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

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Summary

Background Linezolid plays a crucial role in the first-line treatment of drug-resistant tuberculosis globally. Its prolonged use can lead to neurological and haematological toxicity, highlighting the need for safer oxazolidinones. Delpazolid, a novel oxazolidinone, might be safer. We aimed to evaluate the safety and efficacy of delpazolid and identify an optimal dose.

Methods PanACEA-DECODE-01 was a prospective, randomised, open-label, phase 2b, multicentre, dose-finding trial done in five tuberculosis trial sites in Tanzania and South Africa. Adults aged 18–65 years, who weighed 40–90 kg, and had newly diagnosed, smear positive pulmonary tuberculosis were randomly assigned (1:1:1:1:1) through centralised allocation, using a probabilistic minimisation algorithm to receive no delpazolid (D0), delpazolid 400 mg once daily (D400), delpazolid 800 mg once daily (D800), delpazolid 1200 mg once daily (D1200), or delpazolid 800 mg twice daily (D800BD), all administered orally for 16 weeks with follow-up to week 52. All participants received bedaquiline (400 mg orally once daily for the first 14 days, then 200 mg orally thrice weekly), delamanid (100 mg orally twice daily), and moxifloxacin (400 mg orally once daily). Randomisation was stratified based on bacterial load in sputum as measured by GeneXpert cycle threshold (<16 *vs* ≥16), site, and HIV status. The primary efficacy objective was to establish an exposure–response model with the primary endpoint, measured in the modified intention-to-treat population, of change in mycobacterial load measured by time to positivity using the liquid culture mycobacterial growth indicator tube system. A secondary outcome was the time on treatment to sustained conversion to negative sputum culture in liquid media. The primary safety outcome was the occurrence of oxazolidinone class toxicities defined as peripheral or optical neuropathy, incident leukopenia, anaemia or thrombocytopenia, or adverse events in line with tyramine pressor response, all of grade 2 or higher, possibly, probably or definitely related to delpazolid. This study was registered with ClinicalTrials.gov, NCT04550832.

Findings Between Oct 28, 2021, and Aug 31, 2022, 156 individuals were screened for eligibility, 76 of whom were enrolled and randomly assigned to D0 (n=15), D400 (n=15), D800 (n=15), D1200 (n=16), or D800BD (n=15). 60 (79%) of 76 participants were male and 16 (21%) were female. Population pharmacokinetic–pharmacodynamic modelling suggests maximal microbiological activity at a daily total exposure of delpazolid (area under the concentration curve from 0 h to 24 h [$AUC_{0–24}$]) of 50 mg/L per h; close to the median exposure observed after a 1200 mg dose. This maximal effect was estimated at a 38% (95% CI 4–83; p=0·025) faster decline in bacterial load compared with no delpazolid. In the secondary time-to-event analysis, there was no significant difference in time to culture conversion between treatment arms or exposure tertile. When all delpazolid-containing groups were combined, the hazard ratio for the time to sustained culture conversion to negative, comparing all delpazolid-containing groups with the group without delpazolid was 1·53 (95% CI 0·84–2·76). Two drug-related serious adverse events (one gastritis and one anaemia) occurred in the D800BD group, with high individual $AUC_{0–24}$. Apart from the anaemia and one event of brief, moderate neutropenia observed at only one visit in the D800 group not in line with the characteristics of oxazolidinone class toxicity, no oxazolidinone class toxicities occurred.

Interpretation The pharmacokinetic–pharmacodynamic modelling results suggest that delpazolid adds efficacy on top of bedaquiline, delamanid, and moxifloxacin; and that a dose of 1200 mg once daily would result in exposures with maximum efficacy. That dose was shown to be safe, raising hope that linezolid toxicities could be averted in long-term treatment. Delpazolid is a promising drug for future tuberculosis treatment regimens and could be widely usable if safety and efficacy are confirmed in larger trials.

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See Online for appendix

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Introduction

Tuberculosis remains the leading cause of death from a single infectious agent,[1] despite WHO declaring it a public health emergency in 1993. To control the progression of this epidemic, safer and shorter treatment regimens are urgently needed, as emphasised by the 2023 WHO target regimen profile.[2]

In 2022, WHO made a landmark recommendation for a 6-month regimen for drug-resistant tuberculosis, including bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin, with moxifloxacin excluded if resistance is highly likely or confirmed. This recommendation marked a major breakthrough, reducing the treatment duration for drug-resistant tuberculosis from the previous 9 months or longer (18–20 months).[3,4] A concerning limitation of this regimen is the dose-dependent and duration-dependent toxicity of linezolid, which can result in myelosuppression, optic neuropathy, and peripheral neuropathy.[5] Administering linezolid at 600 mg daily in the ZeNix trial,[5] rather than 1200 mg as in the Nix trial,[6] significantly decreased peripheral neuropathy from 81% to 24%; but a safer alternative would be desirable.[5,6] Furthermore, linezolid at a daily dose of 600 mg is part of a regimen with high cure rates, but might not be at its maximum active dose, as suggested by a 14-day early bactericidal activity and reduced effectiveness at week 8 in the first stage of the TB-PRACTECAL study.[7,8]

Delpazolid is a novel oxazolidinone that targets Gram-positive bacteria, including *Mycobacterium tuberculosis*. It acts by binding to the 23S ribosomal RNA portion of the bacterial 50S subunit, thereby inhibiting protein synthesis. Unlike other oxazolidinones, delpazolid contains a cyclic amidrazone group that promotes more rapid excretion. The rapid clearance of delpazolid prevents plasma accumulation, thus providing adequate

Research in context

Evidence before this study

We searched PubMed for clinical trials published between Jan 1, 2000, and June 6, 2025, using MeSH terms "tuberculosis" AND "oxazolidinones" OR "delpazolid" OR "LCB01-0371" restricted to publications in English. 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 that adding linezolid to an optimised background regimen for patients with extensively drug-resistant tuberculosis improved outcomes: 34 of 38 participants in this difficult-to-treat group had treatment success. Results of the Nix-TB, ZeNix-TB, and TB PRACTECAL studies have shown high treatment success rates, between 84% and 93%, thereby consolidating linezolid's prominence in WHO guidelines for drug-resistant tuberculosis therapy. However, prolonged use of linezolid to treat drug-resistant tuberculosis is associated with substantial neurological and haematological toxicity, necessitating treatment interruption or dose reduction for many patients. Safety data from a multiple ascending dose study suggest that delpazolid, administered at doses up to 1200 mg twice daily for 21 days, might be a better tolerated new oxazolidinone. Early bactericidal activity of delpazolid has been shown in patients with pulmonary tuberculosis with an exposure–response relationship described for doses of 800–1600 mg daily over 14 days. Optimal dosing for use in multidrug anti-tuberculosis regimens requires clarification.

Added value of this study

PanACEA-DECODE-01 was a phase 2b clinical trial conducted in Tanzania and South Africa. The innovative study design allowed administration of a novel backbone of bedaquiline–delamanid–moxifloxacin alongside four doses of delpazolid (ranging from 400 mg once daily to 800 mg twice daily) to 76 adults with drug-susceptible pulmonary tuberculosis for 16 weeks with 52 weeks of follow-up. Integrated clinical, microbiological, and pharmacological analyses advance existing knowledge by showing that the regimen including delpazolid 1200 mg once daily was safe and microbiologically effective. Pharmacokinetic–pharmacodynamic modelling showed that maximal microbiological activity was achieved at a plasma area under the concentration curve from 0 h to 24 h of 50 mg/L per h, close to the median exposure attained by 1200 mg once daily dosing. Taken together, the findings from this study establish a dose for delpazolid to be used in future evaluation, and provide encouraging evidence on safety and efficacy of the drug.

Implications of all the available evidence

New, safer oxazolidinones will improve tuberculosis treatment, accelerating progress towards global TB elimination. Two studies led by the PanACEA consortium, PanACEA-DECODE-01 and PanACEA-SUDOCU-01 (done in parallel to assess sutezolid, reported separately) advance this endeavour. Collectively, the emerging data support assessment of anti-tuberculosis drug regimens containing novel oxazolidinones in late-stage trials and show the possibility of replacing linezolid. Specifically, the PanACEA-DECODE-01 study supports selection of a delpazolid dose of 1200 mg once daily.

time for mitochondria to recover their protein synthesis function and reducing toxicity when compared with linezolid.[9]

Oxazolidinones have a weak, reversible MAO inhibitor effect in vitro, with a similar mechanism as the reversible MAO inhibitor toloxatone.[10] This effect has been associated with serotonin syndrome when used alongside other serotonergic medications or a tyramine pressor effect when combined with tyramine-rich foods. A study evaluating linezolid-associated serotonin toxicity among 1743 hospitalised patients found this toxicity to be very rare even among patients receiving multiple and high doses of serotonergic agents.[11,12]

Non-clinical studies have shown that delpazolid is not metabolised by the major cytochrome P450 enzymes nor does it inhibit them or major transporters, resulting in a very low likelihood of drug–drug interactions.[9] Genetic toxicity and in-vivo animal studies also were negative for delpazolid.[9]

The bactericidal efficacy of delpazolid against *M tuberculosis* was reported in a 14-day early bactericidal activity study, in which delpazolid monotherapy at a dose of 800 mg (once or twice daily) or 400 mg twice daily achieved about 25% reduction in log colony-forming units (logCFU) in sputum compared with the drug combination of pyrazinamide, rifampicin, isoniazid, and ethambutol.[13] Furthermore, an in-vitro study investigating multidrug-resistant (MDR) tuberculosis, found resistance to linezolid at 6·7% and resistance to delpazolid at 0·8%, suggesting an advantage of delpazolid over linezolid in the treatment of MDR tuberculosis.[14]

Delpazolid has undergone clinical testing up to phase 2. In the single-dose phase 1 study, delpazolid was administered up to 3200 mg.[15] In the 7-day and 21-day repeat-dose study, delpazolid was given up to 1600 mg twice daily and 1200 mg twice daily, respectively.[16,17] In the 21-day repeat-dose study, delpazolid had similar safety and haematology profiles to placebo up to a dose of 1200 mg twice daily and there were no signs of clinically significant myelosuppression or neuropathy. All electrocardiogram results were normal or assessed as not clinically significant. No deaths or serious adverse events occurred.[16] Altogether, phase 1 studies found no clinically significant safety concerns for delpazolid.

We aimed to assess the exposure–response and exposure–toxicity relationship of delpazolid, the latter specifically focusing on oxazolidinone class toxicities that occur after weeks and months of treatment, to support dose selection for future studies.

Methods

Study design

PanACEA-DECODE-01 was a prospective, randomised, open-label, phase 2b, multicentre, dose-finding study done by the PanACEA consortium in five dedicated tuberculosis trial sites, each adjacent to a hospital. Three sites were located in Tanzania—NIMR-Mbeya Medical Research Centre, Kibon'goto Infectious Disease Hospital, and Ifakara Health Institute (Bagamoyo Research and Training Centre)—and two in South Africa—The Aurum Institute (Tembisa Clinical Research Centre), and University of Witwatersrand Clinical HIV Research Unit.

An independent data safety and monitoring board acted in an advisory capacity to the trial steering committee to safeguard the interests of trial participants, review safety data, and perform expedited review if specific criteria were met (details of these criteria are in the published protocol;[18] appendix pp 20–136). The trial was approved by independent trial sites ethics committees and regulatory authorities of Tanzania and South Africa (appendix pp 6–7) and the ethics committee of the Medical Faculty of the Ludwig Maximilian University (approval number 20-0812), and conducted according to Good Clinical Practice guidelines. The trial was registered with ClinicalTrials.gov (NCT04550832) before the start of enrolment.

Participants

Eligible participants were aged 18–65 years, weighed 40–90 kg, and had newly diagnosed drug-sensitive pulmonary tuberculosis with a positive smear microscopy of at least 1+ on the International Union Against Tuberculosis and Lung Disease/WHO scale. Participants with HIV were eligible if they had a CD4 count of more than 220 cells per mL, were on antiretroviral therapy (ART) for a minimum of 5 months, and were able to switch to a dolutegravir-based regimen, because other options would have had drug–drug interactions with bedaquiline and delamanid; or, if ART naive, were able to safely postpone commencing ART for 2 months after trial start and then be initiated on a dolutegravir-based regimen. 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, or an alanine aminotransferase or aspartate aminotransferase concentration of more than three times the upper limit of the normal range. The full inclusion and exclusion criteria are in the protocol in the appendix (pp 20–136). All participants provided written informed consent. Sex data were collected by physician decision (male or female).

Randomisation and masking

Participants were randomly assigned (1:1:1:1:1) to one of five treatment groups: a control group without delpazolid (D0), delpazolid 400 mg once daily (D400), delpazolid 800 mg once daily (D800), delpazolid 1200 mg once daily (D1200), or delpazolid 800 mg twice daily (D800BD). Participants were randomly assigned through centralised allocation, using a probabilistic minimisation algorithm created by the trial statistician,

with a password-protected online tool that was used by investigators. Randomisation was stratified based on bacterial load in sputum as measured by GeneXpert cycle threshold (<16 *vs* ≥16), site, and HIV status. Participants and investigators were aware of treatment allocation. Other personnel assessing participants' outcomes, including the sponsor and microbiology laboratory staff, were masked to allocation. Only the data safety monitoring board and trial statisticians preparing reports reviewed unmasked aggregate data by treatment group before database lock.

Procedures

Participants received no delpazolid, delpazolid 400 mg once daily, delpazolid 800 mg once daily, delpazolid 1200 mg once daily, or delpazolid 800 mg twice daily, all administered orally in combination with bedaquiline (400 mg orally once daily for the first 14 days, then 200 mg orally thrice weekly), delamanid (100 mg orally twice daily), and moxifloxacin (400 mg orally once daily) for 16 weeks. Participants had weekly visits during the 16-week treatment period at which they received their allocated treatment. This was followed by four follow-up visits at week 18, week 26, week 38, and week 52. At each visit, a physical examination including assessments of adverse events and concomitant medication was conducted. Detailed neurological examination including central and peripheral system testing (ie, cranial nerves testing, vibration sensitivity using a 128 Hz tuning fork, position, pin prick, and light touch) and vision testing (Snellen chart and Ishihara test) was conducted at each treatment visit. During follow-up visits at week 26, week 38, and week 52, symptom-orientated neurological examination was done to follow up on adverse events. All recruiting sites and investigators received sponsor medical expert training on the conduct, interpretation, and stopping criteria of all assessments including neurological assessments. Weekly safety blood tests (full blood count, liver function and liver enzyme tests, renal function, and serum electrolytes) and urine tests were done during the treatment period. Triplicate electrocardiography (ECG) assessment was done at baseline or if a QTcF of more than 480 ms, or a QTcF prolongation over baseline of more than 50 ms was observed in a single ECG during experimental treatment.

Two sputum samples were collected and processed for culture in liquid media in a mycobacterial growth indicator tube 960 (MGIT; BD, Johannesburg, South Africa) at weekly visits during treatment and follow-up visits. Löwenstein–Jensen culture was performed at baseline, months 2, 3, and 4, and follow-up visits 1–4 from two samples each. Sustained sputum culture conversion was defined as two successive negative liquid media cultures at or before week 8, with no positives to follow by the week 16 visit. If the first negative was at or before week 8, participants completed their treatment at week 16 and were observed until week 52; in case of a later culture conversion, continuation treatment consisting of isoniazid and rifampicin was given to complete 26 weeks of treatment. Study investigational medicinal products were self-administered orally for 16 weeks except for clinic days when treatment was directly observed.

Pharmacokinetic sampling was performed for all participants on day 14 of the trial at 0 h (before dose) and at 1, 2, 4, 8, 12, and 24 h after dosing. Study drugs were taken with standardised meals with similar nutrition value as per site choice and informed by the protocol. Drug and metabolite concentrations were analysed with a validated liquid chromatography tandem mass spectometry assay. Further details about the bioanalysis are in the appendix (p 3).

Outcomes

The primary efficacy objective was to establish an exposure–response model for delpazolid given over 16 weeks in combination with standard-dose bedaquiline, delamanid, and moxifloxacin. The primary endpoint was change in mycobacterial load over time on treatment as quantified by time to positivity in MGIT liquid culture, described by non-linear mixed-effects methodology. Time to positivity was defined as the time it takes for a culture of *M tuberculosis* to have growth detected in the MGIT automated liquid culture system, which senses a fluorescence change of an indicator sensitive to the consumption of oxygen.

The primary safety objective was to describe the safety, tolerability, and exposure–toxicity relationship of delpazolid given over 16 weeks in combination with standard-dose bedaquiline, delamanid, and moxifloxacin compared with standard-dose bedaquiline, delamanid, and moxifloxacin alone. The primary safety outcome was the occurrence of oxazolidinone class toxicities defined as peripheral or optical neuropathy, incident leukopenia, anaemia, or thrombocytopenia, or adverse events in line with tyramine pressor response, all of grade 2 or higher, possibly, probably, or definitely related to delpazolid. Participants were evaluated for adverse events at each study visit. The severity of adverse events was classified following the US National Institutes of Health Common Terminology Criteria for Adverse Events version 5.0. An exception from this grading was the assessment of the severity of QTcF prolongation and stopping of treatment, which from protocol version 2.1 onwards followed the grading applied in ACTG A5343,[19] a phase 2 trial investigating the combination of bedaquiline and delamanid. The investigators assessed causality (delpazolid or the background regimen) on a 5-point scale, ranging from unrelated to definitely related.

Secondary endpoints were the time to culture conversion, the proportion converted to negative culture at different timepoints, and the proportion of participants with recurrent disease or relapse over a follow-up of 52 weeks after randomisation, which was assessed only

in participants completing 16 weeks of treatment and with sustained negative culture conversion by week 8 or earlier. A secondary outcome measure that is not reported is the proportion of patients acquiring drug resistance among those without culture conversion. This analysis is still ongoing and the proportion of patients acquiring drug resistance, if any, among those without culture conversion results will be published separately.

Statistical analysis

Given the novel type of primary endpoint used, based on quantitative measures of bacterial load over 16 weeks, data to inform a formal sample size calculation with the intended analysis method were seen as too sparse and primarily from shorter duration studies. As a proxy we used data from shorter early bactericidal activity studies, which also use a quantitative bacterial load metric as endpoint. A sample size of 15 participants per group (total 75) was determined adequate for population pharmacokinetic modelling, and for exposure–response modelling to detect a clinically meaningful dose-dependent relationship, in line with early bactericidal activity trials. Previous phase 2a early bactericidal activity studies suggest that the between-patient SD of logCFU can be approximately 0·2.[20] Therefore, assuming similar variability in this trial, the expected SEs of group mean early bactericidal activity and corresponding half-width of 95% CIs are 0·052 for a group size of 15, a level of precision considered adequate.[20] This sample size accounts for a drop-out of three per group, a conservative estimate based on previous experience.

The primary analysis was done in the modified intention-to-treat population, which consisted of all randomly assigned participants in the groups to which they were randomly assigned, and who had taken at least one dose of study treatment. The modified intention-to-treat population excluded participants who withdrew from study medications before pharmacokinetic sampling and was used for pharmacokinetic–pharmacodynamic modelling.

The adequate adherence population was defined for secondary analyses. From this population, all randomly assigned patients not meeting the eligibility criteria were excluded, as were participants who missed ten or more doses of their allocated experimental treatment. The secondary endpoint of time to sustained culture conversion in MGIT liquid media was analysed by Cox proportional hazards, both adjusted and unadjusted, separate and combined between all experimental groups, as an exploratory analysis. The combined unadjusted results are reported as the secondary outcome, while the adjusted model serves as a check with the inclusion of covariates of known confounders that, if unbalanced, could introduce bias. We assessed the proportional hazards assumptions using Schoenfeld residuals, which showed no statistically significant violations across the covariates. In our assumption checks, we also analysed the linearity assumption using the Martingale residuals and found that a single value of –42·0 for baseline time to positivity slightly affected the smoothness of these residuals. Given the smaller sample size and the exploratory nature of the adjusted hazard ratios (HRs), we opted to retain this observation for the final model. Analyses were done using R statistical software version 4.3.1.

A sequential pharmacokinetic–pharmacodynamic model for delpazolid was developed with non-linear mixed-effects methodology. For development of the pharmacokinetic model, all delpazolid concentrations available were used. One, two, and three compartment models were tested and covariate analysis was performed to evaluate the effect of demographic parameters on delpazolid pharmacokinetics (see appendix p 9 for tested covariates). With the final pharmacokinetic model (see appendix p 10 for estimates), individual exposure metrics area under the concentration curve from 0 h to 24 h ($AUC_{0–24}$), maximum concentration (C_{max}) and minimum concentration (C_{min}) were generated for use in the exposure–response analysis. For development of the pharmacodynamics model, observations of the mycobacterial load in sputum over time quantified by time to positivity were used. From the modified intention-to-treat population, all time to positivity data from just before the start of treatment and during the 16 weeks of treatment were used for the analysis. For patients interrupting treatment, the time to positivity data in the period after the start of the interruption were removed. Longitudinal linear and bilinear models were tested to describe log-transformed time to positivity data. A bilinear model has two linear parts, with the slope steepness changing at an estimated node point. Covariate analysis including demographic factors, disease severity markers, and individual delpazolid exposure metrics was performed to evaluate their effects on change in mycobacterial load. Further details regarding the analysis are in the appendix (p 5).

Role of the funding source

The sponsor of the study was involved in the study design and data collection. Study design was led by academic authors and was based on a previous study (PanACEA-SUDOCU-01[21]) that the funders were not involved in. The academic authors independently performed data analysis, data interpretation, and writing of the report.

Results

Between Oct 28, 2021, and Aug 31, 2022, 156 individuals were screened for eligibility, 76 of whom were enrolled and randomly assigned to D0 (n=15), D400 (n=15), D800 (n=15), D1200 (n=16), or D800BD (n=15; figure 1). Recruitment continued until the target sample size was attained.

60 (79%) of 76 participants were male and 16 (21%) were female, all were Black African individuals, and the

median age was 34 years (range 20–57; table 1). Some variability in these characteristics between groups was observed. Participants were followed up to week 52 after randomisation.

420 plasma concentrations from the 60 participants receiving delpazolid were used to develop the population pharmacokinetic model. Delpazolid disposition was well described by a two-compartment model with first-order absorption, first-order elimination, a proportional residual error, and allometric scaling based on fat-free mass. Details of the model and model evaluation are in the appendix (pp 4, 10). The derived metrics AUC_{0-24} and C_{max} used in the exposure–response analysis are shown in figure 2. A linear dose–exposure relationship was observed up to 1200 mg. The median AUC_{0-24} in the D800BD group was higher than in the D1200 group, in

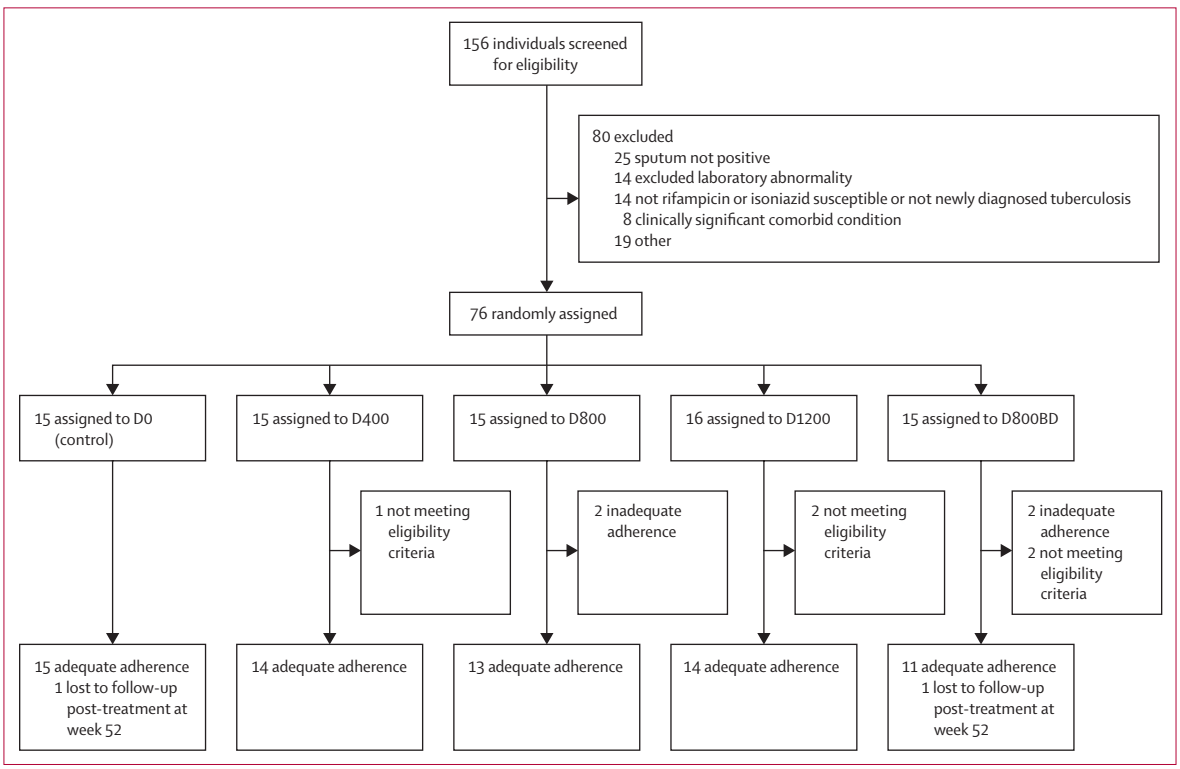

Figure 1: **Trial profile**
D0=no delpazolid. D400=delpazolid 400 mg once daily. D800=delpazolid 800 mg once daily. D1200=delpazolid 1200 mg once daily. D800BD=delpazolid 800 mg twice daily.

	D0 (n=15)	D400 (n=15)	D800 (n=15)	D1200 (n=16)	D800BD (n=15)	Total (n=76)
Sex						
Female	2 (13%)	0	3 (20%)	7 (44%)	4 (27%)	16 (21%)
Male	13 (87%)	15 (100%)	12 (80%)	9 (56%)	11 (73%)	60 (79%)
Age, years	33 (20–50)	41 (22–57)	29 (23–57)	34 (24–51)	32 (23–53)	34 (20–57)
Black African race	15 (100%)	15 (100%)	15 (100%)	16 (100%)	15 (100%)	76 (100%)
Weight, kg	48·3 (43·6–61·0)	51·0 (43·7–70·1)	53·9 (40·2–80 ·0)	57·4 (40·2–70·0)	54·0 (42·9–69·7)	52·9 (40·2–80·0)
BMI, kg/m²	18·2 (15·4–22·1)	18·7 (15·8–23·2)	20·0 (13·9–28·3)	19·3 (16·3–28·0)	19·8 (13·8–26·9)	19·2 (13·9–28·3)
HIV positive	2 (13%)	1 (7%)	3 (20%)	3 (19%)	2 (13%)	11 (14%)
GeneXpert cycle threshold						
<16	3 (20%)	3 (20%)	3 (20%)	3 (19%)	3 (20%)	15 (20%)
≥16	12 (80%)	12 (80%)	12 (80%)	13 (81%)	12 (80%)	61 (80%)
Baseline time to positivity, days	4·9 (3·5–12·2)	5·4 (3·1–19·8)	5·3 (3·6–25·0)	5·8 (3·5–40·0)	5·6 (2·9–10·6)	5·4 (2·9–40·0)

Data are n (%) or median (range). D0=no delpazolid. D400=delpazolid 400 mg once daily. D800=delpazolid 800 mg once daily. D1200=delpazolid 1200 mg once daily. D800BD=delpazolid 800 mg twice daily.

Table 1: **Demographic and baseline characteristics**

line with a higher total dose. The median C_{max} in the D800BD group is similar to the median C_{max} in the D800 group.

At baseline, liquid culture was positive in 76 (100%) of 76 samples and solid culture was positive in 74 (97%) samples (appendix p 8). Median change in time to positivity in MGIT over time on treatment is shown in the appendix (p 12), with culture conversion by week 8 in the sensitivity analysis varying from seven (48%) of 15 participants to 12 (75%) of 16 participants.

2312 time to positivity results from 75 participants (modified intention-to-treat population) were used for developing the pharmacodynamic model. Participants in all treatment groups showed a significant decrease in mycobacterial load (represented by increase in time to positivity) in sputum. A bilinear model (two linear parts with slope steepness changing at an estimated node point) described log_{10}-transformed time to positivity data well (figure 3A). This model had an upper limit of quantification at 25 days and an estimated node point at approximately 7–8 days. Further details and model evaluation are in the appendix (pp 5, 11, 17).

Exposure–response modelling estimated a linear effect of delpazolid AUC_{0-24} on the second slope (starting after the first week) with a maximal effect at an AUC_{0-24} of 50 mg/L per h (figure 3B). This maximal effect was estimated at a 38% (95% CI 4–83; p=0·025) faster decline in bacterial load compared with no delpazolid (figure 3A). These results suggest that delpazolid adds efficacy on top of bedaquiline, delamanid, and moxifloxacin.

39 (51%) of 76 participants had at least one treatment-emergent adverse event during treatment (table 2). The most frequent adverse events were gastrointestinal disorders: 11 (15%) participants had nausea and eight (11%) had vomiting. Only mild aminotransferase elevations were observed during treatment in all groups.

No deaths occurred during the study period. Five (7%) of 76 participants had grade 3 treatment-emergent adverse events: ECG QT prolongation (not related to delpazolid, D800 group), nausea (probably related, D1200 group), anaemia (serious adverse event; possibly related, D800BD group), endoscopically diagnosed gastritis (serious adverse event; possibly related, D800BD group), and hyponatraemia (not related, D800BD group). Two (3%) participants had grade 4 events: diabetic ketoacidosis (serious adverse event; not related, D800 group) and hypernatraemia (not related, D800 group).

Of these higher-grade events, three were reported as serious adverse events in three (4%) participants: one was unrelated to study treatment (grade 4 diabetic ketoacidosis in the D800 group), and two events were possibly related to delpazolid (grade 3 anaemia and endoscopically diagnosed gastritis, both occurring in the D800BD group).

Treatment-emergent adverse events of oxazolidinone class toxicities, at least grade 2 in severity and possibly, probably, or definitely related to delpazolid, included the serious adverse event of anaemia reported in the D800BD group. In addition, in one participant in the D800 group, a moderate neutropenia was observed at one visit, but values had returned to normal on the next visit with continued dosing. No other class toxicities, including peripheral or optic neuropathy of any grade, were reported. No drug-related tyramine pressure response (hypertension) nor serotonine syndrome occurred.

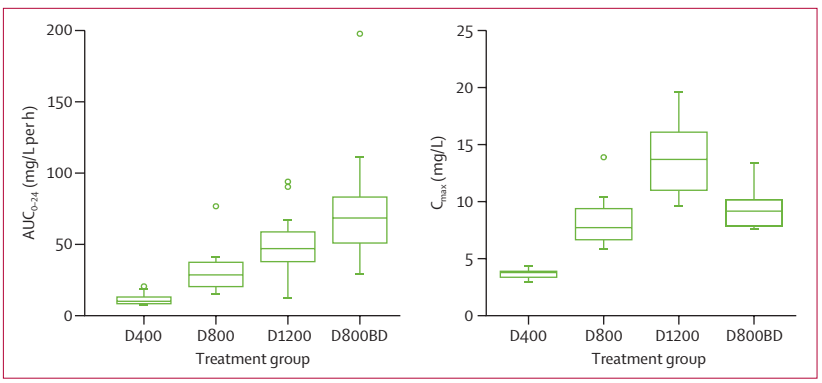

Figure 2: **Boxplots of delpazolid exposure metrics AUC_{0-24} and C_{max} per group derived from the population pharmacokinetics model**

The boxes represent the IQR, with the midline showing the median. The lines outside the boxes extend to the minimum and maximum, excluding outliers, which are represented by the dots. AUC_{0-24}=area under the concentration curve from 0 h to 24 h. C_{max}=maximum concentration. D400=delpazolid 400 mg once daily. D800=delpazolid 800 mg once daily. D1200=delpazolid 1200 mg once daily. D800BD=delpazolid 800 mg twice daily.

Treatment-emergent adverse events of interest for bedaquiline, delamanid, and moxifloxacin included QT interval prolongations, which were reported for eight participants—one participant presented a QT interval of more than 500 ms in the D800 group. This episode occurred after two doses of the study medication, had no clinical repercussion, and was considered not related to delpazolid. In addition, the participant had been included in error, as the QTcF interval at screening was 457 ms (>450 ms).

The study treatment was interrupted temporarily in two participants with adverse events (hyponatraemia and gastritis, both in the D800BD group) and discontinued in three participants due to adverse events (included in error due to too long QTcF interval at baseline in the D800 group, anaemia in the D800BD group, and diabetic ketoacidosis in the D800 group, the latter being rated as unrelated to study treatment). One pregnancy was reported 155 days after the last dose of the study treatment, with a normal pregnancy and neonatal outcome.

In the D800BD group, the two individuals with serious adverse events had relatively high delpazolid AUC_{0-24} values (appendix p 18). The participant with gastritis had an AUC_{0-24} of 198 mg/L per h and C_{max} of 13·4 mg/L (which was the highest observed AUC_{0-24} in the study and highest C_{max} of this group) and the participant with anaemia had an AUC_{0-24} of 112 mg/L per h (C_{max} 9·27 mg/L,

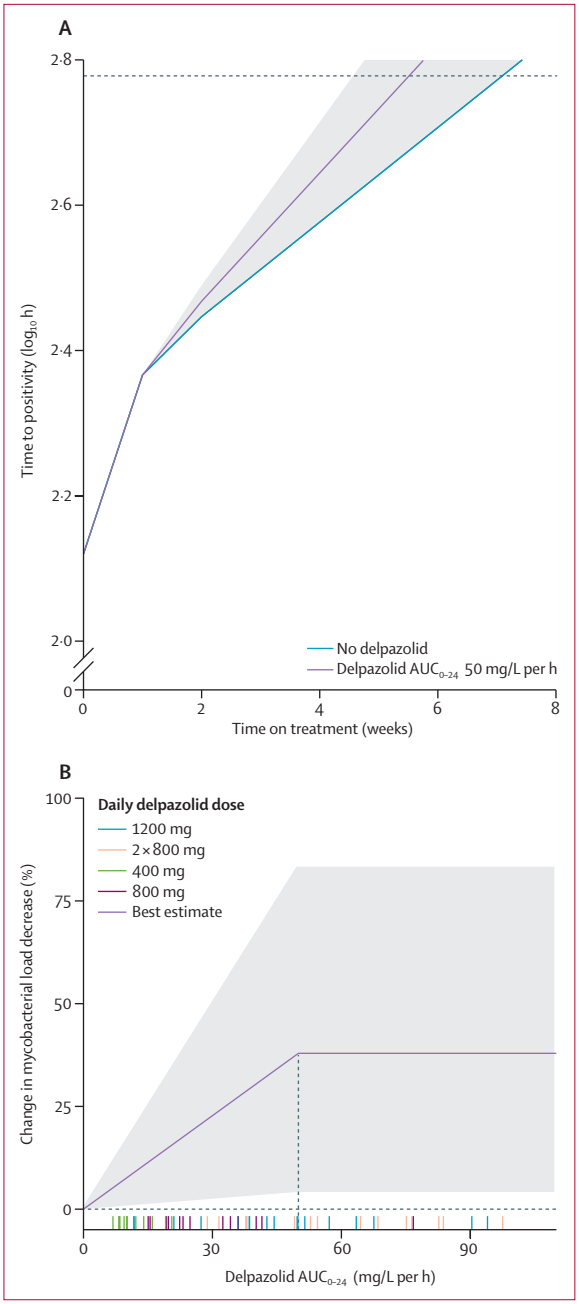

Figure 3: **Exposure–response analysis**
(A) Model-predicted time to positivity over time for a typical individual without delpazolid exposure (D0 group) and one with a delpazolid AUC_{0-24} of 50 mg/L per h, which is close to the median exposure in the D1200 group. The horizontal dashed line represents the upper limit of quantification (25 days). (B) Model-predicted delpazolid exposure effect. Observed exposures are shown with tick marks along the x axis. The x axis is cut at 110 mg/L per h, excluding one AUC_{0-24} at 198 mg/L per h for visibility purposes. The version of this figure with all data included is in the appendix (p 18). The grey shaded area represents the 95% CI on both charts and the dashed line emphasises the exposure achieving maximum effect. AUC_{0-24}=area under the concentration curve from 0 h to 24 h. D0=no delpazolid. D1200=delpazolid 1200 mg once daily.

close to median of this group). Their C_{min} values were within the normal range (appendix p 18).

There was no evidence for a difference in time to culture conversion between treatment groups or exposure tertiles (appendix pp 9, 12–14). When combining all delpazolid treatment groups together compared with the control group (D0), the HR for time to sustained sputum culture conversion to negative compared with the D0 group was 1·53 (95% CI 0·84–2·76).

One participant each in the D0 and D800BD groups did not have sustained sputum culture conversion to negative by week 16, with no identification of adherence issues or potential food–drug interactions (appendix p 8). The participant in the D800BD group was classified as having unsuccessful treatment outcome by week 16 and was restarted on a course of standard tuberculosis treatment, whereas the participant in the D0 group was considered cured at the end of the 26-week treatment course. Of 74 participants who completed 16 weeks of experimental treatment, 41 did not receive additional treatment with isoniazid and rifampicin, so had a shorter treatment and were followed up for disease recurrence. No participant had disease recurrence.

Discussion

Exposure–response modelling resulted in a bilinear model for log_{10} time to positivity increase, with an estimated node point at day 7–8, similar to the model for sutezolid, which was developed in the sister study PanACEA-SUDOCU-01.[21]

This bilinearity could be due to a biphasic killing kinetic that would traditionally be expected from isoniazid-containing regimens whereby a subpopulation of rapidly replicating bacteria is killed first, followed by slow-reproducing resilient mycobacteria killed at a slower rate. It could also be due to the carry-over of drugs with a long half-life and high protein binding such as bedaquiline or delamanid into culture. Whereas the cultures from baseline, before the first dose of treatment, would be unaffected, all those from subsequent timepoints would be affected, resulting in a relatively longer time to positivity.[22] Together, population pharmacokinetic modelling and exposure–response modelling suggest that a plateau in efficacy is reached at an AUC_{0-24} of 50 mg/L per h; which is close to the median exposure at a dose of 1200 mg. Conventional comparison between groups in this study might have suggested the lower dose of 800 mg once daily to be equally efficacious, or been inconclusive due to the overlapping CIs. Longitudinal, quantitative modelling as performed here maximises the information derived from the collected data, and this approach, which was pioneered by PanACEA, is currently being implemented in multiple studies of novel tuberculosis treatments.

Although the pharmacokinetic–pharmacodynamic modelling shows there is a statistically significant relationship between delpazolid exposure and response,

	D0 (n=15)	D400 (n=15)	D800 (n=15)	D1200 (n=16)	D800BD (n=15)	Total (n=76)
Treatment-emergent adverse events	8 (53%)	7 (47%)	8 (53%)	6 (38%)	10 (67%)	39 (51%)
Grade 1 (mild)	4 (27%)	3 (20%)	0	0	1 (7%)	8 (11%)
Grade 2 (moderate)	4 (27%)	4 (27%)	5 (33%)	5 (31%)	6 (40%)	24 (32%)
Grade 3 (severe)	0	0	1 (7%)	1 (6%)	3 (20%)	5 (7%)
Grade 4 (life-threatening)	0	0	2 (13%)	0	0	2 (3%)
Delpazolid-related treatment-emergent adverse events						
Unrelated	5 (33%)	3 (20%)	5 (33%)	3 (19%)	3 (20%)	19 (25%)
Unlikely related	0	1 (7%)	1 (7%)	1 (6%)	2 (13%)	5 (7%)
Possibly related	2 (13%)	1 (7%)	1 (7%)	1 (6%)	5 (33%)	10 (13%)
Probably related	0	1 (7%)	1 (7%)	1 (6%)	0	3 (4%)
Definitely related	1 (7%)	1 (7%)	0	0	0	2 (3%)
Serious adverse events	0	0	1 (7%)	0	2 (13%)	3 (4%)
Grade 3 (severe)	0	0	0	0	2 (13%)	2 (3%)
Grade 4 (life-threatening)	0	0	1 (7%)	0	0	1 (1%)
Delpazolid-related serious adverse events						
Unrelated	0	0	1 (7%)	0	0	1 (1%)
Possibly related	0	0	0	0	2 (13%)	2 (3%)

Treatment-emergent adverse events are defined as adverse events that started at or after the first administration of study drug or that started before the first administration of study drug but worsened after the first administration of study drug, until the last scheduled assessment. For participants who had multiple adverse events, the highest graded event was used to classify seriousness, grade, and relatedness. D0=no delpazolid. D400=delpazolid 400 mg once daily. D800=delpazolid 800 mg once daily. D1200=delpazolid 1200 mg once daily. D800BD=delpazolid 800 mg twice daily.

Table 2: **Overview of adverse events by participant**

the estimates are uncertain and we acknowledge this as a limitation. This is likely to be related to the small sample size of the study. There might also be a relation with the bedaquiline, delamanid, and moxifloxacin backbone, as the strength of this regimen might make it harder to estimate the effect of an additional drug, in this case delpazolid.

The safety profile of delpazolid in our cohort, at doses of up to 1200 mg once daily for 16 weeks seems better than that of linezolid: 81% of patients had neuropathy and 48% had myelosuppression when receiving the same dose of linezolid, although over 6 months.[5] At the dose of 1200 mg of delpazolid, which corresponds best to the plateau in efficacy, no serious adverse events were reported. Six treatment-emergent adverse events were reported in the D1200 group, with one assessed as probably related to delpazolid. No delpazolid-related neuropathy, cardiac toxicity, or liver toxicity was observed in our study. The highest dose of 800 mg twice daily showed two drug-related serious adverse events requiring discontinuation: one was a gastritis event, in keeping with gastric intolerance of higher doses of delpazolid in previous studies, and one was anaemia, which we rated as oxazolidinone class toxicity. In both cases, the individual $AUC_{0–24}$ values were very high whereas C_{min} values were within the normal range (appendix p 18). Despite C_{min} previously being linked to oxazolidinone mitochondrial toxicity, which can lead to bone marrow suppression and anaemia,[23] this study suggests that a high $AUC_{0–24}$ is a key determinant of delpazolid toxicity. The short half-life of delpazolid, which is a third to a half of linezolid half-life, might explain why delpazolid toxicity is more closely associated with $AUC_{0–24}$. A study assessing similar doses of delpazolid as those in our study reported undetectable concentrations of delpazolid within 12 h.[13] Apart from one participant with anaemia, no other oxazolidinone class toxicity adverse event was reported.

The PanACEA consortium carried out this study as one of two dose-ranging studies of novel oxazolidinones, the other being PanACEA-SUDOCU-01.[21] Previously, dose selection for tuberculosis drugs was done in 14-day monotherapy studies. We deliberately chose to extend treatment with experimental drugs beyond 14 days, included a wide range of doses, and chose population pharmacokinetic modelling, exposure–response modelling, and exposure–toxicity modelling if any specific toxicity was encountered, rather than using frequentist statistics. Also, the exposure–response profile of a drug might be different between early and late treatment, and between monotherapy and combination therapy. Here, our innovative design should be closer to the actual use that dosing needs to be optimised for. This approach would support dose selection for a new drug as part of a drug combination likely to play a role in future trials. Due to the usually late onset of oxazolidinone class toxicities, the classic 14-day early bactericidal activity design would not have been adequate to judge safety. This innovative trial design has so far been used in two more trials—UNITE4TB DECISION for dose-finding of BTZ-043 (NCT05926466) and a dose-finding trial of quabodepistat (NCT05221502).

To our knowledge, PanACEA-DECODE-01 and PanACEA-SUDOCU-01 were the first trials to use a combination of bedaquiline, delamanid, and moxifloxacin. Comparing between trials conducted within PanACEA in largely the same sites,[24] the PanACEA-DECODE-01 control group of bedaquiline, delamanid, and moxifloxacin had similar slope in time to positivity over time to the MAMS-TB-01 standard of care isoniazid, rifampicin, pyrazinamide and ethambutol control group.[24] However, as this is a historical comparison, caution is warranted in its interpretation, as potential biases might arise from differences in patient populations, changes in laboratory methodologies, and other trial-related factors.

Our study's limitations include the small sample size leading to limited precision of the estimates and to an imbalance in the baseline characteristics of sex, age, and HIV status. However, the effects of these covariates were tested and none of them substantially improved the pharmacokinetic–pharmacodynamic model, suggesting that the observed imbalances do not affect our primary endpoints. Using a larger sample size in future studies might result in a more precise estimate: a learning that is already incorporated in the UNITE4TB-DECISION trial (NCT05926466). Another limitation is the absence of a concurrently randomised standard of care control group for comparison of observed efficacy. A historical comparison was carried out, but a concurrent, randomised control would be a stronger comparator. Bedaquiline, delamanid, and moxifloxacin was a potent combination, but, despite this, we were able to detect an additional effect of delpazolid. The open-label nature of the study was another potential limitation. Assessment of the tuberculosis culture outcome was done in a masked way, limiting the risk for bias. Knowledge of delpazolid dose could have led investigators to more likely attribute causality to delpazolid in higher dose groups, and the proportion of adverse events at least possibly related is in fact slightly higher in the D800BD group than in the other groups. We believe that patient management was not affected, since all treatment interruptions or discontinuations were based on laboratory values or, in the case of the gastritis event, uncontrollable vomiting.

In the combination of delpazolid plus bedaquiline, delamanid, and moxifloxacin, a plateau in efficacy was reached at an $AUC_{0–24}$ of 50 mg/L per h. This exposure corresponded to the median exposure at a dose of 1200 mg. The estimated maximal effect of delpazolid was a 38% steeper decline in bacterial load after the first week, with a wide 95% CI. Thus, delpazolid added efficacy on top of the strong backbone regimen consisting of bedaquiline, delamanid, and moxifloxacin.

This study provides preliminary safety data supporting delpazolid at a 1200 mg once daily dose for 16 weeks, which aligns with the efficacy plateau. However, more phase 2 studies are ongoing and larger studies are necessary to comprehensively assess the safety and tolerability of this dose and address some of the open questions and uncertainties in this trial.

Taken together, evidence suggests that a dose of 1200 mg should be used for future development, which is currently planned in the UNITE4TB PARADIGM4TB trial.

Contributors

Funding acquisition: LG, MJB, Y-LC, NH, and MH. Study design: NH, EMS, LG, and PPJP. Study conduct and data collection: LTM, CM, SM, FM, MS, RSW, MR, NN, AL, BM, TZ, DDP, HM, LWa, TDM, and LWi. Drug management: RA and LtB. Bioanalysis of drug samples: LtB. Data curation: IN. Formal analysis: PPJP, BHA, LtB, IN, IvdF, EMS, and NH. Project administration: LWa. Supervision and validation: IN and NH. Visualisation: BHA, PPJP, EMS, and IvdF. Writing of the original draft: LTM, IvdF, DJS, JAS, MH, EMS, and NH. Review and editing: all authors. Data access and verification: PPJP, EMS, and NH. Decision to submit the manuscript: LTM and NH. Authors with access to the raw data: NH, IN, LWi, BHA, PPJP, IvdF, EMS, and LtB. All authors have read and approved the final version of the manuscript for publication. 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 corresponding author had full access to all the data in the study; all authors did not have access to the data due to General Data Protection Regulation. All authors had final responsibility for the decision to submit for publication.

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/. Study related documents (including case report forms and patient consent forms) are available on request from the corresponding author. The study protocol was previously published.[18]

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