

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213004Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-disciplinary Review and Evaluation NDA 213004
TALICIA (rifabutin, amoxicillin, omeprazole)

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number	213004
Priority or Standard	Priority
Submit Date	05/02/2019
Received Date	05/02/2019
PDUFA Goal Date	11/02/2019
Division/Office	DAIP/OAP
Review Completion Date	10/21/2019
Established/Proper Name	Omeprazole magnesium, Amoxicillin, Rifabutin
(Proposed) Trade Name	TALICIA
Pharmacologic Class	Proton pump inhibitor, penicillin-class antibacterial drug, and rifamycin antibacterial
Code name	RHB-105
Applicant	RedHill Biopharma Ltd.
Doseage form	Oral capsules
Applicant proposed Dosing Regimen	Four TALICIA capsules (rifabutin 50 mg, amoxicillin 1,000 mg and omeprazole 40 mg) every 8 hours with food for 14 days
Applicant Proposed Indication(s)/Population(s)	Treatment (b) (4) of <i>Helicobacter pylori</i> infection in adults
Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Treatment of <i>Helicobacter pylori</i> infection in adults
Recommended Dosing Regimen	Four TALICIA capsules (rifabutin 50 mg, amoxicillin 1,000 mg and omeprazole 40 mg) every 8 hours with food for 14 days

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DMEPA=Division of Medication Error Prevention and Analysis
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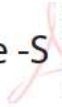
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TALICIA (rifabutin, amoxicillin, omeprazole)

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

RHB-105 (Talicia®) delayed-release capsules for oral use is a fixed dose combination of a rifamycin antibacterial (rifabutin), a penicillin-class antibacterial drug (amoxicillin), and a proton pump inhibitor (omeprazole as omeprazole magnesium). Each RHB-105 capsule contains 12.5 mg of rifabutin, 250 mg of amoxicillin, and 10 mg of omeprazole (equivalent to 10.3 mg of omeprazole magnesium). The proposed dosing regimen of RHB-105 to treat *H. pylori* infection in adults is 4 capsules every 8 hours with food for 14 days.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided adequate information to support the effectiveness of RHB-105 for the treatment of *H. pylori* infection in adults. The efficacy of the RHB-105 relies in part on the FDA's previous findings of efficacy for amoxicillin and omeprazole as part of approved multidrug regimens to eradicate *H. pylori*. Two randomized Phase 3 trials, Study RHB-105-02 and Study RHB-105-01 provide evidence of effectiveness for RHB-105 for the treatment of *H. pylori* infection. The contribution of rifabutin to the efficacy of the RHB-105 combination was demonstrated in Study RHB-105-02 and the added contribution of amoxicillin and omeprazole to the efficacy of RHB-105 triple combination was demonstrated from the literature and previously conducted studies. In Study RHB-105-02, patients were randomized to receive either RHB-105 or a comparator regimen of amoxicillin and omeprazole at the same dose as in RHB-105. RHB-105 therapy was superior to amoxicillin/omeprazole dual therapy for the primary endpoint of *H. pylori* eradication in the Intent to Treat (ITT) population. Study RHB-105-01 was a placebo-controlled study and provided evidence for the efficacy of RHB-105 relative to placebo.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In NDA 213004, the Applicant is seeking approval of RHB-105 (Talicia) for the treatment of *H. pylori* infection in adults. RHB-105 is a fixed dose combination of two antibacterial drugs (rifabutin, amoxicillin) and a proton pump inhibitor (omeprazole as omeprazole magnesium). This 505(b)(2) NDA for RHB-105 relies on the clinical studies completed by the Applicant, the FDA's previous findings of safety and effectiveness for the individual active ingredients in RHB-105 and published literature to support the approval of RHB-105 for the proposed indication. Clinical studies completed by the Applicant consist of two Phase 3 studies in adult patients with *H. pylori* infection (Studies RHB-105-01 and RHB-105-02), and two Phase 1 studies in healthy volunteers (Studies RHB-P2-148 and RHB-105-12). The listed drugs (LDs) include rifabutin (Mycobutin®; NDA 050689), amoxicillin (Amoxil®; NDA 050459), and omeprazole (Prilosec®; NDA 019810). Amoxicillin and omeprazole but not rifabutin are currently approved as part of dual and triple-therapy regimens for the treatment of *H. pylori* infection.

For the finding of efficacy of the RHB-105 for the treatment of *H. pylori* infection, the Applicant is relying in part on literature and published clinical data that support the added contribution of amoxicillin and omeprazole to the RHB-105 triple combination. The contribution of rifabutin to the efficacy of RHB-105 was determined in an active-controlled Phase 3 study (Study RHB-105-02), in which *H. pylori*-positive adults (based on ¹³C urea breath test and gastric biopsy for culture, histology, and/or *Campylobacter*-like organism test) complaining of epigastric pain/discomfort were randomized to receive either RHB-105 or comparator (amoxicillin/omeprazole) at the same dose and duration as RHB-105 but without rifabutin. RHB-105 was superior to amoxicillin/omeprazole dual therapy with *H. pylori* eradication rates of 83.8% vs. 57.7% in the Intent to Treat (ITT) population, a difference of 26.1%, (95% CI; 18.0, 34.1;p-value<0.0001). Findings in the per-protocol and modified ITT populations were of similar magnitude (both with p-value of <0.0001). A smaller placebo-controlled Phase 3 study (Study RHB-105-01) provided supportive evidence for the efficacy of RHB-105. In Study RHB-105-01, *H. pylori*-positive adults (based on ¹³C urea breath test and either fecal antigen test at screening or documented diagnosis of *H. pylori* in gastric biopsy within 12 weeks of screening) complaining of epigastric pain/discomfort were randomized to receive either RHB-105 or placebo. *H. pylori* eradication rates in the ITT population were 76.6% (95% CI; 66.0%, 84.7%) for the RHB-105-treated patients compared to 2.4% for the placebo-treated patients.

The Phase 3 studies and the Phase 1 studies support the safety of RHB-105 for the treatment of *H. pylori* infection. The safety database consisted of 339 subjects treated with RHB-105. Of these, a total of 305 patients were treated with at least 1 dose of RHB-105 at the intended regimen of 4 capsules administered every 8 hours for 14 days in the Phase 3 studies. No new safety signals with RHB-105 were identified in the clinical development program that would not be expected with the individual components of RHB-105. The pharmacokinetic data from the clinical development program also support that the proposed RHB-105 regimen is unlikely to exceed the systemic exposure achieved with the each of the LDs previously demonstrated to be safe.

Overall, RHB-105 demonstrated a favorable benefit-risk profile for the treatment of *H. pylori* infection. There were no new safety issues that would require a Risk Evaluation and Mitigation Strategy (REMS) or postmarketing studies. Safety information is adequately described in product labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<i>H. pylori</i> infection is usually asymptomatic but may have clinically significant manifestations such as dyspepsia (non-ulcer or functional), peptic ulcer disease (duodenal or gastric ulcer), atrophic gastritis, gastric adenocarcinoma, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and iron deficiency anemia. - There is convincing evidence for an etiologic role of <i>H. pylori</i> infection in peptic ulcer disease and gastric cancer.	There is insufficient evidence to support routine testing for and treatment of <i>H. pylori</i> in asymptomatic individuals. Eradication of <i>H. pylori</i> has been shown to reduce the risk of peptic ulcer recurrence. <i>H. pylori</i> is a risk factor for gastric cancer and its elimination is a promising strategy to reduce the incidence of gastric cancer.
Current Treatment Options	- Currently approved regimens to treat <i>H. pylori</i> are multidrug regimens consisting of antibacterial drugs plus an antisecretory drug. - Clarithromycin-based triple therapy or bismuth-based quadruple therapy are recommended first-line treatment options in North America. <i>H. pylori</i> eradication rates have been steadily diminishing in the US as clarithromycin resistance has been increasing worldwide (Thung I <i>et al.</i>, 2016).	Although there are several approved regimens to treat <i>H. pylori</i>, their utility is expected to decline over time due to growing resistance to antibacterial drugs used in standard of care therapies.
Benefit	- Existing clinical literature support the contribution of amoxicillin and omeprazole to the RHB-105 triple combination. Monotherapy with either of these drugs is unable to eradicate <i>H. pylori</i>. - Two randomized Phase 3 trials: Study RHB-105-02 and Study RHB-105-01 provide evidence of effectiveness for RHB-105 treatment of <i>H. pylori</i> infection. - In Study RHB-105-02, RHB-105 triple therapy was significantly	There is sufficient information from the published literature to support the added contribution of amoxicillin and omeprazole in the RHB-105 triple combination. The added contribution of rifabutin to RHB-105 was demonstrated in an adequate and well-controlled Phase 3 trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	superior to amoxicillin/omeprazole dual therapy at the same dose and duration as in RHB-105, with eradication rates of 83.8% and 57.7% in the ITT population, difference of 26.1%, (95% CI; 18.0, 34.1;p-value<0.0001). In Study RHB-105-01, <i>H. pylori</i> eradication rates in the ITT population were 76.6% (95% CI; 66.0%, 84.7%) for RHB-105 treated patients versus 2.4% for placebo-treated patients.	
Risk and Risk Management	No new safety concerns were identified with the RHB-105 therapy. There were no safety signals/potential safety issues identified that would require a Risk Evaluation and Mitigation Strategy (REMS).	The safety of RHB-105 is consistent with the known safety profile of its 3 drug components and is adequately described in labeling. Routine postmarketing surveillance activities will suffice at this time.

1.4. Patient Experience Data

H. pylori eradication was the primary endpoint for the Phase 3 studies (Studies RHB-105-01 and RHB-105-02). Validated (from the Agency perspective) PROs were not part of this application. However, Study RHB-105-01 evaluated severity of dyspepsia assessment (SODA) score as an exploratory endpoint. See Sections 8.1.1 and 8.1.2 for details.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
X	Patient reported outcome (PRO)	8.1.1 and 8.1.2
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

Helicobacter pylori is a gram-negative bacterium that infects the epithelial lining of the stomach and persists in the absence of treatment. It affects over 50% of the adult population worldwide (Lamb A, *et al.*, 2013) and 30-40% of the US population (Chey WD *et al.*, 2007). Although most infected patients are asymptomatic, *H. pylori* is a major cause of peptic ulcer disease and chronic gastritis. Persistent infection with *H. pylori* increases the risk of developing gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma in adults. *H. pylori* may also have a role in uninvestigated and functional dyspepsia, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura (Chey WD *et al.*, 2007). Approximately 20% of those infected with *H. pylori* will develop clinically significant sequelae such as peptic ulcer disease and gastric cancer (El-Serag HB *et al.*, 2018).

The American College of Gastroenterology (ACG) currently recommends “test and treat” approach as standard-of-care for the management of *H. pylori* infection (Chey WD *et al.*, 2017). Testing for and if positive treating for *H. pylori* infection is indicated for the following patients: active peptic ulcer disease, history of peptic ulcer disease without documented cure, low-grade gastric MALT lymphoma, history of endoscopic resection of early gastric cancer, chronic nonsteroidal anti-inflammatory drug therapy initiated, unexplained iron deficiency anemia, adults with idiopathic thrombocytopenia purpura, functional dyspepsia, and age <60 years with uninvestigated dyspepsia without alarm features (i.e., weight loss, anemia, dysphagia, persistent vomiting). There is insufficient evidence to support routine testing for and treatment of *H. pylori* in asymptomatic individuals.

Eradication of *H. pylori* has been shown to reduce the risk of peptic ulcer recurrence. *H. pylori* is a risk factor for gastric cancer and its elimination is a promising strategy to reduce the incidence of gastric cancer. Clarithromycin-based triple therapy or bismuth-based quadruple therapy are standard of care for *H. pylori* eradication. However, clarithromycin-based triple therapies which are approved for the eradication of *H. pylori* have reported cure rates below 80% due to clarithromycin resistance (Chey WD *et al.*, 2017). The current ACG guideline concludes that clarithromycin-based triple therapy remains a first-line treatment option only in regions where clarithromycin resistance is known to be <15%. The global incidence of primary *H. pylori* resistance to clarithromycin has been reported to be >15% (Savoldi A *et al.*, 2008). Although current large scale data on *H. pylori* antibacterial resistance in North America are unavailable, recent data from Houston suggest that clarithromycin resistance rates may now exceed 15% (Shiota S *et al.*, 2015).

2.2. Analysis of Current Treatment Options

Currently available FDA-approved treatment options for *H. pylori* infection are presented in Table 2-1. These multidrug regimens are approved for the treatment of patients with *H. pylori*

infection and duodenal ulcer disease to eradicate *H. pylori*. Dual therapy consists of a proton pump inhibitor (omeprazole) in combination with a macrolide antibacterial drug (clarithromycin), or a proton pump inhibitor (lansoprazole) in combination with a penicillin class antibacterial drug (amoxicillin). Clarithromycin triple therapy consists of a proton pump inhibitor (omeprazole, lansoprazole, esomeprazole, or rabeprazole) in combination with clarithromycin and amoxicillin. Omeclamox-Pak (omeprazole delayed release capsules, clarithromycin tablets, and amoxicillin capsules) and Prevpac (lansoprazole delayed release capsules, amoxicillin capsules, and clarithromycin tablets) are FDA approved co-packaged drug products for *H. pylori*. Bismuth-based quadruple therapy consists of a proton pump inhibitor (omeprazole) in combination with Pylera, a fixed dose combination product containing bismuth subcitrate, a nitroimidazole antibacterial drug (metronidazole), and a tetracycline class antibacterial drug (tetracycline hydrochloride). Another FDA approved treatment regimen consists of a histamine-2 receptor antagonist in combination with Helidac, a co-packaged drug product containing bismuth subsalicylate tablets, metronidazole tablets, and tetracycline hydrochloride capsules. Prevpac and Helidac are no longer marketed in the US and only generic versions of these drug products are available.

Table 2-1: Currently Available Treatment Options for *H. pylori* Infection

Regimen Drugs (doses)	Comment
Dual Therapy	Lower efficacy compared to clarithromycin triple or bismuth quadruple therapies.
Omeprazole 40 mg QD + Clarithromycin 500 mg TID for 14 days	
Lansoprazole 30 mg TID + Amoxicillin 1 g TID for 14 days	
Clarithromycin Triple Therapy	May not be an effective treatment option in regions where <i>H. pylori</i> clarithromycin resistance exceeds 15%
Omeprazole 20 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 10 days	
Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 10–14 days	
Esomeprazole 40 mg QD + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 10 days	
Rabeprazole 20 mg BID + Clarithromycin 500 mg BID + Amoxicillin 1 g BID for 7 days	
Bismuth Quadruple Therapy	
Omeprazole 20 mg BID + Pylera (bismuth subcitrate potassium 140 mg/metronidazole 125 mg/tetracycline hydrochloride 125 mg) 3 capsules QID for 10 days	
Histamine-2 receptor antagonist + co-packaged bismuth subsalicylate 524.8 mg QID, metronidazole 250 mg QID, and tetracycline hydrochloride 500 mg QID for 14 days	

Abbreviations: TID = three times daily; QD = once daily; BID = twice daily; QID = four times daily

**Note: The approved indication for amoxicillin-based dual therapy is limited to patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

RHB-105 is not marketed in the US. The components of RHB-105 (rifabutin, amoxicillin, and omeprazole) have been marketed in the US for several decades. The US FDA initially approved rifabutin in 1992, amoxicillin in 1974, and omeprazole in 1989. Rifabutin is currently approved for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced human immunodeficiency virus (HIV) infection. Amoxicillin and omeprazole are approved for several indications each including multidrug regimens for the treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*.

3.2. Summary of Presubmission/Submission Regulatory Activity

RHB-105 has been studied under IND 114552 which was opened October 10, 2013. A summary of the key regulatory interactions and proceedings with respect to the clinical development program is presented in Table 3-1.

Table 3-1: Summary of Key Regulatory Advice and Agreements on Clinical Development

Event/Date	Summary of Advice/Agreement
Pre-Investigational New Drug (IND) meeting, March 21, 2012	Agreement with the following in relation to the Phase 3 study: use of <i>H. pylori</i> eradication as a surrogate for clinical outcome; use of ¹³ C urea breath test (UBT) with fecal antigen testing to diagnose <i>H. pylori</i> ; follow-up standard of care treatment for patients who remain positive for <i>H. pylori</i> (ethical use of placebo-controlled study); collection of isolates of <i>H. pylori</i> from patients who fail therapy. Agreement with the proposed design of a Phase 1 pharmacokinetic (PK) study. The need to consider: a second PK study to address the effect of food; a second Phase 3 study.
Communication, November 06, 2014	RHB-105 granted a Qualified Infectious Disease Product (QIDP) designation for the treatment of <i>H. pylori</i> infection
Type B meeting, April 07, 2016	Discussions at this meeting plus various email communications provided input from the Agency into the design of the second Phase 3 study. The following agreements were reached with respect to the Phase 3 study: include a single active comparator of high dose amoxicillin/omeprazole; conduct primary analysis on the intent to treat population and sensitivity analysis on the per protocol population; complete the PK studies prior to initiation of the Phase 3 study.
Communication, August 28, 2018	RHB-105 granted a Fast Track Designation for the treatment of <i>H. pylori</i> infection
Pre-NDA meeting, March 18, 2019	Agreement on the content, organization, and regulatory filing strategy to support a 505(b)(2) NDA submission for the treatment of <i>H. pylori</i> infection.
NDA submission, May 02, 2019	NDA 213004 submission for the treatment (b) (4) of <i>H. pylori</i> infection in adults

Source: Adapted from Clinical Overview, Table 4.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted an inspection of five clinical sites from the Phase 3 studies. Sites No. 005 and No. 012 were from Study RHB-105-01, and Sites No. 019, No. 020, and No. 034 were from Study RHB-105-02. These sites were selected due to high enrollment, and thus contributed significantly to the overall efficacy determination. On-site inspections did not demonstrate any significant findings related to data integrity or human subject protection. Overall, OSI determined that the data from Study RHB-105-01 and Study RHB-105-02 appear reliable based on the available information and the conduct of the studies appear to have included appropriate protection of the rights and welfare of the human research subjects.

4.2. Product Quality

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on October 4, 2019.

This NDA describes a fixed dose combination product which contains three drug substances: Amoxicillin trihydrate (DMF (b) (4)), Rifabutin (DMF (b) (4)) and Omeprazole magnesium (DMF (b) (4)). The re-test periods for these three drug substances are (b) (4) months respectively. All three drug substances have corresponding USP monographs and the referenced DMFs for all three were found adequate to support this NDA.

The proposed product, Talicia capsule, is a delayed release capsule. The biopharmaceutics team found that the dissolution and PK characteristics supported the delayed-release claim. Each capsule contains 10 mg of omeprazole as omeprazole magnesium, 250 mg of amoxicillin as amoxicillin trihydrate and 12 mg of rifabutin. The finished capsule contains (b) (4) the immediate release Rifabutin/Amoxicillin (b) (4) and the delayed-release Omeprazole (b) (4). The capsule is orange, opaque and size ‘00’. The capsules are filled into a HDPE bottle with a (b) (4) child-resistant closure. The product is supplied as a carton which contains 2 bottles of Talicia (84 capsules) for a total of 168 capsules. The applicant requested a (b) (4)-month shelf life of the drug product, but a 24-month shelf life was granted. The biopharmaceutics team found that in the requested alcohol dose dumping study, the dissolution of omeprazole increased with the increase in alcohol. The conclusion was that the product should not be given to patients together with alcohol.

Excipient Qualification:

There were no novel excipients in the drug product. The quantitative composition of RHB-105 are provided in Table 4-1.

Table 4-1. Quantitative Composition of RHB-105

Component	Quality Standard	Function	mg per capsule
(b) (4)			
Amoxicillin	USP	Active drug substance	(b) (4)
Rifabutin	USP	Active drug substance	(b) (4)
Pregelatinized starch	NF	(b) (4)	(b) (4)
(b) (4)			
Omeprazole magnesium	USP	Active drug substance	10.3 ^{2) 6)}
Mannitol-starch	In-house	(b) (4)	(b) (4)
Crospovidone	NF	(b) (4)	(b) (4)
Sodium lauryl sulfate	NF	(b) (4)	(b) (4)
Meglumine	USP	(b) (4)	(b) (4)
Magnesium stearate	NF	(b) (4)	(b) (4)
(b) (4)	In-house	(b) (4)	(b) (4)
(b) (4)	In-house	(b) (4)	(b) (4)
(b) (4)	USP	(b) (4)	(b) (4)
Total			
Capsule			
Hard gelatin capsule, Size 00	In-house	Encapsulate contents	(b) (4)
Total			

- 1) Equivalent to 250 mg of Amoxicillin (b) (4) see 3.2.P.2.2.2
- 2) Equivalent to 12.5 mg of Rifabutin, (b) (4) see 3.2.P.2.2.2
- 3) (b) (4)
- 4) (b) (4)
- 5) Equivalent to 10 mg of Omeprazole, (b) (4)
- 6) (b) (4)
- 7) (b) (4)
- 8) (b) (4)
- 9) (b) (4)

Source: 3.2.P.1 Table 1 of Applicant's NDA Submission

NDA 213004, as amended, has provided adequate information to qualify all excipients in RHB-105 for safety. (b) (4) however, two components (b) (4) are excipients used in previous FDA approved products at higher levels per the Agency's Inactive Ingredient Database (IID). (b) (4) is novel, yet all of its components (b) (4) have been previously approved in other products (b) (4) levels of triethyl citrate in RHB-105 exceed amounts in other FDA approved drugs listed in IID, triethyl citrate is classified as Generally Recognized as Safe (GRAS) in foods according to the Agency's

Select Committee of GRAS Substances for Citrates (Report 84; NTIS Accession Number PB280954; 21 CFR Section 184.1911) and is of no safety concern at levels used in this orally administered product. All other excipients are listed in the IID and can be found at higher levels in other FDA approved products.

The capsule formulation of RHB-105 contains meglumine (b) (4). Meglumine, or methylglucamine, is a derivative of glucose and a methylamine sugar of sorbitol. The total daily intake of meglumine in RHB-105 (b) (4) exceeds excipient amounts in other FDA approved drugs per IIG for oral administration. There are approved products with substantially higher levels of meglumine listed in IID that are administered via intravenous (IV) injection; however, these drugs are administered for at most 3 days and, therefore, do not adequately cover the dosing duration of meglumine in RHB-105 (14 days). Additionally, several of these IV drug products with meglumine listed in the IID include meglumine as a component of the drug substance or salt form of the active ingredient (API), and not as a separate excipient. From a Pharmacology/Toxicology perspective the levels of meglumine in RHB-105 are qualified based its structural similarity to sorbitol and its current clinical experience in the Phase 3 studies submitted with this application. Meglumine (C7H17NO5) is a derivative of sorbitol (C6H14O6) with a similar chemical structure: one hydroxyl group in sorbitol is substituted with a methyl amine. Sorbitol is a sugar that is classified as GRAS in 21 CFR Section 184.1835. Due to the structural similarities of meglumine and sorbitol, meglumine would likely have a comparable safety profile as sorbitol. Sorbitol was shown to be generally well tolerated with no significant toxicology findings observed in rhesus monkeys administered 3 g daily for 3 months.¹ Similarly, daily ingestion of 10 g of sorbitol or sorbitol syrup by healthy humans for 1 month showed no evidence of any hematological effects or renal injury, with only minor laxative effects noted.¹

In addition, in the Phase 3 trials submitted by the Applicant (Study RHB-105-101 and RHB-105-102), over 300 patients received RHB-105 or omeprazole containing meglumine in the active comparator for 14 days. There were no adverse events observed in patients that were thought to be related to meglumine. (See Section 10 Review of Safety). Therefore, the Phase 3 trials likely support the safety of meglumine at levels included in RHB-105.

(Reviewer comment: The Applicant described summary results of a 4-week rat toxicology study with oral meglumine located in the European Chemicals Agency (ECHA) registration dossier for meglumine.² The summary table showed a NOAEL of 1000 mg/kg/day (maximum tested dose) for meglumine in this study with no evidence of any toxicological findings related to treatment. Because this is summary data that cannot be verified, and no actual reports of investigations can be independently reviewed in full by the review team, this data cannot be relied upon for qualification of meglumine in Talicia.)

¹ Ellis, F. W., and Krantz, J. C. (1941). J. biol. Chem., 141, 151.

² <https://echa.europa.eu/registration-dossier/-/registered-dossier/18480>

Taken together, based on the safety of sorbitol and the current clinical experience with meglumine, from a Pharmacology/Toxicology perspective the safety of meglumine at levels in RHB-105 are qualified.

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No nonclinical safety toxicology studies were submitted with this NDA. No pharmacology/toxicology information from the literature or other sources was reviewed to support this application. The Applicant relied on FDA's prior findings of safety and effectiveness for amoxicillin (NDA 050459 for Amoxil), rifabutin (NDA 050689 for Mycobutin), and omeprazole (NDA 019810 for Prilosec). The approvals of two of the relied-upon listed drugs, NDA 050459 Amoxil and NDA 019810 Prilosec, have been withdrawn FR effective (Federal Register determination that both products were not discontinued or withdrawn for safety or efficacy reasons). It is permissible for the applicant to refer to the currently approved ANDA labeling for omeprazole (ANDA 76048) and amoxicillin (ANDA 61926) because the listed drugs' labeling is not current. Combination toxicology studies with amoxicillin, rifabutin, and omeprazole were not required as all three drugs are approved and have extensive post-marketing safety information, including clinical experience with co-administration.

5.2. Referenced NDAs and DMFs

NDA 050689 and DMF (b) (4) (Rifabutin), NDA 050459 and DMF (b) (4) (Amoxicillin), NDA 019810, and DMF (b) (4) (Omeprazole)

5.3. Toxicology

5.3.1. General Toxicology

As described in the Mycobutin labeling, rifabutin treatment to mice, rats, and monkeys at doses 0.5, 1, and 3 times the human daily dose of 150 mg rifabutin, resulted in liver abnormalities including increased liver weights and elevated bilirubin.

5.3.2. Genetic Toxicology

The following information is described in the labeling for each listed drug included as a component of RHB-105.

Amoxicillin

- No genetic toxicity studies have been conducted with amoxicillin alone.
- A 4:1 mixture of amoxicillin to potassium clavulanate was negative in an Ames bacterial mutation assay, a yeast gene conversion assay, a mouse micronucleus test, and a dominant lethal assay in mice. The 4:1 mixture was weakly positive in a mouse lymphoma assay.

Rifabutin

- Rifabutin was negative for mutagenicity in an Ames bacterial mutation assay
- Rifabutin was not mutagenic or genotoxic in *Schizosaccharomyces pombe* P1 cells, V-79 Chinese hamster cells, in an in vitro human lymphocytes, or in vivo mouse bone marrow cells.

Omeprazole

- Omeprazole was negative for mutagenicity in an in vitro Ames bacterial mutation assay, an in vitro mouse lymphomas cell forward mutation assay, and negative in an in vivo rat liver DNA damage assay.
- Omeprazole was found to be clastogenic in an in vitro human chromosomal aberration assay and one of two in vivo micronucleus assays.

5.3.3. Carcinogenicity

Due to the short dosing duration for RHB-105, the nonclinical carcinogenicity information is not relevant for this indication. The following information is described in the labeling for each component of RHB-105.

Amoxicillin has not been evaluated for carcinogenicity in nonclinical animal models. Rifabutin was not found to be carcinogenic in mice or rats at doses up to 180 mg/kg/day and 60 mg/kg/day, respectively (approximately 36 and 12 times the recommended human dose of 150 mg of rifabutin). Omeprazole increased gastric enterochromaffin-like (ECL) cell carcinoids and ECL cells hyperplasia in a dose-dependent manner in two year studies in rats at with 1.7-140.8 mg/kg/day. In a one year study in rats, omeprazole was found to slightly increase brain astrocytomas in males at 0.4-16 mg/kg/day; however, in a 2 year study in rats, no astrocytomas were observed following 140.8 mg/kg/day omeprazole. A 78 week mouse study with omeprazole did not show increased tumor occurrence but was not conclusive. In a 26 week study in p53(+/-) mice, omeprazole did not increase tumor occurrence.

5.3.4. Reproductive and Developmental Toxicology

No nonclinical reproductive or developmental toxicity studies were conducted with RHB-105. The following reproductive and developmental information is described in the labeling of each component of RHB-105:

Amoxicillin

NDA Multi-disciplinary Review and Evaluation NDA 213004
TALICIA (rifabutin, amoxicillin, omeprazole)

- Amoxicillin did not cause harm to the fetus in reproduction studies in mice and rats at doses up to 2000 mg/kg in either study (approximately 3 and 6 times the 3 g human dose of amoxicillin in RHB-105).
- In a multi-generational reproduction study in rats, fertility was not affected at doses up to 500 mg/kg (approximately 2 and 3 times the 3 g human dose of amoxicillin in RHB-105). No other reproductive effects were noted at these exposures.

Rifabutin

- Rifabutin did not cause fetal malformations in rats and rabbits when given to pregnant dams at doses up to 80 mg/kg (approximately 6 and 13 times the human dose of 150 mg rifabutin in RHB-105).
- Fetal viability was decreased in rats dosed with 200 mg/kg rifabutin (approximately 6 time the human dose of 150 mg rifabutin in RHB-105). Fetal skeletal variations were observed in rats following 40 mg/kg doses (approximately equivalent to the 150 mg human dose).
- In rabbits, doses of 80 mg/kg rifabutin resulted in maternal toxicity and increased fetal skeletal anomalies (approximately 5 times the human dose of 150 mg rifabutin).
- When dosed with 160 mg/kg rifabutin, male fertility was impaired in rats.

Omeprazole

- Omeprazole was not teratogenic when given to rats and rabbits during organogenesis.
- In rabbits dosed with 6.9- 69 mg/kg/day, omeprazole resulted in dose-dependent increases in embryo lethality, fetal resorptions, and pregnancy disruptions (approximately equivalent to 11 times the human dose of 120 mg omeprazole).
- In rats dosed with 13.8- 138 mg/kg/day omeprazole prior to mating through lactation, dose-dependent increases in embryo/fetal toxicity and postnatal developmental toxicities were observed.
- Reproductive and developmental studies conducted in animal models with esomeprazole, an enantiomer of omeprazole, resulted in decreased neonatal/early postnatal survival, reductions in body weight and body weight gain, neurobehavioral, bone growth and developmental delays in rats exposed in utero to ≥ 138 mg/kg/day (approximately ≥ 11 times the human dose of 120 mg esomeprazole/omeprazole).
- Bone effects were also observed in pregnant and lactating rats dosed with 14-280 mg/kg/day esomeprazole in a prenatal and postnatal toxicity study.
- In a juvenile rat toxicity study, esomeprazole was found to decrease body weight and body weight gains and affect bone development and overall growth at 138- 280 mg/kg/day.
- In a 4 week juvenile rat study, exposure to esomeprazole from postnatal day 7-35 resulted in mortality (280 mg/kg/day), reductions in body weight and body weight gain, bone growth, and overall growth (≥ 140 mg/kg/day).
- Omeprazole did not affect fertility or reproduction in rats at doses up to 138 mg/kg/day.

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology review of this NDA focused on (A) assessment of the relative bioavailability (BA) of Talicia® (RHB-105) components compared to the respective individual drugs, (B) assessment of the need for an alternative dosing regimen or management strategy based on a patient's CYP2C19 phenotype status, and (C) the proposed drug product labeling.

6.1.1. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information provided by the Applicant in NDA 213004 for Talicia® (RHB-105) and recommends approval of this NDA.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Pivotal evidence of effectiveness is derived from a controlled Phase 3 study (Study RHB-105-02) that evaluated the safety and efficacy of the proposed RHB-105 dosing in adults with <i>H. pylori</i> infection. The supportive evidence of effectiveness is derived from a placebo-controlled Phase 3 study (Study RHB-105-01). The Applicant has also conducted two Phase 1 studies: RHB-P2-418 (Relative BA study) and RHB-105-12 (Food effect study). Findings from Study RHB-P2-418 show that at the same daily dose, the systemic bioavailability of three RHB-105 components were similar to or lower than that of the respective individual drugs.
General dosing instructions	The proposed dosing is four RHB-105 capsules administered every eight hours with food for 14 days, which is same as the dosing evaluated in the two Phase 3 studies. The proposed RHB-105 dosing is acceptable from a clinical pharmacology perspective.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The Applicant proposes RHB-105 may be administered regardless of a patient's CYP2C19 phenotype status³. Based on the safety/tolerability and efficacy information in patients with various CYP2C19 phenotypes and considering relatively short duration of the proposed RHB-105 treatment (14 days), the Applicant's proposal is acceptable.

³ CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole.

Review Issue	Recommendations and Comments
	No new information on the effect of other intrinsic or extrinsic factors on RHB-105 has been submitted. To address this aspect in the RHB-105 labeling, the Applicant proposes to rely on FDA’s findings of safety and effectiveness for the listed drugs. The Applicant’s proposal is acceptable.
Labeling	The Applicant proposes to include the clinical pharmacology information from the listed drugs along with the pharmacokinetic information available from the clinical studies conducted with RHB-105. The content and format of the proposed labeling language is not aligned with the current labeling guidance and has been revised.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable as the to-be-marketed formulation was used in Phase 3 studies.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

RHB-105 is a delayed release capsule that contains 10 mg omeprazole (as 10.3 mg omeprazole magnesium), 250 mg amoxicillin, and 12.5 mg rifabutin. The proposed RHB-105 dosing for the treatment of adults with *H. pylori* infection is four RHB-105 capsules administered every eight hours with food for 14 days, equivalent to a unit dose of 40 mg omeprazole, 1000 mg amoxicillin, and 50 mg rifabutin, and a total daily dose of 120 mg omeprazole, 3000 mg amoxicillin, and 150 mg rifabutin. The Applicant has conducted two Phase 3 studies that evaluated the safety and efficacy of RHB-105 in adults with *H. pylori* infection using the proposed dosing. The Applicant has conducted two additional clinical studies that evaluated the pharmacokinetics of RHB-105 in healthy adults: RHB-P2-418 (Comparative BA study) and RHB-105-12 (Food effect study).

Bioavailability Assessment:

Study RHB-P2-418 evaluated the BA of RHB-105 components compared to the respective individual drugs in healthy subjects receiving the following two treatments for one day in a crossover manner. Subjects were fasted with fasting periods of 10 hours pre-first dose, 3.5-4.5 hours post first dose, and 3.5-4.5 hours pre- and post-dose for the subsequent doses.

Treatment-1: Four RHB-105 capsules each containing 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole given three times eight hours apart for one day resulting in respective total daily doses of 150 mg, 3000 mg, and 120 mg

Treatment-2: One Mycobutin® (Rifabutin) 150 mg capsule once in the morning and two Amoxicillin 500 mg capsules as well as one Prilosec® (Omeprazole) 40 mg delayed-release capsule taken concomitantly given three times eight hours apart for one day resulting in respective total daily doses of 150 mg, 3000 mg, and 120 mg

The findings from BA assessments for each component are reported in Table 6-1.

Table 6-1: Summary of the Bioavailability Assessment

Parameters	% Point Estimates RHB-105/Individual Drug (90% CI)
<i>Amoxicillin</i>	
AUC _{0-inf} (µg·h/mL)	111 (105 - 118)
C _{max} (µg/mL)	107 (98 - 116)
<i>Omeprazole</i>	
AUC _{0-inf} (ng·h/mL)	66 (56 - 77)
C _{max} (ng/mL)	94 (77 - 114)
<i>Rifabutin</i>	
AUC _{0-inf} (ng·h/mL)	89 (80 - 98)
C _{max} (ng/mL)	36 (32 - 42)

Source: Reviewer's Analysis

Overall, findings from this study demonstrated that at the same daily dose given under the dosing conditions of the study, the systemic BA of three RHB-105 components are similar to or lower than that of respective individual drugs. See Section 17.3.2.1 for additional details on the study design and findings.

The proposed daily amoxicillin dose (3000 mg) is the same as the FDA approved amoxicillin dose as part of the dual therapy for the treatment of *H. pylori* infection. The proposed rifabutin daily dose is 150 mg, which is lower than the 300 mg daily dose approved for the prevention of disseminated *Mycobacterium avium* complex disease in patients with advanced HIV infection. The proposed daily dose of omeprazole (120 mg) with RHB-105 is higher than the recommended daily dose (40 mg) of Prilosec for the treatment of *H. pylori* infection. However, the relative BA study showed that RHB-105 has 34% lower BA for omeprazole compared to the listed drug at the total omeprazole dose of 120 mg for one day. In addition, the Prilosec labeling recommends higher omeprazole daily doses for the treatment of pathological hypersecretory conditions than for the treatment of *H. pylori* infection, i.e., recommended starting dose is 60 mg once daily, this dose is to be adjusted to the patient's needs and doses up to 120 mg three times a day have been administered. Additional safety information is available from two Phase 3 studies that support the proposed omeprazole dose in RHB-105 treatment.

Food Effect

RHB-105 is proposed to be administered with food to reduce potential for gastrointestinal related side effects associated with rifabutin. RHB-105 was given with food in two Phase 3 studies. It is noteworthy that Prilosec is recommended to be administered before meal (not strictly fasted condition). The food effect study conducted by the Applicant showed that, following a single dose of four RHB-105 capsules, the mean omeprazole $AUC_{0-\infty}$ and C_{max} under fed conditions were 18% and 8%, respectively, of those under fasting conditions. Despite the observed significant reduction in the omeprazole exposure for RHB-105 when given with high-fat meal, the proposed omeprazole daily dose of 120 mg for RHB-105 is expected to have the antisecretory effect due to the following:

- Per the omeprazole drug labeling, the antisecretory effect of omeprazole is exerted after multiple daily dosing of as low as 20 mg (0.17 times the proposed omeprazole daily dose of 120 mg).
- A publication by *Sharma, B K et. al.* 1984 suggests that >80% decrease in 24-hour intragastric H⁺ activity was associated with the omeprazole AUC_{0-24} of approximately > 1.4 $\mu\text{mol}/\text{hour}/\text{L}$. The Reviewer's independent analysis using data from the food effect study showed that mean omeprazole AUC_{0-8h} was 0.78 $\mu\text{mol}/\text{hour}/\text{L}$ in healthy subjects who received four capsules of RHB-105 with high-fat meal. It is expected that the mean AUC_{0-24} following the proposed dosing regimen (four capsules every eight hours for 14 days) would be approximately 2.34 $\mu\text{mol}/\text{hour}/\text{L}$ or higher, which is expected to have the antisecretory effect in *H. Pylori* patients.

Food did not exert significant effect on the BA of amoxicillin and rifabutin. See Section 17.3.2.2 for additional details on the design and findings of the food effect study.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed RHB-105 dosing for the treatment of adults with *H. pylori* infection is four RHB-105 capsules administered every eight hours with food for 14 days, equivalent to a total daily dose of 150 mg rifabutin, 3000 mg amoxicillin, and 120 mg omeprazole.

Therapeutic Individualization

CYP2C19 Genotype-inferred Phenotypes

Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzymes, primarily by CYP2C19, which is a polymorphic enzyme. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. The Applicant proposes that RHB-105 may be administered regardless of CYP2C19 phenotypes. Safety, efficacy, and limited pharmacokinetic data from two Phase 3 trials did not show appreciable differences in patients with various CYP2C19 phenotypes. Based on this information and the relatively short treatment duration (14 days), the Applicant's proposal is acceptable. See sections 6.3.2, 17.3.3, and 17.3.4 for additional details.

The effect of other intrinsic or extrinsic factors on the pharmacokinetics of RHB-105 has not been studied. Clinical pharmacology recommendations related to the therapeutic individualization of RHB-105 are summarized below:

Renal Impairment: The use of RHB-105 should be avoided in patients with severe renal impairment (GFR < 30 mL/min) as amoxicillin is primarily eliminated by the kidney.

Hepatic Impairment: The use of RHB-105 should be avoided in patients with hepatic impairment (Child-Pugh Class A, B, or C) as systemic exposure to omeprazole substantially increased in patients with hepatic impairment compared to healthy subjects.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and pharmacokinetic information of the RHB-105 components is summarized in the table below. The pharmacokinetic parameters and effect of food reported in the table are from clinical studies conducted with RHB-105 in healthy subjects and the information on protein binding, metabolism, and excretion is based on the prescribing information of individual RHB-105 components. The available pharmacokinetic information in adults with *H. pylori* infection is limited. See Section 17.3.3 for additional details.

Pharmacokinetic Information and Parameters	Amoxicillin	Omeprazole	Rifabutin
Mean (SD) C _{max} (ng/mL) ^a	15860 (3340)	1281 (518)	88 (21)
Mean (SD) AUC ₂₄ (ng*hr/mL) ^a	142140 (29216)	7072 (3473)	1320 (306)
Absorption			
Median (range) T _{max} (h) ^b	2 (1.25-3)	1.25 (0.75-1.77)	3 (2-6)
Effect of Food: With high-fat meal ^b (Relative to fasting)	↓30% in C _{max} ↔ AUC ↑T _{max} by 1.5 hr	↓92% in C _{max} ↓82% in AUC ↑T _{max} by 3 hr	↑14% in C _{max} ↑25% in AUC ↑T _{max} by 2 hr
Distribution			
Protein Binding	20%	95%	85%
Elimination			
Mean (SD) t _{1/2} (h)	1.3 (0.2)	1 (0.3)	33 (26)
<i>Metabolism</i>			

Metabolic pathways	Not significantly metabolized	- Extensively metabolized - CYP2C19 (major) responsible for the formation of hydroxyomeprazole - CYP3A4 (minor) responsible for the formation of omeprazole-sulphone - These metabolites have very little or no antisecretory activity	- Of the five metabolites that have been identified, 25-O-desacetyl and 31-hydroxy are the most predominant with a plasma metabolite: parent AUC ratio of 0.10 and 0.07, respectively 25-O-desacetyl rifabutin has an activity equal to the parent drug with up to 10% to the total antimicrobial activity
<i>Excretion</i>			
<i>Major route of elimination</i>	60% of oral dose excreted in urine in 6-8 hours (mostly as unchanged drug)	77% of dose excreted in urine as metabolites and the remainder of the dose recovered in feces	53% of the oral dose was excreted in urine, primarily as metabolites - About 30% of the dose is excreted in feces - Renal and biliary clearance of unchanged drug each contribute approximately 5% to apparent oral clearance

C_{max} = Maximum plasma concentration, AUC_{24} = Area under the concentration vs. 24-hour time curve, T_{max} = Time to reach C_{max} , $t_{1/2}$ = Elimination half-life, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no significant change, ND = No data.

^a C_{max} , and AUC_{24} estimates derived from 15 healthy subjects following administration of four RHB-105 capsules three times (8 hours apart) for one day resulting in the total daily oral doses of 150 mg rifabutin, 3000 mg amoxicillin, and 120 mg omeprazole.

^b Changes in C_{max} , AUC_{∞} , and T_{max} estimates reported from a crossover food-effect study in 18 healthy subjects following the administration of four RHB-105 capsules administered once with a high-fat, high calorie meal consisting approximately 1000 kcal (14% from protein, 53% from fat, and 33% from carbohydrates) compared to when four RHB-105 capsules administered without food. Reported T_{max} and $t_{1/2}$ estimates are from the same study from 18 subjects (for rifabutin, from 17 subjects) who received RHB-105 capsules without food.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Pivotal evidence of effectiveness is derived from a controlled Phase 3 study (Study RHB-105-02) that evaluated the safety and efficacy of RHB-105 in adults with *H. pylori* infection. The

supportive evidence of effectiveness is derived from a placebo-controlled Phase 3 study (Study RHB-105-01).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed RHB-105 dosing is appropriate for the general patient population for the treatment of *H. pylori* infection. In a Phase 3 study (RHB-105-02), the response rate observed in the RHB-105 treatment arm was higher relative to the comparator treatment arm (83.8% versus 57.7%, $p < 0.0001$). In another Phase 3 study (RHB-105-01), the *H. pylori* eradication rate was 76.6% for the RHB-105-treated patients compared to 2.4% for the placebo-treated patients (see Section 8.1). The proposed RHB-105 dosing is same as the dosing evaluated in two Phase 3 studies.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

CYP2C19 Genotype-inferred Phenotype

CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The Applicant evaluated the effect of CYP2C19 genotype-inferred phenotype on the safety and efficacy of RHB-105 as an exploratory endpoint in Phase 3 studies, RHB-105-01 and RHB-105-02, and its effect on omeprazole pharmacokinetics in Study RHB-105-02. Blood samples for genotyping were collected at baseline. The applicant reports genotypes (Table 6-2) from combinations of CYP2C19 *1, *2, *3, and *17 alleles that were classified into phenotypes according to CPIC consensus terms (see section 17.3.4).

Table 6-2: Distribution of CYP2C19 genotype-inferred Phenotypes in Full Analysis Set

Study	Genotype-inferred Phenotype	Treatment Group		
		Comparator (Amoxicillin/Omeprazole)	Placebo	RHB-105
RHB-105-01	Intermediate metabolizers	N/A	8	17
	Normal metabolizers	N/A	27	48
	Poor metabolizers	N/A	2	0
	Rapid metabolizers	N/A	4	11
	Missing	N/A	0	1
RHB-105-02	Intermediate metabolizers	52	N/A	48
	Normal metabolizers	107	N/A	114
	Poor metabolizers	4	N/A	5
	Rapid metabolizers	55	N/A	45
	Ultra-rapid metabolizers	3	N/A	10
	Missing	2	N/A	1
	Not reported	4	N/A	5

N/A= Not applicable

Reviewer's comment: Phenotype frequencies vary across different ethnic populations. Of note, the frequency of poor metabolizers are estimated to be 2.5% in whites, 4.3% in African-Americans, 12.4% in South/Central Asians, 14.5% in East Asians, and up to 46.4% in Oceanian populations (Pharmacogenomics Knowledgebase at :PharmGKB.org at <https://www.pharmgkb.org/page/cyp2c19RefMaterials>). Of the 560 patients with reported CYP2C19 phenotype status in the full analysis set, 11 were CYP2C19 poor metabolizers, 5 of whom received RHB-105.

CYP2C19 Phenotypes vs. Efficacy

Regardless of CYP2C19 status, the rates of *H. pylori* eradication were higher in RHB-105 treatment arm in studies RHB-105-01 and RHB-105-02 compared to the placebo and comparator treatment arms, respectively (See sections 8.1.2 and 8.1.4). In addition, in Study RHB-105-01, efficacy results by the CYP2C19 phenotype status based subgroups are consistent with the overall results (See Section 8.1.2). In Study RHB-105-02, in the groups of rapid, normal, and intermediate metabolizers, eradication rates of the RHB-105 arm were significantly higher than the comparator arm and in the other two subgroups, numbers were too small to make any conclusions (See Section 8.1.4).

CYP2C19 Phenotypes vs. Safety

No notable differences were identified in the rates of treatment-emergent adverse events across the subgroups of patients with different CYP2C19 status in both Phase 3 trials (See Section 10.7). With respect to relationship between a patient's CYP2C19 status and omeprazole exposure/pharmacokinetics, qualitative information is available from Study RHB-105-02. However, this information is very limited to reliably assess the effect of CYP2C19 genotype-inferred phenotype on RHB-105 PK and safety (See Section 17.3.3).

In conclusion, the available efficacy, safety, and PK results together with the proposed relative short treatment duration (14 days), suggest that no alternative dosing regimen or management strategy would be needed based on a patient's CYP2C19 phenotype status.

No new information on the effect of other intrinsic or extrinsic factors on RHB-105 has been submitted.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes, there are clinically relevant food-drug or drug-drug interactions with RHB-105.

Food Effect

A food-effect study demonstrated high fat meal significantly reduced omeprazole C_{max} and AUC by 92% and 82%, respectively, when compared to fasting conditions. High-fat meal did not have a significant effect on amoxicillin and rifabutin BA. Despite the observed notable food-effect on omeprazole, RHB-105 is proposed to be administered with food to reduce potential

for gastrointestinal related side effects associated with rifabutin. Of note, RHB-105 was given with food in two Phase 3 studies.

Drug-Drug Interactions

Drug interaction studies with RHB-105 have not been conducted. Rifabutin is a substrate and inducer of cytochrome P450 (CYP) 3A enzymes. Omeprazole is a substrate and an inhibitor of CYP2C19, and a substrate of CYP3A4. Co-administration of RHB-105 and other drugs that are substrates, inhibitors, and/or inducers of these enzymes may alter concentrations of rifabutin/omeprazole or other co-administered drugs. The drug interaction information to be included in the RHB-105 labeling will be based on the FDA approved prescribing information of respective listed drugs.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

This NDA contains the results of two randomized, double-blinded, controlled, Phase 3 studies with the proposed Talicia (rifabutin 12.5 mg, amoxicillin 250 mg, and omeprazole 10 mg per capsule) regimen of 4 capsules every 8 hours for 14 consecutive days.

Study RHB 105-01 was placebo controlled. Study RHB-105-02 randomized subjects to either Talicia or amoxicillin and omeprazole, at the same doses and duration as Talicia but without the rifabutin component. This study was designed to assess the added contribution of rifabutin to the combination. The Applicant is relying on literature and published clinical data to address how the remaining 2 components, amoxicillin and omeprazole, contribute to the effect of Talicia.

Table 7-1: Listing of Clinical Trials Relevant to this NDA

Study ID	NCT no.	Trial Design	Regimen/ Schedule/ Duration	Study Endpoints	No. Randomized/ Treated	Study Population	No. of Centers/ Countries
Controlled Studies to Support Efficacy and Safety							
RHB-105-01	NCT03198507	Phase 3, MC, R, DB, PC, PG trial	- RHB-105: 4 × RHB-105 (rifabutin/amoxicillin/omeprazole 12.5/250/10 mg) capsules PO q8h for 14 days - Placebo: 4 × Placebo capsules PO q8h for 14 days Follow-up to Day 43 (+7)	<i>H. pylori</i> eradication confirmed via ¹³ C UBT testing at 28-35 days after treatment completion	RHB-105: 78/77 Placebo: 41/41	Adult patients complaining of epigastric pain/discomfort and positive for <i>H. pylori</i> infection ¹	9 centers/ 1 country (USA)
RHB-105-02	NCT01980095	Phase 3, MC, R, DB, AC, PG trial	- RHB-105: 4 × RHB-105 (rifabutin/amoxicillin/omeprazole 12.5/250/10 mg) capsules PO q8h for 14 days - Comparator: 4 × comparator (amoxicillin/omeprazole 250/10 mg) capsules PO q8h for 14 days Follow-up to Day 43 – 71 (+7)	<i>H. pylori</i> eradication confirmed via ¹³ C UBT testing 43-71 days after treatment initiation	RHB-105: 228/228 Comparator: 227/227	Adult patients complaining of epigastric pain/discomfort and positive for <i>H. pylori</i> infection ²	55 centers/ 1 country (USA)
Other studies pertinent to the review of safety (clinical pharmacological studies)							
RHB-P2-418	–	Phase 1, SC, R, OL, single and multiple doses, 2-period, 2-sequence, crossover study	2-arm crossover with 14 day washout between treatments - RHB-105: 4 × RHB-105 (rifabutin/amoxicillin/omeprazole 12.5/250/10 mg) capsules PO q8h – 3 doses - Listed Drugs: 1 × Mycobutin® 150 mg capsule PO (single dose) + 2 × Amoxicillin 500 mg capsules PO	PK/Safety	16/ 16 – RHB-105 15 – Listed Drugs	Healthy adults	1 center/ 1 country (Canada)

NDA Multi-disciplinary Review and Evaluation NDA 213004
TALICIA (rifabutin, amoxicillin, omeprazole)

Study ID	NCT no.	Trial Design	Regimen/ Schedule/ Duration	Study Endpoints	No. Randomized/ Treated	Study Population	No. of Centers/ Countries
			q8h (3 doses) + 1 × Prilosec® 40 mg delayed-release capsule PO q8h (3 doses) Follow-up to Day 18				
RHB-105-12	–	Phase 1, SC, R, laboratory-blinded, single dose, 3-period, 3-sequence, crossover study	3-arm crossover with 14 day washout between treatments • RHB-105 Fed: 4 × RHB-105 (rifabutin/amoxicillin/omeprazole 12.5/250/10 mg) capsules PO under fed conditions – single dose • RHB-105 Fast: 4 × RHB-105 (rifabutin/amoxicillin/omeprazole 12.5/250/10 mg) capsules PO under fasting conditions – single dose • Comparator Fast: 4 × comparator (amoxicillin/omeprazole 250/10 mg) capsules PO under fasting conditions – single dose Follow-up to Day 34	PK/Safety	18/ 18 – RHB-105 Fed 18 – RHB-105 Fast 18 – Comparator Fast	Healthy adults	1 center/ 1 country (Canada)

Abbreviations: MC = multi-centered; R = randomized; DB = double-blinded; PC = placebo-controlled; AC = active-controlled; PG = parallel-group; SC = single-centered; OL = open-label; PO = oral; UBT = urea breath test; PK = pharmacokinetics

¹ Positive for *H. pylori* infection via ¹³C UBT and either fecal antigen test or previous diagnosis by gastric biopsy.

² Positive for *H. pylori* infection via ¹³C UBT and follow-up upper endoscopy (culture, histology, or *Campylobacter*-like organism [CLO] test).

7.2. Review Strategy

This NDA was submitted in eCTD format. Data sources include protocols, reporting and analysis plans, study reports, the integrated summaries of efficacy and safety, and data sets (in both Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) formats). All submitted data sets are available at \\CDSesub1\evsprod\NDA213004\0001.

Overall, the quality of the data and analyses was adequate. It was possible to reproduce the primary analyses, from the original data source, for the two studies we reviewed.

7.3. RHB-105 Component Contribution Review and Assessment

RHB-105 is a fixed dose, oral capsule formulation, a triple combination of two antibacterial drugs rifabutin (12.5 mg) and amoxicillin (250 mg), and a proton pump inhibitor (PPI), omeprazole (10 mg). The intended dose is 4 capsules administered every 8 hours with food for 14 days for a total daily dose of 150 mg rifabutin, 3 g amoxicillin, and 120 mg omeprazole. Given that it is a combination of three drugs, it is important to determine that each of the three components rifabutin, amoxicillin, and omeprazole, contribute to the effect of the combination product. The Applicant submitted a literature review supporting the use of the rifabutin/amoxicillin/omeprazole therapy in the treatment of *H. pylori* infection and rationale to support partial waiver for a full factorial study design. The review team also conducted a search of the publicly available information to support the combination. The following is a summary of this information.

Contribution of Rifabutin

In the randomized, double-blind, controlled phase 3 trial RHB-105-02, RHB-105 triple therapy was significantly superior to amoxicillin/omeprazole dual therapy at the same dose and duration as in RHB-105, with eradication rates of 83.8% and 57.7% in FAS population, respectively (p-value<0.0001). The added effect of rifabutin was well established by this trial.

Contribution of Omeprazole

Omeprazole is a PPI, currently approved for *H. pylori* eradication in combination with antibacterial drugs. The role of PPI in a beta-lactam-centric anti-*H. pylori* regimen is based primarily on the need for acid suppression to maintain consistent, near-neutral gastric pH, thereby maximizing the anti-*H. pylori* activity of a beta-lactam. Previous studies in patients with active or history of duodenal ulcers have shown *H. pylori* eradication rates were less than 5% for monotherapy with a PPI (i.e., omeprazole 40-80 mg/day, lansoprazole 90 mg/day) and

higher with a PPI in combination with amoxicillin.^{4,5}

The added contribution of omeprazole to Talicia would be most directly established by a randomized controlled trial with a Talicia arm and an amoxicillin/rifabutin arm. However, previous studies have shown that the addition of a second (non-bismuth) antibacterial to amoxicillin resulted in consistently low eradication rates, so the amoxicillin/rifabutin arm was not considered. The following table shows results of some amoxicillin-based dual antibacterial therapies.

Table 7-2: Amoxicillin-based dual antibacterial therapy efficacy results

Source	Study Design	Dosage of Amoxicillin/Second Antibacterial	Duration of Treatment (days)	n/N	Eradication Rate (%)
Amoxicillin + Clarithromycin					
Laine 1997 ⁶	R, MC, AC	1 g b.i.d./500 mg b.i.d.	7	11/62	18
Lind 1999 ⁷	R, MC, DB, AC	1 g b.i.d./500 mg b.i.d.	7	34/131	26
Amoxicillin + Ofloxacin					
Burette 1990 ⁸	OL, B	500 mg q.i.d./200 mg b.i.d	8	3/15	20
Amoxicillin + Nitrofurantoin					
DeKoster 1989 ⁹	SC, R, AC	500 mg q.i.d./100 mg q.i.d	7	4/16	25

Abbreviations: AC = active control; B = blinded; b.i.d. = twice a day; DB = double-blind; MC = multicenter; OL = open label; q.i.d. = four times a day; R = randomized; SC = single center

Source: 5.3.5.4 Rationale for RHB-105 Combination, Table 1

The added contribution of omeprazole in an *H. pylori* triple therapy regimen was established according to the following results, in which the triple therapy of omeprazole/clarithromycin/amoxicillin were proved to be superior to the dual therapy of

⁴ Laine L, Johnson E, Suchower L, et al. US Double-blind, Controlled Trials of Omeprazole and Amoxicillin for Treatment of Helicobacter pylori. Aliment Pharmacol Ther 1998;12:377-82.

⁵ Schwartz H, Krause R, Sahba B et al. Triple versus dual therapy for eradicating Helicobacter pylori and preventing ulcer recurrence: a randomized, double-blind, multicenter study of lansoprazole, clarithromycin, and/or amoxicillin in different dosing regimens. Am J Gastroenterol. 1998;93:584-90

⁶ Laine L, Frantz JE, Baker A, et al. A United States multicentre trial of dual and proton pump inhibitor-based triple therapies for Helicobacter pylori. Aliment Pharmacol Ther 1997;11(5):913-917.

⁷ Lind T, Mégraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of Helicobacter pylori with 1-week triple therapies. Gastroenterology 1999;116(2):248-253.

⁸ Burette A, Glupczynski Y, Deprez C. Combined therapy with ofloxacin and amoxicillin on the eradication of Helicobacter pylori. Gastroenterology 1990;98:A26.

⁹ DeKoster E, Nyst J, Glupczynski Y, et al. Amoxicillin + tinidazole vs. amoxicillin + nitrofurantoin: tinidazole is a key drug in Campylobacter pylori treatment. Klin Wochenschr 1989;67(18):16-17.

clarithromycin/amoxicillin.

Table 7-3: *H. pylori* Eradication Rates and 95% CI's for 10-Day Omeprazole Triple Therapy

	Omeprazole (20 mg b.i.d) + Clarithromycin (500 mg b.i.d) + Amoxicillin (1 g b.i.d)		Clarithromycin (500 mg b.i.d) + Amoxicillin (1 g b.i.d)	
	Per-Protocol	Intent-to-Treat	Per-Protocol	Intent-to-Treat
Study 1	0.77* [0.64, 0.86] (N=64)	0.69* [0.57, 0.79] (N=80)	0.43 [0.31, 0.56] (N=67)	0.37 [0.27, 0.48] (N=84)
Study 2	0.78* [0.67, 0.88] (N=65)	0.73* [0.61, 0.82] (N=77)	0.41 [0.29, 0.54] (N=68)	0.36 [0.26, 0.47] (N=83)
Study 3	0.90* [0.80, 0.96] (N=69)	0.83* [0.74, 0.91] (N=84)	0.33 [0.24, 0.44] (N=93)	0.32 [0.23, 0.42] (N=99)

* (p<0.05) versus Clarithromycin + Amoxicillin

Abbreviations: b.i.d. = twice a day

Source: Prilosec® USPI, August 2018

The added contribution of a PPI to rifabutin/amoxicillin combination is most directly addressed in Lim (2014)¹⁰. In this trial, patients with two previous eradication failures were randomized to receive PPI low dose therapy (rifabutin 150mg b.i.d., amoxicillin 1 g t.i.d., lansoprazole 30mg b.i.d.) or PPI high dose therapy (rifabutin 150mg b.i.d., amoxicillin 1 g t.i.d., lansoprazole 60mg b.i.d.) for 7 days. There were 32 patients in low dose group and 27 in high dose group, with corresponding eradication rates of 78.1% and 96.3% in ITT population. The eradication rate was borderline significantly higher with added PPI to the amoxicillin/rifabutin/PPI regimen. In this study, amoxicillin was dosed the same as in Talicia while the dose of rifabutin was double the daily dose as in Talicia. Despite the higher dose of rifabutin a significant dose response with PPI demonstrates its added effect to the rifabutin/amoxicillin/PPI combination therapy. Note that this trial only dosed for 7 days compared to the 14 days of dosing for Talicia. Additionally, lansoprazole was used rather than omeprazole at the same 120 mg/day dosage. Both drugs are approved to treat *H. pylori* in a triple therapy, but at lower dosages (lansoprazole 60 mg/day and omeprazole 40 mg/day).

Contribution of Amoxicillin

Amoxicillin administered as dual therapy with lansoprazole or as triple therapy with clarithromycin plus a PPI (omeprazole, lansoprazole, esomeprazole, or rabeprazole) is currently approved for *H. pylori* eradication. *H. pylori* is very susceptible to amoxicillin *in vitro*. Previous

¹⁰ Lim HC et al. Rifabutin-based High-dose Proton-pump Inhibitor and Amoxicillin Triple Regimen as the Rescue treatment for *Helicobacter pylori*. *Helicobacter* 2014;19(6):455-461.

studies in patients with active or history of duodenal ulcers have shown *H. pylori* eradication rates of less than 5% for monotherapy with amoxicillin 1.5-3 g/day and higher for amoxicillin in combination with a PPI.^{11,12}

The added contribution of amoxicillin to Talicia would be most directly established in a randomized controlled trial of Talicia versus rifabutin/omeprazole. However, as a potential for inducible resistance to rifabutin when used as monotherapy is high (single point mutation in the *rpoB* gene)¹³, a rifabutin/omeprazole arm or rifabutin alone arm were not considered. In contrast, an amoxicillin/omeprazole arm was included because *H. pylori* resistance to amoxicillin usually requires more than a single mutation in the bacterial genome.¹⁴

In a five-arm double-blinded study, patients with active duodenal ulcer (or history of duodenal ulcer within the past year) and *H. pylori* infection were randomized to receive therapies with/without amoxicillin for 14 days. The results shown in the following table showed added effect of amoxicillin in dual and triple therapies. Triple therapy was more effective than all possible dual therapy combinations.

Table 7-4: *H. Pylori* Eradication Rates and 95% CI's for Amoxicillin Triple Therapy

Triple Therapy v.s. Dual Therapy	Lansoprazole (30 mg b.i.d) + Clarithromycin (500 mg b.i.d) + Amoxicillin (1 g b.i.d)		Lansoprazole (30 mg b.i.d) + Clarithromycin (500 mg b.i.d)	
	Per-Protocol	Intent-to-Treat	Per-Protocol	Intent-to-Treat
Rates % [95% CI]	94%* [82.5%, 98.7%]	85%* [73.3%, 93.5%]	57% [42.2%, 71.2%]	50% [36.3%, 63.7%]
Total N	47	55	49	56
Dual Therapy v.s. PPI alone	Lansoprazole (30 mg t.i.d) + Amoxicillin (1 g t.i.d)		Lansoprazole (30 mg t.i.d)	
	Per-Protocol	Intent-to-Treat	Per-Protocol	Intent-to-Treat
Rates % [95% CI]	77%** [62.5%, 87.2%]	70%** [56.8%, 81.2%]	2% [0.0%, 10.1%]	3% [0.0%, 11.5%]

¹¹ Harford W, Lanza F, Arora A, et al. Double-blind, Multicenter Evaluation of Lansoprazole and Amoxicillin Dual Therapy for the Cure of Helicobacter pylori Infection. *Helicobacter* 1996;1:243-50.

¹² Laine L, Johnson E, Suchower L, et al. US Double-blind, Controlled Trials of Omeprazole and Amoxicillin for Treatment of Helicobacter pylori. *Aliment Pharmacol Ther* 1998;12:377-82.

¹³ Hays, C.; Burucoa, C.; Lehours, P.; Tran, C.T.; Leleu, A.; Raymond, J. Molecular characterization of Helicobacter pylori resistance to rifamycins. *Helicobacter* 2018, 23

¹⁴ Megraud F, Trimoulet P, Lamouliatte Het al. Bactericidal effect of amoxicillin on Helicobacter pylori in an in vitro model using epithelial cells. *Antimicrob Agents Chemother* 1991;35:869–72.

Triple Therapy v.s. Dual Therapy	Lansoprazole (30 mg b.i.d) + Clarithromycin (500 mg b.i.d) + Amoxicillin (1 g b.i.d)		Lansoprazole (30 mg b.i.d) + Clarithromycin (500 mg b.i.d)	
	Per-Protocol	Intent-to-Treat	Per-Protocol	Intent-to-Treat
Total N	51	60	53	60

* (p<0.05) compared to Lansoprazole + Clarithromycin

** (p<0.05) compared to Lansoprazole

Abbreviations: b.i.d. = twice a day; t.i.d. = three times a day

Source: H. Schwartz et al. Triple Versus Dual Therapy for Eradicating *Helicobacter pylori* and Preventing Ulcer Recurrence: A Randomized, Double-Blind, Multicenter Study of Lansoprazole, Clarithromycin, and/or Amoxicillin in Different Dosing Regimens. The American Journal of Gastroenterology 1998; 93(4); 584-590

As discussed in Borody (2006)¹⁵, a trial in Australia of previous eradication failure patients evaluated two different doses of amoxicillin: 54 patients received an amoxicillin 3g/day dose regimen (rifabutin 150mg q.d., amoxicillin 1g t.i.d., and pantoprazole 80mg t.i.d) for 12 days and 60 patients received an amoxicillin 4.5 g/day regimen (rifabutin 150 mg q.d., amoxicillin 1.5 g t.i.d., and pantoprazole 80 mg t.i.d) for 12 days. In the ITT population, the eradication rate was 90.7% and 96.6%, respectively.

Some studies investigated 7-day regimens with rifabutin 300 mg, standard dose of PPI and high dose of amoxicillin. Results of these studies are listed in the following table. The regimen with 3 g daily dosage of amoxicillin (same daily dosage as Talicia) shows higher eradication rate (in a harder-to-treat patient population) compared to regimens with 2 g daily dosage of amoxicillin.

Table 7-5: *H. pylori* Eradication with Rifabutin/Amoxicillin/PPI 7-day Regimens

First Author, Year, Previous Therapy	Number of Patients	Daily Dosage	Eradication Rate
Amoxicillin at 3 g daily			
Lim, 2014 (South Korea), Third-line treatment ¹⁶	32	Rifabutin 300 mg Amoxicillin 3 g Lansoprazole 60 mg	78.1% (ITT) 80.6% (PP)
Amoxicillin at 2 g daily			
Bock, 2000 (Germany), ≥1 treatments ¹⁷	25	Rifabutin 300 mg Amoxicillin 2 g	72% (ITT) 86% (PP)

¹⁵ Borody TJ. Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant *Helicobacter pylori* infection. Alimentary Pharmacology and Therapeutics 2006;23:481-488.

¹⁶ Lim HC, Lee YJ, An B, et al. Rifabutin-based high-dose proton-pump inhibitor and amoxicillin triple regimen as the rescue treatment for *Helicobacter pylori*. Helicobacter 2014;19(6):455-461.

¹⁷ Bock H, Koop H, Lehn N, Heep M. Rifabutin-based triple therapy after failure of *Helicobacter pylori* eradication treatment: preliminary experience. J Clin Gastroenterol 2000;31: 222-5.

First Author, Year, Previous Therapy	Number of Patients	Daily Dosage	Eradication Rate
		Lansoprazole 60 mg	
Navarro-Jarabo, 2007 (Spain), Second-line treatment ¹⁸	45	Rifabutin 300 mg Amoxicillin 2 g Omeprazole 40 mg	44.4% (ITT) 46.5% (PP)
Veldhuyzen van Zanten, 2010 (Canada), ≥1 treatments ¹⁹	16	Rifabutin 300 mg Amoxicillin 2 g standard dose PPI	63% (ITT) 67% (PP)
Perri, 2000 (Italy), ≥1 treatments ²⁰	41	Rifabutin 300 mg Amoxicillin 2 g Pantoprazole 80 mg	71% (ITT) 74% (PP)
Miehlke, 2006 (Germany) , ≥1 treatments ²¹	73	Rifabutin 300 mg Amoxicillin 2 g Esomeprazole 40 mg	74.0% (ITT) 78.3% (PP)

Source: Reviewer's literature search

Unge (1989)²² conducted a double-blinded study in which 24 *H. pylori* positive patients were assigned to 14 days treatment of only amoxicillin (750 mg b.i.d), only omeprazole (40 mg q.d.), or a combination of amoxicillin and omeprazole (omeprazole 40 mg q.d. + amoxicillin 750 mg b.i.d.). In the group receiving omeprazole and amoxicillin in combination, 5/8 patients were negative for *H. pylori* 4 weeks after stopping treatment, while 1/7 and 0/8 patients were negative for *H. pylori* in the amoxicillin and the omeprazole alone groups, respectively. This also shows added benefit of amoxicillin when combined with omeprazole.

¹⁸ Navarro-Jarabo JM, Fernández N, Sousa FL et al. Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate helicobacter pylori infection. BMC Gastroenterol. 2007;25:7:31.

¹⁹ Veldhuyzen van Zanten S, Desai S, Best L, et al. Rescue therapy using a rifabutin-based regimen is effective for cure of Helicobacter pylori infection. Can J Gastroenterol 2010;24(5):303-306.

²⁰ Perri F, Festa V, Clemente R et al. Rifabutin-based 'rescue therapy' for Helicobacter pylori infected patients after failure of standard regimens. Aliment Pharmacol Ther. 2000;14:311-6.

²¹ Miehlke S, Hansky K, Schneider-Brachert W et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. Aliment Pharmacol Ther. 2006;24:395-403.

²² Unge P et al. Does omeprazole improve antimicrobial therapy directed towards gastric *campylobacter pylori* in patients with antral gastritis? A pilot study. Scand J Gastroenterol Suppl. 1989;167:49:54.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. RHB-105-01 Design

Trial Design

This study was a randomized, double-blinded, placebo-controlled, parallel group, phase 3 trial to assess the safety and efficacy of Talicia in the treatment of confirmed *H. pylori* infection in dyspepsia patients. The study was planned to be conducted in up to 14 sites in the USA. A total of 120 patients were planned to be randomized in a ratio of 1:2 to receive:

- Talicia 4 capsules every 8 hours for 14 days (total daily dosage: rifabutin 150mg, amoxicillin 3g, and omeprazole 120mg)
- Placebo 4 capsules every 8 hours for 14 days

Study Objectives

The primary objective was to assess the effectiveness of Talicia to eradicate *H. pylori* as indicated by ¹³C UBT for *H. pylori*.

The secondary objective was to assess the safety profile of Talicia.

Inclusion Criteria

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

- 1) males and females aged 18 – 65 years, inclusive;
- 2) positive for *H. pylori* by ¹³C UBT and either fecal antigen test (at Screening) or documented diagnosis of *H. pylori* in gastric biopsy within 12 weeks of Screening or prior to randomization (local laboratory results);
- 3) no clinical evidence of any other disease that might interfere with the patient's ability to enter the study;
- 4) symptoms consistent with dyspepsia of at least 2 weeks duration (defined as recurrent pain or discomfort centered in the upper abdomen, often with a relation to meals);
- 5) females were instructed not to become pregnant or lactating and:
 - at no risk of pregnancy for 1 of the following reasons: post-menopausal for at least 1 year from the date of informed consent, hysterectomy, or tubal ligation, OR
 - were prepared and agreed to practice double method birth control (barrier plus spermicide) from Screening through to 30 days post-end-of-treatment (EOT);
- 6) males were required to be surgically sterilized or were prepared and agreed to practice double method (barrier plus spermicide) birth control from Screening through to 30 days post-EOT;

- 7) were not to consume alcohol, grapefruit, or any other food or supplement known to significantly affect cytochrome P450 (CYP) 3A4 or CYP 2C19 activity during the study;
- 8) able to communicate well with the Investigator and to comply with the requirements of the entire study;
- 9) provided written informed consent .

Exclusion Criteria

Patients were required to have met none of the following exclusion criteria to be eligible for participation in the study:

- 1) informed consent not obtained;
- 2) had alarm symptoms/signs (including unexplained anemia [iron deficiency], melena / hematemesis, anorexia, dysphagia, jaundice, weight loss);
- 3) use of any antibacterial drugs in the 4 weeks immediately prior to Screening Visit;
- 4) use of any bismuth-containing medications (such as peptobismol) or proton pump inhibitors (PPIs) within the 2 weeks immediately prior to screening;
- 5) use of any of the following medications within 7 days prior screening: roflumilast, apixabin, latuda, lovastatin, atorvastatin, amlodipine diltiazem, felodipine, nifedipine, nisoldipine, nitrendipine, fluconazole, ketoconazole, itraconazole voriconazole, colchicine, anti-retroviral agents, probenecid, allopurinol, digoxin, carbamazepine, phenytoin, clopidrogel and other oral anticoagulants, dapson, anti-herpes agents, astemizole, alfentanil, aprepitant, aripiprazole, boceprevir, buspirone, gleevec, mycophenolate mofetil, pimozone, quinine, clomipramine, imipramine, proguanil, amiodarone, citalopram dosed greater than 20 mg/d; and hormonal contraceptives that were not exclusively norethindrone or norgestrel;
- 6) use of amiodarone;
- 7) presence of any of the following: active gastric and duodenal ulcers; 3 or more active ulcers; gastric outlet obstruction; or hypersecretory state (eg, Zollinger-Ellison Syndrome);
- 8) history of esophageal or gastric surgery, except for simple closure of perforated ulcer;
- 9) history of gastric cancer;
- 10) positive screening laboratory results for hepatitis B surface antigen (HBs Ag), hepatitis C antibody (HCV Ab), or human immunodeficiency virus (HIV) antibody (HIV1 or HIV2);
- 11) history or current drug or alcohol abuse;
- 12) pregnant or lactating females or those who were unwilling to use double contraceptive methods; or had not been postmenopausal for at least the past 12 months from informed consent, or had not had a hysterectomy or tubal ligation;
- 13) males who refused to use double contraception methods, or were not surgically sterilized;
- 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 patient's ability to participate in the trial;

- 16) unable to comply with the requirements of the entire study;
- 17) unable to communicate well with the Investigators and to comply with the study requirements;
- 18) involved in any other experimental drug or device protocol (outside of this RHB-105-01 study) within the 4 weeks immediately prior to Screening Visit through end of study;
- 19) had received prior *H. pylori* eradication therapy.

Study Visit

The visit schedule was designed as follows:

- Visit 0: Screening, Day -12 to -2
- Visit 1: Baseline, Day 0, randomization and drug dispensed
- Visit 2: On therapy, Day 8 (± 1 day)
- Visit 3: End of Treatment (EOT), Day 15 (± 1 day)
- Visit 4: Test of Cure, Day 43 (+7 days)
- Visit 4A: Telephone Visit, Unblinding, Day 44 (+7 days)

Subjects were unblinded upon completion of the Visit 4 ^{13}C UBT analysis. Subjects in the placebo arm were entitled to receive standard-of-care following unblinding. Eradication failures in the active study drug arm underwent upper endoscopy and were offered culture and sensitivity-directed therapy. They continued on the following schedule:

- Visit 5: Standard of Care (SOC) Baseline Visit, Day 45 (+10 days), endoscopy in active drug eradication failures, SOC initiation for placebo failures
- Visit 5A: Standard of Care Post-Endoscopy Visit, Day 46 (+54 days), SOC initiation for active treatment failures
- Visit 6: Telephone Visit, Day 46 (+47 days) for placebo failures, Day 47 (+61 days) for active treatment failures
- Visit 7: Telephone Visit, Day 53 (+47 days) for placebo failures, Day 54 (+61 days) for active treatment failures
- Visit 8: SOC Test of Cure, Day 81-100 (+7 days) for placebo failures, Day 82-143 (+7 days) for active treatment failures

Comment: By unblinding individual subjects upon their completion of the trial the study was unblinded before it was completed. This is a possible concern regarding the integrity of the trial because of the availability of ongoing study results to those in a position to alter the trial. However, the subjects and physicians were blinded while the subjects were receiving treatment and assessed for primary outcomes, and given the large expected difference between treatment and placebo, it is less of an issue for this trial.

Study Endpoints

The primary efficacy endpoint was the occurrence of *H. pylori* eradication confirmed via ^{13}C UBT testing 28-35 days after completion of treatment.

Subjects with negative test results were considered treatment successes. Subjects who tested positive for *H. pylori* infection, those with indeterminate, not assessable, or missing results, or those not completing the test of cure visit were considered treatment failures.

Secondary endpoints included:

- Safety: The occurrence and severity of adverse events during the study and changes from baseline in hematology and chemistry laboratory values;
- Pharmacokinetics: The trough concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl-rifabutin on Days 8 and 15 will be summarized and compared with baseline values.

The Applicant also listed exploratory endpoints including:

- Patient reported outcome: Severity of Dyspepsia Assessment (SODA) score prior to and after treatment with study drug (Baseline, visit 3 and visit 4);
- Pharmacogenetic: cytochrome P450 (CYP) 2C19 status.

Statistical Analysis Plan

Analysis Populations

The study had the following analysis populations:

- Safety Population: all subjects who received at least one dose of randomized study treatment
- Intent-to-Treat (ITT) Population: all subjects who received at least one dose of randomized study treatment
- Modified Intent-to-Treat (mITT) Population: all subjects who received at least one dose of randomized study treatment and underwent a ¹³C UBT test at Visit 4
- Per Protocol (PP) Population: all subjects who consumed at least 75% of planned study treatment received, underwent a ¹³C UBT test at Visit 4, and did not have any major protocol violations.

The primary analysis was conducted using the mITT population. The analysis was repeated using the ITT and PP populations for sensitivity analysis.

Comment: We used the ITT population as the primary efficacy analysis population. Exclusions based on information that occurred after randomization and treatment, such as undergoing a ¹³C UBT test at Visit 4, can lead to differences in treatment arms and difficulty in interpreting the trial results.

Statistical Methods

The placebo arm was not expected to provide any relevant comparative effectiveness measure, as the effectiveness of placebo on *H. pylori* eradication was known to be approximately 0%.

Therefore, rather than merely showing a statistically significant difference between the test arm and placebo, the protocol defined an alternative null hypothesis. The null hypothesis was that the eradication rate in the active treatment arm is less than or equal to 70%. The hypothesis was tested using a one-sample one-sided Z test at significance level 0.025.

Protocol Amendments

There were 4 amendments. Amendment 1 (dated October 14th, 2013) was made prior to the start of the trial (November 25th, 2013). It updated inclusion criteria and exclusion criteria related to [REDACTED] (b) (4). All other amendments were made after trial initiation. Amendment 2 (dated May 13th, 2014) included updated visit windows and gastric biopsy pathology report that demonstrates presence of *H. pylori*. Amendment 3 (dated August 19th, 2014) added definition of mITT population and used mITT for primary efficacy analysis. It also changed estimated sample size from 90 to 120, and clarified prohibited and excluded medications. The reason for sample size change was “to account for drop-out, protocol violations, and other potential issues”. Amendment 4 (dated January 19th, 2015) removed “have at least one post-treatment assessment” from the definition of the ITT population, and we agree with the change. It also extended screening test time and updated schedule for diagnostic endoscopic exam.

8.1.2. Study Results for RHB-105-01

Compliance with Good Clinical Practices

The Study Report states that the study was conducted in accordance with Good Clinical Practices.

Financial Disclosure

No disclosable financial interests were reported for this study. See Section 17.2.

Patient Disposition

The study was conducted between November 2013 and August 2015 in the United States. A total of 13 sites participated in the study. 11 sites screened patients, in which 9 sites had patients enrolled and randomized. The following table shows the numbers of subjects screened, randomized, and completed the main study, and the reasons for early termination.

A total of 277 patients were screened in the study, of which 119 patients were randomized. One patient ([REDACTED] (b) (6)) randomized to the RHB-105 treatment group was not treated in the study was not included in any analysis set. The study coordinator entered the patient as eligible and randomized the patient. The patient was later found to be a Screen Failure and discontinued from the study. The monitor confirmed that no kit was dispensed to the patient.

Approximately 79% of patients in the ITT analysis set completed the main study, with the most

common reason for early termination being lost to follow-up.

Table 8-1: Subject Disposition for Study RHB-105-01

Category	RHB-105 N (%)	Placebo N (%)
Subjects randomized	78	41
Randomized per error and not treated	1	0
Treated patients (ITT population)	77	41
mITT population	66 (85.7%)	37 (90.2%)
PP population	63 (81.8%)	36 (87.8%)
Completed main study	63 (81.8%)	30 (73.2%)
Discontinued from main study	14 (18.2%)	11 (26.8%)
Reason for early termination:		
Patient was lost to follow-up	6 (7.8%)	7 (17.1%)
Poor compliance (defined as < 75%) with study medications	5 (6.5%)	0
Withdrawal of informed consent	2 (2.6%)	3 (7.3%)
Safety issue leading to inability to continue on study drug	0	1 (2.4%)
Subject has nausea and vomiting and no longer wanted to continue the study medication	1 (1.3%)	0

All percentages are calculated from treated patients

Source: Clinical Study Report, Table 10.1, Table 14.1.1, Figure 10.1

Protocol Violations/Deviations

A total of 49 patients (33 [42.9%] RHB-105 patients and 16 [39.0%] placebo patients) had at least 1 protocol deviation. The two groups were comparable in terms of proportions of total violations. The majority of protocol deviations belonged to the category of other (n=46, 39%), followed by patient receiving incorrect dose (1 RHB-105 patient and 2 placebo patients) and patients received excluded concomitant treatment (1 patient in each group). The “other” category included but was not limited to drug accountability issues (2 RHB-105 patients vs. 3 placebo patients), patient diary not returned (2 patients in each group), out-of-window visits as specified in the protocol (21 RHB-105 patients vs. 11 placebo patients), PK samples collected at later date than specified in protocol (2 RHB-105 patients vs. 1 placebo patient), laboratory evaluations and vital signs not done on assigned visits and as specified in the protocol (8 RHB-105 patients vs. 2 placebo patients), later date ICF was used (1 patient in each group), different pregnancy strip was used for testing (1 placebo patient) and waiver for negative fecal antigen test (1 RHB-105 patient).

Demographic Characteristics

Demographic characteristics are listed in the following table. The two groups had similar distributions in these characteristics. All subjects were between 24 and 65 years of age. Approximately 63% of patients were female. The majority of the subjects were Hispanic or Latino and white.

Table 8-2: Demographic characteristics of the primary efficacy analysis

Demographic Parameters	RHB-105 (N=77) n (%)	Placebo (N=41) n (%)
Sex		
Male	28 (36.4%)	16 (39.0%)
Female	49 (63.6%)	25 (61.0%)
Age		
Mean years (SD)	46.2 ± 10.56	45.8 ± 9.52
Median (years)	46.0	48.0
Min, max (years)	24, 65	26, 63
Race		
White	71 (92.2%)	38 (92.7%)
Black or African American	6 (7.8%)	3 (7.3%)
Ethnicity		
Hispanic or Latino	60 (77.9%)	35 (85.4%)
Not Hispanic or Latino	17 (22.1%)	6 (14.6%)

Source: Clinical Study Report, Table 11.2

Other Baseline Characteristics

All patients enrolled in the study were positive for *H. pylori* by ¹³C UBT and either fecal antigen test (at Screening) or documented diagnosis of *H. pylori* at gastric biopsy within 12 weeks of Screening. At Screening (Visit 0), all patients enrolled in the study were non-reactive for the hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus antibody.

Almost all patients reported at least one condition involving past medical history. The highest incidence of past medical history conditions was in gastrointestinal category (96.6%), which was expected for an *H. pylori* infection study. The two treatment arms were generally well-balanced with respect to the past medical histories. Minor imbalances can be noticed in neurological, genitourinary/reproductive, and musculoskeletal categories. These were deemed to be of little clinical significance.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance reported as percent of planned medication taken is shown in the following table. The compliance was high and comparable between the two groups. Five patients (all from RHB-105 group) were discontinued early from the study due to poor compliance (<75%).

Table 8-3: Summary of Medication Compliance

Category	Variables	RHB-105, N = 77	Placebo, N = 41
Visit 2 Compliance [1]	N	75	40
	Mean %	95.6	93.5

Category	Variables	RHB-105, N = 77	Placebo, N = 41
	SD	16.83	12.51
	Median	100.0	97.6
	Min, Max	29, 119	43, 115
Visit 3 Compliance [1]	N	70	36
	Mean %	96.2	100.4
	SD	16.86	19.21
	Median	100.0	100.0
	Min, Max	5, 119	5, 119
Overall Compliance [2]	N	75	37
	Mean %	92.7	95.3
	SD	19.89	15.73
	Median	100.0	100.0
	Min, Max	14, 111	21, 107

[1] Subjects are provided with 100 capsules per visit, but are expected to use only 84 (12 capsules per day for 7 days). Compliance is therefore calculated at each visit as follows: $(84 - (\text{number of capsules returned} - 16))/84$.

[2] Overall compliance is calculated as follows: $(168 - (\text{number of capsules returned} - 32))/168$.

Source: Clinical Study Report, Table 11.5

Efficacy Results – Primary Endpoint

The table below displays results for the primary endpoint analysis. The eradication rates of RHB-105 were significantly higher than placebo in all analysis populations. The Applicant was mainly interested in the primary efficacy among subjects randomized to active treatment arm, given that the untreated *H. pylori* has approximately 0% cure rate (97.3% of the placebo group in mITT population were eradication failures). The Applicant compared the eradication rate of RHB-105 group to 70%. 89.4% of RHB-105 patients in mITT population were reported with negative test results for ¹³C UBT at Visit 4. In the test with null hypothesis of $\leq 70\%$ success rate in RHB-105 group in the mITT population, the result was statistically significant with P-value < 0.001. The alternative of RHB-105 success rate > 70% using the mITT population was concluded by the Applicant. The same conclusion was drawn using the PP population.

The ITT population which does not exclude subjects based on post-randomization/post-treatment information (subjects who did not have visit 4 test results) is the more appropriate population to assess efficacy. In this population, the 95% confidence interval of the eradication rate for RHB-105 could exclude a rate of 67%.

Table 8-4: Primary Efficacy Result for Trial RHB-105-01

Analysis Set	<i>H. pylori</i> Eradication	RHB-105	Placebo	Difference (RHB-105 – placebo) 95% CI
ITT		N=77	N=41	
	Success	59 (76.6%)	1 (2.4%)	74.2% (61.5%, 83.6%)
	Failure	7 (9.1%)	36 (87.8%)	
	Missing	11 (14.3%)	4 (9.8%)	

	95% CI ^a P-value ^b	67.2%, 86.1% 0.102 ^c		
mITT		N=66	N=37	
	Success	59 (89.4%)	1 (2.7%)	86.7% (74.3%, 93.9%)
	Failure	7 (10.6%)	36 (97.3%)	
	95% CI ^a P-value ^b	82.5%, 96.3% <0.001		
PP		N=63	N=36	
	Success	56 (88.9%)	1 (2.8%)	86.1% (72.7%, 93.6%)
	Failure	7 (11.1%)	35 (97.2%)	
	95% CI ^a P-value ^b	81.1%, 96.6% <0.001		

^a Confidence interval for eradication success rate

^b One-sample Z-test (RHB-105 subjects only) for Ho: Proportion of success ≤ 70% vs. Ha: Proportion of success > 70%.

^c Reviewer's result is based on score test. The Applicant concluded a p-value of 0.085 using Wald test.

Source: Clinical Study Report, Table 11.7, Table 11.8, Table 11.9, Reviewer's analysis

In ITT population, 11 patients in the active treatment group and 4 in the placebo group didn't have a visit 4 test of cure result. Among the 11 in RHB-105 group, 5 patients had poor compliance with study medication, 5 were lost to follow-up, and one had nausea and vomiting and didn't want to continue study medication. Among the 4 in placebo group, 2 were withdrawal of informed consent, one was lost to follow-up, and one had safety issue leading to inability to continue on study drug.

Comment: The design of this trial does not demonstrate the contribution of each component of the regimen. This is particularly important for rifabutin which does not currently have a labeled indication for eradication of H. pylori.

Data Quality and Integrity

The datasets for Study RHB-105-01 and documentation were generally acceptable. It was possible to reproduce the Applicant's major analyses without complex manipulations.

Efficacy Results – Exploratory PRO as measured by the Severity of Dyspepsia Assessment (SODA)

The Applicant reports the results of the Severity of Dyspepsia Assessment (SODA) which consisted of 3 separate scores: SODA Pain Intensity, SODA Non-Pain Symptoms, and SODA Satisfaction. Subjects were measured at Screening, Baseline, Visit 3 and Visit 4. Though all of scores showed improvement from Baseline/Screening to both visit 3 and visit 4, there was no difference seen at any time point between the RHB-105 arm and the placebo arm.

Additional Analyses Conducted on the Individual Trial

Pharmacogenetic Analysis: Cytochrome P450 (CYP) 2C19 Status

Enzyme CYP 2C19 is responsible for the metabolism of many proton pump inhibitors (PPI), including omeprazole. Plasma PPI levels and gastric pH are highest among slow metabolizers and lowest among rapid metabolizers, potentially resulting in lower cure rates in the latter group. The summary of eradication rates by CYP 2C19 genotype is presented in the following table. Results by the subgroups are consistent with the overall results.

Table 8-5: *H. pylori* eradication rates by CYP 2C19 Status

Genotype	RHB-105 (N = 73)	Placebo (N = 39)
Ultra-rapid	11/11 (100%)	1/4 (25%)
Rapid/Extensive	32/48 (66.7%)	0/27
Intermediate	13/14 (92.9%)	0/6
Poor	0/0	0/2

Source: Reviewer's analysis

By Site Analysis

All participated sites were in US. A summary of *H. pylori* eradication rates for ITT population by site is presented in the following table. Results by sites are consistent with the overall results.

Table 8-6: *H. pylori* eradication rates by site

Site No.	State	RHB-105 (N = 77)	Placebo (N = 41)
001	NC	3/4 (75%)	0/1
002	CA	18/25 (72%)	1/14 (7.1%)
004	LA	4/4 (100%)	0/2
005	CA	21/28 (75%)	0/15
006	NC	0/1	0/0
008	GA	0/1	0/1
009	MD	2/3 (66.7%)	0/2
010	NV	3/3 (100%)	0/2
012	CA	8/8 (100%)	0/4

Source: Reviewer's analysis

By Demographics Analysis

A summary of *H. pylori* eradication rates for ITT population by baseline demographics (gender, race) is presented in the following table. Results by the subgroups are consistent with the overall results.

Table 8-7: *H. pylori* eradication rates by demographics

Demographic Parameters	RHB-105 (N=77)	Placebo (N=41)
Sex		
Male	22/28 (78.6%)	0/16

Female	37/49 (75.5%)	1/25 (4%)
Race		
White	56/71 (78.9%)	0/38
Black or African American	3/6 (50%)	1/3 (33.3%)
Ethnicity		
Hispanic or Latino	45/60 (75%)	0/35
Not Hispanic or Latino	14/17 (82.4%)	1/6 (16.7%)

Source: Reviewer's analysis

All participants but two were less than 65 years of age. Two patients were 65 years old and in the RHB-105 group. They both had successful eradications of *H. pylori* at Visit 4.

For Visit 8 Analysis

At Visit 4, subjects were unblinded and the placebo subjects and the active drug subjects who did not achieve *H. pylori* eradication were offered SOC treatment. At Visit 8, only those patients who were treatment failures at Visit 4, and were not withdrawn prior to Visit 8, were expected to have a ¹³C UBT. Of the 7 failure patients in the RHB-105 treatment group, 5 received SOC medications, and only 4 patients had Visit 8. Of these 4, 50% had *H. pylori* eradication. Of the 36 failure patients in the placebo treatment group, 33 received SOC medications, and only 27 patients had Visit 8. Of these 27, 17 (63%) had *H. pylori* eradication.

Susceptibility and Resistance Analysis

Eradication failures (¹³C UBT positive) in the RHB-105 treatment group were to undergo upper endoscopy with sampling for culture and susceptibility testing to rifabutin, amoxicillin, clarithromycin, and metronidazole (Visit 5A). Of the 7 failure patients, 3 patients ((b) (6)) were tested for susceptibility and resistance to above listed antibacterial drugs. The other 4 patients were not tested, as 1 ((b) (6)) refused the endoscopy, another ((b) (6)) was lost to follow-up and 2 ((b) (6)) patients were not tested due to an error in unblinding that labeled these subjects as having been randomized to placebo. The summary of susceptibility/resistance results is provided in the following table.

Table 8-8: Summary of Susceptibility and Resistance to Antibacterial Drugs (mITT population)

	RHB-105 (N = 3)					
	Amoxicillin	Clarithromycin	Metronidazole	Levofloxacin	Tetracycline	Rifabutin
Susceptible	3	3	2	3	3	3
Resistant	0	0	1	0	0	0

Source: Clinical Study Report, Table 11.12

8.1.3. RHB-105-02 Design

Trial Design

This study was a randomized, double-blinded, comparator controlled phase 3 trial to assess the safety and efficacy of Talicia in the treatment of confirmed *H. pylori* infection in patients

complaining of epigastric discomfort. The study was planned to be conducted in up to 65 sites in the USA. A total of 444 patients were planned to be randomized in a ratio of 1:1 to receive:

- Talicia: 4 capsules every 8 hours for 14 days (total daily dosage: rifabutin 150mg, amoxicillin 3g, and omeprazole 120mg)
- Comparator: 4 capsules every 8 hours for 14 days (total daily dosage: amoxicillin 3g, and omeprazole 120mg)

This study was designed to evaluate the added effect of rifabutin in Talicia triple therapy by comparing a regimen containing rifabutin with a regimen without rifabutin where all subjects in both treatment arms received the same doses of amoxicillin and omeprazole. Amoxicillin and omeprazole are both approved for treatment of *H. pylori* infection. Currently approved omeprazole regimens for *H. pylori* eradication include triple therapy (omeprazole 20mg, amoxicillin 1g, clarithromycin 0.5g, all twice daily for 10 days) and dual therapy (omeprazole 40 mg once daily, clarithromycin 0.5g three times daily, for 14 days). Currently approved amoxicillin regimens for *H. pylori* eradication include triple therapy (lansoprazole 30mg, amoxicillin 1g, clarithromycin 0.5g, all twice daily for 14 days) and dual therapy (lansoprazole 30mg, amoxicillin 1g, both three times daily for 14 days).

Study Objectives

The primary objective was to assess the effectiveness of Talicia to eradicate *H. pylori* as indicated by ¹³C UBT or fecal antigen test (under pregnancy exception). Confirmation of the *H.pylori* eradication based on fecal antigen testing in case of pregnancy was added in the protocol amendment #3.

The secondary objective was to assess the primary endpoint, the occurrence of *H. pylori* eradication, within subgroups of subjects based on the antibacterial resistance and susceptibility prior to therapy.

The safety objective was to assess the safety profile of RHB-105.

Inclusion Criteria

Subjects had to meet all of the following criteria to be eligible for inclusion in the double-blind phase of the study:

- 1) Be aged 18 to 70, inclusive; non-Asian males and females (this population has been demonstrated to have significantly elevated omeprazole levels as per the prescribing information for other omeprazole products). A person who had 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 were to be considered Asian, and for this study Asian was defined as having at least 1 Asian grandparent
- 2) Positive for *H. pylori* by ¹³C UBT and confirmed positive via gastric biopsy for Campylobacter-like organisms (CLO; rapid urease test), or *H. pylori* culture or histology

- 3) Symptoms were consistent with dyspepsia of at least 2 weeks duration (defined as recurrent pain or discomfort centered in the upper abdomen, often with a relation to meals)
- 4) Females must not have been pregnant or lactating and:
 - a) were at no risk of pregnancy for one of the following reasons: had been postmenopausal for at least 1 year from the date of informed consent, status post hysterectomy or tubal ligation
OR
 - b) were prepared to and agreed to use of an intrauterine device or practice double method birth control (barrier plus spermicide) from screening through to 30 days post-EOT; acceptable double contraceptive methods included barrier (condoms or diaphragms) plus spermicide
 - c) hormonal contraceptives (birth control pills and hormone implants) were not acceptable contraception methods under this protocol
- 5) Males had to have been surgically sterilized or were prepared to and agreed to practice double method (barrier plus spermicide) birth control from screening through to 30 days post-EOT
- 6) Agreed to refrain from consuming alcohol from 1 week prior to screening to test of cure/Visit 5
- 7) Agreed 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) Agreed to refrain from taking H₂ blockers at least 24 hours prior to screening ¹³C 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) Agreed to refrain from taking sucralfate from 1 week prior to screening through test of cure/Visit 5
- 10) Agreed to refrain from taking bismuth-containing medications such as Pepto-Bismol™ or other PPIs from 2 weeks prior to screening through test of cure/Visit 5
- 11) Agreed to refrain from consuming grapefruit, or any other food or supplement known to significantly affect cytochrome P450 (CYP)3A4 or CYP2C19 activity from screening to Day 15
- 12) Provided written informed consent.

Exclusion Criteria

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

- 1) Had alarm symptoms/signs (including unexplained anemia [iron deficiency], melena / hematemesis, anorexia, dysphagia, jaundice, weight loss)
- 2) Had received prior *H. pylori* eradication therapy
- 3) Had used antibacterial drugs in the 4 weeks immediately prior to screening ¹³C UBT
- 4) Had used any PPIs or bismuth-containing medications (such as Pepto-Bismol) within the

2 weeks immediately prior to screening ¹³C UBT

- 5) Had used any of the following medications within 7 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/day, 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, pimozone, probenecid, proguanil, quinine, roflumilast, terfenadine, and voriconazole
- 6) Was using amiodarone
- 7) Had more than 2 active gastric and/or duodenal ulcers
- 8) Had a history of gastric outlet obstruction; or hypersecretory state (e.g., Zollinger-Ellison Syndrome)
- 9) Had a history of esophageal or gastric surgery, except for simple closure of perforated ulcer
- 10) Had a history of gastric cancer
- 11) Had a history of malignancy within the past 5 years except for basal cell carcinoma of the skin or carcinoma in situ of the cervix that had been treated with no evidence of recurrence
- 12) Had positive screening laboratory results for human immunodeficiency virus (HIV) antibody (HIV-1 or HIV-2), or hepatitis B surface antigen (HBsAg), or hepatitis C virus antibody (HCVAb), unless the subject had documented sustained viral response evidenced by prior and/or current absence of viral RNA at least 24 weeks after completing antiviral therapy
- 13) Had current drug or alcohol abuse or a history of drug or alcohol abuse in the past 5 years from screening
- 14) Had a known hypersensitivity or suspected history of hypersensitivity reactions to any of the study drugs or related drugs, including cephalosporins and penicillin
- 15) Had clinical evidence of any disease that in the opinion of the investigator might have interfered with the subject's ability to participate in the study
- 16) Had a history of QT prolongation (QTc greater than 450 ms in males and 460 ms in females), or ventricular arrhythmia, including torsades de pointes
- 17) Had aspartate transferase (AST) or alanine transferase (ALT) >3 × upper limit of normal (ULN), or APO₄ >2 × ULN, or total bilirubin (TB) >2 × ULN. Subjects with a confirmed diagnosis of Gilbert's Syndrome were excluded if TB >2.5 × ULN
- 18) Was unable to communicate well with the investigators and to comply with the study requirements
- 19) Was 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 who had a 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

Study Visit

The visit schedule was designed as follows.

- Visit 0: Screening, Day -42 to -2
- Visit 1: Baseline, Day 1, randomization and drug dispensed
- Visit 2: Phone Follow-up, Day 8 (±1 day)
- Visit 3: Safety Visit, Day 13 (±2 day)
- Visit 4: Phone Follow-up, Day 28-60 (±2 day)
- Visit 5: Test of Cure, Day 43-71 (+7 days)
- Visit 5A: ¹³C UBT Follow-up, Day 44-72 (+7 days)
- Visit 6: Standard of Care (SOC) Baseline and Endoscopy, 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)

Only subjects evaluable for the standard-of-care phase continued study participation past visit 5A. There was a primary database lock after the last subject completed visit 5A. Unblinding of the study was completed at this stage.

Study Endpoints

The primary endpoint was eradication of *H. pylori* as confirmed via ¹³C UBT test results at the test of cure Visit 5 (Day 43 to 71) or fecal antigen test (under pregnancy exception, added in the protocol amendment #3).

Subjects with negative test results were considered treatment successes. Subjects who tested positive for *H. pylori* infection were considered treatment failures, and subjects with indeterminate, not assessable, or missing results from the test of cure visit underwent a repeat ¹³C UBT test. Persistent indeterminate results and subjects without any ¹³C UBT test after baseline were considered as treatment failures.

Secondary endpoints included:

- Antibacterial resistance and susceptibility subgroup analyses: The primary endpoint was summarized within subgroups based on *H. pylori* susceptibility and resistance to amoxicillin, clarithromycin, metronidazole, and rifabutin based upon samples obtained prior to initiating study drug. The proportion of subjects with eradication of *H. pylori* was tested between 2 treatment groups.
- Assess the difference in antibacterial resistance: The difference in antibacterial resistance and susceptibility of *H. pylori* after treatment with study drug in subjects with treatment failure was summarized by treatment group. No formal statistical tests were performed for group comparisons.

Statistical Analysis Plan

Analysis Populations

The study had the following analysis populations:

- Full Analysis Set (FAS) / Safety Population: all subjects who received at least one dose of randomized study treatment
- Modified Intent-to-Treat (mITT) Population: all subjects who received at least one dose of randomized study treatment and underwent a ^{13}C UBT test at Visit 5 (with the allowed exception for female women becoming pregnant and refusing the breath test)
- Per Protocol (PP) Population: all subjects who consumed at least 75% of planned study treatment received, underwent a ^{13}C UBT test at Visit 5 (with the allowed exception for female women becoming pregnant and refusing the breath test), and had no major protocol violations that led to exclusion.
- Pharmacokinetic Population (PKP): subjects in the FAS that had demonstrable presence of any component of investigational drug at Visit 3 or for whom the PK assessment at Visit 3 was performed more than 250 hours after the last dose of randomized study drug before this assessment.

Comment: FAS is also the Intent-to-treat (ITT) population. We used the ITT population as the primary efficacy analysis population. Exclusions based on information that occurred after randomization and treatment, such as undergoing a ^{13}C UBT test at Visit 5, can lead to differences in treatment arms and difficulty in interpreting the trial results.

The primary analysis was conducted using the FAS population. The analysis was repeated using the mITT and PP populations as sensitivity analyses.

Statistical Methods

Let p_0 denote the response rate under Talicia and p_P denote the response rate under the comparator, then the primary 2-sided hypothesis tested was:

Null hypothesis (H_0): $p_0 - p_P = 0$ versus Alternate hypothesis (H_1): $p_0 - p_P \neq 0$.

The proportion of subjects with success (negative test results) was tested between 2 treatment groups using the Chi-square test at the 5% level of significance.

Protocol Amendments

There were 3 amendments, all made after trial initiation. Amendment 1 deleted hypersensitivity to macrolides in exclusion criteria. It added inclusion criterion about use of sucralfate, rationale for restricting Asian population from participation, Creatinine clearance in clinical chemistry list, unblinding culture susceptibility results of eradication failures in SOC phase, and certain clarifications. Amendment 2 added inclusion criterion about use of antacids, exclusion criterion about malignancy, correction of drug/alcohol use history, *H. pylori* pre-

screening and certain clarifications. It deleted exclusion criterion of bismuth medication. Amendment 3 removed pre-screening, added exceptional visit 5 due to pregnancy, and defined PK population. Use of fecal antigen test was added after enrollment of a pregnant patient.

8.1.4. Study Results for RHB-105-02

Compliance with Good Clinical Practices

The Study Report states that the study was conducted in accordance with Good Clinical Practices.

Financial Disclosure

No disclosable financial interests were reported for this study. See Section 17.2.

Patient Disposition

The study was conducted between July 2017 and November 2018 in the United States. A total of 62 sites participated in the study, in which 55 sites had patients enrolled and randomized. The following table shows the numbers of subjects screened, randomized, and who completed the main study, and the reasons for early termination. A total of 1295 patients were screened in the study, of which 840 were screen failures. 455 patients were randomized, 226 into the RHB-105 treatment group and 227 into the comparator group. All randomized subjects received at least one dose of treatment.

Table 8-9: Subject Disposition

Category	RHB-105 N (%)	Comparator N (%)
Subjects randomized	228	227
Treated patients (FAS/ITT population)	228	227
mITT population ^a	227 (99.6%)	227 (100%)
PP population ^a	212 (93.0%)	212 (93.4%)
Subjects with a test of cure after the double-blind phase ^a	227 (99.6%)	227 (100%)
Test of cure and compliance with study drug $\geq$ 75% ^a	218 (95.6%)	219 (96.5%)
Test of cure and compliance with study drug $<$ 75% ^a	9 (3.9%)	8 (3.5%)
In case of compliance $<$ 75%, reason for not completing treatment ^a		
Adverse Event	2 (0.9%)	1 (0.4%)
Death	0	0
Lost to follow-up	0	0
Physician decision	0	1 (0.4%)
Withdrawal of subject	2 (0.9%)	1 (0.4%)
Protocol deviation	0	0
Randomized in error	0	0
Other: subject wanted to stop taking IP	0	1 (0.4%)

Category	RHB-105 N (%)	Comparator N (%)
No reason documented	6 (2.6%)	4 (1.8%)
Subjects eligible for the standard-of-care phase	36	96
Subjects eligible for the standard-of-care phase and entered the standard-of-care phase ^b	27 (75.0%)	67 (69.8%)
Subjects completed the standard-of-care phase ^c	26 (96.3%)	64 (95.5%)

^a Percentage based on number of randomized subjects

^b Percentage based on number of subjects who were eligible for the standard-of-care phase

^c Percentage based on number of subjects who entered the standard-of-care phase

Source: Clinical Study Report, Table 6, Table 8, Reviewer's analysis

Reviewer's Comment: A total of 18 patients (10 in treatment group and 8 in placebo group) had <75% treatment compliance. One of these subjects had a test of cure visit. Reasons for lack of compliance were not documented in all patients.

Protocol Violations/Deviations

Major protocol deviations leading to exclusion from the PP population are summarized in the following table.

Table 8-10: Major protocol deviations leading to exclusion from the PP population

Deviation	RHB-105 N=228 n (%)	Comparator N=227 n (%)
Number of subjects with any major protocol deviation during study	16 (7.0)	15 (6.6)
Subject randomized and did not meet inclusion/exclusion criteria	0	1 (0.4)
Subject was not fasting from food and drink 1 hour before ¹³ C UBT test at Visit 5	1 (0.4)	2 (0.9)
<75% of planned study drug received	10 (4.4)	8 (3.5)
Received excluded concomitant medications	6 (2.6)	3 (1.3)
Visit 5 performed earlier than 42 days from Visit 1	1 (0.4)	3 (1.3)
No assessment of primary efficacy at Visit 5	1 (0.4)	0

Percentages are based on the number of subjects in the FAS. Subjects that deviated from a major criterion more than once were counted once for the corresponding criterion. Any subjects who had more than 1 major protocol deviation were counted once in the overall summary.

Source: Clinical Study Report, Table 7

A total of 31 patients had at least 1 major protocol deviation. The two groups were comparable in terms of proportions of total violations. The majority of protocol deviations belonged to the category of <75% of planned study drug received (n=18, 4.0%), followed by received excluded concomitant medications (n=9, 2.0%).

Demographic Characteristics

Demographic characteristics are listed in the following table. The two groups had similar distributions in these characteristics. All subjects were between 18 and 70 years of age. Approximately 62% of patients were female. The majority of the subjects were Hispanic or Latino and white.

Table 8-11: Demographic characteristics of the primary efficacy analysis population (FAS)

Demographic Parameters	RHB-105 (N=228) n (%)	Comparator (N=227) n (%)
Sex		
Male	96 (42.1)	76 (33.5)
Female	132 (57.9)	151 (66.5)
Age		
Mean years (SD)	45.9 (12.77)	47.2 (13.13)
Median (years)	47.0	49.0
Min, max (years)	18, 70	18, 70
Age Group		
< 65 years	214 (93.9)	207 (91.2)
≥ 65 years	14 (6.1)	20 (8.8)
Race		
White	184 (80.7)	167 (73.6)
Black or African American	35 (15.4)	53 (23.3)
Asian	0	0
American Indian or Alaska Native	0	3 (1.3)
Native Hawaiian or Other Pacific Islander	2 (0.9)	0
Other	7 (3.1)	4 (1.8)
Ethnicity		
Hispanic or Latino	149 (65.4)	124 (54.6)
Not Hispanic or Latino	79 (34.6)	103 (45.4)

Source: Clinical Study Report, Table 9

Other Baseline Characteristics

Baseline and disease characteristics

Biopsy for CLO, histology and culture were performed on all patients in the FAS population. Baseline and disease characteristics were listed in the following table.

Table 8-12: Baseline and disease characteristics

Characteristics	RHB-105 (N=228) n (%)	Comparator (N=227) n (%)
CLO Results		

Characteristics	RHB-105 (N=228) n (%)	Comparator (N=227) n (%)
Positive	225 (98.7)	223 (98.2)
Negative	3 (1.3)	4 (1.8)
Histology Results		
Positive	224 (98.2)	222 (97.8)
Negative	4 (1.8)	4 (1.8)
Not evaluable	0	1 (0.4)
Culture Results		
Positive	183 (80.3)	182 (80.2)
Positive, Susceptibility test results available	174 (76.3)	171 (75.3)
Positive, Susceptibility test results not available	9 (3.9)	11 (4.8)
Negative	40 (17.5)	42 (18.5)
Not evaluable	5 (2.2)	3 (1.3)
Antimicrobial susceptibility, amoxicillin MIC (µg/mL)^a		
n	174	171
≤0.125 (Susceptible)	161 (92.5)	162 (94.7)
>0.125 (Resistant)	13 (7.5)	9 (5.3)
Missing	54	56
Antimicrobial susceptibility, clarithromycin MIC (µg/mL)^a		
n	174	171
≤0.25 (Susceptible)	149 (85.6)	136 (79.5)
0.5 (Intermediate)	0	0
>0.5 (Resistant)	25 (14.4)	35 (20.5)
Missing	54	56
Antimicrobial susceptibility, metronidazole MIC (µg/mL)^a		
n	174	170
≤8 (Susceptible)	103 (59.2)	91 (53.5)
>8 (Resistant)	71 (40.8)	79 (46.5)
Missing	54	57
Antimicrobial susceptibility, rifabutin MIC (µg/mL)^a		
n	174	171
≤1 (Susceptible)	174 (100.0)	171 (100.0)
>1 (Resistant)	0	0
Missing	54	56
CYP2C19 status^b		
Ultra-rapid metabolizers	10 (4.4)	3 (1.3)
Rapid metabolizers	45 (19.7)	55 (24.2)
Normal metabolizers	114 (50.0)	107 (47.1)
Intermediate metabolizers	48 (21.1)	52 (22.9)
Poor metabolizers	5 (2.2)	4 (1.8)

Characteristics	RHB-105 (N=228) n (%)	Comparator (N=227) n (%)
Not reported	5 (2.2)	4 (1.8)
Missing	1 (0.4)	2 (0.9)

^a Percentages for antimicrobial susceptibility were calculated with the number of subjects with non-missing assessment as denominator.

^b For CYP2C19 status Not reported indicates samples that arrived in an expired container and were not processed. Missing are samples that were not taken and 1 sample that arrived in the wrong condition.

Source: Clinical Study Report, Table 10

Clinical reviewer comment: The interpretive criteria for susceptibility of H. pylori to antibacterial drugs are currently established only for clarithromycin. Interpretability of the breakpoints used by the Applicant to amoxicillin, metronidazole or rifabutin provided in the table above is questionable.

Medical History

According to the clinical study report, almost all patients reported at least one condition in their past medical history. The two treatment arms were well-balanced with respect to the medical histories reported. Among conditions reported the most prevalent were dyspepsia (80.4% in total population, 82.9% in RHB-105 group and 78.0% in the comparator group), hypertension (27.0% in total population, 25.9% in RHB-105 group and 28.2% in the comparator group), and gastroesophageal reflux disease (26.6% in total population, 25.0% in RHB-105 group and 28.2% in the comparator group).

Treatment Compliance Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance is shown in the following table. The compliance was high and comparable between the two groups.

Table 8-13: Summary of treatment compliance

	RHB-105 (N=228) n (%)	Comparator (N=227) n (%)
Subjects completed all doses n (%)		
Yes	111 (48.7)	128 (56.4)
No	117 (51.3)	99 (43.6)
Compliance (%)^a		
n	228	227
Mean (SD)	97.5 (14.2)	97.9 (13.2)
Median	100.000	100.000
Min, Max	4.8, 157.1	7.1, 119.1

	RHB-105 (N=228) n (%)	Comparator (N=227) n (%)
Compliance category, n (%)^a		
<75%	10 (4.4)	8 (3.5)
≥75%-90%	9 (3.9)	2 (0.9)
>90%-100%	178 (78.1)	186 (81.9)
>100%	31 (13.6)	31 (13.7)

^a Compliance = 100 × ([total number of capsules dispensed] – [total number of capsules returned])/168
Source: Clinical Study Report, Table 11

Concomitant Medication

During the double-blind phase of the study, 339 (74.5%) subjects received non-study concomitant medications; 163 (71.5%) subjects in the RHB-105 group and 176 (77.5%) subjects in the comparator group. Of those reported, the most common concomitant medications were:

- Propofol (27 [11.8%] subjects in the RHB-105 group, 51 [22.5%] subjects in the comparator group).
- Lidocaine (15 [6.6%] subjects in the RHB-105 group, 35 [15.4%] subjects in the comparator group).
- Metformin (30 [13.2%] subjects in the RHB-105 group, 20 [8.8%] subjects in the comparator group).

Prescribed Standard-of-Care Medications

Standard-of-care medication was offered to subjects who did not achieve eradication. A total of 94 patients (27 in the RHB-105 group and 67 in the comparator group) entered the standard-of-care phase of the study. Overall, 92 (97.9%) subjects received standard-of-care medications; 26 (96.3%) subjects in the RHB-105 group and 66 (98.5%) in the comparator group.

Efficacy Results – Primary Endpoint

Primary Analysis

The primary analysis was conducted in the FAS population. The response rate in the RHB-105 group (83.8%) was significantly higher than the comparator group (57.7%) with p-value < 0.001. The detailed results are listed in the following table.

Table 8-14: Primary Efficacy Result for Trial RHB-105-02

Eradication of <i>H. pylori</i>	RHB-105 (N=228)	Comparator (N=227)	Treatment Difference^a, 95% CI, p-value
Responder, n(%)	191 (83.8)	131 (57.7)	26.1 (18.0, 34.1) <0.0001
Non-responder, n (%)	37 (16.2)	96 (42.3)	
Positive test result	36 (15.8)	96 (42.3)	

Eradication of <i>H. pylori</i>	RHB-105 (N=228)	Comparator (N=227)	Treatment Difference^a, 95% CI, p-value
Missing post-baseline test result	1 (0.4)	0	

^a Difference of response rates (RHB-105 – Comparator), p-value was based on Chi-square test
Source: Clinical Study Report, Table 12

Only one patient had missing eradication result, which would not affect the test between the two groups. One patient in the RHB-105 group was pregnant and underwent fecal antigen test (test negative) instead of ¹³C UBT test. One patient in RHB-105 group took a ¹³C UBT test outside of the trial (the test was negative before Visit 5). Excluding these patients or considering them as failures would not impact the results.

The applicant has identified 7 subjects in the comparator group in Study RHB-105-02 that had plasma levels of rifabutin at Visit 3. Of those 7 subjects, 3 were eradication successes and 4 were failures. The applicant conducted a GCP audit of involved sites. It was revealed that the cross-contamination of the plasma specimens might have occurred at the time of batching. An ad-hoc sensitivity analyses was performed in the FAS excluding patients from the comparator group that had a measurable rifabutin concentration at Visit 3 (eradication rate of comparator arm was 58.2% after removing the 7 patients). Another ad-hoc sensitivity analysis was performed in the PK population excluding patients from the comparator group that had a measurable rifabutin concentration at Visit 3. Both analyses showed similar results as the primary analysis in FAS population. RHB-105 group had significantly higher responder rates in the two ad-hoc sensitivity analyses with p-values < 0.0001. If all those 7 subjects were considered treatment successes in the comparator group, the eradication rate of comparator arm would be 59.5%, which is significantly lower than RHB-105 group with p-value < 0.0001. After removing the 6 sites that had patients with detectable rifabutin in the comparator group, the eradication rate of treatment group is 162/181 (89.5%) and the rate of comparator group is 62/160 (38.8%). RHB-105 group has significantly higher responder with p-values < 0.0001.

Sensitivity analyses – mITT, PP and PK populations

The comparison of responder rates of RHB-105 group and the comparator group using primary endpoint was performed in the mITT, PP, and PK populations. The results were similar to the primary analysis in the FAS population. RHB-105 group had significantly higher responder rates in all population with p-values < 0.0001. Detailed results are listed in the following table.

Table 8-15: Efficacy Result for Trial RHB-105-02 in mITT, PP and PK populations

	RHB-105	Comparator	Treatment Difference^a, 95% CI, p-value
mITT Population	(N=227)	(N=227)	
Responder, n(%)	191 (84.1)	131 (57.7)	26.4 (18.4, 34.4) <0.0001
PP Population	(N=212)	(N=212)	
Responder, n(%)	179 (84.4)	123 (58.0)	26.4 (18.2, 34.7) <0.0001

PK Population	(N=207)	(N=184)	
Responder, n(%)	187 (90.3)	119 (64.7)	25.7 (17.7, 33.7) <0.0001

^a p-value was based on Chi-square test

Source: Clinical Study Report, Table 13, Table 14, Table 15

Subgroup analyses

A summary of *H. pylori* eradication rates for the FAS population by baseline demographics (region, gender, age group, race, and ethnicity) is presented in the following table. All study sites were located in the US.

Table 8-16: *H. pylori* eradication rates by demographics

Demographic Parameters	RHB-105 (N=228)	Comparator (N=227)
Region		
South	45/49 (91.8%)	35/54 (64.8%)
Northeast	11/13 (84.6%)	6/12 (50%)
Southeast	66/86 (76.7%)	49/89 (55.1%)
West	62/73 (84.9%)	38/68 (55.9%)
Central	7/7 (100%)	3/4 (75%)
Sex		
Male	81/96 (84.4%)	38/76 (50%)
Female	110/132 (83.3%)	93/151 (61.6%)
Age Group		
< 65 years	179/214 (83.6%)	119/207 (57.5%)
≥ 65 years	12/14 (85.7%)	12/20 (60%)
Race		
White	155/184 (84.2%)	101/167 (60.5%)
Black or African American	29/35 (82.9%)	24/53 (45.3%)
American Indian or Alaska Native	0/0	3/3 (100%)
Native Hawaiian or Other Pacific Islander	2/2 (100%)	0/0
Other	5/7 (71.4%)	3/4 (75%)
Ethnicity		
Hispanic or Latino	125/149 (83.9%)	69/124 (55.6%)
Not Hispanic or Latino	66/79 (83.5%)	62/103 (60.2%)

Source: Reviewer's analysis

Data Quality and Integrity

The datasets for Study RHB-105-02 and documentation were generally acceptable. It was possible to reproduce the applicant's major analyses without complex manipulations.

Efficacy Results – Secondary endpoints

Subgroup Analyses by Baseline Susceptibility

As stated previously in this review, the interpretive criteria for susceptibility of *H. pylori* to amoxicillin, metronidazole or rifabutin have not been established. Interpretability of the breakpoints used by the Applicant in the study is of questionable. The efficacy analyses based on Applicant’s proposed cut-off values for the baseline presented in this section of the review are for completeness purposes. The primary endpoint was summarized within subgroups based on the presence of *H. pylori* susceptibility or resistance to amoxicillin, clarithromycin, metronidazole, and rifabutin in samples obtained prior to taking study drug. In patients with any antibacterial resistance and in patients with metronidazole resistance, eradication rates of the RHB-105 arm were significantly higher than the comparator arm.

Table 8-17: *H. pylori* eradication rates by baseline susceptibility

Eradication of <i>H. pylori</i>	RHB-105	Comparator	Treatment Difference, 95% CI, p-value^a
Resistance to Any Antibacterial Drug			
Resistant	69/85 (81.2)	55/98 (56.1)	25.1 (12.2, 37.9), 0.0003
Suceptibility to Rifabutin			
Suceptible	147/174 (84.5)	99/171 (57.9)	26.6 (17.4, 35.7), <0.0001
Suceptibility to Amoxicillin			
Suceptible	138/161 (85.7)	95/162 (58.6)	27.1 (17.8, 36.4), <0.0001
Resistant	9/13 (69.2)	4/9 (44.4)	24.8 (-16.2, 65.8), 0.2450
Suceptibility to Clarithromycin			
Suceptible	126/149 (84.6)	77/136 (56.6)	27.9 (17.8, 38.1), <0.0001
Resistant	21/25 (84)	22/35 (62.9)	21.1 (-0.4, 42.7), 0.0732
Suceptibility to Metronidazole			
Suceptible	90/103 (87.4)	53/91 (58.2)	29.1 (17.1, 41.1), <0.0001
Resistant	57/71 (80.3)	45/79 (57.0)	23.3 (9.0, 37.6), 0.0022

^a p-value was based on Chi-square test

Source: Clinical Study Report, Table 19-23

Antibacterial Resistance and Susceptibility in Treatment Failures

A summary of antibacterial resistance and susceptibility to amoxicillin, clarithromycin, metronidazole, and rifabutin in treatment failures is presented in the following table.

Table 8-18: Antibacterial resistance and susceptibility in treatment failures

Antibacterial Drug		RHB-105	Comparator
Amoxicillin	N	27	72
	Resistant, n (%)	4 (14.8)	5 (6.9)
	Susceptible, n (%)	23 (85.2)	67 (93.1)
Clarithromycin	N	27	72
	Resistant, n (%)	4 (14.8)	13 (18.1)
	Susceptible, n (%)	23 (85.2)	59 (81.9)

Antibacterial Drug		RHB-105	Comparator
Metronidazole	N	27	72
	Resistant, n (%)	14 (51.9)	34 (47.2)
	Susceptible, n (%)	13 (48.1)	38 (52.8)
Rifabutin	N	27	72
	Resistant, n (%)	0	0
	Susceptible, n (%)	27 (100.0)	72 (100.0)

Source: Clinical Study Report, Table 24

Subgroup analyses by CYP2C19 Status

Based on baseline CYP2C19 status, subjects were categorized as ultra-rapid, rapid, normal, intermediate, or poor metabolizers.

Analysis of eradication of *H. pylori* by CYP2C19 status is presented in the following table. In groups of rapid, normal, and intermediate metabolizers, eradication rates of the RHB-105 arm were significantly higher than the comparator arm. The other two subgroups were too small to make any conclusions.

Table 8-19: *H. pylori* eradication rates by CYP2C19 Status

Eradication of <i>H. pylori</i>	RHB-105 (N=222)	Comparator (N=221)	Treatment Difference, 95% CI, p-value ^a
Ultra-rapid metabolizer			
	8/10 (80.0)	1/3 (33.33)	46.7 (-12.2, 100.0), 0.1245
Rapid metabolizer			
	36/45 (80.0)	28/55 (50.9)	29.1 (11.5, 46.7), 0.0026
Normal metabolizer			
	98/114 (86.0)	64/107 (59.8)	26.2 (14.9, 37.4), <0.0001
Intermediate metabolizer			
	41/48 (85.4)	30/52 (57.7)	27.7 (11.0, 44.5), 0.0023
Poor metabolizer			
	3/5 (60.0)	4/4 (100.0)	-40.0 (-82.9, 2.9), 0.1515

^a p-value was based on Chi-square test

Source: Clinical Study Report, Table 26

Chi-square test for association was also performed for different responder rates by CYP2C19 phenotype within treatment groups (P-value=0.5323 for RHB-105, P-value=0.2993 for Comparator). No significant difference was observed.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

Given the use of the different comparators and randomization ratios, results were not pooled across studies.

8.3. Statistical Issues

Study RHB-105-01 and RBH 105-02 are reviewed for analysis of efficacy.

The applicant needed to show added contribution of each component of Talicia. Trial RHB-105-02 provided evidence for the added contribution of rifabutin, which was not previously approved for *H. pylori* eradication. The justification for omeprazole and amoxicillin contributions was conducted through literature review.

Trial RHB-105-01 shows that Talicia is effective, with placebo eradication rate close to 0%. The applicant planned to exclude 70% eradication rate based on a comparative effect, which was established using MITT/PP population. Our analysis focuses on ITT population, which excludes a 67% eradication rate.

In RHB-105-02, 7 patients (from 6 different sites) in the active comparator arm had plasma levels of rifabutin at Visit 3. The superiority of Talicia compared to the active comparator was still established in the post hoc analysis excluding those 7 patients. One of the 7 patients came from site 20 and this site was selected for audit. According to the clinical inspection summary dated 09/18/2019, on-site inspections demonstrated no significant findings related to data integrity at the audited site.

8.4. Conclusions and Recommendations

Two randomized, double-blinded, controlled studies provided evidence for efficacy of Talicia for *H. pylori* eradication.

Study RHB-105-01 evaluated the efficacy of Talicia and showed superiority to placebo control.

Study RHB-105-02 compared Talicia triple regimen to omeprazole/amoxicillin dual therapy and the superiority was established. This trial showed added benefit of rifabutin to the triple therapy, with an overall eradication rate of 83.8% for Talicia treated patients and 57.7% for omeprazole/amoxicillin dual therapy in ITT population.

There is sufficient evidence from the published literature that amoxicillin contributes to the eradication of *H. pylori* in combination with omeprazole. Previous studies in the US have shown *H. pylori* eradication rates of less than 5% for monotherapy with amoxicillin or omeprazole and this is well below what was observed for omeprazole/amoxicillin dual therapy in Study RHB-105-02. According to literature review, regimen of two antibacterial drugs (i.e., amoxicillin plus clarithromycin) without omeprazole showed significantly lower *H. pylori* eradication rate, which justifies the added contribution of omeprazole. Regimen including rifabutin and PPI with lower amoxicillin dosage also showed lower eradication rate, which supports added contribution of amoxicillin.

This review supports the conclusion that Talicia was effective in treatment of *H. pylori* infection.

9 Clinical Microbiology Review

9.1. Nonclinical Microbiology

Mechanism of Action

TALICIA is a combination of antibacterial agents (rifabutin and amoxicillin) plus omeprazole a proton pump inhibitor.

Rifabutin inhibits DNA-dependent RNA polymerase in susceptible bacteria. In *H. pylori*, rifabutin inhibits the beta-subunit of the DNA-dependent RNA polymerase encoded by *rpoB* with subsequent inhibition of the initiation complex. This results in inhibition of protein synthesis. Rifabutin does not inhibit mammalian RNA synthesis.

Amoxicillin is an analog of penicillin. It is a semisynthetic antibacterial drug that demonstrates a bactericidal action against susceptible bacteria during the stage of active multiplication. It acts through the inhibition of cell wall biosynthesis that leads to the death of the bacteria.

Omeprazole is a substituted benzimidazole, a class of antisecretory compounds that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell and blocks the final step of acid production. This effect is dose-dependent and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Omeprazole can also exhibit antibacterial activity depending on the culture conditions. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for at least one day.

9.1.1. Antibacterial Activity

The antibacterial activity to rifabutin in *H. pylori* is caused by inhibition of the β subunit of DNA dependent RNA polymerase affecting the initiation of transcription with the eventual inhibition of protein synthesis.

The antibacterial activity of amoxicillin is accomplished through the inhibition of the biosynthesis of the bacterial cell wall.

9.1.2. Resistance and Cross-Resistance

Rifabutin is active against *H. pylori* with low rates of resistance. Resistance of *H. pylori* to rifabutin was shown to be < 2% in Europe (O'Connor et al., 2013²³, Megraud et al., 2013²⁴, Ciccaglione et al., 2016²⁵, Di Giulio et al., 2016²⁶), and approximately 3% among patients who were previously treated with the drug. Heep et al., 1999²⁷, found that when induced, in vitro, rifabutin resistant variants occurred at a rate of approximately 1 in 10⁵.

In the U.S.A., a study by Megraud, 2004²⁸ found that between 1995 to 1999 *H. pylori* resistance to amoxicillin was less than 0.08%. Resistance to amoxicillin is associated with mutations in the penicillin binding protein-1A gene (*pbp-1A*). Glocker et al., 2007²⁹ found that in *H. pylori*, cross resistance occurs between rifabutin and rifampicin which belong to the same drug class.

9.2. Clinical Microbiology

9.2.1. Assay Descriptions and Methodologies

Specimen Collection, Storage, Shipping and Handling

A 2 cm biopsy specimen was collected from a single corpus and a single antrum specimen, and frozen appropriately for subsequent culture and susceptibility testing.

For culture, appropriately prepared specimens were plated on non-select and selective horse blood agar and incubated at 37°C for 72 hours in a microaerophilic atmosphere. Negative cultures were re-incubated for up to 14 days; positive cultures were identified using Gram stain, catalase, oxidase and urease tests.

Isolates that resulted from positive cultures were frozen until susceptibility tests could be performed.

²³ O'Connor, et al., *Helicobacter pylori* resistance rates for levofloxacin, tetracycline and rifabutin among Irish isolates at a reference centre. *Ir J Med Sci* (2013) 182:693–695

²⁴ Megraud et al., *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic Consumption. *GUT*(2013) gut.bmj.com on May 15, 2012 as 10.1136/gutjnl-2012-302254-

²⁵ Ciccaglione et al., Rifabutin Containing Triple Therapy and Rifabutin with Bismuth Containing Quadruple Therapy for Third-Line Treatment of *Helicobacter pylori* Infection: Two Pilot Studies. (2016) John Wiley & Sons Ltd, *Helicobacter* 21: 375–381

²⁶ Di Giulio et al., *In vitro* antimicrobial susceptibility of *Helicobacter pylori* to nine antibiotics currently used in Central Italy (2016) *Scandinavian Journal of Gastroenterology*. Volume 51, 2015 - Issue 3

²⁷ Heep et al., Rifampin and Rifabutin Resistance Mechanism in *Helicobacter pylori* (1999) *Antimicrob Agents Chemother*; 43(6): 1497–1499.

²⁸ Megraud, F. *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004;53:1374–1384. doi: 10.1136/gut.2003.022111

²⁹ Glocker et al., Characterization of rifampicin-resistant clinical *Helicobacter pylori* isolates from Germany. *J Antimicrob Chemother*. 2007 May;59(5):874-9.

Susceptibility Testing

Susceptibility tests were performed using the E-test and agar dilution tests. The latter recommended by the Clinical and Laboratory Standards Institute.

The agar dilution test uses Mueller Hinton Agar supplemented with aged (>2 weeks) sheep blood.

10 Review of Safety

10.1. Safety Review Approach

The safety of RHB-105 was evaluated in 4 clinical trials, including 2 Phase 1 studies in healthy adults (RHB-P2-418 and RHB-105-12) and 2 Phase 3 studies (RHB-105-01 and RHB-105-02) in treatment-naïve *H. pylori* positive adult patients complaining of epigastric pain/discomfort. Table 7-1 provides an overview of the clinical studies referenced in the clinical review of safety. This safety review will focus on the data from the 2 Phase 3 studies. Where relevant, data from the Phase 1 studies will also be presented.

10.2. Review of the Safety Database

Overall Exposure

Table 10-1 provides a summary of the overall exposures in the clinical studies used to evaluate safety of RHB-105. The safety database consisted of 339 subjects exposed to RHB-105, and all these subjects received the proposed dose (4 capsules) for *H. pylori* infection. A total of 305 patients were treated with at least 1 dose of RHB-105 at the intended regimen of 4 capsules administered every 8 hours (q8h; total daily dose of rifabutin 150 mg, amoxicillin 3,000 mg, and omeprazole 120 mg) for 14 days.

Table 10-1: Safety Database for RHB-105 Development Program

Clinical Trial Group Study ID	RHB-105 Dosing Regimen	RHB-105 ¹ N	Active Comparator ² N	Placebo N
Phase 3 Studies conducted for <i>H. pylori</i> infection		305	227	41
RHB-105-01	4 capsules q8h with food for 14 days	77	0	41
RHB-105-02	4 capsules q8h with food for 14 days	228	227	0
Phase 1 Studies in healthy adults		34	/	/
RHB-P2-418	4 capsules q8h – 3 doses under fasting conditions	16		
RHB-105-12	4 capsules – single dose under fasting and fed conditions	18		
Grand Total		339	227	41

¹ Each dose (4 capsules) of RHB-105 includes rifabutin 50 mg, amoxicillin 1,000 mg, and omeprazole 40 mg (equivalent to omeprazole magnesium 41.2 mg).

² Each dose (4 capsules) of active comparator includes amoxicillin 1,000 mg and omeprazole 40 mg (equivalent to omeprazole magnesium 41.2 mg).

Source: Adapted from Summary of Clinical Safety, Table 2; Clinical Reviewer’s Analysis.

The Phase 3 studies had 305 patients treated with RHB-105 (25% from Study RHB-105-01 and 75% from Study RHB-105-02), 41 patients treated with matching placebo (all from Study RHB-105-01), and 227 patients treated with active comparator (all from Study RHB-105-02). The

study drug exposures in each treatment group are summarized in Table 10-2. In Study RHB-105-01, the mean treatment duration was 13.2 days in the RHB-105 group and 13.5 days in the placebo group. The mean treatment duration was 14.6 days in both treatment groups in Study RHB-105-02. In the pooled analysis, treatment compliance was $\geq 75\%$ for 287 (94.1%) patients in the RHB-105 treatment group, 35 (85.4%) patients in the placebo group, and 219 (96.5%) patients in the active comparator group.

Table 10-2: Treatment Exposure – Phase 3 Studies (Safety Population)

Parameter	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 N=77	Placebo N=41	RHB-105 N=228	Active Comparator N=227	RHB-105 N=305
Patient Exposure (Capsules)¹					
Mean (SD)	156 (33)	160 (26)	164 (24)	164 (22)	162 (27)
Min, Max	24, 187	36, 180	8, 264	12, 200	8, 264
Missing	2	4	0	0	2
Treatment Duration (Days)²					
Mean (SD)	13.2 (2.7)	13.5 (2.2)	14.6 (1.7)	14.6 (1.7)	14.2 (2.1)
Min, Max	2, 16	3, 15	1, 17	1, 18	1, 17
Missing	2	4	0	0	2
Treatment Compliance³					
< 50%	5 (6.5)	2 (4.9)	6 (2.6)	6 (2.6)	11 (3.6)
50% to < 75%	1 (1.3)	0	4 (1.8)	2 (0.9)	5 (1.6)
$\geq 75\%$	69 (89.6)	35 (85.4)	218 (95.6)	219 (96.5)	287 (94.1)
Missing	2 (2.6)	4 (9.8)	0	0	2 (0.7)

¹ Exposure to study medication is derived as the number of capsules taken between the first dosing date and the last dosing date.

² Treatment Duration (Days) = Date of last randomized study medication intake – Date of first randomized study medication intake + 1. For Study RHB-105-01 (and 1 patient in Study RHB-105-02), the end of treatment date was calculated based on the drug accountability data (number of capsules returned) and expected 4 capsule every 8 hours study drug administration.

³ Compliance = $100 \times [(Total\ number\ of\ capsules\ dispensed) - (Total\ number\ of\ capsules\ returned)] / 168$.

Source: Adapted from Summary of Clinical Safety, Table 17; Clinical Reviewer's Analysis

Reviewer Comment: *The end date of treatment was not specifically collected on the case report form (CRF) employed in Study RHB-105-01. For all patients in Study RHB-105-01, the Applicant calculated the end date of treatment based on the drug accountability data (number of capsules returned) and expected 4 capsule q8h study drug administration. This reviewer also used the drug accountability data to calculate the end date of treatment for 1 patient in Study RHB-105-02. The extent of exposure and number of patients in the safety database are sufficient to conduct a safety review for the H. pylori indication. The mean duration of exposure and treatment compliance was balanced across treatment groups in the Phase 3 studies.*

Relevant characteristics of the safety population:

Table 10-3 summarize the demographic and baseline characteristics for the treatment groups in the Phase 3 studies. Demographic and baseline characteristic were similar across the treatment groups. In Study RHB-105-01, the mean age was 46.2 years in the RHB-105 group and 45.8 years in the placebo group. The mean age for Study RHB-105-02 was 45.9 years and 47.2 years in the RHB-105 and active comparator groups, respectively. The majority of patients in each treatment group were female, white, and of Hispanic or Latino ethnicity. The most common CYP2C19 phenotype category was normal metabolizer and reported in at least 50% of patients in each treatment group.

Table 10-3: Demographic and Baseline Characteristics – Phase 3 Studies (Safety Population)

Parameter	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 N=77 n (%)	Placebo N=41 n (%)	RHB-105 N=228 n (%)	Active Comparator N=227 n (%)	RHB-105 N=305 n (%)
Age (years)					
Mean (SD)	46.2 (10.6)	45.8 (9.5)	45.9 (12.8)	47.2 (13.1)	45.9 (12.2)
Min, Max	24, 65	26, 63	18, 70	18, 70	18, 70
Age categories, n (%)					
18 – 64 years	75 (97.4)	41 (100)	214 (93.9)	207 (91.2)	289 (94.8)
≥65 years	2 (2.6)	0	14 (6.1)	20 (8.8)	16 (5.2)
Gender, n (%)					
Female	49 (63.6)	25 (61.0)	132 (57.9)	151 (66.5)	181 (59.3)
Male	28 (36.4)	16 (39.0)	96 (42.1)	76 (33.5)	124 (40.7)
Race, n (%)					
White	71 (92.2)	38 (92.7)	184 (80.7)	167 (73.6)	255 (83.6)
Black or African American	6 (7.8)	3 (7.3)	35 (15.4)	53 (23.3)	41 (13.4)
Other	0	0	9 (3.9)	7 (3.1)	9 (3.0)
Ethnicity, n (%)					
Hispanic/Latino	60 (77.9)	35 (85.4)	149 (65.4)	124 (54.6)	209 (68.5)
Not Hispanic/Latino	17 (22.1)	6 (14.6)	79 (34.6)	103 (45.4)	96 (31.5)
Body Mass Index, n (%)					
<25 kg/m ²	10 (13.0)	1 (2.4)	44 (19.3)	34 (15.0)	54 (17.7)
25 - <30 kg/m ²	32 (41.6)	16 (39.0)	74 (32.5)	81 (35.7)	106 (34.8)
≥30 kg/m ²	35 (45.5)	24 (58.5)	110 (48.2)	112 (49.3)	145 (47.5)
Creatinine Clearance¹, n (%)					
45 – <60 ml/min	2 (2.6)	0	2 (0.9)	2 (0.9)	4 (1.3)
60 – <90 ml/min	6 (7.8)	2 (4.9)	29 (12.7)	32 (14.1)	35 (11.5)
≥90 ml/min	69 (89.6)	39 (95.1)	196 (86.0)	193 (85.0)	4 (86.9)
Missing	0	0	1 (0.4)	0	1 (0.3)
CYP2C19 Status, n (%)					
Ultra-rapid metabolizers	0	0	10 (4.4)	3 (1.3)	10 (3.3)

Parameter	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 N=77 n (%)	Placebo N=41 n (%)	RHB-105 N=228 n (%)	Active Comparator N=227 n (%)	RHB-105 N=305 n (%)
Rapid metabolizers	11 (14.3)	4 (9.8)	45 (19.7)	55 (24.2)	56 (18.4)
Normal metabolizers	48 (62.3)	27 (65.9)	114 (50.0)	107 (47.1)	162 (53.1)
Intermediate metabolizers	17 (22.1)	8 (19.5)	48 (21.1)	52 (22.9)	65 (21.3)
Poor metabolizers	0	2 (4.9)	5 (2.2)	4 (1.8)	5 (1.6)
Missing/Not reported	1 (1.3)	0	6 (2.6)	6 (2.6)	7 (2.3)

¹ Creatinine clearance calculated using Cockcroft-Gault equation.

Source: Adapted from Integrated Summary of Safety, Table 14.1.2.1; Clinical Reviewer's Analysis

Reviewer Comment: Demographic characteristics at baseline were generally balanced between treatment groups in the Phase 3 studies.

Adequacy of the safety database:

The Phase 3 studies include 573 adults who received at least one dose of study drug for treatment of *H. pylori*. All of the patient with *H. pylori* infection were enrolled in the United States. The Phase 1 studies include 34 healthy volunteers who received at least one dose of RHB-105. The healthy volunteers were all enrolled in Canada. The overall size of the safety database is adequate and applicable to the U.S. population.

10.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This reviewer has not identified any concerning findings regarding the quality and integrity of the data.

Categorization of Adverse Events

No significant issues were identified with respect to the Applicant's process for recording, coding, and categorizing adverse events. Standard regulatory definitions were used to categorize treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). TEAEs were considered as any event that arises after the first dose of study drug and before the standard of care (SOC) phase. In order to be consistent with the individual study analysis, adverse events in Study RHB-105-02 that started later than 28 days after the last dose of study drug were not considered as TEAEs.

All adverse events in the Phase 3 studies were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. Adverse events were coded using the most updated MedDRA version available when the studies were performed (i.e., MedDRA Versions 16 and 21.1 used in

Studies RHB-105-01 and RHB-105-02, respectively). The CYP2C19 phenotype for patients in Study RHB-105-01 was re-classified based on the reporting standard used in Study RHB-105-02 (Caudle KE *et al.*, 2017). The original CYP2C19 status terminology for Study RHB-105-01 was current at the time of the report.

Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns for RHB-105 was adequate in the design and conduct of the clinical studies. Safety assessment included monitoring of TEAEs and SAEs, vital sign measurements (blood pressure, heart rate, respiratory rate, and temperature), physical examination, and clinical laboratory tests (chemistry, hematology, and urinalysis). The schedules for the noteworthy procedures performed during the Phase 3 studies RHB-105-01 and RHB-105-02 are presented in Table 10-4 and Table 10-5, respectively.

Table 10-4: Noteworthy Procedures for Study RHB-105-01

Procedure	Screening	Baseline	Safety Visit	End of Therapy	Test of Cure	Phone Follow-up
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 4A
	Day -21 to -2	Day 0	Day 8 (±1 day)	Day 15 (±1 day)	Day 43 (+7 days)	Day 44 (+7 days)
Informed Consent	X					
Medical History	X	X				
Physical Examination with Vital Signs	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	
Urine Pregnancy Test	X	X	X	X	X	
Chemistry, Hematology, Urinalysis	X	X	X	X	X	
¹³ C UBT	X ^a				X ^a	
Fecal antigen test for <i>H. pylori</i> IgG	X					
Review of gastric biopsy pathology report for presence of <i>H. pylori</i> if available (within 12 week of screening)	X					
Schedule of upper endoscopy if applicable	X					
CYP2C19 Genotyping		X				
Pharmacokinetic assessments		X ^b	X ^b	X ^b		
Electrocardiogram	X					
Study Drug Dispensed		X	X			
Adverse event assessment		X	X	X	X	
Unblinding of ¹³ C UBT Results						X
Study Site Personnel Contact Patients to Schedule Standard of Care Therapy ^c or Endoscopy ^d or notify of study completion ^e						X

^a Performed following a one hour fast from solid food.

^b Blood samples taken prior to first dose at visit 1, prior to AM dose at visit 2, and in the AM of visit 3 to assess trough levels of amoxicillin, omeprazole, rifabutin, and 25-O-desacetyl-rifabutin.

^c All placebo treated patients will be entitled to receive standard of care therapy as prescribed by the investigator after unblinding.

^d Eradication failures (¹³C UBT-positive patients) in the active study drug arm will be scheduled to undergo upper endoscopy with sampling for culture/susceptibility, and follow up standard of care treatment as prescribed by the investigator.

^e Eradication successes (¹³C UBT-negative patients) in active study arm.

Source: Adapted from clinical study report for Study RHB-105-01

Table 10-5: Noteworthy Procedures for Study RHB-105-02

Procedure	Screening	Baseline	Phone Follow-up	Safety Visit	Phone Follow-up	Test of Cure	Phone Follow-up
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 5A
	Day -42 to 0	Day 1	Day 8 (±1 day)	Day 13 (±2 day)	Day 28 – 60 (±2 days)	Day 43 – 71 (+7 days)	Day 44 – 72 (+7 days)
Informed Consent	X						
Medical History	X	X					
Physical Examination with Vital Signs	X	X		X		X	
Concomitant Medications	X	X		X		X	
Urine Pregnancy Test	X	X		X		X	
Chemistry, Hematology, Urinalysis	X			X		X ^a	
¹³ C UBT	X ^b					X ^{b,c}	
Upper Endoscopy to determine <i>H. pylori</i> status ^d	X						
CYP2C19 Genotyping		X					
Pharmacokinetic assessments		X ^e		X ^e			
Electrocardiogram	X						
Study Drug Dispensed		X					
Adverse event assessment		X	X	X	X	X	
Unblinding of ¹³ C UBT Results							X ^f

^a For patients with abnormal results at Visit 3.

^b Performed following a one hour fast from solid food.

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

^d Scheduled endoscopy with gastric biopsies for rapid urease test (CLO), histology, and culture/susceptibility.

^e 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. Also to be performed on patients who early terminate during 14 day course of treatment if possible.

^f Patients with positive results will be scheduled to undergo upper endoscopy with sampling for culture/susceptibility, and follow up standard of care treatment as prescribed by the investigator. Patients with negative results will have Visit 5 be their end-of-study visit.

Source: Adapted from clinical study report for Study RHB-105-02

10.4. Safety Results

Overall Incidence

The overall incidence of TEAEs in the Phase 3 studies is summarized in Table 10-6. In each Phase 3 study, a greater percentage of patients in the RHB-105 treatment group compared with the placebo or active comparator groups experienced at least 1 TEAE. The incidence of TEAE in various TEAE categories were generally well balanced between treatment groups in each study. Overall, most of the TEAEs were mild or moderate in severity, non-serious, and resolved without leading to discontinuation of study drug. No deaths were reported in either Phase 3 study.

Table 10-6: Overview of TEAEs – Phase 3 Studies (Safety Population)

TEAE Category	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 N=77 n (%)	Placebo N=41 n (%)	RHB-105 N=228 n (%)	Active Comparator N=227 n (%)	RHB-105 N=305 n (%)
Any TEAE	39 (50.6)	17 (41.5)	83 (36.4)	72 (31.7)	122 (40.0)
Any severe TEAE	3 (3.9)	2 (4.9)	4 (1.8)	4 (1.8)	7 (2.3)
Any SAE	1 (1.3)	1 (2.4)	1 (0.4)	1 (0.4)	2 (0.7)
Any TEAE leading to discontinuation of study drug	2 (2.6)	1 (2.4)	2 (0.9)	1 (0.4)	4 (1.3)

Source: Adapted from Summary of Clinical Safety, Table 18; Clinical Reviewer's Analysis

The overall incidence of TEAEs for RHB-105 treatment in the Phase 1 studies is summarized in Table 10-7. All of the TEAEs were mild or moderate in severity, non-serious, and resolved without discontinuation of RHB-105 treatment. No deaths were reported in either Phase 1 study.

Table 10-7: Overview of TEAEs – Phase 1 Studies (Safety Population)

TEAE Category	Study RHB-P2-418	Study RHB-105-12
	RHB-105 Multiple Doses N=16 n (%)	RHB-105 Fed/Fast Single Dose N=18 n (%)
Any TEAE	3 (18.8)	4 (22.2)

Source: Adapted from Summary of Clinical Safety, Tables 5 and 9; Clinical Reviewer's Analysis

Deaths

No deaths were reported during the Phase 1 or Phase 3 studies.

Serious Adverse Events

A total of 4 patients experienced SAEs in the overall safety population. The SAEs reported in Study RHB-105-01 included 1 case of anemia in the RHB-105 treatment group and 1 case of perirectal abscess in the placebo treatment group. In Study RHB-105-02, there was 1 SAE of diabetic ketoacidosis in the RHB-105 group and 1 SAE of encephalopathy secondary to benzodiazepine overdose in the active comparator group. All of the SAEs in Studies RHB-105-01 and RHB-105-02 were reported as serious because they required hospitalization. All of the SAEs resolved and none were considered by the investigator to be related to study drug. Brief narratives for the SAEs in the patients treated with RHB-105 are presented below.

Narrative of SAEs in the patients treated with RHB-105 in the Phase 3 studies (n=2)

- **Patient** (b) (6): This was a 49 year old female who completed a 14-day course of RHB-105 treatment in Study RHB-105-01. She had a medical history of anemia which was thought to be due to heavy menstrual bleeding. Low hemoglobin levels of 7.5 g/dL and 7.0 g/dL (reference range, 12.0 – 15.6 g/dL) were noted at the screening and baseline visits, respectively. On Day 5, she was referred to the emergency department for treatment of anemia and hospitalized for 1 day. She received 1 unit of blood during her hospitalization and started iron supplementation on Day 9. Follow-up hemoglobin levels were 9.1 g/dL on Day 10, 9.3 g/dL on Day 15, and 11.1 g/dL on Day 44. The investigator recorded the event as resolved on Day 12. According to the investigator, the SAE of anemia was related to a preexisting condition and unrelated to study drug. The Applicant also considered the event to be a non-treatment emergent SAE.

Reviewer Comment: *The investigator's assessment that the anemia may have been attributed to a preexisting condition is reasonable. However, this reviewer disagrees with the Applicant's assessment that the SAE was not a treatment emergent event. It is unclear if the anemia worsened after starting the study treatment and no post-baseline hemoglobin levels were available to review before her transfusion on Day 5. This reviewer included this event in the analyses of the overall incidence of TEAEs.*

- **Patient** (b) (6): This was a 45 year old male who completed a 14-day course of RHB-105 treatment in Study RHB-105-02. He had a medical history of type 1 diabetes mellitus and experienced the treatment emergent SAE of diabetic ketoacidosis on Day 11. Symptoms and laboratory abnormalities consistent with diabetic ketoacidosis were noted at the time of admission. He also reported variable compliance with his mealtime insulin prior to admission. The patient was admitted to the intensive care unit where he was started on an insulin drip and intravenous fluids. He was transitioned to subcutaneous insulin on Day 12. The diabetic ketoacidosis was considered to be resolved on Day 13 because the patient had clinically improved and was medically stable. The patient was discharged from the hospital on the same day. The investigator considered the event to be unrelated to study drug.

Reviewer Comment: *This reviewer agrees with the investigator's assessment that the diabetic ketoacidosis was not related to study drug. The patient exhibited symptoms and*

laboratory abnormalities consistent with diabetic ketoacidosis and reported variable compliance with insulin at home.

None of the patients in the Phase 1 studies with RHB-105 experienced SAEs.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 10-8 summarizes the premature treatment discontinuations and/or early study withdrawals during the Phase 3 studies. In Study RHB-105-01, 2 (2.6%) patients in the RHB-105 group and 1 (2.4%) patient in the placebo group had TEAEs that led to premature discontinuation of the study drug and study. The TEAEs were non-serious and included 1 case of nausea and vomiting (RHB-105 group), 1 case of nasopharyngitis (RHB-105 group), and 1 case of diarrhea and vomiting (placebo group). Study RHB-105-02 had 2 (0.9%) patients in the RHB-105 group and 1 (0.4%) patient in the active comparator group who experienced TEAEs that led to premature discontinuation of the study drug only. The TEAEs were non-serious and included 1 case of nausea (RHB-105 group), 1 case of nasal congestion (RHB-105 group), and 1 case of headache (active comparator group). There were no dropouts due to adverse events during Study RHB-105-02. All the TEAEs that led to premature discontinuation of study drug in the Phase 3 studies were resolved by study completion.

Table 10-8: Subject Disposition – Phase 3 Studies (Safety Population)

	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 N=77 n (%)	Placebo N=41 n (%)	RHB-105 N=228 n (%)	Active Comparator N=227 n (%)	RHB-105 N=305 n (%)
Number of Patients Prematurely Discontinuing Study Drug					
n (%)	8 (10.4)	4 (9.8)	6 (2.6)	5 (2.2)	14 (4.6)
Primary Reason for Premature Discontinuation of Study Drug					
Adverse Event	2 (2.6)	1 (2.4)	2 (0.9)	1 (0.4)	4 (1.3)
Non-Compliance with Study Drug	4 (5.2)	0	2 (0.9)	1 (0.4)	6 (2.0)
Lost to Follow-Up	2 (2.6)	1 (2.4)	0	0	2 (0.7)
Pregnancy	0	0	1 (0.4)	0	1 (0.3)
Other ¹	0	0	1 (0.4)	0	1 (0.3)
Physician's Decision	0	0	0	1 (0.4)	0
Withdrawal by Subject	0	2 (4.9)	0	2 (0.9)	0
Number of Patients Prematurely Withdrawing from Study before Test of Cure					
n (%)	11 (14.3)	4 (9.8)	1 (0.4)	0	12 (3.9)
Primary Reason for Premature Withdrawal from Study before Test of Cure					
Adverse Event	2 (2.6)	1 (2.4)	0	0	2 (0.7)
Non-Compliance with Study Drug ²	4 (5.2)	0	0	0	4 (1.3)
Lost to Follow-Up	5 (6.5)	1 (2.4)	0	0	5 (1.6)
Withdrawal by Subject	0	2 (4.9)	1 (0.4)	0	1 (0.3)

¹ The "other" reason includes 1 patient not dispensed Day 14 afternoon and evening dose in error.

² Non-compliance with study drug (defined as less than 75%) was a protocol defined criteria for study discontinuation during Study RHB-105-01 only.

Source: Adapted from Integrated Summary of Safety, Table 14.1.1; Clinical Reviewer's Analysis

Reviewer Comment: *There were minor discrepancies between this reviewer's analysis and that of the Applicant. For example, this reviewer included 2 patients in the RHB-105 treatment group who prematurely discontinued both the study drug and study due to adverse events. Both patients were in Study RHB-105-01 and discontinued the study because of TEAE(s) leading to premature discontinuation of study drug. One of the patients (Patient (b) (6)) discontinued the study drug because of nasopharyngitis from Day 3 to Day 6. The other patient (Patient (b) (6)) discontinued the study drug because of nausea and vomiting from Day 7 to Day 8. The Applicant's disposition table included these patients in a different reason for early termination from the study ("non-compliance with study drug" for Patient (b) (6) and "other" for Patient (b) (6)).*

None of the patients in the Phase 1 crossover studies experienced TEAEs that led to premature discontinuation of RHB-105 treatment. However, 1 patient in Study RHB-P2-418 was withdrawn from the study for safety reasons (increased ALT and AST) prior to starting treatment with the individual listed drugs for rifabutin, amoxicillin, and omeprazole. This patient completed the RHB-105 three times a day treatment on Day 1 and was withdrawn by the investigator following elevated liver tests of ALT 102 U/L (reference range, 25 – 70 U/L) and AST 95 U/L (reference range, 0 – 38 U/L) at the end of the washout period on Day 15. The laboratory abnormalities were reported as non-serious TEAEs and repeat liver tests were normal 1 week later. Study RHB-105-12 had 1 patient prematurely discontinue the study due to withdrawal of consent. This patient received a single dose of active comparator on Day 1, a single dose of RHB-105 under fed conditions on Day 15, and a single dose of RHB-105 under fasting conditions on Day 26. The patient withdrew consent after the last dose of study treatment and did not report any new or ongoing TEAEs at that time.

Significant Adverse Events

There were no additional significant adverse events identified within the clinical studies with RHB-105.

Treatment Emergent Adverse Events and Adverse Reactions

Table 10-9 summarizes the common TEAEs reported during the Phase 3 studies, and defined as TEAEs experienced by at least 1% patients treated with RHB-105. Diarrhea and headache were the most common TEAEs. The respective events were reported in 34 (11.1%) and 29 (9.5%) patients treated with RHB-105, 18 (7.9%) and 16 (7.0%) patients treated with active comparator, and 4 (9.8%) patients each treated with placebo.

Table 10-9: TEAEs Experienced by at least 1% of Patients in the Pooled RHB-105 Treatment Group – Phase 3 Studies (Safety Population)

Preferred term	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 N=77 n (%)	Placebo N=41 n (%)	RHB-105 N=228 n (%)	Active Comparator N=227 n (%)	RHB-105 N=305 n (%)
Diarrhea	11 (14.3)	4 (9.8)	23 (10.1)	18 (7.9)	34 (11.1)
Headache ¹	12 (15.6)	4 (9.8)	17 (7.5)	16 (7.0)	29 (9.5)
Nausea	3 (3.9)	1 (2.4)	11 (4.8)	12 (5.3)	14 (4.6)
Abdominal pain ²	3 (3.9)	2 (4.9)	8 (3.5)	11 (4.8)	11 (3.6)
Chromaturia	10 (13.0)	1 (2.4)	0	0	10 (3.3)
Rash ³	4 (5.2)	0	6 (2.6)	2 (0.9)	10 (3.3)
Abdominal tenderness	5 (6.5)	3 (7.3)	1 (0.4)	1 (0.4)	6 (2.0)
Dizziness	3 (3.9)	3 (7.3)	3 (1.3)	5 (2.2)	6 (2.0)
Dyspepsia ⁴	1 (1.3)	0	5 (2.2)	3 (1.3)	6 (2.0)
Urinary tract infection ⁵	2 (2.6)	1 (2.4)	4 (1.8)	5 (2.2)	6 (2.0)
Vomiting	1 (1.3)	2 (4.9)	5 (2.2)	5 (2.2)	6 (2.0)
Oropharyngeal pain	3 (3.9)	0	2 (0.9)	2 (0.9)	5 (1.6)
Vulvovaginal candidiasis ⁶	0	0	5 (2.2)	5 (2.2)	5 (1.6)
Abdominal distention	0	1 (2.4)	4 (1.8)	3 (1.3)	4 (1.3)
Flatulence	2 (2.6)	3 (7.3)	2 (0.9)	2 (0.9)	4 (1.3)

¹ Headache includes: headache and migraine.

² Abdominal pain includes: abdominal pain, abdominal pain upper, and abdominal pain lower.

³ Rash includes: rash, rash erythematous, rash follicular, rash maculo-papular, rash morbilliform, and urticaria.

⁴ Dyspepsia includes: dyspepsia and epigastric discomfort.

⁵ Urinary tract infection includes: urinary tract infection and cystitis.

⁶ Vulvovaginal candidiasis includes: vulvovaginal candidiasis, vulvovaginal mycotic infection, fungal infection, and vaginal discharge + vulvovaginal burning sensation + vulvovaginal pruritus.

Source: Clinical Reviewer's Analysis

Reviewer Comment: The common TEAEs that occurred in at least 1% of patients in the pooled RHB-105 group and with incidences greater than placebo or active comparator were diarrhea, headache, nausea, chromaturia, rash, abdominal tenderness, dyspepsia, oropharyngeal pain, vulvovaginal candidiasis, and flatulence. Some of these TEAEs (i.e., abdominal tenderness, flatulence) occurred more frequently in the placebo group in Study RHB-105-01 and less than 1% of patients in any treatment group in Study RHB-105-02. Riboflavin was administered in Study RHB-105-02 to prevent unintentional unblinding and may have contributed to underreporting of chromaturia. In addition, all patients enrolled in Study RHB-105-02 were made aware of the potential for chromaturia with rifabutin and/or riboflavin.

A total of 7 patients (20.6%) in the Phase 1 studies reported one or more TEAEs after RHB-105 treatment. In Study RHB-P2-418, the TEAEs reported for RHB-105 three times a day treatment included 1 patient with feces hard, 1 patient with fatigue, and 1 patient with ALT and AST increased. The TEAEs reported in Study RHB-105-12 for single dose RHB-105 treatment included

1 patient with fatigue, 1 patient with somnolence, 1 patient with procedural dizziness, and 1 patient with multiple TEAEs (dizziness, headache, hot flush, nausea, pallor, peripheral coldness, and vessel puncture site pain).

Laboratory Findings

Chemistry

Chemistry laboratory values assessed in Phase 3 studies included ALT, albumin, AST, amylase, alkaline phosphatase, bilirubin, calcium, carbon dioxide/bicarbonate, chloride, cholesterol, creatine phosphokinase, creatinine, gamma glutamyl transferase, lactate dehydrogenase, magnesium, phosphorus, potassium, protein, sodium, urate, and urea nitrogen. Mean changes from baseline were generally small and no meaningful trends were observed between the treatment groups.

Summary of peak post-baseline ALT, AST, and total bilirubin values during the double-blind phase are presented in Table 10-10. Individual elevations in ALT, AST, or total bilirubin occurred in the treatment groups at similar frequencies. No patients in any of the clinical studies with RHB-105 satisfied Hy's Law laboratory criteria for potential drug-induced liver injury (ALT or AST $\geq 3 \times$ ULN, alkaline phosphatase $\leq 2 \times$ ULN, and total bilirubin $\geq 2 \times$ ULN).

Table 10-10: Summary of Liver Test Results – Phase 3 Studies (Safety Population)

	Study RHB-105-01				Study RHB-105-02			
	RHB-105		Placebo		RHB-105		Active Comparator	
ALT (U/L)	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	73	94.8%	39	95.1%	220	96.5%	219	96.5%
Between 2x and 5x ULN	1	1.3%	1	2.4%	4	1.8%	6	2.6%
Between 5x and 10x ULN	1	1.3%	0	0.0%	0	0.0%	0	0.0%
Missing Test Result	2	2.6%	1	2.4%	4	1.8%	2	0.9%
All	77	100.0%	41	100.0%	228	100.0%	227	100.0%
AST (U/L)								
Less than 2x ULN	73	94.8%	39	95.1%	221	96.9%	219	96.5%
Between 2x and 5x ULN	2	2.6%	1	2.4%	5	2.2%	6	2.6%
Missing Test Result	2	2.6%	1	2.4%	2	0.9%	2	0.9%
All	77	100.0%	41	100.0%	228	100.0%	227	100.0%
Bilirubin (umol/L)								
Less than 2x ULN	75	97.4%	40	97.6%	225	98.7%	225	99.1%
Missing Test Result	2	2.6%	1	2.4%	3	1.3%	2	0.9%
All	77	100.0%	41	100.0%	228	100.0%	227	100.0%

Source: Clinical Reviewer's Analysis

Hematology

Hematology laboratory values assessed in the Phase 3 studies included WBC count with differential, hemoglobin, hematocrit, and platelet count. Mean changes from baseline were generally small and no meaningful trends were observed between the treatment groups.

Vital Signs

Vital signs descriptive summary statistics and change from baseline visit for the Phase 3 studies were reviewed. Mean changes from baseline visit in heart rate, systolic blood pressure, diastolic blood pressure, and respiratory rate were small and no meaningful trends were observed between the treatment groups. There were no individuals with changes in their vital sign

parameters that were considered clinically significant by the investigator.

Electrocardiograms (ECGs)

ECGs were performed at screening in the Phase 1 and Phase 3 studies. A total of 2 patients, one each belonging to the RHB-105 and active comparator groups in Study RHB-105-02, had abnormal ECG results that were considered clinically significant by the investigator. Both of these patients underwent cardiology consultation and were found to have no significant abnormalities or evidence of cardiac disease prior to treatment.

QT

Not applicable.

Immunogenicity

Not applicable.

10.5. Analysis of Submission-Specific Safety Issues

No submission specific safety issues were identified. A summary of the safety information from literature and the prescribing information of each of the active ingredients in RHB-105 were reviewed. Anaphylactic reactions and *Clostridioides difficile*-associated diarrhea have been reported with the use of nearly all antibacterial agents as well as proton pump inhibitors. Acute interstitial nephritis and uveitis have been reported with the use of amoxicillin and rifabutin, respectively. None of these potentially serious adverse events were observed during the clinical program for *H. pylori* therapy with RHB-105.

10.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

10.7. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were performed using the integrated dataset inclusive of the two Phase 3 studies. The intrinsic factors of age, gender, race, ethnicity, BMI, and CYP2C19 phenotype were investigated. No formal analyses were conducted for extrinsic factors.

The incidence of any TEAE by age, gender, race, ethnicity, and CYP2C19 status are presented in Table 10-11. Overall the safety profile was similar in all the subgroups irrespective of gender, race, ethnicity, BMI, or CYP2C19 status. The number of patients who experienced SAEs or TEAEs leading to discontinuation of study drug were too low to allow a meaningful subgroup analysis for these TEAE categories.

Table 10-11: Adverse Event Rate by Baseline Characteristic – Phase 3 Studies (Safety Population)

Any TEAE by Baseline Characteristic	Study RHB-105-01		Study RHB-105-02		Pooled Analysis
	RHB-105 n/N (%)	Placebo n/N (%)	RHB-105 n/N (%)	Active Comparator n/N (%)	RHB-105 n/N (%)
Overall	39/77 (51)	17/41 (41)	83/228 (36)	72/227 (32)	122/305 (40)
Age categories					
18 – 64 years	39/75 (41)	17/41 (41)	79/214 (37)	66/207 (32)	118/289 (41)
≥65 years	0/2 (0)	–	4/14 (29)	6/20 (30)	4/16 (25)
Gender					
Female	26/49 (53)	11/25 (44)	54/132 (41)	45/151 (30)	80/181 (44)
Male	13/28 (46)	6/16 (38)	29/96 (30)	27/76 (36)	42/124 (34)
Race					
White	36/71 (51)	14/38 (37)	63/184 (34)	58/167 (35)	99/255 (39)
Black/African American	3/6 (50)	3/3 (100)	16/35 (46)	9/53 (17)	19/41 (46)
Other	–	–	4/9 (44)	5/7 (71)	4/9 (44)
Ethnicity					
Hispanic or Latino	30/60 (50)	13/35 (37)	50/149 (34)	40/124 (32)	80/209 (38)
Not Hispanic or Latino	9/17 (53)	4/6 (67)	33/79 (42)	32/103 (31)	42/96 (44)
Body Mass Index					
<25 kg/m ²	5/10 (50)	0/1 (0)	17/44 (39)	9/34 (26)	22/54 (41)
25 - <30 kg/m ²	13/32 (41)	8/16 (50)	21/74 (28)	27/81 (33)	34/106 (32)
≥30 kg/m ²	21/35 (60)	9/24 (38)	45/110 (41)	36/112 (32)	66/145 (46)
CYP2C19 Status					
Ultra-rapid metabolizers	–	–	4/10 (40)	1/3 (33)	4/10 (40)
Rapid metabolizers	6/11 (55)	2/4 (50)	19/45 (42)	11/55 (20)	25/56 (45)
Normal metabolizers	24/48 (50)	9/27 (33)	37/114 (32)	40/107 (37)	61/162 (38)
Intermediate metabolizers	8/17 (47)	4/8 (50)	19/48 (40)	16/52 (31)	27/65 (42)
Poor metabolizers	–	2/2 (100)	1/5 (20)	3/4 (75)	1/5 (20)
Missing/Not reported	1/1 (100)	–	3/6 (50)	1/6 (17)	4/7 (57)

Source: Clinical Reviewer’s Analysis

10.8. Specific Safety Studies/Clinical Trials

There were no specific studies for review.

10.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There have been no formal studies in humans to assess human carcinogenicity development with RHB-105. Carcinogenicity studies were not conducted because of the short-term, intermittent use of RHB-105.

Human Reproduction and Pregnancy

The clinical studies with RHB-105 did not enroll pregnant or lactating women. One pregnancy was reported during Study RHB-105-02. This was a 30 year old female patient who received the RHB-105 three times a day treatment until a positive pregnancy test was noted on Day 10. The pregnancy was suspected to be within the first trimester based on the anticipated due date. She refused to provide further information or follow-up regarding her pregnancy.

Pediatrics and Assessment of Effects on Growth

The clinical studies with RHB-105 did not enroll pediatric patients or evaluate the effects of RHB-105 on growth. The Applicant submitted an initial Pediatric Study Plan (iPSP) which includes documentation in support of a full waiver from conducting pediatric studies for the treatment of *H. pylori* infection.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The clinical studies with RHB-105 did not investigate doses higher than the proposed marketing dose of 4 capsules, equivalent to 50 mg of rifabutin, 1,000 mg of amoxicillin, and 40 mg of omeprazole. Furthermore, no adverse reactions specifically associated with RHB-105 overdose were reported in the clinical studies. RHB-105 does not have a known potential for drug abuse or dependence. No cases of drug abuse, withdrawal, or rebound were reported during the clinical studies with RHB-105.

10.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not Applicable – no postmarket experience.

Expectations on Safety in the Postmarket Setting

There are no potential safety concerns expected beyond the risks conveyed in the proposed labeling.

10.11. Integrated Assessment of Safety

The safety of RHB-105 for the treatment of *H. pylori* infection in adults was primarily based on data from 2 Phase 3 studies comparing RHB-105 treatment to either placebo or active comparator (same doses of amoxicillin and omeprazole without rifabutin). The pooled data from the Phase 3 studies included 305 patients treated with at least 1 dose of RHB-105 at the intended regimen of 4 capsules of RHB-105 administered every 8 hours for 14 days. The demographic and baseline characteristics were comparable between the treatment groups in the pooled analysis. Most of the patients were female, white, and of Hispanic or Latino ethnicity. The CPY2C19 status for a majority of patients was normal metabolizers. All of the

patients were from the US.

The percentage of patients who experienced TEAEs were similar between the pooled RHB-105 and placebo groups (40.0% versus 41.5%) and lower in the active comparator group (31.7%). The most common TEAEs that occurred in at least 1% of patients in the pooled RHB-105 group and with incidences greater than placebo or active comparator were diarrhea, headache, nausea, chromaturia, rash, abdominal tenderness, dyspepsia, oropharyngeal pain, vulvovaginal candidiasis, and flatulence. These events were not a tolerability issue because the majority were mild or moderate in severity and infrequently led to discontinuation of study drug. There were no major imbalances between the treatment groups in terms of number of SAEs and no deaths were reported in any of the clinical studies. No new safety signals with RHB-105 were observed in the clinical development program that would not be expected with the use of the individual components of RHB-105.

10.12. Conclusions and Recommendations

The efficacy and safety of RHB-105 for the treatment of *H. pylori* infection is supported by 2 randomized, double-blind Phase 3 studies comparing RHB-105 to placebo or an active comparator of amoxicillin/omeprazole (without rifabutin). Efficacy data from these studies demonstrate that RHB-105 was superior to placebo control and to amoxicillin/omeprazole dual therapy at the same dose and duration as in RHB-105. No new safety signals were identified in the Phase 3 studies with RHB-105. There were also no important risks identified in the 2 Phase 1 studies with healthy volunteers. In conclusion, review of the available safety information demonstrate that the proposed RHB-105 formulation is safe and well tolerated and support its use to treat *H. pylori* infection in adult patients.

11 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this NDA as there were no issues that needed input from external experts.

12 Pediatrics

There were no pediatric studies included in the NDA. The Applicant's request for a full waiver from conducting pediatric studies in patients less than 17 years of age will be granted given the questionable utility of eradication in pediatric patients with *H. pylori* infection. Eradication of *H. pylori* is not recommended to prevent sequela of chronic infection in children because gastric adenocarcinoma or precancerous lesions that predispose to gastric cancer is rarely reported in *H. pylori*-infected children. The waiver request was discussed at the Pediatric Review Committee (PeRC) on September 10, 2019 and the committee agreed with granting the full waiver.

13 Labeling Recommendations

13.1. Prescription Drug Labeling

NDA 213004 for Talicia relies on FDA’s findings of safety and effectiveness for amoxicillin (NDA 050459 for Amoxil), omeprazole (NDA 19810 for Prilosec), and rifabutin (NDA 050689 for Mycobutin). The approvals of two of the relied-upon listed drugs, NDA 050459 Amoxil and NDA 019810 Prilosec, have been withdrawn FR effective (Federal Register determination that both products were not discontinued or withdrawn for safety or efficacy reasons). It is permissible for the applicant to refer to the currently approved ANDA labeling for omeprazole (ANDA 76048) and amoxicillin (ANDA 61926) because the listed drugs’ labeling is not current.

Summary of Significant Labeling Changes		
Section	Applicant Proposed Labeling	FDA Proposed Labeling Changes
HIGHLIGHTS OF PRESCRIBING INFORMATION	(b) (4)	TALICIA is a three-drug combination of omeprazole, a proton pump inhibitor, amoxicillin, a penicillin-class antibacterial, and rifabutin, a rifamycin antibacterial, indicated for the treatment of <i>Helicobacter pylori</i> infection in adults.
INDICATIONS AND USAGE	(b) (4)	(b) (4). This section is not intended to be a description of the data supporting the determination of effectiveness. - Added statement consistent with the regulatory required statement 21 CFR 201.24 (b).
DOSAGE AND ADMINISTRATION		- Added instructions to not crush or chew TALICIA capsules. - Added instructions to not take TALICIA with alcohol.
WARNINGS AND PRECAUTIONS		Revised to include all the drug interactions under one subsection heading (risk of adverse reactions or loss of efficacy due to drug interactions).
ADVERSE REACTIONS	Summary of clinical trials experience, other important adverse reactions from the labeling of the individual components of TALICIA, and post-marketing experience with components of TALICIA.	- Minor modifications to adverse event totals. - Combined related adverse event terms. - Split adverse reactions from each trial because the study designs were different.
DRUG INTERACTIONS		Added table for interactions with drugs and diagnostics to improve the readability.
USE IN SPECIFIC POPULATIONS		- Revised pregnancy and lactation subsections to comply with PLLR. - Added animal data with esomeprazole in Section 8.1 as it is included in the labeling for the

		omeprazole LD. - For the animal data related to omeprazole and esomeprazole, the multiples and doses were adjusted to reflect the higher fixed dose of 120 mg omeprazole/esomeprazole in RHB-105. Therefore multiples to the human equivalent dose have decreased. - Included information in Section 8.3 on infertility based on animal findings with rifabutin from Section 13.1 to comply with PLR. - Added esomeprazole juvenile rate toxicity data into Section 8.4 from the listed drug omeprazole with revised language to comply with PLR. (b) (4) The effect of CYP2C19 phenotypes was described in Section 12.5.
CLINICAL PHARMACOLOGY		- Revised table for pharmacokinetic parameters of the components of TALICIA. - Added table for the absorption, distribution, and elimination related pharmacokinetic information on the components of TALICIA
NONCLINICAL TOXICOLOGY		- Added information related to esomeprazole in Section 13.1 as it is included in the labeling for the omeprazole LD - Added detailed data from esomeprazole juvenile rat toxicity study from the LD omeprazole into 13.2 since this product is not indicated for children.
CLINICAL STUDIES	Summary of efficacy data in the ITT and PK population of one Phase 3 trial. (b) (4) (b) (4)	(b) (4) Added efficacy data from a second clinical trial to provide supportive evidence for efficacy of TALICIA for the treatment of <i>H. pylori</i> infection.

14 Risk Evaluation and Mitigation Strategies (REMS)

No risk evaluation and mitigation strategies are recommended at this time.

15 Postmarketing Requirements and Commitment

There are no postmarketing requirements or commitments at this time.

16 Division Director Comments

I concur with the review team's assessment.

17 Appendices

17.1. References

Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Whirl-Carrillo M, Scott SA, Rehm HL, Williams MS, Klein TE, Relling MV, Hoffman JM. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genetics in Medicine* 2017;19(2):215-223.

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Thung I, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. Review article: the global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment Pharmacol Ther* 2016;43(4):514-533.

17.2. Financial Disclosure

Financial disclosure information was provided for the investigators who conducted the Phase 3 clinical studies (Studies RHB-105-01 and RHB-105-02). The Applicant determined there were no financial interests or arrangements to disclosure for the investigators in these studies.

Covered Clinical Study (Name and/or Number): RHB-105-01 and RHB-105-02

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Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: Study RHB-105-01: 9 investigators Study RHB-105-02: 55 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in Sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ N/A	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ N/A	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐ N/A	No ☐ (Request explanation from Applicant)

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

17.3.1. Summary of Bioanalytical Method Validation and Performance

Review of the bioanalytical methods utilized to quantify Talicia (RHB-105) components and 25-O-Desacetyl-Rifabutin³⁰ (25ODR) in the clinical pharmacology studies are summarized in Table 17-1 below.

Table 17-1: Bioanalytical Method Validation & Performance Findings

Study	Study RHB-P2-418	
Analyte/Assessment	Amoxicillin	
Method	HPLC-MS/MS	
Validation Report	Validation report provided: AOI-V3-487(R1)	☒ Yes ☐ No
	Validation report acceptable Range: 0.2 µg/mL to 40 µg/mL	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable QC: 0.6, 5, 8, 20, and 30 µg/mL	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No
Analyte/Assessment	Omeprazole	
Method	HPLC-MS/MS	
Validation Report	Validation report provided: OEL-V9-713	☒ Yes ☐ No
	Validation report acceptable Range: 5 ng/mL to 2500 ng/mL	☒ Yes ☐ No
Performance Report	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable QC: 15, 225, 400, 850, and 1875 ng/mL	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No
Analyte/Assessment	Rifabutin & 25ODR	
Method	HPLC-MS/MS	
Validation Report	Validation report provided: RFI-V3-624 (for rifabutin), RFI-V3-723 (for 25ODR)	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No

³⁰ 25-O-Desacetyl-Rifabutin (25ODR) is one of the five rifabutin metabolites and has antimicrobial activity equal to the parent drug. 25ODR is the most predominant metabolite with a plasma metabolite to parent AUC ratio of 0.10 and thereby, contributing to up to 10% of the total antimicrobial activity.

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TALICIA (rifabutin, amoxicillin, omeprazole)

	Range: 8 ng/mL to 800 ng/mL (for rifabutin), 0.2 ng/mL to 100 ng/mL (for 25ODR)	
Performance Report	Samples analyzed within the established stability period Reported long term stability in plasma: 79 days for both rifabutin and 25ODR	☒ Yes ☐ No
	Quality control samples range acceptable QC: 6, 30, 100, 150, 400, and 600 ng/mL for rifabutin and 0.6, 3, 10, 20, 50, and 75 ng/mL for 25ODR	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No
Study	Study RHB-105-12	
Analyte/Assessment	Amoxicillin	
Method	HPLC-MS/MS	
Validation Report	Validation report provided: AOI-V3-487(R5)	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
	Range: 0.2 µg/mL to 40 µg/mL	
Performance Report	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable QC: 0.6, 3, 5, 9, 20, and 30 µg/mL	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No
Analyte/Assessment	Omeprazole	
Method	HPLC-MS/MS	
Validation Report	Validation report provided: OEL-V9-561 (R10)	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
	Range: 2 ng/mL to 1500 ng/mL	
Performance Report	Samples analyzed within the established stability period	☒ Yes ☐ No
	Quality control samples range acceptable QC: 6, 150, 300, 750, and 1200 ng/mL	☒ Yes ☐ No
	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No
Analyte/Assessment	Rifabutin & 25ODR	
Method	HPLC-MS/MS	
Validation Report	Validation report provided: RFI-V3-723 (R4) (for rifabutin and for 25ODR)	☒ Yes ☐ No
	Validation report acceptable	☒ Yes ☐ No
	Range: 2 ng/mL to 800 ng/mL (for rifabutin), 0.2 ng/mL to 100 ng/mL (for 25ODR)	
Performance Report	Samples analyzed within the established stability period Reported long term stability in plasma: 765 days at -20°C nominal.	☒ Yes ☐ No
	Quality control samples range acceptable QC: 6, 25, 70, 100, 400, and 600 ng/mL for rifabutin and 0.6, 2.5, 7, 10, 50, and 75 ng/mL for 25ODR	☒ Yes ☐ No

NDA Multi-disciplinary Review and Evaluation NDA 213004
TALICIA (rifabutin, amoxicillin, omeprazole)

	Chromatograms provided	☒ Yes ☐ No
	Accuracy and precision of the calibration curve acceptable	☒ Yes ☐ No
	Accuracy and precision of the quality control samples acceptable	☒ Yes ☐ No
	Incurred sample reanalysis (ISR) acceptable	☒ Yes ☐ No
	Overall performance reasonable Rifabutin and 25ODR quantification was repeated for samples from five subjects that were analyzed together in a follow-up to a suspicion of inverted period ID for one of those subjects. Based on the duplicated reassay findings that were in agreement, concentration values were revised. For six 25ODR concentration values, the duplicate values from reassay were not in agreement and were noted as Not Reportable.	☒ Yes ☐ No
Inspection	Will the bioanalytical site be inspected?	☐ Yes ☒ No

The analytical methods have evaluated the potential for cross-interference of various RHB-105 components and 25ODR by evaluating the specificity of methods for each analyte in the presence of other analytes and the findings show no significant interference.

Study RHB-105-02, which was a controlled pivotal Phase 3 study for this application, included PK assessments. The method validation reports cited in the study report suggest that the methods used are similar to the methods summarized in the tables above. In this study, rifabutin was detected in seven PK samples collected from seven patients who received the comparator (without rifabutin). The Applicant has submitted an investigation report confirming that carryover (during sample analysis) was not an issue and reassay confirmed the original results. In addition, during the conduct of the study, the comparator drug was packaged and dispensed in accordance with cGMP and drug supply was reconciled for each of the impacted subjects. Therefore, the Applicant concludes that rifabutin and metabolite in the clinical samples may have been introduced via cross-contamination (e.g. via a transfer pipette) at some point during sample processing as 25ODR is not a known impurity of the drug product. From a clinical pharmacology perspective, these findings do not have any significant consequences as the sensitivity analysis submitted by the Applicant demonstrated no effects of these findings on the efficacy related conclusions drawn from this study.

17.3.2. Pharmacokinetics in Healthy Adults

17.3.2.1. Study RHB-P2-418

Overview: This was a single center, randomized, open-label, 2-period, 2-sequence, crossover bioavailability study. This study enrolled 16 subjects including eight females (50%). The mean age of enrolled subjects was 45 years (Range: 23 to 63 years). Majority of the enrolled subjects were White (n=14, 87.5%). From 16 subjects enrolled, 15 subjects completed the study and one subject withdrew due to safety reasons following receiving RHB-105 (due to mild increase in aspartate aminotransferase increased and alanine aminotransferase). The enrolled subjects received the following two treatments three times eight hours apart for one day in a crossover manner after a 10-hour of fast:

Treatment A: Four RHB-105 capsules each containing 12.5 mg rifabutin, 250 mg amoxicillin, and 10 mg omeprazole given three times in a day eight hours apart resulting in respective total daily doses of 150 mg, 3000 mg, and 120 mg

Treatment B: One Mycobutin® 150 mg capsule (Rifabutin) once in the morning and two Amoxicillin 500 mg capsule as well as Prilosec® 40 mg delayed-release capsule (Omeprazole) taken concomitantly given three times in a day eight hours apart resulting in respective total daily doses of 150 mg, 3000 mg, and 120 mg

Following a morning dose, fasting continued for at least 3.5 hours, after which a standardized lunch was served. A supper was served at approximately 3.5 hours following the afternoon drug administration. The evening drug administration followed thereafter.

For pharmacokinetic assessments, 26 blood samples were collected between pre-dose to 72 hours post-dose. These samples were assayed for rifabutin, 25ODR, amoxicillin, and omeprazole. The reported mean plasma concentration-time profiles for all analytes on linear and semi-logarithmic scales are presented for both the treatment groups in Figure 17-1 to Figure 17-4. Pharmacokinetic parameter estimates were derived using noncompartmental analysis for each analyte. The resultant estimates are reported and compared (for bioavailability assessments) in Table 17-2 and Table 17-3, respectively.

Figure 17-1: Mean±SE Amoxicillin Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

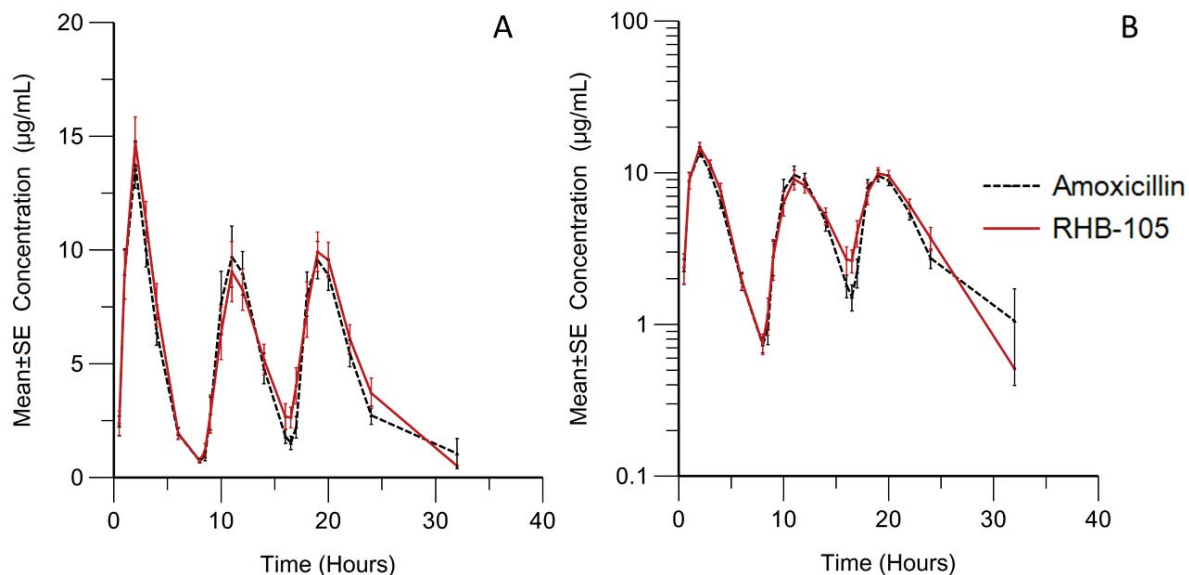


Figure 17-2: Mean±SE Omeprazole Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

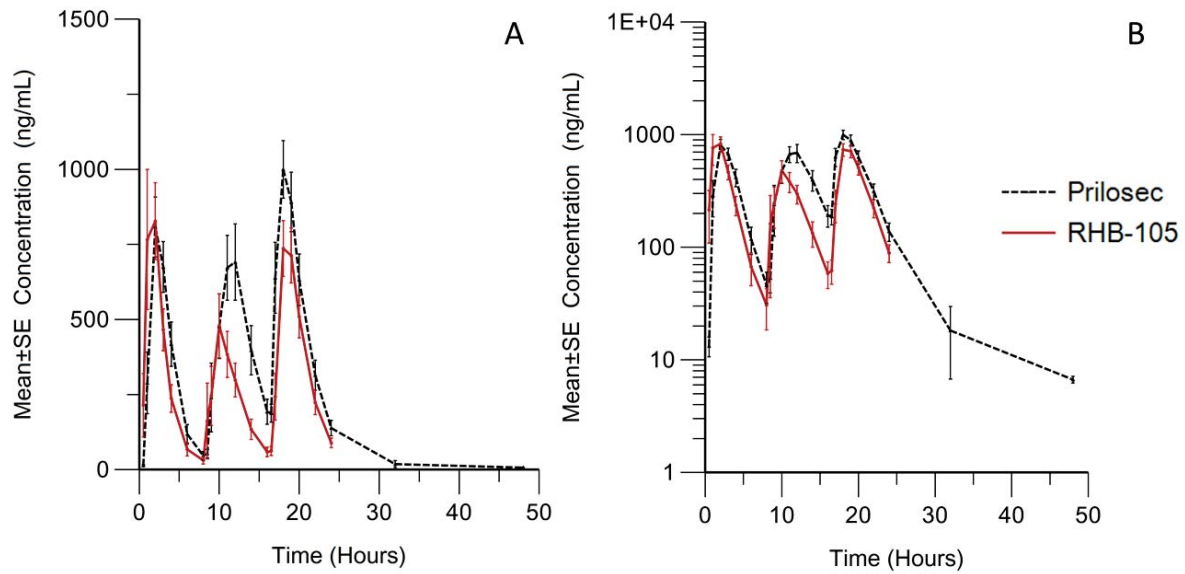


Figure 17-3: Mean±SE Rifabutin Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

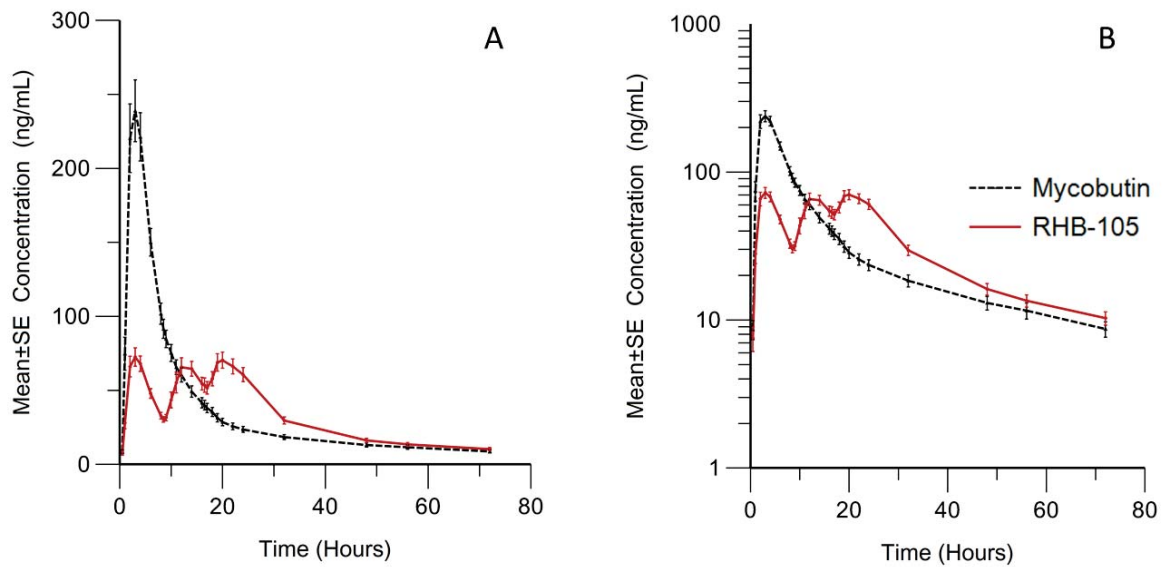


Figure 17-4: Mean±SE 25-O-desacetylriofabutin Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

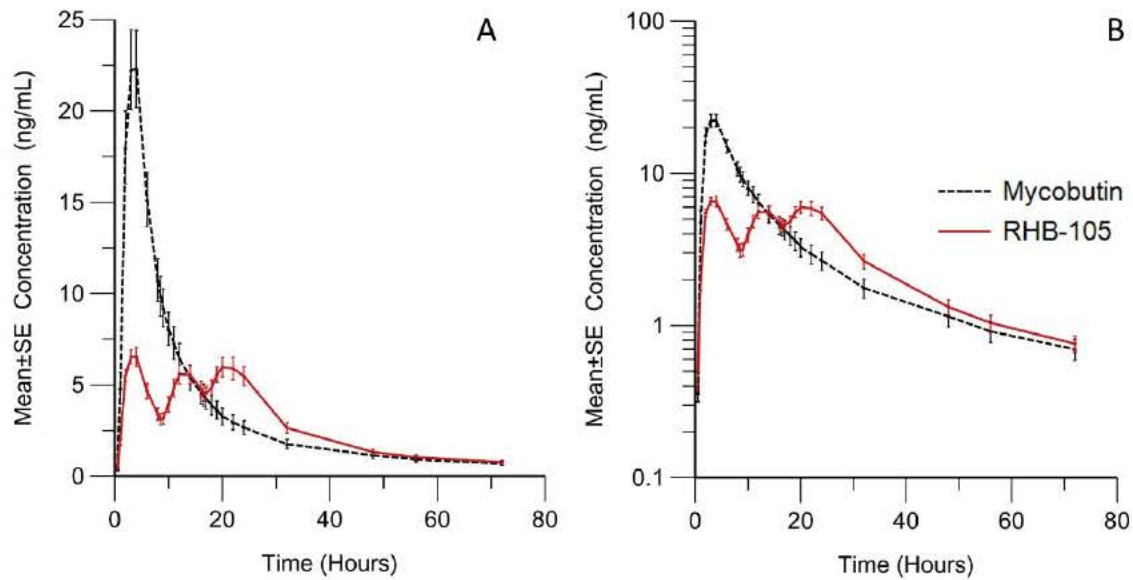


Table 17-2: Mean±SD Exposure and Pharmacokinetic Parameter Estimates

	Treatment A (RHB-105) (n=15)		Treatment B (Individual Drugs) (n=15)	
	Amoxicillin			
AUC _{0-inf} (µg·h/mL)	163±44		145±33	
C _{max} (µg/mL)	16±3		15±4	
T _{max} ^a (h)	2 [2-18]		2 [1-19]	
T _{1/2} (h)	3±2		2.4±1	
	Omeprazole			
AUC _{0-inf} (ng·h/mL)	7288±3606		10367±3761	
C _{max} (ng/mL)	1281±518		1295±356	
T _{max} ^a (h)	2 [1-18]		12 [2-18]	
T _{1/2} (h)	1.5±0.4		2±1.5	
	Rifabutin	25ODR	Rifabutin	25ODR
AUC _{0-inf} (ng·h/mL)	2790±778	237±79	3205±1048	293±134
C _{max} (ng/mL)	88±21	8±2	248±81	23±8
T _{max} ^a (h)	17 [3-22]	4 [2-20]	3 [2-4]	3 [3-4]
T _{1/2} (h)	30±8	30±20	40±12	28±11

a: Median [Range], h: Hours
Source: Reviewer's Analysis

Table 17-3: Summary of the Bioavailability Assessment

Parameters	% Point Estimates Treatment A/ Treatment B (90% CI)	
	Amoxicillin	
AUC _{0-inf} (µg·h/mL)	111 (105 - 118)	
C _{max} (µg/mL)	107 (98 - 116)	
Omeprazole		
AUC _{0-inf} (ng·h/mL)	66 (56 - 77)	
C _{max} (ng/mL)	94 (77 - 114)	
Rifabutin		25ODR
AUC _{0-inf} (ng·h/mL)	89 (80 - 98)	85 (76 - 95)
C _{max} (ng/mL)	36 (32 - 42)	33 (29 - 38)

Source: Reviewer's Analysis

Conclusions:

- For rifabutin and 25ODR, relatively lower mean C_{max} and higher C_{min} were observed with RHB-105 than those with Mycobutin; however, given the difference in the rifabutin dosing regimens between the two treatment groups, i.e., Once a day (QD) for Mycobutin and three times a day (TID) for RHB-105, these results were anticipated.
- Amoxicillin bioavailability was comparable between the treatment groups.

For omeprazole, mean C_{max} estimates were comparable from both the treatment groups, however, overall systemic exposure to omeprazole (AUC) was lower from RHB-105 compared to Prilosec.

Reviewer's Comments: Overall, the systemic bioavailability of three RHB-105 components were similar to or lower than that of the individual drugs evaluated in this study at the same daily dose. It appears that the observed differences between omeprazole AUC estimates from two treatment arms stem from the relatively lower exposures following the second and the third dose in RHB-105 treatment arm. The second and third doses were not administered under strict fasted conditions. However, following the first doses in both the treatment arms omeprazole systemic exposures were relatively comparable. The first doses were administered following a 10-hour of fast. Therefore, the observed differences in omeprazole BA could be due to formulation dependent differential food effect.

17.3.2.2. Study RHB-105-12

Overview: This was a single center, randomized, single dose, 3-period, 3-sequence, crossover food-effect and bioavailability study. This study enrolled 18 subjects including five females (28%). All the enrolled subjects were White with the mean age of 42 years (Range: 25 to 57 years). All 18 subjects received all the assigned treatments. One subject withdrew consent

after dosing of Period 3 (approximately 7.5 hours after dosing). All subjects received the following three treatments succeeding to overnight fast in a crossover manner:

Treatment-1: RHB-105 Fed

Four RHB-105 capsules (12.5 mg rifabutin/250 mg amoxicillin/10 mg omeprazole) given concomitantly under fed (with high fat meal³¹) conditions; total single dose of 50 mg rifabutin/1000 mg amoxicillin/40 mg omeprazole

Treatment-2: RHB-105

Four RHB-105 capsules (12.5 mg rifabutin/250 mg amoxicillin/10 mg omeprazole) given concomitantly under fasting conditions (at least for 10 hours); total single dose of 50 mg rifabutin/1000 mg amoxicillin/40 mg omeprazole

Treatment-3: RHB-105LITE

Four RHB-105LITE comparator capsules³² (250 mg amoxicillin/10 mg omeprazole) given concomitantly under fasting conditions (at least for 10 hours); total single dose of 1000 mg amoxicillin/40 mg omeprazole

Following receiving the treatments, subjects were fasted for at least four hours.

For pharmacokinetic assessments, 20-25 blood samples were collected between pre-dose to up to 12-120 hours post-dose. Samples from all 18 subjects were assayed for rifabutin, 25ODR, amoxicillin, and omeprazole. For all RHB-105 components and a rifabutin metabolite: 25ODR, mean plasma concentration-time profiles on linear and semi-logarithmic scales are presented by treatment group in Figure 17-5 to Figure 17-8. For the purposes of this review, pharmacokinetic parameter estimates were derived using noncompartmental analysis (NCA) of all the available drug concentration data except for the concentration data from one discontinued subject. In the NCA, rifabutin and 25ODR concentrations were excluded for the discontinued subject as the values were available for only up to 7.5 hours after dosing. The resultant estimates are reported and compared in Table 17-4 and Table 17-5, respectively.

³¹ The high-fat, high-calorie meal contained 1011 kcal with 14% from protein, 53% from fat, and 33% from carbohydrate.

³² RHB-105LITE formulation was used in the safety and efficacy trial RHB-105-02 as a comparator. RHB-105LITE formulation does not contain rifabutin.

Figure 17-5: Mean±SE Amoxicillin Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

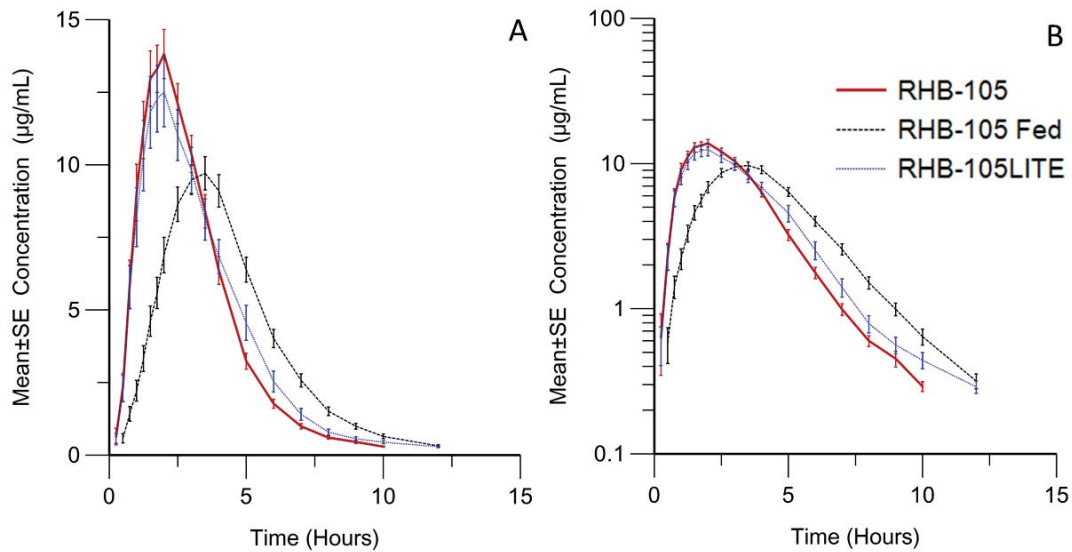


Figure 17-6: Mean±SE Omeprazole Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

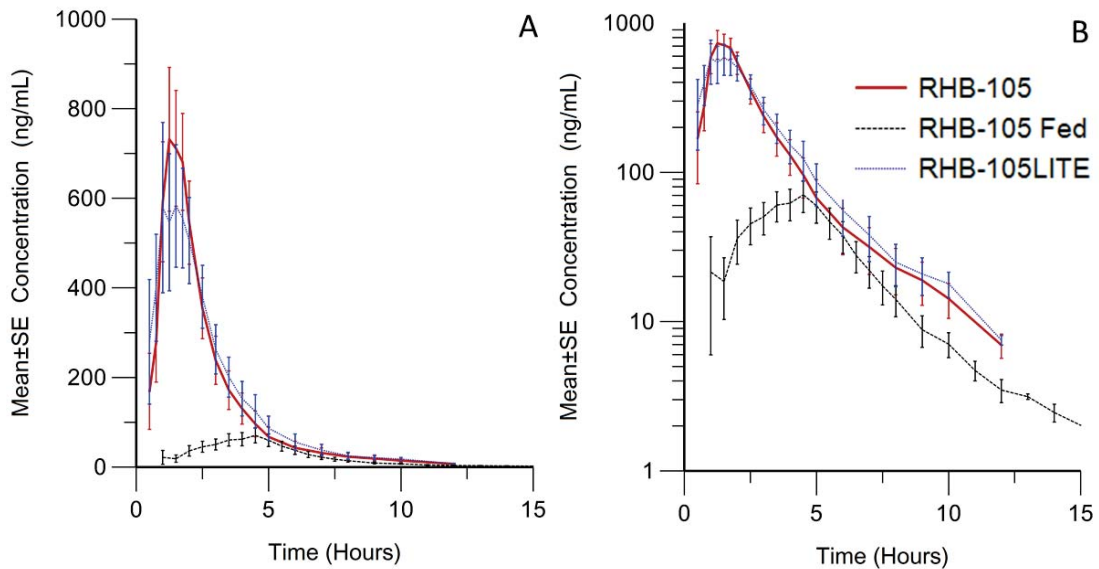


Figure 17-7: Mean±SE Rifabutin Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

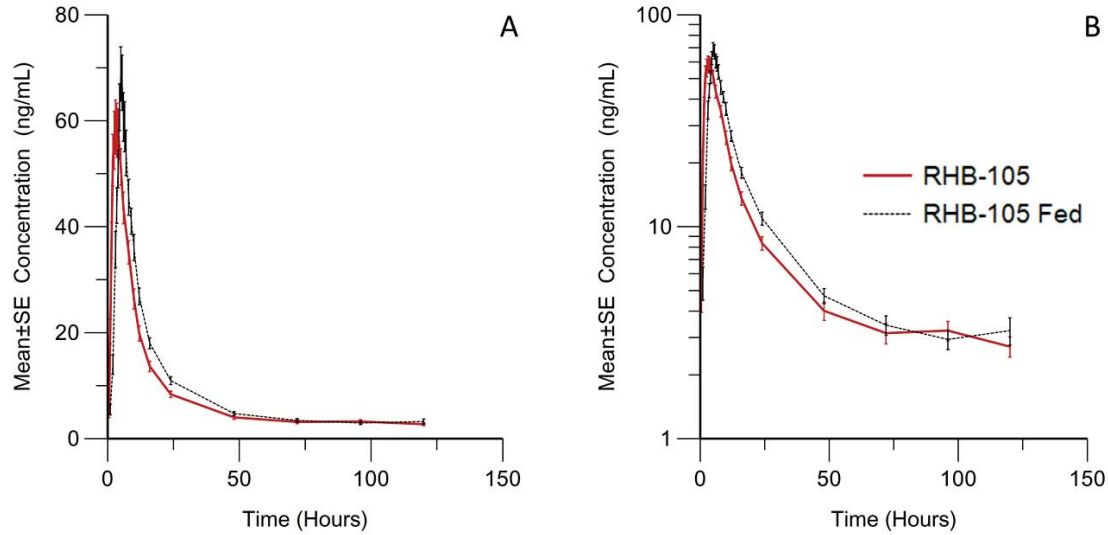


Figure 17-8: Mean±SE 25-O-desacetyl-rifabutin Plasma Concentration-Time Profiles on Linear (A) and Semi-logarithmic (B) Scale

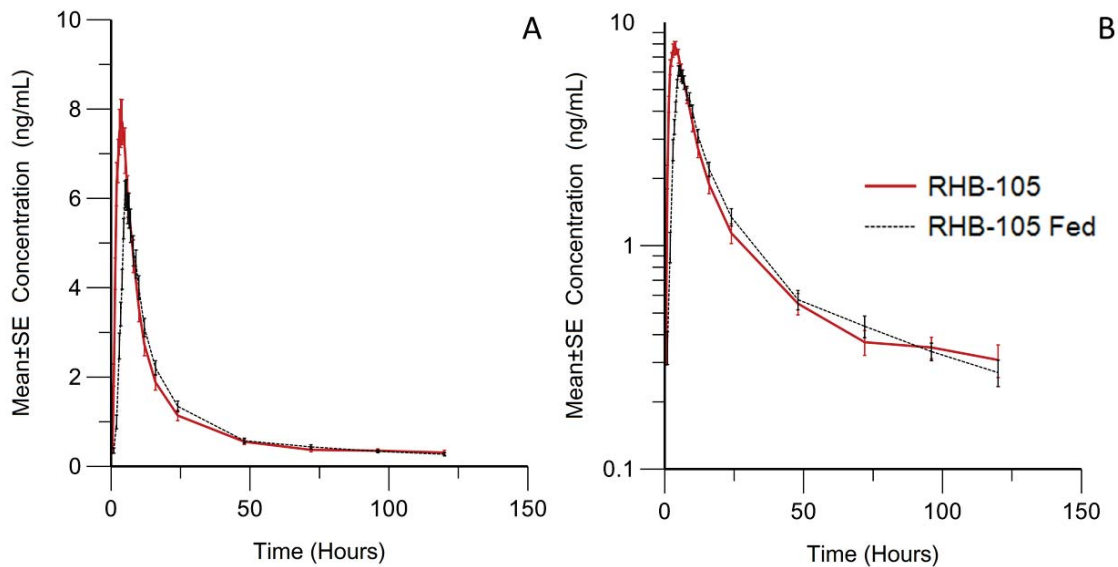


Table 17-4: Mean±SD Exposure and Pharmacokinetic Parameter Estimates

	RHB-105 Fasting (n=18 ^b)	RHB-105 Fed (n=18 ^b)	RHB-105LITE Fasting (n=18 ^b)	
Amoxicillin				
AUC _{0-inf} (µg·h/mL)	46±9	44±7	48±13	
C _{max} (µg/mL)	15±4	11±3	14±5	
T _{max} ^a (h)	2 [1.3-3]	3.5 [2-5]	2 [1.3-5]	
T _{1/2} (h)	1.3±0.2	1.4±0.3	1.6±0.7	
Omeprazole				
AUC _{0-inf} (ng·h/mL)	1632±1367	303±255	1611±1405	
C _{max} (ng/mL)	983±604	86±73	909±655	
T _{max} ^a (h)	1.3 [0.8-1.8]	4 [2.5-6]	1.5 [0.8-4.5]	
T _{1/2} (h)	1±0.3	1.3±0.4	1±0.3	
	Rifabutin	25ODR	Rifabutin	25ODR
AUC _{0-inf} (ng·h/mL)	956±421	121±55	1152±456	118±46
C _{max} (ng/mL)	62±21	8±2	71±22	6±1.5
T _{max} ^a (h)	3 [2-6]	3.5 [2-6]	5 [4-6.5]	5 [4.5-6.5]
T _{1/2} (h)	33±26	27±17	41±26	29±17

a: Median [Range], b: n=17 for rifabutin and 25 ODR, h: Hours

Source: Reviewer's Analysis

Table 17-5: Summary of the Bioavailability Assessment

Parameters	% Point Estimates	
	RHB-105 Fed/RHB-105 (90% CI)	RHB-105LITE/RHB-105 (90% CI)
Amoxicillin		
AUC _{0-inf} (µg·h/mL)	96 (90 - 102)	101 (95 - 107)
C _{max} (µg/mL)	70 (63 - 78)	90 (81 - 100)
Omeprazole		
AUC _{0-inf} (ng·h/mL)	18 (15 - 22)	101 (95 - 107)
C _{max} (ng/mL)	8 (6 - 10)	89 (65 - 121)
	Rifabutin	25ODR
AUC _{0-inf} (ng·h/mL)	122 (113 - 132)	99 (91 - 109)
C _{max} (ng/mL)	116 (106 - 126)	80 (75 - 85)

Source: Reviewer's Analysis

Conclusions:

Food Effect

- For all three RHB-105 components, food delayed T_{max} by 1.5-3 hours.
- Food decreased amoxicillin C_{max} by about 30% and omeprazole C_{max} by about 92% and AUC by about 82%. Food increased Rifabutin C_{max} and AUC by 10-20%.

Bioavailability Assessment: RHB-105LITE vs. RHB-105

- C_{max} and AUC estimates of amoxicillin and omeprazole were comparable between the two treatment groups.

17.3.3. Pharmacokinetics in Patient Population

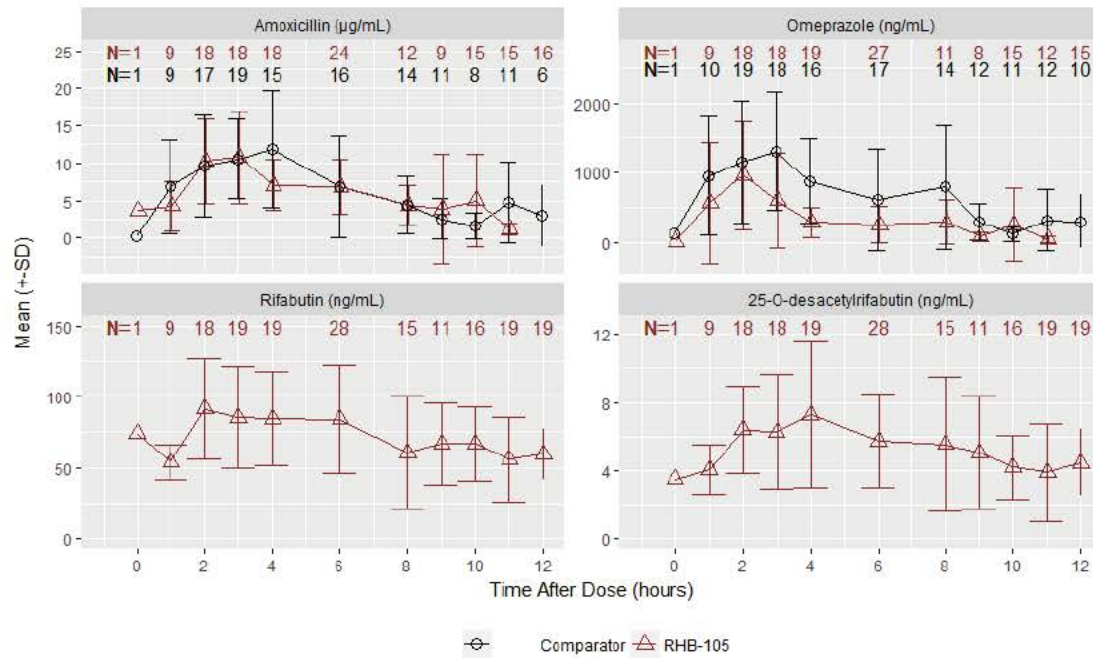
Overview: Limited pharmacokinetic information on RHB-105 in patients with *H. pylori* infection is available from Study RHB-105-02. Study RHB-105-02 was a randomized, double-blind, comparator-controlled study that evaluated safety and efficacy of RHB-105 in adults found to be positive for *H. pylori* infection via ¹³C UBT and follow-up upper endoscopy (culture, histology, or urease test). For detailed information on the study design, see the relevant section of this review. Patients were randomized in a ratio of 1:1 to one of the following treatments for 14 days:

- RHB-105 Treatment: Four RHB-105 capsules every eight hours with food, equivalent to a unit dose of 50 mg rifabutin, 1000 mg amoxicillin, and 40 mg omeprazole and a total daily dose of 150 mg rifabutin, 3000 mg amoxicillin, and 120 mg omeprazole
- Comparator Treatment: Four capsules of comparator every eight hours with food, equivalent to a unit dose of 1000 mg amoxicillin and 40 mg omeprazole and a total daily dose of 3000 mg amoxicillin and 120 mg omeprazole

In total, 227 patients were randomized to the comparator treatment and 228 patients were randomized to the RHB-105 treatment.

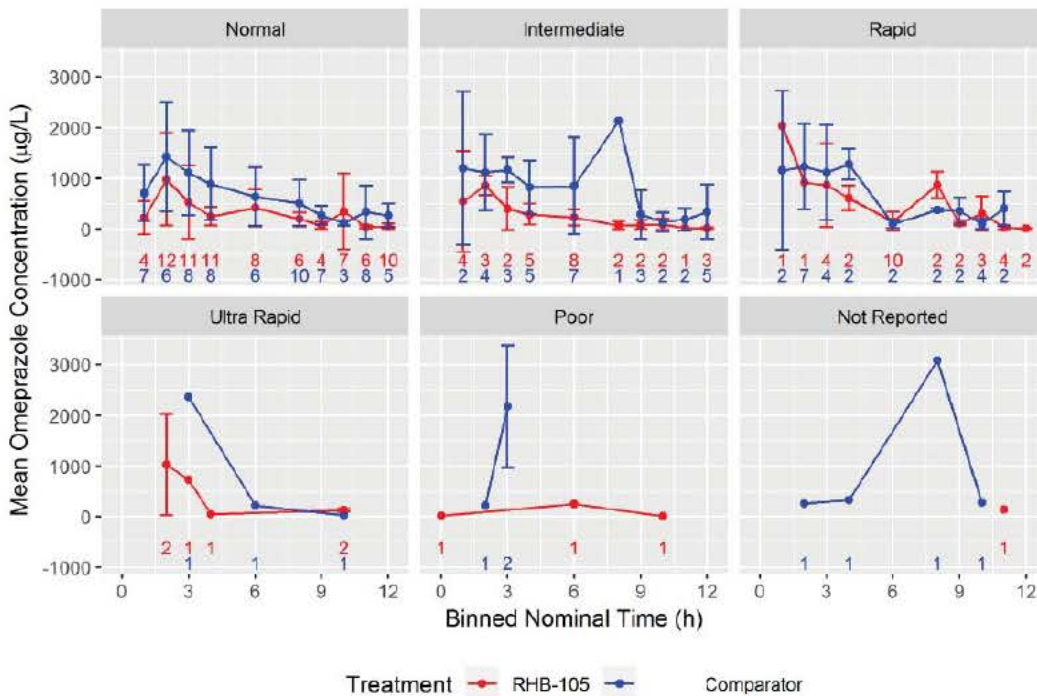
For pharmacokinetic assessments, plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite, 25ODR, were assessed in two blood samples from each patient, i.e., one pre-treatment sample at Baseline (Visit 1 [Day 1]) before the first dose and one pre-dose sample at Visit 3 (Approximately on Day 13). At Visit 3, 221 to 222 samples and 214 to 216 samples were analyzed for each analyte from the RHB-105 treatment group and the comparator group, respectively. Based upon the time of collection for each sample with respect to the dose administration, they were binned into 11 nominal time point groups: 0 hour (h) (samples collected between -1 to 0h of dosing), 1 (>0-1h), 2 (>1-2h), 3 (>2-3h), 4 (>3-4h), 6 (>4-6h), 8 (>6-8h), 9 (>8-9h), 10 (>9-10h), 11 (>10-11h), 12 (>11-12h). Using these binned groups, mean plasma concentration-time profiles were derived for all RHB-105 components and 25ODR (Figure 17-9).

Figure 17-9: Mean±SD Plasma Concentration-Time Profiles for RHB-105 Components and 25-O-desacetylriofabutin



The study also included pharmacogenetic testing to assess enrolled patients' CYP2C19 Genotype-inferred Phenotype status and its effect on response to the RHB-105 treatment as well as relationship to pharmacokinetics of omeprazole. Mean omeprazole concentrations at Visit 3 from the RHB-105 and the comparator treatment groups are compared across different CYP2C19 status in Figure 17-10. Efficacy and safety results across the different CYP2C19 phenotypes are discussed in sections 8.1.4 and 10.7.

Figure 17-10: Mean±SD Omeprazole Concentrations at Visit 3 in the RHB-105 and Comparator Treatment Groups Across Patients with Different CYP2C19 Phenotypes



Note: numbers in plot area represent the number of data points by binned nominal time

Regarding the efficacy assessments in this study, the primary efficacy endpoint was eradication of *H. pylori* infection determined based on ¹³C UBT testing conducted between 43 and 71 days after initiation of therapy. Applicant conducted exposure-response analysis by evaluating the relationship of efficacy with the concentrations of each analyte. Specifically, logistic regression analysis was performed by the Applicant to assess associations between concentrations of each analyte and the probability of cure (Defined as eradication of *H. pylori* as indicated by ¹³C UBT for *H. pylori* in this study). Given that (A) The RHB-105 dosing evaluated in this Phase 3 study is derived from empirical evidence and (B) The findings from the Applicant’s exposure-response analysis does not appear to have any implications on the proposed RHB-105 dosing for general patient population or for subpopulations, no further clinical pharmacology review of the submitted exposure-response analysis was ensued.

Conclusions:

- The impact of the RHB-105 rifabutin component did not appear to influence amoxicillin pharmacokinetics.
- Due to, in part to the mix of CYP2C19 status, omeprazole concentrations from both RHB-105 and comparator treatment groups were quite variable, however, there was a trend towards lower omeprazole concentrations in the RHB-105 treatment group, relative to the comparator group, likely as a consequence of rifabutin mediated induction of

CYP2C19 (or other CYP enzymes involved in omeprazole biotransformation) and/or differential food effect.

Reviewer's Comments: Overall, the pharmacokinetic assessments performed in this study are very limited; particularly, the omeprazole pharmacokinetic data in patients with different CYP2C19 status. Therefore, pharmacokinetic information from this study appears to be inadequate to assess the effect of CYP2C19 status on omeprazole pharmacokinetics.

17.3.4. Pharmacogenomics Summary

Pharmacogenetic analysis of CYP2C19 status was an exploratory endpoint in studies RHB-105-01 and RHB-105-02. Blood samples were collected to assess CYP2C19 genotype and effect on response to RHB-105 at baseline. Use of any listed prohibited medications, (apart from antibacterial drugs, bismuth or PPI), medications or dietary supplements known to be CYP3A4 or CYP2C19 substrates, inhibitors, or inducers within 1 week of the screening visit was an exclusion criterion. The assay methodology and CYP2C19 alleles tested in both studies were not specified. However, in study RHB-105-01, the applicant indicated the genotypes resulting from *1 (wild type ([WT]), *2, *3, and *17 allele combinations were used to infer the following phenotypes: ultrarapid metabolizers, extensive metabolizers, intermediate metabolizer, and poor metabolizers. These classifications were later changed to match classification used in subsequent study RHB-105-02 (Figure 17-11).

Figure 17-11 Updates Reported to CYP2C19 Genotypes and Inferred-Phenotypes in RHB-105-01 and Classification Used in RHB-105-02

Study RHB-105-01 Phenotype classification	Genotype	Match to RHB-105-02 classification*
PM - Poor Metabolizer	*2/*2 *3/*3 *2/*3	Poor
IM - Intermediate Metabolizer	*1/*2 *2/WT *3/WT *2/*17 *3/*17	Intermediate
Indeterminate	*2/*17	Intermediate
EM - Extensive Metabolizer	*1/*1 WT/WT	Normal
UM - Ultra Extensive	*1/*17 *17/WT	Rapid
Ultra Rapid Metabolizer	*17/*17	Ultra Rapid

*Based on CAUDLE et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genetics in Medicine* 2017; 19(2): 215-223

in Study RHB-105-01, *2/*17 genotype appears to have been classified both as indeterminate and intermediate. In the updated classification, phenotypes inferred from the *2/*17 genotype previously identified as indeterminate was updated to intermediate metabolizer classification, those inferred from *1/*1 or WT/WT previously extensive metabolizer were updated to normal metabolizer, those inferred from *1/*17 or *17/WT previously classified as ultra-extensive were updated to rapid metabolizer status.

Key Questions and Summary of Findings

Are the CYP2C19 phenotypes inferred from genotypes appropriate?

Published literature

CYP2C19 *2, *3, and *17 are commonly described variants of the polymorphic CYP2C19. The *2 and *3 alleles result in no functional activity of CYP2C19, while *17 results in increased function of CYP2C19 when compared to the *1, normal function, allele. Many other CYP2C19 alleles that impact enzyme function have been reported, however, *2, *3, and *17 have been proposed as the minimum variants to be tested in a pharmacogenetic assay of CYP2C19 (PMID: 29474986). The selection of these variants was based on their well-established functional impact on CYP2C19 activity and drug response and their appreciable minor allele frequency in major ethnic populations and the availability of reference materials (PMID: 29474986). Efforts to standardize terms for allele functional status and phenotype have been published and standardized phenotypes for drug metabolizing enzymes such as CYP2C19 are as follows: Poor Metabolizer (PM) phenotype is inferred if 2 copies of a non-functional allele is present; Intermediate Metabolizer (IM) phenotype is inferred when one copy of a normal function allele and one copy of a no function allele are present; normal metabolizer phenotype is inferred when 2 copies of a functional allele are present; rapid metabolizer phenotype is inferred when one copy of a normal function allele and one copy of an increased function allele are present; and an ultrarapid metabolizer phenotype is inferred when two copies of an increased function allele are present (PMID: 27441996). *Phenotype frequencies vary across different ethnic populations. Of note, the frequency of poor metabolizers is estimated to be 2.5% in Whites, 4.3% in African-Americans, 12.4% in South/Central Asians, 14.5% in East Asians, and up to 46.4% in Oceanian populations (Pharmacogenomics Knowledgebase at :PharmGKB.org at <https://www.pharmgkb.org/page/cyp2c19RefMaterials>).*

Reviewer's Comments:

The phenotypes predicted from the genotypes in RHB-105-02 and the updates to the assignment in RHB-105-01 were consistent with prevailing assignments in the literature (CPIC standardization suggestions).

Applicant Proposed Labeling Language

The applicant has proposed a Use in Specific Populations section in the label to define the use of RHB-105 [REDACTED] ^{(b) (4)} as follows:

(b) (4)

The applicant proposed labeling also includes a pharmacogenomics section 12.5 as follows:

12.5: Pharmacogenomics

*CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or (b) (4). Patients carrying two fully functional alleles are (b) (4) metabolizers and those carrying two (b) (4) alleles are poor metabolizers. (b) (4) The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > (b) (4). Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers.*

(b) (4)

Recommended Language

Deletion of proposed section (b) (4).

Section 12.5

CYP2C19, a polymorphic enzyme, is involved in the metabolism of omeprazole. The CYP2C19*1 allele is fully functional while the CYP2C19*2 and *3 alleles are nonfunctional. There are other alleles associated with no or decreased CYP2C19 function. Patients carrying two fully functional alleles are normal metabolizers and those carrying two nonfunctional alleles are poor metabolizers. The systemic exposure to omeprazole varies with a patient's metabolism status: poor metabolizers > intermediate metabolizers > normal metabolizers. Approximately 3% of Caucasians and 15 to 20% of Asians are CYP2C19 poor metabolizers.

In a pharmacokinetic study of a single 20 mg omeprazole dose, the AUC of omeprazole in Asian subjects was approximately four times higher than in Caucasians. In Study 1, the safety and tolerability of Talicia was not substantially different in CYP2C19 poor metabolizers (n = 5) and intermediate metabolizers (n = 48) compared to normal metabolizers (n = 114).

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