Sutezolid in combination with bedaquiline, delamanid, and moxifloxacin for pulmonary tuberculosis (PanACEA-SUDOCU-01): a prospective, open-label, randomised, phase 2b dose-finding trial

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Summary

Background Linezolid is a key component globally in first-line therapy for drug-resistant tuberculosis but has considerable toxicity. New and safer alternative oxazolidinones are needed. Sutezolid is one such promising alternative. We aimed to evaluate preliminary efficacy and safety of sutezolid and to identify an optimal dose.

Methods PanACEA-SUDOCU-01 was a prospective, open-label, randomised, phase 2b dose-finding study in four tuberculosis trial sites in Tanzania and South Africa. Adults aged 18–65 years with newly diagnosed, drug-sensitive, smear-positive tuberculosis were enrolled and randomly assigned (1:1:1:1:1) by a probabilistic minimisation algorithm using a web-based interface, stratified by site, sex, and HIV status, to receive no sutezolid (U0), sutezolid 600 mg once daily (U600), sutezolid 1200 mg once daily (U1200), sutezolid 600 mg twice daily (U600BD), or sutezolid 800 mg twice daily (U800BD), all administered orally for 12 weeks followed by standard therapy for 6 months. All participants received oral bedaquiline (400 mg once daily for 14 days followed by 200 mg thrice weekly), oral delamanid (100 mg twice daily), and oral moxifloxacin (400 mg once daily). For the primary endpoint, measured in the modified intention-to-treat population, sputum samples were taken weekly to measure the change in bacterial load measured by time to positivity using the mycobacterial growth indicator tube system. Safety was assessed through weekly electrocardiography, safety blood tests, vision testing, and physical and neurological examinations. Intensive pharmacokinetic measurements were done on day 14 to determine exposure to sutezolid, bedaquiline, delamanid, and moxifloxacin. This trial is registered with ClinicalTrials.gov (NCT03959566).

Findings Between May 20, 2021, and Feb 17, 2022, 186 individuals were screened for eligibility, 75 of whom were enrolled and randomly assigned to U0 (n=16), U600 (n=15), U1200 (n=14), U600BD (n=15), or U800BD (n=15). 56 (75%) participants were male and 19 (25%) were female. The final pharmacokinetic–pharmacodynamic model showed a benefit of sutezolid, with an increase in time to positivity slope steepness of 16·7% (95% CI 0·7–35·0) at the maximum concentration typical for the 1200 mg dose, compared with no sutezolid exposure. A maximum effect of sutezolid exposure was not observed within the investigated dose range. Six (8%) participants (one in the U600 group, two in the U600BD group, one in the U800BD group, and two retrospectively identified in the U600 group) had an increase in a QT interval using Fridericia correction greater than 60 ms from baseline. Two (3%) participants in the U600BD group had grade 4 adverse events, one each of neutropenia and hepatotoxicity, but they were not deemed associated with the use of sutezolid by the investigators. No neuropathy was reported.

Interpretation Sutezolid, combined with bedaquiline, delamanid, and moxifloxacin, was shown to be efficacious and added activity to the background drug combination, although we cannot make a final dose recommendation yet. This study provides valuable information for the selection of sutezolid doses for future studies, and described no oxazolidinone class toxicities at the doses used.

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Introduction

Tuberculosis was the leading cause of deaths from any infectious pathogen in 2023.[1] Better treatment regimens are needed to successfully curb this global health emergency. A 2024 WHO target regimen profile emphasises the urgent need for regimens of shorter duration, better safety, and less pre-existing resistance.[2]

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English between Jan 1, 2000, and July 26, 2024, using MeSH terms "tuberculosis" AND "oxazolidinones" OR "sutezolid" OR "PNU-100480". Linezolid, the first oxazolidinone antibiotic, was approved in 2000 to treat Gram-positive bacterial infections. In 2012, a randomised controlled trial from South Korea showed improved patient outcomes by adding linezolid to drug-resistant tuberculosis therapy. Further studies have consolidated linezolid's prominence in WHO guidelines for drug-resistant tuberculosis. Oxazolidinones inhibit bacterial protein synthesis, a mechanism of action not targeted by any drugs in current first-line tuberculosis treatment, so there is no known cross-resistance with other tuberculosis drug classes. However, prolonged linezolid use is associated with neurological and haematological toxicity, necessitating treatment interruption or dose reduction for many patients with tuberculosis. In-vitro studies of the alternative oxazolidinone, sutezolid, have shown a lower minimum inhibitory concentration for *Mycobacterium tuberculosis* than linezolid, and less inhibition of mitochondrial protein synthesis, which is expected to translate to improved safety. Sutezolid was more effective than linezolid in mouse models of tuberculosis treatment. A 14-day study confirmed early bactericidal activity in humans. However, that duration is too short for relevant toxicity assessments, and the optimal sutezolid dose for anti-tuberculosis regimens remains unknown.

Added value of this study

PanACEA-SUDOCU-01 was a phase 2b clinical trial conducted at four locations in Tanzania and South Africa. The innovative study design allowed administration of a novel backbone of bedaquiline–delamanid–moxifloxacin alone and together with four sutezolid doses (ranging from 600 mg once daily to 800 mg twice daily) to 75 adults with drug-susceptible pulmonary tuberculosis for 12 weeks. Clinical, microbiological, and pharmacokinetic–pharmacodynamic modelling analyses showed that the regimen was safe and microbiologically effective at all doses. Relationships between sutezolid dose and plasma exposure (including a key active metabolite), and between exposure and bacteriological response were identified, but maximal effect plateaus were not reached within the evaluated dose range.

Implications of all the available evidence

New, safer oxazolidinones will improve tuberculosis treatment. Two studies led by the PanACEA consortium, PanACEA-SUDOCU-01 (assessing sutezolid, reported here) and PanACEA-DECODE-01 (performed in parallel to assess delpazolid) advance this endeavour. Specifically, the PanACEA-SUDOCU-01 data do not suggest a final dose for use but show that sutezolid is safe and efficacious, adding to the bactericidal activity of a bedaquiline–delamanid–moxifloxacin backbone.

Linezolid is an oxazolidinone that, when added to failing treatment for drug-resistant tuberculosis in a landmark trial in South Korea,[3] resulted in cure in the majority of participants, with unsuccessful outcome only in four of 38 patients. This led to the development of a new regimen for rifampicin-resistant tuberculosis composed of bedaquiline, pretomanid, and linezolid, supplemented by moxifloxacin if susceptibility can be ascertained, for 6 months.[4] This regimen is a substantial improvement for patients and the health-care system. Linezolid, when given over this duration, still has substantial toxicity; in the ZeNIX trial,[5] linezolid toxicity was mitigated by recommending a lower dose of 600 mg once daily (original dose 1200 mg), but 24% of participants still had peripheral neuropathy at that dose. The 14-day bactericidal activity study[6] and a low culture conversion rate at week 8 in the bedaquiline, pretomanid, and linezolid group of the TB-PRACTECAL trial that used the lower 600 mg dose for linezolid,[7] suggest that this dose might be suboptimally active.

New oxazolidinones have been under development for tuberculosis to provide a safer alternative that retains or improves on efficacy. Sutezolid is a linezolid analogue with a 2–4-fold lower minimum inhibitory concentration (MIC) than linezolid. In humans, the main (active) metabolite of sutezolid, known as PNU-101603, circulates at concentrations several times higher than sutezolid.[8] The MIC of this metabolite is similar to that of linezolid.[9,10] In vitro, this metabolite is less active at inhibiting mitochondrial protein synthesis than linezolid, which might translate to a lower risk for neuropathy or myelosuppression, the two key toxic effects of linezolid.

Sutezolid and its main metabolite have a half-life of less than 4 h and undergo oxidative metabolism by multiple pathways, including flavin monooxygenases, CYP3A4, and other unknown mechanisms. In-vitro assessments suggest no relevant inhibition, and only minor induction, if any, of CYP enzymes, similar to linezolid. This makes sutezolid an attractive combination partner drug, both with newer anti-tuberculosis medications, and with antiretroviral therapy (ART).[11]

Linezolid has been shown to occasionally cause serotonin syndrome when combined with medications affecting serotonin metabolism,[12] or tyramine pressor response, an increase in blood pressure through increased intestinal uptake of tyramine (inhibition of MAO-A).[13] In-vitro analysis found that sutezolid and its main metabolite might still have MAO-A inhibition potential, while the potential to inhibit MAO-B seems to be lower than that of linezolid.

Clinically, sutezolid has been evaluated up to 14 days as monotherapy in a phase 2a study that compared a daily dose of 1200 mg given as a single dose or in two doses. This study found the drug to be active, with only minimal

differences in bactericidal activity between the two groups.[8] A final dose for further clinical development, to achieve maximal efficacy and good safety, was not established. In the phase 2a study, 14% of participants had a mild or moderate increase in the liver enzyme alanine aminotransferase. However, the main oxazolidinone class toxicities, neuropathy and myelosuppression, have a delayed onset and will occur only after weeks of dosing. Therefore, to evaluate safety, monotherapy, which is limited to 14 days, is not the correct approach and dosing as part of a combination is required.

We aimed to evaluate different doses of sutezolid in combination with bedaquiline, delamanid, and moxifloxacin—a combination of second-line tuberculosis drugs that was safe and effective, had little pre-existing resistance, and was thought to be a promising option for treatment of drug resistant tuberculosis. The combination of bedaquiline, pretomanid, and linezolid, with or without moxifloxacin had not yet been recommended when the trial was designed. The primary aim was to evaluate safety and efficacy of sutezolid as part of a novel combination of drugs and support the choice of a dose for further development. Efficacy was to be described by population pharmacokinetic and pharmacokinetic–pharmacodynamic modelling, a more powerful method than conventional comparisons between treatment groups. The pharmacokinetic–pharmacodynamic model provides information to support the choice of a dose with the highest efficacy at acceptable safety.

Methods

Study design

PanACEA Sutezolid Combination Development (PanACEA-SUDOCU-01) was a prospective, open-label, randomised, phase 2b dose-finding study. The trial was conducted by the PanACEA consortium in four dedicated tuberculosis trial sites, each of which is adjacent to a hospital. Sites in Tanzania were the National Institute for Medical Research—Mbeya Medical Research Centre (Mbeya); Kibong'oto Infectious Diseases Hospital and Kilimanjaro Clinical Research Institute (Moshi); and Ifakara Health Institute—Bagamoyo Research and Training Unit, Mwananjamala Hospital, Dar es Salaam; and in South Africa, Aurum Institute, Tembisa site, in Johannesburg. The study protocol was very similar to the previously published protocol for the PanACEA-DECODE-01[14] study that started soon after PanACEA-SUDOCU-01.[15]

The trial was approved by institutional, local, and national ethics boards and regulatory authorities of participating countries. Written informed consent was obtained from participants before study-specific screening procedures. All authors approved the submitted version and attest to the accuracy and completeness of the data and fidelity of the trial to the protocol. The trial was registered with ClinicalTrials.gov (NCT03959566) before the start of enrolment. The trial is now closed for enrolment.

Participants

Adults aged 18–65 years with newly diagnosed, smear-positive, drug-sensitive tuberculosis who weighed 40–90 kg were recruited. People living with HIV were eligible if they had more than 220 CD4 cells per mL and were either ART-naive or were on or able to switch to a dolutegravir-based ART regimen. Screening laboratory assessments, vital signs, and electrocardiography were performed to rule out substantial pre-existing comorbidities. Participants were required not to be on concomitant medication associated with QT prolonging effects, affecting serotonin metabolism, or causing hepatic drug–drug interactions, and had to abstain from consuming tyramine-rich foods during their experimental treatment (appendix p 7). Female participants of childbearing potential were required to use effective contraception. Participants were excluded if they were pregnant or breastfeeding, had current or clinically relevant neuropathy, had a QT interval using Fridericia correction (QTcF) greater than 450 ms, arterial hypertension (≥140/90 mm Hg), serum albumin less than 2·8 g/dL, haemoglobin concentration less than 7·0 g/dL, and an alanine aminotransferase or aspartate aminotransferase concentration greater than three times the upper limit of the normal range (ULN). The full list of inclusion and exclusion criteria are in the appendix (pp 3–6). Participant sex data (male or female) were collected by physician decision.

Randomisation and masking

Participants were randomly assigned (1:1:1:1:1) by a probabilistic minimisation algorithm using a web-based interface, to receive no sutezolid (U0), sutezolid 600 mg once daily (U600), sutezolid 1200 mg once daily (U1200), sutezolid 600 mg twice daily (U600BD), or sutezolid 800 mg twice daily (U800BD). The algorithm stratified assignment by sex, site, and HIV status. Sponsor staff and tuberculosis laboratory staff who assessed the outcomes were masked to treatment assignment, whereas patients and investigators were aware of treatment assignment. Only the data safety monitoring board and trial statisticians preparing reports reviewed unblinded aggregate data by treatment group before database lock.

Procedures

Participants received no sutezolid, sutezolid 600 mg once daily, sutezolid 1200 mg once daily, sutezolid 600 mg twice daily, or sutezolid 800 mg twice daily, all administered orally for 12 weeks. In addition to sutezolid, all patients received bedaquiline, delamanid, and moxifloxacin at licensed doses for 12 weeks. The duration of combined treatment was limited to 12 weeks due to an absence of preclinical data to support longer use of sutezolid in humans. The dose for bedaquiline was 400 mg once daily for 14 days, followed by 200 mg thrice weekly. Delamanid was administered at 100 mg twice daily and moxifloxacin at 400 mg once daily. After

the end of experimental treatment, participants continued to receive isoniazid and rifampicin continuation phase treatment at doses specified in national tuberculosis treatment guidelines through the local tuberculosis clinic to complete a total of 26 weeks of treatment.

At screening, a chest x-ray was performed. Severity of changes were graded using a published chest x-ray score.[16] At the baseline visit, triplicate electrocardiograms (ECGs) were taken as baseline readings before the first dose of study treatment. Single ECGs were taken at all successive visits, and two more ECGs were done if the participants had a QTcF greater than 480 ms or if a prolongation of more than 50 ms over baseline was seen in the single ECG. Cardiac safety stopping criteria were defined as QTcF-prolongation of grade 3 according to US National Institutes of Health Common Terminology for Adverse Events version 5.0 (absolute QTcF value >500 ms or a change from the baseline QTcF >60 ms; the latter was requested by the US Food and Drug Administration [FDA] in feedback to the protocol). In such events, study medication was to be withheld, and the participants were to be admitted to hospital for diagnostics and observation.

Safety laboratory assessments were done weekly. The individual participant stopping criteria for drug-induced liver injury was set following FDA guidance,[17] to discontinue study drug if alanine aminotransferase or aspartate aminotransferase increased to more than 8 times ULN; alanine aminotransferase or aspartate aminotransferase increased to more than 5 times ULN for more than 2 weeks; alanine aminotransferase or aspartate aminotransferase increased to more than 3 times ULN and total bilirubin increased to more than twice ULN or international normalised ratio more than 1·5; or alanine aminotransferase or aspartate aminotransferase increased to more than 3 times ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%). Visual acuity, colour perception, and vibration sense were tested weekly.

Intensive pharmacokinetic sampling was done at day –1 for the U800BD group for midazolam probe drug pharmacokinetics, and at treatment day 14 for all participants, after taking study drugs with standardised meals. Participants in the U800BD group received 2 mg of midazolam orally at both pharmacokinetic days. Plasma samples were drawn at 1 h, 2 h, 4 h, 8 h, 12 h (±10 min) and 24 h (±30 min) after the morning dose of experimental treatment. Concentrations of sutezolid and the main metabolite (sutezolid-sulfoxide, PNU-101603) were measured for all samples using a validated liquid chromatography-tandem mass spectrometry assay. Details about the bioanalysis are in the appendix (p 7). Chest x-rays were centrally read and severity of abnormalities was graded following the published score by Ralph and colleagues.[16]

Outcomes

The primary efficacy endpoint was the change of sputum bacterial load over time, measured by a change in the time from inoculation to a culture flagging positive in the mycobacterial growth indicator tube (MGIT; BD, Johannesburg, South Africa) system, which has been shown to correlate with long-term outcomes.[18] Duplicate weekly sputum samples were collected from week 0 to week 12 and at week 14 and quantitatively cultured using the MGIT automated liquid culture system, as previously described.[19] This readout was to be used for pharmacokinetic–pharmacodynamic modelling.

Secondary outcomes were the dose–response relationships for sutezolid, based on secondary efficacy endpoints culture status at different timepoints and time to culture conversion to negative (defined as the time to the first of two successive visits with at least one negative and no positive culture per visit, without an intervening positive culture). We also aimed to assess the relative efficacy of increasing sutezolid doses compared with the background regimen without sutezolid. The pharmacokinetics of companion drugs, and mycobacterial characterisation were also to be performed. These will be reported separately.

Another objective was to assess the potential of sutezolid for CYP450 3A4 enzyme induction, as measured by its influence on the ratio of area under the curve of the CYP 3A4 probe drug midazolam at day –1 before the start of sutezolid and at day 14 of sutezolid dosing. This will be reported separately.

The primary safety endpoint was the occurrence of adverse events reported by the participant and those measured in safety assessments that included physical, neurological, and visual acuity examination, ECGs, haematology and clinical chemistry laboratory, and performance of the Hunter score for serotonin syndrome. Severity of adverse events was graded following Common Terminology for Adverse Events version 5.0.

Statistical analysis

Given the novel type of primary endpoint used, based on quantitative measures of bacterial load over 12 weeks, data to inform a formal sample size calculation with the intended analysis method were not available. As a proxy, we used data from shorter early bactericidal activity studies,[19] which also used a quantitative bacterial load metric as an endpoint. Assuming a between-patient SD of log colony-forming unit per mL of sputum of 0·2, for 75 participants distributed into five groups (15 participants each) the expected SE of group mean early bactericidal activity is 0·052, which is a level of precision considered adequate.[19] The sample size was calculated allowing for up to three participants to be lost to follow-up per group.

The modified intention-to-treat population consisted of all randomly assigned participants who had taken at least one dose of study treatment, analysed according to treatment assigned. All participants who had taken at

least one dose of study medication were included in the safety analysis set, which was analysed according to treatment received. Efficacy and pharmacokinetic–pharmacodynamic analyses included all participants up to the scheduled last study visit while on experimental treatment, or a permanent withdrawal from study treatment.

A sequential pharmacokinetic–pharmacodynamic model was developed using non-linear mixed-effects methods. All available sutezolid and metabolite concentrations during the intensive pharmacokinetic sampling period were used to develop the pharmacokinetic model. One, two, and three compartmental disposition models were evaluated. Covariate analysis was performed to assess the effects of demographic and disease-severity parameters on the pharmacokinetics of sutezolid (evaluated relationships are listed in appendix p 10). The final pharmacokinetic model was used to generate exposure metrics to be used in the pharmacokinetic–pharmacodynamic analysis.

The decrease in mycobacterial load over time was analysed using a model-based approach. Linear, bilinear, and semi-mechanistical models were considered to describe the change in bacterial load (quantified by $\log_{10}$-transformed time to positivity) over time on treatment. Covariate analysis was performed to assess the effects of demographic and disease-severity parameters on the change in mycobacterial load over time on treatment. The exposure–response relationship of sutezolid and the metabolite was investigated using individual pharmacokinetic model-derived estimates of the area under the curve from 0 h to 24 h (AUC_{0-24}), maximum concentration (C_{max}), and minimum concentration during the intensive pharmacokinetic sampling at day 14. Details on the pharmacokinetic–pharmacodynamic modelling are in the appendix (pp 9–13, 23–27).

The pharmacokinetic and pharmacokinetic–pharmacodynamic models were developed using NONMEM version 7.5 with Pirana version 2.9.9 as graphical interface and Perl speaks NONMEM version 5.3.0 for additional functionalities[20–22] Data management was performed in R version 4.1.3 using R Studio version 2022.02.[23] Goodness-of-fit plots and visual predictive checks were made for the graphical evaluation of the model fit. An objective function value decrease of more than 3·84 was considered statistically significant, corresponding to $p<0·05$. Parameter precision for the pharmacokinetic and pharmacodynamic models was determined using the sampling importance resampling method.[24]

An analysis of the time to sustained culture conversion in MGIT liquid media, a secondary endpoint, corrected for gender, age, BMI, HIV status, and baseline bacterial load is described in the appendix (pp 18–20).

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 20, 2021, and Feb 17, 2022, 186 individuals were screened for eligibility, 75 of whom were enrolled and randomly assigned to U0 (n=16), U600 (n=15), U1200 (n=14), U600BD (n=15), or U800BD (n=15; figure 1). Recruitment continued until the target sample size was

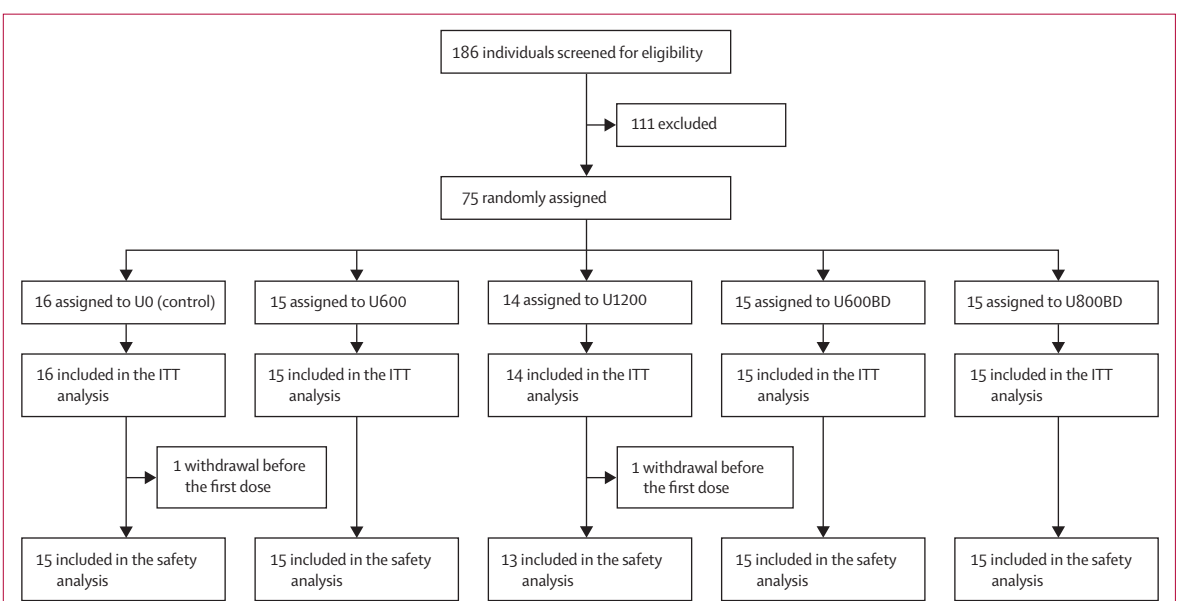

Figure 1: **Trial profile**
ITT=intention to treat. U0=no sutezolid. U600=sutezolid 600 mg once daily. U1200=sutezolid 1200 mg once daily. U600BD=sutezolid 600 mg twice daily. U800BD=sutezolid 800 mg twice daily.

	U0 (n=16)	U600 (n=15)	U1200 (n=14)	U600BD (n=15)	U800BD (n=15)	Total (n=75)
Sex						
Female	3 (19%)	4 (27%)	3 (21%)	5 (33%)	4 (27%)	19 (25%)
Male	13 (81%)	11 (73%)	11 (79%)	10 (67%)	11 (73%)	56 (75%)
Age, years	30·0 (25·5–36·2)	33·0 (26·0–37·0)	35·0 (28·8–41·5)	36·0 (25·5–46·0)	34·0 (28·5–38·5)	33·0 (27·0–39·5)
Black race	16 (100%)	15 (100%)	14 (100%)	15 (100%)	15 (100%)	75 (100%)
Weight, kg	54·9 (49·4–61·0)	50·0 (45·4–57·2)	55·2 (50·8–56·2)	54·8 (49·4–57·5)	49·1 (47·8–52·8)	53·0 (48·5–57·2)
Person living with HIV	1 (6%)	0	0	1 (7%)	0	2 (3%)
Time to positivity, days	4·9 (4·0–6·0)	4·4 (3·7–6·6)	4·9 (4·5–6·7)	5·0 (4·3–6·4)	4·6 (3·9–5·6)	4·8 (4·0–6·3)
Ralph score*	62 (42–70)	62 (59–71)	70 (38–90)	52 (34–71)	70 (60–83)	62 (52–80)

Data are n (%) or median (IQR). U0=no sutezolid. U600=sutezolid 600 mg once daily. U1200=sutezolid 1200 mg once daily. U600BD=sutezolid 600 mg twice daily. U800BD=sutezolid 800 mg twice daily. *Ralph score is a published scoring system to rate the severity of chest x-ray abnormalities in individuals with tuberculosis.

Table 1: **Baseline characteristics**

	U600 (n=15)	U1200 (n=13)	U600BD (n=14)	U800BD (n=15)
Geometric mean sutezolid $AUC_{0\text{-}24}$, mg/L per h (geoSD)	3·64 (1·59)	6·42 (1·36)	7·08 (1·66)	10·4 (1·57)
Geometric mean sutezolid C_{max}, mg/L (geoSD)	0·59 (1·57)	1·00 (1·33)	0·69 (1·62)	0·92 (1·60)
Geometric mean metabolite $AUC_{0\text{-}24}$, mg/L per h (geoSD)	19·2 (1·22)	33·0 (1·27)	38·2 (1·31)	51·9 (1·36)
Geometric mean metabolite C_{max}, mg/L (geoSD)	2·39 (1·24)	3·91 (1·27)	2·93 (1·29)	3·72 (1·40)

$AUC_{0\text{-}24}$=area under the curve from 0 h to 24 h. C_{max}=maximum concentration. geoSD=geometric SD. U600=sutezolid 600 mg once daily. U1200=sutezolid 1200 mg once daily. U600BD=sutezolid 600 mg twice daily. U800BD=sutezolid 800 mg twice daily.

Table 2: **Summary statistics of sutezolid and metabolite exposure at day 14 per dosing group derived from the population pharmacokinetic model**

attained. Baseline demographic and clinical characteristics are shown in table 1. 56 (75%) participants were male, 19 (25%) were female, all were Black, and the median age was 33·0 years (range 20·0–58·0).

372 observations each for sutezolid and the main metabolite (PNU-101603) were available for the development of the population pharmacokinetic model. The pharmacokinetics of sutezolid and the metabolite were both best described by two-compartment disposition models (appendix p 10). No plateau in the extent of sutezolid absorption was observed within the investigated dose range, demonstrating dose linearity up to doses of 1200 mg daily. Saturation of sutezolid or metabolite clearance was not identified. Except for scaling with total bodyweight, no statistically significant covariates were identified. The final model parameters and visual predictive checks are shown in the appendix (pp 11–13). The pharmacokinetic model-derived sutezolid and metabolite exposure metrics at day 14 are shown in table 2. Findings on the interaction potential of sutezolid with midazolam (a substrate of CYP3A4) will be published separately.

Median change in MGIT time to positivity by group is shown in the appendix (p 17). All participants had an adequate response to treatment and transitioned to continuation therapy after week 12. Culture conversion to negative by week 8 varied between groups, from six (40%) of 15 in the U800BD group to 11 (73%) of 15 in the U600 group (appendix p 19). There was no evidence of a difference between groups in time to culture conversion to negative (appendix p 20).

1651 time to positivity observations were available for the primary efficacy analysis with pharmacokinetic–pharmacodynamic modelling. In a bilinear model on a log scale, with the node estimated at 9·18 days (95% CI 7·30–11·61), mycobacterial killing showed a faster decline in the days up to the node compared with thereafter. The extent of lung damage, as characterised by the Ralph score, correlated with the second slope of bacterial-load decrease, suggesting lower killing with higher lung damage.

We identified evidence for a relationship between sutezolid exposure and decrease in mycobacterial load. Both sutezolid $AUC_{0\text{-}24}$ (p=0·056) and C_{max} at week 2 (p=0·041) were correlated with the rate of mycobacterial load decrease (appendix p 23). The exposure–response model driven by the C_{max} fitted the data slightly better than the model driven by the $AUC_{0\text{-}24}$.

Participants in the group with the highest single dose (U1200) were predicted by the pharmacokinetic–pharmacodynamic model to typically have 16·7% (95% CI 0·7–35·0) faster decrease in mycobacterial load compared with participants not receiving sutezolid (U0). A maximum effect of sutezolid exposure was not observed within the investigated dose range. Figure 2 shows the model-predicted increase in mycobacterial killing rate versus the maximum sutezolid concentration, and figure 3 shows the typical time to positivity trajectory for treatment with bedaquiline, delamanid, and moxifloxacin without sutezolid compared with when 1200 mg sutezolid daily is added (assuming typical C_{max}). No exposure–response relationship was found for the metabolite of sutezolid (PNU-101603) or for a joint sutezolid plus metabolite metric as a driver of the antimicrobial effect.

A summary of treatment-emergent adverse events is in table 3, and all serious or higher-grade adverse events are

listed in the appendix (p 27). The mean prolongation of QTcF over baseline while on study treatment was 23·7 ms (95% CI 22·5–24·8). There was no significant difference in the QTcF interval between the treatment groups (ie, higher sutezolid doses did not lead to a significantly higher QTcF). Although the absolute QTcF values remained below 470 ms for all participants throughout the study (appendix p 28), four (5%) of 73 participants had grade 3 adverse events due to a QTcF change from baseline greater than 60 ms: two (13%) of 15 in the U600BD group, one (7%) of 15 in the U600 group, and one (7%) of 15 in the U800BD group. Three of the four participants were asymptomatic and one participant reported recurring palpitations and weakness; the palpitations had already been felt before the start of study medications. ECG recorded during an episode of palpitations showed sinus tachycardia. In one participant, study medication was successfully reintroduced and the remaining three participants were switched to standard of care. During retrospective analysis, two additional participants (both in the U600 group) had brief episodes of QTcF prolongation over 60 ms compared with baseline values that had been overlooked, with no further complications.

Clinical chemistry found some participants with increased aminotransferases without clinical significance (appendix p 29). One (7%) of 15 participants in the U600BD group had grade 4 drug-induced liver toxicity with clinical nausea, fulfilling stopping criteria at week 2 (appendix p 30). Study treatment was successfully reintroduced after aminotransferases had normalised. There were no other cases of drug-induced liver injury with aminotransferases greater than three times the ULN during experimental treatment, but one (7%) of 15 patients in the U600 group developed increased aminotransferases after being switched to continuation phase therapy (appendix p 29).

One (7%) of 15 participants in the U600BD group had a haematological adverse event (grade 4 neutropenia) with a minimum of 370 cells per µL (lower limit of normal 1200 cells per µL)[25] at 1 week after treatment start. After stopping study treatment, the neutrophil count improved but not to normal values despite following up for 11 months. One (7%) of 15 participants in the U0 group had a neutropenia event with a minimum of 840 cells per µL (grade 3) and recovered despite continued dosing. One (7%) of 15 participants in the U600BD group had a brief event of grade 3 neutropenia (minimum count 970 cells per µL) concurrent with liver toxicity; the neutrophil count recovered. One (7%) of 15 participants in the U800BD group had anaemia, with a decrease in haemoglobin from 11·3 g/dL to 9·9 g/dL (grade 2) at week 2, and recovery to 14·2 g/dL at the end of experimental treatment despite continued dosing. No other haematological adverse events, nor cases of peripheral or optic neuropathy were observed.

One (7%) of 15 participants in the U600BD group died due to COVID-19. There were 17 other adverse events of grade 3 and higher, which were considered unrelated or unlikely to be related to sutezolid by the investigator (appendix p 27). In view of the small number of adverse effects related to study medication, no evaluation of a possible exposure–toxicity relationship for sutezolid or its metabolite was done.

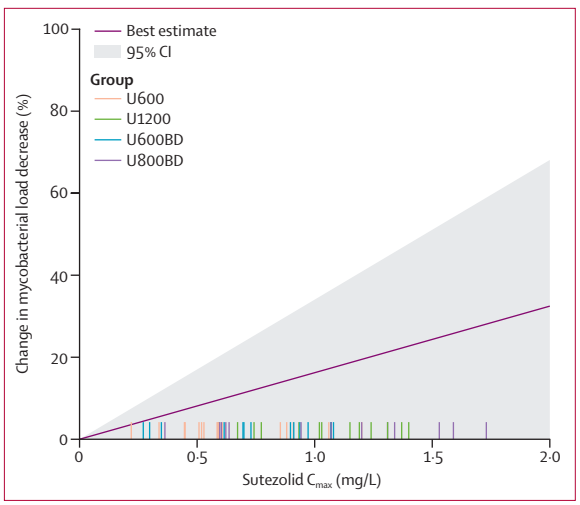

Figure 2: **Model-predicted sutezolid exposure–response effect**
The x-axis shows the individual pharmacokinetic model-predicted sutezolid C_{max} and the y-axis shows the decrease in the mycobacterial load relative to the group without sutezolid. Coloured dashes show the C_{max} for individual patients, coloured coded by treatment group. The 95% CI is based on the uncertainty in the estimated exposure–response effect. C_{max}=maximum concentration. U600=sutezolid 600 mg once daily. U1200=sutezolid 1200 mg once daily. U600BD=sutezolid 600 mg twice daily. U800BD=sutezolid 800 mg twice daily.

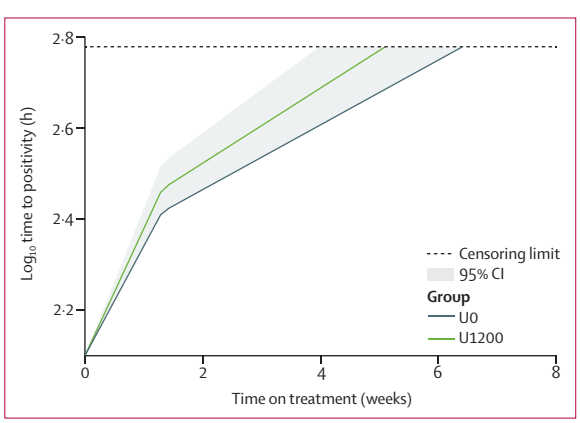

Figure 3: **Predicted time to positivity trajectories for a participant in the U0 group compared with a participant in the U1200 group**
The participant in the U1200 group was predicted to have a C_{max} of 1·03 mg/L (table 2). 95% CIs are based on the uncertainty in the estimated exposure–response effect. The node is at 9·18 days. C_{max}=maximum concentration. U0=no sutezolid. U1200=sutezolid 1200 mg once daily.

Discussion

To our knowledge, PanACEA-SUDOCU-01 was the first randomised dose-finding study that was primarily designed to allow dose-finding for a tuberculosis drug by pharmacokinetic–pharmacodynamic modelling.

	U0 (n=15)	U600 (n=15)	U1200 (n=13)	U600BD (n=15)	U800BD (n=15)	Overall (n=73)
Summary						
Any adverse event	6 (40%)	5 (33%)	7 (54%)	7 (47%)	4 (27%)	29 (40%)
Serious adverse event	0	1 (7%)	1 (8%)	4 (27%)	1 (7%)	7 (10%)
Severity grade						
Grade 1, mild	3 (20%)	2 (13%)	2 (15%)	4 (27%)	1 (7%)	12 (16%)
Grade 2, moderate	3 (20%)	4 (27%)	4 (31%)	4 (27%)	1 (7%)	16 (22%)
Grade 3, severe	1 (7%)	2 (13%)	3 (23%)	5 (33%)	2 (13%)	13 (18%)
Grade 4, life threatening	1 (7%)	1 (7%)	0	3 (20%)	0	5 (7%)
Grade 5, death	0	0	0	1 (7%)	0	1 (1%)
Relatedness to sutezolid						
Unrelated	4 (27%)	4 (27%)	6 (46%)	7 (47%)	3 (20%)	24 (33%)
Unlikely related	1 (7%)	1 (7%)	1 (8%)	4 (27%)	2 (13%)	9 (12%)
Possibly related	0	0	1 (8%)	4 (27%)	0	5 (7%)
Probably related	1 (7%)	1 (7%)	1 (8%)	1 (7%)	0	4 (5%)
Definitely related	0	0	0	0	0	0
Relatedness to other drugs of the regimen						
Unrelated	3 (20%)	4 (27%)	6 (46%)	7 (47%)	3 (20%)	23 (32%)
Unlikely related	2 (13%)	0	1 (8%)	1 (7%)	2 (13%)	6 (8%)
Possibly related	1 (7%)	0	1 (8%)	4 (27%)	1 (7%)	7 (10%)
Probably related	1 (7%)	1 (7%)	1 (8%)	1 (7%)	0	4 (5%)
Definitely related	0	0	0	1 (7%)	0	1 (1%)

Severity grading by Common Terminology Criteria for Adverse Events version 5.0. One participant from the U0 group and one from the U1200 group withdrew before the start of treatment and are thus not included in the safety population; they had no recorded adverse events. One participant from the U600BD group died due to COVID-19 and is the one grade 5 event recorded. A participant may have experienced more than one adverse event and be counted in multiple categories of severity or relatedness. U0=no sutezolid. U600=sutezolid 600 mg once daily. U1200=sutezolid 1200 mg once daily. U600BD=sutezolid 600 mg twice daily. U800BD=sutezolid 800 mg twice daily.

Table 3: **Summary of all treatment-emergent adverse events in PanACEA-SUDOCU-01**

The pharmacokinetic–pharmacodynamic model identified an effect of sutezolid exposure on the rate of mycobacterial load decrease, with an increase in steepness of 16·7% at the median C_{max} in the U1200 group compared with the U0 group. Both sutezolid C_{max} and $AUC_{0–24}$ were identified as potential drivers of the antimycobacterial effect in addition to the effect of the companion drugs, including bedaquiline, delamanid, and moxifloxacin. The model-based evaluation did not identify a distinct difference between sutezolid C_{max} or the $AUC_{0–24}$ as a driver of the antimycobacterial effect, suggesting that a more practical once-daily dose might be most suitable. Furthermore, the pharmacokinetic model did not identify a plateau in sutezolid absorption within the investigated dose range, strengthening the rationale for once daily dosing; however, a plateau in exposure identified in the phase 1a study for doses greater than 1000 mg should be considered.[26] No exposure–response relationship was identified using the metabolite or a joint sutezolid plus metabolite metric as the driver of the antimicrobial effect; previous studies had described higher MICs of the metabolite for intracellular bacteria.[9]

The decrease in bacterial load was biphasic, with a faster initial decrease up to the node point at 9 days and a slower decrease thereafter. A possible explanation for this effect is that a fast-replicating subpopulation of mycobacteria are rapidly killed off in the first part of the treatment, whereafter more resilient, slow-reproducing mycobacteria are killed at a slower rate, or that a build-up of the long-acting drugs bedaquiline and delamanid would lead to carry over into sputum culture, and thus cause changes in the culture outcome after baseline.

No activity maximum for sutezolid was identified, suggesting that higher doses might lead to an increased antimycobacterial effect. Together with the observed dose–exposure linearity and the safety profile shown in this study, higher, once-daily sutezolid doses might be both safe and efficacious. The final model showed a negative influence of more extensive lung involvement as rated by the Ralph score.[16] This was not found in the sister study PanACEA-DECODE-01,[14] which examined delpazolid, potentially due to the narrower range of Ralph score present among participants in PanACEA-DECODE-01.

To our knowledge, this study is the first to report a combination of bedaquiline, delamanid, and moxifloxacin as a potential backbone for a regimen containing sutezolid or other drugs. Our historical comparison of time to positivity data suggests a similar efficacy compared with the isoniazid, rifampicin, pyrazinamide, and ethambutol control group of the PanACEA-MAMS-TB-01 study.[27] PanACEA-MAMS-TB-01 was similar to PanACEA-SUDOCU-01 in terms of study sites and participant entry

criteria, specifically the requirement for sputum smear positivity (appendix p 17). Also, the median time to culture conversion in the PanACEA-MAMS-TB-01 isoniazid, rifampicin, pyrazinamide, and ethambutol control group was 62 days (IQR 41–83)[27] and in this study it was 63 days (42–77) for bedaquiline, delamanid, and moxifloxacin. Due to the small number of patients in PanACEA-SUDOCU-01 and the between-trial nature of the comparison, this finding should be interpreted with caution.

Safety findings for sutezolid, in combination with bedaquiline, delamanid, and moxifloxacin, were promising. The combination of three drugs with a potential to prolong the QT interval resulted in a mean prolongation of QTcF of 23·7 ms while on treatment; this is similar to the 20·7 ms (95% CI 16·1–25·3) found for a combination of bedaquiline and delamanid previously.[28] Sutezolid had shown low affinity for hERG in vitro and previous studies did not identify an effect on the QTcF. Therefore, it is likely that the QTcF prolongation observed is due to the background drugs. We identified four participants (and two were identified retrospectively) with prolongation of QTcF of more than 60 ms over baseline, which was a stopping criterion requested by the FDA. However, patients with tuberculosis have shorter baseline QTcF than when they have undergone successful treatment due to a high heart rate with higher body temperature before treatment, which is under-corrected by the Fridericia formula.[29] A prolongation of QTcF to greater than 500 ms is a better indicator for risk of torsade de pointes, but no patient in our study exceeded a QTcF of 470 ms at any point.

Haematological toxicity assessments in PanACEA-SUDOCU-01 showed one participant with grade 4 neutropenia. In retrospect, the early onset and lack of recovery over a long observation in this participant suggest a benign ethnic neutropenia rather than an oxazolidinone-associated myelosuppression.[30] Other events were a temporary anaemia that resolved despite continued dosing in the control group, and neutropenia associated with the hepatotoxicity event, both of which have clear other causes. We therefore conclude that sutezolid in our trial did not cause haematological toxicity of concern. Likewise, participants did not report symptoms of neuropathy, and neurological examinations did not describe those; also, no case of serotonin syndrome was identified. This raises the hope that sutezolid will be a safer oxazolidinone than linezolid; however, the risk of serotonin syndrome occurring when sutezolid is combined with drugs affecting serotonin metabolism cannot be ruled out.

Hepatotoxicity requiring treatment interruption was seen in one (2%) of 60 participants receiving sutezolid, which suggests that the finding of raised amino-transferases seen in seven (14%) of 50 participants in the phase 2a study did not translate into a similar frequency of higher-grade events in our study.[8]

The limitations of this study were the small sample size leading to a wide CI for the estimated sutezolid effect, and the short dosing duration to 12 weeks due to lack of preclinical data to support longer use in humans. More than half of the linezolid dose modifications required by toxicity in the ZeNiX trial occurred before week 12;[5] so the absence of such a signal in our trial is encouraging. Furthermore, because the study population was restricted through inclusion and exclusion criteria, mainly to limit spurious, confounding adverse events, a more generalisable patient population might encounter more safety events, although many of these will not be related to study treatment. A final conclusion on the efficacy of the regimens tested to achieve cure, versus long-term unfavourable outcome in a general patient population, can therefore not be drawn from this study. Ongoing studies with sutezolid are testing a combination with bedaquiline, delamanid or pretomanid, and quabodepistat (NCT05971602), and higher doses of 1600 mg once daily (NCT05686356) in combination with pretomanid and bedaquiline with N-acetylcysteine as host-directed therapy, both for a duration of 4 months. These studies will describe the cure rates of regimens that contain sutezolid. A further limitation of our study might have been the potency of the three-drug backbone, which might have masked the full effect of sutezolid.

Although the findings from this study did not suggest a final dose to be used, we were able to show that sutezolid is a safe and efficacious oxazolidinone over a dosing period of 12 weeks and seemed to add to the activity of bedaquiline, delamanid, and moxifloxacin, as measured by our surrogate endpoint of change of quantitative culture over time. In comparison with the historical data from PanACEA-MAMS-TB-01,[27] the combination of sutezolid with bedaquiline, delamanid, and moxifloxacin seems to be a treatment option for patients that is at least as effective as isoniazid, rifampicin, pyrazinamide, and ethambutol, if confirmed in larger trials.

Contributors

Funding acquisition: MB, NH, and MH. Study design: EMS, NH, LtB, and PPJP. Study conduct and data collection: CM, SM, FM, MS, RSW, NN, AL, BH, LTM, TZ, IN, LWi, LWa, DDP, LtB, and REA. Data curation: IN, BHA, PPJP, SEK, KS, LtB, and NH. Formal analysis: BHA, SEK, EMS, PPJP, LtB, MH, and NH. Project administration: LWa and HM. Supervision/validation: NH, LWi, KS, IN, TDM, and LWa. Visualisation: BHA, SEK, and EMS. Writing original draft: NH, SEK, KS, EMS, DJS, PPJP, and LtB. Review and editing: all authors. Accessed and verified the data: PPJP, EMS, BHA, and NH. All authors had final responsibility for the decision to submit for publication. NH had full access to all the data in the study. All authors did not have access to all the data due to General Data Protection Regulations.

Declaration of interests

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Data sharing

Data collected for the study include individual participant data and a data dictionary defining each field in the set. PanACEA will make de-identified data available through the TB PACTS trial repository at the latest by the end of 2025. Access to this can be applied for under https://c-path.org/.

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References

1 WHO. Global Tuberculosis Report 2024. Geneva: World Health Organization, 2024.
2 Lienhardt C, Dooley KE, Nahid P, et al. Target regimen profiles for tuberculosis treatment. *Bull World Health Organ* 2024; **102:** 600–07.
3 Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; **367:** 1508–18.
4 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment: drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization, 2022.
5 Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; **387:** 810–23.
6 Diacon AH, De Jager VR, Dawson R, et al. Fourteen-day bactericidal activity, safety, and pharmacokinetics of linezolid in adults with drug-sensitive pulmonary tuberculosis. *Antimicrob Agents Chemother* 2020; **64:** e02012-19.
7 Nyang'wa B-T, Berry C, Kazounis E, et al. Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med* 2024; **12:** 117–28.
8 Wallis RS, Dawson R, Friedrich SO, et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. *PLoS One* 2014; **9:** e94462.
9 Wallis RS, Jakubiec W, Kumar V, et al. Biomarker-assisted dose selection for safety and efficacy in early development of PNU-100480 for tuberculosis. *Antimicrob Agents Chemother* 2011; **55:** 567–74.
10 Tasneen R, Betoudji F, Tyagi S, et al. Contribution of oxazolidinones to the efficacy of novel regimens containing bedaquiline and pretomanid in a mouse model of tuberculosis. *Antimicrob Agents Chemother* 2015; **60:** 270–77.
11 Wallis RS, Jakubiec W, Mitton-Fry M, et al. Rapid evaluation in whole blood culture of regimens for XDR-TB containing PNU-100480 (sutezolid), TMC207, PA-824, SQ109, and pyrazinamide. *PLoS One* 2012; **7:** e30479.
12 Ramsey TD, Lau TT, Ensom MH. Serotonergic and adrenergic drug interactions associated with linezolid: a critical review and practical management approach. *Ann Pharmacother* 2013; **47:** 543–60.
13 Antal EJ, Hendershot PE, Batts DH, Sheu WP, Hopkins NK, Donaldson KM. Linezolid, a novel oxazolidinone antibiotic: assessment of monoamine oxidase inhibition using pressor response to oral tyramine. *J Clin Pharmacol* 2001; **41:** 552–62.
14 Minja LT, van der Feltz I, Manyama C, et al. Delpazolid in combination with bedaquiline, delamanid, and moxifloxacin for pulmonary tuberculosis (PanACEA-DECODE-01): a prospective, randomised, open-label, phase 2b, dose-finding trial. *Lancet Infect Dis* 2025; published online July 8. https://doi.org/10.1016/S1473-3099(25)00289-0.
15 Dierig A, Hoelscher M, Schultz S, et al. A phase IIb, open-label, randomized controlled dose ranging multi-centre trial to evaluate the safety, tolerability, pharmacokinetics and exposure-response relationship of different doses of delpazolid in combination with bedaquiline delamanid moxifloxacin in adult subjects with newly diagnosed, uncomplicated, smear-positive, drug-sensitive pulmonary tuberculosis. *Trials* 2023; **24:** 382.
16 Ralph AP, Ardian M, Wiguna A, et al. A simple, valid, numerical score for grading chest x-ray severity in adult smear-positive pulmonary tuberculosis. *Thorax* 2010; **65:** 863–69.
17 US Food and Drug Administration. Guidance for industry: drug-induced liver injury: premarketing clinical evaluation. US Food and Drug Administration, 2009.
18 Phillips PP, Mendel CM, Burger DA, et al. Limited role of culture conversion for decision-making in individual patient care and for advancing novel regimens to confirmatory clinical trials. *BMC Med* 2016; **14:** 19.
19 Diacon AH, Maritz JS, Venter A, van Helden PD, Dawson R, Donald PR. Time to liquid culture positivity can substitute for colony counting on agar plates in early bactericidal activity studies of antituberculosis agents. *Clin Microbiol Infect* 2012; **18:** 711–17.
20 Beal S, Sheiner LB, Boeckmann A, Bauer RJ. NONMEM user's guides (1989–2009). Icon Development Solutions, 2009.
21 Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. *CPT Pharmacometrics Syst Pharmacol* 2013; **2:** e50.
22 Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. *Comput Methods Programs Biomed* 2005; **79:** 241–57.
23 R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, 2021.
24 Dosne AG, Bergstrand M, Karlsson MO. An automated sampling importance resampling procedure for estimating parameter uncertainty. *J Pharmacokinet Pharmacodyn* 2017; **44:** 509–20.
25 Saathoff E, Schneider P, Kleinfeldt V, et al. Laboratory reference values for healthy adults from southern Tanzania. *Trop Med Int Health* 2008; **13:** 612–25.
26 Wallis RS, Jakubiec WM, Kumar V, et al. Pharmacokinetics and whole-blood bactericidal activity against *Mycobacterium tuberculosis* of single doses of PNU-100480 in healthy volunteers. *J Infect Dis* 2010; **202:** 745–51.
27 Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis* 2017; **17:** 39–49.
28 Dooley KE, Rosenkranz SL, Conradie F, et al. QT effects of bedaquiline, delamanid, or both in patients with rifampicin-resistant tuberculosis: a phase 2, open-label, randomised, controlled trial. *Lancet Infect Dis* 2021; **21:** 975–83.
29 Olliaro PL, Merle C, Mthiyane T, et al. Effects on the QT interval of a gatifloxacin-containing regimen versus standard treatment of pulmonary tuberculosis. *Antimicrob Agents Chemother* 2017; **61:** e01834-16.
30 Mpofu R, Otwombe K, Mlisana K, et al. Benign ethnic neutropenia in a South African population, and its association with HIV acquisition and adverse event reporting in an HIV vaccine clinical trial. *PLoS One* 2021; **16:** e0241708.