CONFIDENTIAL

A Randomized Double Blind Active Comparator Controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed *Helicobacter pylori* (*H. pylori*) Infection

ERADICATE Hp2 Study

Protocol Number:	**RHB-105-02**
Sponsor's Medical Director:	[redacted]
Principal Investigator:	[redacted]
Version and Date:	**Final Version, dated 26 February 2017**
	Amendment No. 1, dated 15 August 2017
	Amendment No. 2, dated 02 October 2017
	Amendment No. 3, dated 22 March 2018

STATEMENT OF COMPLIANCE

This study will be carried out in accordance with Good Clinical Practices (GCP) as identified and/or required by the following regulations and guidance:

- Declaration of Helsinki (Fortaleza, 2013)
- US Code of Federal Regulations: 45 CFR Part 46, 21 CFR Parts 50, 56, and 312
- ICH E6; Consolidated Guidelines on Good Clinical Practices (1997)

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LIST OF ABBREVIATIONS

ACG	American College of Gastroenterology
AE	Adverse Event
AGA	American Gastroenterological Association
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
APO_4	Alkaline Phosphatase
BL	Baseline
BUN	Blood Urea Nitrogen
CDC	Centers for Disease Control and Prevention
CE	Covered Entity
CIOMS	Council for International Organizations of Medical Sciences
CLO	Campylobacter-like organism
CRA	Clinical Research Associate
CRE	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
DHHS	Department of Health and Human Service
DO	Doctor of Osteopathy
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCGF	estimated Cockcroft-Gault (eCGF) formula
EDC	Electronic Data Capture
EOT	End-of-treatment
FAP	Full Analysis Population
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GMP	Good Manufacturing Practices
HBs Ag	Hepatitis B surface antigen
HCV Ab	Hepatitis C Viral antibody

HDPE	High-density Polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
NCR	No Carbon Required
NSAID	Nonsteroidal Anti-inflammatory Drug
PA	Physician's Assistant
PIPEDA	Personal Information Protection and Electronic Documents Act
PHI	Personal Health Information
PI	Principal Investigator
PKP	PK Population
PP	Per Protocol
PPI	Proton Pump Inhibitor
QTc	Corrected Q-T Interval
REB	Research Ethics Board
RHB	RedHill Biopharma
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOC	Standard of Care
SOP	Standard Operating Procedure
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
^{13}C UBT	^{13}Carbon Urea Breath Test
ULN	Upper Limit of Normal
USA	United States of America
WBC	White Blood Cell
WHO	World Health Organization

PROTOCOL SYNOPSIS	
Title:	A randomized, double blind, active comparator controlled phase III study to assess the safety and efficacy of RHB-105 in the treatment of confirmed *Helicobacter pylori (H. pylori)* infection
Phase:	Phase III
Study Population:	Main Inclusion Criteria To be eligible for this protocol, subjects must: 1. Be ages 18 – 70, inclusive; non-Asian males and females (This population has been demonstrated to have significantly elevated omeprazole levels as per the prescriber information for other omeprazole products). A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam should be considered Asian, and for this study Asian is defined as having at least one Asian grandparent (Shektar et al, 2014, FDA Guidance for Industry 2016); 2. Positive for *H. pylori* by ^{13}C Urea Breath Test (UBT) and confirmed positive via gastric biopsy for CLO (Rapid Urease Test), or *H. pylori* culture or histology; 3. Symptoms consistent with dyspepsia of at least two weeks duration (defined as recurrent pain or discomfort centered in the upper abdomen, often with a relation to meals); 4. Females must not be pregnant or lactating and: a. at no risk of pregnancy for one of the following reasons: postmenopausal for at least one year from the date of informed consent, status post hysterectomy or tubal ligation, OR b. are prepared to and agree to use of an intrauterine device (IUD) or practice double method birth control (barrier plus spermicide) from screening through to 30 days post-end of-treatment (EOT); Acceptable double contraceptive methods include barrier (condoms or diaphragms) plus spermicide c. Hormonal contraceptives (birth control pills and hormone implants) are not acceptable contraception methods under this protocol. 5. Males must be surgically sterilized or are prepared to and agree to practice double method (barrier plus spermicide) birth control from screening through to 30 days post-EOT; 6. Agree to refrain from consuming alcohol from 1 week prior to screening to Test of Cure/Visit 5; 7. Agree to refrain from taking antacids from screening through day 15 and for at least 24 hours prior to Test of Cure/Visit 5 and if applicable at least 24 hours prior to Visit 8/Test of Cure; 8. Agree to refrain from taking H2 blockers at least 24 hours prior to screening ^{13}C UBT and at least 24 hours prior to Test of Cure/Visit 5 and if applicable at least 24 hours prior to Visit 8/Test of Cure; 9. Agree to refrain from taking sucralfate from one week prior to screening through Test of Cure/Visit5;

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	10. Agree to refrain from taking bismuth containing medications such as Pepto-Bismol™ or other proton pump inhibitors (PPIs) from two weeks prior to screening through Test of Cure/Visit 5; 11. Agree to refrain from consuming grapefruit, or any other food or supplement known to significantly affect CYP3A4 or CYP2C19 activity from screening to day 15; 12. Provide written informed consent to participate as shown by a signature of subject on the consent form. Main Exclusion Criteria To be eligible for this protocol, subjects must not: 1. Have alarm symptoms/signs (including unexplained anemia [iron deficiency], melena / hematemesis, anorexia, dysphagia, jaundice, weight loss); 2. Have received prior *H. pylori* eradication therapy 3. Use of antibiotics in the 4 weeks immediately prior to screening ^{13}C UBT; 4. Use of any proton pump inhibitors (PPIs) or bismuth-containing medications (such as Pepto-Bismol™) within the 2 weeks immediately prior to screening ^{13}C UBT; 5. Use of any of the following medications within seven days prior screening: alfentanil, allopurinol, amlodipine, anti-herpes agents, anti-retroviral agents, apixaban, aprepitant, aripiprazole, astemizole, atorvastatin, boceprevir, buspirone, carbamazepine, cisapride, citalopram dosed greater than 20 mg /d, clomipramine, clopidogrel and other oral anticoagulants, colchicine, dapsone, dihydroergotamine, digoxin, diltiazem, ergotamine, felodipine, fluconazole, imatinib, hormonal contraceptives that are not exclusively norethindrone or norgestrel, imipramine, itraconazole, ketoconazole, lurasidone, lovastatin, mycophenolate mofetil, nifedipine, nisoldipine, nitrendipine, phenytoin, pimozide, probenecid, proguanil, quinine, roflumilast, terfenadine and voriconazole; 6. Use of amiodarone; 7. Presence of more than two active gastric and/or duodenal ulcers; 8. History of gastric outlet obstruction; or hypersecretory state (e.g., Zollinger Ellison Syndrome); 9. History of esophageal or gastric surgery, except for simple closure of perforated ulcer; 10. History of gastric cancer; 11. History of malignancy within the past five years except for basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been treated with no evidence of recurrence; 12. Positive screening laboratory results for human immunodeficiency virus (HIV) antibody (HIV1 or HIV2), or hepatitis B surface antigen (HBs Ag), or hepatitis C antibody (HCV Ab), unless patient has documented sustained viral response evidenced by prior and/or current absence of viral RNA at least 24 weeks after completing antiviral therapy; 13. Current drug or alcohol abuse or history of drug or alcohol abuse in the past 5 years from screening; 14. Known hypersensitivity or suspected history of hypersensitivity reactions to any of the study drugs or related drugs, including cephalosporins and penicillin;

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15. Clinical evidence of any disease that in the opinion of the investigator might interfere with the subject's ability to participate in the trial;
16. History of QT prolongation (QTc greater than 450ms in males and 460ms in females), or ventricular arrhythmia, including torsades de pointes;
17. AST or ALT >3x ULN, or APO4 >2x ULN, or TB >2x ULN. Subjects with confirmed diagnosis of Gilbert's Syndrome are excluded if TB > 2.5x ULN;
18. Unable to communicate well with the Investigators and to comply with the study requirements;
19. Involved in any other experimental drug or device protocol (outside of this RHB-105-02 study) within the 4 weeks immediately prior to screening visit through end of study.
20. Subjects with creatinine clearance less than 30 ml/min at screening via estimated Cockcroft-Gault formula (eCGF):

    eCGF or estimated creatinine clearance = [140 - age in years] * weight (kg) / 72 * Serum Creatinine (mg/dl) [multiply estimated rate by 0.85 for women], using actual body weight at screening.

Number of Subjects:	Estimated total: 444 subjects will be randomized into the study.
Number of Sites:	The study will be conducted at up to 65 sites in the United States of America (USA).
Study Design:	This is a, randomized, double blind, active comparator-controlled study of RHB-105 in adult subjects complaining of epigastric discomfort that have been screened and found to be positive for H. *pylori* infection via ^{13}C UBT and gastric biopsy. The biopsy samples will also be used to conduct *H. pylori* antibiotic susceptibility/resistance assessment. The study will be conducted at up to 65 sites in the USA. Once consent has been obtained and upon positive screening and enrollment into the study, eligible subjects will be randomized in a ratio of 1:1 between Test (RHB-105) arm (n=222) and the active comparator arm (n=222). Subjects will receive RHB-105 or active comparator for 14 consecutive days. Eradication of *H. pylori* infection will be determined at Visit 5 based on ^{13}C UBT testing conducted between 43 and 71 days after initiation of study drug therapy. All subjects who meet inclusion and exclusion criteria and have positive^{13}C UBT will undergo upper endoscopy with sampling for culture and sensitivity testing (to rifabutin, amoxicillin, clarithromycin, and metronidazole) prior to randomization. After test of cure at Visit 5, all *H. pylori* eradication failures will receive susceptibility directed standard of care therapy based on initial culture results for subjects, and undergo repeat upper endoscopy for post treatment antibiotic susceptibility/resistance assessment.

Study Visit Schedule:

Screening	Baseline	Phone	Safety	Phone	Test of Cure	^{13}C UBT Follow-up	SOC Endo	Phone	Test of Cure
Day -42 to 0	Day 1	Day 8 +1	Day 13 +/-2	Day 28-60 +/-2	Day 43-71 +7	Day 44-72 +7	After Day 44-72 +14	Day 50-79+/-2	Day 85 - 140 +14
Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 5a	Visit 6	Visit 7	Visit 8

Subject Participation Duration:	Subjects may participate for up to 154 days.

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Treatment:	RHB-105 is an 'all-in-one' combination oral capsule consisting of 2 different antibiotics and a proton pump inhibitor combined in a single capsule. Dose per RHB-105 capsule: 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole. Active comparator is RHB-105 without rifabutin, an 'all-in-one' combination oral capsule consisting of amoxicillin and a proton pump inhibitor combined in a single capsule. Dose per active comparator capsule: 250 mg amoxicillin, and 10 mg omeprazole. All subjects will also be administered a single 50 mg dose of riboflavin dispensed as a separate tablet in order to maintain study blind.
Route of Administration:	Oral capsule.
Dosage Regimen for Investigational Product:	The intended dose is RHB-105 (12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole) 4 capsules every eight hours with food, equivalent to 50 mg rifabutin, 1000 mg amoxicillin and 40 mg omeprazole for a total daily dose of: • Rifabutin 150 mg • Amoxicillin 3000 mg • Omeprazole 120 mg Subjects will take RHB-105 every 8 hours with food for 14 consecutive days.
Dosage Regimen for Active Comparator:	The intended dose active comparator is 250 mg amoxicillin, and 10 mg omeprazole 4 capsules every eight hours with food, equivalent to 1000 mg amoxicillin and 40 mg omeprazole for a total daily dose of: • Amoxicillin 3000 mg • Omeprazole 120 mg Subjects will take active comparator every 8 hours with food for 14 consecutive days.
Outcome Measures	Primary Endpoint: The occurrence of *H. pylori* eradication is confirmed via ^{13}C Urea Breath Test (UBT) testing 43-71 days after initiation of treatment. Secondary Endpoints: 1) Antibiotic Resistance and Susceptibility Subgroup Analyses - The primary endpoint will be summarized within subgroups formed by the presence of H. pylori susceptibility and resistance to amoxicillin, clarithromycin, metronidazole and rifabutin determined based upon samples obtained prior to initiating study treatment. The proportion of subjects with failure to eradicate H. pylori and the treatment effect (difference in the proportions) will be estimated within each subgroup along with 95% 2-sided confidence intervals where there are an adequate number of subjects in the subgroup (e.g., at least 20 subjects per subgroup). 2) Pharmacokinetics – The plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl-rifabutin on Day 13 will be summarized by time following most recent dose 3) Assess the difference in antibiotic resistance and susceptibility of *H. pylori* after treatment with study drug in treatment failure subjects Safety:

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	The occurrence and severity of treatment emergent adverse events during the study and changes from baseline in hematology and chemistry laboratory values. Exploratory Endpoints: 1) Upon study completion and unblinding of all subjects, CYP2C19 status will also be summarized and subgroup analyses of efficacy based on CYP2C19 status and pharmacokinetics will be performed using descriptive methods 2) Eradication rates in failure to eradicate subjects who receive susceptibility directed standard of care will be analyzed descriptively.
Objectives:	Primary Objective: To assess the effectiveness of RHB-105 to eradicate *H. pylori* as indicated by ^{13}C UBT for *H. pylori.* Secondary Objective: The primary endpoint, the occurrence *of H. pylori* eradication, will be examined within subgroups of subjects formed by the occurrence of antibiotic resistance and susceptibility prior to therapy. Safety Objective: To assess the safety profile of RHB-105.
Study Completion:	Upon completion of clinical activities and safety follow-up.
Statistical Considerations	Sample size for this study has been calculated based on a superiority comparison assuming 83% effectiveness for the new treatment, and 70% effectiveness for the control, with 90% power and a 2-sided alpha of 5%. Using these specifications, 222 subjects per arm will be required. The primary analysis will use the Full Analysis Population defined as all randomized subjects who received at least one dose of study drug. The primary efficacy endpoint is eradication of *H. pylori* via ^{13}C UBT test at Test of Cure Visit 5. The treatment groups will be compared for the primary endpoint using a chi-squared test. Other endpoints, including safety endpoints, will be summarized using descriptive methods. The primary endpoint, the occurrence *of H. pylori* eradication, will be examined within subgroups of subjects formed by the occurrence of antibiotic resistance and susceptibility prior to therapy.

RESPONSIBLE PERSONNEL

Sponsors and Contacts

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1.0 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1. Background Information

1.1.1 *Helicobacter pylori*

Helicobacter pylori is a common and important transmissible (human-to-human) bacterial human pathogen. The prevalence of this infection varies worldwide from as low as 10% in some developed western nations to higher than 80% among the indigent populations of many developing countries. The World Health Organization (WHO) estimates that *H. pylori* is present in about half of the world's population while the Centers for Disease Control and Prevention (CDC) estimates a total of 30-40% of Americans harbor the infection, with the highest prevalence rates in minority subgroups (Wannmacher 2011, Barzilay 2011, Graham 1991, Cardenas 2006a).

The major concerns of *H. pylori* as an infectious agent are as follows:

- It is continuously infectious throughout an initial, clinically latent and often asymptomatic stage.
- It induces a pattern of acute-on-chronic gastric inflammation, resulting in disordered gastric physiology and progressive gastric mucosal damage.
- It can produce serious pathological effects and clinical sequelae in infected patients.

Patients with *H. pylori* infection may present with mild dyspepsia. One of the major current reasons for *H. pylori* testing is the presence of dyspepsia (Malfertheiner 2012, Graham 2010a), as many *H. pylori*-related diseases are associated with this symptom. In addition, more than 50% of dyspeptic patients with no evidence of ulcer disease (non-ulcer dyspepsia or functional dyspepsia) are infected with *H. pylori* (Maconi 2009, Moayyedi 2006) and are at risk for progression of gastric mucosal damage (Graham 1997a).

Approximately 20% of patients infected with *H. pylori* will develop clinically significant sequelae (Axon, 1997), including atrophic gastritis, gastric atrophy, duodenal ulcer disease, gastric ulcer disease, primary gastric B-cell lymphoma, gastric adenocarcinoma, iron deficiency anemia, and vitamin B_{12} deficiency (Rimbara 2011; Cardenas 2006a; Cardenas 2006b; DuBois 2005; Graham 1997b; Dholakia, 2005).

In 1994, *H. pylori* was classified as a Group 1 agent (carcinogenic to humans) by the WHO's International Agency for Research on Cancer and it is now accepted as a major cause of gastric cancer worldwide. Gastric cancer is amongst the most frequent cancers worldwide and is associated with a poor prognosis (5-year survival rate of only 10-15% in patients with advanced disease) (Selgrad 2010, Ekstrom 2001). In the first half of the 20th century, gastric cancer was the most common cancer in many Western countries including the United States of America (USA). Despite the decreased incidence of gastric cancer since the mid-20th century, the

National Cancer Institute [NCI] (Surveillance Epidemiology and End Results [SEERS]) estimates that >21,000 Americans will be diagnosed with and almost 11,000 will die of gastric cancer in 2012 (NCI 2012). As such, identification and eradication of *H. pylori* before pre-neoplastic lesions are present is vital if gastric cancer is to be prevented (Malfertheiner 2005). For example, population-based eradication of *H. pylori* in an area where the infection is endemic (Taiwan) showed a 67% reduction in new ulcers, 77% reduction in the incidence of gastric atrophy, and 25% reduction in gastric cancer, comparing the period before (1995-2003) to the *H. pylori* eradication period (2004-2008) (Lee 2013).

1.1.2 *Current Treatment Options for the Eradication of H. pylori*

H. pylori eradication is a well-established therapy for patients with ulcer disease (Chey 2007). Other commonly cited recommendations for treatment include recurrent ulcer hemorrhage, uninvestigated dyspepsia (depending upon *H. pylori* prevalence), plan to start therapy with proton pump inhibitors (PPIs) or nonsteroidal anti-inflammatory drugs (NSAIDs) in high-risk patients, after endoscopic resection of early gastric cancer, and whenever the infection is diagnosed. This “test and treat” strategy is the recommendation of the American Gastroenterological Association (AGA) and American College of Gastroenterology (ACG) (Talley 2005, Chey 2007). Given the potential morbidity of *H. pylori* infection, which may range from non-serious to life-threatening disease states, and given the steady rise in clarithromycin and metronidazole resistant *H. pylori* strains (De Francesco 2010), a therapy that will reliably eradicate *H. pylori* upon detection is sorely needed.

H. pylori infection can be cured using suitable antimicrobial therapies, and a success rate ≥ 85% should be achieved (Graham et al, 2007, Graham 2010b). Unfortunately, this degree of success is often clinically impossible to achieve using standard-of-care therapies, due to the increased prevalence of antimicrobial resistance. Physicians are often unaware of the resistance rates within their region (Graham, 2009) making the empiric selection of effective therapies difficult. Due to this, a step-wise approach is commonly used to achieve treatment success by providing, as needed, first-line, second-line, third-line, and fourth-line therapies to patients. However, according to the ACG, the first (or primary) course of treatment offers the greatest chance at eradication of *H. pylori*. Therefore, the first treatment regimen is the most important and should include only those therapies with proven effectiveness (Graham and Calvet 2012).

Currently approved triple and quadruple therapies often achieve sub-optimal eradication. Two separate meta-analyses have demonstrated that effectiveness of both clarithromycin- and metronidazole-based triple therapies has decreased to unacceptably low levels of <85% (Per Protocol) effectiveness (Graham 2010b). A meta–analysis of 2751 patients revealed that the failure rate for *H. pylori* eradication with triple therapy in non-ulcer dyspeptic patients and duodenal ulcer patients was 33.7% and 21.9%, respectively (a difference which was found to be statistically significant). This demonstrates that the high rate of eradication failure is an issue in *H. pylori* infection regardless of the status of ulcer disease secondary to *H. pylori*. If anything, it would seem that triple therapy is less effective in eradication of *H. pylori* in non-ulcer dyspeptic patients as compared to duodenal ulcer patients (Broutet 2003).

The Food and Drug Administration (FDA) approved bismuth quadruple therapy Pylera® in 2006 for the treatment of patients with *H. pylori* infection and duodenal ulcer disease). This therapy offers bismuth, tetracycline, metronidazole (within a single capsule), and the PPI omeprazole. There are broadly varying reports (75-90%) regarding the effectiveness of bismuth-containing quadruple therapy in eradication of *H. pylori* (Chey 2007). In 2010, a meta-analysis of randomized studies comparing triple therapy to quadruple therapy reported an average eradication rate of 78.3% using bismuth-based quadruple therapy, which included a PPI, and 77.0% eradication using clarithromycin triple therapy (Luther 2010). Quadruple therapy regimen also requires four times daily (qid) dosing, potentially reducing compliance and treatment success. (Malfertheiner 2011, Salazar 2012).

Prevpac®, (amoxicillin, clarithromycin and lansoprazole) wrapped individual daily administration pack was approved by the US Food and Drug Administration in February 1999 for the treatment of *h pylori* infection and duodenal ulcer disease. In April 2002, duration of therapy was reduced to 10 days. The Prevpac® PI reports eradication rates of 81-86% and these have been steadily decreasing. The American College of Gastroenterology Clinical Guideline: Treatment of *Helicobacter pylori* Infection states that for first line therapy, clarithromycin triple therapy should be restricted to patients from areas where clarithromycin resistance is low (<15%) and or have no previous history of macrolide exposure (Chey 2017).

No US trial of dual antibiotic therapy [Attumi et al 2014, Graham et al 2010, Graham et al 1995, Harford et al 1996, Laine et al 1995, Laine et al 1998, Malaty et al 1996] has successfully achieved the 85% ITT eradication rate targeted in the literature [Graham et al 2007). High dose amoxicillin/lansoprazole dual therapy is already an FDA approved therapy to eradicate *H. pylori* to reduce recurrence of duodenal ulcer. The dosing of this approved regimen is amoxicillin 1 g t.i.d. and lansoprazole 30 mg t.i.d. administered for 14 days. This dosing regimen is equivalent to RHB-105 without rifabutin and with omeprazole replacing lansoprazole as per ability to raise intragastric pH over 24 hours, and 67% bioavailability of omeprazole in RHB-105 vs reference omeprazole (RedHill Biopharma Study RHB-P2-418). Two studies noted in the Prevacid PI report *H. pylori* eradication rates of 77% and 66% in the evaluable data sets and 70 and 61% in the intent to treat analyses in those same studies. On the basis of these and published studies, first line dual amoxicillin/PPI therapy is not recommended in current treatment guidelines. The Prevacid prescribing information states that triple therapy was shown to be more effective than all possible dual therapy combinations and that amoxicillin dual therapy is indicated only for patients who are either allergic or intolerant to clarithromycin.In summary, there is growing consensus among the scientific and medical communities that the currently approved therapies for the eradication of *H. pylori* no longer provide adequate therapy for over 20% of treated patients. Indeed, ineffective treatment may lead to generally increased bacterial resistance as well as complicate future treatment attempts to eradicate the *H. pylori* infection and thus cause greater medical and financial burdens. Given the morbidity associated with *H. pylori* infection and the decline in effectiveness of standard-of-care therapies, there is a clear need for a new

highly effective first-line therapy that will reduce treatment burden on the patient and consistently achieve a high rate of eradication.

1.1.3 RHB-105

RHB-105 is an antibiotics (rifabutin and amoxicillin) and proton pump inhibitor (omeprazole) proprietary drug combination under investigation for the treatment of *H. pylori* infection.
H. pylori has been shown to be highly sensitive to rifabutin (a derivative of rifamycin). Rifabutin-based therapy offers an alternative to clarithromycin- or metronidazole-based therapies and could establish improved effectiveness of *H. pylori* eradication, including metronidazole- and/or clarithromycin-resistant strains.

Resistance of *H. pylori* to amoxicillin or rifabutin is very rare (Van Der Poorten 2007). The mean rate of *H. pylori* resistance to rifabutin (calculated from 11 studies including 2982 patients) was 1.3% in general and 0.6% for patients' naïve to *H. pylori* eradication treatment (Gisbert 2011).
Combining rifabutin, amoxicillin, and a PPI (pantoprazole) has achieved eradication rates of 96.6% (in the highest dose group), regardless of clarithromycin or metronidazole resistance status (Borody 2006). In his study of *H. pylori*-infected patients who previously failed standard clarithromycin-based triple therapy, Borody demonstrated that a 12-day course of rifabutin (150 mg qd), amoxicillin (1 – 1.5 g tid), and a PPI (pantoprazole; 80 mg tid) was well tolerated and highly effective, providing a high eradication rate of 90.7 - 96.6% (Borody 2006). Therefore, RHB-105 can potentially overcome the current resistance issues that are problematic with the approved clarithromycin and metronidazole based therapies and may provide efficient and widespread *H. pylori* eradication to treat and prevent the numerous and life-threatening diseases associated with *H. pylori* infection.

RHB-105 has recently completed investigation in RedHill Biopharma Study RHB-105-01. This study, entitled **A Randomized Placebo-controlled Phase III Study to Assess the Safety and Efficacy of RHB-105 in the Treatment of Confirmed *Helicobacter pylori* (*H. pylori*) Infection in Dyspepsia Patients,** compared RHB-105 to placebo in a double blind fashion to assess safety only. The effectiveness of any combination of 2 out of 3 API components of RHB-105 was projected to be no more than 70% given the information in the Prevacid and Prilosec Prescriber Information. The new regimen was expected to be superior to the 70% historical comparator. Subjects noted to be endoscopically and ^{13}C UBT positive were treated with blinded RHB-105 (or placebo) for 14 days and had test of cure via ^{13}C UBT performed at day 28-35 post completion of therapy. Subjects who experienced failure to eradicate *H. pylori* received standard of care triple or quadruple therapy as per the local investigator.

Following treatment with the 3-in-1 combination RHB-105, the success rate of eradication (based on ^{13}C UBT) of *H. pylori* 28 days post-EOT was 89.4% based on the primary endpoint of mITT (Modified Intent to Treat). The mITT population included all subjects who received at least 1 dose of randomized study treatment and underwent a ^{13}C UBT test at 28-35 days post completion of therapy. The PP (Per Protocol) Population included all subjects who consumed at least 75% of planned study treatment, underwent a ^{13}C UBT test at 28-35 days post completion

of therapy, and did not have any major protocol violations. Efficacy in this group was 88.9% due to the exclusion of three treatment successes who were assessed for *H. pylori* eradication outside the protocol defined treatment windows. This rate was statistically significantly superior to 70%, which was the projected effectiveness of any combination of 2 out of 3 the components of RHB-105 given the data in the Prevacid and Prilosec prescribing Information. In placebo subjects who had failure to eradicate *H. pylori*, and were treated with standard of care therapy, there was a 63% (17/27) eradication rate with standard of care therapy. Fifty percent (2/4) of RHB-105 subjects who received standard of care demonstrated eradication of *H. pylori* with standard of care.

RHB-105 was shown to be safe and well-tolerated. The majority of treatment-related AEs were mild to moderate; only one RHB-105-treated patient had a treatment-emergent SAE, and this was assessed as not related to study treatment. The AE profile, laboratory values, and other safety assessments did not indicate any safety concerns with respect to the use of RHB-105 in this patient population.

FDA prescribing information for omeprazole and omeprazole containing products note up to a fourfold increase in AUC in Asian subjects compared with Caucasians and suggest dose reduction in this patient population. Given the fixed dose combination present in RHB-105 this population is excluded from the ERADICATE Hp2 study.

1.1.4 Study Rationale

Standard treatments fail to eradicate *H. pylori* in over 20% of infected patients. These patients constitute a significant medical problem as they harbor strains resistant to clarithromycin and/or metronidazole, which are major components of the therapies currently available.

In the USA, standard second-line therapy is bismuth, tetracycline and metronidazole in conjunction with a PPI or H_2 receptor antagonist. While this therapy is effective, compliance is an issue due to the fact that this therapy must be administered four times daily for 10 to 14 days (due to metronidazole resistance).

Combining rifabutin with amoxicillin and a PPI, such as omeprazole, overcomes the problem of clarithromycin and metronidazole resistance, as this therapy does not contain either; *H. pylori* strains resistant to rifabutin are rare and, rifabutin is effective against clarithromycin and metronidazole resistant strains.

RedHill has developed an “all-in-one” capsule formulation, containing 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole (RHB-105). Details about the formulation and its components are available in the Investigator’s Brochure. RHB-105 is intended to maintain or improve upon the current demonstrated *H. pylori* eradication effectiveness, maintain or improve the tolerability of anti-*H. pylori* treatment, and simplify the anti-*H. pylori* dosing schedule. It is

being investigated against an active comparator ‘all-in-one' combination oral capsule consisting of 250 mg amoxicillin and 10 mg omeprazole. Both the investigational drug (RHB-105) and the active comparator will be administered as 4 capsules three times daily with food.

Rifabutin has been demonstrated to discolor body fluids and in an effort to maintain the study blind, all subjects will be administered 50 mg of riboflavin (Vitamin B2) to be taken once daily in addition to blinded study drug.

2. OUTCOME MEASURES AND OBJECTIVES

2.1. Study Outcome Measures

Primary Endpoint:
The occurrence of *H. pylori* eradication is confirmed via ^{13}C Urea Breath Test (UBT) testing 43-71 days after initiation of treatment.

Secondary Endpoints:
The secondary endpoints are as follows and will be assessed using descriptive measures:

1) Antibiotic Resistance and Susceptibility Subgroup Analyses **-**
   The primary endpoint will be summarized within subgroups formed by the presence of *H. pylori* susceptibility and resistance to amoxicillin, clarithromycin, metronidazole and rifabutin determined based upon samples obtained prior to initiating study treatment. The proportion of subjects with failure to eradicate *H. pylori* and the treatment effect (difference in the proportions) will be estimated within each subgroup along with 95% 2-sided confidence intervals where there are an adequate number of subjects in the subgroup (e.g., at least 20 subjects per subgroup).
2) Pharmacokinetics – The plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl-rifabutin on Day 13 will be summarized by time following most recent dose
3) Assess the difference in antibiotic resistance and susceptibility of *H. pylori* after treatment with study drug in treatment failure subjects

Safety:
The occurrence and severity of treatment emergent adverse events during the study and changes from baseline in hematology and chemistry laboratory values.

Exploratory Endpoints:

1) Upon study completion and unblinding of all subjects, CYP2C19 status will also be summarized and subgroup analyses of efficacy based on CYP2C19 status and pharmacokinetics will be performed using descriptive methods.
2) Eradication rates in failure to eradicate subjects who receive susceptibility directed standard of care will be analyzed descriptively.

2.2. Study Objectives

Primary Objective:
The primary objective is to assess the effectiveness of RHB-105 to eradicate *H. pylori* as indicated by ^{13}C UBT for *H. pylori*.

Secondary Objective:

The primary endpoint, the occurrence *of H. pylori* eradication, will be examined within subgroups of subjects formed by the occurrence of antibiotic resistance and susceptibility prior to therapy.

Safety Objective
The safety objective is to assess the safety profile of RHB-105.

3. STUDY DESIGN

This is a randomized, double blind, active comparator controlled study of RHB-105 in adult subjects complaining of epigastric discomfort that have been screened and found to be positive for *H. pylori* infection via ^{13}C UBT and follow up upper endoscopy (culture, histology or urease test). All subjects who meet inclusion and exclusion criteria and have positive^{13}C UBT will undergo upper endoscopy with three biopsies taken from each of the antrum and corpus of the stomach. One biopsy from both the corpus and antrum will be combined and tested for *H. pylori* via a rapid urease test at the point of care. One biopsy from both the corpus and antrum will be combined and sent for *H. pylori* testing at the central histology laboratory. One biopsy from both the corpus and antrum will be combined and sent to the central laboratory for *H. pylori* culture with susceptibility testing assessing amoxicillin, clarithromycin, metronidazole and rifabutin. Subject specific pretreatment culture susceptibility and resistance results will be provided to the investigator in those subjects who fail to eradicate *H. pylori* upon post treatment ^{13}C UBT analysis. All other susceptibility results will remain blinded until study completion. The active comparator arm is expected to demonstrate an approximate 70% efficacy rate and RHB-105 is being investigated for superiority with an expected approximate 83% efficacy rate.

The study will be conducted at up to 65 sites in the USA. Once informed consent has been obtained and upon positive screening and enrollment into the study, eligible subjects will be randomized in a ratio of 1:1 between active comparator arm (n=222 and the active investigational arm (RHB-105) (n=222). Subjects will receive RHB-105 or active comparator (RHB-105-LT) for 14 days. Eradication of *H. pylori* infection will be determined based on ^{13}C UBT testing conducted between 43 and 71 days after initiation of therapy.

Subjects who fail to eradicate *H. pylori* upon post treatment ^{13}C UBT analysis will receive investigator prescribed susceptibility directed therapy based on culture and sensitivity results from biopsy samples prior to therapy. The investigator may prescribe local standard of care therapy if susceptibility results are not contributory or are unavailable. These subjects will also undergo repeat endoscopy to assess changes in susceptibility and resistance. All information related to therapy including drugs, doses and duration administered will be collected, and subjects will be reassessed for eradication of *H. pylori* 28 - 60 days following completion of therapy, ideally between 43 and 71 days after initiation of therapy. Susceptibility data will only be provided for those subjects who fail to eradicate *H. pylori.*

4. STUDY ENROLLMENT AND WITHDRAWAL

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1 Inclusion Criteria

The subject must meet all of the following criteria to be eligible for inclusion in the double-blind phase of the trial:

1. Be ages 18 – 70, inclusive; non-Asian males and females (This population has been demonstrated to have significantly elevated omeprazole levels as per the prescriber information for other omeprazole products). A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam should be considered Asian, and forr this study Asian is defined as having at least one Asian grandparent (Shektar et al, 2014, FDA Guidance for Industry 2016)
2. Positive for *H. pylori* by ^{13}C Urea Breath Test (UBT) and confirmed positive via gastric biopsy for CLO (Rapid Urease Test), or *H. pylori* culture or histology;
3. Symptoms consistent with dyspepsia of at least two weeks duration (defined as recurrent pain or discomfort centered in the upper abdomen, often with a relation to meals);
4. Females must not be pregnant or lactating and:
    a. at no risk of pregnancy for one of the following reasons: postmenopausal for at least one year from the date of informed consent, status post hysterectomy or tubal ligation, OR
    b. are prepared to and agree to use of an intrauterine device (IUD) or practice double method birth control (barrier plus spermicide) from screening through to 30 days post-end of-treatment (EOT); Acceptable double contraceptive methods include Barrier (condoms or diaphragms) plus spermicide
    c. Hormonal contraceptives (birth control pills and hormone implants) are not acceptable contraception methods under this protocol.
5. Males must be surgically sterilized or are prepared to and agree to practice double method (barrier plus spermicide) birth control from screening through to 30 days post-EOT;
6. Agrees to refrain from consuming alcohol from 1 week prior to screening to Test of Cure/Visit 5;
7. Agree to refrain from taking antacids from screening through day 15 and for at least 24 hours prior to Test of Cure/Visit 5 and if applicable at least 24 hours prior to Visit 8/Test of Cure;

8. Agree to refrain from taking H2 blockers at least 24 hours prior to screening ^{13}C UBT and at least 24 hours prior to Test of Cure/Visit 5 and if applicable at least 24 hours prior to Visit 8/Test of Cure
9. Agree to refrain from taking sucralfate from one week prior to screening through Test of Cure/Visit5.
10. Agrees to refrain from taking bismuth containing medications such as Pepto-Bismol™ or other proton pump inhibitors (PPIs) from two weeks prior to screening through Test of Cure/Visit 5;
11. Agrees to refrain from consuming grapefruit, or any other food or supplement known to significantly affect CYP3A4 or CYP2C19 activity from screening to day 15;
12. Provide written informed consent to participate as shown by a signature of subject on the consent form.

4.2 Exclusion Criteria

The subject must be excluded from the double-blind phase of the study for any of the following reasons:

1. Have alarm symptoms/signs (including unexplained anemia [iron deficiency], melena / hematemesis, anorexia, dysphagia, jaundice, weight loss);
2. Have received prior *H. pylori* eradication therapy;
3. Use of antibiotics in the 4 weeks immediately prior to screening ^{13}C UBT;
4. Use of any proton pump inhibitors (PPIs) or bismuth-containing medications (such as Pepto-Bismol™) within the 2 weeks immediately prior to screening ^{13}C UBT;
5. Use of any of the following medications within seven days prior screening: alfentanil, allopurinol, amlodipine, anti-herpes agents, anti-retroviral agents, apixaban, aprepitant, aripiprazole, astemizole, atorvastatin, boceprevir, buspirone, carbamazepine, cisapride, citalopram dosed greater than 20 mg /d, clomipramine, clopidogrel and other oral anticoagulants, colchicine, dapsone, dihydroergotamine, digoxin, diltiazem, ergotamine, felodipine, fluconazole, imatinib, hormonal contraceptives that are not exclusively norethindrone or norgestrel, imipramine, itraconazole, ketoconazole, lurasidone, lovastatin, mycophenolate mofetil, nifedipine, nisoldipine, nitrendipine, phenytoin, pimozide, probenecid, proguanil, quinine, roflumilast, terfenadine and voriconazole;
6. Use of amiodarone;
7. Presence of more than two active gastric and/or duodenal ulcers;
8. History of gastric outlet obstruction; or hypersecretory state (e.g., Zollinger Ellison Syndrome);
9. History of esophageal or gastric surgery, except for simple closure of perforated ulcer;
10. History of gastric cancer;

11. History of malignancy within the past five years except for basal cell carcinoma of the skin or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
12. Positive screening laboratory results for human immunodeficiency virus (HIV) antibody (HIV1 or HIV2), or hepatitis B surface antigen (HBs Ag), or hepatitis C antibody (HCV Ab), unless patient has documented sustained viral response evidenced by prior and/or current absence of viral RNA at least 24 weeks after completing antiviral therapy;
13. Current drug or alcohol abuse or history of drug or alcohol abuse in the past 5 years from screening;
14. Known hypersensitivity or suspected history of hypersensitivity reactions to any of the study drugs or related drugs, including cephalosporins and penicillin;
15. Clinical evidence of any disease that in the opinion of the investigator might interfere with the subject's ability to participate in the trial;
16. History of QT prolongation (QTc greater than 450ms in males and 460ms in females), or ventricular arrhythmia, including torsades de pointes;
17. AST or ALT >3x ULN, or APO4 >2x ULN, or TB >2x ULN. Subjects with confirmed diagnosis of Gilbert's Syndrome are excluded if TB > 2.5x ULN;
18. Unable to communicate well with the Investigators and to comply with the study requirements;
19. Involved in any other experimental drug or device protocol (outside of this RHB-105-02 study) within the 4 weeks immediately prior to screening visit through end of study.
20. Subjects with creatinine clearance less than 30 ml/min at screening via estimated Cockcroft-Gault formula (eCGF):
    eCGF or estimated creatinine clearance = [140 - age in years] * weight (kg) / 72 * Serum Creatinine (mg/dl) [multiply estimated rate by 0.85 for women], using actual body weight at screening.

No waivers will be provided during the conduct of this study. Subjects may be rescreened following discussion with medical monitor. Rescreens must be treated like a newly screened patient with a new consent and new screening number.

4.3 Treatment Assignment Procedures

A list of subjects screened but deemed ineligible will be maintained indicating reason(s) for exclusion.

Treatment assignments will be based on a centralized computer-generated randomization scheme using permuted block randomization without additional stratification.

Each subject will have a randomization code assigned that corresponds to treatment assignment and a unique identifier for drug packaging purposes. Once a subject number and treatment have

been assigned to a subject, the subject identification number cannot be reused even if the subject discontinues the study early or withdraws prior to receiving any study medication. Subjects who discontinue from the study or who have previously participated in the study will not be permitted to re-enroll. Subjects may be rescreened if endoscopic results for *H pylori* are unavailable during the screening window. Subjects will be randomized to one of the following groups:

Treatment Arms:

444 Subjects Randomized	Arm 1	222 Subjects	RHB-105
	Arm 2	222 Subjects	Active Comparator

4.3.1 Randomization Procedures

Subjects will be assigned to treatment using permuted block randomization without additional stratification.

4.3.2 Post-treatment Standard of Care

Subjects who fail to eradicate *H. pylori* will receive susceptibility directed standard of care therapy as prescribed by the treating investigator based on initial pretreatment results, and will undergo upper endoscopy with culture to assess changes in susceptibility and resistance. The investigator may prescribe local standard of care therapy if susceptibility results are not contributory or are unavailable. Susceptibility data will only be provided for those subjects who fail to eradicate *H. pylori.*

4.3.3 Reasons for Discontinuation of Study Treatment

Subjects may be withdrawn from treatment at any time for the following reasons:

- Withdrawn consent by the subject to continue receiving study medication
- Any safety issue leading to inability to continue on study drug
- Lost to follow up
- Administrative decision of investigator or sponsor that It is compulsory to remove the subject from the study
- If the subject becomes pregnant

Subjects discontinuing treatment will continue with routine study visits unless the subject requests that follow-up be discontinued.

4.3.4 Handling of Withdrawals

Maximal effort will be made to follow up with all subjects starting study treatment. These subjects will be strongly encouraged to attend post treatment ^{13}C UBT visits to undergo primary efficacy analysis.

4.3.5 Premature Termination or Suspension of Study

The sponsor reserves the right to temporarily suspend or prematurely discontinue this study or individual study sites.

The reasons that the sponsor may terminate the study or clinical sites include, but are not limited to, any of the following reasons:

- Development of unexpected laboratory toxicities which preclude further investigation of the investigational product
- Reporting of unexpected serious adverse events (SAEs) which preclude further investigation of the investigational product
- The observation of any new third-party findings related to any of the active agents which would preclude further investigation of the investigational product
- The sponsor's inability to provide sufficient resources to continue the investigation

If this study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. Each Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB)/Helsinki Committee will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

If the investigator terminates or suspends the study without prior agreement of the sponsor, the investigator must inform the institution, where required by the regulatory requirements and the investigator/institution must promptly inform the sponsor and the IRB/IEC/REB/Helsinki Committee, and should provide the sponsor and the IRB/IEC/REB/Helsinki Committee a detailed written explanation of the termination or suspension. If the IRB/IEC/REB/Helsinki Committee terminates or suspends its approval/favorable opinion of the study, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

5. INVESTIGATIONAL PRODUCT

5.1 Study Drug Description

5.1.1 Formulation, Packaging, and Labeling

The study drug will be manufactured in accordance with Good Manufacturing Practices (GMP) guidelines. The required quantity of blinded formulation, either RHB-105 or active comparator, will be encapsulated in opaque capsules to prevent identification.

The necessary quantity of capsules will be prepackaged in high-density polyethylene (HDPE) bottles with child-resistant closures.

The study drug, packaged by-subject in accordance with the randomization code, will be labeled in accordance with US FDA requirements for clinical trial supplies.

The Investigator will have access to perform emergency unbinding through the IWRS system in order to determine what treatment arm the patient was assigned.

5.1.2 Study Drug Storage and Stability

All study drug is to be stored at temperature up to 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) (see USP Controlled Room Temperature). Each study drug kit will include two bottles containing either RHB-105 or active comparator. Each of the bottles will contain 100 capsules (adequate study medication for 8 days).

Riboflavin will be provided in bottles of 20 tablets according to the manufacturer's instructions and labeled in accordance with US FDA requirements.

5.1.3 Supply, Handling, and Accountability

The sponsor will be responsible for supplying the investigators/institutions with the study drug. The study drug will be supplied once the sponsor obtains all required documentation from the study site. The sponsor will ensure timely delivery of investigational product(s) to the investigator(s) and maintain records within IWRS that document shipment, receipt, disposition, return, and destruction of the study drug.

The qualified/principal investigator (PI) is responsible for study drug accountability, reconciliation, and record maintenance at his/her site. The PI or designated trained study site personnel will document all aspects of drug receipt, inventory, dispensing, return, reconciliation, and shipment within IWRS.

All study drug must be kept in a locked area with access restricted to designated study personnel. At the baseline visit a full course of study medication will be dispensed. A list of the exact supply of study drug dispensed to each subject at each visit will be included in the supplied drug accountability log that will need to be completed at each study visit and maintained within EDC. All product containers, with and without residual study drug, will be returned by the subject to the clinic in the packaging in which it was provided to the subject. The investigator or delegated staff will reconcile all capsules returned with those recorded as being dispensed and account for any inconsistencies in writing in the drug accountability log or similar document maintained in the investigator study file/Pharmacy Manual. The site monitor will routinely check the supplies of study drug to ensure accountability of all study medication used and record findings within EDC.

At the conclusion of the study, all unused study drug and all bottles will be returned to the sponsor. The sponsor will ensure that a final report of drug accountability is prepared and that unused medications are appropriately destroyed.

5.2 Dosage and Administration of Study Drug

The intended dose of RHB-105 (12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole) is 4 capsules every eight hours, equivalent to 50 mg rifabutin, 1000 mg amoxicillin and 40 mg omeprazole for a total daily dose of:

- Rifabutin 150 mg
- Amoxicillin 3000 mg
- Omeprazole 120 mg

The intended dose of active comparator is (250 mg amoxicillin, and 10 mg omeprazole) 4 capsules every eight hours, equivalent to 1000 mg amoxicillin and 40 mg omeprazole for a total daily dose of:

- Amoxicillin 3000 mg
- Omeprazole 120 mg

Study treatment will be taken orally every 8 hours with food for 14 consecutive days beginning on Day 1. Subjects may begin their study drug intake in the afternoon or evening of the first study day. In these cases, the study treatment may extend to 15 days to complete the full course of the treatment (42 doses, 168 capsules). Subjects will be instructed to take 4 capsules every 8 hours at approximately the same time each day.

The first morning dose is to be taken as soon upon awakening, with food. The next dose should be taken 8 hours later with food and the last dose 8 hours later or before going to bed if that is closer, again with food.

Example of Administration Times	RHB-105	Active Comparator
6 AM	4	4
2 PM	4	4
10 PM	4	4

Any missed dose must be taken as soon as possible and no later than within 2 hours of the next scheduled dose. Subjects should maintain their regular dosing schedule in all situations.
Subjects are to be instructed to and are expected to note the date and time of their last dose prior to Visit 3.

All subjects will be provided with riboflavin 50 mg tablets to be taken once daily throughout the 14-day study period. Subject may take riboflavin for up to 15 days if the study drug dosing schedule requires 15 dosing days. This should be taken with the morning dose of study drug but can be taken with afternoon or evening doses if not taken with the AM dose.

5.3 Assessment of Subject Compliance with Study Drug

Subjects will be instructed to bring the remainder study drug and all empty packaging to each clinic visit. Compliance will be assessed by capsule counts, conducted by the investigator or delegate at each visit. Details will be recorded and reconciled against expected study drug use. Compliance will be calculated as a percentage (%) of expected usage in the final analysis and the capsule count will be entered on the appropriate page of the case report form (CRF) at each applicable study visit.

5.4 Past Medical History, Concomitant Illnesses and Medications

5.4.1 Past Medical History and Concomitant Illnesses

Past medical history and concomitant illnesses present at the time of informed consent, will be will be documented on the appropriate pages of the CRF (see Section 7.3.1, Adverse Events).

5.4.2 Concomitant Medications

All concomitant and rescue medications will be recorded on the CRF as to the identity of the agent (trade and generic names), start date, dose, route, reason for use, and stop date. No concomitant medication should be started or stopped without the instructions of the investigator.

All medications being taken by the subjects from the time of informed consent signature until the last study visit are regarded as concomitant medications and must be documented preferably by generic name on the appropriate pages of the CRF.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the subject's welfare and are not likely to interfere with the study, they may be given at the discretion of the Investigator.

5.4.3 Prohibited Medications

Subjects will not consume grapefruit or any other food or supplement known to significantly affect CYP3A4 or CYP2C19 from screening through study day 15.

Subjects will not consume alcohol from one week prior to screening through study Visit 5.

Subjects will not take any antibiotics in the 4 weeks immediately prior to screening ^{13}C UBT visit and through Visit 5 except for the study medications.

Subjects will not take any bismuth-containing medications (such as Pepto-Bismol) or proton pump inhibitors (PPIs) within the 2 weeks immediately prior to screening ^{13}C UBT through Visit 5.

Subjects will not take any sucralfate containing medications within one 1 week immediately prior to screening through Visit 5.

Subjects will not take any H2 blockers for at least 24 hours prior to any ^{13}C UBT collection (Screening, Test of Cure/Visit 5 or Visit 8).

Subjects will not take any antacids from screening through study day 15 and for at least 24 hours prior to Test of Cure/Visit 5 and if applicable at least 24 hours prior to Visit 8/Test of Cure;

Subjects will not take any of the following medications through visit 3: alfentanil, allopurinol, amlodipine, anti-herpes agents, anti-retroviral agents, apixaban, aprepitant, aripiprazole, astemizole, atorvastatin, amiodarone, boceprevir, buspirone, carbamazepine, cisapride, citalopram dosed greater than 20 mg /d, clomipramine, clopidogrel and other oral anticoagulants, colchicine, dapsone, dihydroergotamine, digoxin, diltiazem, ergotamine, felodipine, fluconazole, imatinib, imipramine, itraconazole, ketoconazole, lurasidone, lovastatin, mycophenolate mofetil, nifedipine, nisoldipine, nitrendipine, phenytoin, pimozide, probenecid, proguanil, quinine, roflumilast, terfenadine and voriconazole.

Hormonal contraceptives that are not exclusively norethindrone or norgestrel are prohibited through visit 3 and subjects on norethindrone or norgestrel contraception may continue these medications but must practice double method contraception.

If a subject is discovered to have taken a prohibited medication after screening, the Investigator should immediately consult the Medical Monitor or his/her designee and the Medical Monitor will

discuss with the sponsor as appropriate. Subjects will not be discontinued from study treatment due to use of prohibited medications unless there is a safety concern.

5.4.4 Warning for CYP Interacting Medications

RHB-105 is a CYP3A4 inducer and substrate as well as a CYP2C19 substrate. Active comparator is a CYP2C19 substrate. Subjects receiving CYP3A4 and CYP2C19 interacting drugs may have diminished or elevated plasma levels of these medications and should be monitored for potential interactions and clinical effects. See Appendix 4 for a listing of CYP3A4 and CYP2C19 interacting drugs.

6. STUDY SCHEDULE

6.1 Visit 0 - Screening

Subjects will be assessed for study eligibility during the screening visit (Day -42 to 0). The following study procedures will be performed at the screening visit:

- Provide subject with study information and obtain subject informed consent and ^{13}C UBT patient information sheet
- Assessment of individual inclusion/exclusion criteria
- Basic subject demographic information
- Medical history
- Physical examination including vital signs
- Concomitant medication assessment
- Hematology, biochemistry and urinalysis testing
- Electrocardiogram (ECG)
- Urine pregnancy test on all females of child-bearing potential
- ^{13}C UBT following a one hour fast (no liquid or solid intake)
- Hepatitis B surface antigen and hepatitis C antibody
- HIV1 and HIV2 antibody
- Schedule of upper endoscopy for
    - Determination of presence of *H. pylori* via CLO, culture or histology - results must be available by Baseline (V1)/Day 1 Visit
    - *H. pylori* culture with susceptibility testing (to amoxicillin, clarithromycin, metronidazole, and rifabutin) – results to be blinded until study completion except in those subjects who fail to eradicate H pylori at visit 5 or who fail eradication at Visit 8 Standard of Care

Only upon successful completion of all screening activities including review of safety data and ^{13}C UBT, will subjects undergo scheduled upper endoscopy.

6.2 Visit 1 - Baseline - Day 1

At visit 1, the subject's eligibility will be confirmed. Eligible subjects will then be enrolled in the study and randomized to a treatment arm.

The following study procedures will be performed at Visit 1 (Baseline):

- Review of inclusion/exclusion criteria
- Medical history
- Physical examination with vital signs
- Concomitant medications assessment
- Urine pregnancy test on all females of child-bearing potential

- Adverse event assessment (captured for descriptive purposes prior to drug administration)
- Randomization
- Blood sample will be collected to assess CYP2C19 genotyping
- Blood sample will be collected for PK assessment of pretreatment amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin plasma levels prior to initial dose
- Dispense paper and electronic diaries and instruct subject on how to complete the diaries (record daily time of administration of each dose and any other concomitant medications taken every day)
- Study drug dispensing (study drug to begin on Day 1)

6.3 Visit 2 - Telephone follow-up - Day 8 (± 1 day)

Telephone Call to Stress Compliance, Remind Subjects to Report Adverse Events, Note the Time of Last 3 Doses Administered Prior to Next Visit, and Reiterate the Importance of attending next study visits.

6.4 Visit 3 - Safety Visit - Day 13 (± 2 days)

The following study procedures will occur at visit 3:

- Physical examination with vital signs
- Concomitant medication assessment
- Urine pregnancy test on all females of child-bearing potential
- Blood samples will be collected for PK and timed in relation to most recent dose of study drug to assess plasma levels of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin
- Hematology, biochemistry and urinalysis testing
- Assess diary and record date and time of last three most recent doses of study drug
- Adverse events assessment
- Subject reminded that antibiotics, bismuth, and PPI are prohibited through Visit 5 and that H2 blockers are prohibited at least 24 hours prior to Visit 5
- Study drug accountability/compliance and review of last day/s of scheduled drug administration if not day 15
    - Subjects seen prior to Day 15 will be instructed to return their study drug upon completion of full 14-day course of therapy and compliance will be finalized at that time

6.5 Visit 4 - Telephone follow-up - Day 28-60 (± 2 days)

Telephone Call to Stress Importance of Follow-Up ^{13}C UBT Testing (at least a 1 hour fast – no liquid or solid intake) and Remind of Upcoming Appointment and

Adverse Event Assessment. Subjects will be reminded that antibiotics, bismuth, and PPI are prohibited through Visit 5 and that H2 blockers are prohibited at least 24 hours prior to Visit 5.

6.6 Visit 5 – Test of Cure - Day 43 - 71 (+ 7 days)

The following study procedures will occur at visit 5:

- Physical examination with vital signs
- Concomitant medication assessment with specific question related to antibiotic use, bismuth, PPI or H2 blockers
- Urine pregnancy test on all females of child-bearing potential
- Follow-up hematology, biochemistry and urinalysis testing in subjects with clinically significant abnormal results at Visit 3
- ^{13}C UBT following a one hour fast (no liquid or solid intake)
- Adverse events assessment
- Study drug accountability/compliance if not performed to date

Exceptional Visit 5 due to pregnancy

In the event a female subject becomes pregnant during the course of the double-blind phase of the study and refuses to undergo the ^{13}C UBT assessment, then a fecal antigen test may be performed at the local lab. Results of the fecal antigen test will substitute for the ^{13}C UBT test of cure for this subject in all efficacy analyses.

6.6.1 Visit 5A – ^{13}C UBT Telephone Follow-up - Day 44 – 72 (+7 days)

This visit will be performed after Visit 5 ^{13}C UBT test results have been received. Delays in visits due to delayed results will not be considered protocol deviations.

- Study site personnel will contact subjects following ^{13}C UBT test results reporting and arrange for follow-up care
    - Subjects with positive ^{13}C UBT test results will be scheduled for upper endoscopy to be performed at visit 6, with *H. pylori* culture with susceptibility testing (to amoxicillin, clarithromycin, metronidazole, and rifabutin)
    - Subjects with negative ^{13}C UBT test results will be noted to have completed the study and will be informed that Visit 5 is considered their End of Study Visit.

6.7 Visit 6 – Standard of Care Baseline Visit - Endoscopy After Day 44-72 (+14 days)

Subjects who are determined to be ^{13}C UBT positive post treatment with investigational drug will undergo upper endoscopy, with sampling for *H. pylori* culture and susceptibility testing to amoxicillin, clarithromycin, metronidazole, and rifabutin.

The following study procedures will occur at Standard of Care visit 6:

- Assess vital signs
- Concomitant medication assessment
- Urine pregnancy test on all females of child bearing potential
- Susceptibility directed initiation of standard of care therapy based on initial culture results for subjects
- Endoscopy with biopsy for *H. pylori* culture and susceptibility
- Schedule Visit 8 for ^{13}C UBT (Standard of Care Test of Cure visit), remind subject that he/she must be tested following at least a one hour fast (no liquid or solid intake) and that he/she should not take PPI, antibiotics, bismuth through Visit 8 or H2 blockers 24 hours prior to Visit 8.

6.7.1 Visit 7 - Standard of Care Telephone follow-up - Day 50-79 (± 2 days)

- Telephone Follow-up to Stress Compliance, Follow-up and Schedule ^{13}C UBT Testing (at least a 1 hour fast – no liquid or solid intake) and reminded that antibiotics, bismuth, and PPI are prohibited through Visit 8 and that H2 blockers and antacids are prohibited 24 hours prior to Visit 8

6.8 Visit 8 - Standard of Care Test of Cure - Day 85 - 140 (+ 14 days)

- Post treatment ^{13}C UBT Testing

6.9 Early Termination Visit

In the event of an early termination for any reason, the investigator will perform all procedures as described for Visit 5. All subjects will be asked to return for post treatment ^{13}C UBT assessment 28-60 days after last dose of study drug, ideally between 43 and 71 days after initiation of study drug. Every effort will be made to obtain ^{13}C UBT assessment as this is the primary efficacy data point. The investigator will record the reasons for any early termination or deviation from required procedures within the CRF.

All subjects who early terminate from the study, during a clinic visit or hospitalization for SAE (if possible), while in the 14-day course of study drug administration, will have amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin levels drawn at that date with best efforts made at capturing exact date and time of most recent study drug administration.

6.9.1 Unscheduled Visit

If, in the investigator's opinion, the subject for medical reasons is required to be seen outside of the proposed visit schedule, then an unscheduled visit may be performed. Additional CRFs will be

provided to accommodate such visits. Activities at these visits will be dependent upon the investigator's concerns. The investigator will record the reasons for the unscheduled visit.

7. STUDY PROCEDURES/EVALUATIONS

7.1 Clinical Evaluations

The following clinical evaluations will be conducted according to the study schedule described in Appendix 2:

Screening
An initial assessment of subject demographics, review of ICF, inclusion/exclusion criteria and concomitant medications will be conducted.

Upper Endoscopy and biopsies
All subjects who meet inclusion and exclusion criteria and have positive ^{13}C UBT will undergo upper endoscopy with three biopsies taken from each of the antrum and corpus of the stomach.

One biopsy from both the corpus and antrum will be combined in a single container and tested for *H. pylori* via a rapid urease test at the point of care. Rapid urease tests (CLO) must be completed within 24 hours of sample collection.

One biopsy from both the corpus and antrum will be combined in a single container and sent for *H. pylori* testing at the central histology laboratory.

One biopsy from each the corpus and antrum will be combined in a single container and sent to the microbiology central laboratory for *H. pylori* culture with susceptibility testing assessing amoxicillin, clarithromycin, metronidazole and rifabutin prior to therapy and after therapy in those subjects with persistent positive ^{13}C UBT

All samples should be handled as detailed within the laboratory manual.

Post treatment endoscopies in subjects with persistent positive ^{13}C UBT will require two biopsies – one from each of the antrum and corpus. These will be combined in a single container and sent to the microbiology central laboratory for *H. pylori* culture with susceptibility testing assessing amoxicillin, clarithromycin, metronidazole and rifabutin following treatment with RHB-105.

Laboratory Testing
Includes hematology, chemistry, pregnancy test, urinalysis, viral serologies, *H. pylori status,* and PK assessment of amoxicillin, omeprazole, rifabutin, and 25-o-desacetyl-rifabutin.

Medical History
An initial medical history will be obtained during the interview with the study subject to evaluate the subject's suitability for consent and baseline assessment. At baseline, a focused follow-up medical history and related medications will be obtained by interview and review of medical records. Medical history should include review of the inclusion/exclusion criteria, and ensure that current medications are not prohibited or unstable in dose. Medical histories obtained during standard of care treatment will assess subjects for non-treatment emergent adverse events, drug compliance, and concomitant medications via direct questioning.

Physical Examination
A physical examination will non-invasively assess the subject's major body systems: general appearance, head/eyes/ears/nose/throat, neck, lungs, heart, abdomen, genitourinary, if clinically indicated, extremities, neurological, skin, and lymphatics.

Vital Signs
Vital signs will be recorded - height, weight, respiratory rate, temperature, supine blood pressure and pulse. Height measurement should be measured once during the screening visit. All other vital signs measurements should be measured as detailed in the study schedule.

Electrocardiogram (ECG)
An ECG will be performed at the screening visit.

Diary
Diaries will be used by subjects to note missed doses, concomitant medications, and adverse events or changes in well-being while administered study drug.

Drug Compliance
Study drug compliance will be based upon capsule counts after return of drug and final drug accountability.

7.2 Efficacy Evaluations

7.2.1 ^{13}C Urea Breath Test

The ^{13}C UBT (BreathTek®, Otsuka America Pharmaceutical Inc.) will be conducted at screening visit, visit 5 and visit 8 if applicable. This will be used to verify *H. pylori* status prior to study drug administration and to determine if *H. pylori* has been successfully eradicated. Subjects will be asked to fast (no liquid or solid intake) for at least 1 hour prior to their visit. They must not have had any other antibiotics for 4 weeks prior to screening through test of cure Visit5 and Visit 8, or proton pump inhibitors or bismuth preparations two weeks prior to screening through Test of cure Visit 5 or Visit 8 or H2 receptor antagonists or antacids 24 hours prior to any ^{13}C UBT testing (screening visit, visit 5 and visit 8 if applicable). Step-by-step procedures are presented in the BreathTek® Package Insert (provided in the laboratory manual).

7.2.2 Laboratory Studies

Pharmacogenetics
Pharmacogenetic testing to assess cytochrome P450 (CYP) 2C19 status and effect on response to RHB-105 as well as relationship to pharmacokinetics.

7.3 Assessment of Safety

7.3.1 Adverse Events

7.3.1.1 Definition of Treatment Emergent Adverse Event

Timely accurate and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and is mandated by regulatory agencies worldwide. In this study a treatment emergent adverse event (TEAE) is defined as any unfavorable and unintended sign, symptom, physical finding or disease, whether or not believed to be related to the investigational product that arises after the first dose of study drug was administered. This includes any occurrence that was new in onset or aggravated in severity or frequency from the time the first dose of study drug was administered.

Any event reported between signature of Informed Consent form and first dose of study drug will be considered medical history and will be reported as such.

Abnormal results of diagnostic procedures, or laboratory test abnormalities, should also be considered as TEAEs, ONLY if they result in any of the following:

- Discontinuation of study drug
- Require treatment or any other therapeutic intervention and/or
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)

All events, TEAEs and SAEs, regardless of severity or causality, that occur between the time of first study drug administration and within 28 days following the last dose of blinded study drug are to be documented on the adverse event case report form with indications of onset, duration, severity (mild, moderate, and severe), seriousness, relationship to study drug (unrelated, unlikely, possible, probable, definite), remedial actions taken, and outcome.

All SAEs occurring during the administration of standard of care (SOC) drug are to be documented as SAEs on serious adverse event case report form (for SOC) with indications of onset, duration, severity (mild, moderate, and severe), relationship to SOC drug (unrelated, unlikely, possible, probably, definite), remedial actions taken, and outcome. If the SAE is deemed to be related to any of the standard of care drugs, it is the responsibility of the investigator to report the event to the manufacturer of the related drug, through the manufacturer's post-marketing surveillance system. Determination of eradication of *H. pylori* infection will be based on

^{13}C UBT testing done between 43 and 71 days after initiation of blinded therapy. Due to this delay in time of 28-60 days, any SAEs that occur during the SOC dosing period will NOT be considered related to the study treatment regimen of RHB-105 or Active comparator.

A TEAE is considered associated with the use of the study drug if the attribution was possible, probable, or definite (see Appendix 3 for Definitions for Clinical and Laboratory Adverse Events). Abnormal laboratory values that qualify as TEAEs will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant. Any positive pregnancy test result must be repeated, study drug withdrawn, and any pregnancy must be followed to term.

7.3.1.2 Definition of Serious Adverse Event

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect
- is considered medically significant

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such medical events include those events requiring intensive treatment in an emergency room or at home, that do not result in inpatient hospitalization, or the development of drug dependency or treatment-related substance abuse.

7.3.1.3 Definition of Unexpected Adverse Drug Reaction

An adverse drug reaction is generally defined as all noxious and unintended responses to a medicinal product related to any dose. An unexpected adverse drug reaction is one that is not consistent with the current Investigator’s Brochure.

7.3.1.4 Adverse Event/Serious Adverse Event Recording and Reporting

Treatment-emergent adverse events (TEAEs) will be recorded up to 28 days after completion of the blinded study period in the source documents and in the CRFs. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor. Adverse events will be clinically assessed only by those with the training and authority to make a diagnosis and medical

evaluation, which would include an MD, Physician's Assistant (PA), Nurse Practitioner, or Doctor of Osteopathy (DO).

Any medical condition that is present at the time that the subject is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE or SAE when appropriate.

All AEs and/or TEAEs including local and systemic reactions, should be captured on the appropriate CRF. The investigator will rate AEs for severity, causality, action taken, and outcome. Severity will be rated on a three-point scale as mild, moderate, or severe.

- Mild is noticeable to the subject, does not interfere with the subject's daily activities and usually does not require additional therapy or dose adjustment.
- Moderate may interfere with the subject's daily activities and may require additional therapy.
- Severe may severely limit the subject's daily activities and typically requires therapy or intervention.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity noted. Causality will be based upon medical assessment of the suspected relationship to the study medication.

Relationship	Causality	Description
Not related to investigational agent	Unrelated	The AE is clearly not related to the investigational agent.
	Unlikely	The AE is doubtfully related to the investigational agent.
Related to investigational agent	Possible	The AE may be related to the investigational agent.
	Probable	The AE is likely to be related to the investigational agent.
	Definite	The AE is clearly related to the investigational agent.

AEs considered unrelated or unlikely will be deemed not related, and AEs considered possible, probable, or definite will be deemed related. Any actions taken to ameliorate the AE will be recorded such as dose withdrawn, pharmacological intervention, and no action taken. Outcome will provide information as to whether the event was resolved, resolved with sequelae, or remains ongoing.

Any SAE, including death from any cause that occurs during this investigation, whether or not related to the investigational drug, must be reported on the SAE pages of the CRF. In case of unavailability of electronic CRF, the SAE form provided must be filled out and send via fax to CRO Pharmacovigilance/Safety (contact details below) within 24 hours. In addition, CRO Pharmacovigilance/Safety group, including the medical monitor should be notified immediately for any death or life-threatening event believed to be possibly related to study drug.

[redacted]

Any change in well-being defined as any unfavorable and unintended sign, symptom, physical finding or disease that occurs following initiation of standard of care therapy will NOT be considered a TEAE. This data will be captured via medical history for descriptive purposes only.

Laboratory abnormalities in hematology or chemistry will be reviewed by the investigator for clinical significance and will be reported only if considered significant.

Other supporting documentation of the event may be requested by the medical monitor and should be provided as soon as possible.

Expedited regulatory reporting by the sponsor/medical monitor is required for serious unexpected adverse drug reactions. The time frame for reporting is as follows: for fatal or life-threatening unexpected drug reactions regulatory agencies will be informed no later than 7 days after the CRO or sponsor's first knowledge of the reaction, followed by as complete a report as possible within 8 additional days. In the case of non-fatal, non-life-threatening unexpected drug reactions, these events must be reported no later than 15 days after the CRO or sponsor's first knowledge of the reaction. All other SAEs that do not meet expedited regulatory reporting will be reported to the regulatory agencies at least annually in a summary format. This includes SAEs thought to be not related as well as expected, related SAEs and unexpected, not related SAEs.
If expedited reporting is required (due to a safety event/ Serious Adverse Event reporting), the Pharmacovigilance/Safety representative will request emergency unblinding in order to comply with the FDA regulatory requirements, as described in the section 4.3.1, in order to include the subject's treatment assignment within the report. Only the CRO Pharmacovigilance/Safety representative will have access to the unblinded code; all other study personnel (including site personnel) will remain blinded.

7.3.1.5 Adverse Event Follow-up

AEs and TEAEs will be followed until resolution or the last study visit, whichever comes first. All SAEs will be followed until event resolution, until the condition stabilizes, until the event is otherwise explained, or until the patient is lost to follow-up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be reasonably indicated to elucidate the nature and/or causality of the SAE. Any follow-up information regarding SAEs must be reported to within 24 hours.

7.3.1.6 Reporting of Pregnancy

Pregnancy occurring in a female subject, or in the partner of a male subject, must be reported to the sponsor. Pregnancies are considered immediately reportable (within 24 hours, and must be

captured up to 30 days after completion of the blinded study period) and are to be documented on the Pregnancy Form. In the event of pregnancy in a female subject, the investigational treatment will be immediately discontinued and treated in the way least likely to harm both subject and fetus. The investigator and/or primary care physician will follow the pregnancy to term, and document the maternal and fetal outcomes. This information will be provided to the sponsor as soon as possible thereafter.

7.3.2 Clinical Laboratory Tests

7.3.2.1 Identification of the Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in the following table according to the schedule in Appendix 2. Clinical laboratory tests (hematology, biochemistry, urinalysis, pharmacokinetic, genotyping, and gastric biopsy histology and microbiology) will be performed at a central laboratory. Central lab collections, processing and shipping will be detailed within the lab manual. Urine pregnancy test and CLO testing will be performed at each local site. Tests performed at unscheduled visits will be at the discretion of the investigator.

Laboratory Assessments

Hematology	Clinical Chemistry	Special Testing	Urinalysis
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood urea nitrogen (BUN) Creatinine Total bilirubin (Direct and indirect fractionated) Lactate Dehydrogenase (LDH) Serum glutamic-pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) Serum glutamic-oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST) Creatine phosphokinase eCGF or estimated creatinine clearance Alkaline phosphatase Sodium Potassium Chloride Gamma-glutamyltransferase (GGT) Bicarbonate Calcium Magnesium Inorganic phosphorus Amylase Uric acid Total cholesterol Total protein Glucose Albumin	CYP 2C19 genotyping HBs Ag HCV Ab HIV1 antibody HIV2 antibody Pharmacokinetic testing for: amoxicillin, omeprazole, rifabutin, and 25-O-desacetylrifabutin Urine pregnancy ^{13}C Urea Breath Test Culture and Resistance/ Susceptibility for *H. pylori* CLO – Chlamydia Like Organism (Rapid Urease Test) Histology for H. pylori	Leucocytes Nitrite Protein pH Blood Specific gravity Ketones Glucose Sediment microscopy, If indicated by the dipstick

7.3.2.2 Recording of Clinical Laboratory Tests

All laboratory values will be filed in the source documents. The lab report must be interpreted by the investigator (i.e., signed and dated with the clinical significance of any abnormal values indicated).

Abnormal laboratory findings or other abnormal assessments (e.g., vital signs) that are judged by the investigator as clinically significant must be recorded as AEs or SAEs, if they meet the definition of an AE/SAE. The investigator should exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Laboratory findings that are considered adverse or serious adverse events will be reported and followed-up in the same manner as previously described.

7.4 Pharmacokinetic Evaluations

Blood samples for the determination of pretreatment and Visit 3 plasma concentrations of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin will be collected as described in Sections 6.2 and 6.4. The following will be recorded in the CRF:

- Date and time of the three most recent doses of study drug before collection of PK sample
- Date and time of collection of PK sample

Time of blood sample collection will be noted and determined relative to most recent dose of study drug. All PK samples will be collected and processed according to the procedure outlined in the laboratory manual. Plasma samples will be analyzed using validated methodology.

Plasma concentration data for each analyte will be summarized through data tabulations and descriptive statistics.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis Populations

8.1.1 Full Analysis Population (FAP)

The full analysis population (based upon the intention-to-treat principle as described in ICH-E9) will include all subjects who received at least one dose of randomized study treatment and will be identical with the safety population.

8.1.2 Modified Intent-to-Treat (mITT) Population

The mITT population will include all subjects who received at least one dose of randomized study treatment and undergo a ^{13}C UBT test at Visit 5.

8.1.3 Per Protocol (PP) Population

The PP population will include all subjects who consume at least 75% of planned study treatment received and undergo a ^{13}C UBT test at Visit 5.

8.1.4 PK Population (PKP)

The PKP will include those subjects in the full analysis population (FAP) that have demonstrable presence of any component of investigational drug at Visit 3.

8.2 Statistical Analyses

8.2.1 Primary Endpoint

The primary efficacy endpoint in this study is eradication of *H. pylori* among subjects, documented by ^{13}C UBT test results at the test of cure visit (Visit 5). Subjects with negative test results will be considered treatment successes. Subjects who test positive for *H. pylori* infection will be considered treatment failures. Those subjects with indeterminate, not assessable, or missing results from actual test of cure visits will undergo repeat ^{13}C UBT testing. Persistent indeterminate results will be considered treatment failures.

The primary endpoint will be assessed statistically in the full analysis population data set. The treatment groups will be compared with respect to the difference between the two treatment arms for the proportion of subjects with negative test results using a chi-squared test at the 5% level of significance (2-sided). The primary analysis will be repeated using the mITT and PP populations as sensitivity analyses.

Those subjects lost to follow-up or who fail to complete the test of cure visit will be excluded from the MITT and PP analyses. All efforts will be made to obtain data from the test of cure visit for each subject receiving randomized treatment.

8.2.2 Secondary Endpoints

The secondary endpoints are as follows and will be assessed using descriptive measures:

1) Antibiotic Resistance and Susceptibility Subgroup Analyses **-**
   The primary endpoint will be summarized within subgroups formed by the presence of *H. pylori* susceptibility and resistance to amoxicillin, clarithromycin, metronidazole and rifabutin determined based upon samples obtained prior to initiating study treatment. The proportion of subjects with failure to eradicate *H. pylori* and the treatment effect (difference in the proportions) will be estimated within each subgroup along with 95% 2-sided confidence intervals where there are an adequate number of subjects in the subgroup (e.g., at least 20 subjects per subgroup).
2) Pharmacokinetics – The plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl-rifabutin on Day 13 will be summarized by time following most recent dose

3) Assess the difference in antibiotic resistance and susceptibility of *H. pylori* after treatment with study drug in treatment failure subjects

8.2.3 Safety

The occurrence and severity of treatment emergent adverse events during the study and changes from baseline in hematology and chemistry laboratory values

8.2.4 Exploratory Endpoints

1) Upon study completion and unblinding of all subjects, CYP2C19 status will also be summarized and subgroup analyses of efficacy based on CYP2c19 status and pharmacokinetics will be performed using descriptive methods.
2) Eradication rates in failure to eradicate subjects who receive susceptibility directed standard of care will be analyzed descriptively.

8.3 Interim Analysis

No interim analysis is planned for this study.

8.4 Sample Size

Sample size for this study has been calculated based on a superiority comparison assuming 83% effectiveness for the new treatment, and 70% effectiveness for the control, with 90% power and a 2-sided alpha of 5%. Using these specifications, 222 subjects per arm will be required.

9. QUALITY CONTROL AND QUALITY ASSURANCE

RedHill Biopharma (RHB) and its CRO delegate shall implement and maintain quality control procedures in accordance with written standard operating procedures (SOPs) to ensure that the study, and specifically that the study data, are being generated, documented, and reported in compliance with the protocol, GCP and applicable laws and regulations. Central to the assurance of a high standard of quality of the data at the acquisition stage is study monitoring.

During study conduct, RHB or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow RHB monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Committee/Helsinki Committee, and/or to quality assurance audits performed by RHB, or companies working with or on behalf of RHB, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

RHB reserves the right to temporarily suspend or prematurely discontinue this study or individual study sites based on the findings of quality assurance audits. If such action is to be taken, RHB will discuss the specific reasons with the investigator(s). The investigator(s) must inform their IRB/IEC/REB/Helsinki Committee in a timely fashion, and provide them with the reason for the suspension or termination.

If the study is prematurely discontinued, all study materials and data must be returned to RHB once a final disposition assessment of all unused study drug and materials is performed, in accordance with the required study procedures.

The investigator and RHB share the responsibility to ensure data quality and integrity. The investigator will personally ensure the quality of the data by overseeing all study activities, including the timely review of both source data and CRF data as transferred from source. The investigator, or medically responsible delegate, will sign and date a declaration for each CRF attesting to his/her responsibility for the quality of all data recorded, stating that the data represents a complete and accurate record of each subject's participation in the study, and that the data has been medically reviewed in a timely fashion throughout the data acquisition period.

All processes and procedures undertaken by RHB once the data have been sequestered from the investigational sites will be subject to a rigorous quality control program. This includes data management (Section 12), statistics (Section 8), and Medical Writing (ICH E3).

10. ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Standard

The sponsor, investigator, and institution will ensure that this study is conducted in full conformity with the principles set forth in the following documents and guidance:

- the Declaration of Helsinki (Tokyo, 2004)
- the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research; The USA National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979)
- the USA Code of Federal Regulations: 45 CFR Part 46, 21 CFR Parts 50, 56, and 312

- the Canadian Food and Drug Regulations F-27 – C.R.C., c. 870: Division 5 (C.05.)
- ICH E6; Consolidated Guidelines on Good Clinical Practices (1997)
- International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 2002)

10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/ Research Ethics Board (REB)/Helsinki Committee

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by a properly constituted IRB/IEC/REB/Helsinki Committee that is functioning and operating in accordance with CFR Part 56 requirements and in accordance with the ICH GCP Guidelines in Section 3.2. The IRB/IEC/REB/Helsinki Committee must also review and approve the site's informed consent form (ICF) and any other written information provided to the subject, as well as any advertisement that will be used for subject recruitment. The investigator or his/her designee must forward to RHB or its delegate, copies of the IRB/IEC/REB/Helsinki Committee study approval(s) and the approved informed consent materials, specific versions being duly identified and dated by the IRB/IEC/REB/Helsinki Committee as being approved (e.g., signed, stamped, electronic signature).

If, during the study, it is necessary to amend the protocol and/or the ICF, or any other salient review documents, the investigator will be responsible for ensuring that the IRB/IEC/REB/Helsinki Committee reviews and approves these amended documents. IRB/IEC/REB/Helsinki Committee approval of the amended ICF must be obtained before new subjects can provide their consent to take part in the study using the revised versions of the form. Copies of all approvals must be forwarded to RHB or its' delegates as soon as available.

10.3 Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the study subject. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB/IEC/REB/Helsinki Committee approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject as well as answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study.

The subject should have reasonable opportunity to discuss the study with their family, physician, and/or surrogates prior to giving their consent to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subject for their records.

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic updates on the conduct of the study at his/her site to the IRB/IEC/REB/Helsinki Committee. Such timely periodic updates and notifications are the responsibility of the investigator.

10.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover the testing of biological samples and genetic tests, in addition to the clinical information relating to participating subjects. Any records sent to RHB will not identify the subjects. All subjects' identities will be restricted to their initials and a unique subject number.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor (or other authorized representatives of the sponsor), regulatory agencies or representatives of the IRB/IEC/REB/Helsinki Committee may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The confidentiality of personal health information has been the subject of recent laws and regulations in the US and Canada.

In the US, investigators and their affiliated institutions that are considered covered entities (CE) under the Health Insurance Portability and Accountability Act (HIPAA) will request that the subject sign a fully informed authorization that will accompany the consent form. The authorization will include the Authorization Core Elements (see Privacy Rule, 45 CFR §164.508I(1)) and the Authorization Required Statements (see Privacy Rule, 45 CFR § 164.508(c)(2)). These activities are intended to ensure that subjects understand how their Protected Health Information (PHI) arising from this research study is to be handled. The Privacy Rule is an additional but similar obligation to those that have been required under the Department of Health and Human Services (DHHS) or the Food and Drug Administration (FDA) Protection of Human Subjects Regulations (e.g., 45 CFR part 46 or 21 CFR parts 50 and 56, respectively) to take measures to protect such PHI from inappropriate use or disclosure.

The investigator's and other study site personnel's obligations do not apply to:

- Information that becomes publicly available through no fault of the investigator or study site personnel;

- Information that it is necessary to disclose in confidence to an IRB/IEC/REB/Helsinki Committee solely for the evaluation of the study;
- Information that it is necessary to disclose in order to provide appropriate medical care to a study subject; or
- Study results that may be published as described under the Publication Section.

10.5 Future Use of Stored Specimens

The *de facto* assumption of the donor of any biomaterial is that nothing will be done in regards to any specimen(s) to his or her detriment, or to that of his/her family. To ensure that this is so, the consent form is central to the donor's need to be apprised of certain details as to the fate of the sample. The investigator and REB/institution (specimen custodians) have an obligation to ensure that the subject is fully informed in this regard. To do so, the consent form will include the following information:

- purpose of research on the biomaterial
- type and amount of blood and tissue biopsies
- manner in which blood/tissue will be taken, safety/invasiveness of procedure, and conditions/duration of preservation
- potential uses for the blood/tissue
- safeguards to privacy and confidentiality
- identifying information and traceability (linkage)
- how blood/tissue use could affect privacy

In summary, all biological samples provided by the subject for the purposes of this study are to be used only for assessments and testing that have been explicitly agreed to in the consent form. The degree to which any retained samples will be protected for identification to a given individual will be specified.

11. DATA HANDLING AND RECORD KEEPING

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. CRO will be responsible for the design of the electronic case report form (eCRF), monitoring the trial according to GCP guidelines, preparation of data queries and reports to assist the clinical monitoring, and training each study site staff member entering data in the eCRF. CRO will also be responsible for preparation of analysis files from the database prior to analyses, assisting with the statistical analyses and statistical report, and preparation of the integrated clinical study report.

11.1 Documentation of Data

The electronic data capture (EDC) will be used for electronic data acquisition and storage. EDC will provide eCRFs for transfer of all research data by site personnel from data source

documentation to the study database. Each responsible person at a site will have user access to EDC through their unique username and password, with permissions providing each person their needed access. Some personnel will have data entry, data review, and query resolution permissions, while others may only have data read permissions, based on their individual study roles. EDC is flexible to allow customizable permissions as needed for study personnel.

11.2 Coding

The following coding dictionaries will be used:

Coding Dictionaries

Diseases:	Medical Dictionary for Regulatory Activities (MedDRA)
Adverse events:	MedDRA
Drugs:	World Health Organization (WHO) Drug Reference List

11.3 Data-Handling

Study data will be checked for completeness and correctness as it is entered by the real-time online checks applied by EDC. Off-line checks will also be run to perform any additional data review required. Any issues identified will be transferred to the study site via query for resolution by the investigator or his/her designee. All queries will be managed through EDC and audit trails of all queries and their resolution, along with any data changes, will be recorded.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Clinical research associates (CRAs) will monitor the data, verifying all captured data against its source. Monitoring will be enhanced by computer assisted data management identifying missing or possibly erroneous data as soon as data is entered into the system. This approach will allow initial remote monitoring, and communication between CRAs and site personnel before and between site visits, and will expedite data review and cleaning. Missing data and identified data errors (or possible errors) will be communicated by the CRAs to site investigators using the Query feature in EDC for correction or acknowledgement that data is correct as entered. As each subject's data entry is completed and fully monitored with all queries resolved, that subject's data will be locked by Data Management to only allow read access for the remainder of the study.

EDC and all study data are housed in a secure computing environment. EDC further provides a complete audit trail of all data entry, monitoring, and query activity. EDC is compliant with HIPAA and meets all requirements for 21 CFR Part 11.

11.4 Reporting

The statistical team will create a dedicated statistical report to support the clinical study report (CSR). The CSR will be written in accordance with the ICH E3 guidance.

11.5 Study Records Retention

As per US regulations, study documents will be retained at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least when 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations.

At the end of the retention period, the investigator or medical institution can arrange with the sponsors for continued retention at the sponsors' facilities. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

12. FINANCIAL, INSURANCE AND OWNERSHIP

12.1 Financial Disclosure

As described in CFR Title 21, Part 54, RHB will obtain a completed Form FDA 3454 attesting to the absence of financial interests by the investigator, or a completed Form FDA 3455 disclosing completely and accurately the following:

- Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial.
- Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- Any proprietary interest in the tested product held by any clinical investigator involved in a study;
- Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and
- Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

The investigator must update this information if any relevant changes occur in the course of the study, or for one year following completion of the study.

12.2 Ownership

All data and records provided by RHB or generated during the study (other than a subject's medical records/source documents) and all inventions discovered in the course of conducting the study are the property of RHB.

13. PUBLICATION POLICY

Data derived from the trial are the exclusive property of RHB. Any publication or presentation related to the trial must be reviewed and approved by RHB before submission of the manuscript. Prior to submitting for publication, presentation, use for instructional purposes, or other disclosure of the results of the study, the investigator(s) shall allow RHB a period of at least 30 days (or, for abstracts, at least 10 working days) to review the proposed publication or disclosure prior to its submission. Publications or disclosures of study results shall not include confidential information belonging to RHB. Publication or disclosure of study results must include the results from all sites combined. If the proposed publication/disclosure risks RHB's ability to patent any invention related to the study or seriously impairs its competitive strategy with respect to regulatory submission, licensing, or marketing of the final product, the publication or disclosure will be modified or delayed a sufficient time to allow RHB to seek patent protection of the invention or to realize its expected benefits, in so far as such requirement is reasonable. This statement does not give RHB any editorial rights over the content of a publication or disclosure, other than to restrict the disclosure of RHB's confidential information.

A clinical study report will be prepared by RHB in accordance with the ICH E3 guidance. RHB will retain final editorial control over the final clinical report.

14. LITERATURE REFERENCES

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15. APPENDICES

APPENDIX 1 SPONSOR APPROVAL AND SIGNATURES

APPENDIX 2 SCHEDULE OF EVENTS

APPENDIX 3 DEFINITIONS FOR CLINICAL AND LABORATORY ADVERSE EVENTS

APPENDIX 4 CYP-INTERACTING DRUGS

APPENDIX 1 SPONSOR APPROVAL AND SIGNATURES

The signatures below indicate the approval of this protocol and its attachments, and provide the necessary assurances that this trial will be conducted according to all requirements of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable Canadian and US regulations and to ICH guidelines.

MEDICAL DIRECTOR SIGNATURE:

_____ Date: _____

[redacted]

[redacted]

CHIEF EXECUTIVE OFFICER SIGNATURE:

_____ Date: _____

[redacted]

[redacted]

INVESTIGATOR'S APPROVAL

The signature below indicates the approval of this protocol and its attachments, and provides the necessary assurances that this trial will be conducted according to all requirements of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable Canadian and US regulations and to ICH guidelines.

INVESTIGATOR SIGNATURE:

_____ Date: _____

Signature

_____

Print Name

APPENDIX 2
SCHEDULE OF EVENTS – DOUBLE-BLIND PHASE OF STUDY

Assessments and Recordings	**Visit 0 Screening Day -42 to 0**	**Visit 1 Baseline Day 1**	**Visit 2 Phone follow-up Day 8 (±1 day)**	**Visit 3 Safety Visit Day 13 (±2 days)**	**Visit 4 Phone follow-up Day 28-60 (±2 days)**	**Visit 5 Test of Cure Day 43-71 (+7 days)**
Subject Information and Demographics	X					
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Urine Pregnancy Test on Females of Child Bearing Potential	X	X		X		X
Medical History	X	X				
Physical Examination with Vital Signs	X	X		X		X
Concomitant Medications	X	X		X		X
Laboratory Studies						
• Hematology, Chemistry, Urinalysis	X			X		X[b]
• ^{13}C UBT[a]	X[a]					X[a]
• HBs Ag, HCV Ab, HIV_1 /HIV_2 Abs	X					
Upper Endoscopy to determine *H pylori* status) • Biopsy for CLO • Biopsy for histology • Biopsy for culture and susceptibility	 X X X					
• CYP2C19 Genotyping		X				
Blood Sample for PK Assessment of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin – TO BE PERFORMED ON SUBJECTS WHO EARLY TERMINATE DURING 14 DAY COURSE OF TREATMENT IF POSSIBLE)		X[c]		X[c]		
Electrocardiogram	X					
Diary Dispensed		X				
Randomization		X				
Study Drug Dispensed		X				
Critical Review of Diary for: • Missed Doses • Concomitant Medications				 X X		
Drug Accountability/Compliance				X		X

Assessments and Recordings	Visit 0 Screening Day -42 to 0	Visit 1 Baseline Day 1	Visit 2 Phone follow-up Day 8 (±1 day)	Visit 3 Safety Visit Day 13 (±2 days)	Visit 4 Phone follow-up Day 28-60 (±2 days)	Visit 5 Test of Cure Day 43-71 (+7 days)
Adverse Event Assessment (SAEs through Visit 5/43-71 days post initiation of study drug). (Reminder at Visits 2 and 4)		**X**	**X**	**X**	**X**	**X**
Stress Compliance and Follow-up			**X**			
Stress ^{13}C UBT Testing and Reminder of Upcoming Appointment					**X**	

[a] Subject is to fast (no liquid or solid intake) for at least one hour for ^{13}C UBT prior to blood draw.

[b] For subjects with abnormal results at Visit 3.

[c] Blood samples taken prior to first dose at visit 1, and at visit 3 to assess plasma levels of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin.

SCHEDULE OF EVENTS – STANDARD OF CARE PHASE OF STUDY

Assessments and Recordings	**Visit 5A Phone ^{13}C UBT Follow-up Day 44-72 (+7 days)**	**Visit 6 SOC Baseline and Endoscopy After Day 44-72 (+ 14 days)**	**Visit 7 Phone follow-up Day 50 - 79 (±2 days)**	**Visit 8 SOC Test of Cure Day 85 – 140 (+14 days)**
Urine Pregnancy Test on Females of Child Bearing Potential		**X**		
Vital Signs		**X**		
Concomitant Medications		**X**		
Unblinded ^{13}C UBT Results: • Subjects with positive result – schedule upper endoscopy • Subjects with negative result – Visit 5 is their end-of-study visit	**X**			
Susceptibility Directed (initial endoscopy samples) or Standard of Care Therapy to Eradication Failure Subjects with Positive ^{13}C UBT		**X**		
Endoscopy with Biopsy (x2) for Culture and Susceptibility in Subjects with Positive ^{13}C UBT		**X**		
Stress Compliance Follow-up and Schedule ^{13}C UBT			**X**	
^{13}C UBT[a]				**X**

APPENDIX 3
DEFINITIONS FOR CLINICAL AND LABORATORY ADVERSE EVENTS

All adverse events (clinical and laboratory) will be rated as follows:

Severity (Clinical Events Only)

Severity of clinical events are to be **graded** as follows:

1 = Mild: Event Is noticeable to the subject, does not interfere with the subject's daily activities and usually does not require additional therapy or dose adjustment.

2 = Moderate: Event may interfere with the subject's daily activities and may require additional therapy

3 = Severe: Event may severely limit the subject's daily activities and typically requires therapy or intervention.

Causal Relationship

The investigators are to assess the **causal relationship** of all AEs using the following five categories:

Relationship	Causality	Description
Not related to investigational agent	Unrelated	The AE is clearly not related to the investigational agent.
	Unlikely	The AE is doubtfully related to the investigational agent.
Related to investigational agent	Possible	The AE may be related to the investigational agent.
	Probable	The AE is likely to be related to the investigational agent.
	Definite	The AE is clearly related to the investigational agent.

APPENDIX 4
CYP-INTERACTING DRUGS

CYP2C19						
INDUCERS	**INHIBITORS**			**SUBSTRATES**		
artemisinin carbamazepine norethindrone prednisone rifampicin	allicin (garlic derivative) armodafinil carbamazepine, chloramphenicol cimetidine esomeprazole etravirine	fluconazole fluvoxamine human growth hormone indomethacin ketoconazole lansoprazole moclobemide modafinil	omeprazole oral contraceptives oxcarbazepine pantoprazole probenecid rabeprazole ticlopidine topiramate	amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide diazepam hexobarbital	indomethacin lansoprazole S-mephenytoin Rmephobarbital moclobemide nelfinavir nilutamide omeprazole	phenobarbitone phenytoin primidone progesterone proguanil propranolol rabeprazole teniposide R-warfarin
	felbamate fluoxetine		voriconazole	imipramine NDeME	pantoprazole	

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CYP3A						
INDUCERS	**INHIBITORS**		**SUBSTRATES**			
amprenavir aprepitant armodafinil avasimibe barbiturates bosentan carbamazepine echinacea efavirenz etravirine glucocorticoids modafinil nafcillin nevirapine oxcarbazepine phenobarbital phenytoin pioglitazone prednisone rifabutin rifampin rufinamide St. John's wort troglitazone	alprazolam amiodarone amlodipine amprenavir aprepitant atazanavir atorvastin bicalutamide boceprevir chloramphenicol clarithromycin cilostazol cimetidine ciprofloxacin conivaptan cyclosporine darunavir/ ritonavir delaviridine diethyl- dithiocarbamate diltiazem erythromycin fluconazole fluoxetine fluvoxamine fosamprenavir gestodene ginkgo	goldenseal grapefruit juice imatinib indinavir indinavir isoniazid itraconazole ketoconazole lopinavir/ritonavir mibefradil mifepristone nefazodone nelfinavir nilotinib norfloxacin norfluoxetine oral contraceptives posaconazole ranitidine ranolazine ritonavir saquinavir starfruit telithromycin telaprevir tipranavir/ritonavir verapamil voriconazole zileuton	alfentanil alprazolam amlodipine aprepitant aripiprazole astemizole atorvastatin boceprevir budesonide buspirone cafergot cerivastatin chlorpheniramine clarithromycin cilostazol cisapride cocaine codeine-N- demethylation conivaptan cyclosporine dapsone darifenacin darunavir	dasatinib dexamethasone dextromethorphan diazepam dihydroergotamin e diltiazem docetaxel domperidone dronedarone eletriptan erythromycin ergotamine eplerenone estradiol everolimus felodipine fentanyl finasteride fluticasone imatinib haloperidol hydrocortisone indinavir irinotecan	LAAM lercanidipine lidocaine lopinavir lovastatin lurasidone methadone maraviroc midazolam nateglinide nelfinavir nifedipine nisoldipine nitrendipine ondansetron pimozide progesterone propranolol quetiapine quinidine quinine risperidone ritonavir salmeterol	saquinavir sildenafil simvastatin sirolimus sorafenib sunitinib tacrolimus tamoxifen taxol telaprevir telithromycin terfenadine testosterone tipranavir tolvaptan torisel trazodone triazolam vardenafil verapamil vincristine zaleplon ziprasidone zolpidem

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