ERADICATE *Hp*: A Randomized, Double-Blind, Placebo-Controlled Phase III Study to Assess the Safety and Efficacy of Rifabutin Triple Therapy (RHB-105) for *Helicobacter pylori* (*H. pylori*) Infection in Dyspepsia Patients

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The Problem

"...the only good *H. pylori* is a dead *H. pylori*..."[1]

- *H. pylori* is an infectious disease[2] (Kyoto)
- Eradication is recommended for patients with active *H. pylori* infections
  - Irrespective of symptoms and stage of disease
- A test-and-treat strategy is appropriate for uninvestigated dyspepsia[3] (Maastricht V)
- Important caveats to "test and treat"
  - Age, alarm symptoms and *H. pylori* prevalence/susceptibility
- Up to 30% eradication failure with standard-of-care (SOC) triple therapy in infected patients
- Increasing global resistance to clarithromycin and metronidazole

The Solution

RHB-105

- All-in-One capsule formulation of:
  - Amoxicillin (AMX) 250 mg
  - Rifabutin (RIF) 12.5 mg
  - Omeprazole 10 mg
- Subjects received four (4) capsules three times a day (TID)
- > 90% efficacy in AMX/RIF/PPI single site SOC failed treatment study[4]
- Historically, minimal resistance to amoxicillin and rifabutin has been observed

Methods

Study design

This was a Phase III, double-blind, 2:1 randomized, placebo-controlled study of RHB-105 in adult subjects complaining of epigastric discomfort that were screened and found to be positive for *H. pylori* infection via ^{13}C UBT and by fecal antigen test or gastric biopsy (CLO).

- Eligible subjects were randomized to receive study drug for 14 consecutive days with a total daily dose of:
  - Amoxicillin 3000 mg
  - Rifabutin 150 mg
  - Omeprazole 120 mg
- Test of Cure via ^{13}C UBT was performed 28 to 35 days post completion of treatment
- Treatment failures received investigator-directed, non-rifabutin based therapy (SOC)
- 2:1 Randomization
- RHB-105:Placebo = 77:41
- 9 active sites

Inclusion Criteria

- Aged 18 to 65 years
- Positive for *H. pylori* by ^{13}C UBT and fecal antigen test or gastric biopsy within six (6) weeks
- Dyspeptic symptoms for at least two (2) weeks; recurrent pain/discomfort in upper abdomen

Exclusion Criteria

- Alarm symptoms or signs
- Antibiotics four (4) weeks prior to screening
- Bismuth or PPI two (2) weeks prior to screening
- History of prior *H. pylori* eradication therapy
- History of previous esophageal or gastric surgery
- History of gastric outlet obstruction
- History of hypersecretory states such as Zollinger-Ellison Syndrome
- History of gastric cancer
- Presence of active gastric and duodenal ulcers or presence of three or more active ulcers

Statistical analysis

The effectiveness of any combination of 2 out of 3 API components of RHB-105 was projected to be no more than 70% given the information in the Prevacid® and Prilosec® Prescriber Information. The new regimen was expected to be at least 20% more effective than the previous regimen. The per protocol defined primary endpoint comparator efficacy was 70% based on the reported effectiveness of SOC treatment. This study design was based on 90% power and single-sided *p*-value 0.025.

The eradication rate with placebo was expected to be minimal and hence not informative.

Objectives

Primary

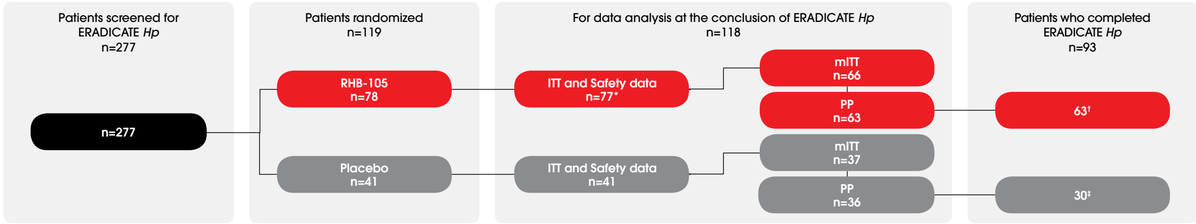
H. pylori eradication as confirmed via ^{13}C UBT testing at 28 to 35 days after treatment completion.

The efficacy analyses were to be performed on the modified-intent-to-treat (mITT) population as primary analysis and repeated on the intent-to-treat (ITT) and per-protocol (PP) populations as sensitivity analyses.

Secondary and Exploratory

Safety of RHB-105 and CYP2C19 genotyping related to efficacy.

Disposition of Subjects



* 1 patient erroneously randomized and not treated
† 14 RHB-105 subjects did not complete protocol: 6 lost to follow-up; 5 non-compliant to regimen; 2 withdrew consent; 1 other
‡ 11 placebo subjects did not complete protocol: 7 lost to follow-up; 3 withdrew consent; 1 safety issue

ITT - Intent to Treat Population includes all patients who received at least one dose of randomized study treatment
mITT - Modified Intent to Treat Population includes all patients who received at least one dose of randomized study treatment AND underwent a ^{13}C UBT test at Visit 4
PP - Per Protocol Population includes all patients who received at least 75% of randomized study treatment AND underwent a ^{13}C UBT test at Visit 4 AND did not have any major protocol violations

Results

PRIMARY EFFICACY ANALYSIS

H. pylori eradication by population	RHB-105	Comparator	*p*-value vs comparator[2]	Placebo
mITT[1]	89.4% (59/66)	Historical 70%	p<0.001	2.7% (1/37)

[1]Success defined as *H. pylori* infection eradication, confirmed by ^{13}C UBT 28-35 days after double-blind therapy
[2]One-sample Z-test (RHB-105 subjects only) for Ho: Proportion of success ≤70% vs. Ha: Proportion of success >70%

Seventy-seven subjects received RHB-105 and 41 received FDA-mandated placebo for assessment of safety. The *H. pylori* eradication rate (based on ^{13}C UBT) in the protocol defined, modified intent-to-treat (mITT) patient population was 89.4% (59/66 subjects). This rate was statistically significantly superior to 70%, *p*<0.001, which was the reported effectiveness of SOC treatment. Placebo patients underwent physician-choice, non-rifabutin based *H. pylori* therapy with eradication rates of 63% (17/27) irrespective of chosen therapy, *p*=0.006, and 60.9% (14/23) in SOC triple therapy, *p*=0.004. A sensitivity analysis based on the intent-to-treat (ITT) population demonstrated a mean success rate of eradication of *H. pylori* of 79%, while a sensitivity analysis based on the per protocol (PP) population showed results similar to the main analysis (success rate=88.9%, *p*<0.001).

Results of CYP2C19 genotyping in the mITT population showed the majority of subjects treated with RHB-105 (n=38, 61.3%) were extensive or rapid metabolizers and 32 (84.2%) successfully eradicated *H. pylori*. All ultra-rapid (n=11) and intermediate (n=13) metabolizers were *H. pylori* successes. While not all subjects were assessed, there was no statistically significant difference observed between the success and failure groups based on the subject's CYP2C19 status for the subjects randomized to the RHB-105 treatment group (*p*=0.123).

The adverse event profile, laboratory values, and other safety assessments did not indicate any safety concerns.

Sensitivity Analyses

	RHB-105	Comparator	*p*-value	Placebo
PP[1]	88.9% (56/63)	**Historical 70%**	<0.001[3]	2.8% (1/36)
ITT[1]	76.6% (59/77)	**Historical 70%**	0.085[3]	2.4% (1/41)
Physician-Directed SOC (Previous Placebo Subjects)				
mITT[2]	89.4% (59/66)	61% (14/23) Triple Tx	0.004[4]	
mITT[2]	89.4% (59/66)	63% (17/27) All Tx	0.006[4]	
ITT[2]	76.6% (59/77)	52.0% (17/33) All Tx	0.009[4]	

[1]Success defined as *H. pylori* infection eradication, confirmed by ^{13}C UBT 28-35 days after double-blind therapy
[2]Success defined as *H. pylori* infection eradication, confirmed by ^{13}C UBT 28-35 days after SOC therapy
[3]One-sample Z-test (RHB-105 subjects only) for Ho: Proportion of success ≤70% vs. Ha: Proportion of success >70%
[4]Chi-squared test

Summary of CYP2C19 Status For RHB-105 Subjects (mITT Population)

CYP2C19 Status (RHB-105 subjects only)	Success[1]	Failure	*p*-value[2]
Ultra-Extensive or Ultra-Rapid Metabolizer	11 (100%)	0	0.123
Rapid/Extensive Metabolizer	32 (84.2%)	6 (20.8%)	
Intermediate Metabolizer	13 (100%)	0	
Poor Metabolizer	0	0	
Ultra-Rapid + Rapid/Extensive	43 (87.8%)	6 (12.2%)	
Ultra-Rapid + Rapid/Extensive + Intermediate	56 (90.3%)	6 (9.7%)	
Rapid/Extensive + Intermediate	45 (88.2%)	6 (11.8%)	

[1]Success defined as *H. pylori* infection eradication, confirmed by ^{13}C UBT 28-35 days after double-blind therapy
[2] Chi-squared test

Genotyping

In the mITT population, 97 subjects (62 RHB-105, 35 placebo) had CYP2C19 status data. Based on CYP2C19 genotypes, there were 14 ultra-rapid (11 RHB-105, 3 placebo), 64 extensive or rapid (38 RHB-105, 26 placebo), and 17 intermediate (13 RHB-105, 4 placebo) metabolizers. Two poor metabolizers were identified in the placebo group, and none in the RHB-105 group.

There was no statistically significant difference observed between the success and failure groups based on the CYP2C19 status (while assessing the distribution over the different genotypes) for the subjects randomized to RHB-105 treatment group (*p*=0.123).

Results

Safety

- 151 adverse events (AEs) in 55 of 118 subjects
  - 103 AEs in RHB-105 arm
  - 48 AEs in placebo arm
- 55 patients experienced Treatment-Related Adverse Events (TEAEs)
  - 51 mild to moderate
  - Four (4) severe
    - RHB-105: Rash / diarrhea
    - Placebo: Anemia / perirectal abscess
    - One (1) additional anemia noted at baseline in RHB-105 subject

Summary of Treatment-Related TEAES (> 5% Safety Population)

	RHB-105 n=77		Placebo n=41	
Category	# Pts (%)	# AEs	# Pts (%)	# AEs
All System Organ Classes	38 (49.4%)	103	17 (41.5%)	48
Related	23 (29.9%)	40	8 (19.5%)	23
Not related	15 (19.5%)	63	9 (22.0%)	25
Diarrhea	9 (11.7%)	9	4 (9.8%)	4
Headache	4 (5.2%)	5	3 (7.3%)	3
Chromaturia	9 (11.7%)	9	1 (2.4%)	1

Related = Possibly, Probably, or Definitely Related; Unrelated = Unlikely, Unrelated
Treatment emergent AEs are defined as those beginning on or after the first dose of study treatment

ERADICATE *Hp* Conclusions

- RHB-105 is a novel All-in-One new therapy to eradicate *H. pylori*
- RHB-105's 89.4% efficacy was significantly more effective than 70% efficacy of historical triple therapy or 63% efficacy of physician-directed, non-rifabutin based therapy
- RHB-105 was safe and well tolerated
- No significant difference noted beween success and failure groups based on CYP2C19 status
- Confirmatory Phase III study is planned

References

1. Graham D. The only good Helicobacter pylori is a dead Helicobacter pylori. *Lancet*. 1997;350(9070):70-1.
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4. Borody TJ, Pang G, Wettstein AR, et al. Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. *Aliment Pharmacol Ther*. 2006;23(4):481-488.

Disclosures

Ira Kalfus, MD is a consultant for RedHill Biopharma Ltd; Gilead Raday, MSc is employed at RedHill Biopharma Ltd; Reza Fathi, PhD is employed at RedHill Biopharma Ltd; David Y. Graham, MD is a consultant for RedHill Biopharma Ltd.