Low-dose Rifabutin (50 mg) Triple Therapy for *H. pylori* Is Efficacious and Well Tolerated in Patients with Obesity or Diabetes

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BACKGROUND

- The overall US prevalence of *Helicobacter pylori (H. pylori)* infection is ~35% but higher among non-Hispanic Black and Mexican Americans.[1,2]
  - **The estimated prevalence of** obesity in non-Hispanic Black adults **is 49.9% and 45.6% in** Hispanic adults.[3]
  - **The estimated prevalence of diabetes in non**-Hispanic Blacks **is** 12.1% and **11.8% in** Hispanics.[4]
- *H. pylori* eradication has become more challenging due to rising antibiotic resistance.[5-7]
- Diabetes and obesity may further complicate the successful treatment of the infection.[8-12]
  - A meta-analysis confirmed a higher **risk of *H. pylori* eradication failure in** patients with diabetes vs. those without diabetes.[13]
    - Total diabetes prevalence in the US is estimated to be 11.3%[4], which is mostly type 2 diabetes.
  - Obesity decreases the efficacy of clarithromycin triple therapy by nearly 50%.[12]
- A potential contributing factor to eradication success is intragastric antibiotic concentration time at or above the MIC_{90} for *H. pylori*.[14]

OBJECTIVES

- We aimed to assess if the efficacy of low-dose rifabutin (50 mg Q8H) triple therapy, RHB-105 (Talicia®) (50 mg rifabutin, 1000 mg amoxicillin, 40 mg omeprazole, Q8H for 14 days) for *H. pylori* infection was affected by patient obesity or diabetic status.

METHODS

- We conducted a *post hoc* analysis of pooled, modified-intent to treat data from 293 subjects in the Phase 3 RHB-105 clinical trials (NCT01980095/NCT03198507) analyzing the efficacy and safety of RHB-105 for *H. pylori* infection.
- We compared *H. pylori* eradication rates, safety, demographics, and body mass index (BMI) in patients with and without diabetes.
- We used physiologically based pharmacokinetic (PBPK) modeling to assess intragastric antibiotic concentration time above the MIC_{90} for *H. pylori* (0.008 µg/ml) in normal, overweight, and obese patients.

RESULTS

Of the 293 subjects, 84% were white; 68% were Hispanic; 59% were women. Average BMI was 30.5 kg/m². Patients with diabetes (n=48) were older (54 vs. 45 years), were more often black or African American (21% vs. 12%) and had higher BMI (33 vs. 30 kg/m²) compared to patients without diabetes (n=245).

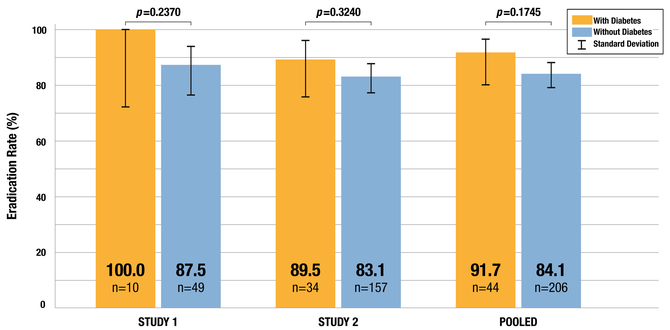
Table 1: Subject Demographics Between Patients With and Without Diabetes

		SEX		AGE	BMI	RACE				ETHNICITY		
Diabetes		M	F			White	Black/ AA	Native American	Other	Hispanic	Non-Hispanic	N
No	n	101	144	44.6	30.1	210	29	1	5	167	78	245
	%	41%	59%			86%	12%	0%	2%	68%	32%	
Yes	n	19	29	53.9	32.6	35	10	1	2	32	16	48
	%	40%	60%			73%	21%	2%	4%	67%	33%	

AA: African American

- Pooled eradication rates for RHB-105 were 91.7% (N=44) and 84.1% (N=206) (p=0.175) in subjects with vs. without diabetes, respectively (Figure 1).

Figure 1: *H. pylori* Eradication Rates with Low-Dose Rifabutin (50 mg) Triple Therapy Unaffected by Presence of Diabetes

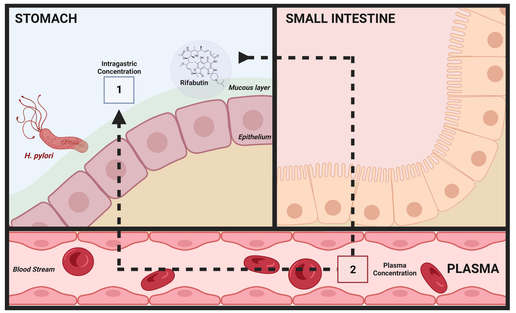


- Treatment naïve subjects with and without diabetes showed similar resistance profiles, respectively: clarithromycin 21% vs. 17%; metronidazole 45% vs. 43%; amoxicillin 4% vs. 7%; and no resistance was shown to rifabutin.
- The most frequently reported adverse events were diarrhea, headache, and nausea; no cases of hypoglycemia were reported (Table 2).

Table 2: Safety and Tolerability of Low-Dose Rifabutin (50 mg Q8H) Triple Therapy Generally Similar Between Patients With and Without Diabetes

	STUDY 1		STUDY 2		POOLED	
	With Diabetes	Without Diabetes	With Diabetes	Without Diabetes	With Diabetes	Without Diabetes
Adverse Reaction	N=12	N=65	N=38	N=190	N=50	N=225
Diarrhea	0 (0.0%)	11 (16.9%)	3 (7.9%)	20 (10.5%)	3 (6.0%)	31 (13.8%)
Headache	1 (8.3%)	9 (13.8%)	4 (10.5%)	13 (6.8%)	5 (10.0%)	22 (9.8%)
Nausea	0 (0.0%)	3 (4.6%)	4 (10.5%)	7 (3.7%)	4 (8.0%)	12 (5.3%)
Abdominal Pain	1 (8.3%)	1 (1.5%)	1 (2.6%)	3 (1.6%)	2 (4.0%)	4 (1.8%)
Chromaturia	1 (8.3%)	9 (13.8%)	0 (0.0%)	0 (0.0%)	1 (2.0%)	9 (4.0%)
Rash	0 (0.0%)	2 (3.1%)	1 (2.6%)	2 (1.1%)	1 (2.0%)	4 (1.8%)
Dyspepsia	0 (0.0%)	1 (1.5%)	1 (2.6%)	3 (1.6%)	1 (2.0%)	4 (1.8%)
Vomiting	0 (0.0%)	1 (1.5%)	0 (0.0%)	6 (3.2%)	0 (0.0%)	7 (3.1%)
Oropharyngeal Pain	0 (0.0%)	3 (4.6%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	5 (2.2%)
Vulvovaginal Candidiasis	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (0.5%)	1 (2.0%)	1 (0.4%)

Figure 2: Simplified Schematic of Rifabutin Transit Highlighting the Two Sites of Pharmacokinetic Modeling: (1) Intragastric Rifabutin Concentrations and (2) Plasma Rifabutin Concentrations



- Figure 2 is a simplified representation of the path of orally administered rifabutin, which must **exit** the stomach **to be** absorbed **from** the small intestine, enters the plasma, and is then secreted **back** into the gastric lumen (site of infection). Intragastric antibiotic concentrations have been shown to be important to eradication success.[15]
- In a *post hoc* analysis of pooled Phase 3 clinical trial data, patient BMI had no statistically significant impact on eradication outcomes with RHB-105.[16] To explore a mechanism supporting these outcomes, PBPK modeling was used to assess intragastric rifabutin concentrations over time (Figure 3).
  - **Increasing BMI had minimal impact on maximal plasma concentration (C_{max}), a parameter known to influence** intragastric rifabutin concentration (data on file).
  - Increasing BMI had minimal impact on the intragastric rifabutin concentration time ≥MIC_{90} over 24 hours (approximately 22 hours of the day for normal, overweight, or obese subjects) (Figure 3).

Figure 3: Modeled Intragastric Rifabutin Concentrations Similar Regardless of Patient BMI

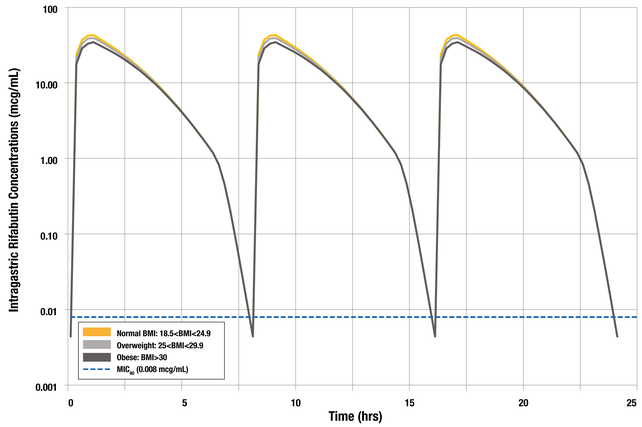


Figure 3 represents day 6 (steady state) of a 14 day therapy.

CONCLUSIONS

- **Low-dose rifabutin (50mg Q8H) triple therapy for 14 days produced high eradication rates and displayed favorable safety and tolerability across all subjects.**
- **Despite higher mean age and BMI, and a different racial and ethnic distribution in patients with vs. without diabetes, eradication rates with RHB-105 remained high supporting its use in populations with unmet needs.**
- **PBPK modeling supports minimal differences in intragastric rifabutin concentration time above MIC_{90} for *H. pylori* between patients with normal BMI or who are overweight or obese, supporting the minimal differences seen in eradication outcomes with RHB-105 between patients irrespective of BMI status.**
- **This study supports the efficacy and safety of low-dose rifabutin triple therapy as empiric first-line treatment for *H. pylori* infection in patients regardless of obesity or diabetic status.**

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