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Long-term efficacy and safety of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): extended follow-up of an open-label, multicentre, randomised, non-inferiority trial

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Summary

Background STREAM stage 2 showed that two bedaquiline-containing regimens (a 9-month all-oral regimen and a 6-month regimen with 8 weeks of aminoglycoside) had superior efficacy to a 9-month injectable-containing regimen for rifampicin-resistant tuberculosis up to 76 weeks after randomisation. Our objective in this follow-up analysis was to assess the durability of efficacy and safety, including mortality, at 132 weeks.

Methods We report the long-term outcomes from STREAM stage 2, a randomised, phase 3 non-inferiority (10% margin) trial in participants (aged ≥15 years) with rifampicin-resistant tuberculosis without fluoroquinolone or aminoglycoside resistance at 13 clinical sites in seven countries (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda). Participants were randomly assigned 1:2:2:2 (via permuted blocks and stratified by site and HIV status plus CD4 cell count) to the 2011 WHO long regimen (terminated early), a 9-month control regimen, a 9-month oral regimen with bedaquiline (primary comparison), or a 6-month regimen with bedaquiline and 8 weeks of an injectable antituberculous drug. Participants and clinicians were aware of treatment-group assignments, but laboratory staff were masked. The primary outcome, reported previously, was favourable status (negative cultures for *Mycobacterium tuberculosis* without a preceding unfavourable outcome; any death, bacteriological failure or recurrence, and major treatment change were considered unfavourable) at week 76. Here we report efficacy outcomes at week 132, analysed in the modified intention-to-treat (mITT) population. Safety assessments continued to 132 weeks and were in all participants who received at least one dose of the study regimen. All comparisons used concurrently randomised participants. This trial is registered on ISRCTN (ISRCTN18148631) and is now completed.

Findings Between March 28, 2016, and Jan 28, 2020, 588 participants were randomly assigned to the long (n=32), control (n=202), oral (n=211), or 6-month (n=143) treatment regimens; 352 (60%) were male and 236 (40%) were female. Of the 556 participants on the three shorter regimens, 517 were included in the mITT population (187 in control group, 196 in oral group, and 134 in 6-month group) and 465 in the per-protocol analyses. Six additional participants had an unfavourable outcome that occurred between week 76 and the end of efficacy follow-up (one in control group, four in oral group, one in 6-month group). In the mITT population, the proportion of patients with an unfavourable outcome at the end of follow-up was 19·6% (95% CI 14·3 to 24·9) in the oral group and 29·3% (23·3 to 36·5) in the control group (–9·7 percentage points difference [95% CI –18·7 to –1·8]; $p_{superiority}$=0·024). An estimated 9·8% (95% CI 4·6 to 14·9) of participants on the 6-month regimen had an unfavourable outcome, which was significantly lower than for those concurrently on the control regimen (32·5% [23·7 to 40·2]; $p_{superiority}$<0·0001) or the oral regimen (23·8% [16·9 to 31·1]; $p_{superiority}$=0·013). Few serious or severe adverse events were reported after week 76, with no indication of a difference between the regimens. At week 132, treatment-emergent hearing loss was recorded in significantly fewer participants on the oral regimen (7/205; 3%) than the control regimen (16/198; 8%; p=0.041); there was no significant difference in severe hearing loss between the oral regimen (6/139; 4%) and the 6-month regimen (5/143; 4%; p=0·72). Death rates were low: 1·01 (95% CI 0·48 to 2·12) per 100 person-years in participants allocated to bedaquiline (ie, oral and 6-month regimen, n=287) compared with 1·52 (0·63 to 3·66) in participants on the control regimen (n=140; p=0·49).

Interpretation Both of the bedaquiline-containing regimens maintained superiority to the control regimen, without evidence of increased mortality, providing two additional evidence-based treatment options for patients; previous mortality concerns for bedaquiline were not substantiated.

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See Comment page 939

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See Online for appendix

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Introduction

The management of multidrug-resistant tuberculosis is a global challenge; until the past few years, the disease was treated with long regimens of toxic medications resulting in poor outcomes and frequent losses to follow-up. STREAM stage 1, the first international phase 3 trial of a new regimen for multidrug-resistant tuberculosis, showed that a shorter, 9-month, regimen had non-inferior outcomes to the 20-month regimen that had been recommended by WHO since 2011, but concerns about toxicity remained.[1]

STREAM stage 2 was designed to assess whether the inclusion of bedaquiline instead of the aminoglycoside kanamycin in the shortened regimen would be equally effective and would reduce the incidence of treatment-emergent hearing loss found in stage 1. A second experimental regimen given for only 6 months included bedaquiline throughout and 8 weeks of kanamycin and high-dose isoniazid in a short intensive phase. At 76 weeks after randomisation, the primary efficacy outcome timepoint, both experimental regimens containing bedaquiline were found to be not only non-inferior but also superior to the 9-month regimen when assessed through the primary composite outcome and a secondary tuberculosis-related outcome.[2]

Three other phase 3 trials,[3–5] also evaluating all-oral regimens for multidrug-resistant tuberculosis, published their results in the same year as STREAM stage 2, although the choice of both the experimental and control regimens differed from those in STREAM. The NExT trial, with 111 participants in South Africa, found that 51% of participants assigned to a 6-month all-oral regimen composed of WHO group A antituberculous drugs plus two other group B or C antituberculous drugs had a favourable outcome at 24 months compared with 23% assigned to the injectable-based standard-of-care regimen.[3] The MDR-END trial, with 214 participants in South Korea, showed that a 9-month oral regimen with delamanid, linezolid, levofloxacin, and pyrazinamide was non-inferior to treatment based on the 2014 WHO guidelines; at 24 months after treatment initiation, 71% in the control group had treatment success according to WHO outcome definitions, compared with 75% on the shorter regimen.[4] TB-PRACTECAL, an international trial with 301 participants in Belarus, South Africa, and Uzbekistan, published in late 2022, found that 11% of

Research in context

Evidence before this study

Few randomised phase 3 clinical trials in participants with rifampicin-resistant tuberculosis have been completed and published, and none before STREAM stage 2 was initiated. We searched PubMed for randomised treatment trials with clinical outcomes in rifampicin-resistant or multidrug-resistant tuberculosis, published from Jan 1, 2000, to Sept 14, 2023. We used the search terms "trial" AND "tuberculosis" AND "rifampicin resistance" OR "MDR" OR "multi-drug" OR "multidrug" OR "rifampicin-resistance", with no language restrictions. This search yielded 259 results; studies that were not randomised controlled trials reporting clinical outcomes were excluded, as was one trial that included only regimens over 20 months in length, leaving only six trials.
STREAM stage 2 was designed in 2016, before publication of the STREAM stage 1 results showed the study regimen (the control regimen in STREAM stage 2) to be non-inferior to the treatment based on 2011 WHO guidelines. In 2019, a trial comparing delamanid to placebo added to an optimised background showed no difference in sputum culture conversion or long-term outcome.

In 2022, NExT, a small South African trial, found that 51% of participants assigned to a 6-month all-oral regimen based on WHO group A antituberculous drugs had a favourable outcome at 24 months compared with 23% assigned to the injectable-based standard of care. In the same year, the South Korean MDR-END trial showed that a 9-month oral regimen with delamanid, linezolid, levofloxacin, and pyrazinamide was non-inferior to treatment based on 2014 WHO guidelines; 71% had treatment success on the control regimen compared with 75% on the shorter regimen at 24 months. The TB-PRACTECAL trial, published in late 2022, found that 11% of participants assigned to a 24-week regimen with bedaquiline, pretomanid, linezolid, and moxifloxacin had an unfavourable outcome compared with 48% on concurrent standard of care.

Added value of this study

The STREAM stage 2 study shows that at 132 weeks from randomisation, both a 9-month oral bedaquiline-containing regimen and a 6-month bedaquiline-containing regimen with 8 weeks of a second-line injectable had superior favourable outcomes compared with a 9-month injectable-based regimen, with very little acquisition of phenotypic resistance to core drugs and no evidence that bedaquiline increases the risk of death. STREAM stage 2 currently has the longest follow-up data of a randomised comparison of bedaquiline to a robust control regimen.

Implications of all the available evidence

The findings of the STREAM stage 2 trial, combined with results of previous trials, show that shorter bedaquiline-containing regimens are an effective and safe treatment for patients with multidrug-resistant tuberculosis. These data confirm the value of the 9-month regimen recommended in current WHO guidelines and support the use of a 6-month regimen.

participants assigned to a 24-week all-oral regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin had an unfavourable outcome compared with 48% on a 9–20-month standard-of-care regimen.[5] The definition of an unfavourable outcome included treatment discontinuation, which accounted for the majority of events in TB-PRACTECAL; there were no treatment failures or recurrences reported in either treatment group.

This Article reports the STREAM stage 2 long-term efficacy and safety outcomes, 132 weeks after randomisation, to assess whether the outcomes seen at week 76 are maintained and to assess whether there are any mortality risks associated with bedaquiline, as was suggested by the phase 2b trial C208.[6] STREAM stage 2 is a specific obligation linked to the conditional European Medicines Agency approval of bedaquiline and a post-marketing requirement related to the US Food and Drug Administration accelerated approval of bedaquiline. We also report on acquired drug resistance over the long-term; there is concern that regimens containing bedaquiline, although short, could drive resistance even when the regimen is stopped, given the very long half-life of the drug.

Methods

Study design and participants

STREAM stage 2 was a phase 3, open-label, randomised, non-inferiority trial conducted at 13 clinical sites in seven countries (Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda). The trial methods and primary results at week 76 have been published.[2,7] The Union Ethics Advisory Group was the global ethics committee. Ethical approvals were also obtained from national and institutional ethics committees of participating sites. This trial is registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN18148631).

In brief, eligible participants were recruited at clinical sites when presenting for care and randomly assigned to a treatment group between March 28, 2016, and Jan 28, 2020. Eligible participants were aged 15 years or older (where approved, otherwise aged 18 years or older) and had pulmonary tuberculosis with evidence of resistance to rifampicin, regardless of susceptibility to isoniazid. Participants were ineligible if they were infected with a strain of *Mycobacterium tuberculosis* with evidence of resistance to a second-line injectable drug or fluoroquinolones on a line-probe assay. Written informed consent was obtained from all participants.

Randomisation and masking

Participants were randomly assigned in a 1:2:2:2 ratio to one of four treatment regimens: long, control, oral, and 6-month. Randomisations were stratified by site and HIV status plus CD4 cell count (HIV negative, HIV positive with CD4 count ≥350 cells/mm³, HIV positive with CD4 count <350 cells/mm³). Separate randomisation lists for each combination of strata were prepared by an independent masked statistician with permuted blocks of varying sizes. Participants were randomly assigned through a web-based randomisation system accessed by site personnel; if web access was not available at the time of randomisation, a manual alternative with sealed envelopes was provided. Participants and clinicians were aware of treatment-group assignments, but laboratory staff were not. Only the independent data monitoring committee and the unmasked trial statisticians saw data by treatment group.

Procedures

The long regimen was the 20-month regimen recommended by WHO from 2011 to 2018;[23] the control regimen was a 9-month regimen of moxifloxacin (at higher-than-standard dose), clofazimine, ethambutol, and pyrazinamide for 40 weeks, with kanamycin, high-dose isoniazid, and protionamide given for the 16-week intensive phase; the oral regimen was a 9-month regimen identical to the control regimen except that bedaquiline, given for 40 weeks, replaced kanamycin given for 16 weeks and levofloxacin replaced moxifloxacin; the 6-month regimen consisted of bedaquiline, clofazimine, pyrazinamide, and levofloxacin prescribed for 28 weeks, supplemented by high-dose isoniazid with kanamycin for an 8-week intensive phase. All drugs in all regimens were administered orally, except for kanamycin, which was administered by intramuscular injection. All regimens included the option to extend the intensive phase by up to 8 weeks for delayed sputum smear conversion. Full details, including dosing schedules, are given in the appendix (pp 4–6).

In April 2018, a protocol amendment substituted levofloxacin for moxifloxacin in the control regimen when the results of stage 1 became known, with the aim of collecting data on whether the use of levofloxacin reduced the number of participants having QT prolongation and the need for intensive monitoring.

The 2018 protocol amendments also closed recruitment to the long and 6-month regimens. Use of the long regimen in routine practice had declined rapidly as sites adopted shorter regimens in response to the 2016 WHO treatment guidelines.[8] We decided to stop randomisation to the 6-month regimen early to ensure that sufficient participants would be recruited to the main comparison of the control and oral regimens. The use of an injectable in the 6-month regimen made this regimen less likely to be adopted than the entirely oral regimen by some national treatment programmes because of concerns about ototoxicity. The cessation of randomisation of participants to the 6-month regimen and change of the fluoroquinolone in the control regimen were implemented in all countries except India; the Central Drugs Standard Control Organization headed by the Drugs Controller General of India did not approve these changes.[7]

Baseline and follow-up demographic and clinical data were collected on the case report form by clinical staff at each site. Sputum samples for smear and culture were obtained at the randomisation visit, then every 4 weeks until week 52, then once every 8 weeks until week 76, and then once every 12 weeks up to and including a participant's last scheduled efficacy visit. Thereafter, sputum was collected only if clinically indicated. The trial reference laboratory tested *M tuberculosis* isolates obtained from sputum specimens collected at screening, at randomisation, and from week 8 onwards for phenotypic drug susceptibility and genotyped strains to distinguish true relapses from exogenous reinfections. Regular electrocardiographic (ECG) monitoring with centralised calculation of the corrected QT through Fridericia's formula (QTcF) was recorded until week 76; thereafter regular ECG monitoring was limited to participants whose QTcF had not normalised by week 76 or if clinically indicated—eg, if taking a salvage regimen with potential for QT prolongation. Routine safety blood tests were also stopped after week 76 but the investigators could undertake them whenever clinically indicated. Tablet-based audiometry was done regularly to the end of follow-up (appendix pp 7–10).

After the week 76 visit, the time of the primary outcome assessment, participants were seen at week 84 and then at intervals of once every 12 weeks until week 132. Safety assessments were continued to the end of follow-up; efficacy assessments were terminated at a participant's last efficacy visit, defined as their last scheduled visit on or before Nov 30, 2021 (the projected week 96 visit of the last participant to be randomly assigned).

The window for the last efficacy visit was defined as no more than 6 weeks before and up to 6 weeks after the scheduled visit (window censored on Nov 30, 2021, if this was earlier). The end dates of the visit window were extended for any participants whose scheduled last efficacy visit was during the COVID-19 pandemic and did not occur due to restrictions on movement, unacceptable risk of exposure to COVID-19 in connection with the scheduled visit, or any other reason related to the pandemic. For these participants, the window for the last sputum samples was extended to 12 weeks after the scheduled visit date.

A comprehensive in-trial health economics analysis was done at selected STREAM clinical sites (chosen to reflect diversity) and is reported separately.[24]

Outcomes

The primary outcome of the trial, reported previously,[2] was favourable status (ie, negative cultures for *M tuberculosis* without a preceding unfavourable outcome) at 76 weeks. Here we report the long-term efficacy outcomes, which were unfavourable outcome at week 132 after randomisation; time to unfavourable outcome; time to probable or definite treatment failure or recurrence (FOR) of tuberculosis; tuberculosis outcome at week 132 irrespective of any interim events; and treatment outcome according to the WHO classification.[9] A participant's outcome at their last scheduled efficacy visit was classified as unfavourable if their outcome was unfavourable at week 76, they had started any multidrug-resistant tuberculosis treatment, they had died between their week 76 and their last scheduled efficacy visit, or they had a positive culture from one of their two most recent samples. A participant who did not have a culture result within the window for their last scheduled efficacy visit, having not otherwise been classified as having an unfavourable outcome, was regarded as non-assessable if their last two cultures, from specimens taken at least 1 day apart, were negative. For the FOR (tuberculosis-related) outcome, clinical and microbiological data to the time of the unfavourable efficacy outcome were reviewed by an independent clinician, unaware of treatment-group assignment, to determine the likelihood of FOR. Participants were assigned to one of five categories depending on the likelihood of their treatment outcome being FOR: definite, probable, possible, likely, or highly unlikely. The tuberculosis outcome ignoring interim events was defined according to the participants' culture status at week 132 regardless of treatment changes or intermediate culture results—similar to a simplistic intention-to-treat analysis. A participant's tuberculosis outcome was classified as cured at week 132 if their last two cultures were negative, with the last sputum collected no earlier than the week 132 analysis window; other categories included death before week 132, last positive culture at week 132, last negative culture before week 132, last positive culture before week 132, or no cultures after baseline. WHO treatment outcomes for drug-resistant tuberculosis were determined at the end of treatment with the 2021 update of the definition.[9] Participant outcomes were classified as cured, treatment completed, treatment failed, died, lost to follow-up, or not evaluated, with the first two categories considered together as treatment success.

Long-term safety outcomes were death due to any cause, grade 3 and grade 4 treatment-emergent adverse events (defined according to Division of AIDS, US National Institute of Allergy and Infectious Diseases criteria), serious adverse events, normalised QT prolongation (defined as QTcF <450 ms or within 10 ms of baseline), and treatment-emergent hearing loss detected by audiometry as per Brock's criteria. Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 21.0, except for COVID-19-related events with version 23.0). An independent death review committee (two infectious disease specialists and a cardiologist), with members unaware of treatment-group assignments, classified the probable causes of death as cardiac structural, cardiac arrhythmic (ie, probable or possible sudden cardiac death), tuberculosis-related, HIV-related, or other.

Statistical analysis

We estimated that a sample of 200 participants allocated to each regimen would give 80% power to show the non-inferiority of the oral regimen versus the control regimen at a one-sided significance level of 0·025 with a 10% margin of non-inferiority. This power calculation assumed a favourable efficacy outcome at 76 weeks in 80% of participants in the control group and 82% of those in the oral group and assumed that 14% of participants would be excluded from the per-protocol analysis.

We analysed non-inferiority of the oral regimen compared with the control regimen at week 132 by estimating the proportions of participants with unfavourable outcomes with the Kaplan–Meier product limit estimator using time to unfavourable outcome, thereby using information on all participants and not just those randomly assigned at least 132 weeks before Nov 30, 2021 (appendix p 11). Data from participants whose last scheduled efficacy visit was before week 132 were censored at the time of their last visit, unless they had already had an unfavourable outcome. Non-assessable participants were included in the time-to-event analysis and censored at the time of their last visit. CIs for the difference in the proportion of participants with

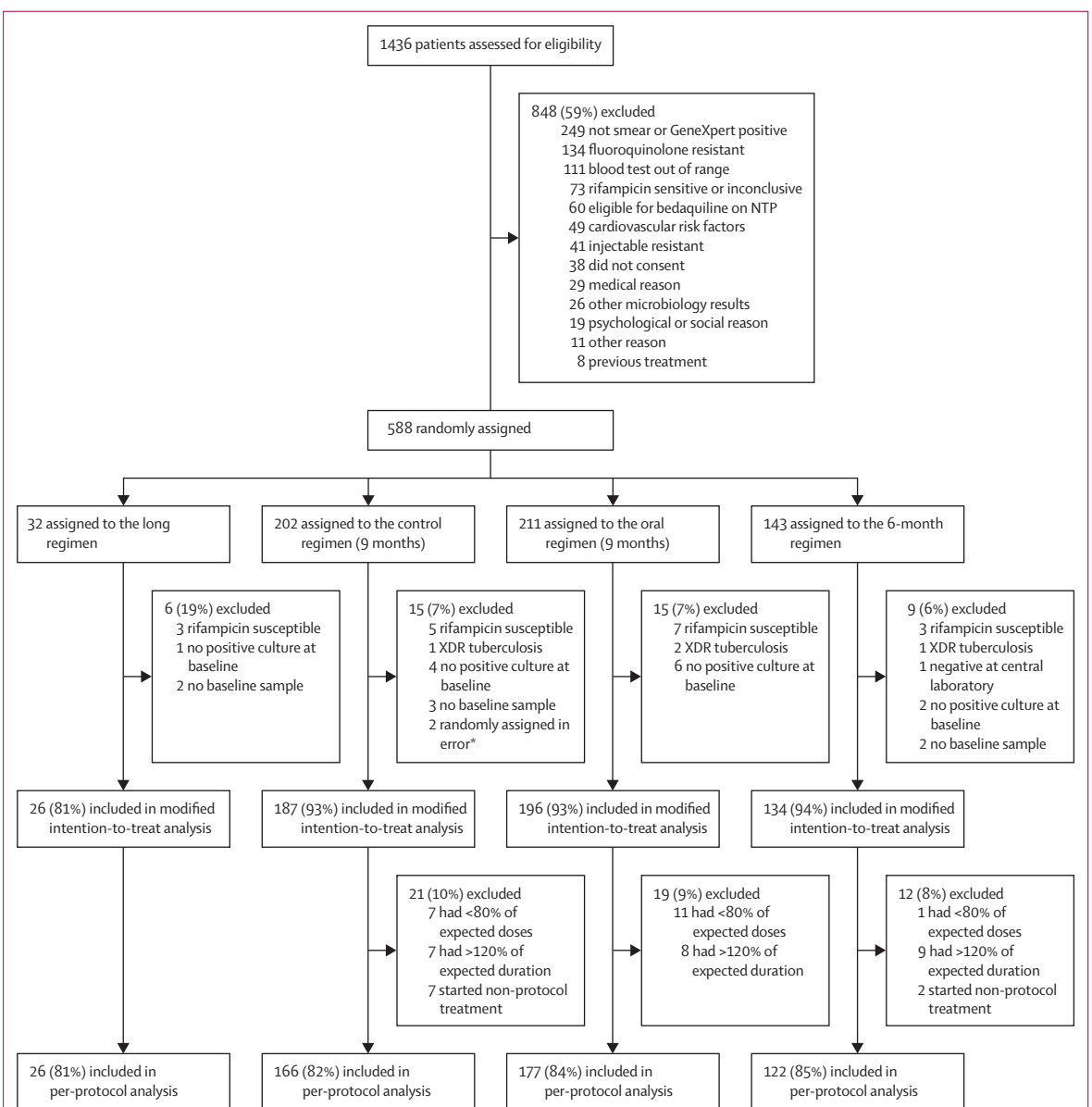


Figure 1: **CONSORT trial flow diagrams**

All participants randomly assigned treatment received at least one dose of trial treatment and are included in the safety population. NTP=national tuberculosis programme. XDR=extensively drug resistant. *One patient had QT corrected with Fridericia's formula of more than 450 ms and one patient had pre-existing hearing loss.

	Oral regimen *vs* control regimen		6-month regimen *vs* concurrent oral and control regimens		
	Control (n=187)	Oral (n=196)	Control (n=127)	Oral (n=131)	6-month (n=134)
Country					
Ethiopia	20 (11%)	19 (10%)	18 (14%)	18 (14%)	18 (13%)
Georgia	13 (7%)	12 (6%)	7 (6%)	7 (5%)	7 (5%)
India	42 (22%)	46 (23%)	42 (33%)	46 (35%)	47 (35%)
Moldova	24 (13%)	24 (12%)	8 (6%)	6 (5%)	8 (6%)
Mongolia	45 (24%)	46 (23%)	23 (18%)	22 (17%)	24 (18%)
South Africa	22 (12%)	25 (13%)	22 (17%)	25 (19%)	21 (16%)
Uganda	21 (11%)	24 (12%)	7 (6%)	7 (5%)	9 (7%)
Sex					
Men	115 (61%)	124 (63%)	77 (61%)	83 (63%)	81 (60%)
Women	72 (39%)	72 (37%)	50 (39%)	48 (37%)	53 (40%)
Race					
Asian	87 (47%)	92 (47%)	65 (51%)	68 (52%)	71 (53%)
Black or African American	63 (34%)	68 (35%)	47 (37%)	50 (38%)	48 (36%)
White	37 (20%)	36 (18%)	15 (12%)	13 (10%)	15 (11%)
Age, years					
<25	44 (24%)	33 (17%)	31 (24%)	24 (18%)	32 (24%)
25–44	105 (56%)	119 (61%)	73 (57%)	79 (60%)	79 (59%)
≥45	38 (20%)	44 (22%)	23 (18%)	28 (21%)	23 (17%)
Weight, kg					
<33	1 (1%)	2 (1%)	1 (1%)	2 (2%)	3 (2%)
33–50	64 (34%)	86 (44%)	50 (39%)	59 (45%)	55 (41%)
>50	122 (65%)	108 (55%)	76 (60%)	70 (53%)	76 (57%)
BMI, kg/m²					
<16·0	21 (11%)	29 (15%)	14 (11%)	24 (18%)	23 (17%)
16·0–18·4	52 (28%)	60 (31%)	38 (30%)	34 (26%)	31 (23%)
18·5–24·9	96 (51%)	92 (47%)	66 (52%)	60 (46%)	72 (54%)
≥25·0	18 (10%)	15 (8%)	9 (7%)	13 (10%)	8 (6%)
HIV status and CD4 count					
Negative	162 (87%)	169 (86%)	106 (83%)	110 (84%)	113 (84%)
Positive and 50–349 cells/mm³	12 (6%)	13 (7%)	10 (8%)	9 (7%)	10 (7%)
Positive and ≥350 cells/mm³	13 (7%)	14 (7%)	11 (9%)	12 (9%)	11 (8%)
Smoking status					
Never smoked	119 (64%)	114 (58%)	87 (69%)	77 (59%)	96 (72%)
Ex-smoker	40 (21%)	51 (26%)	18 (14%)	28 (21%)	22 (16%)
Current smoker	28 (15%)	31 (16%)	22 (17%)	26 (20%)	16 (12%)
Previous tuberculosis treatment					
None	60 (32%)	40 (20%)	33 (26%)	18 (14%)	26 (19%)
Drug-sensitive tuberculosis	65 (35%)	93 (47%)	49 (39%)	72 (55%)	55 (41%)
Second-line	62 (33%)	63 (32%)	45 (35%)	41 (31%)	53 (40%)
Radiographic extent of disease					
None or minimal	23/176 (13%)	13/184 (7%)	15/117 (13%)	7/121 (6%)	12/124 (10%)
Moderate	100/176 (57%)	103/184 (56%)	65/117 (56%)	68/121 (56%)	66/124 (53%)
Advanced	53/176 (30%)	68/184 (37%)	37/117 (32%)	46/121 (38%)	46/124 (37%)
Unavailable or non-assessable	11	12	10	10	10
Radiographic extent of cavitation					
None	48/176 (27%)	45/184 (24%)	29/117 (25%)	36/121 (30%)	31/124 (25%)
Single cavity	46/176 (26%)	24/184 (13%)	34/117 (29%)	14/121 (12%)	22/124 (18%)
Multiple cavities	82/176 (47%)	115/184 (63%)	54/117 (46%)	71/121 (59%)	71/124 (57%)
Unavailable or non-assessable	11	12	10	10	10

Data are n (%) or n/N (%).

Table 1: **Baseline characteristics of the modified intention-to-treat population**

unfavourable outcomes were estimated with bootstrapped SEs (appendix pp 11–12). The same analysis was completed for the comparison of participants in the 6-month group versus the control group who were concurrently randomised. Only a small proportion of participants were not followed up for efficacy to week 132; it is unlikely that outcomes will have been affected since the reduction in the total person-years of follow-up was only 3% for the comparison of the oral and control regimens.

A sensitivity analysis directly estimated the proportion of participants with unfavourable outcomes at week 132 in the subset of participants whose scheduled week 132 visit was on or before Nov 30, 2021. For this analysis, non-assessable participants were excluded. This difference in proportions (with 95% CI) and all others (except in the analyses of the proportion of participants with an unfavourable outcome at week 132 described in the previous paragraph) were calculated with the use of Cochran–Mantel–Haenszel weights, stratifying for randomisation protocol.[10]

Non-inferiority was found if the upper bound of the 95% CI of the difference in the proportion of participants with an unfavourable outcome at week 132 between the control and oral groups was less than the 10% margin of non-inferiority in the modified intention-to-treat (mITT) population. The mITT population included all randomly assigned participants with a positive culture for *M tuberculosis* at screening or randomisation, except for participants with sputum taken before randomisation that was subsequently found on phenotypic drug-susceptibility testing to contain isolates that were susceptible to rifampicin or resistant to both fluoroquinolones and second-line injectables, or participants who had been randomly assigned treatment in error. We repeated analyses in the per-protocol population, which was the same as the mITT population with the exclusion of participants who did not complete a protocol-adherent course of treatment, other than for treatment failure, change of treatment for an adverse event, or death. We did one-sided tests for non-inferiority. Prespecified tests for superiority were done when non-inferiority was shown.

All other secondary efficacy analyses were in the mITT population and included data from all visits up to a participant's last scheduled efficacy visit. We analysed time-to-event outcomes with the Kaplan–Meier product limit estimator (with SE estimated through Greenwood's formula), log-rank tests for difference between groups, and Cox proportional hazards models; these were displayed through the KMunicate format.[11] We tested assumptions for proportional hazards models with Schoenfield residuals. We assessed the difference in proportion of participants with two-sided tests of superiority. For the analysis of time to FOR, participants with a FOR outcome in the definite or probable categories were considered to have evidence of FOR at the time of their unfavourable outcome, with all other participants censored at the time of their primary endpoint (ie, at the time they were unfavourable or at the time they were last seen if never unfavourable). Analyses of the tuberculosis outcome ignoring interim events excluded all participants whose scheduled last efficacy visit was before week 132.

Mortality rates and the number of deaths, severe adverse events, serious adverse events, abnormal QT prolongation, and hearing loss adverse events were calculated in the safety population, which comprised all participants who received at least one dose of a trial medication, with two-sided tests of superiority.

All comparisons were restricted to participants concurrently randomised. All analyses were prespecified in the statistical analysis plan. Details of the study database and data handling procedures are provided in the appendix (p 11).

Analyses were stratified by randomisation protocol, except those of the WHO outcome and hearing loss. All analyses were done in STATA version 17.0. A trial steering committee oversaw this study, which was monitored by an independent data monitoring committee.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis or interpretation, or writing of the report, with the exception of Janssen Research & Development, which, as the developer of bedaquiline, provided a consultancy service upon request of the trial sponsor Vital Strategies in relation to bedaquiline, the eligibility criteria, safety investigations, and the pharmacokinetic component to fulfil the regulatory requirements of the trial.

Results

Between March 28, 2016, and Jan 28, 2020, 1436 patients were screened and 588 were randomly assigned to a regimen as follows: 32 to the long, 202 to the control, 211 to the oral, and 143 to the 6-month group. Participants were recruited in Ethiopia (n=67), Georgia (n=32), India (n=148), Moldova (n=63), Mongolia (n=130), South Africa (n=92), and Uganda (n=56). Reasons for exclusion from the analysis population are described in the CONSORT flow diagram (figure 1). Missing data were minimal, as evidenced by the high retention rate (appendix p 13); a complete case analysis was therefore sufficient.

Only 32 participants were randomly assigned to the long regimen due to early termination of recruitment to that regimen and the lower probability of allocation. Of these, 26 participants were included in the mITT population. In the week 132 comparison restricted to participants concurrently randomised, an estimated 36·7% (95% CI 16·2 to 57·7) of participants on the long regimen had an unfavourable outcome compared with 31·0% (20·2 to 41·7) in the control group, a difference of 5·7 percentage points (95% CI –15·5 to 29·9; p=0·62). No deaths were observed on the long regimen over 80

	Oral regimen *vs* control regimen			6-month regimen *vs* concurrent oral and control regimens			
	Control	Oral	Percentage points difference (95% CI; p value)	Control	Oral	6-month	Percentage points difference (95% CI; p value)
Favourable or unfavourable outcome at week 132							
Total mITT population							
Randomised	187	196	..	127	131	134	..
Estimated favourable outcome*	70·7%	80·4%	..	67·5%	76·2%	90·2%	..
Estimated unfavourable outcome*	29·3% (23·3 to 36·5)	19·6% (14·3 to 24·9)	−9·7 (−18·7 to −1·8; $p_{superiority}$=0·024)	32·5% (23·7 to 40·2)	23·8% (16·9 to 31·1)	9·8% (4·6 to 14·9)	Control *vs* 6-month 22·8 (13·7 to 32·2; $p_{superiority}$<0·0001); oral *vs* 6-month 14·0 (5·1 to 22·6; $p_{superiority}$=0·013)
Week 132 subgroup†							
Randomised	145	148	..	112	113	114	..
Non-assessable	1	4	..	0	4	2	..
Excluding non-assessable	144	144	..	112	109	112	..
Favourable outcome	96 (67%)	115 (80%)	..	74 (66%)	82 (75%)	100 (89%)	..
Unfavourable outcome	48 (33%)	29 (20%)	−12·7 (−22·7 to −2·7; $p_{superiority}$=0·013)	38 (34%)	27 (25%)	12 (11%)	Control *vs* 6-month 23·2 (12·8 to 33·6; $p_{superiority}$<0·0001); oral *vs* 6-month 14·0 (4·2 to 23·7; $p_{superiority}$=0·0056)
Week 132 status irrespective of treatment changes							
Randomised	145	148	..	112	113	114	..
Culture negative	126 (87%)	131 (89%)	1·4 (−6·0 to 8·9; $p_{superiority}$=0·71)	98 (88%)	97 (86%)	107 (94%)	Control *vs* 6-month −6·4 (−13·9 to 1·1; $p_{superiority}$=0·093); oral *vs* 6-month −8·0 (−15·6 to −0·4; $p_{superiority}$=0·039)
Culture negative when last seen‡	7 (5%)	9 (6%)	..	5 (4%)	9 (8%)	3 (3%)	..
On treatment	2	3	..	2	3	0	..
After treatment	5	6	..	3	6	3	..
Culture positive	2 (1%)	0	..	1 (1%)	0	2 (2%)	..
Culture positive when last seen‡	1 (1%)	1 (1%)	..	1 (1%)	1 (1%)	0	..
Died	6 (4%)	5 (3%)	..	4 (4%)	4 (4%)	2 (2%)	..
No culture since baseline	3 (2%)	2 (1%)	..	3 (3%)	2 (2%)	0	..

Data are n, n (%), %, or % (95% CI), unless otherwise specified. Participants are compared with the subset of control participants who were randomised concurrently. *Percentage favourable at week 132 estimated from analyses of time to unfavourable outcome, with non-assessable and favourable participants censored at their final efficacy visit; the model estimated the percentage of participants with unfavourable outcomes (with 95% CIs), from which we calculated the percentage of participants with favourable outcomes. †Week 132 subgroup consists of the participants randomised more than 132 weeks before Nov 30, 2021, who therefore completed efficacy follow-up without censoring. ‡Last seen before week 132.

Table 2: **Long-term efficacy outcomes in the modified intention-to-treat population**

person-years of follow-up. All results reported subsequently focus on the three shorter regimens only.

Of the 556 participants randomly assigned to the three shorter regimens, 517 were included in the mITT and 465 in the per-protocol analyses. Baseline characteristics of the mITT population are shown in table 1. Of those in the mITT population, 407 (79%) had a last efficacy visit at week 132 (appendix p 13). Retention in all groups was good; 488 (94%) of 517 participants in the mITT population were seen at or were known to have died before the last efficacy visit, and 527 (95%) of the 556 participants in the safety population were seen at or were known to have died before week 132 (appendix p 13).

Only six (1%) of the 417 participants with a favourable outcome at week 76 had an unfavourable outcome between week 76 and their final efficacy visit. Of those, two received further treatment (one in the oral group and one in the 6-month group) and four died (one in the control group and three in the oral group; appendix p 14). The proportion of participants in the mITT population with an unfavourable outcome at week 132 was estimated as 19·6% (95% CI 14·3 to 24·9) for the oral regimen and 29·3% (23·3 to 36·5) for the control regimen, a difference of −9·7 percentage points (−18·7 to −1·8; $p_{superiority}$=0·024; table 2, figure 2A). The corresponding results for the per-protocol analysis were an estimated proportion unfavourable of 14·8% (10·2 to 20·4) in the oral regimen and 24·8% (19·0 to 32·4) in the control regimen, a difference of −10·0 percentage points (−18·1 to −1·8; $p_{superiority}$=0·018). The results were similar in the sensitivity analyses restricted to participants randomly assigned more than 132 weeks before Nov 30, 2021 (table 2), with

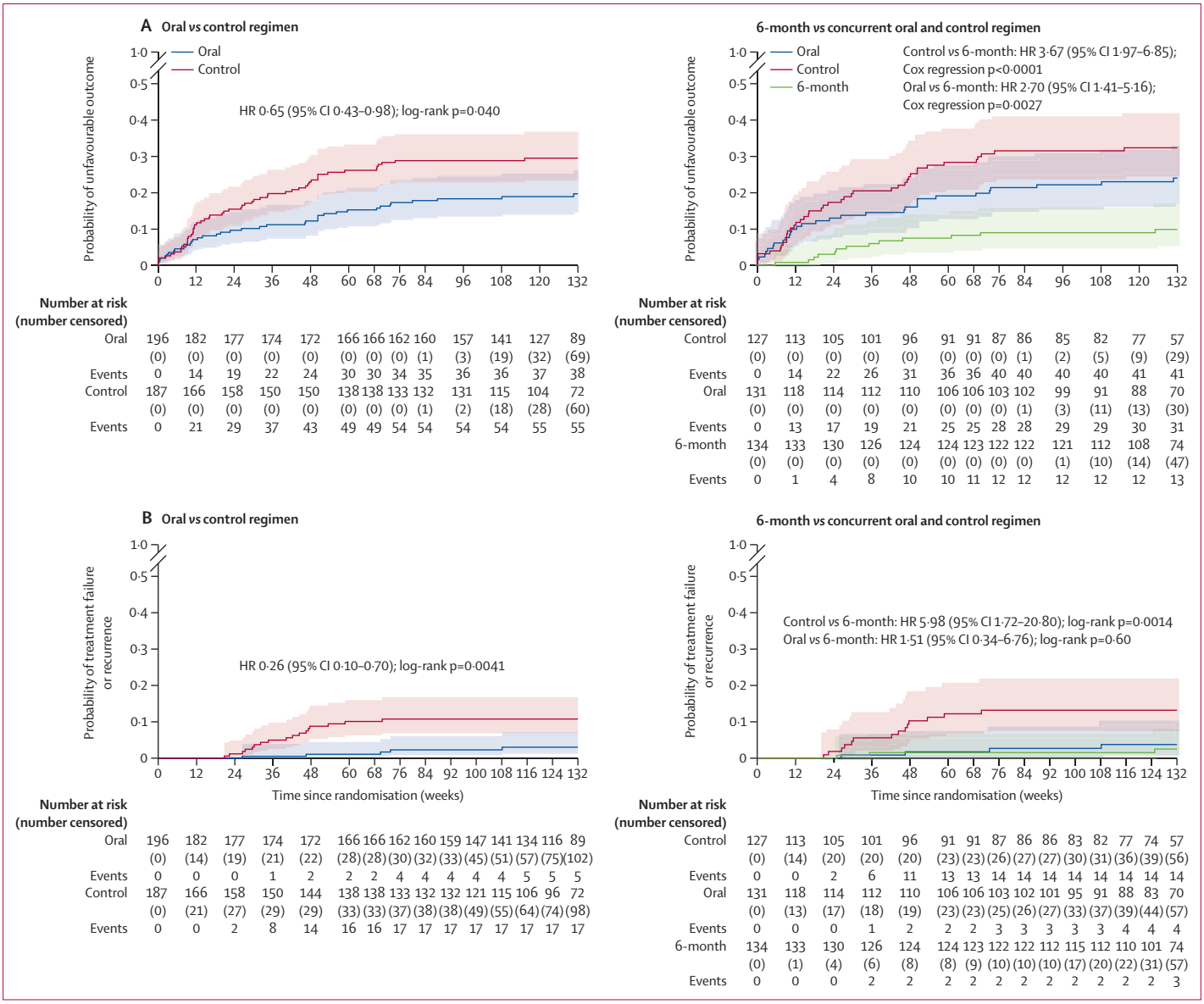


Figure 2: **Kaplan–Meier curves of efficacy outcomes**
Time to unfavourable outcome (A) or time to treatment failure or recurrence (B). Graphs show comparisons between the oral and control groups or the control vs 6-month group and oral *vs* 6-month group. HR=hazard ratio.

a difference between oral and control groups in the mITT population of –12·7 percentage points (–22·7 to –2·7; $p_{superiority}$=0·013) and a difference of –12·3 percentage points (–22·3 to –2·4) in the per-protocol population ($p_{superiority}$=0·015; appendix pp 15–16).

Only two participants with a new unfavourable outcome occurring after week 76 had an unfavourable outcome due to bacteriological reasons (both participants restarted treatment due to recurrence); drug-susceptibility testing before starting salvage treatment was available in one of these participants, who developed resistance to pyrazinamide. Therefore, resistance in the trial remained low overall, with little development of resistance in those in whom treatment failed based on bacteriology (appendix p 17). Only one participant developed resistance to bedaquiline (in the oral group), and six participants acquired resistance to fluoroquinolones (one in the control, two in the oral, and three in the 6-month group). The percentage of participants in the mITT population acquiring resistance in the long term was 3% or lower in all groups.

In the FOR analysis, which focuses on outcomes that are likely to be related to tuberculosis (figure 2B), the cumulative percentage of participants with a definite or probable FOR event by 132 weeks was significantly lower on the oral regimen (3·1% [95% CI 1·3 to 7·2]) than on

	Oral regimen *vs* control regimen			6-month regimen *vs* concurrent oral and control regimens				6-month regimen plus concurrent oral regimen* *vs* concurrent control regimen		
	Control	Oral	Difference (95% CI; p value)	Control	Oral	6-month	Difference (95% CI; p value)	Control	Oral and 6-month	Difference (95% CI; p value)
Randomised, n	202	211	..	140	144	143	..	140	287	..
Safety population, n	202	211	..	140	144	143	..	140	287	..
Person-years	478·8	497·1	..	328·3	338·9	354·5	..	328·3	693·4	..
Deaths, n	8	11	..	5	5	2	..	5	7	..
Death rate per 100 person-years (95% CI)	1·67 (0·84 to 3·34)	2·21 (1·23 to 4·00)	0·54 (–1·20 to 2·29; p=0·56)	1·52 (0·63 to 3·66)	1·47 (0·51 to 3·54)	0·56 (0·14 to 2·26)	Control *vs* 6-month 0·96 (–0·59 to 2·51; p=0·24); oral *vs* 6-month 0·91 (–0·60 to 2·42; p=0·26)	1·52 (0·63 to 3·66)	1·01 (0·48 to 2·12)	–0·51 (–2·04 to 1·02; p=0·49)

*Both the 6-month and oral regimens contained bedaquiline.

Table 3: **All-cause mortality in the safety population**

the control regimen (10·8% [6·9 to 16·8]; log-rank p=0·0041). However, in the analysis ignoring interim events (table 2), the proportion of participants who were culture negative at week 132 was not significantly different (131 [89%] of 148 in the oral group *vs* 126 [87%] of 145 in the control group; difference 1·4 percentage points, [95% CI –6·0 to 8·9]; $p_{superiority}$=0·71). According to the WHO classification of treatment outcome, 168 (86%) of 196 participants on the oral regimen had outcomes classified as cured or completed treatment compared with 142 (76%) of 187 on the control regimen (difference 9·8 percentage points [95% CI 1·9 to 17·6]; p<0·0001; appendix p 17).

In the mITT analysis of the concurrently randomised participants, the estimated proportion of participants with an unfavourable outcome at week 132 was significantly lower on the 6-month regimen than on the control regimen (difference 22·8 percentage points [95% CI 13·7–32·2]; $p_{superiority}$<0·0001) or the oral regimen (14·0 percentage points [5·1–22·6]; $p_{superiority}$=0·013; table 2, figure 2A).

The cumulative probability of a definite or probable FOR event by week 132 was significantly lower on the 6-month regimen (2·5% [95% CI 0·8–7·7]) than the control regimen (13·2% [8·0–21·3]), with participants in the control group significantly more likely to have an FOR event (figure 2B). There was no evidence of a difference in the cumulative probability of an FOR event between the oral regimen (3·8% [95% CI 1·4–9·8]) and 6-month regimen (2·5% [0·8–7·7]; figure 2B).

The percentage of participants with a negative culture at week 132 irrespective of interim events was 107 (94%) of 114 in the 6-month group compared with 98 (88%) of 112 in the control group (difference –6·4 percentage points [95% CI –13·9 to 1·1]; p=0·093) or 97 (86%) of 13 in the oral group (difference –8·0 percentage points–[15·6 to –0·4]; p=0·039; table 2). In the analysis according to the WHO outcome definition, significantly more participants had outcomes classified as cured or having completed treatment on the 6-month regimen than the control regimen (127 [95%] of 134 in the 6-month group *vs* 94 [74%] of 127 in the control group; difference –20·8 percentage points [–29·3 to –12·3]; p<0·0001; appendix p 17).

In the safety population, we observed no indication of a difference between the regimens in the proportion of participants who had a serious adverse event or a severe adverse event, with very few adverse events reported after week 76 (appendix p 18).

Table 3 presents the all-cause mortality data in the safety population. The percentage of deaths was low in all regimens, with no statistically significantly differences in the percentage of deaths between groups. When comparing participants receiving bedaquiline-containing regimens (the oral and 6-month regimens combined) with participants who were not allocated to receive bedaquiline, we found no evidence to suggest that mortality was higher in the participants receiving bedaquiline. Death rates were 1·01 (95% CI 0·48–2·12) per 100 person-years in participants allocated to bedaquiline (n=287) compared with 1·52 (0·63–3·66) in participants on the control regimen (n=140; p=0·49). The appendix (p 18) gives the results of the independent review of deaths. Notably, the reviewers considered tuberculosis to be the cause of death for only seven of the 21 deaths.

Treatment-emergent hearing loss on audiogram that was graded 3 or 4 on the Brock scale, indicating severe sensorineural hearing loss, was recorded in significantly fewer participants on the oral regimen than the control regimen at week 132 (table 4). At week 132, five (4%) participants allocated to the 6-month regimen had Brock grade 3 or 4 hearing loss compared with 11 (8%) allocated to the control regimen (table 4). There was also no significant difference in severe hearing loss between the oral and 6-month regimens (table 4).

The proportion of participants with QTcF levels that normalised (within 10 ms of a participant's baseline

	Oral regimen *vs* control regimen			6-month regimen *vs* concurrent oral and control regimens			
	Control (n=198)	Oral (n=205)	Difference* (95% CI; p value)	Control (n=136)	Oral (n=139)	6-month (n=143)	Difference* (95% CI; p value)
Grade 0†	116 (59%)	180 (88%)	..	78 (57%)	120 (86%)	102 (71%)	..
Grade 1	41 (21%)	6 (3%)	..	30 (22%)	5 (4%)	20 (14%)	..
Grade 2	25 (13%)	12 (6%)	..	17 (13%)	8 (6%)	16 (11%)	..
Grade 3	12 (6%)	3 (2%)	..	7 (5%)	3 (2%)	3 (2%)	..
Grade 4	4 (2%)	4 (2%)	..	4 (3%)	3 (2%)	2 (1%)	..
Severe hearing loss	16 (8%)	7 (3%)	−4·7 (−9·2 to −0·1; p=0·041)	11 (8%)	6 (4%)	5 (4%)	6-month *vs* control −4·6 (−10·1 to 0·9; p=0·10); oral *vs* 6-month 0·85 (−3·7 to 5·3; p=0·72)

Data are n (%) unless otherwise specified. Audiogram readings were graded with Brock's criteria. *Difference in percentage points (pairwise comparison with Wald test). †Six (two in the control group and four in the oral group) participants who had non-gradable test results with Brock's criteria for all visits (due to non-monotonic shape of their decibel readings across test frequencies at the same visit) were assumed to be grade 0.

Table 4: **Treatment-emergent hearing loss at last visit in the safety population**

value or below 450 ms) by week 76 was more than 95% on all regimens (appendix p 18). When considering the last available ECG, this rose to 99% on both the control and oral regimens (appendix p 19). Only nine participants did not have a normal QTcF value at their last ECG, four of whom were on salvage treatment.

Discussion

The results of this long-term follow-up of STREAM stage 2 participants show that the primary efficacy findings were sustained up to 132 weeks.[2] Very few additional unfavourable events occurred between week 76 and week 132, and the conclusions remain regarding the significantly superior efficacy of both the fully oral regimen (similar to one of the regimens currently recommended by WHO) and the shorter 6-month regimen when compared with the 9-month control regimen, previously assessed in STREAM stage 1 and recommended by WHO.[1,8] We found no indication of a difference between the regimens in the proportion of participants who had a serious adverse event or a severe adverse event, consistent with results previously reported,[2] with very few adverse events occurring after week 76.

When the results of the C208 phase 2 trial of bedaquiline were published,[6] concerns were expressed regarding the significant increase in all-cause mortality observed in the bedaquiline-containing group compared with those receiving placebo; these concerns were reflected in the US Food and Drug Administration conditional recommendation of 2012.[12,13] There is no evidence in the data presented here that bedaquiline is responsible for an increase in mortality; the slight increase in reported mortality in the oral regimen compared with the control regimen is non-significant and is probably due to chance. This conclusion is supported by the low mortality seen in the 6-month regimen; there was no suggestion of any excess mortality when mortality in both bedaquiline-containing regimens were combined and compared with the control regimen.

The absence of a mortality risk is further supported by findings from a large retrospective observational cohort of South African patients, which showed that participants treated with a bedaquiline-containing regimen had a decreased risk of both short-term and long-term mortality compared with a multidrug-resistant tuberculosis regimen not containing bedaquiline.[14]

Long-term outcomes, as assessed with the composite efficacy endpoint, were best among those receiving the 6-month regimen, and this finding was also true when efficacy outcomes ignoring treatment changes were considered. In addition to being shorter than the other two regimens, the 6-month regimen included bedaquiline, a reduced duration of kanamycin, and a higher dose of isoniazid, which has a rapid early bactericidal activity;[15] neither ethambutol nor protionamide were included, which could have improved the tolerability of the regimen. Hearing loss, identified by audiometry rather than clinically apparent change, occurred in 4% of participants in the 6-month group and 8% in the control group (non-significant difference), but occurred significantly more frequently in the control group than in the oral group; grade 3 or 4 hearing loss events were similar in the two bedaquiline-containing regimens. A more detailed analysis of the audiometry data will be reported separately.

Assessments of efficacy according to the current WHO definition reflected a level of benefit and relative differences between the three regimens similar to that described so far. It is important to note, however, that the WHO definition relates to status at the end of allocated treatment as opposed to the end of the post-treatment follow-up period in the trial.

As already described, tuberculosis-related unfavourable outcomes were a minority component of the primary outcome. Both the oral and 6-month regimens were found to be highly effective with respect to FOR, with very low rates of definite or probable FOR events.

Although acquired levels of drug resistance were low in the present study, there are increasing concerns about the extent to which bedaquiline resistance is being reported

from field studies[14,16] and there is clearly a need to evaluate drug combinations that will minimise the risk of developing resistance. Therefore, new regimens for rifampicin-resistant or multidrug-resistant tuberculosis, such as those presented here, need to be assessed not only for their safety and efficacy, but also for their drug composition and the possibility of emergence of resistance, especially in the population in which they are being introduced. Drugs currently recommended by WHO include not only bedaquiline but also linezolid, and it is worth noting that a meta-analysis from 14 different countries reported a frequency of 4·2% (95% CI 3·5–5·0%) for linezolid resistance in patients with multidrug-resistant tuberculosis.[17] In addition, a cohort study in India reported linezolid resistance in 72 (20%) of 365 patients with multidrug-resistant tuberculosis with no documented exposure to linezolid in 16 of the 72 patients with resistance.[18]

As has been noted, strengths of STREAM stage 2 were the diversity of sites and the high rate of retention; a limitation was the open-label nature of the trial, which could have influenced some of the clinical decisions that were made. We observed a higher-than-expected unfavourable outcome rate for the control regimen (higher than assumed in the sample size calculations), which we believe is partly due to the difference in location of trial sites and changes in clinical practice between stages 1 and 2. The long-term findings have substantiated that the two bedaquiline-containing regimens are both safe and effective and provide valuable treatment options for rifampicin-resistant tuberculosis.

For the **data repository** see https://c-path.org/programs/tb-pacts/

Before the introduction of new and repurposed drugs for rifampicin-resistant tuberculosis, outcomes were generally poor, with successive WHO reports describing favourable outcomes of little more than 50% success, although under well managed programmes, such as the one in Taiwan, high rates of long-lasting cure were achievable.[19,20]

In December, 2022, WHO endorsed the use of the bedaquiline, pretomanid, linezolid, and moxifloxacin regimen for the treatment of most patients with rifampicin-resistant tuberculosis, including those with fluroquinolone-resistant tuberculosis in whom moxifloxacin is not given.[21] Clinicians treating rifampicin-resistant tuberculosis now have a choice of 9-month or 6-month regimens, which have been found to be effective in randomised controlled trials.[2,4,5] Most programmes have moved away from injectable-based regimens, but the results in the 6-month regimen raise the possibility that a shortened intensive phase that includes an aminoglycoside (eg, amikacin, which is now the WHO recommended drug in this class) could warrant further consideration. It is possible that a shortened intensive phase that includes an aminoglycoside would provide protection during the early stages of treatment before bedaquiline has reached therapeutic concentrations, thereby mitigating the risk of acquired bedaquiline resistance.

It will be very important to monitor outcomes in programme conditions and to continue to develop regimens that are highly effective with reduced instances of adverse drug-related events and protect against the development of acquired resistance. In addition to evaluating adverse effects, time to culture conversion, and cure rates, future trials of rifampicin-resistant tuberculosis treatments should assess outcomes important to patients, such as speed of symptom resolution, quality of life, and mental health outcomes, in addition to health economic implications of new regimens.[22]

Contributors

RLG, SKM, AJN, C-YC, MG, KS, SBS, GT, AVD, and IDR designed the trial and study protocol. AB, AKB, FC, NG, BK, NK, DM, RM, NN, MR, RS, MT, BT, and ET enrolled participants and oversaw all clinical follow-up and data collection at their sites. GT oversaw all microbiology processes. This paper was initially drafted by RLG, SKM, and AJN. RLG and KS accessed and verified the study data. All authors contributed to data interpretation, critical review, and revision of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. RLG oversaw the statistical analysis and vouches for the fidelity of this report to the study protocol and statistical analysis plan.

Declaration of interests

MR sat on the South African Bedaquiline, Pretomanid and Linezolid Clinical Access Program data monitoring committee and the BEAT Tuberculosis Trial data monitoring committee. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, are available through the TB—Platform for Aggregation of Clinical TB Studies data repository; they will provide de-identified participant data, data dictionary, study protocol, a set of blank case record forms, and the informed consent form.

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