# A Phase I Study of Intravenously Administered Tedizolid Phosphate in Subjects with Advanced Renal Impairment

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## Abstract

**Purpose**
The objective of the study was to characterize the safety of tedizolid phosphate (TR-701 FA) and the pharmacokinetics of tedizolid (TR-700), its microbiologically active moiety, in subjects with advanced renal impairment (eGFR <30 mL/min/ 1.73m$^2$, not on dialysis) compared with matched subjects with normal renal function (eGFR ≥80.0 mL/min/1.73 m$^2$).

**Methods**
Eight subjects with advanced renal impairment and 8 matched controls (by age, gender, and body mass index) received a single intravenous infusion of 200 mg tedizolid phosphate. Serial plasma PK samples were collected from pre-dose through 72 hours post-dose. Plasma samples were analyzed for tedizolid and the following pharmacokinetic parameters were calculated: $C_{max}$, $t_{max}$, $AUC_{0-\infty}$, $AUC_{0-t}$, $\lambda_z$, $CL_{sys}$, and plasma $t_{1/2}$.

**Results**
Baseline eGFR ranged from 7 to 28 mL/min/1.73m$^2$ (including 3 subjects with eGFR <15 mL/min/1.73m$^2$). The pharmacokinetics of tedizolid were essentially unchanged in subjects with advanced renal impairment relative to a matched control group. Approximately 8% lower AUC and nearly identical $C_{max}$ values were observed in renal impaired subjects relative to matched controls, and other pharmacokinetic parameters were also similar between groups.

**Conclusions**
The tedizolid plasma pharmacokinetic results from this study provide support that no dose adjustment is needed in subjects with advanced renal impairment.

This is an Encore Presentation. These data were originally presented at the ICAAC meeting September 9-12, 2012, San Francisco, CA.

## Introduction

Tedizolid phosphate (TR-701 Free Acid [FA]) is a novel oxazolidinone prodrug antibiotic of the active moiety tedizolid (TR-700), currently being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI). Tedizolid phosphate 200 mg QD has been selected as the therapeutic regimen for ABSSSI in adults. The objective of the study was to characterize the safety and pharmacokinetics of tedizolid in subjects with advanced renal impairment compared with matched subjects with normal renal function.

## Study Design

An open-label, single-dose study was performed in subjects with advanced renal impairment and in subjects with normal renal function. Subjects were recruited based on their estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease Study, 4-variable formula (MDRD4). Subjects with renal impairment not receiving hemodialysis (eGFR <30 mL/min/1.73m$^2$) were assigned to the Severe Renal Impairment Group, and control subjects with normal renal function (eGFR ≥80.0 mL/min/1.73 m$^2$) were matched to the Severe Renal Impairment Group by age (±10 years), sex, and body mass index (±15%).

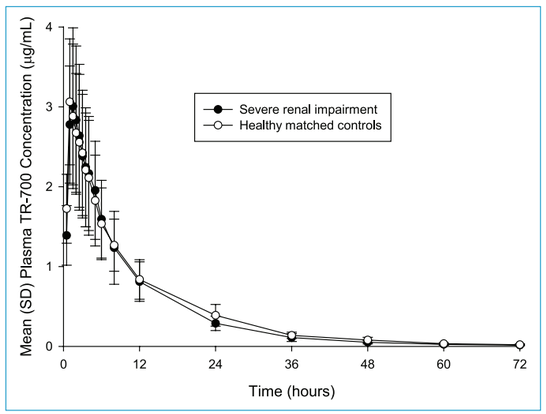
Eight subjects in the Severe Renal Impairment Group and 8 subjects in the Control Group received a single intravenous infusion of 200 mg tedizolid phosphate on Day 1. Serial plasma PK samples were collected from pre-dose through 72 hours post-dose. Plasma samples were analyzed for tedizolid and the following PK parameters were calculated: $C_{max}$, $t_{max}$, $AUC_{0-\infty}$, $AUC_{0-t}$, and $t_{1/2}$. Clinical and laboratory safety evaluations were performed pre- and post-dose.

## Demographics

**Table 1. Baseline Demographics**

| Demographics | Statistics | Severe Renal Impairment | Control Group |
|---|---|---|---|
| Age (years) | Mean (range) | 61 (40-74) | 58 (44-68) |
| Sex | Male (%) | 4 (50) | 4 (50) |
| | Female (%) | 4 (50) | 4 (50) |
| Ethnicity | Non Hispanic (%) | 6 (75) | 7 (87.5) |
| | Hispanic | 2 (25) | 1 (12.5) |
| Race | White (%) | 4 (50) | 7 (87.5) |
| | Black (%) | 3 (37.5) | 1 (12.5) |
| | American Indian/ Alaska Native (%) | 1 (12.5) | 0 (0) |
| BMI (kg/m$^2$) | Mean (SD) | 29.4 (5.4) | 28.7 (3.9) |
| eGFR (mL/min/1.73m$^2$) | Mean (SD) | 18.3 (6.5) | 92.6 (9.1) |

## Tedizolid Plasma Concentration-Time Profiles




## Pharmacokinetic Results

**Table 2. Tedizolid Mean (SD) Plasma Pharmacokinetic Parameters**

| | Severe Renal Impairment | Control Group |
|---|---|---|
| $C_{max}$ (µg/mL) | (0.85) | (0.75) |
| $AUC_{0-t}$ (µg·hr/mL) | 29.69 | 32.02 |
| | (8.93) | (9.33) |
| $AUC_{0-\infty}$ (µg·hr/mL) | 29.99 | 32.43 |
| | (8.97) | (9.53) |
| $T_{max}$ (hr) [median (min-max)] | 1.26 | 1.0 |
| | (1.00-2.00) | (1.00-2.50) |
| $t_{1/2}$ (hr) | 12.8 | 12.3 |
| | (2.28) | (2.04) |

**Table 3. Statistical Analysis of Pharmacokinetic Data: Intravenous Tedizolid Phosphate in Severe Renal Impairment**

| Parameter (Units) | Geometric Mean (GM) | | GM Ratio (Renal Impaired/ Control) | 90% Confidence Interval | |
|---|---|---|---|---|---|
| | Severe Renal Impairment | Control | | Lower | Upper |
| $C_{max}$ (µg/mL) | 3.01 | 3.02 | 0.99 | 0.78 | 1.27 |
| $AUC_{0-t}$ (µg·hr/mL) | 28.4 | 30.7 | 0.93 | 0.70 | 1.23 |
| $AUC_{0-\infty}$ (µg·hr/mL) | 28.7 | 31.1 | 0.93 | 0.70 | 1.23 |

## Results

Pharmacokinetics of tedizolid were essentially unchanged in subjects with advanced renal impairment relative to a matched control group. Approximately 8% lower AUC and nearly identical $C_{max}$ values were observed in renal impaired subjects relative to matched controls. Other pharmacokinetic parameters were also similar between groups. These results were as expected given tedizolid is primarily eliminated hepatically, highly permeable, not extensively metabolized, and moderately protein bound.

Three adverse events were related to tedizolid phosphate in renally impaired subjects: nausea, vomiting, and head-ache. There were no discontinuations due to an adverse event. One SAE of an epidural lumbar abscess, not related to study drug, was reported in a control subject.

## Conclusions

The tedizolid plasma pharmacokinetic results from this study support the contention that no dose adjustment is needed in tedizolid phosphate treated subjects with severe renal impairment. tedizolid phosphate was well-tolerated in renally impaired subjects.

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