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Low-Dose Rifabutin Triple Therapy (RHB-105) Demonstrates High *Helicobacter pylori (H. pylori)* Eradication Rates

(Physiologically-Based Pharmacokinetic Modeling Supports Favorable Intragastric Rifabutin Concentrations for 50 mg Q8H Dosing vs 150 mg QD)

Poster Number
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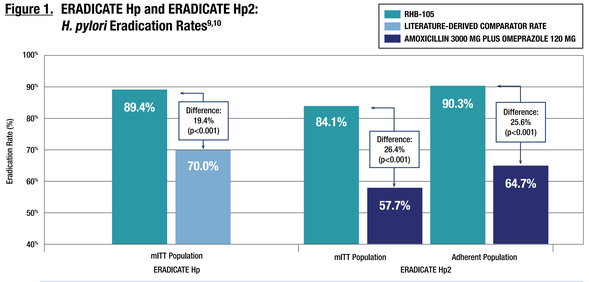
INTRODUCTION

- *H. pylori* is the strongest risk factor for peptic ulcer disease and non-cardia gastric cancer, and is also associated with dyspepsia, iron deficiency anemia, and vitamin B12 deficiency.[1,2,3,4]
- Achieving and maintaining adequate local gastric antibiotic concentrations (at or above the relevant MIC_{90} for *H. pylori)* are important for successful eradication.[5,6]
- Variable eradication rates (~70%) have been reported when generic rifabutin (typically 150 mg QD or BID) was used as a component of *H. pylori* treatment.[7,8]
- RHB-105 is formulated as an all-in-one combination of low-dose rifabutin 50 mg/amoxicillin 1000 mg/omeprazole 40 mg in 4 capsules to be given Q8H for 14 days, and was proven safe and efficacious in two Phase 3 trials (ERADICATE Hp [NCT01980095]; ERADICATE Hp2 [NCT03198507])[9,10,11]
- Eradication rates in Phase 3 trials (Figure 1): [9,10,11]
  - ERADICATE Hp: 89.4% for RHB-105 vs. 70% for literature-derived comparator rate (p<0.001) in the modified intent-to-treat patient population (mITT).[a,b,c]
  - ERADICATE Hp2: 84.1% for RHB-105 vs. 57.7% for amoxicillin 1000 mg and omeprazole 40 mg Q8H (p<0.001) for mITT analysis and 90.3%for confirmed adherent population vs 64% for the same comparator (p<0.001).

[a]Clarithromycin, amoxicillin, and proton pump inhibitor (omeprazole or lansoprazole). [b]Metronidazole, bismuth subcitrate potassium, and tetracycline. [c]Bismuth subcitrate potassium, metronidazole, tetracycline, and omeprazole.

Figure 1. ERADICATE Hp and ERADICATE Hp2: *H. pylori* Eradication Rates[9,10]



NOTE: - mITT, modified intent-to-treat
- Adherent Population, a subset of ITT patients who underwent ^{13}C UBT and demonstrated presence of any component of study drug at end of treatment (day 13)

- RHB-105 was generally well tolerated. Most frequently reported adverse events were diarrhea (10.1 – 14.3%), headache (7.5 – 15.6%), and nausea (3.9 – 4.8%).

DEMOGRAPHICS

ERADICATE Hp Study

- The study was conducted between November 25, 2013 and August 24, 2015, and enrolled 118 subjects. Key demographics included mean age (46 ± 10.18 years), female (62.7%), White (92.4%), and Black (7.6%); 80.5% were Hispanic/Latino.

ERADICATE Hp2 Study

- The study was conducted between July 2017 and November 2018, and enrolled 445 subjects. Key demographics included mean age (45.9 ± 12.77 years), female (62.2%), White (77.1%), and Black (19.3%); 60% were Hispanic/Latino.

OBJECTIVE

- To use physiologically-based pharmacokinetic (PBPK) modeling to compare intragastric rifabutin concentrations when administered as 50 mg Q8H (the dose for RHB-105) and 150 mg QD.

METHODS

- Plasma pharmacokinetic (PK) data for rifabutin were obtained from the RHB-105 Phase 1 clinical development program for rifabutin 50mg Q8H (as RHB-105) and rifabutin 150 mg QD (co-administered with omeprazole and amoxicillin Q8H) and two Phase 3 RHB-105 studies.[9,10]
- Key chemical and biological properties of the formulations were obtained from literature or calculated using quantitative structure-activity relationship models.
- The remaining parameters were estimated by fitting model predictions to a subset of the plasma PK data.
- The final parameterized PBPK model was validated against the plasma PK data not used for fitting.
- The final PBPK model was constructed to predict rifabutin concentrations in the gastric lumen that would be at or above the MIC_{90} for *H. pylori* during a 24-hour period at steady state based on rifabutin 50 mg Q8H and rifabutin 150 mg QD regimens.

RESULTS

Pharmacokinetic Properties of RHB-105 from PBPK Modeling

Intragastric Rifabutin Concentrations Based on Dosing Regimen (Table 1, Figure 2)

- Based on steady state simulations, time above MIC_{90} (mean ± SD) in the gastric lumen was approximately 3 times longer for rifabutin 50 mg Q8H than rifabutin 150 mg QD, irrespective of meal status:
  - Without meals: rifabutin 50 mg Q8H achieved 2.73-times longer time above MIC_{90} in the gastric lumen vs. rifabutin 150 mg QD.
  - With meals: rifabutin 50 mg Q8H achieved 2.68-times longer time above MIC_{90} in the gastric lumen vs. rifabutin 150 mg QD.

Plasma Rifabutin Concentrations Based on Dosing (Figure 3)

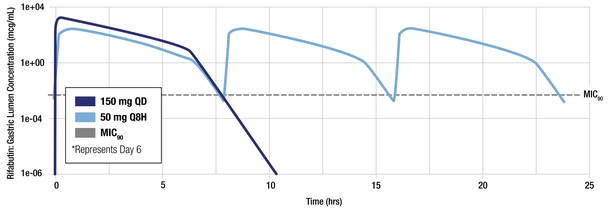
- Plasma rifabutin concentrations and AUC_{0-24} were similar between 50 mg Q8H and 150 mg QD.
- However, there were differences in peak plasma concentrations between dosing regimens. Rifabutin 150 mg QD yielded a single higher C_{max} (about 3-hrs after each dose) and the plasma concentrations declined rapidly.
  - The rapid decline of plasma rifabutin concentration with 150 mg QD is consistent with the rapid decline of the intragastric rifabutin concentration during a 24-hr period at steady state.
- In contrast, rifabutin 50 mg Q8H yielded three consistent C_{max} values (about 3-hrs after each dose) and the plasma concentrations declined steadily.
  - Consistent and sustained plasma rifabutin concentrations with 50 mg Q8H are similar to the increased time above MIC_{90} for intragastric rifabutin concentrations during a 24-hr period at steady state.
- Thus, rifabutin 50 mg Q8H provides optimal intragastric rifabutin concentrations compared with 150 mg QD.

Table 1. Predicted Intragastric Luminal Rifabutin Concentrations: Time Above MIC_{90} During a 24-hr Period at Steady State with 50 mg Q8H vs. 150 mg QD in Subjects without Meals and with Meals (Cumulative Time Above MIC_{90})*

REGIMENS PARAMETERS		Intragastric Rifabutin Concentration: Time Above MIC_{90}	
		WITHOUT MEALS	WITH MEALS
Rifabutin 50 mg Q8H	Mean (SD), hr	10.85 (4.69)	22.25 (1.08)
	% Day	45.21	92.71
Rifabutin 150 mg QD	Mean (SD), hr	3.98 (2.68)	8.29 (1.67)
	% Day	16.6	34.54
Ratio of Intragastric Time Above MIC_{90}: Rifabutin 50 mg Q8H/ Rifabutin 150 mg QD		2.73	2.68

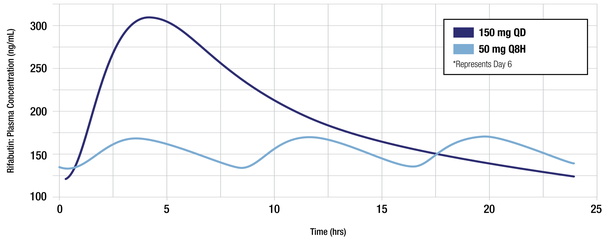
Note: SD, Standard Deviation *Represents Day 6

Figure 2: Predicted 24-hr Intragastric Rifabutin Concentrations at Steady State with 50 mg Q8H vs. 150 mg QD Over Time with Meals (Cumulative Time Above MIC_{90})*



NOTE: - Rifabutin 50 mg Q8H: time above MIC_{90} in the gastric lumen was 22.25 ± 1.08 hr; 92.71% of the day
- Rifabutin 150 mg QD: time above MIC_{90} in the gastric lumen was 8.29 ± 1.67 hr; 34.54% of the day
- MIC_{90} for *H. pylori*: 0.008 µg/mL

Figure 3. Predicted 24-hr Plasma Rifabutin Concentrations at Steady State with 50 mg Q8H vs. 150 mg QD in Subjects with Meals*



CONCLUSION

- Adequate intragastric antibiotic concentrations are imperative for eradication of *H. pylori*.
- Dosing rifabutin at 150 mg QD does not replicate the sustained intragastric concentrations predicted when dosing rifabutin at 50 mg Q8H.
- Low-dose rifabutin 50 mg Q8H (as in RHB-105) maintains intragastric concentrations at or above the MIC_{90} nearly 3-fold longer than 150 mg QD irrespective of fasting or fed conditions.
  - Approximately 93% of the day for RHB-105 vs. approximately 35% of the day for rifabutin 150 mg QD in the fed condition.
- This could explain the lower published eradication rates for QD dosing (~ 70%) than were seen in the clinical trials of RHB-105 with Q8H dosing (about 84% – 90%).
- There may be a link between sustained high intragastric rifabutin exposure and the high eradication rates seen with low-dose rifabutin 50 mg given Q8H (RHB-105).

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