

## INTRODUCTION

**Background:** The prodrug TR-701 is a novel oxazolidinone antibiotic that is rapidly converted in vivo by blood and tissue phosphatases, to the microbiologically-active molecule torezolid (TR-700). TR-700 is active against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and other drug-resistant gram-positive organisms.

**Methods:** A randomized, open label, 2-period, 2-treatment crossover, single oral dose study was performed to evaluate the safety, tolerability, and effect of food on the pharmacokinetics (PK) of TR-701/TR-700 in 12 healthy adult subjects. Subjects received a single oral dose of 600 mg TR-701 after a 10-hr fast or after eating a high-fat breakfast preceded by a 10-hr fast.

**Results:** Median TR-700 T<sub>max</sub> values increased from 2.0 hours in the fasted state to 8.0 hours in the fed state, and mean C<sub>max</sub> values decreased 26% in fed (4,786 ng/mL) as compared to the fasted (6,502 ng/mL) state. However, AUC<sub>0-inf</sub> values of 81,992 ng·hr/mL in the fasted state and 85,043 ng·hr/mL in the fed state indicate that the extent of TR-700 exposure is not significantly affected by food. TR-701 was well-tolerated and no significant clinical or laboratory abnormalities were reported.

**Conclusions:** Administration of TR-701 after a high-fat meal increased T<sub>max</sub> and decreased C<sub>max</sub>, but did not affect the extent of TR-700 exposure. These results support dosing of oral TR-701 irrespective of the timing of meals.

## STUDY DESIGN

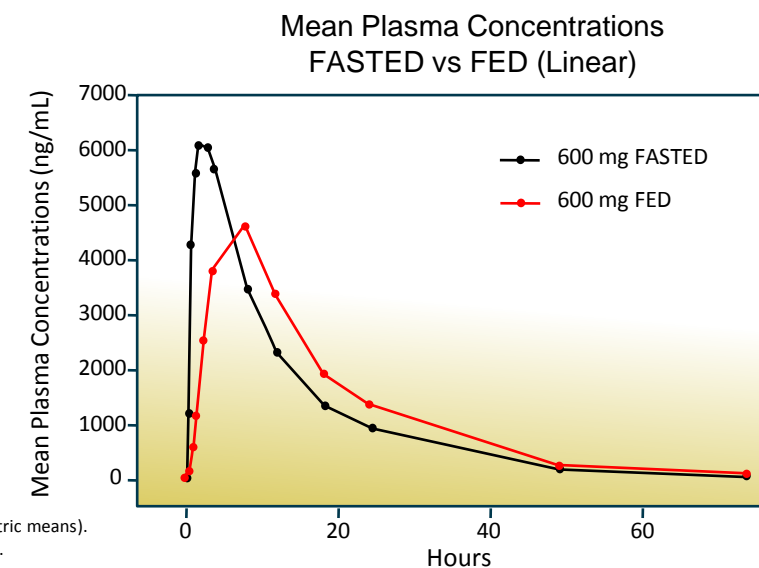
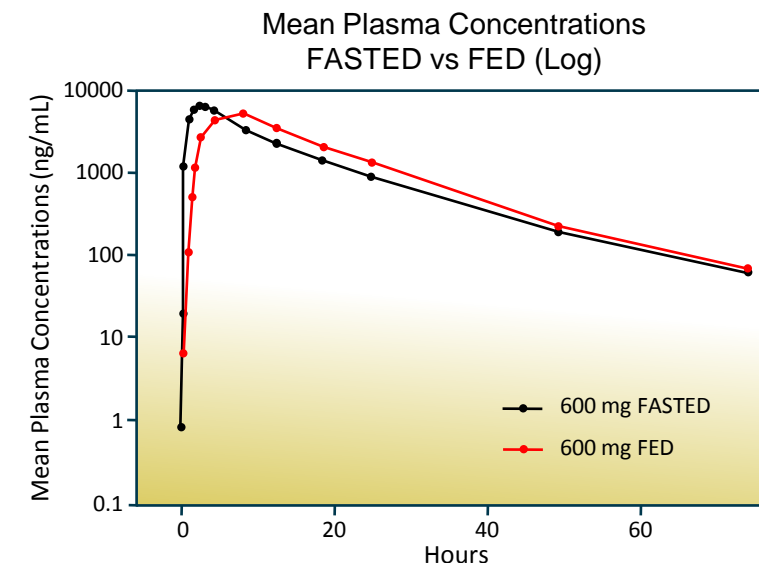
This was a Phase 1, open-label, randomized, 2-sequence, 2-treatment, 2-period, crossover design study investigating the PK of TR-701 and TR-700 and the effects of a high-fat meal following administration of TR-701 in 12 healthy male (n=8) and female (n=4) volunteers. Subjects were confined to the Covance Phase 1 Clinical Research Unit (CRU) in San Diego, CA from approximately 24 hrs predose to approximately 72 hrs postdose. Subjects received a single 600 mg oral dose of TR-701 (equivalent to 450 mg TR-700) after a 10-hr fast or after eating a high-fat breakfast preceded by a 10-hr fast.

## RESULTS

| TR-700 Parameter (units)               | FED Mean (SD)   | FASTED Mean (SD) |
|--|-----------------|------------------|
| N                                      | 11              | 11               |
| C <sub>max</sub> (ng/mL)               | 4786 (1117)     | 6502 (1362)      |
| T <sub>max</sub> (hr) [Median (range)] | 8.00 (4.0-12.0) | 2.00 (1.5-3.0)   |
| AUC <sub>0-24</sub> (ng·hr/mL)         | 62656 (17471)   | 65397 (15546)    |
| AUC <sub>0-t</sub> (ng·hr/mL)          | 84139 (27141)   | 81176 (22575)    |
| AUC <sub>0-inf</sub> (ng·hr/mL)        | 85043 (27690)   | 81992 (23111)    |
| t <sub>1/2</sub> (hr)                  | 10.4 (0.88)     | 10.9 (0.90)      |

| TR-700 Parameter (units)        | Least Squares Means <sup>a</sup> |       |    |        | 90% Confidence Interval <sup>d</sup>            |
|---------------------------------|----------------------------------|-------|----|--------|---|
|                                 | N <sup>b</sup>                   | FED   | N  | FASTED |   |
| C <sub>max</sub> (ng/mL)        | 11                               | 4746  | 11 | 6438   | FED/FASTED (%) <sup>c</sup> 73.7 (67.81, 80.12) |
| AUC <sub>0-t</sub> (ng·hr/mL)   | 11                               | 81026 | 11 | 79189  | 102 (98.09, 106.74)                             |
| AUC <sub>0-inf</sub> (ng·hr/mL) | 11                               | 81822 | 11 | 79912  | 102 (98.18, 106.79)                             |

a. Least squares mean from ANOVA. Natural log (ln) transformed parameter means transformed back to the linear scale (i.e., geometric means).  
b. TR-700 concentrations for one subject were below the limit of quantification in both periods and were not included in the analysis.  
c. Ratio of parameter means (expressed as a percent). Natural log transformed ratios transformed back to linear scale.  
d. 90% confidence interval for ratio of parameter means (expressed as a percent). Natural log transformed confidence limits transformed back to scale.



## SUMMARY AND CONCLUSIONS

- Following oral administration in the fed and fasted states, TR-701 was rapidly and extensively converted to TR-700. TR-701 was detected at just above the LLQ in two subjects at one timepoint each (at 6.76 and 5.38 ng/mL).
- After single oral administration of 600 mg TR-701, a 6 hr delay in TR-700 median T<sub>max</sub> was observed in the fed compared to the fasted state.
- In the fed state, the mean TR-700 C<sub>max</sub> was significantly (26%) lower than that observed in the fasted state.
- Mean TR-700 AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> values after administration of TR-701 in the fed state were similar (within 2%) to the corresponding values after administration in the fasted state.
- Since AUC/MIC is the main PK/PD driver of efficacy for oxazolidinones the present study provides evidence that the TR-701 dosing regimen will not need to be modified whether administered in fasting or fed conditions.
- Based on AEs, clinical laboratory evaluations, 12-lead ECGs, vital signs measurements, and physical examinations, single doses of 600 mg TR-701 administered in the fed or fasted state were well tolerated in this group of healthy males and females.