Tedizolid Plasma Pharmacokinetics Are Comparable in Obese and Nonobese Patients and Healthy Subjects

Shawn Flanagan[1], Sonia L. Minassian[2], Julie A. Passarell[3], Jill B. Fiedler-Kelly[3], Philippe Prokocimer[1]

[1]Cubist, San Diego, CA; [2]Minassian Biostatistics, Inc., San Diego, CA; [3]Cognigen Corporation, Buffalo, NY

Shawn Flanagan
6310 Nancy Ridge Dr
San Diego, CA 92121
858 452 0370 extension 270
shawn.flanagan@cubist.com

P1703

INTRODUCTION

- Tedizolid phosphate is a novel oxazolidinone prodrug antibacterial being investigated for the treatment of Gram-positive infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Tedizolid phosphate is rapidly converted by endogenous phosphatases to tedizolid, the microbiologically active moiety.[1,2]
- In 2 recent Phase 3 trials in patients with acute bacterial skin and skin structure infections (ABSSSI), tedizolid (200 mg once daily for 6 days) demonstrated noninferior efficacy to linezolid (600 mg twice daily for 10 days), and was generally well tolerated.[3,4]
- Obesity is a key patient characteristic shown to alter dose-exposure relationships with some drugs, thus resulting in the need for dose adjustments for this particular patient population.[5]
- Available data suggest that linezolid systemic exposure is lower in obese than in nonobese patients.[6-9] The reason for this difference has not been determined, and it is not currently known whether linezolid dose modification is warranted in obese patients.
- Previous studies have shown that, following oral or intravenous (IV) administration of tedizolid phosphate 200 mg, tedizolid exposure in elderly persons, adolescents, and subjects with severe hepatic or renal impairment (including those requiring hemodialysis) was similar to that of control groups.[10,11]
- In the current analysis, the influence of body weight and body mass on tedizolid plasma pharmacokinetics (PK) was evaluated to determine whether plasma exposure parameters of tedizolid are comparable in obese and nonobese individuals.

METHODS

- The analysis population consisted of 821 individuals who received either oral or IV tedizolid phosphate. It included healthy subjects who participated in Phase 1 clinical studies and patients with ABSSSI who participated in Phase 3 clinical studies.
- In all analyses, obese was defined as body mass index (BMI) ≥30 kg/m^2 and nonobese was defined as BMI <30 kg/m^2. Severe obesity was defined as BMI ≥35 kg/m^2. Noncompartmental analysis (NCA) and population PK (popPK) methodologies were used to assess tedizolid plasma concentration data obtained from extensive or sparse blood sampling.
- The NCA used data from 174 subjects without ABSSSI who participated in Phase 1 clinical studies (obese = 38, nonobese = 136). Using these data, geometric mean ratios (GMRs) of the observed tedizolid plasma single-dose PK exposure parameters were calculated for single-dose oral and IV administration of tedizolid phosphate, along with associated 90% confidence intervals. Parameters of interest were maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$). Nonobese subjects were used as the reference population.
- PopPK modeling analysis used data from 647 patients with ABSSSI (obese = 193, nonobese = 454) who participated in Phase 3 studies. In this analysis, anthropometric subject measures (BMI, total body weight [TBW], and ideal body weight [IBW]) were evaluated as continuous variables for predicting variability in tedizolid plasma PK parameters after single and multiple oral or IV dosing. PopPK model predicted tedizolid plasma exposure parameters were then compared between obese and nonobese patients using descriptive statistics. Parameters of interest were area under the concentration-time curve at steady state from 0 to 24 hours ($AUC_{ss(0-24)}$) and maximum plasma concentration at steady state ($C_{max,ss}$).

RESULTS

- NCA assessments showed that observed plasma exposure measures ($AUC_{0-\infty}$ and C_{max}) were similar for obese and nonobese healthy subjects who had received either oral or IV tedizolid phosphate (**Table 1**). All GMRs were within the 80% to 125% no-effect boundary.

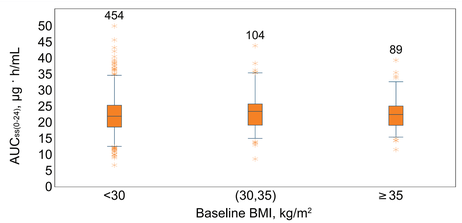
Table 1. Observed Plasma Tedizolid Exposure Measures for Obese and Nonobese Healthy Subjects Who Received Oral or IV Tedizolid Phosphate in Phase 1 Clinical Trials

Parameter	Route	Weight Classification	n	GM	GM Ratio[a]	GM Ratio 90% CI Limits	
						Lower	Upper
C_{max}[b]	Oral	Obese	31	1.86	0.82	0.75	0.89
		Nonobese	91	2.28			
	IV	Obese	7	2.49	0.88	0.72	1.07
		Nonobese	60	2.85			
$AUC_{0-\infty}$[c]	Oral	Obese	31	25.4	0.89	0.80	0.99
		Nonobese	86	28.5			
	IV	Obese	7	25.4	0.88	0.73	1.07
		Nonobese	59	28.7			

$AUC_{0-\infty}$, area under the plasma concentration-time curve from zero to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GM, geometric mean; IV, intravenous.
[a]GM ratio = (GM obese)/(GM nonobese).
[b]C_{max} units are µg/mL.
[c]AUC units are µg · h/mL.

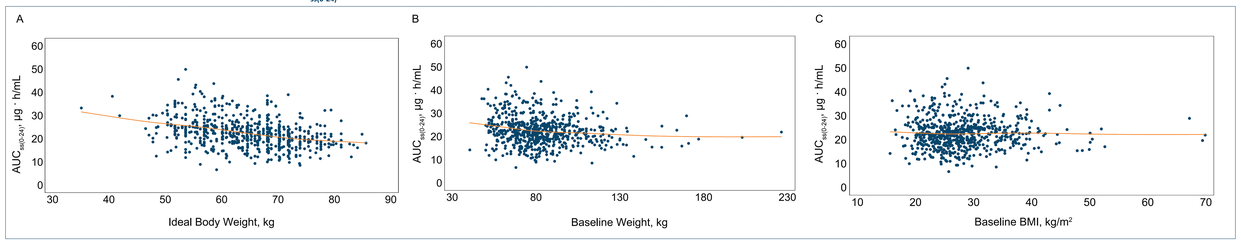
- PopPK analysis showed that only IBW had a statistically significant effect on tedizolid plasma PK. However, this effect was not considered clinically meaningful.
- PopPK model–predicted steady state PK ($AUC_{ss(0-24)}$ and $C_{max,ss}$) were similar between obese and nonobese patients.
- $AUC_{ss(0-24)}$ values were also similar for patients with more severe and less severe obesity (**Figure 1**).
- **Figure 2** and **Figure 3** illustrate the apparent relationship between tedizolid exposure ($AUC_{ss(0-24)}$ and $C_{max,ss}$, respectively) and IBW, as well as the lack of relationship between tedizolid exposure and baseline weight and BMI.

Figure 1. Population Pharmacokinetics: Tedizolid Exposure Was Similar in Nonobese, Obese, and Severely Obese Patients[a]



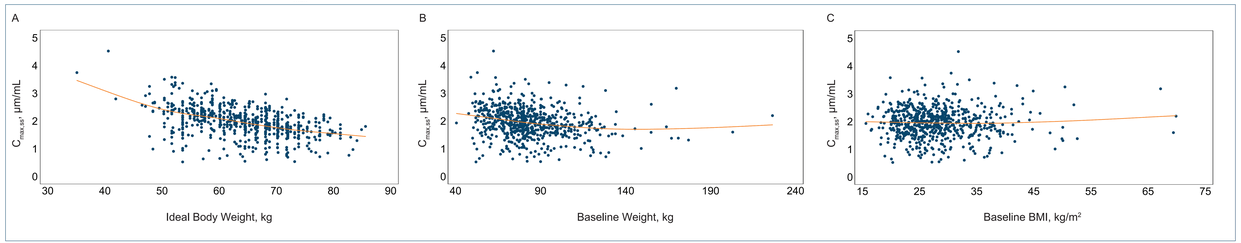
[a]Boxes represent the 25th, 50th, and 75th percentiles, with whiskers extending to the 5th and 95th percentiles. Asterisks show data points outside this range. The number of patients is above each box.

Figure 2. Relationship Between Tedizolid Plasma $AUC_{ss(0-24)}$ and Anthropometric Measures for (A) Ideal Body Weight, (B) Baseline Weight, and (C) Baseline BMI



The line represents a smoothing spline fit to the data.
$AUC_{ss(0-24)}$, area under the concentration-time curve at steady state from 0 to 24 hours; BMI, body mass index.

Figure 3. Relationship Between Tedizolid Plasma C_{max} and Anthropometric Measures for (A) Ideal Body Weight, (B) Baseline Weight, and (C) Baseline BMI



The line represents a smoothing spline fit to the data.
$C_{max,ss}$, maximum plasma concentration at steady state; BMI, body mass index.

CONCLUSIONS

- Observed tedizolid plasma levels were similar for obese and nonobese individuals who received tedizolid phosphate.
- PopPK analysis showed that baseline weight and BMI had no statistically significant effect on tedizolid plasma exposures and that the effect of IBW was not clinically meaningful.
- These findings suggest that tedizolid phosphate could be administered to obese patients without dose adjustment.

REFERENCES

1. Shaw KJ, et al. *Antimicrob Agents Chemother.* 2008;52(12):4442-4447.
2. Schaadt R, et al. *Antimicrob Agents Chemother.* 2009;53(8):3236-3239.
3. Prokocimer P, et al. *JAMA.* 2013;309(6):559-569.
4. Moran GJ, et al. *Lancet Infect Dis.* In Press.
5. Hanley MJ, et al. *Clin Pharmacokinet.* 2010;49(2):71-87.
6. Mersfelder TL, et al. *Am J Health Syst Pharm.* 2005;62(5):464-467.
7. Meagher AK, et al. *Antimicrobial Agents Chemother.* 2003;47(2):548-553.
8. Hamilton R, et al. *J Antimicrob Chemother.* 2013;68(3):666-673.
9. Stein GE, et al. *Ann Pharmacother.* 2005;39(3):427-432.
10. Flanagan S, et al. Presented at: ICAAC 2012; September 9-12, 2012; San Francisco, CA. Poster A-1294.
11. Flanagan S, et al. Presented at: ID Week 2013; October 2-6, 2013; San Francisco, CA. Poster 707.

ACKNOWLEDGMENTS

Editorial support for this poster was provided by ApotheCom ScopeMedical and funded by Cubist.

DISCLOSURES

- Shawn Flanagan and Philippe Prokocimer are employees of Cubist.
- Sonia L. Minassian is a consultant to Cubist and was compensated for supporting this research.
- Jill Fiedler-Kelly and Julie Passarell are employees of Cognigen; Cognigen received consulting fees to perform the analyses described herein.

This study was funded by Cubist

24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)

10-13 May 2014; Barcelona, Spain