# Modeling Gastric Luminal Rifabutin Concentrations: RHB-105 (Rifabutin 50 mg Q8H) Provides More Favorable Exposure for *H. pylori* Eradication than Generic Rifabutin 150 mg BID or 300 mg QD

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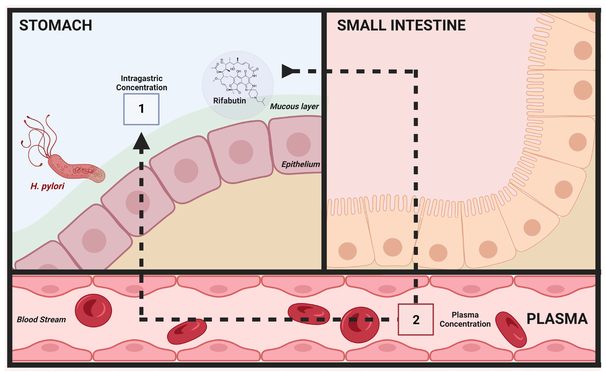
## BACKGROUND

- *Helicobacter pylori* (*H. pylori*) is the strongest risk factor for peptic ulcer disease and non-cardia gastric cancer, and has been linked to dyspepsia, iron deficiency anemia, and vitamin B12 deficiency.[1-4]
- Topical gastric antibiotic exposure is important for successful eradication of *H. pylori*.[5,6]
- Variable success has been reported with rifabutin when used off-label (typically dosed at 150 mg QD, 150 mg BID, or 300 mg QD) as a component of treatment.[7]
- In two phase 3 trials in treatment-naïve subjects, low dose rifabutin (50 mg Q8H) triple therapy, RHB-105, (Talicia®), (50 mg rifabutin, 1000 mg amoxicillin, 40 mg omeprazole Q8H for 14 days) demonstrated eradication rates of 89.4% (NCT03198507; modified intention-to-treat) and 83.8% ITT (NCT01980095; 90.3% in confirmed adherent subjects).[8,9]
- Previous work has demonstrated that RHB-105 (50 mg rifabutin Q8H) achieved intragastric rifabutin concentrations ≥$MIC_{90}$ for ~93% of the day compared to generic substitution (150 mg rifabutin QD) which only achieved rifabutin concentrations ≥$MIC_{90}$ for ~35% of the day.[10]
- Our aim was to use physiologically based pharmacokinetic (PBPK) modeling to assess how generic rifabutin dosing (150 mg BID and 300 mg QD) affects intragastric rifabutin concentrations and any potential impact on *H. pylori* eradication.

## METHODS

- Plasma pharmacokinetic (PK) data for rifabutin following 50 mg Q8H or 150 mg QD triple therapy were obtained from literature sources and clinical studies.
- Key chemical and biological properties for the rifabutin were obtained from literature sources 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 validated PBPK model was then used to simulate 150 mg BID, 300 mg QD, or 50 mg Q8H at steady state and assess both plasma and intragastric rifabutin concentrations (Figure 1).
- Simulated concentrations were used to predict time above the rifabutin $MIC_{90}$ for *H. pylori* in the gastric lumen.
- Since RHB-105 includes omeprazole, the impact of intragastric pH on rifabutin absorption was explored along with the impact of rifabutin autoinduction on time above $MIC_{90}$.

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

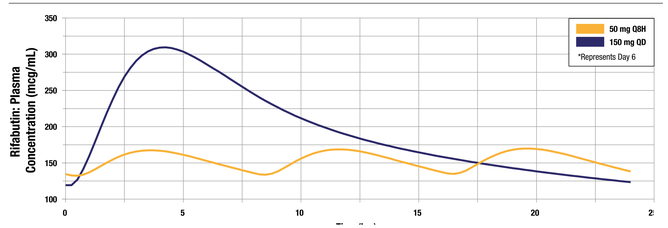



Rifabutin given orally must exit the stomach into the small intestine where it is absorbed and enters the blood stream (box 1; intragastric concentration) and is then re-secreted into the gastric lumen (box 2; plasma concentration).

## RESULTS

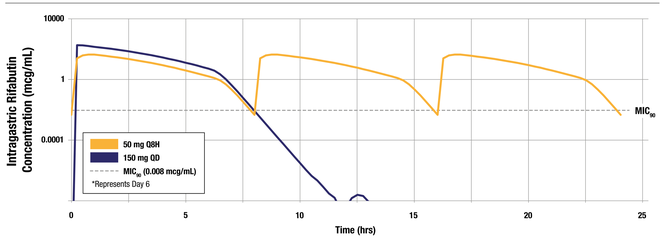
- Plasma rifabutin concentrations comparing 50 mg Q8H vs. 150 mg QD were modeled with equivalent doses of omeprazole in each regimen (Figure 2).
- Subsequently, time when intragastric concentration was ≥$MIC_{90}$ were modeled (Figure 3); time ≥$MIC_{90}$ was 22.25±1.08 hrs (93% of the day) for 50 mg Q8H vs. 8.29±1.67 hrs (35% of the day) for 150 mg QD (Table 1).

**Figure 2: Plasma Rifabutin Concentrations Comparing 50 mg Q8H (RHB-105) and 150 mg QD Over a 24-hour Period**




Steady state mean plasma rifabutin concentrations over 24 hours modeled on day 6 of a 14-day regimen comparing rifabutin 50 mg Q8H (orange) and rifabutin 150 mg QD (blue).

**Figure 3: Intragastric Rifabutin Concentrations Comparing 50 mg Q8H (RHB-105) and 150 mg QD Over a 24-hour Period**




Steady state mean local intragastric rifabutin concentrations over 24 hours modeled on day 6 of a 14-day regimen comparing 50 mg Q8H (orange) and 150 mg QD (blue).

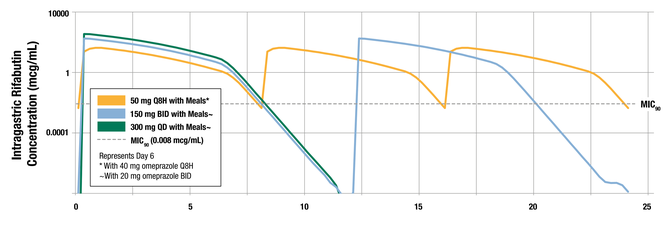
**Table 1: Time Intragastric Rifabutin Concentration ≥$MIC_{90}$ with 50 mg Q8H vs. 150 mg QD**

| Regimens Parameters | | Intragastric Rifabutin Concentrations: 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 Time Intragastric Rifabutin Concentration above $MIC_{90}$: 50 mg Q8H / 150 mg QD | | 2.73 | 2.68 |

Note: SD, Standard Deviation; Represents Day 6

- Other generically dosed regimens were assessed and showed intragastric concentrations ≥$MIC_{90}$ of 16.32±2.25 hrs for rifabutin 150 mg BID (68% of day), and 8.51±1.86 hrs (35% of the day) for 300 mg QD (Figure 4 and 5; Table 2). **Model reflects commonly used generic regimens composed of differing omperazole and rifabutin concentrations.**
- Although both generic regimens contain twice the total daily dose of rifabutin than RHB-105, both failed to achieve the prolonged time intragastric rifabutin concentration was ≥$MIC_{90}$ (22.25±1.08 hrs; 93% of the day) seen with RHB-105 (50 mg Q8H).

**Figure 4: Intragastric Rifabutin Concentrations Comparing 50 mg Q8H (RHB-105), 150 mg BID, and 300 mg QD Over a 24-hour Period**




Steady state mean intragastric rifabutin concentrations over 24 hours modeled on day 6 of a 14-day regimen comparing 50 mg Q8H (orange), 150 mg BID (blue), and 300 mg QD (green).

**Figure 5. Proportion of Day (%) Intragastric Rifabutin Concentration is ≥$MIC_{90}$ Comparing 50 mg Q8H (RHB-105), 150 mg BID, and 300 mg QD**

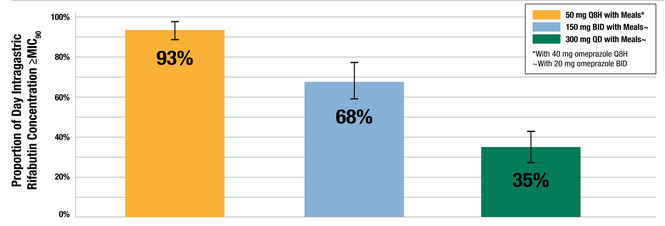



**Table 2: Time Intragastric Rifabutin Concentration ≥$MIC_{90}$ with 50 mg Q8H vs. 150 mg BID or 300 mg QD**

| Regimens Parameters | | Intragastric Rifabutin Concentrations: Time above $MIC_{90}$ | |
|---|---|---|---|
| | | Without Meals | With Meals |
| Rifabutin 50 mg Q8H* | Mean (SD), hr | 10.85 (4.69) | 22.25 (1.08) |
| | % Day | 42.21 | 92.71 |
| Rifabutin 150 mg BID** | Mean (SD), hr | 7.24 (4.44) | 16.32 (2.25) |
| | % Day | 30.16 | 68.0 |
| Rifabutin 300 mg QD** | Mean (SD), hr | 3.96 (2.84) | 8.51 (1.86) |
| | % Day | 16.50 | 35.46 |

Note: SD, Standard Deviation
*40 mg omeprazole, given Q8H
**20 mg omeprazole, given BIDz

## CONCLUSIONS

- **Key determinants of intragastric rifabutin concentrations include gastrointestinal transit time, time required for systemic absorption, and dosing frequency.**
- **Rifabutin 50 mg Q8H (RHB-105) maintains intragastric rifabutin concentrations above its $MIC_{90}$ for 3.12-fold longer than 150 mg QD.**
- **Here, we show that two other generically substituted rifabutin regimens (150 mg BID and 300 mg QD) fail to achieve and maintain intragastric rifabutin concentrations seen with rifabutin 50 mg Q8H (RHB-105) (Table 2) despite comprising twice the total daily dose of rifabutin.**
  - **50 mg rifabutin Q8H 22.25±1.08 hrs (93% of the day).**
  - **150 mg rifabutin BID 16.32±2.25 hrs (68% of the day).**
  - **300 mg rifabutin QD 8.51±1.86 hrs (35% of the day).**
- **With 150 mg QD, 150 mg BID or 300 mg QD dosing, the shorter duration of time with intragastric rifabutin concentration above its $MIC_{90}$ for *H. pylori* could explain the lower eradication rates than seen with RHB-105.**
- **Moreover, generically substitued 150 mg BID and 300 mg QD rifabutin regimens fail to achieve intragastric concentrations seen with RHB-105, while doubling the daily dose of rifabutin, potentially exposing patients to serious dose-related adverse events.**

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