Fourteen-Day Bactericidal Activity, Safety, and Pharmacokinetics of Linezolid in Adults with Drug-Sensitive Pulmonary Tuberculosis

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Abstract

Background

Linezolid is increasingly used for the treatment of tuberculosis resistant to first-line agents, but the most effective dosing strategy is yet unknown.

Methods

Between November 2014 and November 2016, we randomised 114 drug-sensitive treatment-naïve pulmonary tuberculosis patients from Cape Town, South Africa, to one of six 14-day treatment arms containing linezolid 300 mg once daily (qd), 300 mg twice daily (bd), 600 mg qd, 600 mg bd, 1200 mg qd, 1200 mg three times per week (tiw) or a combination of isoniazid, rifampicin, pyrazinamide and ethambutol. Sixteen-hour sputum samples were collected overnight, and bactericidal activity characterized by the daily percentage change in time to positivity (TTP) and colony forming units (CFU). We also assessed the safety and pharmacokinetics of the study treatments.

Results

Bactericidal activity increased with increasing doses of linezolid. Based on the daily percentage change in TTP, activity was highest for 1200 mg qd (4.5; 95% Bayesian confidence interval [BCI]: 3.3-5.6), followed by 600 mg bd (4.1; BCI: 2.5-5.7), 600 mg qd (4.1; BCI: 2.9-5.3), 300 mg bd (3.3; BCI: 1.9-4.7), 300 mg qd (2.3; BCI: 1.1-3.5) and 1200 mg tiw (2.2; BCI: 1.1-3.3). Similar results were seen with bactericidal activity characterized by the daily rate of change in CFU count. Antimycobacterial activity correlated positively with plasma drug exposure and percentage time over minimum inhibitory concentration. There were no unexpected adverse events.

Conclusion

All linezolid doses showed bactericidal activity. For the same total daily dose, once daily dosing proved to be at least as effective as a divided twice daily dose. An intermittent dosing regimen, with 1200 mg given three times weekly, showed the least activity.

[268 words]

Introduction

Tuberculosis (TB) continues to be a major public health problem globally, with the number of persons infected with TB resistant to first line drug therapy continuing to increase (1). Together with the novel nitroimidazole class of anti-TB agents, pretomanid and delamanid, and the novel diarylquinoline bedaquiline, linezolid is a good candidate for inclusion in a much-needed new regimen for treatment of drug-resistant TB. Previous studies have shown that linezolid may play a valuable role in improving the rate of culture conversion in patients with drug-resistant TB (2). In a prospective, randomised, controlled trial performed in South Korea, 87% of patients with extensively drug-resistant TB, unresponsive to TB chemotherapy within 6 months prior to study enrolment, achieved sputum culture conversion within 6 months after linezolid (600 mg/d) was added to their background regimen (2). Four patients acquired drug resistance to linezolid in this study, of whom three showed relatively low exposures of linezolid.

Despite the inclusion of linezolid in current drug-resistant TB regimens (3), there is limited information about the relationship between the dose of linezolid and its mycobactericidal activity. While linezolid is approved at a dose of 600 mg every 12 hours for up to 28 days to treat selected bacterial infections (4), the toxicities of myelosuppression and peripheral neuropathy, in particular, have raised concerns about using this dose long term for the treatment of TB infections. Key toxicities of linezolid are thought to be related to inhibition of mitochondrial protein synthesis, and drug exposures above a threshold for this inhibition may have greater risk of causing toxicity. In reports of use of linezolid beyond two months to treat TB, adverse events were primarily related to haematological, neurological and gastrointestinal disorders. Based on a review of the literature, haematological disorders were generally moderate and reversible upon discontinuation of linezolid. Peripheral neuropathy often resolved or partially resolved with dosage reduction or discontinuation of linezolid, although cases of irreversible peripheral neuropathy have been reported (5, 6, 7, 8). In a systematic review and meta-analyses of prolonged use of linezolid, Agyeman and Ofori-Asenso found that myelosuppression occurred in a higher proportion of patients than neuropathy, but that in most studies this could be managed by temporarily or permanently discontinuing linezolid therapy (9). These authors also reported that the incidence of myelosuppression was dose related, with lower

doses being associated with lower incidence, while neuropathy was not highly associated with higher doses of linezolid.

Preclinical studies in a mouse model of infection have shown that drug exposure equivalent to a 1200 mg total daily dose in humans is required to have mycobacterostatic activity (10). Consequently, this study was undertaken to provide rigorous information about the bactericidal activity of varying dosing schemes in humans with new TB infections over the first 14 days of treatment. The results will allow a better assessment of the potential risks and benefits as linezolid continues to be incorporated in TB treatment regimens.

Methods

Participants

The study was conducted at two sites in Cape Town, South Africa: TASK Applied Science Tuberculosis Clinical Research Centre and the University of Cape Town Lung Institute. Local ethics and regulatory approvals were received prior to conduct of the study. The study is registered on www.clinicaltrials.gov, with study identifier: NCT02279875. Between November 2014 and November 2016, we included 114 patients with rifampicin-sensitive pulmonary TB showing at least 1+ positive for acid-fast bacilli on sputum microscopy (as per the WHO/International Union Against Tuberculosis and Lung Disease scale). Participants were treatment-naïve, aged between 18 and 75 years, with body weight of 35 to 100 kg, had a chest X-ray compatible with pulmonary TB and were able to produce at least 10 mL of sputum during a 16-hour collection. Patients with evidence of extrathoracic TB, poor general condition requiring immediate initiation of anti-TB therapy, diabetes mellitus, human immunodeficiency virus (HIV) infection with a CD4+ cell count ≤250 cells/μL, or significant cardiac arrhythmias were excluded. After completion of the 14-day study treatment, all participants were started on standard-of-care anti-TB therapy and followed up after 14 days to exclude late signs of toxicity and to ascertain that they were receiving standard TB treatment at their community clinics.

Treatments

Eligible participants were randomly assigned to one of five linezolid treatment groups with approximately 15 participants each: 300 mg once daily (qd); 300 mg twice daily (bd); 600 mg

qd; 600 mg bd; 1200 mg qd; or a smaller control group receiving standard combination-drug therapy (weight-banded isoniazid, rifampicin, pyrazinamide, and ethambutol [HRZE] combination tablets according to South African National TB Programme guidelines). After completion of the once-daily and twice-daily dosing groups, two additional groups of approximately 15 patients each were included, receiving linezolid 1200 mg three times per week (tiw) or 600 mg qd (for temporal comparison with the previous group). Therapy was administered for 14 consecutive days by study staff 1 hour before or 2 hours after meals, with 250 mL water, at approximately the same time daily throughout the study period.

Safety and toxicity

Participants were hospitalised for the duration of study treatment and assessed daily by the study physicians for adverse events that were graded according to the Division of Microbiology and Infectious Diseases Adult Toxicity Table. Regular monitoring for specific laboratory toxicities was based on target organs defined in preclinical toxicity studies and included, among others, elevations in transaminases (alanine- and aspartate aminotransferase), amylase, lipase, features of myelosuppression and lactic acidosis. Adverse events were elicited by means of open-ended questions. Participants who experienced signs or symptoms of peripheral neuropathy, optic neuropathy or seizures were to permanently discontinue study treatment and be managed according to standard medical practice. Impairment of human mitochondrial protein synthesis (MPS) is suspected to be the underlying mechanism associated with these common toxicities of long-term linezolid use. For each participant, we calculated the percentage time linezolid concentration exceeded MPS IC50, the concentration of linezolid required to inhibit 50% of MPS. The value of MPS IC50 we used was 2.7 μg/mL, the median of 25 independent assessments derived from an in vitro study (internal data).

Microbiology

Before patients were included in the study, susceptibility to rifampicin was ascertained with the Genotype MTBDRplus line probe assay (Hain, Nehren, Germany). For endpoint assessments, sputum was collected for 16 consecutive hours overnight for 2 days prior to study therapy initiation and daily from day 1 to 14 during therapy. Sputum samples were kept at 2 to 8°C before transport to the central laboratory at the Department of Medical Biochemistry, Faculty of

Health Sciences, Stellenbosch University, Cape Town. For time to positivity (TTP), sputum was homogenised by magnetic stirring, decontaminated with NaOH-NALC (AlphaTec NAC-PAC *Red*; AlphaTec, Vancouver, WA, USA), and incubated in duplicate in a standardized liquid culture system (Bactec MGIT 960; BD, Franklin Lakes, NJ, USA). TTP was recorded in hours. Additionally, homogenised non-decontaminated sputum was inoculated in 10-fold dilutions in quadruplicate onto 7H11S agar plates (BD) made selective with the addition of Selecatab (MAST, Merseyside, UK) and incubated for 3 to 4 weeks for colony forming unit (CFU) counting. Phenotypical susceptibility to first-line anti-TB agents was ascertained with the MGIT system (BD). Minimal inhibitory concentrations of participants' isolates to linezolid were assessed with the agar proportion method.

Pharmacokinetics and pharmacodynamics

Blood draws for pharmacokinetic measurements occurred on day 14 of study therapy for all participants in the linezolid-containing treatment groups. Sampling occurred pre-dose and at 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose. At each time point, approximately 9 mL of blood was collected in a lithium-heparin blood collection tube, placed on ice, and centrifuged within 45 minutes of collection in a refrigerated centrifuge at 1,500 g for 10 minutes. Plasma was then transferred into two polypropylene tubes and stored at -20°C until shipment and analysed using a validated method. Pharmacodynamics were assessed by determining the percentage time over minimum inhibitory concentration (T_{MIC}).

Statistical analyses

This was an observational study with no prespecified hypothesis testing. Bactericidal activity was characterised by the daily percentage change in TTP and the daily rate of change in $\log_{10}$(CFU) count over fourteen treatment days using Bayesian non-linear mixed effects regression modelling (11, 12). This model has been designed specifically for this type of data and can handle missing data due to contamination, early participant withdrawal, or culture conversion. The model accounts for correlations between the random intercepts and slopes over time (e.g. bacterial load at baseline is typically associated with the rate of change in CFU count or TTP over time (13)). Dose response was assessed using the Jonckheere-Terpstra (J-T) test (14). For safety and tolerability endpoints, we determined the incidence and severity of adverse

events. Pharmacokinetic parameters included maximum linezolid plasma concentration (C_{max}), time of C_{max} (t_{max}), area under the plasma concentration–time curve over the dosing intervals ($AUC_{(0\text{-}tau)}$), from zero to 24 hours ($AUC_{(0\text{-}24)}$), and until 168 hours ($AUC_{(0\text{-}168)}$) for the three-times-weekly dosing group, as well as the average plasma concentration over the total dosing interval (C_{avg}). Spearman correlation coefficients were evaluated between 14-day bactericidal activity and C_{max}, C_{avg}, $AUC_{(0\text{-}24)}$, TMIC, Time over MPS IC50, C_{max}/MIC, C_{avg}/MIC, and $AUC_{(0\text{-}24)}$/MIC. PK indices were calculated using Phoenix WinNonlin (Certara, Princeton, NJ, USA).

Results

Participants

Of the 114 enrolled participants, 107 completed the study until the final follow-up visit. Seven participants were withdrawn from the study (Figure 1). Among all enrolled participants, the mean age was 33 years, 83% were male, and 96% were HIV negative (Table 1).

Bactericidal activity

The highest mean bactericidal activity over 14 days was seen with the highest once daily dose of linezolid, 1200 mg qd, while 600 mg qd and 300 mg qd had lower mean activities. Confidence intervals for mean responses of the dose groups overlapped (Tables 2 and 3); but the J-T test was significant ($p < 0.001$), providing evidence for an ordered dose response. For those receiving the same total daily dose, twice daily dosing did not show any advantage over once daily dosing. The two linezolid 600 mg qd groups, analyzed separately and pooled, showed similar bactericidal activity for both TTP and CFU. The pooled data in the final analysis thus resulted in a group size twice that of the other linezolid groups. The control group receiving standard therapy (HRZE) showed the expected change in viable mycobacterial load for both bactericidal activity endpoints, change over time in TTP and CFU count. All infecting bacteria were identified as *Mycobacterium tuberculosis* (*M.tb*) and all patients on HRZE were susceptible to all anti-TB agents.

Safety and toxicity

All adverse events seen were expected for linezolid from experience in other indications. The most commonly reported adverse events included rash and pruritus (8.8% each), diarrhoea (7.1%), vomiting (5.3%), headache (4.4%), dizziness (3.5%), and increases in liver transaminases (4.4%) and amylase (5.3%). Seventy-one treatment-related adverse events were recorded during the trial, of which the majority were mild or moderate in severity. Adverse events were evenly distributed amongst the dose groups, with no obvious relationship between linezolid exposure/dose and number of events. Participants dosed only three times per week (linezolid 1200 mg tiw) experienced no less serious or frequent adverse events than participants receiving daily or twice-daily linezolid. As expected, critical events related to myelosuppression or neuropathy were not seen over the relatively short 2-week treatment period.

Four of 114 participants (3.5%) who started on linezolid were withdrawn due an adverse event (Figure 1), two of whom developed a grade 3 elevation in transaminases (600 mg qd) and drug induced liver injury (DILI) (600 mg bd), and another two with grade 4 elevated transaminases (300 mg qd) and DILI (1200 mg tiw). One participant in the 1200 mg tiw group died early in treatment due to massive haemoptysis. Two participants withdrew consent from further study participation for reasons not related to an adverse event.

In terms of MPS inhibition, a clear dose-response relationship was observed. The twice-daily treatment regimens had higher mean Time over MPS IC50 (%) than their once-daily counterparts with the same total daily dose, as follows: 99.9% for 600 mg bd, 77.3% for 300 mg bd, 88.9% for 1200 mg qd, 54.8% for 600 mg qd, 24.8% for 300 mg qd, and 38.6% for 1200 mg tiw.

Pharmacokinetics and pharmacodynamics

Over the 300 mg to 1200 mg dose range, plasma C_{max} and AUC increased more than proportionally to dose (Table 4). Half-life also increased with dose, consistent with non-linear pharmacokinetics of linezolid previously observed by some investigators (15, 16, 17, 18) but not all (19, 20). In comparison to once-daily regimens with the same total daily dose, twice-daily administration provided comparable AUC, lower C_{max}, and higher trough concentrations. There were no consistent gender effects. MIC values of 91 participants treated with linezolid (86.7%) were 0.25, 0.5, and 1 µg/mL in 10, 61, and 20 participants, respectively, which is within the

expected range of 0.125 to 1 µg/mL (21). Linezolid 1200 mg qd, 300 mg bd, and 600 mg bd reached 100% time above MIC in all participants, while 300 mg qd and 600 mg qd reached a mean of 58% and 89% time above MIC, respectively. Spearman correlation coefficients for TTP were positive and statistically significant ($p < 0.05$) for C_{max}, C_{avg}, $AUC_{(0-24)}$, TMIC, Time over MPS IC50, and C_{avg}/MIC, and were moderately large in magnitude (> 0.4) for C_{avg}, TMIC, and Time over MPS IC50. These findings suggest that linezolid has concentration-dependent bactericidal activity against *M.tb*.

Discussion

In this 2-week monotherapy study with increasing doses of linezolid, the greatest antimycobacterial activity was found with the once-daily 1200 mg dose, with lower activity seen when smaller daily doses were given. Twice-daily dosing appeared to have no clear advantage over once-daily dosing. Linezolid once-daily regimens also showed a lower mean percentage Time over MPS IC50 and may thus be associated with relatively less toxicity over a prolonged treatment period.

The bactericidal activity of the highest tested dose, 1200 mg daily, with a daily mean $\log_{10}$(CFU) decline of 0.104 (BCI: 0.052-0.158), is in the range of that found previously for established anti-TB agents such as rifampicin 10 mg/kg or pyrazinamide 2g (22) and more recently evaluated novel compounds such as bedaquiline 400 mg, pretomanid 200 mg, meropenem-amoxicillin-clavulanic acid three times daily, and sutezolid 600 mg bd (23, 24, 25, 26, 27). In an ongoing study in participants with highly drug-resistant TB treated with a combination of bedaquiline, pretomanid and linezolid, an overall cure rate of approximately 90% has been observed, with this all-oral triple drug combination recently receiving US FDA approval for use in this patient population (28).

Based on our study findings, higher doses of linezolid appeared more active, at least during the first 2 weeks of treatment, and the same total daily dose is at least as effective given once daily as when given in a divided twice daily dose. As an alternate dosing strategy to exploit its early bactericidal potential while maintaining an acceptable toxicity profile, one may consider linezolid treatment initiation at the highest tested dose, 1200 mg daily, for the first 2 to 4 weeks,

followed by dose de-escalation to 600 mg or 300 mg once daily based on individual tolerability. However, further studies are needed to explore the long-term linezolid safety profile at such high doses, while the need for dose modifications should continue to be guided by individual risk/benefit assessments.

This study adds to the mounting evidence that the oxazolinidones continue to have their place in antituberculosis treatment regimens, provided that long-term toxicity can be managed.

279 **References**

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368 **Table 1**. Baseline characteristics of study participants.

Treatment group	n	Males n (%)	Mixed ethnicity n (%)	Age (yrs) Mean (SD)	BMI (kg/M^2) Mean (SD)	HIV positive n (%)	Baseline CFUs (log_{10}/mL sputum) Mean (SD)		Baseline log_{10}(TTP) (hrs) Mean (SD)	
LIN 300 qd	14	12 (85.7)	11 (78.6)	29.7 (7.66)	18.94 (1.755)	0	5.931	1.460	2.033	0.106
LIN 300 bd	15	14 (93.3)	10 (66.7)	30.7(11.32)	19.38 (2.549)	0	5.469	1.218	2.064	0.134
LIN 600 qd	30	22 (73.3)	14 (46.7)	33.1 (10.63)	18.99 (2.181)	1 (3.3)	6.272	0.876	2.027	0.096
LIN 600 bd	15	13 (86.7)	7 (46.7)	32.3 (10.44)	18.45 (2.572)	0	5.424	1.632	2.061	0.155
LIN 1200 qd	16	13 (86.7)	8 (53.3)	34.0 (14.44)	20.00 (3.339)	2 (13.3)	5.769	1.391	2.068	0.184
LIN 1200 tiw	16	13 (81.3)	6 (37.5)	35.1(12.81)	19.39 (2.882)	0	6.172	0.947	2.046	0.105
HRZE	8	7 (87.5)	3 (37.5)	35.9 (8.97)	19.70 (3.829)	1 (12.5)	6.046	0.803	2.070	0.085
All	114	94 (83.2)	59 (52.2)	32.9 (11.06)	19.21 (2.619)	4 (3.5)	5.869	1.189	2.052	0.123

CFU = colony-forming unit; HIV = human immunodeficiency virus; LIN = linezolid; TTP = time to positivity. HRZE is a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol. Mixed ethnicity refers to the multiracial ethnic group native to Southern Africa, commonly referred to as Coloured.

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372 **Table 2**. Bactericidal activity per treatment arm expressed as the daily percentage change in
373 TTP from Day 0 to Day 14

		Period (days)		
		0-14	0-2	7-14
Treatment arm	**n**	**Posterior estimate (95% BCI)**	**Posterior estimate (95% BCI)**	**Posterior estimate (95% BCI)**
LIN 300 qd	14	2.269 (1.071; 3.535)	2.073 (–0.535; 4.840)	2.477 (–0.375; 5.270)
LIN 300 bd	15	3.303 (1.949; 4.663)	2.268 (–3.809; 8.091)	3.557 (1.945; 5.083)
LIN 600 mg qd	30	4.128 (2.943; 5.342)	6.392 (4.763; 8.173)	2.746 (1.032; 4.505)
LIN 600 mg bd	15	4.071 (2.521; 5.666)	5.962 (3.759; 8.517)	2.337 (0.171; 4.593)
LIN 1200 mg qd	15	4.458 (3.301; 5.630)	5.518 (2.729; 8.156)	3.585 (2.127; 5.156)
LIN 1200 mg tiw	15	2.178 (1.101; 3.253)	3.832 (1.401; 6.598)	1.595 (0.232; 2.889)
HRZE	8	6.918 (4.825; 9.141)	20.189 (10.200; 30.240)	4.174 (1.755; 6.685)

BCI = Bayesian credibility interval; LIN = linezolid; TTP = time to positivity. HRZE is a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol.

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Table 3. Bactericidal activity per treatment arm expressed as the daily rate of change in log_{10}(CFU) count from Day 0 to Day 14

		Period (days)		
		0-14	0-2	7-14
Treatment arm	**n**	**Posterior estimate (95% BCI)**	**Posterior estimate (95% BCI)**	**Posterior estimate (95% BCI)**
LIN 300 qd	14	0.024 (–0.020; 0.071)	0.006 (–0.138; 0.116)	0.032 (–0.038; 0.103)
LIN 300 bid	15	0.060 (0.008; 0.114)	0.110 (0.026; 0.230)	0.025 (–0.054; 0.100)
LIN 600 mg qd	30	0.094 (0.060; 0.126)	0.177 (0.121; 0.238)	0.035 (–0.021; 0.090)
LIN 600 mg bid	15	0.072 (0.014; 0.127)	0.093 (0.008; 0.178)	0.053 (–0.031; 0.133)
LIN 1200 mg qd	15	0.104 (0.052; 0.158)	0.071 (–0.071; 0.189)	0.116 (0.048; 0.188)
LIN 1200 mg tiw	15	0.069 (0.034; 0.105)	0.076 (–0.051; 0.191)	0.067 (0.023; 0.112)
HRZE	8	0.167 (0.088; 0.245)	0.238 (0.096; 0.457)	0.132 (0.029; 0.228)

CFU = colony forming unit; BCI = Bayesian credibility interval; LIN = linezolid. HRZE is a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol.

395 **Table 4.** Pharmacokinetics of linezolid

Parameter (unit)	LIN 300 mg qd (n = 13)[1]	LIN 600 mg qd (n = 28)[2,3]	LIN 1200 mg qd (n = 15)	LIN 300 mg bd (n = 15)	LIN 600 mg bd (n = 14)	LIN 1200 mg tiw (n = 13)
C_{max} (mcg/mL)	7.056 (21.1)	14.46 (23.9)	30.25 (20.5)	9.266 (29.6)	23.92 (20.9)	26.01 (25.4)
t_{max} (h)[4]	1.03 (0.50 - 4.00)	2.00 (0.50 - 4.03)	1.00 (0.50 - 2.02)	1.00 (0.50 - 2.05)	1.01 (0.50 - 2.00)	2.00 (0.92 - 4.00)
$AUC_{(0\text{-}tau)}$ (mcg×h/mL)	40.67 (35.5)	106.8 (36.5)	287.7 (30.4)	54.90 (24.7)	167.9 (26.8)	244.7 (37.3)
$AUC_{(0\text{-}24)}$ (mcg×h/mL)	40.67 (35.5)	106.8 (36.5)	287.7 (30.4)	109.7 (24.7)	335.6 (26.8)	228.4 (31.1)
$AUC_{(0\text{-}168)}$ (mcg×h/mL)	ND	ND	ND	ND	ND	736.5 (37.7)
C_{avg} (mcg/mL)	1.694 (35.6)	4.450 (36.4)	12.00 (30.4)	4.602 (24.8)	14.08 (26.9)	4.386 (37.7)
$C_{(predose)}$ (mcg/mL)	0.1653 (75.6)	0.5278 (147.0)	2.419 (83.8)	2.487 (38.7)	8.819 (42.1)	0.3134 (48.5)
$t_{1/2}$ (h)	3.598 (31.3)	4.573 (38.6)	6.446 (28.8)	4.982 (23.3)	6.340 (28.5)	5.351 (45.4)

LIN = linezolid; ND = not determined.
[1]n = 11 for $t_{1/2}$.
[2]Results of pooled data for participants recruited before and after Amendment 02 of the protocol are presented for linezolid 600 mg qd.
[3]n = 26 for $t_{1/2}$.
[4]Median (minimum – maximum).
Unless indicated otherwise, all values are given as the geometric mean and (percent coefficient of variation [% CV]).

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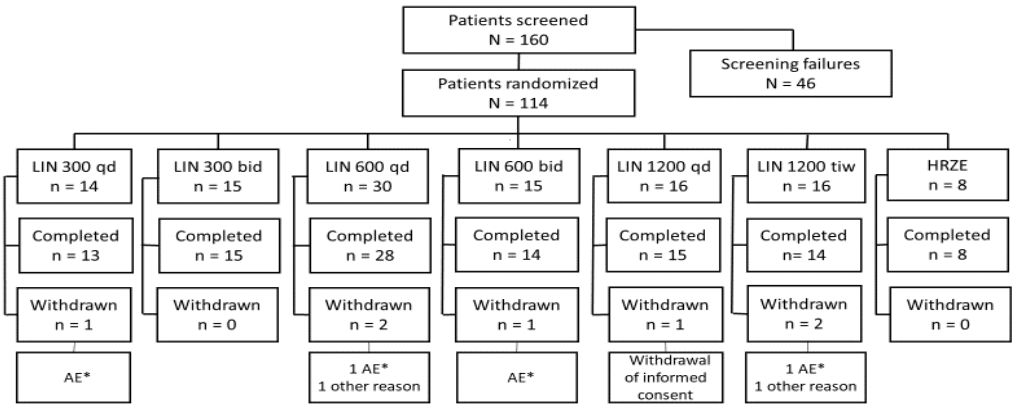
401 **Figure 1.** Participant disposition



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One participant (receiving linezolid 1200 mg tiw) died from massive haemoptysis (not related to study treatment). Four participants (one each receiving 300 mg qd, 600 mg qd, 600 mg bd, and 1200 mg tiw) were withdrawn for elevations in liver enzymes (ALT and/or AST) that reached grade 4 in two cases and grade 3 in another two cases. Two participants withdrew consent from further study participation (1200 mg qd and 600 mg qd) for personal reasons not related to an adverse event.

LIN = linezolid, qd = once daily, bid = twice daily, tiw = three times weekly. HRZE is a fixed-dose combination of rifampicin, isoniazid, pyrazinamide, and ethambutol.

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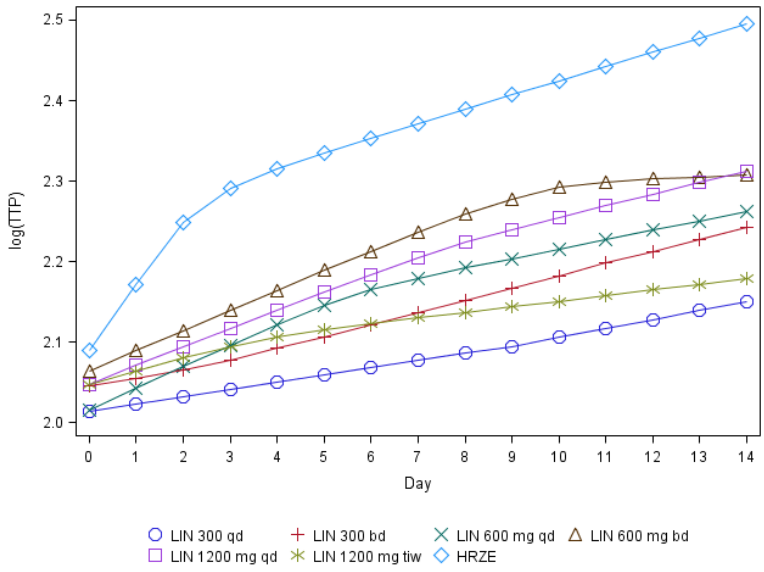

LIN = linezolid, qd = once daily, bd = twice daily, tiw = three times weekly. TTP = time to positivity. HRZE is a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol.

405 **Figure 2.** Posterior estimates of mean $\log_{10}$(TTP) over 14 treatment days.

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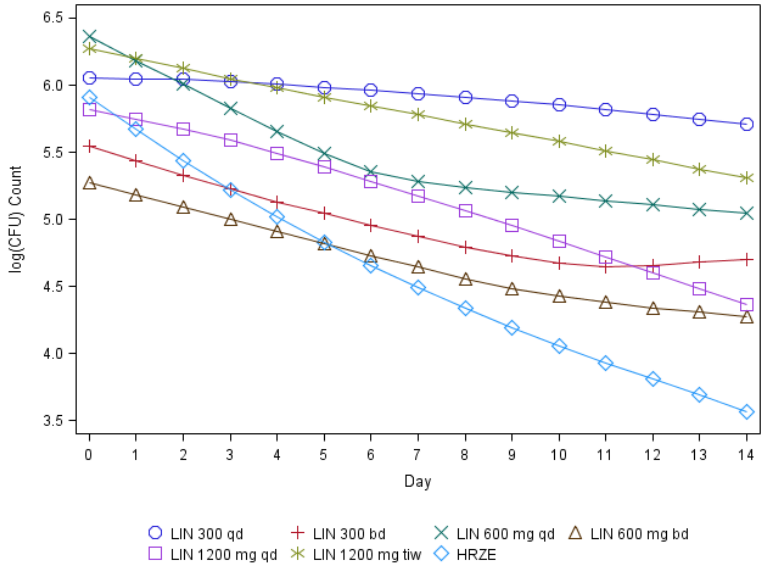

CFU = colony forming unit; LIN = linezolid, qd = once daily, bd = twice daily, tiw = three times weekly. HRZE is a fixed-dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol.

406 **Figure 3.** Posterior estimates of mean $\log_{10}$(CFU) count over 14 treatment days.