmacovigilance.

The Investigator is required to follow SAEs until resolution or stabilization for up to a maximum of 30 days after last dose. Resolution is defined as:

- Resolved with or without residual effects (sequelae)
- A return to baseline for a preexisting condition
- The Investigator does not expect any further improvement or worsening of the event
- Fatal outcome: If an autopsy is performed on a deceased subject, the autopsy report and death certificate must be provided to Ironwood as soon as it is available.

3.5.1.3.1 Reporting of SAEs to the IRB

The Investigator will receive prompt notification of SAEs, with the use of the study product, that are both unexpected and related, or any finding that suggests a significant risk for patients. The Investigator will promptly inform the IRB of the notification and insert the notification in the Investigator's Regulatory Binder in accordance with local regulations.

All applicable expedited safety reports will be forwarded, by Ironwood, to the Investigator.

The Investigator will inform Ironwood of any local regulatory or IRB requirements not covered by the procedures in this or the prior section.

3.5.1.3.2 Reporting of Pregnancy

Any female patient who becomes pregnant while participating in the study will be withdrawn from the study.

Information on any pregnancies in female patients, or the female partner of a male patient, will be collected from the Screening Visit until the completion of the Follow-up Phone Call.

If the patient or the female partner of a male patient becomes pregnant after receiving study drug during the study, the Investigator will collect and record the pregnancy information on the Pregnancy Reporting Form and submit it via fax or e-mail to Ironwood Pharmacovigilance within 24 hours of learning of the pregnancy. (Note: If the female partner of a male patient becomes pregnant, the Investigator must attempt to obtain consent to collect pregnancy information [including status of the newborn, if applicable] before reporting information to Ironwood). If not all information on the Pregnancy Reporting Form is available at the time of the initial report, follow-up Pregnancy Reporting Forms will be completed and submitted via fax or e-mail to Ironwood Pharmacovigilance within 24 hours of becoming aware of new information.

The Investigator is required to attempt follow-up on the pregnancy until the completion of the pregnancy. Information on the status of the mother and newborn will be forwarded to Ironwood within 24 hours of the Investigator becoming aware. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be an SAE and reported as such. A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the Investigator, will be reported to Ironwood as described in Section 3.5.1.3. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

3.5.1.4 Recording Requirements

Severity

The Investigator or delegated physician 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*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. Severity will be assessed according to the following scale:

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

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

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

AEs should be recorded using the maximum intensity of the event (eg, if a patient reported nausea lasting 3 days, one start date and stop date should be recorded along with the maximum intensity experienced for that event over that 3-day timeframe).

Relationship to Study Drug and to PPI

The Investigator must assess the relationship of each AE (including SAEs) to the use of study drug or to ongoing PPI therapy using a 2-category scale (not related or related) based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, preexisting conditions, concomitant use of other drugs, and presence of environmental or genetic factors
- The temporal association between study drug/PPI exposure and onset of the AE
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product or PPI
- Whether the AE resolved or improved with stopping use of the study drug; judgment should be used if multiple products are discontinued at the same time

The causality assessment must be recorded in the patient's source documentation and on the AE page of the patient's CRF. The causal relationship between study drug and the AE will be assessed using the categories shown in Table 2.

Table 2. Adverse Event Causality

Category	Definition
Not related	An AE is not associated with study medication or PPI if: - Lack of a temporal relationship to study drug administration makes a causal relationship improbable (eg, the event did not occur within a reasonable time frame following administration of the study medication); and/or - Other causative factor(s) (eg, a preexisting clinical condition, other concomitant treatments) more likely explain the occurrence of the event, and - The event did not improve with stopping of the investigational product, and/or - The event did not recur upon re-exposure with investigational product
Related	An AE is attributed to the study medication or PPI if: - A temporal relationship to study drug administration makes a causal relationship plausible (eg, the event occurred within a reasonable time frame following administration of study medication); and/or - Other causative factor(s) (eg, the patient's clinical condition, other concomitant treatments) either do not explain the event or are less equally likely to have led to the occurrence of the event, or - The event improved with stopping of the investigational product, and/or - The event recurred upon re-exposure with investigational product

Laboratory Abnormalities

The Investigator will review clinical laboratory values for significance and consideration as an AE. All the following laboratory abnormalities should be captured as AEs:

- Any laboratory test result that meets criteria for an SAE
- Any laboratory abnormality that results in study discontinuation
- Any laboratory abnormality that requires the patient to receive specific corrective therapy
- Any laboratory abnormality that the Investigator considers to be clinically significant

Ongoing abnormal laboratory values/conditions that are being treated at baseline will be captured as an AE if the condition increases in severity and/or frequency during the study or if the condition requires more frequent treatment. If a patient is treated for an abnormal laboratory value just before the Screening Visit, then the medical history should reflect the severity of the condition before treatment.

3.5.1.5 Termination of Patients from the Study

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator will make reasonable efforts to keep each patient in the study. However, if the Investigator removes a patient from the study or if the patient declines further participation, the evaluations required at the Week 8/EOT Visit should be performed, if possible. All evaluations and observations, together with the description of the reason(s) for study withdrawal, must be recorded in the patient's source documentation and subsequently on the appropriate page of the patient's eCRF. The reasons for patient withdrawal from the study are provided in Section 3.3.3.

An effort must be made to determine why a patient fails to return or is dropped from the study. Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up should be recorded in source documents and reported where applicable on the eCRF. All reasons for discontinuation of treatment should be documented.

If a patient cannot be reached at the end of the trial for the Safety Phone Call, the site should make every effort to contact the patient, including sending a certified letter. In every case, the patient outcome, including lost to follow-up information, will be documented.

3.5.2 Medical and Disease History

A complete medical and disease history will be obtained as defined in the Schedule of Evaluations within the protocol synopsis.

3.5.3 Physical Examination, Body Weight, and Height

A physical examination will be obtained as defined in the Schedule of Evaluations. The physical examination of each patient should include examination and assessment of the following:

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

3.5.4 Electrocardiograms

A 12-lead ECG will be performed as defined in the Schedule of Evaluations within the protocol synopsis and documented on the eCRF. Electrocardiograms should be obtained after the patient has been supine for at least 5 minutes.

3.5.5 Vital Signs

Vital signs will be collected at the visits defined in the Schedule of Evaluations within the protocol synopsis. Respiratory rate, pulse, and BP readings will be taken after the patient has been seated for at least 5 minutes.

3.5.6 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected at the visits defined in the Schedule of Evaluations within the protocol synopsis. The clinical laboratory evaluations will include the clinical chemistry, hematology, coagulation, and urinalysis parameters presented in Table 3.

Table 3. Clinical Laboratory Tests

Clinical Chemistry	Hematology (CBC)	Complete Urinalysis
Albumin	Hematocrit	pH and specific gravity
Alkaline phosphatase	Hemoglobin	Bilirubin
ALT	Platelet count	Glucose
AST	MPV	Ketones
Bicarbonate	RBC count	Leukocytes
BUN	WBC count	Nitrites
Calcium	WBC differential	Occult blood
Chloride	(% and absolute)	Protein
Total cholesterol	Basophils	Urobilinogen
HDL cholesterol	Eosinophils	
LDL cholesterol	Lymphocytes	
Creatinine	Monocytes	
GGT	Neutrophils	
Glucose	RBC indices	
HbA1C	MCH	
Iron	MCHC	
LDH	MCV	
Magnesium	RDW	
Phosphorus	**Coagulation**	
Potassium	aPTT	
Sodium	PT	
Total bilirubin		
Total protein		
Triglycerides		
Uric acid		

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; GGT = gamma glutamyl transferase; HbA1C = glycated hemoglobin; 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 pregnancy test will be administered to all female patients of childbearing potential (ie, women who are not postmenopausal or who have not had a bilateral oophorectomy, hysterectomy, or tubal ligation) at the Screening, Randomization (prior to dosing), Week 4, and EOT Visits. These pregnancy test results must be negative for patient eligibility. All positive urine pregnancy tests results will be confirmed by a serum pregnancy test.

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

3.5.7 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.

3.5.7.1 Daily Assessments

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

- GERD symptom assessments (mRESQ-eD, Appendix 1) will be completed by the patient once daily, in the evening before bed.

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

  - 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
  - Difficulty swallowing
  - Hoarseness
  - Cough

  The following GERD symptoms 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

- Assessment of sleep disturbance due to GERD symptoms (Daily Sleep Disturbance due to GERD, Appendix 2), completed once daily upon getting up each morning (5:00 a.m. to 12:00 p.m.)
    - Last night, did you have trouble falling asleep because of GERD symptoms? [Yes/No]
    - Last night, how many times did you wake up during the night because of GERD symptoms? [0,1, 2, 3-5, 6 or more times]

- Use of per-protocol rescue medicine (antacid) will be completed by the patient once daily, in the evening before bed.
    - "How many times did you use your rescue medicine (liquid antacid) during the past 24 hours?"

- Heartburn severity is assessed once daily in the evening before bed on a 0-5 severity scale: 0=Did not have, 1=Very mild, 2=Mild, 3=Moderate, 4=Moderately severe, 5=Severe

3.5.7.2 Weekly Assessments

The following information will be entered into the eDiary once each week during an entry of the evening diary (see Appendix 3):

- Degree of relief assessment

  The following 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 pain or 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?

How would you rate your overall GERD symptoms over the past 7 days?

Compared to before you started this study, how would you rate your heartburn (a pain or burning sensation in your chest, behind the breastbone) over the past 7 days?

Compared to before you started this study, 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?

- Bothersomeness Assessment.

  The following items are 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 pain or burning sensation in your chest, behind the breastbone) over the past 7 days?

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 7 days?

How much were you bothered by your overall GERD symptoms over the past 7 days?

- Treatment Satisfaction Assessment

  The following items are 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?

3.5.7.3 Study Visit Assessments

The following assessments will be performed at the study visits indicated:

- WPAI-Sleep Disturbance-GERD

  The Work Productivity and Activity Impairment Questionnaire: Sleep Disturbance-GERD (WPAI-Sleep-GERD) includes questions about time lost from work, reduced productivity while at work, and reduced productivity while doing regular daily activities resulting from sleep disturbance due to GERD symptoms. Patients will complete the WPAI-Sleep-GERD at the Randomization Visit, the Week 4 Visit, and at the EOT Visit and will record their responses in the eDiary.

- EQ-5D-3L

  The EuroQol (EQ)-5D-3L is a generic measure of health widely used in Europe.(13) 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.(14) 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 and will record their responses in the eDiary.

3.5.8 Other Assessments

3.5.8.1 Esophagogastroduodenoscopy

All patients will be required to undergo an EGD during the Screening Period. There should be a minimum of 7 days between the EGD and the start of the Pretreatment Period to allow for pH testing and patient stabilization. EGDs will be interpreted by the local site personnel and by a central reader. Details are provided in a separate study manual (Image Acquisition Guidelines for Ironwood Pharmaceuticals, Inc. Protocols C3718-301/C3718-302; WorldCare Clinical).

An EGD will be performed at the Week 8 / EOT Visit in all patients who completed at least 4 weeks of treatment and had erosive esophagitis on the EGD obtained during the Screening Period (based on the Los Angeles [LA] classification of esophagitis [Appendix 5], as determined by either the site personnel or the central reader).

3.5.8.2 Bravo™

At all sites, all patients will undergo up 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. All patients will return to the site with their Bravo pH monitor after approximately 96 hours (or 48 hours where applicable) to return the recording device. To determine eligibility, a centralized review of pH monitoring will be conducted for each patient. Please refer to the Bravo Site Manual for specific instructions.

3.6 SCHEDULE OF EVENTS

The schedule of study procedures and assessments is presented by visit in the Schedule of Evaluations within the Protocol Synopsis. Procedures and assessments by study visit are provided in the following sections.

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

3.6.1.1 Screening Visit (Visit 1) Procedures

- Review of inclusion and exclusion criteria
- Signing of ICF
- Register visit in IWRS
- Demographics
- Medical and disease history
- Physical examination
- Body weight and height
- Begin H2RA and antacid washout (for 5 days before the EGD and Bravo pH monitoring [H2RA] and 1 calendar day before the EGD and Bravo pH monitoring [antacids])
- EGD (see Section 3.5.8.1)
- Up 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)
- 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, antacid, and PPI)
- Collection of blood and urine samples for clinical laboratory test, including:

  Clinical chemistry

  Hematology (complete blood count [CBC])

  Coagulation

  Urinalysis

- Pregnancy test for all female patients of childbearing potential (must be confirmed negative; positive urine test results will be confirmed via serum pregnancy test)
- Drug and alcohol screening, including a urine drug screen for selected drugs of abuse (cocaine, barbiturates, amphetamines, opiates, benzodiazepines, cannabinoids, and phencyclidine) and a serum alcohol screen
- AE evaluation (throughout the Screening Period)

3.6.1.2 Pretreatment Visit (Visit 2) Procedures

- Register visit in IWRS
- Review of inclusion and exclusion criteria
- Body weight
- Prior and concomitant medications and procedures
- AE evaluation (throughout the Pretreatment Period)
- Liquid antacid rescue medicine dispensation
- eDiary training and dispensation (for recording daily and weekly evaluations throughout the Pretreatment and Treatment Periods)

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 and procedures
- Collection of blood and urine samples for clinical laboratory tests, including:

  Clinical chemistry

  Hematology (CBC)

  Coagulation

  Urinalysis
- Pregnancy test for all female patients of childbearing potential (must be confirmed negative; positive urine test results will be confirmed via serum pregnancy test)
- AE evaluation (throughout the Treatment Period)

- Liquid antacid rescue medicine dispensation (if needed)
- Review eDiary
- WPAI-Sleep Disturbance-GERD
- 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 4 (Visit 4) Procedures

- Register visit in IWRS
- Body weight
- Seated vital signs
- Concomitant medications and procedures
- Collection of blood and urine samples for clinical laboratory tests, including:

  Clinical chemistry

  Hematology (CBC)

  Coagulation

  Urinalysis
- Pregnancy test for all female patients of childbearing potential (must be confirmed negative; positive urine test results will be confirmed via serum pregnancy test)
- AE evaluation (throughout the Treatment Period)
- Liquid antacid rescue medicine dispensation (if needed)
- Review eDiary
- WPAI-Sleep Disturbance-GERD
- EQ-5D-3L
- Study medication dispensed
- Return of all unused study medication

3.6.2.3 Week 8/End-of-treatment (Visit 5) Procedures

- Register visit in IWRS
- Physical examination
- Body weight
- EGD (A repeat EGD will be performed at the Week 8 / EOT Visit for all patients who have completed at least 4 weeks of treatment and had erosive esophagitis on the screening EGD [based on the LA classification of esophagitis, see Appendix 5] as determined by either the site personnel or the central reader; see Section 3.5.8.1)
- Seated vital signs
- 12-lead ECG
- Concomitant medications and procedures
- Collection of blood and urine samples for clinical laboratory tests, including:

  Clinical chemistry

  Hematology (CBC)

  Coagulation

  Urinalysis
- Pregnancy test for all female patients of childbearing potential (must be confirmed negative; positive urine test results will be confirmed via serum pregnancy test)
- AE evaluation (throughout the Treatment Period)
- Review eDiary
- WPAI-Sleep Disturbance-GERD
- EQ-5D-3L
- Return of all unused study medication
- Return eDiary

3.6.3 Follow-up Phone Call

The study site will contact all patients via telephone 7 days following the EOT Visit to collect information regarding ongoing AEs/SAEs/concomitant medications and any new AEs/SAEs/concomitant medications and procedures since the EOT Visit (Section 3.6.2.3). This information will be recorded via EDC.

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 3.6.2.3) at the time of their discontinuation.

3.7 STATISTICAL METHODS

Statistical analysis methods are summarized in the following sections. 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

Screened Population consists of all patients who signed informed consent and received a patient identification (PID) number.

Randomized Population consists of all patients who were assigned to a treatment group (placebo or IW-3718) via randomization.

Safety Population consists of all randomized patients who received at least 1 dose of study drug.

Modified Intent-to-Treat (mITT) Population consists of all randomized patients who received at least 1 dose of study drug and had at least 1 postbaseline primary efficacy assessment.

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 count and proportion of patients in each category. Unless otherwise specified, all confidence intervals will be 2-sided and with a confidence level of 95%. Details of the data handling methods will be specified in the SAP. Unless otherwise specified, the week prior to randomization will be considered the baseline for efficacy analyses. For safety analyses, the baseline value is defined as the last non-missing value measured before administration of study treatment. All statistical analyses will be performed using SAS® Version 9.4 (or later) for Windows.

3.7.3 Patient Disposition, Demographics, and Baseline Characteristics

The count and proportion of patients included in the Randomized, Safety, and mITT 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 (ie, patients who enter the Screening Period but not the Pretreatment Period) and pretreatment failures (ie, patients who enter the Pretreatment Period but are not randomized), along with the associated reasons for failure, will be tabulated overall for the Screened Population.

The count and proportion of patients who complete the study and who prematurely discontinue will be presented for each treatment group and overall for the Randomized 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 Randomized Population.

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

3.7.4 Efficacy Analyses

Table 4 and Table 5 provide the analysis time windows allowed for the efficacy analyses in the Pretreatment and Treatment Periods.

Table 4. Analysis Time Windows for Efficacy Analysis – Daily Assessments

Period	Analysis Week	Begins[a]	Ends[a]
Pretreatment (Baseline[b])	Week -2	Day -14	Day -8
	Week -1	Day -7	Day -1 (Day before randomization)
Treatment	Week 1	Day 1 (Day of Randomization)	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
	Week 9	Day 57	Day 63
	•••	•••	•••

a. Relative to the day of randomization (Day 1). There is no Day 0.
b. Baseline for efficacy parameters will be derived from the daily eDiary collected for Pretreatment Week -1 (Week -2 if data for Week -1 not available); specifically for the proportion endpoints (defined as days with the event of interest divided by the number of diary entry days), the last 14 days (Week -2 to Week -1) prior to day of randomization will be used.

Table 5. Analysis Time Windows for Efficacy Analysis – Weekly Assessments

Period	Analysis Week	Begins[a]	Ends[a]
Pretreatment (Baseline[b])	Week -2	Day -11	Day -5
	Week -1	Day -4	Day -1 (Day before randomization)
Treatment	Week 1	Day 7	Day 10
	Week 2	Day 11	Day 17
	Week 3	Day 18	Day 24
	Week 4	Day 25	Day 31
	Week 5	Day 32	Day 38
	Week 6	Day 39	Day 45
	Week 7	Day 46	Day 52
	Week 8	Day 53	Day 59
	Week 9	Day 60	Day 66
	•••	•••	•••

a. Relative to the day of randomization (Day 1). There is no Day 0.
b. Baseline for efficacy parameters will be derived from the eDiary collected for Pretreatment Week -1 (Week -2 if data for Week -1 not available)

3.7.4.1 Primary Efficacy Parameter

The primary efficacy parameter of the study is defined as the change from baseline at Week 8 in WHSS.

- The WHSS for a week is the average of the non-missing Daily Heartburn Severity Scores (DHSS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock.
- The DHSS for a day is the greater score of the 2 mRESQ items assessing heartburn severity ("Burning feeling behind the breastbone or in the center of the upper stomach" and "Pain behind the breastbone or in the center of the upper stomach") for that day. Where 1 of the 2 mRESQ heartburn severity items is missing for the day, the maximum will be the score of the remaining item; where both items are missing for the day, the DHSS will be missing.

3.7.4.2 Key Secondary Efficacy Parameters

There are 3 key secondary efficacy parameters. Hypothesis testing of these key secondary efficacy parameters (and the primary efficacy parameter) will be controlled for multiplicity.

1. Change from baseline at Week 8 in Weekly Regurgitation Frequency Score (WRFS)
   - The WRFS for a week is the average of the non-missing Daily Regurgitation Frequency Scores (DRFS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock.
   - The DRFS for a day is the greater score of the 2 mRESQ items assessing regurgitation frequency ("Regurgitation [liquid or food moving upwards toward your throat or mouth]" and "An acid or bitter taste in the mouth") for that day.
2. Overall Heartburn Responder: a patient who is a weekly heartburn responder for at least 4 weeks, including at least 1 of the last 2 weeks (Weeks 7 and 8), during the 8-week Treatment Period.
   - A weekly heartburn responder is a patient with a decrease from baseline of ≥ 45% in Weekly Heartburn Severity Score (WHSS).
   - Rules for missingness of data will be prespecified in the SAP finalized before database lock.
3. Proportion of heartburn-free days during the 8-week Treatment Period
   - Proportion of heartburn-free days is calculated as the number of heartburn-free (DHSS=0) days divided by the number of diary entry days.

3.7.4.3 Analysis Methods for Primary and Key Secondary Efficacy Parameters

For analysis of the primary efficacy and first key secondary efficacy parameters, continuous parameters (eg, change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. The IW-3718 group will be compared with the placebo group by employing a linear mixed-effects model for repeated measures (MMRM) framework with week (categorical), treatment group, week-by-treatment group and week-by-baseline value interactions, baseline esophagitis status (present vs. not present), and baseline WHSS (<3 vs. ≥3) as fixed-effect terms and baseline value as a covariate, with patient as a random effect. An unstructured covariance structure will be used. Least-squares mean (LSM) for each treatment group, LSM difference between the IW-3718 group and the

placebo group and a 95% confidence interval for the difference at Week 8, as well as the p-value for comparison versus placebo will be presented.

For analysis of responder parameters (ie, responder vs. non-responder), the counts and proportions of responders will be calculated for each treatment group. The proportions of responders between the IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for baseline esophagitis status (erosive esophagitis vs. no erosive esophagitis) and baseline WHSS (<3 vs. ≥3). The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between the IW-3718 group and the placebo group, as well as the CMH estimate of the odds ratio (IW-3718 over placebo) and a 95% confidence interval for the odds ratio, will also be presented.

Time-dependent proportion parameters, defined as days the event of interest occurs, divided by the number of eDiary entry days within the 8-week Treatment Period (eg, proportion of heartburn-free-days), will be analyzed using a Poisson model which is appropriate for count data. The analysis includes the treatment, the baseline esophagitis status (present vs. not present), baseline WHSS (<3 vs. ≥3), covariate of baseline proportion of event-free days, with the eDiary entry days adjusted in the model. In the case of overdispersion, a negative binomial model instead of Poisson regression will be implemented. Model estimates in difference between the rates for IW-3718 and placebo groups will be calculated with corresponding 95% confidence interval and p-value associated with the comparisons to placebo .

3.7.4.4 Controlling Type-I Error

To maintain an overall type-I error rate of 0.05, the primary and 3 key secondary efficacy parameters will be tested sequentially according to the following order, each at a 2-sided significance level of 0.05.

Order	Parameter
1	Change from Baseline at Week 8 in WHSS (primary)
2	Change from Baseline at Week 8 in WRFS
3	Overall Heartburn Responder
4	Proportion of Heartburn-free Days during the 8-week Treatment Period

Testing of subsequent parameters will not be performed unless all previous parameters have been tested statistically significant ($p \leq 0.05$).

3.7.4.5 Sensitivity Analysis of Primary Efficacy Parameter

For the primary parameter, change from baseline in WHSS at Week 8, a sensitivity analysis will be conducted; details will be provided in the SAP.

3.7.4.6 Handling of Missing Data

For the primary efficacy analysis, change from baseline at Week 8 in WHSS, no imputation will be performed on missing data. The WHSS will be computed as the average of daily scores for that week. Rules for the average calculation will be prespecified in the SAP finalized before database lock.

A pattern-mixture model with control-based pattern imputation will be implemented as a multiple imputation method to explore the effects of missing data on the primary efficacy parameter. The details of this approach will be provided in the SAP.

3.7.4.7 Exploratory Efficacy Parameters and Analysis Methods

Exploratory efficacy parameters will be explored outside of the formal testing procedures and not controlled for multiplicity.

Change or percent change for continuous parameters will be analyzed using the MMRM approach as described for the primary efficacy parameter, change from baseline at Week 8 in WHSS.

Categorical responder parameters will be analyzed using the CMH testing method as described for the key secondary efficacy analysis for Overall Heartburn Responder.

Time-dependent proportion parameters, defined as days the event of interest occurs, divided by the number of diary entry days within the 8-week Treatment Period (eg, proportion of heartburn-free-days), will be analyzed using a Poisson model which is appropriate for count data. The analysis is similar to that described for the key secondary efficacy analysis for the proportion of heartburn-free days during the 8-week Treatment Period.

The exploratory efficacy endpoints and proposed analysis methods are listed below:

Item No.	Exploratory Efficacy Endpoints	Analysis Methods
1.	Percent change from baseline at Week 8 in WHSS	MMRM for change from baseline at Week 8.
2.	Overall Heartburn Responders with baseline WHSS ≥3	CMH
3.	Change from baseline in proportion of days when heartburn did not occur (DHSS = 0) or was very mild (DHSS = 1) during the 8-week Treatment Period	Analysis of covariance (ANCOVA)
4.	Proportion of days when heartburn did not occur (DHSS=0) or was very mild (DHSS=1) during the 8-week Treatment Period	Poisson regression for proportions
5.	Percent change from baseline at Week 8 in WRFS	MMRM for change from baseline at Week 8.
6.	Change from baseline in proportion of days when regurgitation did not occur (DRFS = 0) or rarely occurred (DRFS = 1) during the 8-week Treatment Period	ANCOVA
7.	Proportion of regurgitation free (DRFS = 0) days during the 8-week Treatment Period	Poisson regression for proportions
8.	Proportion of days when regurgitation did not occur (DRFS=0) or rarely occurred (DRFS=1) during the 8-week Treatment Period	Poisson regression for proportions
9.	Overall Regurgitation Responder: a patient who is a Weekly Regurgitation Responder for at least 4 weeks, including at least 1 of the last 2 weeks (Weeks 7 and 8), during the 8-week Treatment Period • A Weekly Regurgitation Responder is a patient with a decrease of ≥ 45% from baseline in WRFS • A patient who reports DRFS for less than 4 days during a week will not be considered a Weekly Regurgitation Responder for that week	CMH
10.	Change from baseline at Week 8 in each mRESQ item	MMRM for change from baseline at Week 8.
11.	Proportion of nights with difficulty falling asleep due to GERD during the 8-week Treatment Period	Poisson regression for proportions
12.	Proportion of days with nighttime awakening (≥1 time) due to GERD during the 8-week Treatment Period	Poisson regression for proportions
13.	Degree of relief of heartburn/regurgitation/overall GERD symptoms responder: • Degree of relief responder: patient who reported a score of 1-Significantly Relieved or 2-Moderately Relieved on the Degree of Relief question for at least 4 weeks, including at least 1 of the last 2 weeks (Weeks 7 and 8), during the 8-week Treatment Period	CMH
14.	Change from baseline at Week 8 in heartburn/regurgitation/overall GERD symptoms bothersomeness	MMRM for change from baseline at Week 8.
15.	Proportion of days with rescue medication use during the 8-week Treatment Period	Poisson regression for proportions

Item No.	Exploratory Efficacy Endpoints	Analysis Methods
16.	Erosive esophagitis (EE) healed (not present) at Week 8	CMH
17.	Proportion of patients with erosive esophagitis (EE) improved by at least 1 grade at Week 8	CMH

Descriptive supportive summary for following variables will be generated for mITT population.

Item No.	Description of Summary
1.	Percent change from baseline in WHSS by week
2.	Percent change from baseline in WRFS by week
3.	Change from baseline in WHSS by week
4.	Change from baseline in WRFS by week
5.	Change from baseline in each mRESQ item by week
6.	Proportion of heartburn-free (DHSS=0) days by week
7.	Proportion of regurgitation-free (DRFS=0) days by week
8.	Proportion of days when heartburn did not occur (DHSS=0) or was very mild (DHSS=1) by week
9.	Proportion of days when regurgitation did not occur (DRFS=0) or rarely occurred (DRFS=1) by week
10.	Proportion of nights with difficulty falling asleep due to GERD by week
11.	Proportion of days with nighttime awakening (≥1 time) due to GERD by week
12.	Proportion of days with rescue medication use by week
13.	Degree of relief of heartburn/regurgitation/overall GERD symptoms by week
14.	Heartburn/regurgitation/overall GERD symptoms bothersomeness by week
15.	Treatment satisfaction by week
16.	Shift in erosive esophagitis (EE) grade from baseline at Week 8

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, clinical laboratory evaluations, vital signs, ECGs, and physical examination. For each safety parameter, the last non-missing assessment made before the first dose of study drug 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 occurred 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 severe TEAEs, study drug-related AEs, AEs leading to study drug discontinuation, and treatment-emergent SAEs will also be tabulated by SOC, preferred term, and treatment group. Listings will be provided for deaths (if any), SAEs, and AEs leading to study drug 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.

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 time point post baseline will also 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 calculations for the primary and key secondary efficacy parameters are based on results from patients with evidence of pathological acid reflux (positive baseline Bravo status) in Study ICP-3718-202, which had a similar study population as the current study.

The primary efficacy parameter is Change from Baseline at Week 8 in WHSS, and key secondary efficacy parameters include:

- Change from Baseline at Week 8 in WRFS
- Overall Heartburn Responder
- Proportion of Heartburn-free Days during the 8-week Treatment Period

Using data from patients in Study ICP-3718-202, we derived the estimated results at end of the study as follows:

Order of Hypothesis Testing	Parameter	Placebo (+ PPIs)	1500 mg IW-3718 (+ PPIs)
1	Change from Baseline at Week 8 in WHSS	N = 43 Mean = -1.58 SD = 1.20	N =51 Mean = -2.01 SD = 1.29
2	Change from Baseline at Week 8 in WRFS	N = 43 Mean = -0.81 SD = 1.12	N = 51 Mean = -1.26 SD = 0.91
3	Overall Heartburn Responder	18/49 = 36.7%	31/55 = 56.4%
4	Proportion of Heartburn-free Days during the 8-week Treatment Period	N = 48 Mean = 0.195 SD = 0.2822	N = 55 Mean = 0.268 SD = 0.2928

The efficacy parameters will be tested sequentially according to the above order at a 2-sided significance level of 0.05 so that the overall type-I error rate is maintained at 0.05 Based on bootstrap simulations, a sample size of 330 patients per group will provide approximately 99% power to detect a treatment difference between 1500-mg IW-3718 (while receiving PPIs) and placebo (while receiving PPIs) for the primary efficacy parameter, assuming the randomized population in this study is consistent with the selected population from Study ICP-3718-202. Power that is based on simulations for all type-I error controlling key efficacy parameters are presented in the table below. The 2-sample t-test was used for continuous parameters and the Chi-square test was used for the responder parameter.

Order of Hypothesis Testing	Parameters	Power for Fixed Sequence Testing
1	Change from Baseline at Week 8 in WHSS	99%
2	Change from Baseline at Week 8 in WRFS	99%
3	Overall Heartburn Responder	99%
4	Proportion of Heartburn-free Days during the 8-week Treatment Period	88%

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/IEC) must be approved by the IRB/IEC 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/IEC review and approval. However, the IRB/IEC 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 (ie, 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, the European Directive 2001/20/EC relating to the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use, and applicable regulatory requirements.

4.1 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE

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/IEC.

All IRB/IEC approvals must be dated and signed by the IRB/IEC Chairman or his or her designee and must identify the IRB/IEC 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/IEC approvals should be forwarded to Ironwood. All correspondence with the IRB/IEC should be maintained in the Investigator File.

No drug will be released to the site to dose a patient until written IRB/IEC 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/IEC. The Investigator must supply Ironwood with written documentation of the approval of the continued clinical research.

The IRB/IEC 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/IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC 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/ IEC for the purposes of obtaining and documenting consent.

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 trial will include approximately 100 study centers in the US and Canada. 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/IEC 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/IEC, 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 and the study monitoring plan. 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

This trial is one of 2 similar studies of IW-3718 that plan to enroll a combined population of approximately 1300 patients. 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, or qualified designee, 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.

The clinical site monitor (Ironwood or qualified designee) 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/IEC, or regulatory authority, the Investigator should make all requested study-related records available for direct access.

Ironwood or its designee will monitor the study in compliance with applicable government regulations with respect to GCP, the study monitoring plan, 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/IEC approval letter for the protocol and ICF
6. IRB/IEC-approved ICF to be used
7. IRB/IEC approval of recruitment advertising (if applicable)
8. A list of IRB/IEC 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/IEC 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/IEC 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/IEC. An Investigator must not make any changes in a study without IRB/IEC and Sponsor approval, except when necessary to eliminate apparent immediate hazards to the subjects. All protocol amendments must be submitted to the IRB/IEC and approved.
14. Responsibility Log
15. Other logs (eg, 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, 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/IEC, 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

1. Safaie-Shirazi S, DenBesten L, Zike WL. Effect of bile salts on the ionic permeability of the esophageal mucosa and their role in the production of esophagitis. Gastroenterology. 1975;68:728-33.
2. Kivilaakso E, Fromm D, Silen W. Effect of bile salts and related compounds on isolated esophageal mucosa. Surgery. 1980;87(3):280-5.
3. Nishijima K, Miwa K, Miyashita T, Kinami S, Ninomiya I, Fushida S, et al. Impact of the biliary diversion procedure on carcinogenesis in Barrett's esophagus surgically induced by duodenoesophageal reflux in rats. Ann Surg. 2004;240(1):57-67.
4. Nehra D, Howell P, Williams CP, Pye JK, Beynon J. Toxic bile acids in gastro-oesophageal reflux disease: influence of gastric acidity. Gut. 1999;44(5):598-602.
5. Bachir GS, Leigh-Collis J, Wilson P, Pollak EW. Diagnosis of incipient reflux esophagitis: a new test. South Med J. 1981;74(9):1072-4.
6. Vaezi MF, Richter JE. Contribution of acid and duodenogastro-oesophageal reflux to oesophageal mucosal injury and symptoms in partial gastrectomy patients [see comment]. Gut1468-3288. 1998;41:297-302.
7. Kono K, Takahashi A, Sugai H, Iizuka H, Fujii H. Trypsin activity and bile acid concentrations in the esophagus after distal gastrectomy. Dig Dis Sci. 2006;51(6):1159-64.
8. Gerson LB, Kahrilas PJ, Fass R. Insights Into Gastroesophageal Reflux Disease-Associated Dyspeptic Symptoms. Clin Gastroenterol Hepatol. 2011;9(10):824-33.
9. Cohen E, Bolus R, Khanna D, Hays RD, Chang L, Melmed GY, et al. GERD symptoms in the general population: prevalence and severity versus care-seeking patients. Dig Dis Sci. 2014;59(10):2488-96.
10. Friedenberg FK, Hanlon A, Vanar V, Nehemia D, Mekapati J, Nelson DB, et al. Trends in gastroesophageal reflux disease as measured by the National Ambulatory Medical Care Survey. Dig Dis Sci. 2010;55(7):1911-7.
11. Dickman R, Boaz M, Aizic S, Beniashvili Z, Fass R, Niv Y. Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. Journal of neurogastroenterology and motility. 2011;17(4):387-94.
12. Tack J, Koek G, Demedts I, Sifrim D, Janssens J. Gastroesophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's esophagus: acid reflux, bile reflux, or both? Am J Gastroenterol. 2004;99(6):981-877.
13. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy. 1990;16:199-208.
14. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care. 2005;43(3):203-20.

9. SPONSOR SIGNATURE

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial of Oral IW-3718 Administered to Patients with Gastroesophageal Reflux Disease while receiving Proton Pump Inhibitors
Study Number:	C3718-301
Final Date:	14 August 2020

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

If an electronic signature was obtained, it will appear on the final page of this document.

Signed: _____ Date: _____

[redacted]

10. INVESTIGATOR SIGNATURE

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Trial of Oral IW-3718 Administered to Patients with Gastroesophageal Reflux Disease while receiving Proton Pump Inhibitors
Study Number:	C3718-301
Final Date:	14 August 2020

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 MODIFIED REFLUX SYMPTOM QUESTIONNAIRE ELECTRONIC DIARY (MRESQ-ED)

Instructions: Please answer the following questions to help us understand the symptoms you experienced over the past 24 hours because of your reflux disease. For each question, please choose the answer most appropriate for you.

1.	Over the past 24 hours, how would you rate the severity of your burning feeling behind the breastbone or in the center of the upper stomach? *Did not have/ Very mild/ Mild/ Moderate/ Moderately severe/ Severe*
2.	Over the past 24 hours, how would you rate the severity of your pain behind the breastbone or in the center of the upper stomach? *Did not have/ Very mild/ Mild/ Moderate/ Moderately severe/ Severe*
3.	Over the past 24 hours, how would you rate the severity of your difficulty swallowing? *Did not have/ Very mild/ Mild/ Moderate/ Moderately severe/ Severe*
4.	Over the past 24 hours, how would you rate the severity of your hoarseness? *Did not have/ Very mild/ Mild/ Moderate/ Moderately severe/ Severe*
5.	Over the past 24 hours, how would you rate the severity of your cough? *Did not have/ Very mild/ Mild/ Moderate/ Moderately severe/ Severe*
6.	Over the past 24 hours, how often did you experience regurgitation (liquid or food moving upwards towards your throat or mouth)? *Never/ Rarely/ Sometimes/ Often/ Very often*
7.	Over the past 24 hours, how often did you experience an acid or bitter taste in the mouth? *Never/ Rarely/ Sometimes/ Often/ Very often*
8.	Over the past 24 hours, how often did you experience burping? *Never/ Rarely/ Sometimes/ Often/ Very often*

APPENDIX 2 OTHER DAILY ASSESSMENTS

Heartburn

The following question will be answered by the patient in the evening diary.

Over the past 24 hours, how would you rate the severity of your heartburn?

0=Did Not Have, 1=Very Mild, 2=Mild, 3=Moderate, 4=Moderately Severe, 5=Severe

Sleep Disturbance due to GERD

The following questions will be answered by the patient upon getting up each morning (5:00 a.m. to 12:00 p.m.) using the eDiary:

Falling Asleep

Last night, did you have trouble falling asleep because of GERD symptoms?

[Yes, No]

Awakenings

Last night, how many times did you wake up during the night because of GERD symptoms?

0
1 time
2 times
3-5 times
6 or more times

APPENDIX 3 WEEKLY ASSESSMENTS

Degree of Relief Assessments

***Administered weekly during Pretreatment and Treatment Periods*:**

How would you rate your heartburn (a pain or 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?

How would you rate your overall GERD symptoms over the past 7 days?

Compared to before you started this study, how would you rate your heartburn (a pain or burning sensation in your chest, behind the breastbone) over the past 7 days?

Compared to before you started this study, 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?

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

Bothersomeness Assessments

***Administered weekly during Pretreatment and Treatment Periods*:**

How much were you bothered by heartburn (a pain or burning sensation in your chest, behind the breastbone) over the past 7 days?

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 7 days?

How much were you bothered by your overall GERD symptoms over the past 7 days?

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

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

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 days before the EGD and Bravo pH monitoring; a 14-day washout means that the particular medicine is not allowed during the 14 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]) (eg, cimetidine, ranitidine, famotidine, and nizatidine).

14-DAY WASHOUT

- Bile acid sequestrants (eg, Welchol [colesevelam], cholestyramine, and colestipol)
- Drugs with a known drug-drug interaction or a potential for a drug-drug interaction with colesevelam (cyclosporine, olmesartan medoxomil, phenytoin, warfarin)
- Drugs with a narrow therapeutic index (eg, warfarin, theophylline)
- Prokinetic agents (eg, metoclopramide, tegaserod, erythromycin); anti-cholinergic and anti-muscarinic agents (eg, dicyclomine, flavoxate, scopolamine, hyoscyamine, propantheline, oxybutynin, tolterodine, solifenacin, darifenacin, and trospium)
  [Note: inhaled ipratropium and tiotropium are permitted]
- Antipsychotic agents (eg, risperidone, haloperidol, droperidol, chlorpromazine, perphenazine, all phenothiazines, quetiapine, olanzapine, clozapine)
- GABAergics (eg, baclofen, valproic acid, gabapentin, pregabalin, benzodiazepine)

- Calcium channel blockers (eg, verapamil, nifedipine, diltiazem, amlodipine, felodipine, nicardipine, nimodipine, nisoldipine)
- Beta blockers (eg, metoprolol, timolol, atenolol, betaxolol)
- All narcotics either alone or in combination (eg, tramadol, codeine, morphine, propoxyphene, loperamide, diphenoxylate)
  [Note: narcotics used as anesthesia for an EGD require a 7-day wash-out prior to the patient entering into the Pretreatment Period.]
- Tricyclic antidepressants (eg, amitriptyline, imipramine, and nortriptyline)
  [Note: Patients may take another single antidepressant (such as a selective serotonin reuptake inhibitor, 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 (eg, 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 and continue to take their PPI through the EOT visit. PPIs that are formulated in combination with other drugs are not permitted (eg, Zegerid® [omeprazole/sodium bicarbonate], Vimovo® [esomeprazole/naproxen]).

Daily use of estrogens and/or low-dose aspirin (up to 162 mg/day) is permitted if, after an appropriate evaluation (eg, 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.

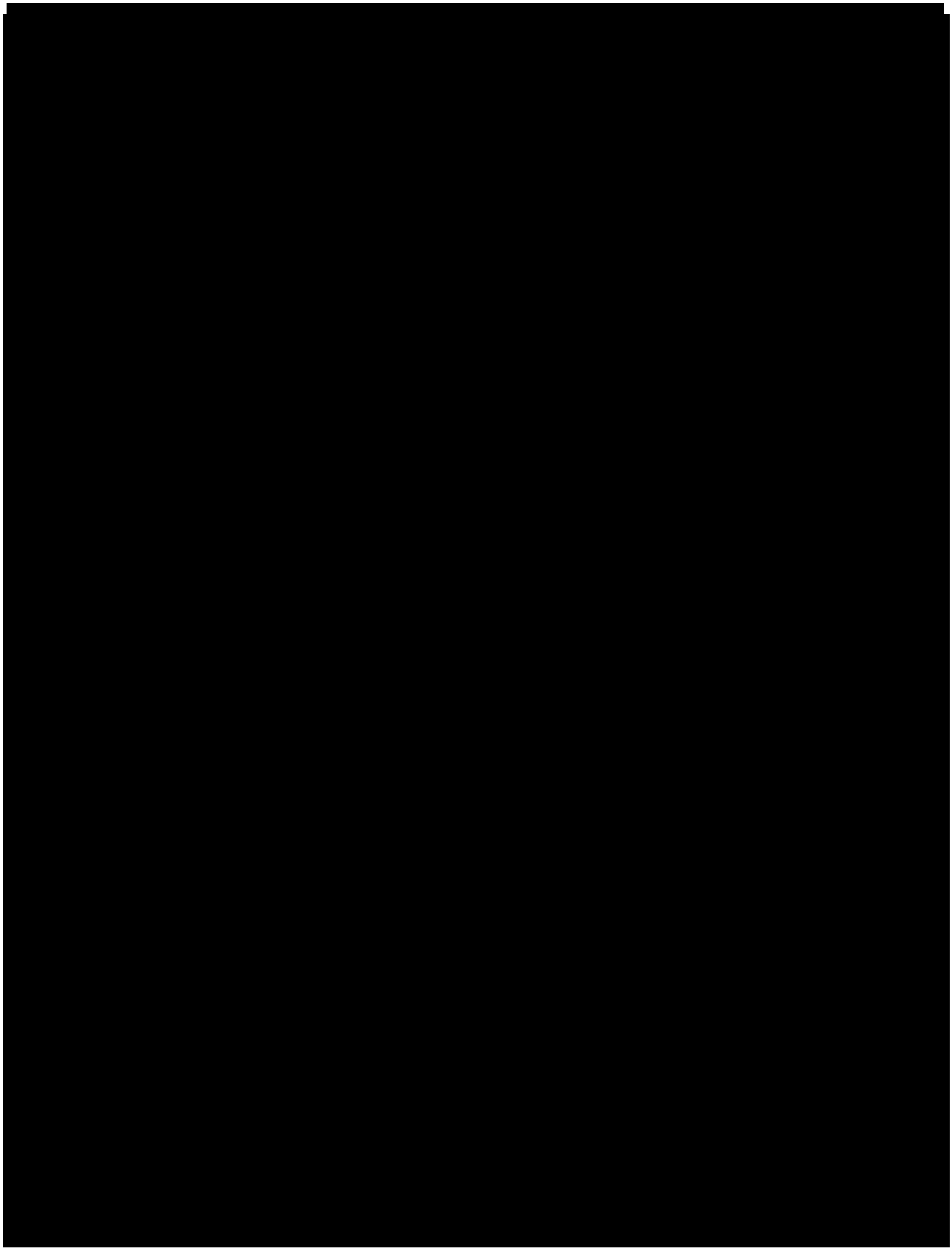
Oral contraceptives containing ethinyl estradiol and norethindrone were shown not to have a drug-drug interaction with IW-3718 (see the IW-3718 Investigator's Brochure, Edition 5, dated 10 March 2020). All female patients of childbearing potential may use oral contraceptives with the ingredients listed above as birth control and must agree to use an additional form of contraception, from the date they sign the ICF until 24 hours after their final dose of study drug (eg, condom).

APPENDIX 5 LOS ANGELES CLASSIFICATION OF ESOPHAGITIS

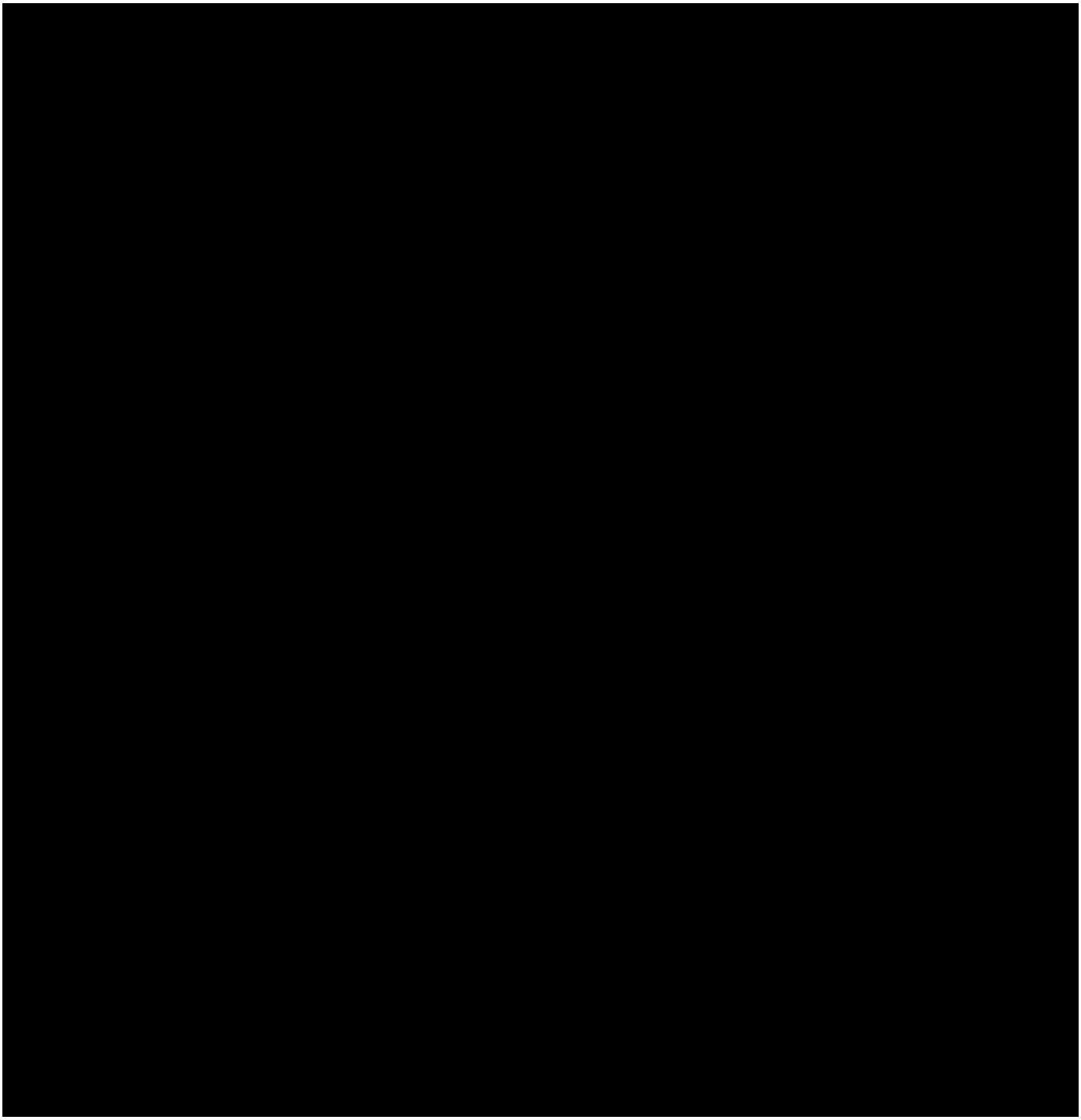
Classification	Definition
Not Present	No breaks (erosions) in the esophageal mucosa. (However, edema, erythema, or friability may be present.)
Grade A	One or more mucosal breaks not more than 5 mm in maximum length.
Grade B	One or more mucosal breaks more than 5 mm in maximum length, but not continuous 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 IN-CLINIC ASSESSMENTS

EQ-5D-3L



Work Productivity and Activity Index (WPAI) - Sleep Disturbance - GERD



APPENDIX 7 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 they represent standard, labeled-dose PPI treatment.
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.

The data and information related to my line function, which has been included with this file, are truthful and accurate.

Approval	[redacted]
Approval	[redacted]

Signature Page for VV-CLIN-001305
v3.0

Summary of Changes for Protocol Amendment 1: C3718-301

Final Version, 23 June 2018

Ironwood Substance Identifier:		IW-3718	
Protocol Number:		C3718-301	
Original Protocol Date:		15 March 2018	
Protocol Amendment 1	**Date** 23 June 2018	**Regions** United States Canada EU	**Sites** All Sites

SPONSOR SIGNATURE

If an electronic signature was obtained, it will appear on the final page of this document.

Signature: _____ Date: _____

TABLE OF CONTENTS

SPONSOR SIGNATURE 2
1. SUMMARY OF THE PROTOCOL AMENDMENT 4
2. PROTOCOL SECTION(S) CHANGED 5

1. SUMMARY OF THE PROTOCOL AMENDMENT

A summary of the protocol sections that have been amended are listed below:

- Updated proposed indication wording & sponsor contact on protocol cover page
- Revision of the Study Schema
- Specified rescue medication to be used and that sites will obtain and provide it to patients
- Clarified that patients will be stratified by the presence or not of erosive esophagitis and their baseline heartburn severity
- Noted where appropriate that an EGD must be completed at the End-of-Treatment (EOT) Visit for all patients who had evidence of erosive esophagitis
- Clarified that patients with cholecystectomy are eligible if procedure was ≥6 months prior to Screening
- Updated list of key secondary and additional endpoints
- Made additional updates to the statistical methods, including updates to sample size calculations
- Clarified that SAEs will be followed to adequate resolution or stabilization for up to a maximum of 30 days after last dose
- Expanded reference to collection of concomitant medications to “concomitant medication/therapy”
- Updated sections regarding the recording of screen failures and patients who prematurely discontinue from the trial
- Updated AE recording to capture of the relationship of AEs to to ongoing PPI therapy
- Other editorial and formatting changes to improve protocol readability and utility

2. PROTOCOL SECTION(S) CHANGED

The protocol sections that were amended are detailed in the table below. The relevant section and page number is referenced as well as the description of the change.

The table below contains a list of major changes from original clinical protocol C3718-301 to amended protocol C3718-301.

Item #	Section	Description of Change
1	Cover Page - Indication	*New Text:* "IW-3718 is indicated as an adjunct to proton pump inhibitors to treat persistent gastroesophageal reflux disease symptoms such as heartburn and regurgitation that are not resolved with proton pump inhibitor therapy alone." *Old Text:* "Gastroesophageal reflux disease (GERD) with persistent symptoms such as heartburn and regurgitation while receiving proton pump inhibitor (PPI) therapy"
2	Sponsor Contact & Identification	*New Sponsor Contacts:* [redacted]
3	Sudy Synopsis - Study Schema	The study schema was updated for clarity.
4	Sections: Synopsis, Schedule of Evaluations, and Sections 3.1, 3.4.1, 3.6.1, 3.6.2	Clarified information regarding rescue medication type (liquid aluminum hydroxide / magnesium hydroxide) and that the clinical sites will supply to enrolled study patients.

Item #	Section	Description of Change
5	Synopsis, and Sections 3.1, 3.4.4, 3.7.4.4,	Clarified that patients will be stratified by the presence or not of erosive esophagitis and their baseline heartburn severity. *Revised text (Synopsis):* "Patients will be stratified by whether they have, or do not have, erosive esophagitis on the screening EGD, and by their baseline heartburn severity level (average heartburn severity score over the last 7 days prior to randomization of <3 vs. ≥3; see Criteria for Evaluation) and randomly assigned within each stratum to placebo or 1500 mg IW-3718 BID (1:1)."
6	Synopsis, Sections 3.1, 3.5.8.1, 3.6.2.3	Clarified that an EGD must be completed at the End-of-Treatment (EOT) Visit for all patients who had evidence of erosive esophagitis and who completed at least 4 weeks of study drug treatment. *Revised text (Section 3.1):* "At the end of the treatment period study medication will be discontinued and patients will return for an End-of-Treatment (EOT) Visit. All patients who have erosive esophagitis (LA classification A-D) on EGD at Screening and completed ≥4 weeks of treatment will have a repeat EGD at their EOT Visit."
7	Synopsis, Section 3.3.1.2	Study Eligibility Criteria: Revised inclusion criteria wording to permit a single weekly eDiary entry during the 14 days prior to the Treatment Period. Revised Inclusion Criteria #10: Patient is able to successfully use the eDiary, and has adequately completed the eDiary questions on at least 5 days each week and the weekly questions at least once during the 14 days before the start of the Treatment Period.

Item #	Section	Description of Change
		Corrected wording of exclusion criteria #9 that patients who had cholecystectomy within 6 months before the Screening Visit were ineligible. Corrected wording in Section 3.3.1.1 to match criteria within the Study Synopsis. Revised Text Exclusion Criteria #9: 1. 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
8	Synopsis and Section 3.7.4.2 and 3.7.4.3	Modified the Key and Additional Secondary Endpoints: *Added* Overall Heartburn Responder – patients with a baseline weekly heartburn severity score (WHSS) ≥ 3 and the first key secondary endpoint. *Replaced* Overall Regurgitation Responder with the Proportion of Heartburn-free Days during the 8-week Treatment Period and the 4th key secondary endpoint. Made changes to the list of planned additional secondary endpoints.
9	Section 3.7.4.4	*Revised wording:* "Cumulative distribution function (CDF) of percent change from baseline to Week 8 in WHSS and WRFS will be plotted by treatment group."
10	Synopsis, and Sections 3.7.4.8, 3.7.7	Revised sample size calculations based on Phase 2b study results and the addition of the Overall Heartburn Responder as a key secondary endpoint. Added details regarding the

Item #	Section	Description of Change
		handling of missing data. Updated list of planned additional efficacy parameters.
11	Sections 3.5.1.2	Clarified that SAEs will be followed for a maximum of 30 days following the last dose of study drug. *Revised text:* "All SAEs will be followed to adequate resolution or stabilization for up to a maximum of 30 days after last dose."
12	Sections 3.5.1.2, 3.6	Expanded reference to collection of concomitant medications to "*concomitant medication/therapy*"
13	Section 3.3.2 and Section 3.5.1.5	*Added* Screen Failures (Section 3.3.2) detailing instructions for recording screen failure information on the eCRF. Modified Section 3.5.1.5 to eliminate redundance with new section.
14	Section 3.3.3	Updated wording regarding the reasons for removal of patients from therapy or assessment.
15	Section 3.5.1	Updated AE recording to include the capture of the relationship of AEs to study drug and to ongoing protocol pump inhibitor (PPI) therapy.
16	Section 3.5.7	Updated wording and layout of Efficacy Assessment section for clarity.
17	Appendix 1	Reformatted mRESQ-eD tool for clarity.
18	Entire Document	Small editorial and formatting changes were made to improve protocol readability.

The data and information related to my line function, which has been included with this file, are truthful and accurate.

Approval	[redacted]

Signature Page for VV-CLIN-002056
v2.0

Summary of Changes for Protocol Amendment 2: C3718-301

Final Version, 14 August 2020

Ironwood Substance Identifier:		IW-3718	
Protocol Number:		C3718-301	
Original Protocol Date:		27 March 2018	
Protocol Amendment 1	Date 23 June 2018	Regions United States Canada EU	Sites All Sites
Protocol Amendment 2	Date 14 August 2020	Regions United States Canada	Sites All Sites

SPONSOR SIGNATURE

If an electronic signature was obtained, it will appear on the final page of this document.

Signature: _____ Date: _____

[redacted]

TABLE OF CONTENTS

SPONSOR SIGNATURE....2
1. SUMMARY OF THE PROTOCOL AMENDMENT....4
2. PROTOCOL SECTIONS CHANGED....5

1. SUMMARY OF THE PROTOCOL AMENDMENT

The major protocol revisions are listed below:

- In accordance with guidance from the US FDA, the primary and key secondary efficacy endpoints have been changed. The analytical methods, including sequential testing to control Type-I error, have been updated accordingly.
- To support the anchor-based analyses corresponding to the 'Change from baseline at Week 8' endpoints, 3 weekly 'Degree of Relief' patient-reported items were added. These 3 new items ask the patient to compare their current degree of relief to that experienced before the start of the study.
- The power calculations for the sample size were recalculated to reflect the new primary and key secondary efficacy parameters.
- Endpoints listed as "Additional Secondary Efficacy Parameters" and the "Additional Efficacy Parameters" were consolidated into a new section "Exploratory Efficacy Parameters". New exploratory endpoints were added.
- Changes were made to one of the study's eligibility criteria for consistency between the synopsis and body of the protocol.
- Enrollment of patients without esophageal erosions was revised to state that the study will aim to enroll up to 50% of patients with esophageal erosions.
- Updates were made to the prohibited medication and concomitant medication guidance.
- The Sponsor's study contact information was updated.

2. PROTOCOL SECTIONS CHANGED

The table below contains a list of changes from Protocol C3718-301 Amendment 1 to Protocol C3718-301 Amendment 2.

Item #	Section	Page #	Description of Change
1.	Sponsor Contact & Identification	1, 17	*New address:* Ironwood Pharmaceuticals, Inc. 100 Summer Street, Suite 2300 Boston, MA 02110, USA *New Medical Monitor:* [redacted] *New Drug Safety Physician (Serious Adverse Event [SAE] Reporting):* [redacted]

Item #	Section	Page #	Description of Change
2.	Study Synopsis, Study Centers	2	The European Union (EU) was removed from the list of countries with study centers.
3.	Study Synopsis, Methodology	2	The figure showing the Overview of Study Design indicated that randomization will be stratified by baseline erosive esophagitis. This was updated to denote that randomization will be stratified by baseline erosive esophagitis status (present, not present) and by Weekly Heartburn Severity Score (WHSS; <3, ≥3).
4.	Study Synopsis, Methodology, Screening Period	3	A correction was made to the duration of time that patients must be adherent to their PPI regimen (*italic* and ~~strikethrough~~ text represent a change from the previous version): The patient must have been adherent to their standard PPI dosage regimen (as per product label) for the ~~30 days~~ *8 weeks* prior to the Screening Visit and during the entire Screening Period.
5.	Study Synopsis, Study Population	4	Enrollment of patients without esophageal erosions was revised to state that the study will aim to enroll up to 50% of patients with esophageal erosions.
6.	Study Synopsis, Criteria for Evaluation, Other Efficacy Assessments	9	Three weekly 'Degree of Relief' patient-reported items were added. These 3 new items ask the patient to compare their current degree of relief to that experienced before the start of the study: Degree of Relief of heartburn, regurgitation, and overall GERD symptoms on 7-point patient global impression of change scale (compared to before you started the study; 1=significantly relieved, 4=unchanged, 7=significantly worse)
7.	Study Synopsis, Statistical Methods, Analysis Populations	10	The Analysis Populations were modified as follows (*italic* and ~~strikethrough~~ text represent a change from the previous version): The **Screened Population** consists of all patients who *signed informed* consent *and received a patient identification (PID) number* ~~to participate in the study~~. The **Randomized Population** consists of all patients who ~~are randomly~~ *were* assigned *to a treatment group (placebo or IW-3718) via randomization* ~~either placebo or 1500 mg IW-3718~~. The **Safety Population** consists of all *randomized* patients who receive*d* at least 1 dose of study *drug* ~~treatment~~.

Item #	Section	Page #	Description of Change
			The **modified Intent-To-Treat (mITT) Population** consists of all randomized patients who receive*d* at least ~~one~~ *1* dose of study ~~treatment~~ *drug* and ~~have~~ *had* at least *1 postbaseline primary efficacy assessment.* ~~one daily heartburn severity assessment post baseline~~ ~~The Per-Protocol (PP) Population is defined as those patients in the mITT Population who have a minimum of 6 weeks of daily heartburn severity assessments and ≥80% compliance with study treatment and the PPIs for the period during which they are on study.~~
8.	Study Synopsis, Statistical Methods, Primary Efficacy Parameter	10	The Primary Efficacy Parameter was changed from "Overall Heartburn Responder" to: Change from baseline at Week 8 in Weekly Heartburn Severity Score (WHSS). • The WHSS for a week is the average of the non-missing Daily Heartburn Severity Scores (DHSS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock. • The DHSS for a day is the greater score of the 2 mRESQ items assessing heartburn severity ("Burning feeling behind the breastbone or in the center of the upper stomach" and "Pain behind the breastbone or in the center of the upper stomach") for that day. Where 1 of the 2 mRESQ heartburn severity items is missing for the day, the maximum will be the score of the remaining item; where both items are missing for the day, the DHSS will be missing.
9.	Study Synopsis, Statistical Methods, Key Secondary Efficacy Parameters	10-11	The Key Secondary Efficacy Parameters were changed from: 1. Overall Heartburn Responder – patients with a baseline WHSS ≥ 3 2. Percent change from baseline to Week 8 in WHSS 3. Percent change from baseline to Week 8 in Weekly Regurgitation Frequency Score (WRFS) 4. Proportion of heartburn-free days during the 8-week Treatment Period. to: 1. Change from baseline at Week 8 in Weekly Regurgitation Frequency Score (WRFS)

Item #	Section	Page #	Description of Change
			• The WRFS for a week is the average of the non-missing Daily Regurgitation Frequency Scores (DRFS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock. • DRFS for a day is the greater score of the 2 mRESQ items assessing regurgitation frequency ("Regurgitation [liquid or food moving upwards toward your throat or mouth]" and "An acid or bitter taste in the mouth") for that day. 2. Overall Heartburn Responder: a patient who is a weekly heartburn responder for at least 4 weeks, including at least 1 of the last 2 weeks (Weeks 7 and 8), during the 8-week Treatment Period. • A weekly heartburn responder is a patient with a decrease from baseline of ≥ 45% in Weekly Heartburn Severity Score (WHSS). • Rules for missingness of data will be prespecified in the SAP finalized before database lock. 3. Proportion of heartburn-free days during the 8-week Treatment Period. • Proportion of heartburn-free days is calculated as the number of heartburn-free (DHSS=0) days divided by the number of diary entry days.
10.	Study Synopsis, Efficacy Analysis Methods	11	*Previous text:* For analysis of the primary efficacy parameter and other 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 the IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for esophagitis status (erosive esophagitis vs. no erosive esophagitis), baseline heartburn severity level (<3 vs. ≥3), and geographic region. The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between the IW-3718 group and the placebo group, as well as the CMH estimate of the odds ratio (IW-3718 over placebo) and a 95% confidence interval for the odds ratio, will also be presented. For analysis of continuous parameters (e.g., percent change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. The IW-3718 group will be compared with the placebo group by employing a mixed model for repeated

Item #	Section	Page #	Description of Change
			measures (MMRM) framework with week (categorical), treatment group, week-by-treatment group, esophagitis status, and geographic region as fixed-effect terms and baseline value as a covariate (if applicable). A compound symmetry covariance structure will be used. Least-squares mean (LSM) for each treatment group, LSM difference between the IW-3718 group and the placebo group and a 95% confidence interval for the difference, as well as the p-value for comparison versus placebo will be presented. Cumulative distribution function (CDF) of percent change from baseline to Week 8 in WHSS and WRFS will be plotted by treatment group. To interpret the graphical representation of the CDF across treatment, a two-sample Kolmogorov-Smirnov test will be conducted. *Revised text:* For analysis of the primary efficacy and first key secondary efficacy parameters, continuous parameters (eg, change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. The IW-3718 group will be compared with the placebo group by employing a linear mixed-effects model for repeated measures (MMRM) framework with week (categorical), treatment group, week-by-treatment group and week-by-baseline value interactions, baseline esophagitis status (present vs. not present), and baseline WHSS (<3 vs. ≥3) as fixed-effect terms and baseline value as a covariate, with patient as a random effect. An unstructured covariance structure will be used. Least-squares mean (LSM) for each treatment group, LSM difference between the IW-3718 group and the placebo group and a 95% confidence interval for the difference at Week 8, as well as the p-value for comparison versus placebo will be presented. For analysis of responder parameters (ie, responder vs. non-responder), the counts and proportions of responders will be calculated for each treatment group. The proportions of responders between the IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for baseline esophagitis status (erosive esophagitis vs. no erosive esophagitis) and baseline WHSS (<3 vs. ≥3). The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between the IW-3718 group and the placebo group, as well as the CMH estimate of the odds ratio (IW-3718 over placebo) and a 95% confidence interval for the odds ratio, will also be presented.

Item #	Section	Page #	Description of Change
			Time-dependent proportion parameters, defined as days the event of interest occurs, divided by the number of eDiary entry days within the 8-week Treatment Period (eg, proportion of heartburn-free-days), will be analyzed using a Poisson model which is appropriate for count data. The analysis includes the treatment, the baseline esophagitis status (present vs. not present), baseline WHSS (<3 vs. ≥3), covariate of baseline proportion of event-free days, with the eDiary entry days adjusted in the model. In the case of overdispersion, a negative binomial model instead of Poisson regression will be implemented. Model estimates in difference between the rates for IW-3718 and placebo groups will be calculated with corresponding 95% confidence interval and p-value associated with the comparisons to placebo.
11.	Synopsis, Sample Size Determination and Controlling for Type-I Error	12-13	The sample size power calculations were revised to reflect the new primary and key secondary efficacy parameters using data from previously completed Phase 2b Study ICP-3718-202 which enrolled a similar study population. The revised text is as follows: The sample size calculations for the primary and key secondary efficacy parameters are based on results from patients with evidence of pathological acid reflux (positive baseline Bravo status) in Study ICP-3718-202, which had a similar study population as the current study. The primary efficacy parameter is Change from Baseline at Week 8 in WHSS, and key secondary efficacy parameters include: • Change from Baseline at Week 8 in WRFS • Overall Heartburn Responder • Proportion of Heartburn-free Days during the 8-week Treatment Period Using data from patients in Study ICP-3718-202, we derived the estimated results at end of the study as follows:

<table>
<tr><th>Item #</th><th>Section</th><th>Page #</th><th>Description of Change</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Order of Hypothesis Testing</th><th>Parameter</th><th>Placebo (+ PPIs)</th><th>1500 mg IW-3718 (+ PPIs)</th></tr>
<tr><td>1</td><td>Change from Baseline at Week 8 in WHSS</td><td>N = 43
Mean = -1.58
SD = 1.20</td><td>N =51
Mean = -2.01
SD = 1.29</td></tr>
<tr><td>2</td><td>Change from Baseline at Week 8 in WRFS</td><td>N = 43
Mean = -0.81
SD = 1.12</td><td>N = 51
Mean = -1.26
SD = 0.91</td></tr>
<tr><td>3</td><td>Overall Heartburn Responder</td><td>18/49 = 36.7%</td><td>31/55 = 56.4%</td></tr>
<tr><td>4</td><td>Proportion of Heartburn-free Days during the 8-week Treatment Period</td><td>N = 48
Mean = 0.195
SD = 0.2822</td><td>N = 55
Mean = 0.268
SD = 0.2928</td></tr>
</table>
The efficacy parameters will be tested sequentially according to the above order at a 2-sided significance level of 0.05 so that the overall type-I error rate is maintained at 0.05.
Based on bootstrap simulations, a sample size of 330 patients per group will provide approximately 99% power to detect a treatment difference between 1500-mg IW-3718 (while receiving PPIs) and placebo (while receiving PPIs) for the primary efficacy parameter, assuming the randomized population in this study is consistent with the selected population from Study ICP-3718-202. Power that is based on simulations for all type-I error controlling key efficacy parameters are presented in the table below. The 2-sample t-test was used for continuous parameters and the Chi-square test was used for the responder parameter.
</td></tr>
</table>

<table>
<tr><th>Item #</th><th>Section</th><th>Page #</th><th>Description of Change</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Order of Hypothesis Testing</th><th>Parameters</th><th>Power for Fixed Sequence Testing</th></tr>
<tr><td>1</td><td>Change from Baseline at Week 8 in WHSS</td><td>99%</td></tr>
<tr><td>2</td><td>Change from Baseline at Week 8 in WRFS</td><td>99%</td></tr>
<tr><td>3</td><td>Overall Heartburn Responder</td><td>99%</td></tr>
<tr><td>4</td><td>Proportion of Heartburn-free Days during the 8-week Treatment Period</td><td>88%</td></tr>
</table>
</td></tr>
<tr><td>12.</td><td>Schedule of Events, EGD (esophagogastroduodenoscopy), Footnote E</td><td>14-15</td><td>Text was revised as per an Administrative Letter dated 28 May 2019 to clarify which patients will have a repeat EGD (italic and ~~strikethrough~~ text represent a change from the previous version):
A repeat EGD will be performed at the Week 8 / EOT Visit for all patients who have completed at least 4 weeks of treatment and had erosive esophagitis on the screening EGD (based on the Los Angeles [LA] classification of esophagitis, see Appendix 5) as determined by either the site personnel or the central reader. ~~An EGD will be performed at the Week 8 / EOT Visit in all patients who have Grades A, B, C, or D esophagitis (based on the Los Angeles [LA] classification of esophagitis) on the EGD obtained during the Screening Period and have completed ≥4 weeks of treatment.~~</td></tr>
<tr><td>13.</td><td>Schedule of Events, Drug and Alcohol Screen Footnote L</td><td>14-15</td><td>Phencyclidine had been required in the previous version of the protocol and was added to the list of drugs of abuse included in the urine screen.</td></tr>
<tr><td>14.</td><td>Section 1.2, IW-3718</td><td>27</td><td>Depomed, the manufacturer of Acuform®, was updated to its current name, Assertio.</td></tr>
</table>

Item #	Section	Page #	Description of Change
15.	Section 3.1, Overall Study Design and Plan: Description (Figure and Treatment Period)	34, 36	Figure 1, Overview of Study Design, was updated to denote that randomization will be stratified by baseline EE status (present, not present) and Weekly Heartburn Severity Score (WHSS; <3, ≥3). Text was updated for clarity (*italic* and ~~strikethrough~~ text represent a change from the previous version): Patients will be stratified by whether they have, or do not have, EE on the screening EGD, and by their baseline *weekly* heartburn severity ~~level~~ *score* (*WHSS, defined as the* average heartburn severity score over the last 7 days prior to randomization of <3 vs. ≥3; see Section 3.5.7.1) and randomly assigned within each stratum to placebo or 1500 mg IW-3718 BID (1:1).
16.	Section 3.1, Overview of Study Design and Plan: Description (Screening Period)	35	A correction was made to the duration of time that patients must be adherent to their PPI regimen (*italic* and ~~strikethrough~~ text represent a change from the previous version): The patient must have been adherent to their standard PPI dosage regimen (as per product label) for the ~~30 days~~ *8 weeks* prior to the Screening Visit and during the entire Screening Period.
17.	Section 3.1, Overview of Study Design and Plan: Description (Treatment Period)	36	Text was revised as per an Administrative Letter dated 28 May 2019 to clarify which patients will have a repeat EGD (*italic* and ~~strikethrough~~ text represent a change from the previous version): *A repeat EGD will be performed at the Week 8 / EOT Visit for all patients who have completed at least 4 weeks of treatment and had erosive esophagitis on the screening EGD (based on the Los Angeles [LA] classification of esophagitis, see Appendix 5) as determined by either the site personnel or the central reader.* ~~All patients who have erosive esophagitis (LA classification A–D) on EGD at Screening and completed ≥4 weeks of treatment will have a repeat EGD at their EOT Visit.~~
18.	Section 3.3, Selection of Study Population	37	Text was updated to reflect the new sample size and the stratification by baseline EE status and WHSS (*italic* and ~~strikethrough~~ text represent a change from the previous version): Patients will be stratified for treatment assignment at the time of randomization based on the presence of esophageal erosions (erosions, no erosions) *and by baseline WHSS (<3 vs. ≥3).* ~~Enrollment of patients without esophageal erosions will be capped at approximately~~ *The study will aim to enroll up to* 50% of ~~total~~

Item #	Section	Page #	Description of Change
			~~enrollment~~ *patients with esophageal erosions*. Patients must be receiving 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 labelling. Approximately 660 patients (330 patients per treatment arm) will be randomized to treatment.
19.	Section 3.3.1.2, Exclusion Criteria	40	Criterion # 14 was modified to reflect the criterion as listed in the Synopsis and guidance from an Administrative Letter dated 10 October 2018. Only elevated serum bilirubin at Screening (and not during the Pretreatment Period) is exclusionary.
20.	Section 3.4.4; Method of Assigning Patients to a Treatment Group	45	Text was updated to reflect the stratification by baseline EE status and WHSS (*italic* and ~~strikethrough~~ text represent a change from the previous version): Eligible patients will be stratified by whether they have or do not have erosive esophagitis on the screening EGD, and by their baseline ~~heartburn severity level~~ *WHSS* (<3 vs. ≥3), and then randomized through central randomization in a 1:1 ratio to receive either 1500 mg IW-3718 BID or placebo BID, *both administered in addition to the patient's per-label QD PPI therapy*.
21.	Section 3.5.1.3, Procedures for Collecting and Reporting Serious Adverse Events	50	References to XML file formats were deleted.
22.	Section 3.5.6, Clinical Laboratory Determinations	59	Phencyclidine had been required in the previous version of the protocol and was added to the list of drugs of abuse included in the urine screen.
23.	Section 3.5.7.2, Weekly Assessments	60-61	Three weekly 'Degree of Relief' patient-reported items were added. These 3 new items ask the patient to compare their current degree of relief to that experienced before the start of the study: • Compared to before you started this study, how would you rate your heartburn (a pain or burning sensation in your chest, behind the breastbone) over the past 7 days? • Compared to before you started this study, 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?

Item #	Section	Page #	Description of Change
24.	Section 3.5.8.1, Esophagogastroduodenoscopy	62	The following operational details were added for the EGD interpretation (*italic* and ~~strikethrough~~ text represent a change from the previous version): All patients will be required to undergo an EGD during the Screening Period. There should be a minimum of 7 days between the EGD and the start of the Pretreatment Period to allow for pH testing and patient stabilization. *EGDs will be interpreted by the local site personnel and by a central reader. Details are provided in a separate study manual (Image Acquisition Guidelines for Ironwood Pharmaceuticals, Inc. Protocols C3718-301/C3718-302; WorldCare Clinical).* An EGD will be performed at the Week 8 / EOT Visit in all *patients who completed at least 4 weeks of treatment and had* erosive esophagitis on the EGD obtained during the Screening Period ~~patients~~ (based on the Los Angeles [LA] classification of esophagitis~~, [see~~ Appendix 5*]*~~) on the EGD obtained during the Screening Period~~ *as determined by either the site personnel or the central reader)* ~~who completed at least 4 weeks of treatment~~.
25.	Section 3.5.8.2, Bravo™	62	To reflect the use of a central reader, the following text was added: To determine eligibility, a centralized review of pH monitoring will be conducted for each patient.
26.	Section 3.6.1.1, Screening Visit (Visit 1) Procedures	63	Phencyclidine was added to the list of drugs of abuse included in the urine drug screen.
27.	Section 3.6.2.3, Week 8/End-of-treatment (Visit 5) Procedures	66	For EGD, the following clarification was added (*italic* and ~~strikethrough~~ text represent a change from the previous version): EGD *(A repeat EGD will be performed at the Week 8/EOT Visit for all patients who have completed at least 4 weeks of treatment and had erosive esophagitis on the screening EGD [based on the LA classification of esophagitis, see Appendix 5] as determined by either the site personnel or the central reader* ~~patients with erosions [LA Classification Grades A-D] at Screening~~; see Section 3.5.8.1.)
28.	Section 3.7.1, Analysis Populations	67	The Analysis Populations were modified as follows (*italic* and ~~strikethrough~~ text represent a change from the previous version): The **Screened Population** consists of all patients who *signed informed* consent *and received a patient identification (PID) number* ~~to participate in the study~~.

Item #	Section	Page #	Description of Change
			The **Randomized Population** consists of all patients who ~~are randomly~~ *were* assigned *to a treatment group (placebo or IW-3718) via randomization* ~~either placebo or 1500 mg IW-3718~~. The **Safety Population** consists of all *randomized* patients who receive*d* at least 1 dose of study *drug* ~~treatment~~. The **modified Intent-To-Treat (mITT) Population** consists of all randomized patients who receive*d* at least ~~one~~ *1* dose of study ~~treatment~~ *drug* and ~~have~~ *had* at least *1 postbaseline primary efficacy assessment.* ~~one daily heartburn severity assessment post baseline~~ ~~The Per-Protocol (PP) Population is defined as those patients in the mITT Population who have a minimum of 6 weeks of daily heartburn severity assessments and ≥80% compliance with study treatment and the PPIs for the period during which they are on study.~~
29.	Section 3.7.3, Patient Disposition, Demographics, and Baseline Characteristics	68	Text was changed to reflect the deletion of the Per Protocol (PP) population (*italic* and ~~strikethrough~~ text represent a change from the previous version): The count and proportion of patients included in the Randomized, ~~mITT, PP,~~ ~~and~~ Safety*, and mITT* Populations will be presented overall and by treatment group. The number of patients in the Screened Population will be presented overall.
30.	Section 3.7.4; Efficacy Analyses, Table 4	69	In Table 4, footnote "b" was revised as follows (*italic* and ~~strikethrough~~ text represent a change from the previous version): b. ~~Unless otherwise specified, b~~*B*aseline for efficacy parameters will be derived from the daily eDiary collected for Pretreatment Week -1 (Week -2 if data for Week -1 not available)*; specifically for the proportion endpoints (defined as days with the event of interest divided by the number of diary entry days), the last 14 days (Week -2 to Week -1) prior to day of randomization will be used*.
31.	Section 3.7.4.1; Primary Efficacy Parameter	70	The Primary Efficacy Parameter was changed from "Overall Heartburn Responder" to: Change from baseline at Week 8 in Weekly Heartburn Severity Score (WHSS). • The WHSS for a week is the average of the non-missing Daily Heartburn Severity Scores (DHSS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock.

Item #	Section	Page #	Description of Change
			• The DHSS for a day is the greater score of the 2 mRESQ items assessing heartburn severity ("Burning feeling behind the breastbone or in the center of the upper stomach" and "Pain behind the breastbone or in the center of the upper stomach") for that day. Where 1 of the 2 mRESQ heartburn severity items is missing for the day, the maximum will be the score of the remaining item; where both items are missing for the day, the DHSS will be missing.
32.	Section 3.7.4.2; Key Secondary Efficacy Parameters	71	The Key Secondary Efficacy Parameters were changed from: 1. Overall Heartburn Responder – patients with a baseline WHSS ≥ 3 2. Percent change from baseline to Week 8 in WHSS 3. Percent change from baseline to Week 8 in Weekly Regurgitation Frequency Score (WRFS) 4. Proportion of heartburn-free days during the 8-week Treatment Period. to: 1. Change from baseline at Week 8 in Weekly Regurgitation Frequency Score (WRFS) • The WRFS for a week is the average of the non-missing Daily Regurgitation Frequency Scores (DRFS) for that week. Rules for missingness of data will be prespecified in the SAP finalized before database lock. • DRFS for a day is the greater score of the 2 mRESQ items assessing regurgitation frequency ("Regurgitation [liquid or food moving upwards toward your throat or mouth]" and "An acid or bitter taste in the mouth") for that day. 2. Overall Heartburn Responder: a patient who is a weekly heartburn responder for at least 4 weeks, including at least 1 of the last 2 weeks (Weeks 7 and 8), during the 8-week Treatment Period. • A weekly heartburn responder is a patient with a decrease from baseline of ≥ 45% in Weekly Heartburn Severity Score (WHSS). • Rules for missingness of data will be prespecified in the SAP finalized before database lock. 3. Proportion of heartburn-free days during the 8-week Treatment Period.

Item #	Section	Page #	Description of Change
			• Proportion of heartburn-free days is calculated as the number of heartburn-free (DHSS=0) days divided by the number of diary entry days.
33.	Section 3.7.4.3, Analysis Methods for the Primary and Key Secondary Efficacy Parameters	71-72	The section was renamed (*italic* text represents an addition):"Analysis Methods *for the Primary and Key Secondary Efficacy Parameters*". *Previous text:* For analysis of the primary efficacy parameter and other 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 the IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for esophagitis status (erosive esophagitis vs. no erosive esophagitis), baseline heartburn severity level (<3 vs. ≥3), and geographic region. The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between the IW-3718 group and the placebo group, as well as the CMH estimate of the odds ratio (IW-3718 over placebo) and a 95% confidence interval for the odds ratio, will also be presented. For analysis of continuous parameters (e.g., percent change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. The IW-3718 group will be compared with the placebo group by employing a mixed model for repeated measures (MMRM) framework with week (categorical), treatment group, week-by-treatment group, esophagitis status, and geographic region as fixed-effect terms and baseline value as a covariate (if applicable). A compound symmetry covariance structure will be used. Least-squares mean (LSM) for each treatment group, LSM difference between the IW-3718 group and the placebo group and a 95% confidence interval for the difference, as well as the p-value for comparison versus placebo will be presented. Cumulative distribution function (CDF) of percent change from baseline to Week 8 in WHSS and WRFS will be plotted by treatment group. To aid in the interpretation of the graphical representation of the CDF across treatment, a two-sample Kolmogorov-Smirnov test will be conducted. *Revised text:*

Item #	Section	Page #	Description of Change
			For analysis of the primary efficacy and first key secondary efficacy parameters, continuous parameters (eg, change from baseline), descriptive statistics (patient number [n], mean, standard deviation, median, and range) will be presented for each treatment group. The IW-3718 group will be compared with the placebo group by employing a linear mixed-effects model for repeated measures (MMRM) framework with week (categorical), treatment group, week-by-treatment group and week-by-baseline value interactions, baseline esophagitis status (present vs. not present), and baseline WHSS (<3 vs. ≥3) as fixed-effect terms and baseline value as a covariate, with patient as a random effect. An unstructured covariance structure will be used. Least-squares mean (LSM) for each treatment group, LSM difference between the IW-3718 group and the placebo group and a 95% confidence interval for the difference at Week 8, as well as the p-value for comparison versus placebo will be presented. For analysis of responder parameters (ie, responder vs. non-responder), the counts and proportions of responders will be calculated for each treatment group. The proportions of responders between the IW-3718 group and the placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for baseline esophagitis status (erosive esophagitis vs. no erosive esophagitis) and baseline WHSS (<3 vs. ≥3). The CMH test is the primary analysis for responder parameters. The difference in the proportion of responders between the IW-3718 group and the placebo group, as well as the CMH estimate of the odds ratio (IW-3718 over placebo) and a 95% confidence interval for the odds ratio, will also be presented. Time-dependent proportion parameters, defined as days the event of interest occurs, divided by the number of eDiary entry days within the 8-week Treatment Period (eg, proportion of heartburn-free-days), will be analyzed using a Poisson model which is appropriate for count data. The analysis includes the treatment, the baseline esophagitis status (present vs. not present), baseline WHSS (<3 vs. ≥3), covariate of baseline proportion of event-free days, with the eDiary entry days adjusted in the model. In the case of overdispersion, a negative binomial model instead of Poisson regression will be implemented. Model estimates in difference between the rates for IW-3718 and placebo groups will be calculated with corresponding 95% confidence interval and p-value associated with the comparisons to placebo.

<table>
<tr><th>Item #</th><th>Section</th><th>Page #</th><th>Description of Change</th></tr>
<tr><td>34.</td><td>Section 3.7.4.4, Controlling Type-I Error</td><td>72-73</td><td>The section was revised to reflect the new primary and 3 key secondary efficacy parameters. The primary and key secondary efficacy parameters will be tested sequentially according to the following order, each at a 2-sided significance level of 0.05:

<table><tr><th>Order</th><th>Parameter</th></tr><tr><td>1</td><td>Change from Baseline at Week 8 in WHSS (primary)</td></tr><tr><td>2</td><td>Change from Baseline at Week 8 in WRFS</td></tr><tr><td>3</td><td>Overall Heartburn Responder</td></tr><tr><td>4</td><td>Proportion of Heartburn-free Days during the 8-week Treatment Period</td></tr></table>
Testing of subsequent parameters will not be performed unless all previous parameters have been tested statistically significant ($p \leq 0.05$)</td></tr>
<tr><td>35.</td><td>Section 3.7.4.5, Sensitivity Analysis of Primary Efficacy Parameter</td><td>73</td><td>Text was revised as follows (italic and ~~strikethrough~~ text represent a change from the previous version):

For the primary ~~and first secondary endpoint,~~ parameter, change from baseline in WHSS at Week 8, a sensitivity analysis will be conducted; details will be provided in the SAP ~~where both a reduction of at least 45% in WHSS and no decrease in proportion of heartburn-free days are required for a patient to be considered a weekly heartburn responder~~.</td></tr>
<tr><td>36.</td><td>Section 3.7.4.6, Handling of Missing Data</td><td>73</td><td>Text was revised as follows (italic and ~~strikethrough~~ text represent a change from the previous version):

~~In the primary analysis of the primary efficacy parameter Overall Heartburn Responder and first key secondary efficacy parameter Overall Regurgitation Responder – patients with a baseline WHSS ≥ 3, a patient who reported daily symptom severity scores for less than 4 days during a week will not be considered a weekly responder for that week. This approach essentially classifies the weekly symptom severity score as missing for any treatment week (intermittent or post-dropout) for which less than 4 daily scores are available. Furthermore, this approach imputes a weekly responder status of "non-responder" for that week.~~</td></tr>
</table>

Item #	Section	Page #	Description of Change
			~~In the primary analysis of the key secondary efficacy parameters Percent Change from Baseline to Week 8 in WHSS and WRFS, no imputation will be performed on missing data. The weekly symptom severity score will be computed as the average of all available daily scores for that week, regardless of the number of daily score available for that week. If there is not a single daily score available for a week, then the weekly score for that week is missing and is included in the MMRM analysis as missing.~~ *For the primary efficacy analysis, change from baseline at Week 8 in WHSS, no imputation will be performed on missing data. The WHSS will be computed as the average of daily scores for that week. Rules for the average calculation will be prespecified in the SAP finalized before database lock.* A pattern-mixture model with control-based pattern imputation will be implemented as a multiple imputation method to explore the effects of missing data on the primary ~~and key secondary~~ efficacy parameters. The details of this approach will be provided in the SAP.
37.	Section 3.7.4.7, Exploratory Efficacy Parameters and Analysis Methods	73-75	The previous Section 3.7.4.3, "Additional Secondary Efficacy Parameters" and the previous Section 3.7.4.8, "Additional Efficacy Parameters" were consolidated into a new section: Section 3.7.4.7, "Exploratory Efficacy Parameters and Analysis Methods". Parameters that were previous "Key Secondary Efficacy Parameters", previous "Additional Secondary Efficacy Parameters", and "Additional Efficacy Parameters", were all preserved in this new consolidated section listing endpoints and descriptive supportive summaries. In addition, 3 new endpoints were added: ▪ Change from baseline of proportion in days when heartburn did not occur (DHSS = 0) or was very mild (DHSS = 1) during the 8-week Treatment Period ▪ Change from baseline in proportion of days when regurgitation did not occur (DRFS = 0) or rarely occurred (DRFS = 1) during the 8-week Treatment Period • Proportion of patients with erosive esophagitis (EE) improved by at least 1 grade at Week 8 Globally, endpoints and descriptive data summaries phrased as "change from baseline *to* Week 8" were rephrased as "change from baseline *at* Week 8".

<table>
<tr><th>Item #</th><th>Section</th><th>Page #</th><th>Description of Change</th></tr>
<tr><td>38.</td><td>Section 3.7.7, Determination of Sample Size</td><td>76-77</td><td>
The sample size power calculations were revised to reflect the new primary and key secondary efficacy parameters using data from previously completed Phase 2b Study ICP-3718-202 which enrolled a similar study population. The revised text is as follows:
The sample size calculations for the primary and key secondary efficacy parameters are based on results from patients with evidence of pathological acid reflux (positive baseline Bravo status) in Study ICP-3718-202, which had a similar study population as the current study.
The primary efficacy parameter is Change from Baseline at Week 8 in WHSS, and key secondary efficacy parameters include:
• Change from Baseline at Week 8 in WRFS
• Overall Heartburn Responder
• Proportion of Heartburn-free Days during the 8-week Treatment Period
Using data from patients in Study ICP-3718-202, we derived the estimated results at end of the study as follows:
<table>
<tr><th>Order of Hypothesis Testing</th><th>Parameter</th><th>Placebo (+ PPIs)</th><th>1500 mg IW-3718 (+ PPIs)</th></tr>
<tr><td>1</td><td>Change from Baseline at Week 8 in WHSS</td><td>N = 43
Mean = -1.58
SD = 1.20</td><td>N =51
Mean = -2.01
SD = 1.29</td></tr>
<tr><td>2</td><td>Change from Baseline at Week 8 in WRFS</td><td>N = 43
Mean = -0.81
SD = 1.12</td><td>N = 51
Mean = -1.26
SD = 0.91</td></tr>
<tr><td>3</td><td>Overall Heartburn Responder</td><td>18/49 = 36.7%</td><td>31/55 = 56.4%</td></tr>
<tr><td>4</td><td>Proportion of Heartburn-free Days during the 8-week Treatment Period</td><td>N = 48
Mean = 0.195
SD = 0.2822</td><td>N = 55
Mean = 0.268
SD = 0.2928</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Item #</th><th>Section</th><th>Page #</th><th>Description of Change</th></tr>
<tr><td></td><td></td><td></td><td>The efficacy parameters will be tested sequentially according to the above order at a 2-sided significance level of 0.05 so that the overall type-I error rate is maintained at 0.05.
Based on bootstrap simulations, a sample size of 330 patients per group will provide approximately 99% power to detect a treatment difference between 1500-mg IW-3718 (while receiving PPIs) and placebo (while receiving PPIs) for the primary efficacy parameter, assuming the randomized population in this study is consistent with the selected population from Study ICP-3718-202. Power that is based on simulations for all type-I error controlling key efficacy parameters are presented in the table below. The 2-sample t-test was used for continuous parameters and the Chi-square test was used for the responder parameter.
<table>
<tr><th>Order of Hypothesis Testing</th><th>Parameters</th><th>Power for Fixed Sequence Testing</th></tr>
<tr><td>1</td><td>Change from Baseline at Week 8 in WHSS</td><td>99%</td></tr>
<tr><td>2</td><td>Change from Baseline at Week 8 in WRFS</td><td>99%</td></tr>
<tr><td>3</td><td>Overall Heartburn Responder</td><td>99%</td></tr>
<tr><td>4</td><td>Proportion of Heartburn-free Days during the 8-week Treatment Period</td><td>88%</td></tr>
</table></td></tr>
<tr><td>39.</td><td>Section 5, Investigators and Study Administrative Structure</td><td>81</td><td>The European Union (EU) was removed from the list of countries with study centers.</td></tr>
<tr><td>40.</td><td>Appendix 3, Weekly Assessments</td><td>96</td><td>For consistency with Protocol Section 3.5.7.2, the following question was added:
“How much were you bothered by your overall GERD symptoms over the past 7 days?”</td></tr>
</table>

Item #	Section	Page #	Description of Change
41.	Appendix 3, Weekly Assessments	95	Three weekly 'Degree of Relief' patient-reported items were added. These 3 new items ask the patient to compare their current degree of relief to that experienced before the start of the study: • Compared to before you started this study, how would you rate your heartburn (a pain or burning sensation in your chest, behind the breastbone) over the past 7 days? • Compared to before you started this study, 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?
42.	Appendix 4, Prohibited Medications, 14-Day Washout	97	In accordance with results from a completed drug-drug interaction study, C3718-103 as described in the Investigator's Brochure (Edition 5, dated 10 March 2020), levothyroxine and digoxin were removed from the list of prohibited medications (~~strikethrough~~ text represents a deletion from the previous version): • 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)
43.	Appendix 4, Prohibited Medications, Notes Regarding Concomitant Medications	98	PPIs formulated in combination with other drugs were prohibited. In accordance with results from a completed drug-drug interaction study, C3718-103, and as described in the Investigator's Brochure (Edition 5, dated 10 March 2020), no drug-drug interaction was observed when IW-3718 was dosed in combination with oral contraceptives containing ethinyl estradiol and norethindrone. As such, this type of medication is now permitted as a single contraceptive modality. Changes were as follows (*italic* and ~~strikethrough~~ text represent changes from the previous version): Patients must have been on once-daily (QD) PPI therapy for at least 8 weeks before the Screening Visit and continue to take their PPI through the EOT visit. *PPIs that are formulated in combination with other drugs are not permitted (eg, Zegerid® [omeprazole/sodium bicarbonate], Vimovo® [esomeprazole/naproxen]).*

Item #	Section	Page #	Description of Change
			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. Oral contraceptives containing ethinyl estradiol and norethindrone ~~have a known~~ *were shown not to have a* drug-drug interaction with ~~colesevelam~~ *IW-3718 (see the IW-3718 Investigator's Brochure, Edition 5, dated 10 March 2020).* All female patients of childbearing potential *may use* ~~using~~ oral contraceptives with the ingredients listed above as birth control and must agree to use ~~*without using another*~~ an additional form of contraception, from the date they sign the ICF until 24 hours after their final dose of study drug (eg, condom).
44.	Entire Document	All	Small editorial and formatting changes were made to improve protocol readability.

The data and information related to my line function, which has been included with this file, are truthful and accurate.

Approval	[redacted]
Approval	[redacted]

Signature Page for VV-CLIN-004512
v1.0