# Pharmacokinetics of Tedizolid Following Oral Administration: Single and Multiple Dose, Effect of Food, and Comparison of Two Solid Forms of the Prodrug

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**Objectives** The single- and multiple-dose pharmacokinetics (PK) of tedizolid were examined after oral administration of tedizolid phosphate disodium (TPD), including the effect of food on PK. The relative bioavailability of TPD to the free acid tedizolid phosphate was determined to bridge the results of these and other studies to the solid form of the prodrug selected for further development.

**Design** Randomized placebo-controlled, double-blind single- and multiple-ascending dose studies and randomized open-label, crossover food effect and relative bioavailability studies.

**Setting** Clinical Research Units.

**Participants** Healthy subjects.

**Intervention** Study TR701-101 enrolled 40 subjects in single-ascending dose (200–1200 mg TPD or placebo) and 40 subjects in 21-day multiple-ascending dose (200, 300, or 400 mg TPD once/day; 600 mg linezolid twice/day; or placebo) arms. Study TR701-103 was a food-effect study in 12 subjects administered 600 mg TPD. Study TR701-108 was a relative bioavailability study in 12 subjects administered 150-mg tedizolid equivalents as TPD or tedizolid phosphate.

**Measurements and Main Results** Plasma concentrations of the prodrug tedizolid phosphate, its active moiety tedizolid, and/or linezolid were collected. After administration of 200 to 600 mg TPD, tedizolid values increased approximately dose proportionally in area under the concentration-time curve (AUC) and maximum plasma concentration ($C_{max}$). Tedizolid half-life values were approximately 2-fold greater compared with linezolid. TPD administration with food delayed tedizolid absorption and reduced $C_{max}$ relative to the fasted state but did not alter AUC. Minimal accumulation was predicted and observed for tedizolid, whereas observed accumulation of linezolid exceeded predictions based on single-dose PK. Comparable PK of tedizolid was observed following oral administration of either TPD or tedizolid phosphate. In the multiple-ascending dose study, 3 of 24 tedizolid subjects were withdrawn under prespecified stopping rules (one each of elevated alanine

Primary Funding Source: Trius Therapeutics, Inc.

This work was supported by Trius Therapeutics, Inc. All authors are employees and shareholders of Trius Therapeutics, Inc., or consultants of Trius Therapeutics, Inc.

Data from study TR701-101 were previously presented at the 19th and 20th European Congress of Clinical Microbiology and Infectious Diseases (2009 and 2010), the 48th Interscience Conference on Antimicrobial Agents and Chemotherapy (2008), and the 2012 American College of Clinical Pharmacy Annual Meeting (encore presentation). Data from study TR701-103 were previously presented at the 19th European Congress of Clinical Microbiology and Infectious Diseases (2009). Trial registration: www.clinicaltrials.gov, NCT00671814, NCT00671359, and NCT00876655.

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aminotransferase, low reticulocyte count, or low white blood cell count), as was 1 of 8 linezolid subjects (low reticulocyte count).

Conclusions Overall, tedizolid has a favorable PK profile, a half-life that supports once daily administration, and no nonlinearities at steady state. Tedizolid phosphate can be administered without regard to food.

Key Words tedizolid phosphate disodium, tedizolid phosphate free acid, TR-700, TR-701, TR-701 FA, pharmacokinetics, food effect, relative bioavailability.

**(Pharmacotherapy 2014;34(3):240–250) doi: 10.1002/phar.1337**

Acute bacterial skin and skin structure infections (ABSSSI), such as cellulitis, major abscesses, and wound infections, are often caused by *Staphylococcus aureus* (*S. aureus*) and *Streptococcus* spp.[1] Community-acquired methicillin-resistant *S. aureus* (MRSA) is of growing clinical concern and often presents as skin and skin structure infections.[2, 3] In cases where adequate coverage requires treatment with the same agent intravenously and orally, the only current option is linezolid.[4, 5] Because early differentiation between MRSA and methicillin-susceptible *S. aureus* (MSSA) skin infections is not reliable[6] and many antibiotics are ineffective against some strains of MRSA,[7–9] oral linezolid use has increased, contributing to the development of linezolid-resistant strains of *Staphylococcus* and *Enterococcus* sp.[10–13] Although still infrequent, resistance to linezolid is likely to increase over time, warranting the development of new antimicrobial agents effective against drug-resistant strains.

Tedizolid phosphate (previously known as torezolid phosphate) is a novel oxazolidinone prodrug antibiotic. Two solid forms of the prodrug have been used in clinical and nonclinical testing: tedizolid phosphate disodium (TPD, TR-701) used in early development studies and the free acid tedizolid phosphate (TR-701 FA) selected for its relative ease of manufacture. Both forms yield tedizolid phosphate in solution, which is rapidly converted in vivo by phosphatases to the microbiologically active moiety tedizolid (TR-700).

Compared with linezolid, tedizolid has greater potency against most MSSA and MRSA strains, including those resistant to linezolid, as well as vancomycin-resistant enterococci.[14–18] Spontaneous resistance rates to tedizolid in *S. aureus* are low ($1-2 \times 10^{-10}$ after serial passage), and tedizolid retains a 4-fold or greater potency advantage over linezolid in mutants selected during serial passage in tedizolid or linezolid.[19] Tedizolid phosphate has equivalent or greater activity relative to linezolid in murine staphylococcal and pneumococcal infection models including immunocompetent and neutropenic mice.[20–24] In humans, after oral administration of tedizolid phosphate, tedizolid is highly available in plasma, interstitial fluids of muscle and adipose tissue, and epithelial lining fluid and alveolar macrophages in the lung.[25, 26] Tedizolid, which is the only circulating metabolite of tedizolid phosphate, does not induce or inhibit CYP450 isozymes (unpublished results), and it is primarily excreted in feces as a sulfate conjugate.[27] Tedizolid phosphate demonstrated clinical and microbiological efficacy with 200-mg once/day dosing and a short course of therapy in patients with ABSSSI and is currently in clinical development for the treatment of ABSSSI.[28–30]

Pharmacokinetic data from three phase I studies conducted in healthy adults are presented here. The pharmacokinetics (PK) of single and multiple doses of TPD administered for up to 21 days were evaluated in Study TR701-101. In Study TR701-103, the effect of food on tedizolid PK was evaluated following a single oral dose of TPD. Study TR701-108 compared the PK of tedizolid following an oral dose of 200 mg of TPD with 182 mg of tedizolid phosphate, both containing 150-mg tedizolid equivalents.

## Materials and Methods

### Study Drugs

Tedizolid phosphate was supplied and manufactured by Pharmatek Laboratories, Inc. (San Diego, CA) as two different immediate-release formulations for oral administration (50- or 200-mg disodium salt capsules and 182-mg free acid powder in capsules). Placebo capsules were also provided by Pharmatek Laboratories. Linezolid (Zyvox, Pfizer, Inc.) was obtained from the University of Wisconsin Health Pharmacy Services (Madison, WI). Study drugs were stored according to the manufacturers' instructions.

### Study Designs

Study TR701-101 was a two-part, nine-cohort, double-blind phase I study conducted at a single

site in the United States (Covance Clinical Research Unit, Madison, WI). The study evaluated the safety, tolerability, and PK of tedizolid phosphate following oral administration in fasted healthy adults.

The single-ascending dose arm of the study consisted of five double-blind cohorts; subjects received 200, 400, 600, 800, or 1200 mg of TPD (six subjects per dose group) or placebo (two subjects per group). Subjects fasted for 10 hours or longer prior to and 4 hours following administration of the study drug.

The multiple-ascending dose arm consisted of three double-blind cohorts in which subjects received 21 days of TPD (200, 300, 400 mg once/day, eight subjects per dose cohort) or placebo (two per cohort) and one single-blind cohort in which eight subjects received 600 mg linezolid twice/day and two received placebo. Subjects fasted for at least 8 hours before administration of the morning dose, 2 hours prior to the evening dose, and 1 hour after each dose. On days 1, 15, and 21, administration of the morning dose was preceded by a 10-hour fast and followed by a 4-hour fast.

All safety and tolerability data and available PK data at each TPD dose level were reviewed by the investigator, medical monitor, and sponsor (blinded, but with access to aggregate data) and were assessed as not posing any safety concerns before a higher dose cohort was initiated. Of note, because this was a first-in-man study and the human safety profile was as yet unknown, the study protocol specified a number of stopping rules. Under these rules, any subject with laboratory parameters that exceeded a conservative predefined threshold was to be withdrawn from the study for maximum safety. These conservative thresholds did not necessarily reflect adverse events or toxicities.

Study TR701-103 was an open-label randomized, 2-sequence, 2-treatment, 2-period crossover phase I study conducted at a single site in the United States (Covance Clinical Research Unit, San Diego, CA). The safety, tolerability, and PK of TPD administered orally as a single 600-mg dose during each treatment period to 12 healthy volunteers under fasted (10 hrs) or fed conditions (a standard high-calorie, high-fat breakfast preceded by 10-hr or longer fast) were investigated. A 4-hour fast followed study drug administration, and there was a 7-day or longer washout between treatments.

Study TR701-108 was an open-label randomized, 2-sequence, 2-treatment, 2-period, crossover phase I study conducted at a single site in the United States (Covance Clinical Research Unit, Austin, TX). The safety, tolerability, and PK of single doses of TPD (200 mg) and tedizolid phosphate (182 mg) administered orally after at least an 8-hour fast with 240 ml room temperature water were evaluated in healthy volunteers. The relative bioavailability of tedizolid phosphate compared with TPD was also evaluated. A 4-hour fast followed study drug administration, and there was a 5-day or longer washout between treatments.

Each study was approved by the Covance Clinical Research Unit institutional review board. All subjects provided written informed consent. The studies were conducted in accordance with the International Conference on Harmonisation and U.S. Food and Drug Administration guidelines and regulations, Good Clinical Practice, and the Declaration of Helsinki. Each study was registered at clinicaltrials.gov: NCT00671814 (TR701-101), NCT00671359 (TR701-103), and NCT00876655 (TR701-108).

### Study Populations

In all studies, subjects eligible for enrollment were in good health based on medical history, physical examination, 12-lead electrocardiogram, vital signs, and laboratory test results, tested negative for drugs of abuse and for pregnancy, and were able to provide written informed consent. Studies TR701-101 and TR701-103 enrolled subjects who were 18–50 years of age with a body mass index (BMI) of 20.0–29.9 kg/$m^2$ (inclusive), whereas Study TR701-108 enrolled subjects who were 18–60 years of age with a BMI of 18.5–32.0 kg/$m^2$ (inclusive). Subjects were assigned to treatment using computer-generated randomization schedules.

### Study Procedures

PK analysis of tedizolid was performed for all three studies, tedizolid phosphate for Studies TR701-101 and TR701-103, and linezolid for Study TR701-101. Blood samples for PK analysis were collected via direct venipuncture and/or an indwelling catheter at the following time points during both treatment periods in Studies TR701-103 and TR701-108 and the single-ascending dose part of Study TR701-101: 0 hour (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 18, 24, 48, and 72 hours postdose.

In the multiple-ascending dose part of Study TR701-101, blood samples were collected at the above time points up to 24 hours on days 1, 15 (no 18-hrs sample), and 21, and predose on days 3–14 and days 16–20.

In Study TR701-101, urine samples were collected for PK analysis of tedizolid phosphate and tedizolid concentrations during the following intervals: −24 to 0 hours (predose) and 0–4, 4–8, 8–12, and 12–24 hours postdose on day 1 (single-ascending dose) and on days 1, 15, and 21 (multiple-ascending dose), and at 24-hour intervals until discharge. Urine samples for PK were not collected from the linezolid cohort.

### Pharmacokinetics

Concentrations of tedizolid phosphate and tedizolid were determined by Covance Bioanalytical Laboratory Services, using validated tandem mass spectrometry methods. Pharmacokinetic calculations were performed using WinNonlin (v.5.2; Pharsight Corporation, Cary, NC). Tedizolid parameters included area under the concentration-time curve (AUC, from time zero to the last quantifiable concentration [t], extrapolated to time infinity [∞], or over the dosing interval [τ], using the linear trapezoidal rule), maximum plasma concentrations ($C_{max}$), time to $C_{max}$ ($T_{max}$), apparent half-life of elimination ($t_{½}$), oral clearance (CL/F), and volume of distribution ($V_z$/F).

The observed extent of accumulation following multiple doses in study TR701-101 was calculated as the ratio of $AUC_{0–\tau}$(day 21) to $AUC_{0–\tau}$ (day 1). The predicted accumulation ratio was calculated as the ratio of $AUC_{0–\infty}$(day 1) to $AUC_{0–\tau}$(day 1). The linearity factor was calculated as the ratio of $AUC_{0–\tau}$(day 21) to $AUC_{0–\infty}$ (day 1). Dose proportionality was assessed graphically. In Study TR701-103, food effect was evaluated by calculating geometric mean ratios for $C_{max}$, $AUC_{0–\tau}$, and $AUC_{0–\infty}$ for the fed state (test) to the fasted state (reference). In Study TR701-108, relative bioavailability was evaluated by calculating least squares mean ratios for $C_{max}$, $AUC_{0–\tau}$, and $AUC_{0–\infty}$ for tedizolid phosphate (test) to TPD (reference).

## Results

### Subject Disposition, Demographics, and Baseline Characteristics

In Study TR701-101, 80 healthy subjects were randomized to treatment in sequential cohorts between the single- and multiple-ascending dose parts of the study. All 40 subjects receiving a single oral dose completed the study, and 36 of 40 subjects (90.0%) completed the multiple-ascending dose part of the study. Four subjects were withdrawn due to prespecified treatment-emergent adverse events (AEs) indicative of potential liver toxicity or myelosuppression. Most of the subjects were white and male, with a mean age of 25 years in the single-ascending dose part and 33 years in the multiple-ascending dose part of the study (Table 1).

In Study TR107-103, 12 healthy subjects were enrolled and completed the study. Most of the subjects were white and male, with a mean age of 35 years (Table 1).

**Table 1. Subject Demographics and Baseline Characteristics**

| | Study TR701-101 | | | |
|---|---|---|---|---|
| Demographic Variable | SAD n=40 | MAD n=40 | Study TR701-103 n=12 | Study TR701-108 n=12 |
| Mean age, yr (range) | 25 (18–41) | 33 (18–49) | 35 (21–50) | 36 (26–59) |
| Mean weight, kg (range) | 73.1 (52.2–92.9) | 80.3 (60.3–100.9) | 73.1 (51.4–104.0) | 75.1 (57.0–95.5) |
| Mean height, cm (range) | 173.7 (158.2–189.1) | 176.0 (159.0–190.0) | 171.5 (154.3–187.0) | 168.5 (154.3–184.2) |
| Mean BMI, kg/m$^2$ (range) | 24.2 (20.1–30.0) | 25.8 (22.2–29.5) | 24.6 (20.2–29.7) | 26.4 (20.4–30.6) |
| Sex, n (%) | | | | |
| Male | 23 (57.5) | 31 (77.5) | 8 (66.7) | 6 (50.0) |
| Female | 17 (42.5) | 9 (22.5) | 4 (33.3) | 6 (50.0) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | 6 (15.0) | 3 (7.5) | 2 (16.7) | 6 (50.0) |
| Not Hispanic or Latino | 34 (85.0) | 37 (92.5) | 10 (83.3) | 6 (50.0) |
| Race, n (%) | | | | |
| White | 36 (90.0) | 28 (70.0) | 9 (75.0) | 12 (100) |
| Black or African American | 3 (7.5) | 8 (20.0) | 2 (16.7) | 0 |
| Other | 1 (2.5) | 4 (10.0) | 1 (8.3) | 0 |

SAD = single-ascending dose part of the study; MAD = multiple-ascending dose part of the study; BMI = body mass index.

In Study TR107-108, 12 healthy subjects were enrolled and completed the study. All subjects were white and half were male, with a mean age of 36 years (Table 1).

## Pharmacokinetics

In Study TR701-101, after oral administration of TPD, the active moiety tedizolid was readily observed in plasma at all doses following single or multiple once/day administration (Figures 1 and 2, respectively) and remained quantifiable at 72 hours after a single dose. Tedizolid phosphate was below the lower limit of quantification at all time points for all subjects but one. That subject received a single dose of 1200 mg TPD and had tedizolid phosphate quantifiable in plasma up to 3 hours after administration with $AUC_{0-t}$ of 0.024 μg × hr/ml and peak concentration of 0.017 μg/ml at 1 hour after administration. Mean half-life of tedizolid was longer than 10 hours for all dose groups.

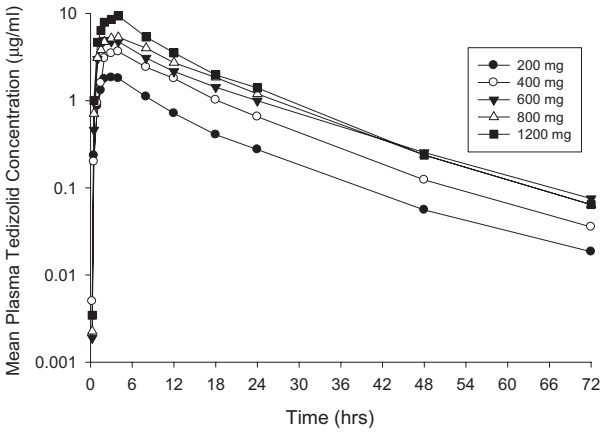


**Figure 1.** Mean plasma concentration-time profiles for tedizolid after a single oral dose of tedizolid phosphate disodium (TPD) at 200, 400, 600, 800, or 1200 mg. Subjects received a single administration of TPD (fasting) in the single-ascending dose arm of Study TR701-101.

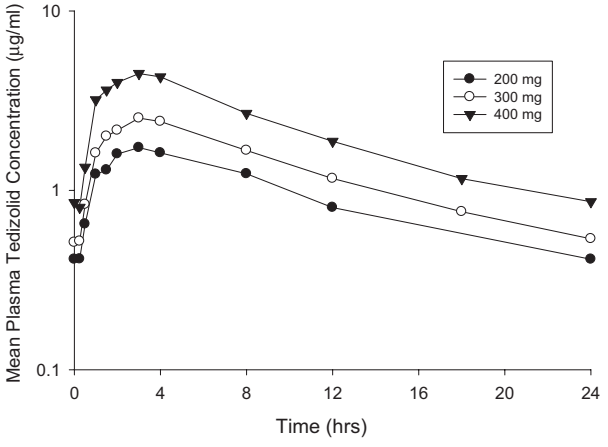


**Figure 2.** Mean plasma concentration-time profiles for tedizolid after multiple oral doses of tedizolid phosphate at 200, 300, or 400 mg/day. Subjects received a single administration of tedizolid phosphate disodium (TPD) each morning after an overnight fast in the multiple-ascending dose arm of Study TR701-101. Plasma concentrations of tedizolid were determined on Day 15 for the 200 mg dose group, or on Day 21 (or last day of dosing in case of earlier withdrawal) for higher dose groups.

Tedizolid PK parameter values were similar for single doses and 21-day multiple doses (Tables 2 and 3). After single-dose 200–1200 mg TPD administration, $C_{max}$ increased with dose but was not dose proportional (Table 2 and Figure 3). $AUC_{0-\infty}$ was more nearly dose proportional, especially at lower doses. In the multiple-ascending dose part of the study, repeated 200, 300, or 400 mg TPD administration resulted in approximately dose-proportional increases in tedizolid $C_{max}$ and AUC values at day 15 (200 mg) or at day 21 (300 and 400 mg; Table 3). Mean half-life (SD) of linezolid 600 mg was 3.80 (1.67) hours on day 1 and 5.75 (1.15) hours on day 21.

CL/F of tedizolid after TPD administration was generally independent of dose and number of administrations (Tables 2 and 3), whereas oral clearance of linezolid decreased by approximately a third following multiple twice/day dosing (Table 3). The apparent $V_z/F$ was similar for linezolid with single or multiple dosing, but there was a trend toward increased Vz/F with multiple-dose tedizolid at 300 or 400 mg. In both single- and multiple-dose portions of the study, less than 1% of the TPD dose was excreted in urine as either tedizolid phosphate or tedizolid (data not shown).

Steady-state tedizolid PK was predicted by single-dose kinetics (Table 3) across the three doses tested in the multidose portion of the study. Predicted accumulation ratios were similar, and the linearity factor was close to 1 for all doses. Accumulation of approximately 31% tedizolid AUC was observed for the therapeutic dose of 200 mg after 15 days of daily TPD administration (Table 3). In contrast, linezolid results indicated greater than predicted accumulation (~72%) after repeated twice/day administration over 21 days, resulting in a linearity factor of approximately 1.6. The mean tedizolid $t_{½}$ was approximately 2-fold that of linezolid, supporting once/day administration of TPD.

In Study TR701-103, following a single TPD administration with a meal, absorption was pro-

**Table 2. Tedizolid Plasma Pharmacokinetic Parameters After a Single Dose of Tedizolid Phosphate Administered Under Fasted Conditions (Study TR701-101)**

| | Tedizolid Phosphate Dose | | | | |
|---|---|---|---|---|---|
| PK Parameter | 200 mg[a] | 400 mg | 600 mg | 800 mg | 1200 mg |
| $C_{max}$, μg/ml[b] | 2.0 (0.4) | 3.8 (1.0) | 5.2 (0.7) | 5.5 (1.2) | 9.5 (1.9) |
| $T_{max}$, hr[c] | 3 (1, 4) | 3.5 (2, 4) | 2.5 (2, 4) | 4 (2, 8) | 4 (2, 4) |
| $AUC_{(0-\infty)}$, μg × hr/ml[b] | 25.4 (4.6) | 56.1 (13.2) | 79.3 (31.3) | 91.8 (12.9) | 123.1 (31.2) |
| $t_{½}$, hr[b] | 11.2 (3.6) | 10.8 (0.80) | 11.4 (2.57) | 10.6 (1.29) | 10.4 (1.43) |
| CL/F, L/hr[b] | 6.08 (1.08) | 5.58 (1.23) | 6.58 (3.00) | 6.65 (0.94) | 7.77 (2.24) |
| $V_z$/F, L[b] | 95.7 (23.5) | 87.0 (18.0) | 101 (23.5) | 101 (14.0) | 116 (29.2) |

PK = pharmacokinetic; $C_{max}$ = maximum plasma concentration; $T_{max}$ = time to maximum plasma concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from 0 to infinity; $t_{½}$ = half-life; CL/F = oral clearance; $V_z$/F = apparent volume of distribution.
[a]Therapeutic dose.
[b]Data are mean (SD).
[c]Data are median (range).

**Table 3. Mean Plasma Pharmacokinetic Parameters for Tedizolid and Linezolid After Multiple-Dose Administrations Under Fasted Conditions (Study TR701-101)**

| | Tedizolid Phosphate Disodium Dose | | | | | | Linezolid Dose | |
|---|---|---|---|---|---|---|---|---|
| | 200 mg once/day[a] | | 300 mg once/day | | 400 mg once/day | | 600 mg twice/day | |
| PK Parameter | Day 1 | Day 15[b] | Day 1 | Day 21 | Day 1 | Day 21 | Day 1 | Day 21 |
| $C_{max}$, μg/ml | 1.8 (1.2) | 1.8 (0.4) | 2.1 (0.5) | 2.7 (0.5) | 4.2 (0.8) | 4.7 (0.5) | 12.2 (3.0) | 16.5 (4.6) |
| $C_{min}$, μg/ml | NA | 0.41 (0.17) | NA | 0.51 (0.14) | NA | 0.85 (0.16) | NA | 5.1 (2.6) |
| $T_{max}$, hr | 3 (1.5–4) | 3 (2–4) | 2 (1.5–4) | 3 (1.5–8) | 4 (1–4) | 2.5 (1.5–4) | 1 (0.5–1.5) | 1.5 (0.5–4) |
| $AUC_{0-\tau}$, μg × hr/ml | 16.7 (3.8) | 22.5 (6.5) | 24.1 (5.4) | 31.2 (6.6) | 46.0 (6.4) | 52.0 (5.1) | 65.9 (19.2) | 114.6 (38.2) |
| $AUC_{0-\infty}$, μg × hr/ml | 21.6 (6.5) | NC | 29.6 (7.5) | NC | 54.0 (8.2) | NC | 78.1 (31.6) | NC |
| CL/F, L/hr | 7.48 (2.12) | 7.16 (1.99) | 7.98 (1.80) | 7.51 (1.60) | 5.66 (0.835) | 5.82 (0.607) | 8.73 (3.09) | 5.76 (1.89) |
| $V_z$/F, L | 117 (21.9) | 108 (38.1) | 116 (27.8) | 127 (22.0) | 64.8 (9.96) | 108 (20.4) | 42.9 (11.2) | 46.1 (12.7) |
| Accumulation ratio | | | | | | | | |
| Observed[c] | 1.31 (0.11) | | 1.31 (1.18) | | 1.18 (0.13) | | 1.72 (0.22) | |
| Predicted[d] | 1.31 (0.08) | | 1.24 (0.05) | | 1.17 (0.06) | | 1.16 (0.14) | |
| Linearity factor[e] | 0.94 (0.37) | | 1.02 (0.10) | | 1.01 (0.10) | | 1.55 (0.32) | |

PK = pharmacokinetic; $C_{max}$ = maximum plasma concentration; $C_{min}$ = minimum plasma concentration; NA = not applicable; $T_{max}$ = time to maximum plasma concentration; $AUC_{(0-\tau)}$ = area under the concentration-time curve from 0 to the dosing interval of 24 hours for tedizolid phosphate or 12 hours for linezolid; NC = not calculated; $AUC_{(0-\infty)}$ = area under the concentration-time curve from 0 to infinity; CL/F = oral clearance; $V_z$/F = apparent volume of distribution.
Day 21 represents day 21 or the last day dosed. Parameters with tedizolid phosphate administration represent tedizolid plasma concentration. All data are mean (SD) with the exception of $T_{max}$, which is median (range).
[a]Therapeutic dose.
[b]Steady-state day 15 and day 21 PK results were comparable for most individuals; day 15 shown for 200-mg dose due to one subject suspected to have missed the day 21 administration.
[c]Observed accumulation ratio = day 21 $AUC_{0-\tau}$/day 1 $AUC_{0-\tau}$.
[d]Predicted accumulation ratio = day 1 $AUC_{0-\infty}$/day 1 $AUC_{0-\tau}$.
[e]Linearity factor = Day 21 $AUC_{0-\tau}$/day 1 $AUC_{0-\infty}$.

longed with reduced mean tedizolid concentrations for several hours relative to TPD administration with fasting (Figure 4). In the fed state, the mean tedizolid $C_{max}$ was reduced by approximately 26% relative to the fasted state with a 6-hour delay in median time to maximum concentration ($T_{max}$) (Table 4). The overall extent of absorption as indicated by tedizolid $AUC_{0-t}$ and $AUC_{0-\infty}$ was virtually unaltered by meal status with a geometric mean ratio of 102% (90% confidence interval [CI] 98–107) for both. The tedizolid mean half-life in plasma was also unaffected by food, with mean half-lives (SD) of 10.9 (0.901) and 10.4 (0.883) hours in the fasted and fed states, respectively.

In Study TR701-108, oral administration of equivalent tedizolid doses from either TPD or tedizolid phosphate resulted in a nearly identical concentration profile (Figure 5). Peak ($C_{max}$) and overall ($AUC_{0-t}$ and $AUC_{0-\infty}$) exposures to tedizolid for both formulations differed by less than 5% with the geometric mean ratios and associated 90% CI falling entirely within the 80–125% bioequivalence range (Table 5). Results were consistent at the individual level with no outliers observed for $AUC_{0-\infty}$ or $C_{max}$ (Figure

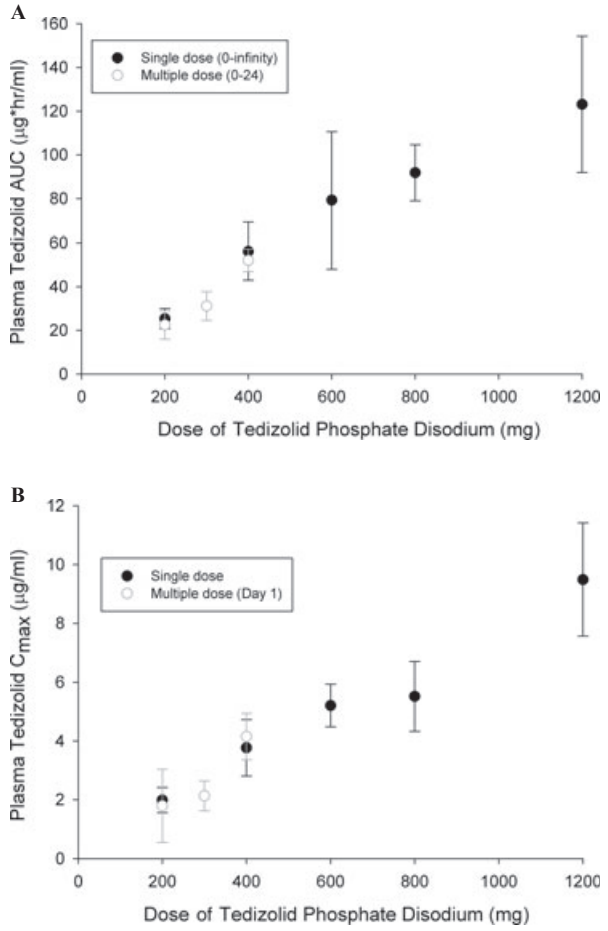


**Figure 3.** Relationship between dose of tedizolid phosphate disodium (TPD) and tedizolid plasma pharmacokinetics. Maximum plasma concentration ($C_{max}$) and area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) were determined after a single dose of TPD in the single ascending dose arm of Study TR701-101 (six subjects per dose group). In the multiple ascending dose arm, $C_{max}$ was determined after the first dose of TPD, and $AUC_{0-24\ hr}$ was determined at steady state. (A) Mean (± SD) $C_{max}$ versus dose. (B) Mean (± SD) AUC versus dose.

6). Compared with TPD, median time to maximum concentration ($T_{max}$) was similar (2.5–3.0 hrs) and the mean half-life ($t_{½}$) was the same for both drug products (11.4 hrs; Table 5).

### Safety

TPD was generally well tolerated. There was no apparent relationship between dose and the number of subjects experiencing AEs in the single-ascending dose part of Study TR701-101. In the multiple-ascending dose part of the study, four subjects were withdrawn due to meeting protocol-specified stopping rules (i.e., they exceeded conservative predefined thresholds in laboratory parameters). These were as follows: more than two times the upper limit of normal alanine aminotransferase after 11 days of TPD 200 mg once/day in one subject, reticulocyte count less than 75% the lower limit of normal in one subject after 18 days of TPD 400 mg once/day and one subject after 18 days of linezolid 600 mg twice/day, and white cell count less than 75% the lower limit of normal in one subject after 10 days of TPD 400 mg once/day. All of these changes in laboratory parameters resolved after discontinuation of the respective study drug. Of the 12 subjects in Study TR701-103, 2 experienced AEs after receiving TPD with fasting, and 5 had AEs after receiving TPD with food. Of the 12 subjects in Study TR701-108, 2 experienced AEs after receiving TPD, and 3 had adverse events after receiving tedizolid phosphate.

## Discussion and Conclusions

Following oral administration of TPD to fasted subjects, plasma tedizolid phosphate was generally undetectable, whereas the active moi-

**Table 4. Tedizolid Pharmacokinetic Parameters After a Single Administration of 600 mg Tedizolid Phosphate Disodium in the Presence or Absence of Food (Study TR701-103)**

| PK Parameter (Units) | | Fasted (Reference) (n=11) | Fed (Test) (n=11) | Geometric Mean Ratio (Test/Reference) (%) | 90% Confidence[a] Interval |
|---|---|---|---|---|---|
| $C_{max}$, µg/ml | Geometric mean | 6.4 | 4.7 | 73.7 | 67.8, 80.1 |
| $AUC_{0-t}$, µg × hr/ml | Geometric mean | 79.2 | 81.0 | 102.3 | 98.1, 106.7 |
| $AUC_{0-\infty}$, µg × hr/ml | Geometric mean | 79.9 | 81.8 | 102.4 | 98.2, 106.8 |
| $T_{max}$, hr | Median (range) | 2.0 (1.5, 3.0) | 8.0 (4.0, 12.0) | – | – |
| $t_{½}$, hr | Mean (SD) | 10.9 (0.901) | 10.4 (0.883) | – | – |

PK = pharmacokinetic; $C_{max}$ = maximum plasma concentration; $AUC_{(0-t)}$ = area under the concentration-time curve from time 0 to the last measurable concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 to infinity; $T_{max}$ = time to maximum plasma concentration; $t_{½}$ = half-life.

Tedizolid concentrations for one subject were below the limit of quantification in periods 1 and 2. As a result, this subject was excluded from the PK analysis and the calculation of descriptive statistics.

[a]90% confidence interval for geometric mean ratio (expressed as a percentage).

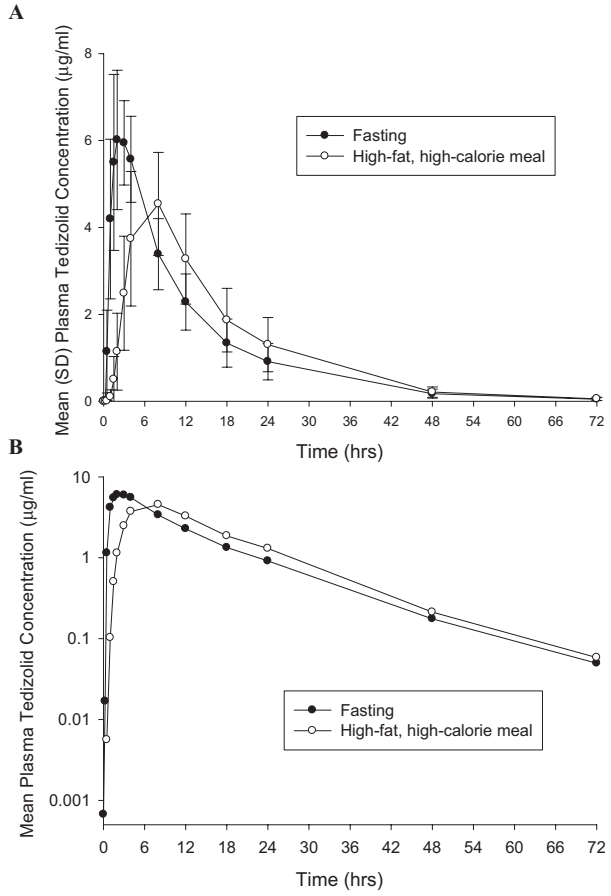


**Figure 4.** Mean plasma concentration-time profiles for tedizolid after a single administration of 600 mg of tedizolid phosphate under fed or fasted conditions. Results from Study TR701-103 are shown in linear (A, mean ± SD) and log (B) scales.

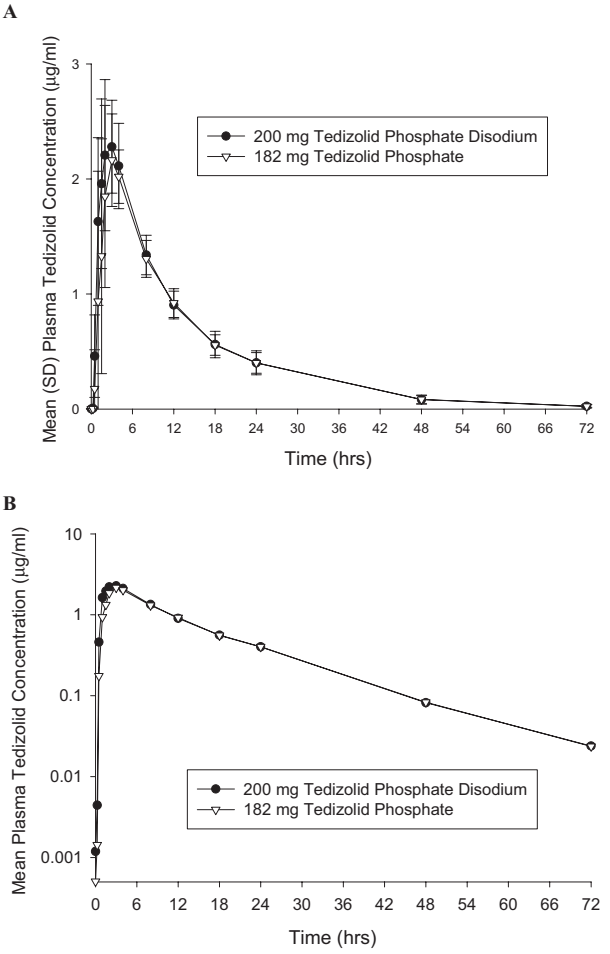


**Figure 5.** Mean plasma concentration-time profiles for tedizolid after a single administration of 150 mg of tedizolid from tedizolid phosphate disodium or tedizolid phosphate under fasted conditions. Results from Study TR701-108 are shown in linear (A, mean ± SD) and log (B) scales.

ety tedizolid was readily detected in plasma within 30 minutes of administration at all doses. Low absorption of tedizolid phosphate is not surprising due to its low predicted distribution coefficient (cLogD) of −4.67 at physiologic pH and ubiquitous expression of phosphatases throughout the body, with especially high expression in the intestine and liver. The reduced $C_{max}$ and delayed $T_{max}$ observed in the fed state result from delayed gastric emptying associated with a solid meal because tedizolid phosphate has low predicted membrane permeability and the stomach does not contain phosphatase enzymes. In vitro studies suggest that tedizolid phosphate is dephosphorylated at the intestinal brush border membrane, after which tedizolid enters into enterocytes without accumulating in the gut lumen. Tedizolid is rapidly absorbed with nearly complete oral bioavailability of 91% (90% CI 87–96) following therapeutic doses (200 mg) of tedizolid phosphate in healthy adults.[31]

Less than dose-proportional increases in AUC and $C_{max}$ were observed for tedizolid after oral administration of 200–1200 mg TPD but appeared linear from 200 to 600 mg TPD. Oral clearance and volume of distribution were greatest at the highest dose (1200 mg), likely due to reduced bioavailability at supratherapeutic doses rather than a true change in either parameter. Supratherapeutic doses of TPD may result in saturation of phosphatases and reduced tedizolid bioavailability; one subject had tedizolid phosphate detectable in plasma between 15 minutes and 3 hours after receiving 1200 mg TPD. The mean $t_{½}$ for tedizolid was approximately twice that of linezolid, allowing tedizolid to be administered by a more convenient once/day dosing schedule.

**Table 5. Tedizolid Pharmacokinetic Parameters and Relative Bioavailability After a Single Administration of 200 mg Tedizolid Phosphate Disodium and 182 mg Tedizolid Phosphate Under Fasted Conditions (Study TR701-108)**

| PK Parameter (Units) | | TPD (Reference) (n=12) | Tedizolid Phosphate (Test) (n=12) | Geometric Mean Ratio (Test/Reference) (%) | 90% Confidence[a] Interval |
|---|---|---|---|---|---|
| $C_{max}$, μg/ml | LS mean | 2.4 | 2.3 | 95.3 | 89.7, 101.3 |
| $AUC_{0-t}$, μg × hr/ml | LS mean | 32.3 | 31.0 | 95.8 | 93.0, 98.8 |
| $AUC_{0-\infty}$, μg × hr/ml | LS mean | 32.7 | 31.4 | 95.9 | 93.1, 98.8 |
| $T_{max}$, hr | Median (range) | 2.5 (1.5, 4.0) | 3.0 (1.0, 4.0) | – | – |
| $t_{½}$, hr | Mean (SD) | 11.4 (1.43) | 11.4 (1.38) | – | – |

PK = pharmacokinetic; TPD = tedizolid phosphate disodium; $C_{max}$ = maximum plasma concentration; LS = least squares; $AUC_{(0-t)}$ = area under the concentration-time curve from time 0 to the last measurable concentration; $AUC_{(0-\infty)}$ = area under the concentration-time curve from time 0 to infinity; $T_{max}$ = time to maximum plasma concentration; $t_{½}$ = half-life.
[a]90% confidence interval for LS mean ratio (expressed as a percentage).

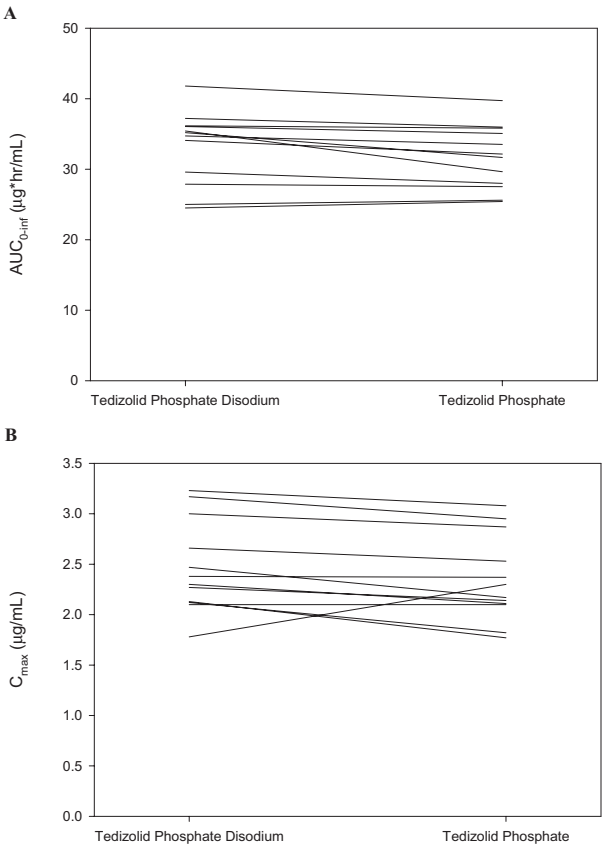


**Figure 6.** Pharmacokinetic parameter values for tedizolid for each subject after a single administration of 150 mg of tedizolid from tedizolid phosphate disodium or tedizolid phosphate under fasted conditions. Results from Study TR701-108 are shown for (A) area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) and (B) maximum plasma concentration ($C_{max}$).

Pharmacokinetic parameters were generally similar for single- and multiple-dose administration and between dose groups in the multiple-dose arm. Minor differences were noted in the 400-mg dose group, which had reduced tedizolid clearance relative to the lower doses and minor changes in Vz/F values between day 1 and day 21 that were not apparent at 200 mg or 300 mg TPD.

Tedizolid accumulation at steady state was minimal and well predicted by single-dose kinetics, with a linearity factor near 1 across the three doses (Table 3). In contrast, accumulation of linezolid was greater than predicted from single-dose kinetics, thus indicating nonlinear kinetics consistent with product labeling and the existing literature.[4] A number of studies have described nonlinear PK of linezolid with parallel linear (from one- or two-compartment models) and Michaelis-Menten elimination pathways.[32, 33] More recently, an inhibition compartment model was proposed to provide better PK predictions with a possible mechanistic interpretation of inhibition of mitochondrial respiratory chain activity resulting in decreased NADPH-dependent metabolism of linezolid.[34] Predictable PK and lack of significant accumulation following multiple doses of tedizolid phosphate may lead to lower potential for side effects related to higher exposures.

Administration of 600 mg tedizolid phosphate in the fed state reduced the geometric mean $C_{max}$ and delayed the median $T_{max}$ relative to fasting, it but had no effect on $AUC_{0-t}$ or $AUC_{0-\infty}$. Because AUC is the main PK/pharmacodynamic driver of efficacy for oxazolidinones,[20–22] the results suggest that tedizolid phosphate can be administered without regard to food.

The relative bioavailability of tedizolid with administration of tedizolid phosphate versus TPD was within the 80–125% bioequivalence acceptance window. Early studies with TPD including TR701-101, TR701-103, a microdialysis study,[26] and a phase II study,[28] suggested the 200-mg dose had the most favorable pharmacokinetic, safety, and efficacy profile for therapeutic dosing. When tedizolid phosphate was selected as the intended commercial drug

substance due to manufacturing advantages (nonhygroscopic, with no special storage or handling requirements), the nominal dose level of 200 mg tedizolid phosphate (164 mg tedizolid equivalent) was retained for simplicity, which resulted in a minor (less than 10%) increase in the dose of the active moiety compared with a 200-mg dose of TPD (150 mg tedizolid equivalent). However, the tedizolid exposures with the 200-mg dose of tedizolid phosphate would be expected to be nearly equal to those from the 200-mg dose of TPD and well within the range of doses evaluated clinically for TPD. Perhaps not surprisingly, this lowest dose was also associated with the best safety profile. TPD was generally well tolerated, but there were a few discontinuations due to conservative stopping rules (as specified in the study protocol) in the multiple-ascending dose arm. With the exception of an elevated liver enzyme in one subject receiving 200 mg, the other two tedizolid treated subjects that were discontinued (due to changes in blood work) received doses higher than the 200 mg used in a recent clinical trial.[30] All laboratory abnormalities that led to withdrawal from the study resolved after discontinuation of the respective study drug. It should be noted that the stopping rules were predefined for maximum safety because little was known about tedizolid's safety profile at this early stage of clinical development.

Overall, these studies indicate that tedizolid presents a favorable PK profile, with an elimination half-life that supports once/day administration and no nonlinearities at steady state. No modification of the TPD dosing regimen appears necessary for fasting or fed conditions. Because the PK of tedizolid are similar for oral administration of tedizolid phosphate or TPD, the pharmacokinetic conclusions determined from studies with TPD should apply to tedizolid phosphate.

## Acknowledgments

This study was sponsored by Trius Therapeutics and conducted by Covance, Inc. Employees of the study sponsor were involved in study design, data analysis, interpretation of the results, and review/writing of the manuscript. All authors had full access to the data. The authors had final responsibility for the decision to submit for publication. Shawn D. Flanagan, Paul A. Bien, Kelly A. Muñoz, and Philippe G. Prokocimer are employees of Trius Therapeutics. Sonia L. Minassian was a consultant to Trius Therapeutics and compensated for supporting this research. Medical writing support was provided by Synchrogenix Information Strategies (Wilmington, DE) and Brenda Clapper (BioMedCom, Santee, CA), funded by Trius Therapeutics, and by Sharon Dana, an employee of Trius Therapeutics.

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