Lack of an effect of standard and supratherapeutic doses of linezolid on QTc interval prolongation

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Running title: Linezolid and lack of QT prolongation
ABSTRACT

A double-blind, placebo-controlled, four-way crossover study was conducted in 40 subjects to assess the effect of linezolid on corrected QT (QTc) interval prolongation. Time-matched, placebo-corrected QT intervals were determined predose and at 0.5, 1 (end of infusion), 2, 4, 8, 12, and 24 hours after intravenous dosing of linezolid 600 and 1,200 mg. Oral moxifloxacin 400 mg was used as an active control. The pharmacokinetic profile of linezolid was also evaluated. At each time point, the upper bound of the 90% confidence interval (CI) for placebo-corrected QTcF values for linezolid 600 and 1,200 mg doses were <10 ms, which indicates an absence of clinically significant QTc prolongation. At 2 and 4 hours after moxifloxacin dose, corresponding to the population T\textsubscript{max}, the lower bound of the two-sided 90% CI for QTcF when comparing moxifloxacin to placebo was >5 ms, indicating that the study was adequately sensitive to assess QTc prolongation. The pharmacokinetic profile of linezolid 600 mg was consistent with previous observations. Systemic exposure to linezolid increased in a slightly more than dose-proportional manner at supratherapeutic doses, but the degree of nonlinearity was small. At a supratherapeutic single dose of 1,200 mg linezolid, no treatment-related increase in adverse events was seen compared to 600 mg linezolid, and no clinically meaningful effects on vital signs and safety laboratory evaluations were noted.
INTRODUCTION

Linezolid, a totally synthetic oxazolidinone antibiotic, is indicated for the treatment of infections known or suspected to be caused by susceptible strains of aerobic gram-positive bacteria. Approved indications are community-acquired or nosocomial pneumonia, complicated skin and soft-tissue infections (cSSTIs), and enterococcal infections, including those caused by vancomycin-resistant Enterococcus faecalis and Enterococcus faecium. The antibacterial activity of linezolid is due to inhibition of protein synthesis by its binding to the bacterial 23S ribosomal RNA of the 50S subunit, thus blocking the formation of the functional 70S initiation complex; linezolid does not inhibit peptidyl transferase. Linezolid is available as both oral and intravenous (IV) formulations, allowing the initiation of treatment of serious infections using the IV formulation and subsequent switching to the oral formulation without the need for any dose adjustment. The standard adult IV linezolid dose is 600 mg every 12 hours infused over 1 hour.

Studies in healthy volunteers and patients with gram-positive infections have evaluated the pharmacokinetics of linezolid after single and multiple doses administered orally (375, 500, 600, and 625 mg) or IV (375, 600, and 625 mg). There appears to be a tendency toward slightly higher exposure with increasing doses due to nonlinearity of clearance; however, the degree of nonlinearity is small. After single or multiple IV doses, the clearance of linezolid averages about 125 ml/min. About 30% of the dose is eliminated unchanged in the urine; renal clearance averages about 40 ml/min. Linezolid exhibits low (30%) binding to plasma proteins. Steady-state volume of distribution (V_{ss})
averages about 50 liters. The plasma elimination half-life \( t_{1/2} \) of linezolid is in the range of 3.5 to 6.0 hours (7). Linezolid is primarily metabolized by oxidation of the morpholine ring, resulting in two inactive ring-opened metabolites.

Numerous drugs, including some antibacterial agents, have been associated with QT prolongation, which may be exacerbated by underlying metabolic abnormalities such as hypokalemia, and by medical conditions such as congenital long QT syndrome. The phenomenon of quinolone-induced QT prolongation, for example, is well recognized (2). A formal evaluation of the potential of linezolid to prolong the QT interval has not been conducted; therefore, the present study was performed to assess the effect of IV linezolid on the QT/QTc interval and to examine the pharmacokinetics, safety, and tolerability of escalating single doses. Although the maximum therapeutic dose of linezolid administered orally or via IV infusion is 600 mg every 12 hours, there are very limited clinical pharmacokinetic and safety data at linezolid doses beyond 600 mg. Therefore, prior to evaluation of QTc interval prolongation at a supratherapeutic dose of linezolid, the safety and pharmacokinetics of higher doses of linezolid were assessed in an initial cohort of healthy subjects.

**METHODS**

**Study design and subjects.** This study was conducted in two sequential cohorts (Clinicaltrials.gov number NCT00795145). No subject was allowed to be included in both cohorts. Subjects were healthy men or women aged 21 to 55 years, weighing >45 kg, and with a body mass index of 18 to 30 kg/m\(^2\). Subjects were screened (detailed
medical history, full physical examination, standard 12-lead electrocardiography [ECG],
86 hematology, blood chemistry, and urinalysis) no more than 28 days before receipt of the
87 first dose. The study was conducted in compliance with the ethical principles originating
88 in or derived from the Declaration of Helsinki and in compliance with all International
89 Conference on Harmonization (ICH) Good Clinical Practice Guidelines. All local
90 regulatory requirements were followed and written informed consent was obtained prior
91 to each subject entering the study. The study was managed by Pfizer Global
92 Pharmaceuticals and was conducted at the Pfizer Clinical Research Unit in Singapore.
93 The protocol was approved by the Singapore General Hospital Ethics Committee.
94
95 Cohort 1 was designed to assess the safety, tolerability, and pharmacokinetics of
96 plausible supratherapeutic doses of linezolid and utilized a double-blind, randomized,
97 single-dose, three-treatment, three-period crossover design. According to a
98 predetermined sequence, the subjects in cohort 1 received IV placebo (0.9% saline 600
99 ml), linezolid 900 mg (Zyvox, Pfizer Inc, IV injection 450 ml plus saline 150 ml), and
100 linezolid 1,200 mg (Zyvox IV solution 600 ml). All treatments were infused at a constant
101 rate over 60 minutes. The washout interval between treatments was at least 48 hours.
102 The subject, investigator, and site personnel involved in the study (except for the
103 pharmacy staff) were blinded to treatment. Subjects remained in-house for the duration
104 of the study.
105
106 Cohort 2 employed a single-dose, randomized, four-treatment, four-period crossover,
107 double-blind (open-label for moxifloxacin [Avelox, Bayer]) design to assess the influence
of linezolid on corrected QT (QTc) interval prolongation. Subjects in cohort 2 randomly received a 60-minute infusion of placebo (0.9% saline 600 ml), linezolid 600 mg (Zyvox IV injection 300 ml plus saline 300 ml), and linezolid 1,200 mg (Zyvox IV solution 600 ml) in a blinded fashion. Each subject also received, in random order, open-label moxifloxacin 400 mg tablet (Avelox) with 240 ml water after an overnight fast. The interval between randomized treatments was extended to a minimum of 96 hours in cohort 2 to ensure adequate washout. Linezolid was administered intravenously to achieve supratherapeutic drug concentrations upon single dose; administering placebo intravenously enabled the maintenance of the study blind between linezolid and placebo.

The primary objective for cohort 2 was to demonstrate the lack of an effect on the QTc interval of single IV doses of linezolid (600 and 1,200 mg), relative to placebo. Secondary objectives were to determine study sensitivity by comparing the QTc effect of moxifloxacin relative to placebo, to evaluate the relationship of the QTc interval with plasma concentrations of linezolid, and to assess safety and tolerability. Subjects remained in-house for each treatment period and were allowed to be furloughed during the washout phase between treatments.

**Electrocardiography.** In cohort 1, single, standard 12-lead ECGs were obtained predose on day 0 and at 0.5, 1, and 3 hours after the start of infusion of each treatment. In cohort 2, triplicate standard 12-lead ECGs were obtained at baseline (1, 0.5, and 0 hours) before and at 0.5, 1, 2, 4, 8, 12, and 24 hours after the start of linezolid/placebo.
infusion or the swallowing of the moxifloxacin tablet. The triplicate ECGs were separated by intervals of 2 minutes. The ECGs were obtained at each time point before blood samples were collected, after subjects rested in the supine position for ≥10 minutes. The QT intervals were determined using a semi-automated program. ECGs were recorded with Philips HP PageWriter Touch. The QT interval measurements were based on the Philips 12-lead algorithm (6). No changes were made to the automated interval annotations; these QT interval measurements were used for analyses. The QT, ventricular rate (VR), PR, QRS, and R-R intervals were collected from the ECG.

Statistical analyses of QT/QTc. A study population of 36 subjects provided 98% power to exclude a 10-ms mean difference for linezolid versus placebo (i.e., 95% one-sided confidence interval [CI] upper bound <10 ms) to demonstrate a lack of effect of linezolid on QTc interval prolongation. Averages of the triplicate ECGs at each time point for subjects in cohort 2 were calculated. QT intervals were adjusted for ventricular rate using the correction methods of Fridericia (QTcF = QT divided by cube root of R-R in seconds) and Bazett (QTcB = QT divided by square root of R-R in seconds); the primary correction utilized was QTcF. Using the derived QTcF and QTcB, the mean differences between the effects of linezolid or moxifloxacin versus placebo for each time point after the start of infusion were calculated. The postdose QTc intervals were analyzed using a mixed-effect, repeated-measures model with sequence, period, treatment, and treatment-by-time interaction as fixed effects, subject within sequence as a random effect, and baseline QTc as a covariate. Baseline was defined as the mean of the three averaged triplicate measurements taken at the following three time points (−1,
–0.5, and 0 hours) before dosing within each period. Estimates of the adjusted mean
treatment differences (active treatment–placebo) and the two-sided 90% CIs for each
treatment and time were obtained from the model. ICH E14 guidance states that a
negative thorough QT/QTc study is defined as one in which the upper bound of the 95%
one-sided CI for the largest mean effect of the drug on the QTc interval excludes 10 ms
(5). The criterion used in this study for the lack of effect of linezolid was that the upper
bounds of the two-sided 90% CIs for all time-matched mean differences between
linezolid and placebo were <10 ms. Validity of the study was confirmed if the lower
bound of the two-sided 90% CI for mean difference between moxifloxacin and placebo
at the historical (3 hours) time of the maximum plasma concentration (\(T_{\text{max}}\)) was >5 ms,
per ICH guidelines. (5)

Pharmacokinetics. Blood samples (5 ml) were collected in tubes containing
tripotassium EDTA from subjects in cohort 1 before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6,
8, 12, 24, and 46 hours after the start of infusion. For subjects in cohort 2, samples were
obtained at predose and at 0.5, 1, 2, 4, 6, 8, and 24 hours after the start of infusion.
Samples from subjects in cohort 2 were collected immediately after obtaining triplicate
ECGs. All samples were kept in an ice bath immediately after collection. Plasma was
separated within 1 hour of collection and kept frozen at −20°C until analyzed. Plasma
samples were assayed for linezolid concentrations using a validated liquid
chromatography tandem mass spectrometry method by Eurofins AvTech Laboratories
(Portage, MI, USA). Samples from subjects who received placebo or moxifloxacin were
not analyzed. A 50-µl plasma aliquot was diluted with water, and proteins were
precipitated with acetonitrile. [D-3]Linezolid was used as the internal standard. Following centrifugation, a 5-µl aliquot of the supernatant was injected into a Sciex API-4000 LC-MS/MS (Applied Biosystems Inc, Foster City, CA, USA) utilizing a heated nebulizer (atmospheric pressure chemical ionization) source set up with a Phenomenex Gemini C18 column (50 × 2.0 mm, 3 µm). The mobile phase consisted of methanol:10 mM:ammonium acetate (60:40, v:v). The mass spectrometer was operated in the positive ion mode and monitored the transition ions m/z 338.1→296.1 and 341.1→297.1 for linezolid and [D-3]linezolid, respectively. The range of the assay was 250 to 50,000 ng/ml. The accuracy (percentage difference from nominal) of the quality control samples used during sample analysis ranged from –4.8 to –2.4%, with a precision (as measured by percentage relative standard deviation) of ≤6.7%.

The pharmacokinetic profile of linezolid was determined by standard noncompartmental methods using an internal validated software system, eNCA (version 2.2.2). Maximum plasma concentration (C<sub>max</sub>) and T<sub>max</sub> were determined based on observed data. Area under the concentration versus time curve to last quantifiable time point (AUC<sub>0–last</sub>) was determined using the linear-log trapezoidal method. The elimination rate constant (λ<sub>z</sub>) was estimated by linear regression of the linear portion of the natural log (ln) concentration versus time curve. AUC<sub>0–∞</sub> was calculated as the sum of AUC<sub>0–last</sub> and predicted last concentration/λ<sub>z</sub>, where the predicted concentration at the last quantifiable time point was estimated from the log-linear regression. The t<sub>1/2</sub> was calculated as ln(2)/λ<sub>z</sub>. Total body clearance (CL<sub>t</sub>) was calculated as dose divided by
AUC was calculated as MRT · CL, where MRT is the mean residence time extrapolated to infinity.

Pharmacokinetic–pharmacodynamic analyses. Three separate analyses were conducted to evaluate the data from this study. First, to assess whether a relationship exists between linezolid plasma concentration and heart rate (HR), an analysis was conducted using a linear mixed-effect model with time and linezolid plasma concentration as fixed effects and subject-specific random effects on intercept and slope. The means of triplicate R-R intervals were used as the response variable for this analysis. This analysis provides information on whether estimation of a study-specific HR correction factor for the QT intervals using baseline data would be appropriate for measurements of QT during placebo treatment or active treatment with linezolid.

Secondly, using the natural log-transformed singlet QT and R-R interval observations obtained at baseline, estimation of a study-specific correction factor was performed using a linear mixed-effect model with R-R interval (in seconds) as a fixed effect and subject-specific random effects on intercept and slope. The study-specific correction factor was then applied to calculate the study-specific corrected QT interval (QTcP) by the following equation:

\[
QTcP = QT \left( \frac{RR}{1000} \right)^{-\beta}
\]

, where \( \beta \) is the estimated study-specific correction factor.
A graphical assessment was used to evaluate how well each correction factor (uncorrected QT, QTcB, QTcF, and QTcP) removes the relationship between the QTc interval and HR. Additionally, a linear mixed effect model with R-R interval as a fixed effect and subject specific random effects on intercept and slope was fitted to the QT R-R data for each correction. The mean predicted values were overlaid on the observed data to aid in the graphical assessment.

Lastly, the same QTcF data from cohort 2 used in the statistical analysis were used to characterize the relationship between linezolid plasma concentrations and QTcF interval. The concentration-QTcF relationship was modeled using a linear mixed-effect model with sex, time, and linezolid plasma concentration as fixed effects and subject-specific random effects for intercept and slope. The means of triplicate QTcF interval values were used as the response variable for this analysis. Adequacy of the model fit was assessed graphically and model parameter estimates with two-sided 90% CIs were obtained.

All linear mixed-effect models used for the pharmacokinetic/pharmacodynamic analyses were implemented in the R software package, Version 2.11.1 (http://www.r-project.org) using the nlme package.

Safety assessment. Voluntarily reported or observed adverse events, vital signs, hematology, blood chemistry, and urinalysis were monitored for the duration of the
study in both cohorts 1 and 2. Information on the intensity of all adverse events and considered relationship to treatment were recorded.

RESULTS

Demographics. Across the two cohorts, a total of 49 healthy subjects were enrolled, 25 of whom were male. Among 9 participants in cohort 1, 4 were women (3 of these premenopausal) and all were Asian. In cohort 1, ranges for age, weight, and body mass index were 22 to 52 years (mean, 30.1 years), 49.0 to 83.0 kg (mean, 69.0 kg), and 19.2 to 28.7 kg/m$^2$ (mean 23.8 kg/m$^2$), respectively. Among 40 participants in cohort 2, 20 were women (17 of these premenopausal) and all were Asian except for 2 men. In cohort 2, ranges for age, weight, and body mass index were 21 to 48 years (mean, 29.9 years), 46.0 to 83.0 kg (mean, 60.2 kg), and 18.2 to 30.3 kg/m$^2$ (mean 22.3 kg/m$^2$), respectively. All subjects in both cohorts completed the study.

Electrocardiography. In cohort 2, time-matched differences in QTcF intervals, corrected for the placebo effect, for the standard dose of linezolid 600 mg and the supratherapeutic dose of 1,200 mg over the 24 hours following the start of infusion were similar (Fig. 1). At each time point, the upper bounds of the 90% CIs for placebo corrected QTcF values for linezolid 600 and 1,200 mg were <10 ms (linezolid 600 mg range –3.36 to 3.64 ms; linezolid 1,200 mg range –5.34 to 5.64 ms), thus satisfying the criterion for a negative thorough QT/QTc study and the absence of clinically significant QTc prolongation due to linezolid. Additionally, it should be noted that the mean change from placebo in QTcF intervals at each time point post-dose was <5 ms for both doses of linezolid.
The population $T_{\text{max}}$ for moxifloxacin is approximately 3 hours. While QTc assessment was not done at 3 hours post moxifloxacin, at 2 and 4 hours postdose the lower bound of the two-sided 90% CI when comparing moxifloxacin to placebo was $>5$ ms. Therefore, according to ICH guidelines (5), the study was deemed adequately sensitive to assess QTc prolongation.

There was a small and transient shortening of the QTcF interval after both dose levels of linezolid in cohort 2. The mean difference at 1 and 2 hours after the start of infusion with linezolid 600 mg was $-2.96$ and $-5.53$ ms, respectively, and with linezolid 1,200 mg it was $-1.78$ and $-7.51$ ms, respectively. By 4 hours after the start of linezolid infusion, QTc shortening was no longer apparent.

Postbaseline ECG values were examined based on predefined criteria. In both cohorts, no subjects had a maximum absolute QTcF interval $\geq 480$ ms or a change from baseline $\geq 60$ ms. In cohort 1, one subject had absolute QTcF value between 450 and 480 ms following treatment with linezolid 900 mg. One subject each after linezolid 900 mg and placebo treatment in cohort 1 had QTcF change from baseline between 30 and 60 ms. In cohort 2, one subject each after linezolid 600 and 1,200 mg and seven subjects after moxifloxacin had absolute QTcF values between 450 and 480 ms. One subject in the moxifloxacin group had QTcF change from baseline between 30 and 60 ms. No ECG abnormalities were recorded as being clinically significant in either cohort.
Pharmacokinetics. Mean (SD) plasma concentration profiles for linezolid in cohorts 1 and 2 are shown in Fig. 2. Pharmacokinetic parameters are summarized in Table 1. In cohort 1, a 33% dose increment of linezolid from 900 to 1,200 mg resulted in an increase in the mean $C_{\text{max}}$ and $AUC_{0-\infty}$ values by 31% and 58%, respectively. In cohort 2, an increase in the linezolid dose from 600 to 1,200 mg resulted in an increase in mean $C_{\text{max}}$ and $AUC_{0-\infty}$ values of 104% and 134%, respectively. The arithmetic means (SD) for $C_{\text{max}}$ of linezolid following a single 1-h IV infusion at doses of 600 and 1,200 mg in cohort 2 were 15.0 (2.6) and 30.8 (4.4) µg/ml, respectively. Clearance of linezolid decreased slightly with increasing dose: the mean $CL_t$ was 12.3% and 13.7% lower in cohorts 1 and 2, respectively, for the higher dose compared with the lower dose within each cohort. The $V_{ss}$ values appeared to be reasonably similar across doses within each cohort. The median $T_{\text{max}}$ values were comparable across doses and cohorts, whereas the mean $t_{95}$ values exhibited a slight trend toward being higher with increased dose. Although separate subjects were enrolled in each cohort, $CL$ normalized by body weight was plotted against dose across both cohorts to assess linearity across the entire dose range studied (Fig. 3). The $CL_t$ normalized by body weight showed a slight decreasing trend with increasing dose; however, there was significant overlap in the values across doses.

Pharmacokinetic–pharmacodynamic analysis. The mean (90% CI) slope estimate from the linezolid concentration–R-R interval analysis was $-0.0017 (-0.0022$ to $-0.0011)$ ms/µg/ml. This translates to a mean (90% CI) predicted decrease in heart rate...
of approximately 1.5 (1.0 to 2.0) and 3.0 (2.1 to 4.1) beats/min at the mean $C_{\text{max}}$
following administration of 600 mg and 1,200 mg linezolid doses, respectively.  

The study-specific mean correction factor estimated from baseline data was 0.278,
which is slightly less than Fridericia’s correction (0.333). Evaluation of the various
correction factors showed that QTcF most appropriately resolves the relationship
between QT interval and heart rate in the baseline data from this study. This is evident
upon inspection of Fig. 4 as the slope between QTcF interval and R-R interval is closest
to zero when this correction is applied.

The results from the concentration-QTcF analysis are graphically depicted in Fig. 5. The
mean (90% CI) slope estimate from the linezolid concentration-QTcF analysis was
$-0.0145 (-0.0768$ to $0.0477)$ ms/µg/ml. At the geometric mean $C_{\text{max}}$ following infusion
of linezolid 600 mg (14.9 µg/ml) and 1,200 mg (30.5 µg/ml), the mean (90% CI)
predicted placebo adjusted change from baseline QTcF was $-0.217 (-1.14$ to $0.710)$
and $-0.444 (-2.34$ to $1.45)$ ms, respectively, thus confirming a lack of a relationship
between linezolid concentrations and QTc interval.

Safety and tolerability. In cohort 1, when IV linezolid 900 mg was administered, three
subjects experienced four treatment-related adverse events: somnolence,
hypoesthesia, and two events of injection-site reactions. Two subjects experienced
three adverse events related to IV linezolid 1,200 mg: diarrhea, nausea, and headache.
All adverse events were mild in intensity. One case of diarrhea was reported by a
subject who received placebo. In cohort 2, two subjects experienced a treatment-related adverse event after receiving linezolid 600 mg: eye pruritus and tongue discoloration. Seven subjects who received linezolid 1,200 mg experienced a total of 11 treatment-related adverse events: abdominal distension (one case), nausea (four cases), tongue discoloration (one case), vomiting (one case), headache (two cases), and dysmenorrhea (two cases). All adverse events were mild in intensity. By comparison, nine subjects who received oral moxifloxacin experienced treatment-related adverse events: nausea (one case), headache (two cases), diarrhea (one case), flatulence (two cases), frequent bowel movements (one case), hunger (one case), rash (one case), and decreased urine output (one case). Following administration of placebo, there were two cases of headache, one of diarrhea, and one of eye pruritus. No clinically significant changes in vital signs, hematology, blood chemistry, or urinalysis were observed with the administration of a single IV dose of linezolid 600, 900, or 1,200 mg, or oral moxifloxacin.

**DISCUSSION**

This placebo-controlled crossover study in healthy volunteers was conducted to evaluate the effect on the QT/QTc interval of IV linezolid administered as an infusion at the standard dose of 600 mg and a supratherapeutic dose of 1,200 mg. The tolerability and safety of linezolid observed in the nine subjects in cohort 1 supported the administration of linezolid 1,200 mg to the larger study population in cohort 2. The study was conducted in accordance with the ICH guidance on a thorough QT/QTc study (5). On the basis that the upper bound of the two-sided 90% CI was <10 ms at all time.
points after the start of infusion of linezolid at both the standard and the supratherapeutic doses, no clinically significant prolongation of the QTcF interval was detected in this study following linezolid administration. In accordance with the ICH guidance, the present study used moxifloxacin as an active control (5). The population $T_{\text{max}}$ for moxifloxacin is approximately 3 hours. Although QTc assessment was not performed at 3 hours post moxifloxacin intake in the current study, at 2 and 4 hours postdose the lower bounds of the two-sided 90% CIs when comparing moxifloxacin with placebo were $>5$ ms. Hence, the study was deemed adequately sensitive to assess QTc prolongation.

While the current study conclusively demonstrates the lack of effect of linezolid on QTc interval prolongation, similar findings have been noted in patients. Combined data from two large-scale studies comparing the efficacy of linezolid versus iclaprim in nearly 1,000 patients with cSSTIs found a mean increase in the QTcB interval of 1.5 ms, from a mean baseline value of 424.4 ms, 10 min after a 30-min infusion of linezolid 600 mg. By comparison, IV iclaprim 0.8 mg/kg infused over 30 min brought about a 7.1-ms prolongation 10 min after the completion of the infusion from a baseline of 423.4 ms (4).

In the present study, a shortening of the QTcF interval was observed immediately after completion of the infusion of linezolid at both the standard and supratherapeutic doses in cohort 2. This shortening was transient, being no longer apparent 4 hours after the start of dosing. Although congenital short QT syndrome (QT $<300$ ms) is associated with arrhythmias and sudden death (3), the clinical significance of drug-induced small,
transient shortening of the QT interval is unclear (8). A drug-induced shortening of an average of >20 ms has been suggested to be clinically relevant, although there is no clinical evidence to support this (8). In the current study with linezolid, no subjects reached these purported thresholds for clinical concern.

The pharmacokinetic parameters of the standard IV linezolid dose of 600 mg in this study are consistent with those previously reported from studies conducted in healthy volunteers (10) and patients with gram-positive infections (7). Phase I dose-escalation studies suggested that there was a slight degree of nonlinearity in clearance with increasing doses. The present study showed a similar trend toward decrease in clearance with increasing doses of linezolid from 600 to 1,200 mg, but the degree of nonlinearity was small.

Drug or food interactions that result in clinically meaningful increases in linezolid concentration have not been observed (11). Similarly, no dose adjustments of linezolid are needed for geriatric patients or patients with renal or hepatic insufficiency. Although women exhibit higher plasma linezolid concentrations than men, partly due to differences in body weight, dose adjustments are not necessary based on sex (11). Therefore, during routine clinical use of linezolid 600 mg given every 12 hours, systemic concentrations are unlikely to be markedly elevated. In the current study, the arithmetic means (SD) for $C_{\text{max}}$ of linezolid following a single 1-hour IV infusion at doses of 600 and 1,200 mg in cohort 2 were 15.0 (2.6) and 30.8 (4.4) µg/ml, respectively. Historically, the maximum therapeutic dose of linezolid 600 mg q12 h resulted in mean (SD) steady-
state $C_{\text{max}}$ of 21.20 (5.78) µg/ml after oral administration and 15.10 (2.52) µg/ml after 30-minute IV infusion (11). Therefore, the use of linezolid at a supratherapeutic dose of 1,200 mg in the current study provided greater systemic concentrations for QTc evaluation compared with those observed during routine clinical use of linezolid. It is important to note that the recommended dosage of linezolid for routine clinical use is 600 mg every 12 hours (11).

A marginal decrease in mean heart rate (~–1.5 to 3.0 ms) was predicted across the mean maximum linezolid plasma concentrations in this study. Given the small magnitude of change, the QT–R-R relationship between off-drug and on-drug periods of the study was not thought to be meaningfully different. This finding lends support for estimation of a study-specific correction factor using off-drug data from the current study and subsequent application of the estimated correction factor to all QT–R-R measurement pairs in the study to derive the QTcP interval. Calculation of the QTcP interval and assessment of its performance is a necessary step in evaluating drug effects on QTc, as QTcF is not always the most appropriate correction factor to remove the relationship between QTc and R-R intervals for a given study. However, in our study, QTcF did provide the most appropriate correction for the QT interval. Overall, the exposure-response analysis was in agreement with the statistical results and provides additional support for the claim that administration of linezolid is not expected to affect the QTcF interval.
In conclusion, at the standard dose of 600 mg and a supratherapeutic dose of 1,200 mg, linezolid had no clinically relevant effect on the QT/QTc interval in healthy subjects. Systemic exposure of linezolid increased in a slightly more than dose-proportional manner with increasing doses. The study also showed that linezolid was well tolerated after single IV doses of 600 to 1,200 mg.
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REFERENCES


TABLE 1. Summary statistics for pharmacokinetic parameters for IV linezolid infused over 1 hour at doses of 900 and 1,200 mg in cohort 1, and at doses of 600 and 1,200 mg in cohort 2

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>Cohort 1 (n = 9)</th>
<th>Cohort 2 (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>900 mg</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>AUC_{0–∞}, µg · h/ml</td>
<td>219 (21)</td>
<td>340 (22)</td>
</tr>
<tr>
<td>AUC_{0–last}, µg · h/ml</td>
<td>206 (23)</td>
<td>326 (20)</td>
</tr>
<tr>
<td>C_{max}, µg/ml</td>
<td>22.0 (18)</td>
<td>28.8 (22)</td>
</tr>
<tr>
<td>T_{max}, h</td>
<td>1.0 (1.0–1.5)</td>
<td>1.0 (1.0–1.5)</td>
</tr>
<tr>
<td>t_{1/2}, h</td>
<td>6.9 (22)</td>
<td>7.6 (27)</td>
</tr>
<tr>
<td>CL_{t}, ml/min/kg</td>
<td>1.01 (16)</td>
<td>0.87 (21)</td>
</tr>
</tbody>
</table>
\( V_{ss} \)

<table>
<thead>
<tr>
<th></th>
<th>L/kg</th>
<th>0.60 (11)</th>
<th>0.58 (8)</th>
<th>0.64 (13)</th>
<th>0.62 (11)</th>
</tr>
</thead>
</table>

Geometric mean (CV%) for all parameters, except: median (range) for \( T_{\text{max}} \); arithmetic mean (CV%) for \( t_{\frac{1}{2}} \).

\(^{b} n = 39\) for \( t_{\frac{1}{2}} \); \( n = 38\) for \( \text{AUC}_{0-\infty} \), and \( V_{ss} \).

\(^{c} n = 37\) for \( t_{\frac{1}{2}} \); \( n = 36\) for \( \text{AUC}_{0-\infty} \), CL, and \( V_{ss} \).

CV, coefficient of variation.
FIG. 1. Time-matched differences from placebo in QTcF intervals for IV linezolid 600 mg, IV linezolid 1,200 mg, and oral moxifloxacin 400 mg (n = 40).
FIG. 2. Plasma concentrations of linezolid versus time after IV infusion over 1 hour of (A) linezolid 900 and 1,200 mg in cohort 1 (n = 9) and (B) linezolid 600 and 1,200 mg in cohort 2 (n = 40).
FIG. 3. Clearance of linezolid following administration of single IV doses of 600, 900, and 1,200 mg linezolid in cohort 1 ($n = 9$) and cohort 2 ($n = 40$).
FIG. 4. Evaluation of various heart rate correction factors for QT interval vs R-R interval. Predicted line in each figure represents the fit from a linear mixed-effect model with RR interval as a fixed effect and subject-specific random effects for intercept and slope.
FIG. 5. QTcF interval versus plasma linezolid concentrations.

- Observed QTcF Interval (ms)
- Mean Predicted QTcF Interval (ms)
- 90% CI

Males

Females

Linezolid Plasma Concentration (µg/mL)

Linezolid Plasma Concentration (µg/mL)
The diagram shows the relationship between linezolid plasma concentration (μg/mL) and QTcF interval (ms) for males and females. The plots include observed data points, mean predicted QTcF intervals, and 90% confidence intervals. The x-axis represents linezolid plasma concentration, while the y-axis shows the QTcF interval. The data points are scattered across the graph, indicating variability in the QTcF interval across different plasma concentrations.