Annals of Internal Medicine ORIGINAL RESEARCH

Rifabutin-Based Triple Therapy (RHB-105) for *Helicobacter pylori* Eradication

A Double-Blind, Randomized, Controlled Trial

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Background: Although consensus supports eradication of *Helicobacter pylori* infections, antimicrobial resistance has substantially reduced eradication rates with most current therapies.

Objective: To assess the effectiveness of a novel rifabutin-based therapy (RHB-105) for *H pylori* eradication.

Design: Phase 3, double-blind trial (ERADICATE Hp2). (Clinical Trials.gov: NCT03198507)

Setting: 55 clinical research sites in the United States.

Participants: 455 treatment-naive adults with epigastric discomfort and confirmed *H pylori* infection.

Intervention: RHB-105 (amoxicillin, 3 g; omeprazole, 120 mg; and rifabutin, 150 mg) versus active comparator (amoxicillin, 3 g, and omeprazole, 120 mg), given as 4 capsules every 8 hours for 14 days.

Measurements: Between-group difference for *H pylori* eradication rate, demonstrated by ^{13}C urea breath test 4 weeks after treatment, analyzed by using the χ^2 test.

Results: In the intention-to-treat population, the eradication rate was higher with RHB-105 than with the active comparator (228 vs. 227 patients, respectively; 83.8% [95% CI, 78.4% to 88.0%] vs. 57.7% [95% CI, 51.2% to 64.0%]; $P < 0.001$). Eradication rates were unaffected by resistance to clarithromycin or metronidazole. No rifabutin resistance was detected. The most commonly reported adverse events (incidence ≥5%) were diarrhea (10.1% with RHB-105 vs. 7.9% with active comparator), headache (7.5% vs. 7.0%), and nausea (4.8% vs. 5.3%).

Limitation: Persons of Asian descent were excluded because of their higher prevalence of poor cytochrome P450 2C19 metabolizers.

Conclusion: These findings suggest potential for RHB-105 as first-line empirical *H pylori* therapy, addressing an unmet need in the current environment of increasing antibiotic resistance.

Primary Funding Source: RedHill Biopharma Ltd.

Ann Intern Med. doi:10.7326/M19-3734 **Annals.org**
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This article was published at Annals.org on 5 May 2020.

Helicobacter pylori infection is the major etiologic agent for peptic ulcer, gastritis, and gastric cancer (1). Current guidelines recommend *H pylori* eradication, irrespective of absence of symptoms or clinical manifestations of disease (2–7). This goal has become increasingly difficult because success with previously effective therapies has declined, related largely to the worldwide increase in antimicrobial resistance (4, 5, 7–10). Both the World Health Organization and the U.S. Food and Drug Administration (FDA) have designated clarithromycin-resistant *H pylori* as a focus for new drug development (9, 11, 12), and the FDA included it as a pathogen with "the potential to pose a serious threat to public health" (11). Despite more than 30 years of experience with therapy, *H pylori* remains unique in that local, regional, and population susceptibility testing and reporting remain largely unavailable, forcing clinicians to rely on an empirical treatment approach (2). The prevalence of *H pylori* resistance to clarithromycin, metronidazole, and levofloxacin has increased to a level that, except in a few regions, these antibiotics are not considered appropriate for empirical use in triple therapies (2, 4, 8, 13, 14). Clearly, new *H pylori* therapies are needed.

Rifabutin, a rifamycin derivative most frequently used in treating mycobacterial infections, is an excellent candidate for treating *H pylori* because 1) it has in vitro bactericidal activity against *H pylori* (15–20); 2) it achieves high intracellular and intragastric concentrations (21, 22); and 3) resistance is rare and typically occurs only when rifabutin is administered at high doses for extended durations—for example, to treat atypical mycobacterial infections (23). Rifabutin-resistant mutants of *H pylori* can be induced in vitro, but this typically occurs only after multiple exposures and at a very low rate (estimated at 1 in 10^9) (17). As with other *H pylori* therapies, the risk for antimicrobial resistance is reduced when used with another antibiotic (24, 25).

Clinical experience with rifabutin for treatment of *H pylori* infection has focused on patients in whom 1 or more courses of anti–*H pylori* treatment has previously failed and has utilized rifabutin (typically 300 mg/d) with amoxicillin and a proton-pump inhibitor (PPI). A meta-analysis of 2982 patients by Gisbert and Calvet (23) reported mean eradication rates with rifabutin triple therapy of 73% (range, 66% to 79%) among patients with 1 to 4 prior treatment failures. Of note, clinically relevant side effects were uncommon, generally transient, and dose-related.

On the basis of work by Borody and colleagues (26), we did a pilot study (ERADICATE Hp [NCT01980095]) to test the efficacy of RHB-105, a fixed-dose combination containing a low dose of rifabutin (150 mg/d) plus amoxicillin (3000

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mg/d), and omeprazole (120 mg/d) in *H pylori*–infected patients with dyspepsia. The cure rate with RHB-105 in that small study was 89.4% (95% CI, 79.7% to 94.8%) (59 of 66 patients) (27). The current phase 3 study (ERADICATE Hp2) was done to confirm the efficacy of RHB-105; we report the results of ERADICATE Hp2 here.

METHODS

The study was conducted in accordance with ethical principles of the Declaration of Helsinki and applicable regulatory requirements. The study protocol and all amendments were approved by the respective institutional review boards of participating institutions. All patients provided written informed consent before participating in the study.

Study Population

Treatment-naive adults (aged 18 to 70 years) with dyspepsia (i.e., recurrent epigastric pain or discomfort often related to meals) for at least 2 weeks were enrolled. *Helicobacter pylori* infection was confirmed by using a ^{13}C urea breath test (UBT) plus upper endoscopy with a positive culture, histology, or rapid urease test result before randomization.

Key exclusion criteria included prior anti–*H pylori* therapy; alarm symptoms (i.e., anemia, melena, dysphagia, jaundice, or weight loss); more than 2 active gastric or duodenal ulcers; a history of esophageal or gastric surgery or gastric cancer; and receipt of any antibiotic in the 4 weeks before screening for this study, or a PPI or bismuth-containing medication in the 2 weeks before screening. Persons of Asian descent (i.e., Far East, Southeast Asia, or Indian subcontinent) were excluded because of the potential for lower rates of omeprazole metabolism due to polymorphisms in cytochrome P450 (CYP) 2C19 in these populations (28). A complete list of the inclusion and exclusion criteria can be found in the protocol (**Supplement**, available at Annals.org).

Study Design

This randomized, double-blind, active comparator, controlled study was conducted between July 2017 and November 2018. Patients were screened at 62 clinical research sites in 23 U.S. states and underwent randomization at 55 sites. The study consisted of screening to assess patients' eligibility for study enrollment (days −42 to 0) and a baseline visit on day 1 before initiation of study drug, followed by 14-day double-blind treatment (site visit on day 13), and then a test-of-cure visit (conducted between 43 and 71 days after initiation of therapy).

On the basis of a computer-generated randomization schedule, eligible participants were randomly assigned in a 1:1 ratio to receive RHB-105 or active comparator. Randomization was balanced by using randomly permuted blocks (4 patients per block) without additional stratification. Patients, study staff, investigators, and site personnel were blinded to treatment group assignment.

Study Drug Dosing and Concomitant Medications

Each RHB-105 capsule contained rifabutin, 12.5 mg; amoxicillin, 250 mg; and omeprazole, 10 mg. Matching active comparator capsules contained amoxicillin, 250 mg, and omeprazole, 10 mg. This active comparator, as per FDA requirements, assessed the added contribution of rifabutin versus high-dose amoxicillin–omeprazole therapy. High-dose amoxicillin–lansoprazole therapy is an FDA-approved regimen for patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected (29). RHB-105 and the active comparator were manufactured as identical dark opaque capsules.

Patients were to take 4 capsules of study drug every 8 hours for 14 days (total daily doses of amoxicillin, 3 g; omeprazole, 120 mg; and rifabutin, 150 mg [RHB-105] or amoxicillin, 3 g, and omeprazole, 120 mg [active comparator]). Because rifabutin can cause chromaturia, all patients took riboflavin, 50 mg, once daily with study drug to maintain the study blind.

Antibiotics, PPIs (other than study drug), and bismuth-containing drugs were prohibited during treatment with study drug and after treatment through the test-of-cure visit. Histamine-2 receptor antagonists and antacids were prohibited 24 hours before ^{13}C UBT.

Efficacy and Safety Procedures and Assessments

A ^{13}C UBT (BreathTek) was done at screening to determine *H pylori* status. Patients with a positive ^{13}C UBT result underwent upper endoscopy with 3 paired gastric biopsies of samples obtained from the antrum and the corpus. One biopsy sample each from the corpus and the antrum were combined in 3 individual containers: The contents of one container were tested for *H pylori* with a rapid urease test (*Campylobacter*-like organism test [Halyard]) at the study site; one container was sent to a central histology laboratory (Inform Diagnostics) for histologic examination; and one container was sent to the microbiology central laboratory (Infectious Diseases Research Laboratory, Texas Children's Hospital) for *H pylori* culture. In brief, biopsies were grown on selective and nonselective brain heart infusion agar containing 7% horse blood at 37 °C under microaerophilic conditions. *Helicobacter pylori* was identified according to standard methods (30). Susceptibility testing was performed by using agar dilution according to Clinical and Laboratory Standards Institute guidelines (31). Resistance breakpoints were greater than 0.125 μg/mL for amoxicillin, greater than 8 μg/mL for metronidazole, greater than 1 μg/mL for rifabutin (European Committee on Antimicrobial Susceptibility Testing), and 1 μg/mL or greater for clarithromycin (Clinical and Laboratory Standards Institute) (32, 33).

Patients underwent follow-up ^{13}C UBT at the test-of-cure visit to determine *H pylori* eradication. Those with positive ^{13}C UBT results underwent repeat endoscopy with culture and antibiotic susceptibility testing.

Plasma concentrations of amoxicillin, omeprazole, rifabutin, and the rifabutin metabolite 25-O-desacetyl

rifabutin were determined by using liquid chromatography mass spectrometry detection in blood samples collected at baseline and day 13 visits.

Adverse events were monitored throughout the study. Physical examination, vital signs, and laboratory studies (hematology, serum chemistry, and urinalysis) were performed at screening, day 13, and test-of-cure visits.

Because omeprazole is metabolized by CYP 2C19, pharmacogenetic testing was performed on blood samples collected at baseline to assess CYP 2C19 status. Patients were classified according to metabolizer categories (ultrarapid, rapid, normal, intermediate, or poor), and both efficacy and safety data were analyzed to determine whether metabolizer status affected efficacy or safety.

Statistical Analysis

All randomly assigned participants who received at least 1 dose of randomized study drug were included in the safety analysis data set and in the intention-to-treat (ITT) analysis data set for efficacy. Prespecified sensitivity analyses on the primary end point were conducted in modified ITT (mITT) and per protocol (PP) analysis populations. The mITT population included all participants who received at least 1 dose of study drug and underwent ^{13}C UBT at the test-of-cure visit. The PP population included all participants who consumed 75% or more of planned study drug, had no protocol violations that led to exclusion, and underwent ^{13}C UBT at the test-of-cure visit. The primary end point was also analyzed in a subset of ITT patients who had demonstrated presence of any component of study drug at end of treatment (day 13), referred to as the "confirmed adherent population."

Sample Size Determination

Sample size was calculated on the basis of a superiority comparison assuming 83% effectiveness for the new treatment, 70% effectiveness for the active comparator, and a 2-sided significance level of 5%. Approximately 222 patients were to be randomly assigned to each treatment group to achieve 90% power.

Efficacy End Points and Analyses

All statistical testing was 2-sided and was performed by using SAS, version 9.4 (SAS Institute), with a significance (α) level of 0.05. Two-sided 95% CIs were provided when relevant.

The primary efficacy end point was eradication of *H pylori,* as determined by the ^{13}C UBT result at the test-of-cure visit, assessed in the ITT data set. The between-group difference for *H pylori* eradication rate was analyzed by using a χ^2 test. Patients with persistent indeterminate results or no ^{13}C UBT after baseline were classified as having had treatment failure. Sensitivity analyses on the primary end point in the mITT and PP populations, as well as the confirmed adherent population, were also performed by using a χ^2 test.

Analyses of eradication rates based on antibiotic sensitivity findings at baseline (susceptible or resistant to amoxicillin, clarithromycin, metronidazole, or rifabutin) were performed if there were 20 or more patients per subgroup, and eradication rates based on CYP 2C19 status were tested by using the χ^2 test (exploratory end point).

Role of the Funding Source

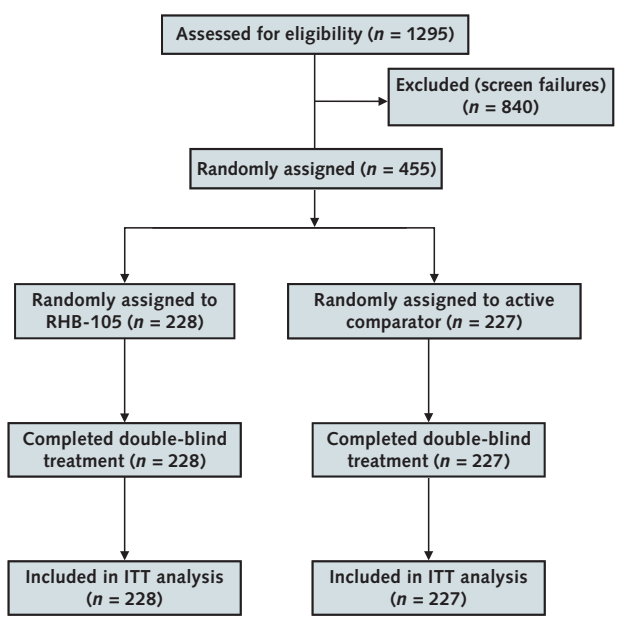
This study was funded by RedHill Biopharma Ltd., Tel Aviv, Israel. RedHill Biopharma was involved in study design, data collection, data analysis and interpretation, and writing (I.N.K.) and review of the manuscript.

RESULTS

A total of 455 patients were randomly assigned (228 to receive RHB-105 and 227 to receive the active comparator); all received at least 1 dose of study drug (Figure). Of these, all but 1 patient had ^{13}C UBT at the test-of-cure visit, and none had persistently indeterminate results. One participant had fecal antigen testing. Measurable study drug levels at day 13 were obtained in 207 patients (90.8%) in the RHB-105 group and 184 (81.1%) in the active comparator group. Culture and susceptibility results were available for 174 (76.3%) and 171 (75.3%) participants in the respective treatment groups.

The treatment groups were balanced with respect to demographic and other baseline characteristics (Table 1). Overall, mean age was 46.5 years (SD, 13), women accounted for a higher proportion (62.2%) of the study sample, and 60.0% of participants were Hispanic.

Figure. Study flow diagram.



ITT = intention-to-treat.

Table 1. Demographic and Baseline Characteristics

Characteristic	RHB-105 Group (*n* = 228)	Active Comparator Group (*n* = 227)	Overall (*n* = 455)
Mean (SD) age, *y*	45.9 (12.77)	47.2 (13.13)	46.5 (12.95)
Age group, *n (%)*			
<65 y	214 (93.9)	207 (91.2)	421 (92.5)
≥65 y	14 (6.1)	20 (8.8)	34 (7.5)
Sex, *n (%)*			
Male	96 (42.1)	76 (33.5)	172 (37.8)
Female	132 (57.9)	151 (66.5)	283 (62.2)
Race, *n (%)*			
Black or African American	35 (15.4)	53 (23.3)	88 (19.3)
White	184 (80.7)	167 (73.6)	351 (77.1)
Other	9 (4.0)	7 (3.1)	16 (3.5)
Ethnicity, *n (%)*			
Hispanic/Latino	149 (65.4)	124 (54.6)	273 (60.0)
Not Hispanic/Latino	79 (34.6)	103 (45.4)	182 (40.0)
Cytochrome P450 2C19 status, *n (%)*			
Ultrarapid metabolizers	10 (4.4)	3 (1.3)	13 (2.9)
Rapid metabolizers	45 (19.7)	55 (24.2)	100 (22.0)
Normal metabolizers	114 (50.0)	107 (47.1)	221 (48.6)
Intermediate metabolizers	48 (21.1)	52 (22.9)	100 (22.0)
Poor metabolizers	5 (2.2)	4 (1.8)	9 (2.0)
Not reported*	5 (2.2)	4 (1.8)	9 (2.0)
Missing†	1 (0.4)	2 (0.9)	3 (0.7)

* Samples arrived in an expired container and were not processed.
† Includes samples that were not taken, and 1 sample that arrived in the wrong condition.

At baseline, 22 (6.4%), 60 (17.4%), and 150 (43.6%) patients were infected with *H pylori* strains resistant to amoxicillin, clarithromycin, and metronidazole, respectively (Table 2). Thirty-six patients (10.5%) had an isolate resistant to both clarithromycin and metronidazole. No rifabutin resistance was detected.

Overall, study drug adherence, as defined by pill count returned versus expected return, was similar be-

Table 2. Susceptibility Testing Results for *Helicobacter pylori* at Baseline

Antibiotic	RHB-105 Group	Active Comparator Group	Overall
Amoxicillin MIC			
Participants with MIC data*, *n*	174	171	345
≤0.125 μg/mL (susceptible), *n (%)*	161 (92.5)	162 (94.7)	323 (93.6)
>0.125 μg/mL (resistant), *n (%)*	13 (7.5)	9 (5.3)	22 (6.4)
Clarithromycin MIC			
Participants with MIC data*, *n*	174	171	345
≤0.25 μg/mL (susceptible), *n (%)*	149 (85.6)	136 (79.5)	285 (82.8)
0.5 μg/mL (intermediate), *n (%)*	0	0	0
>0.5 μg/mL (resistant), *n (%)*	25 (14.4)	35 (20.5)	60 (17.4)
Metronidazole MIC			
Participants with MIC data*, *n*	174	170	344
≤8 μg/mL (susceptible), *n (%)*	103 (59.2)	91 (53.5)	194 (56.4)
>8 μg/mL (resistant), *n (%)*	71 (40.8)	79 (46.5)	150 (43.6)
Rifabutin MIC			
Participants with MIC data*, *n*	174	171	345
≤0.125 μg/mL (susceptible), *n (%)*	174 (100)	171 (100)	345 (100)
>0.125 μg/mL (resistant), *n (%)*	0	0	0

MIC = minimum inhibitory concentration.
* Percentages for antimicrobial susceptibility were calculated with the number of participants with nonmissing assessment as the denominator. Classifications of MIC values as susceptible, intermediate, or resistant were based on the European Committee on Antimicrobial Susceptibility Testing Breakpoint tables for interpretation of MICs and zone diameters: Version 8.0, 2018 (www.eucast.org) for amoxicillin, metronidazole, and rifabutin and on Clinical and Laboratory Standards Institute, Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria, M45, 3rd edition, 2016, for clarithromycin.

tween treatment groups. Mean adherence rate was 97.5% (SD, 14.20%) in the RHB-105 group and 97.9% (SD, 13.17%) in the active comparator group (**Appendix Table 1**, available at Annals.org).

Efficacy Results

The *H pylori* eradication rate in the ITT data set (primary efficacy end point) was higher with RHB-105 than the active comparator (228 vs. 227 patients; 83.8% [95% CI, 78.4% to 88.0%] vs. 57.7% [95% CI, 51.2% to 64.0%]; treatment difference, 26.1% [95% CI, 18.0% to 34.1%] favoring RHB-105; $P < 0.001$) (**Table 3**). Results of sensitivity analyses conducted on the mITT and PP populations were consistent with the results of the ITT data set, with treatment differences of 26.4% (95% CI, 18.4% to 34.4%) and 26.4% (95% CI, 18.2% to 34.7%), respectively (**Table 3**). In the confirmed adherent population, the eradication rates were 90.3% (95% CI, 85.5% to 93.7%) and 64.7% (95% CI, 57.5% to 71.2%) with RHB-105 (207 patients) and the active comparator (184 patients), respectively ($P < 0.001$).

The eradication rate with RHB-105 remained high, irrespective of the resistance or susceptibility of *H pylori* strains causing infection (**Table 4**). With regard to amoxicillin resistance (minimum inhibitory concentration [MIC] >0.125 µg/mL), only 1 of 4 patients in the active control group infected with an amoxicillin-resistant strain achieved eradication. In the amoxicillin–omeprazole dual therapy group, 9 patients (5.5%) were infected with resistant strains. Of these, 4 of 6 (66.7%) patients infected with a strain having an MIC of 0.250 µg/mL were cured, similar to the rate among those infected with a strain having an MIC of 0.125 µg/mL or less (59.3% [95 of 160 patients]). In contrast, amoxicillin–omeprazole dual therapy failed in all 3 patients infected with a strain having an MIC greater than 0.250 µg/mL.

In analyses of *H pylori* eradication rates by CYP 2C19 status (**Appendix Table 2**, available at Annals.org), with sparse data in some strata (5 and 4 poor metabolizers in the RHB-105 and active comparator groups, respectively), eradication rates were unaffected by clarithromycin or metronidazole resistance.

Treatment Failure

Susceptibility data were available for 174 patients in the RHB-105 group and 171 patients in the active comparator group, including data from 99 patients in whom treatment failed (27 and 72 patients in the respective treatment groups). None had an isolate that developed rifabutin resistance.

Safety Results

The type and incidence of adverse events were similar between treatment groups (**Table 5**). The most commonly reported adverse events with RHB-105 and active comparator were diarrhea (10.1% vs. 7.9%, respectively), headache (7.5% vs. 7.0%), and nausea (4.8% vs. 5.3%). One patient in each treatment group experienced 1 serious adverse event (diabetic ketoacidosis in the RHB-105 group, and encephalopathy secondary to benzodiazepine overdose in the active comparator group); investigators classified these events as unrelated to study drug. No deaths were reported. A targeted search of both adverse events and hematologic studies did not uncover any case of myelotoxicity.

The safety of RHB-105 and active comparator was similar between patients with impaired CYP 2C19 function and those with normal or high metabolizer phenotypes. The proportion of patients with any adverse event did not appear to be related to CYP 2C19 genotype, and there was no difference in serious adverse event reporting across the subgroups (**Appendix Table 3**, available at Annals.org).

DISCUSSION

The principles of antimicrobial stewardship stress the importance of treatment optimization (34, 35). In the case of *H pylori*, individualized treatment is limited

Table 3. *Helicobacter pylori* Eradication Rate, by Treatment Group

Analysis	RHB-105 Group	Active Comparator Group	Treatment Difference	*P* Value*
ITT analysis on the primary efficacy end point†				
Eradication rate, % (*n/N*)	83.8 (191/228)	57.7 (131/227)	26.1	<0.001
95% CI, %	78.4 to 88.0	51.2 to 64.0	18.0 to 34.1	
Sensitivity analyses on the primary efficacy end point				
mITT‡				
Eradication rate, % (*n/N*)	84.1 (191/227)	57.7 (131/227)	26.4	<0.001
95% CI, %	78.8 to 88.3	51.2 to 64.0	18.4 to 34.4	
Per protocol§				
Eradication rate, % (*n/N*)	84.4 (179/212)	58.0 (123/212)	26.4	<0.001
95% CI, %	78.9 to 88.7	51.3 to 64.5	18.2 to 34.7	
Confirmed adherent population‖				
Eradication rate, % (*n/N*)	90.3 (187/207)	64.7 (119/184)	25.6	<0.001
95% CI, %	85.5 to 93.7	57.5 to 71.2	17.7 to 33.7	

ITT = intention-to-treat; mITT = modified intention-to-treat.
* Based on χ^2 test.
† All participants who received at least 1 dose of study drug.
‡ All participants who received at least 1 dose of study drug and underwent ^{13}C urea breath testing at the test-of-cure visit.
§ All participants who consumed ≥75% of planned study drug, had no protocol violations that led to exclusion, and underwent ^{13}C urea breath testing at the test-of-cure visit.
‖ Participants in the ITT population who had demonstrated presence of any component of study drug at end of treatment (day 13) or for whom the end of treatment pharmacokinetic assessment was performed >250 h after the last dose of randomized study drug.

Table 4. *Helicobacter pylori* Eradication Rate, by Antimicrobial Resistance Status at Baseline

Antimicrobial Resistance Status at Baseline	Responders*		Treatment Difference†	*P* Value‡
	RHB-105 Group (*n* = 228)	Active Comparator Group (*n* = 227)		
Resistance to any antibiotic§				
Eradication rate, % (*n/N*)	81.2 (69/85)	56.1 (55/98)	25.1	<0.001
95% CI, %	71.6 to 88.1	46.3 to 65.5	12.2 to 37.9	
Resistance to individual antibiotics				
Amoxicillin only				
Eradication rate, % (*n/N*)	80.0 (4/5)	25.0 (1/4)	55.0	NA
95% CI, %	37.6 to 96.4	4.6 to 69.9	0.0 to 100.0	
Clarithromycin only				
Eradication rate, % (*n/N*)	85.7 (6/7)	57.1 (8/14)	28.6	NA
95% CI, %	48.7 to 97.4	32.6 to 78.6	–8.1 to 65.2	
Metronidazole only				
Eradication rate, % (*n/N*)	80.8 (42/52)	53.6 (30/56)	27.2	0.003
95% CI, %	68.1 to 89.2	40.7 to 66.0	10.3 to 44.1	
Amoxicillin + clarithromycin				
Eradication rate, % (*n/N*)	100.0 (2/2)	100.0 (1/1)	0.0	NA
95% CI, %	34.2 to 100.0	20.7 to 100.0	NA to NA	
Amoxicillin + metronidazole				
Eradication rate, % (*n/N*)	66.7 (2/3)	66.7 (2/3)	0.0	NA
95% CI, %	20.8 to 93.9	20.8 to 93.9	–75.4 to 75.4	
Clarithromycin + metronidazole				
Eradication rate, % (*n/N*)	92.3 (12/13)	68.4 (13/19)	23.9	NA
95% CI, %	66.7 to 98.6	46.0 to 84.6	–1.5 to 49.3	
Amoxicillin + clarithromycin + metronidazole				
Eradication rate, % (*n/N*)	33.3 (1/3)	0 (0/1)	33.3	NA
95% CI, %	6.1 to 79.2	0.0 to 79.3	–20.0 to 86.7	

NA = not applicable (sample size <20 patients per subgroup).
* Defined as eradication of *Helicobacter pylori*, confirmed via ^{13}C urea breath testing or fecal antigen results, at the test-of-cure visit (day 43 to 71).
† RHB-105 minus active comparator.
‡ Based on χ^2 test.
§ Amoxicillin, clarithromycin, or metronidazole (or any combination of these agents).

by the fact that antibiotic sensitivity testing is not routinely available, forcing clinicians to use empirical therapies (9). As with any antimicrobial therapy, the first-line treatment should offer the greatest chance of success (4). Recent consensus statements have recommended either bismuth quadruple or concomitant therapies (PPI, amoxicillin, clarithromycin, and metronidazole) as empirical therapies in regions where resistance has un-

Table 5. Treatment-Emergent Adverse Events

Adverse Event*	Participants, *n (%)*		
	RHB-105 Group (*n* = 228)	Active Comparator Group (*n* = 227)	Overall (*n* = 455)
Any adverse event	83 (36.4)	72 (31.7)	155 (34.1)
Any serious adverse event	1 (0.4)	1 (0.4)	2 (0.4)
Adverse events leading to discontinuation of study drug	2† (0.9)	1‡ (0.4)	3 (0.7)
Death	0	0	0
Most frequently reported adverse events§			
Diarrhea	23 (10.1)	18 (7.9)	41 (9.0)
Headache	17 (7.5)	16 (7.0)	33 (7.3)
Nausea	11 (4.8)	12 (5.3)	23 (5.1)
Vomiting	5 (2.2)	5 (2.2)	10 (2.2)
Abdominal distention	4 (1.8)	3 (1.3)	7 (1.5)
Abdominal pain	4 (1.8)	8 (3.5)	12 (2.6)
Dyspepsia	4 (1.8)	3 (1.3)	7 (1.5)
Urinary tract infection	4 (1.8)	4 (1.8)	8 (1.8)
Upper abdominal pain	3 (1.3)	3 (1.3)	6 (1.3)
Dizziness	3 (1.3)	5 (2.2)	8 (1.8)
Rash	3 (1.3)	0	3 (0.7)

* Adverse events were assessed at study visits from baseline through the test-of-cure visit. Riboflavin was administered to prevent unintentional unblinding; this may have contributed to under-reporting of chromaturia, which is associated with rifabutin use.
† Nausea in 1 participant and nasal congestion in 1 participant.
‡ Headache.
§ "Most frequently reported" was defined as ≥1% of participants in the RHB-105 treatment group. Events are presented in descending order of frequency in the RHB-105 group.

dermined the effectiveness of traditional or standard triple therapies (2, 4, 5, 7). Bismuth quadruple therapy is complex, and patients experience challenges with both adherence and tolerability (36). Concomitant therapy is ineffective in the presence of dual clarithromycin and metronidazole resistance, and all patients receive at least 1 unnecessary antibiotic (2, 37).

This large, double-blind, randomized, controlled trial was designed to confirm the efficacy of a novel rifabutin-based triple therapy for *H pylori*. It was anticipated that combining the 3 drugs into an all-in-one capsule, thereby simplifying the treatment regimen, would enhance adherence and efficacy. RHB-105 proved highly effective and superior to the active comparator. Our design demonstrated a substantial increase in efficacy when rifabutin was added to the high-dose dual regimen of omeprazole and amoxicillin. The tolerability of RHB-105 was favorable, with high adherence and an adverse event profile similar to that of the comparator group. In an era of increasing antimicrobial resistance, it is important to note that the efficacy of RHB-105 was not adversely affected by clarithromycin resistance or by metronidazole resistance, and there was no evidence of development of rifabutin resistance among patients who experienced treatment failure.

Resistance to clarithromycin, metronidazole, and levofloxacin has been associated with low cure rates worldwide, particularly when these drugs are used in triple therapy regimens (2, 4, 5, 7, 8). In this study conducted in the United States, the *H pylori* resistance rates to clarithromycin and metronidazole were 17.4% and 43.6%, respectively. Furthermore, we identified, for the first time, a low rate of amoxicillin resistance in the United States (6.4%) and affirmed the lack of resistance to rifabutin.

This study was not designed to establish clinical breakpoints for the antibiotics used; however, clinical data comparing treatment success and susceptibility to amoxicillin are currently virtually nonexistent. Results from this study suggest that the proposed breakpoint for amoxicillin is probably higher (for example, MIC >0.250 μg/mL) than proposed.

There has not been a new therapy approved by FDA since 1997. Taken together, these findings support the proposed use of RHB-105 as a new first-line empirical treatment strategy for *H pylori*. Ultimately, the place of RHB-105 in anti-*H pylori* treatment will be determined by such factors as treatment success, adherence, cost, and availability.

Our study has limitations. It was conducted in the United States (23 states) and excluded persons of Asian descent because of the higher prevalence of poor CYP 2C19 metabolizers. However, our analysis of non-Asian persons with intermediate or poor metabolizer status did not identify any safety or efficacy differences relating to CYP 2C19 polymorphisms. Conclusions about cure rate based on CYP 2C19 status at baseline and cure rate based on antimicrobial resistance at baseline are limited by the small number of patients in certain categories, as are clinical breakpoints for amoxicillin. We hope our results on these end points prompt others to perform larger studies to confirm our findings.

In conclusion, RHB-105 was developed to overcome the problem of resistance to existing anti–*H pylori* therapies. This study confirmed that a high *H pylori* eradication rate can be achieved with RHB-105. Efficacy was not reduced by the presence of clarithromycin or metronidazole resistance, which suggests that RHB-105 should be considered as a first-line empirical therapy of *H pylori* infection. A new treatment option will help address the unmet need of providing effective, well-tolerated therapy in an environment of clinically significant antibiotic resistance. Studies in Asia (for example, evaluating rifabutin resistance in areas of high current use), head-to-head comparisons against reliably highly effective first-line regimens, and "real-world" experience will expand efficacy and safety data and further define the role of RHB-105 in the treatment of *H pylori* infections.

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Acknowledgment: The authors thank June Almenoff, MD, PhD, RedHill Biopharma Ltd., for valuable editorial contributions; Raymond Panas, PhD, RedHill Biopharma Ltd., and Sandra Norris, PharmD, Norris Communications Group LLC, for medical writing assistance; and Joerg Pawlitschko, PhD, ICON plc, who conducted the statistical analyses. They also thank Michael DeMicco, MD (now deceased), for his substantial contributions, including enrollment of patients and data collection. Finally, they thank the patients and investigators who participated in the ERADICATE Hp2 clinical trial.

Financial Support: By RedHill Biopharma Ltd., Tel Aviv, Israel.

Disclosures: Dr. Graham reports a grant from the Public Health Service (grant DK56338 which funds the Texas Medical Center Digestive Diseases Center) during the conduct of the study and grants from RedHill Biopharma and consultancy for Phathom Pharmaceuticals outside the submitted work. Dr. Hulten reports grants from RedHill Biopharma during the conduct of the study and grants, personal fees, and nonfinancial support from Pfizer outside the submitted work. Dr. Kalfus was the medical director for RedHill Biopharma during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-3734.

Data Sharing Statement: The authors have indicated that they will not be sharing data. Data have been made available to authors based upon requests. Mining of the data continues for additional analyses. It has not been made available as a public resource.

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Appendix Table 1. Treatment Adherence

Adherence*	RHB-105 Group (*n* = 228)	Active Comparator Group (*n* = 227)	Overall (*n* = 455)
Overall, %			
Mean (SD)	97.5 (14.20)	97.9 (13.17)	97.7 (13.68)
Median	100.0	100.0	100.0
Minimum, maximum	4.76, 157.14	7.14, 119.05	4.76, 157.14
By category, *n (%)*			
<75%	10 (4.4)	8 (3.5)	18 (4.0)
≥75%–90%	9 (3.9)	2 (0.9)	11 (2.4)
>90%–100%	178 (78.1)	186 (81.9)	364 (80.0)
>100%	31 (13.6)	31 (13.7)	62 (13.6)

* Calculated as 100 × ([total number of capsules dispensed] – [total number of capsules returned])/168. When a participant returned fewer capsules than expected, whether because of capsule loss or taking an extra dose, for example, adherence was considered greater than 100%.

Appendix Table 2. *Helicobacter pylori* Eradication Rate in Participants With Analyzable Cytochrome P450 2C19 Status at Baseline

Cytochrome P450 2C19 Status	Responders*		Treatment Difference†	*P* Value‡
	RHB-105 Group (*n* = 222)	Active Comparator Group (*n* = 221)		
Ultrarapid metabolizers				
Eradication rate, % (*n*/*N*)	80.0 (8/10)	33.3 (1/3)	46.7	NA
95% CI, %	49.0 to 94.3	6.1 to 79.2	–12.2 to 100.0	
Rapid metabolizers				
Eradication rate, % (*n*/*N*)	80.0 (36/45)	50.9 (28/55)	29.1	0.003
95% CI, %	66.2 to 89.1	38.1 to 63.6	11.5 to 46.7	
Normal metabolizers				
Eradication rate, % (*n*/*N*)	86.0 (98/114)	59.8 (64/107)	26.2	<0.001
95% CI, %	78.4 to 91.2	50.3 to 68.6	14.9 to 37.4	
Intermediate metabolizers				
Eradication rate, % (*n*/*N*)	85.4 (41/48)	57.7 (30/52)	27.7	0.002
95% CI, %	72.8 to 92.8	44.2 to 70.1	11.0 to 44.5	
Poor metabolizers				
Eradication rate, % (*n*/*N*)	60.0 (3/5)	100.0 (4/4)	-40.0	NA
95% CI, %	23.1 to 88.2	51.0 to 100.0	–82.9 to –2.9	

NA = not applicable (sample size <20 patients per subgroup).
* Defined as eradication of *Helicobacter pylori*, confirmed via ^{13}C urea breath testing or fecal antigen results, at the test-of-cure visit (day 43 to 71). Six participants in each treatment group did not have analyzable cytochrome P450 2C19 status information at baseline.
† RHB-105 versus active comparator.
‡ Based on χ^2 test.

Appendix Table 3. Treatment-Emergent Adverse Events in Participants With Analyzable Cytochrome P450 2C19 Status at Baseline

Cytochrome P450 2C19 Status	Participants, *n/N (%)**		
	RHB-105 Group (*n* = 222)	**Active Comparator Group (*n* = 221)**	**Overall (*n* = 443)**
Ultrarapid metabolizers			
Any adverse event	4/10 (40.0)	1/3 (33.3)	5/13 (38.5)
Any serious adverse event	0	0	0
Adverse events leading to discontinuation of study drug	1/10 (10.0)	0	1/10 (7.7)
Death	0	0	0
Rapid metabolizers			
Any adverse event	19/45 (42.2)	11/55 (20.0)	30/100 (30.0)
Any serious adverse event	0	0	0
Adverse events leading to discontinuation of study drug	1/45 (2.2)	0	1/100 (1.0)
Death	0	0	0
Normal metabolizers			
Any adverse event	37/114 (32.5)	40/107 (37.4)	77/221 (34.8)
Any serious adverse event	1/114 (0.9)	0	1/221 (0.5)
Adverse events leading to discontinuation of study drug	0	1/107 (0.9)	1/221 (0.5)
Death	0	0	0
Intermediate metabolizers			
Any adverse event	19/48 (39.6)	16/52 (30.8)	35/100 (35.0)
Any serious adverse event	0	1/52 (1.9)	1/100 (1.0)
Adverse events leading to discontinuation of study drug	0	0	0
Death	0	0	0
Poor metabolizers			
Any adverse event	1/5 (20.0)	3/4 (75.0)	4/9 (44.4)
Any serious adverse event	0	0	0
Adverse events leading to discontinuation of study drug	0	0	0
Death	0	0	0

* Adverse events were assessed at study visits from baseline through the test-of-cure visit. Six participants in each treatment group did not have analyzable cytochrome P450 2C19 status information at baseline.