Comparative Pharmacokinetics of Rifaximin 550 mg and 200 mg Oral Tablets: One Is Not Like the Other

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BACKGROUND

- Rifaximin (Xifaxan®, Salix Pharmaceuticals) is available as 2 different formulations (200-mg and 550-mg oral tablets) and dosages are dependent on the condition being treated[1]
  - Rifaximin 200 mg three times daily (TID; 600 mg/day) for 3 days is indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in patients aged ≥12 years
  - Rifaximin 550 mg TID (1650 mg/d) for 14 days is indicated for the treatment of irritable bowel syndrome with diarrhea in adults (patients who experience recurrence can be retreated for up to 2 times [same regimen])
  - Rifaximin 550 mg two times daily (1100 mg/d) is indicated for reduction in risk of overt hepatic encephalopathy recurrence in adults
- Given the availability of 2 rifaximin formulations (200 mg and 550 mg), questions have arisen regarding the interchangeability of tablets across various disease state dosing regimens

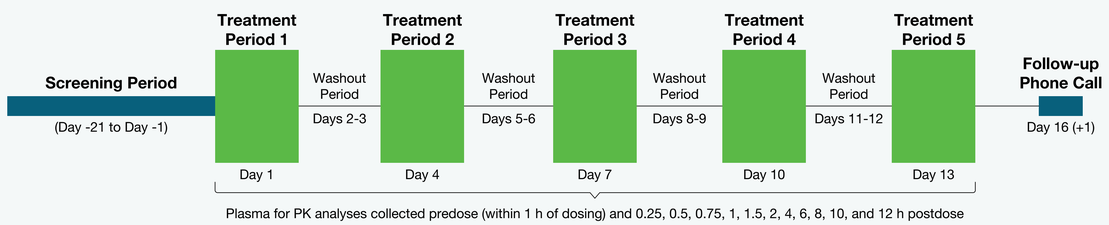
AIM

- To assess the pharmacokinetics (PK) and relative bioavailability of rifaximin 550-mg tablets and rifaximin 200-mg tablets (200, 400, and 600 mg)
- To determine whether rifaximin 200-mg tablets exhibit dose-proportional PK over a dose range of 200 to 600 mg

METHODS

- Phase 1, open-label, 5-treatment crossover PK study (**Figure 1**) in healthy volunteers aged 18 to 45 years with body mass index (BMI) between 18 and 32 kg/m^2
  - Study was approved by an institutional review board, and all individuals provided written informed consent
- Participants were randomly assigned to a prespecified dosing sequence to receive the following treatments during the trial (**Figure 1**; 72-hour washout period between each treatment)
  - Rifaximin 200 mg (one 200-mg tablet)
  - Rifaximin 400 mg (two 200-mg tablets)
  - Rifaximin 600 mg (three 200-mg tablets)
  - Rifaximin 550 mg (one 550-mg tablet)
  - Formulation not commercially available (data not included herein)

Figure 1. Study Design*



*A rifaximin formulation (not commercially available) was evaluated as an arm in the trial (ie, 5th treatment arm); data for this formulation are not reported herein.
PK = pharmacokinetic.

- Plasma samples for PK analyses were collected prior to dosing and periodically through 12 hours postdose during each treatment period (**Figure 1**)
- Geometric mean ratios and 90% CI were calculated to determine dose proportionality
  - Doses were considered proportional if the 90% CI of the dose-normalized PK parameters after administration of rifaximin 400 mg (test) and rifaximin 600 mg (test) were within 80% to 125% (ie, lower and upper boundaries, respectively) compared with rifaximin 200 mg (reference)

RESULTS

- 30 healthy volunteers were included in the trial
  - 66.7% were male, the median age was 35.5 y (range, 20-45 y), 56.7% were black, and the median BMI was 28.1 kg/m^2 (range, 22.6-32.1 kg/m^2)
- Rifaximin C_{max} following oral administration was relatively low across all 4 doses (**Table**)
  - Apparent oral clearance (CL/F) was relatively high due to the low oral bioavailability of rifaximin

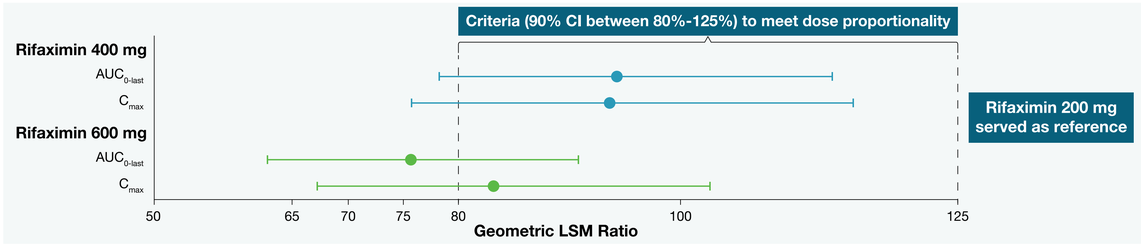
Table. Pharmacokinetic Results (N=30)

Parameter	Rifaximin 200 mg	Rifaximin 400 mg	Rifaximin 600 mg	Rifaximin 550 mg
C_{max}, ng/mL, mean (SD)	0.94 (0.58)	1.83 (1.13)	2.50 (1.76)	0.91 (0.95)
T_{max}, h, median	1.43	0.93	0.97	0.87
$AUC_{0\text{-last}}$, h*ng/mL, mean (SD)	3.23 (1.55)	6.23 (3.04)	7.76 (4.69)	3.65 (3.66)
$t_{1/2}$, h, median	6.17*	5.29‡	6.06¶	6.76**
CL/F, L/h, mean (SD)	45,700 (16,500)†	66,600 (45,100)§	76,000 (45,300)#	142,000 (89,900)**

*n=22. †n=20. ‡n=23. §n=21. ¶n=26. #n=25. **n=17.
$AUC_{0\text{-last}}$ = concentration-time curve from time 0 to last measurement; CL/F = apparent oral clearance; C_{max} = maximum concentration; $t_{1/2}$ = terminal half-life; T_{max} = time to maximum observed serum concentration.

- For rifaximin 550 mg, both C_{max}, T_{max}, and $AUC_{0\text{-last}}$ were lower than dosages using rifaximin 200-mg tablets (C_{max} and T_{max} lower vs 200, 400, and 600 mg; $AUC_{0\text{-last}}$ lower vs 400 and 600 mg) and CL/F was higher with rifaximin 550 mg (**Table**)
- Likewise, dose-normalized proportionality analyses indicated that the 200 mg, 400 mg, and 600 mg rifaximin dosages were not proportional based on 90% CI intervals (**Figure 2**)

Figure 2. Dose Proportionality Analysis



$AUC_{0\text{-last}}$ = concentration-time curve from time 0 to last measurement; C_{max} = maximum concentration; LSM = least-squares mean.

CONCLUSIONS

- PK data showed rifaximin was not dose proportional over the 200- to 600-mg range, suggesting that 200-mg tablet dosages are not interchangeable with the 550-mg tablet
- Increased exposure with intervals of 200-mg tablets may have implications for drug–drug interactions and potential for adverse drug reactions
  - For example, in patients with hepatic impairment, who are already susceptible to increased rifaximin exposure[1]
- Therefore, 200-mg rifaximin tablets should not be substituted for 550-mg rifaximin tablets

Reference: 1. Xifaxan® (rifaximin) tablets, for oral use [package insert]. Salix Pharmaceuticals; 2022.

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