Pharmacokinetics and Safety of Tedizolid after Single and Multiple Intravenous/Oral Sequential Administrations in Healthy Chinese Subjects

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ABSTRACT

Purpose: Tedizolid phosphate is a new antibacterial agent under investigation for the treatment of Gram-positive infections in China. This study was conducted to assess the pharmacokinetic (PK) properties, oral bioavailability, and safety of once daily tedizolid phosphate 200 mg in Chinese subjects to support its further clinical development in China.

Methods: This Phase I single-center study, conducted in 16 healthy Chinese male subjects, consisted of a single-dose administration, 1:1 randomized, two-way, intravenous (IV)/oral (PO) crossover of tedizolid phosphate 200 mg (Part 1) and, after a 7-day washout, a nonrandomized, multiple-dose, 7-day tedizolid phosphate 200 mg once daily administration (IV for 3 days, PO for 4 days; Part 2). Blood samples were collected for up to 72 hours after single dosing and for up to 2 hours on Day 3 and 72 hours on Day 7 of multiple dosing to determine PK parameters. Adverse events (AEs) were recorded throughout the entire study.

Findings: The Cmax and AUC of tedizolid (the active moiety of tedizolid phosphate) were 3.02 μg/mL and 30.50 μg • h/mL after single IV dosing of tedizolid phosphate, and 2.25 μg/mL and 26.10 μg • h/mL after single PO dosing, respectively, and the mean half-life was 10.1 hours for both administration routes. The oral bioavailability of tedizolid was 85.5%. PK parameters of tedizolid were similar after single and multiple dosing of tedizolid phosphate, indicating no time dependency. Only minor accumulation of tedizolid was observed after multiple dosing (expressed as accumulation ratios R_AAUC: 1.18 for PO dosing, and R_ACmax: 1.16 and 1.05 for IV and PO dosing, respectively). Steady state of tedizolid was reached after about 3 days, and trough concentrations remained constant when switching from IV to PO dosing. Tedizolid phosphate was well tolerated with 6 subjects (37.5%) in Part 1 and 5 subjects (31.3%) in Part 2 experiencing an AE; all AEs but one were related to the study drug assessed by the investigator. All AEs were of mild intensity and had recovered or resolved by the end of the study. No serious AEs were observed, and no subjects prematurely discontinued the study due to an AE.

Implications: The results of this Phase I study conducted in Chinese male subjects indicate that no dosage adjustment of tedizolid phosphate 200 mg would be required when switching administration routes in this population. Tedizolid phosphate was well tolerated in healthy Chinese subjects. China Food and Drug Administration clinical trial permission numbers 2014L00360 and 2014L00361. (*Clin Ther.* 2016;38:1869–1879) © 2016 Published by Elsevier HS Journals, Inc.

Key words: healthy Chinese volunteers, multiple sequential administration, pharmacokinetics, safety, single administration, tedizolid.

INTRODUCTION

Serious bacterial infections are a significant problem in inpatient and outpatient settings and represent a growing health care burden worldwide. Acute bacterial skin and skin structure infections (ABSSSIs) are most frequently caused by Gram-positive pathogens,

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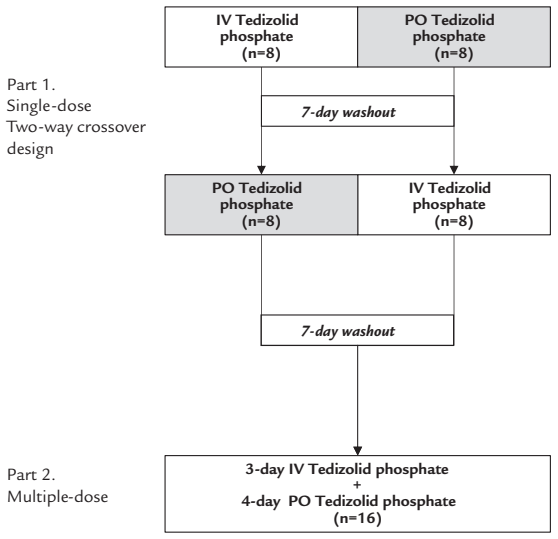

Figure 1. Study design. IV = intravenous; PO = oral.

with methicillin-resistant *Staphylococcus aureus* (MRSA) becoming increasingly common as an important causative pathogen.[1–3]

In China, the prevalence of MRSA has reached 40% to 70% of total *S aureus* isolates based on previous laboratory-based surveillance data, and the latest data from the 2014 CHINET surveillance study find that MRSA accounted for 44.6% of all the *S aureus* isolates collected from 17 clinical hospitals.[4–7] Analysis of Gram-positive bacteria collected from Chinese hospitals between 2005 and 2010 has also revealed that isolates from inpatients exhibited a higher rate of MRSA than that from outpatients (52.3% vs 26.2%, respectively).[4,7] A recent systematic review of available studies found that MRSA accounted for 41.3% of *S aureus* in surgical site infections in China, with isolates tending to be sensitive to vancomycin and linezolid.[8]

Tedizolid phosphate, a new oxazolidinone prodrug antibiotic, 200 mg, once daily, either oral (PO) or intravenous (IV) formulation given for 6 days has recently been approved in the United States,[9] Europe, Canada, and Singapore for the treatment of ABSSSIs when Gram-positive pathogens, including MRSA, are suspected or confirmed causative agents. Two Phase III double-blind, randomized, active-controlled trials found that tedizolid phosphate 200 mg, IV/PO, once daily (QD) treatment for 6 days was as effective as linezolid 600 mg, IV/PO, BID for 10 days in the management of patients with ABSSSIs.[10–12] The studies have demonstrated that tedizolid phosphate was well tolerated in ABSSSI patients with significantly lower incidences of gastrointestinal side effects and abnormal platelet counts. It has been reported that the oral bioavailability of tedizolid (active metabolite of tedizolid phosphate) was 91.7% in Caucasians, thus leading to drug exposures comparable with IV treatment.[13]

The present Phase I study was conducted to evaluate the pharmacokinetic (PK) properties of tedizolid phosphate in healthy Chinese subjects after single IV or PO administration and multiple IV/PO sequential administrations, and to determine the oral bioavailability of tedizolid after IV or PO administration of tedizolid phosphate at the therapeutic dose of 200 mg to support its clinical development in China for the indications of ABSSSI and nosocomial pneumonia.

METHODS

Study Design

This study was an open-label, Phase I study consisting of Part 1, a single-dose crossover part with IV and PO administration of tedizolid phosphate 200 mg (Figure 1), followed by Part 2, a nonrandomized, multiple-dose part involving once daily administration of tedizolid phosphate 200 mg for 7 days (IV administration for 3 days, followed by PO administration for 4 days) (Figure 1). The first, single-dose part had an open-label, 1:1 randomized, 2-way crossover design (Figure 1). After 8-hour fast, healthy male Chinese subjects received tedizolid phosphate either as a single IV dose (infusion of 250 mL solution over 60 minutes) or a single PO dose (tablet). In the study each IV dose was infused for 60 minutes. After a 7-day washout period, subjects received tedizolid phosphate again after a switch in the route of administration. In the second multiple-dose part (Part 2), subjects received sequential tedizolid phosphate 200 mg once daily IV for 3 days and PO for 4 days (Figure 1). The IV/PO sequential administration in Part 2 was conducted for 7 consecutive days.

The study was conducted at a single center in China (Clinical Pharmacology Research Centre of the Peking Union Medical College Hospital, Beijing, China) between June 2014 and July 2014. Written informed consent was obtained from all subjects before undergoing any study-related procedures.