Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Online Supplement

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3 LISTING OF SUPPLEMENTARY TABLES AND FIGURES

4 BACKGROUND

In 2008, the United States Agency for International Development (USAID) called for proposals for a cooperative agreement on tuberculosis research that included a focus on shortened treatment regimens for MDR-TB. The International Union Against TB and Lung Disease (The Union) was successful in securing the award and subsequently partnered with the MRC Clinical Trials Unit, UK and other global agencies to develop the STREAM trial

The International Union Against Tuberculosis and Lung Disease (The Union, and its North American affiliate) was the sponsor of the STREAM trial and The Union's Ethics Advisory Group and all national and local ethics committees approved the study.

A trial steering committee (TSC) with an independent chair supervised the conduct of the trial. An independent data monitoring committee (IDMC) met approximately every six months to oversee the safety of the study participants. Only the IDMC and the unblinded statisticians saw aggregate data by treatment arm during the trial. At each meeting of the IDMC they reviewed all the accumulated safety and efficacy data by study arm. The IDMC was tasked with advising the TSC that the trial should be stopped if in their view there was proof beyond reasonable doubt that one of the trial treatments was clearly indicated or clearly contra-indicated in terms of a net difference in efficacy or adverse events or, there was proof beyond reasonable doubt from other studies to influence clinic staff in their management of patients that was incompatible with continuing the trial. Such proof would require a difference in failure/relapse rates between treatment arms significant at the 0.1% level. In arriving at their recommendations, the IDMC would also take account of outcomes reported from all countries. They could also recommend modification or closure of the study in a country or sub-group of patients, such as those who are HIV-infected.

4.1 STREAM STAGES 1 AND 2

The Evaluation of a **S**tandardised **T**reatment **Re**gimen of **A**nti-Tuberculosis Drugs for Patients with **M**DR-TB (STREAM) Stage 1 was the initial trial that was developed which opened to recruitment in July 2012; a prospective, within trial economic analysis was included. Supplementary details of the methods and results are reported below and published elsewhere.[1]

In November 2014, the trial protocol was amended to add two additional arms to the trial[2]; this 4-arm trial was called STREAM Stage 2. Recruitment to Stage 2 began in March 2016 at which point all 424 participants had been randomized to Stage 1, but many participants were still in follow-up. This second stage of the STREAM trial can therefore be considered a separate trial with separate patient population and is still ongoing in 2018 with results to be reported at a later date.

5 DETAILED METHODS

5.1 RANDOMIZATION

Separate randomization lists for each combination of strata were prepared by an independent statistician using permuted blocks of varying sizes. Participants were randomized using a web-based randomization system; if web access was not available at the time of randomization, a manual alternative using sealed envelopes was provided.

5.2 INTERVENTIONS

Medicines in the Short regimen were quality assured and supplied through The Union procurement mechanisms; supplies for the Long regimen were provided by the National Tuberculosis Programmes of participating countries.

5.2.1 Short regimen

Drugs and doses by weight band in the Short regimen are shown below.

Product	Weight group		
	Less than 33 kg	33 kg to 50 kg	More than 50 kg
Moxifloxacin	400 mg	600 mg	800 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg
Kanamycin	15 mg per kilogramme body weight (maximum 1g)		

All drugs were given in a single dosage daily (seven days a week) except for kanamycin which was given three times per week from week 12. Doses could be changed at the end of the intensive phase if participants had increased weight.

The intensive phase of the Short regimen could be extended from 16 to 20 or 24 weeks for participants whose smear has not converted by 16 or 20 weeks respectively.

Treatment that had been missed (up to 8 weeks in total) in either the intensive or the continuation phase could be made up by extending the relevant phase of the regimen by the number of days missed at the discretion of the treating clinician. Participants who missed more than 8 weeks in total were referred to the National TB Programme for further management but continued in follow-up to 132 weeks.

5.2.2 Long regimen

Any modifications to the locally used standard of care regimen that was used as the Long regimen in the STREAM trial that occurred during the trial are also described below.

1.1.1.1 Mongolia

Policy: The intensive phase was composed of kanamycin, pyrazinamide , ethambutol , levofloxacin, ethionamide , and high-dose isoniazid . This was given for at least 4 months after the participant first converted to sputum culture-negative, and for a minimum duration of 6 months.

The continuation phase was given for at least 12 months, to give a total treatment duration of 18 – 24 months, and was composed of pyrazinamide, ethambutol, levofloxacin and ethionamide.

Intensive phase drugs used in trial participants:

- kanamycin (16mg/kg)
- pyrazinamide (1600 or 2000mg, depending on weight
- levofloxacin 750mg, except 1 participant of 92 kg on 1000mg and 2 who started on ofloxacin 800mg but switched to levofloxacin 750mg within 10 weeks.
- ethionamide or prothionamide 500mg, 750mg, or 1000mg depending weight
- cycloserine 500mg, 750mg, or 1000mg depending weight

1.1.1.2 South Africa

Policy: Prior to August 2015, the intensive phase was composed of ofloxacin , pyrazinamide, ethambutol, kanamycin or amikacin , ethionamide, and one of the following: terizidone , azithromycin or clofazimine . The continuation phase of treatment consisted of ofloxacin, pyrazinamide, ethambutol, and terizidone or clofazimine.

After August 2015, the intensive phase of treatment was changed to moxifloxacin, pyrazinamide, terizidone, ethionamide and kanamycin; para-aminosalicylic acid and isoniazid could also be included based on drug sensitivity testing results. The continuation phase comprised moxifloxacin, pyrazinamide, terizidone and ethionamide .

The intensive phase was given for at least 4 months after the participant first converted to sputum culture-negative, and for a minimum duration of 6 months total. The continuation phase was given for 12 months, to make the total treatment duration at least 18 months.

Intensive phase drugs used in trial participants:

- kanamycin (15mg/kg)
- pyrazinamide (1000, 1500, 1750 or 2000mg, depending on weight
- moxifloxacin 400mg
- ethionamide 500mg or 750mg, depending weight
- terizidone 500mg or 750mg, depending weight
- plus isoniazid 400mg or 600mg and ethambutol 800mg or 1200mg in 7 participants

1.1.1.3 Ethiopia

Policy: Prior to April 2013, the intensive phase was composed of levofloxacin, pyrazinamide, ethambutol, capreomycin , ethionamide, and cycloserine. The continuation phase of treatment consisted of levofloxacin, pyrazinamide, ethambutol, ethionamide, and cycloserine.

After April 2013, the intensive phase of treatment was changed to levofloxacin, pyrazinamide, capreomycin, prothionamide, and cycloserine. The continuation phase comprised levofloxacin, pyrazinamide, prothionamide (study participants were allowed to continue to have ethionamide), and cycloserine.

The intensive phase was given for at least 4 months after the participant first converted to sputum culture-negative, and for a minimum duration of 8 months total. The continuation phase was given

for 10 months before April 2013 and 12 months after April 2013, to make the total treatment duration at least 18 months or 20 months, respectively.

Intensive phase drugs used in trial participants:

- capreomycin (16mg/kg)
- pyrazinamide 1000mg, 1500mg, 1750mg or 2000mg, depending on weight
- levofloxacin 750mg or 1000mg, depending on weight
- ethionamide 500mg or 750mg, depending weight
- cycloserine 500mg or 750mg, depending weight
- In addition, 2 participants had ethambutol 1200mg and 1 participant isoniazid 300mg

1.1.1.4 Vietnam

Policy: The intensive phase was composed of kanamycin, pyrazinamide, levofloxacin, prothionamide, ethambutol and cycloserine. This was given for at least 4 months after the participant first converted to sputum culture-negative, and for a minimum duration of 6 months and a maximum duration of 10 months.

The continuation phase was given for 13 – 14 months after the completion of the intensive phase, and was composed of pyrazinamide, levofloxacin, prothionamide, ethambutol and cycloserine.

Intensive phase drugs used in trial participants:

- kanamycin (15mg/kg)
- pyrazinamide 1250mg, 1500mg, 1750mg or 2000mg, depending on weight
- levofloxacin 750mg
- prothionamide 500mg or 750mg, depending weight
- cycloserine 500mg or 750mg, depending weight
- ethambutol 800mg, 1000mg, 1200mg, 1400mg or 1600mg, depending on weight

5.3 FULL ELIGIBILITY CRITERIA

There were some minor modifications to the eligibility criteria during recruitment, full eligibility criteria with any changes are described here.

5.3.1 Inclusion criteria

A participant will be eligible for entry to the study if he/she:

1. Is willing and able to give informed consent to be enrolled in the trial treatment and follow-up (signed or witnessed consent if the participant is illiterate)
2. Is aged 18 years or older
3. Has smear-positive pulmonary tuberculosis with initial laboratory result of resistance to rifampicin by line probe assay or other DST
    - *changed to add 'or is HIV positive and has GeneXpert-positive pulmonary tuberculosis'*
    - *changed to 'has an initial laboratory result of resistance to rifampicin by line probe assay (Hain Genotype LPA), GeneXpert or culture-based drug susceptibility testing (Version5.0, March 2013)'*
4. Is willing to have an HIV test and, if positive, is willing to be treated with ART in accordance with the national policies.

5. Agrees to use effective barrier contraception or have an intrauterine contraceptive device during treatment phase if a pre-menopausal woman
6. Has an identifiable address and expects to remain in the area for the duration of the study
7. Is willing to adhere to the follow-up schedule and to study procedures

5.3.2 Exclusion criteria

A participant will not be eligible for entry to the study if he/she:

1. Is infected with a strain of *M. tuberculosis* resistant to a second-line injectable drug by line probe assay
2. Is infected with a strain of *M. tuberculosis* resistant to a fluoroquinolone by line probe assay
3. Has tuberculous meningitis or bone and joint tuberculosis
4. Is critically ill, and in the judgment of the investigator, unlikely to survive more than 4 months.
5. Is known to be pregnant or breast-feeding
6. Is unable to attend or comply with treatment or follow-up schedule
7. Is unable to take oral medication
8. Has AST or ALT >5 times the upper limit of normal
9. Has any condition (social or medical) which in the opinion of the investigator would make study participation unsafe.
10. Is taking any medications contraindicated with the medicines in either the trial or control regimen
11. Has a known allergy to any fluoroquinolone antibiotic
12. Is currently taking part in another trial of a medicinal product
13. Has a QTc interval of ≥500msec at screening

5.4 STUDY PROCEDURES

After screening and baseline assessments, participants had scheduled weekly visits for the first 4 weeks, then 4-weekly visits to 132 weeks. Investigations undertaken at screening included sputum samples for smear, culture, rifampicin resistance testing, LPA for second-line injectables and fluoroquinolones. Blood samples were obtained for liver function tests (AST and ALT) and HIV testing. Participants were re-assessed for eligibility prior to randomization in the light of the results of the laboratory tests when they returned after their screening visit. Sputum samples for smear and culture were collected at every visit except the first 4 visits during treatment and follow-up and blood samples for liver function tests and creatinine every four weeks throughout the intensive phase of treatment.

Apart from the line probe assays and tests for rifampicin, fluoroquinolone, and second-line injectable sensitivity conducted prior to enrolment, the enrolling sites were only required to perform smear and culture examinations on sputum samples collected at each participant visit. Those sites which had access to phenotypic drug sensitivity testing were discouraged from acting on results obtained unless clinically indicated.

Standardised, calibrated 12-lead ECG machines with an automated reporting function, including QT and QT corrected for heart rate using the Fridericia formula (QTcF) were provided to each site. Initially ECGs were undertaken at baseline, two and four hours after the first treatment dose, then weekly for the first four weeks and at the end of weeks 12, 24 and 36. This schedule was subsequently modified: the 2-hour post-dose ECG was dropped, and ECGs were undertaken every

four weeks for a year. Guidance was provided to investigators on how to manage QT or QTcF prolongation to 500ms or more. The fluoroquinolone was withheld during investigation and if drugs in the treatment regimen were thought to be the cause, treatment was modified by reduction of moxifloxacin or clofazimine dose or substitution of levofloxacin for moxifloxacin.

Baseline chest radiographs were read by two independent clinicians, discordant assessments were read by a third clinician following published procedures.[3]

A central medical team with expertise in MDR-TB, HIV, clinical microbiology and electrocardiology was set up to advise investigators, when requested, in management of adverse events, guidance in management of participants needing retreatment and the promotion of consistent practice across the sites.

Participants and clinical staff were aware of individual treatment allocations; laboratory staff were blinded to treatment.

5.5 BACTERIOLOGICAL PROCEDURES

The simple culture method (Kudoh) using modified Ogawa medium (acid-buffered) was performed in site laboratories on sputum samples collected at the specified visits.[4] The Line Probe Assays used to detect resistance to first and second line drugs were Genotype MTBDRplus and Genotype MTBDRsl version 1 (Hain Lifescience)[5-8]. All laboratory procedures were carried out according to the STREAM Stage 1 Microbiology Manual (available on request). In addition, the quality of local procedures and results was regularly monitored by the study reference laboratory, (The Institute of Tropical Medicine (ITM) in Antwerp, Belgium.

The *Mycobacterium tuberculosis* isolates were sent to the study reference laboratory, for drug sensitivity testing (DST) and strain genotyping to distinguish relapses from reinfections. The mycobacteria speciation was performed using the SD Bioline Ag TB MPT64 Rapid test and sensitivity test to para-nitro benzoic acid (PNB) to exclude mixed infection with NTM.[9,10]

DSTs were performed by the indirect proportion method on Löwenstein-Jensen medium for first line drugs (isoniazid, rifampicin, streptomycin and ethambutol) and also on Middlebrook 7H11 agar for second line drugs (ofloxacin, kanamycin, capreomycin and ethionamide) according to the standard procedure.[11] The critical concentrations (breakpoints) used were those recommended by WHO with the addition of two more concentrations for isoniazid (1 and 5 µg/ml) and one concentration for ofloxacin (8 µg/ml) with the aim at determining the level of resistance to the respective drugs.[12]

Genotyping by spoligotyping and the Mycobacterial Interspersed Repetitive Units - Variable-Number Tandem Repeats (MIRU-VNTR, 24 loci) were performed on the pair baseline (initial)/recurrent isolates to differentiate relapses or failure from reinfection. Both genotyping procedures were followed according to the standard methods.[13-15]

Reinfection was inferred when the MIRU-VNTR (24 loci) patterns obtained from the baseline and recurrent strains were different in more than one loci and the Spoligotype patterns differed in more than one spacer.

Relapses were inferred when the MIRU-VNTR (24 loci) and Spoligotype patterns from the pair baseline/recurrent strains were identical (0 locus difference with MIRU-VNTR and 0 spacer difference with Spoligotyping). Likely relapse was inferred when the MIRU-VNTR (24 loci) patterns from the pair stains differed in one locus.

Fluorescein diacetate (FDA) vital staining was performed to decide on eligibility of participants who had received treatment for TB in the 3 months prior the screening, other than MDR treatment initiated in the previous seven days, or had taken any of the drugs in the study regimen during that time. FDA, a salt of the green fluorophore fluorescein, is detectable by fluorescence microscopy only after its cleavage by cell esterase present in viable cells and only these cells are stained in fluorescent green colour making this test highly predictive of culture growth.[16,17]

The phenotypic DSTs of *M. tuberculosis* isolates from the Mongolia site were performed in the National Tuberculosis Reference Laboratory (LNR), Ulaanbaatar, due to national restriction for exporting category A Infectious substances. The indirect proportion method on Löwenstein-Jensen for first (isoniazid, rifampicin, streptomycin and ethambutol) and second (ofloxacin, kanamycin and capreomycin) line drugs was performed using the critical concentrations (breakpoints) recommended by WHO.[12] The NRL is a quality assured laboratory which participates in the External Quality Assessment program for phenotypic DST organized by the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association.

5.6 ASSESSMENT SCHEDULE

5.6.1 Protocol version 4.0, March 2011 Assessment Schedule

Observation/ Investigation	Screening (Pre-trial)	Enrolment	Treatment Phase		Post-Treatment Phase
			Intensive Phase	Continuation Phase	Follow-up
Written informed consent	X	X			
Demographics		X			
Medical History		X			
Clinical Examination	X	X	X	X	X
Clinical assessment (including AEs and concomitant medication during treatment)		X	X	X	X
Height		X			
Weight		X	X	X	X
Simple hearing test		X	If clinically indicated		
HIV antibody test	X				
CD4 (in HIV positive participants)		X	According to national guidelines		
Haemoglobin		X			
AST and ALT	X		X		
Serum creatinine		X	X		
Serum potassium		X	X	If clinically indicated	
Blood glucose		X			
Urinalysis		X	X		
Urine: HCG Pregnancy test		X	If clinically indicated		
Chest X-ray		X			
ECG		X[§]	Weeks 1-4 & 12	Weeks 24 & 36	
Sputum smear and culture[‡]	1	2	1[*]	1[*]	1[*]
Rifampicin (& 2nd line) LPA	1				
Participant's costs		X	X	X	X
Blood sample for storage (if participant consents)		X		X[π]	

X indicates assessments required at particular visits

[*] One sample will be collected per visit, except at the final visit of each phase of treatment and at the 27 month follow-up visit, when two samples will be collected.

[‡] all positive strains post-randomization onwards will be shipped to the reference laboratory for full drug susceptibility testing.

[§] one ECG will be done prior to, and another, after administering the first dose of treatment

[π] one sample will be collected for storage at 16 weeks, for participants consenting to sample storage

5.6.2 Major Protocol Changes to the Assessment Schedule

Version 4.0 to 5.0 (March 2013)

- Modification to the enrolment criteria which previously only allowed enrolment of sputum smear positive pulmonary TB patients. Protocol version 5.0 allowed HIV-co-infected patients who are smear negative but are shown to be positive pulmonary TB patients on GeneXpert
- Addition of Fluorescein Diacetate (FDA) vital staining as facultative (optional) test prior to LPA or GeneXpert screening in sites with low prevalence of MDR. To be used when the patient has been on anti-tuberculosis treatment in the previous 3 months; only those patients whose specimens are positive on vital staining are eligible.
- Removal of the limit of 8 weeks as the maximum amount of treatment that can be missed and then made up in the regimen.

Version 5.0 to 5.1 (January 2014)

- Additional 12 lead ECG monitoring added: 12-lead ECG required at weeks 1-4, then every 4 weeks to week 52.

Version 5.1 to 6.2 (February 2015)

- Mandated that all patients should be followed up to week 132 (previously the requirement was that as many patients as possible should be followed up to that time point)

5.7 ANALYSIS DEFINITIONS

5.7.1 Analysis populations

5.7.1.1 Safety population

All randomized participants that have taken at least one dose of treatment will be included in the safety analysis population.

5.7.1.2 Modified intention-to-treat (mITT)

The mITT population is defined as all randomized participants that have a positive culture for M. *tuberculosis* on acidified Ogawa (Kudoh medium) or other culture media if the Ogawa result is not available, at screening or randomization or up to Week 4, with the exception of participants with isolates taken before randomization that are subsequently found to be susceptible to rifampicin, and participants with isolates taken before randomization that are subsequently found to be resistant to both fluoroquinolones and second-line injectables (i.e. XDR-TB) on phenotypic DST. Results from the central reference laboratory will take priority over any results from local laboratories where available.

5.7.1.3 Per protocol (PP)

The PP population will be the same as the mITT population with the exclusion of participants not completing a protocol-adherent course of treatment, other than for treatment failure or death. Treatment failure is defined as failure to attain and maintain culture negativity until the end of allocated treatment.

A participant is considered to have completed a protocol-adherent course of treatment if they have taken 80% of doses within 120% of the minimum duration in both the intensive phase and in the whole treatment period. For this purpose, a dose is defined as all the study medications at the correct dose for that particular day.

For the Short regimen, with or without an extension of the intensive phase, a participant has completed a protocol-adherent course of treatment if they have taken:

- 90 doses (80% of 16 weeks) within 134 days (120% of 16 weeks) in the intensive phase, and
- 224 doses (80% of 40 weeks) within 336 days (120% of 40 weeks) over the whole treatment period (i.e. the combined intensive and continuation phases) regardless of treatment extensions

The same algorithm (80% of doses within 120% of the minimum duration) was applied for the Long regimen.

5.7.2 Primary efficacy outcome

5.7.2.1 Favourable

A participant's outcome will be classified as favourable if their last two culture results are negative unless they have previously been classified as unfavourable. These two cultures must be taken on separate visits (on different days); the latest of which being within the Week 132 window (that is no more than six weeks before 132 weeks since randomisation but with no upper bound).

Participants that don't have a culture result within the Week 132 window because they were unable to produce sputum, will be classified as favourable if their last two cultures before the Week 132

window are negative and they have not previously been classified as unfavourable; such participants will be identified separately in tables.

5.7.2.2 Unfavourable

A participant's outcome will be classified as unfavourable if:

1. They are discontinued from their allocated study treatment and subsequently restarted on a different MDR-TB regimen
2. Treatment is extended beyond the scheduled end of treatment for any reason other than making up of days when no treatment was given (missed treatment) for a maximum of eight weeks. A maximum of 14 days of extra treatment (irrespective of reason) is acceptable before it is classified as treatment extension. In addition, if the intensive phase of treatment has been extended for delayed sputum conversion (maximum 8-week extension permitted) the scheduled end of treatment will also be extended by the same amount, in accordance with Section 7.3.2 of the protocol.
3. They are restarted on any MDR-TB treatment after the scheduled end of treatment, but before 132 weeks after randomization.
4. They change their allocated study treatment for any reason other than (1) the replacement of a single drug or (2) for participants allocated to Regimen A when the change is as a result of changes in local guidelines and not related to any change in the participant's circumstances or condition.
5. Bedaquiline is started where the allocated regimen did not originally contain that drug.
6. A drug from the class of nitroimidazoles is started
7. They die at any point during treatment or follow-up
8. At least one of their last two culture results, from specimens taken on separate occasions, is positive
9. They do not have a culture result within the Week 76 window or thereafter

Providing none of the other criteria above are met, starting a single drug is not considered to be a substantial change to the regimen and therefore does not result in an unfavourable outcome, with the exception of adding bedaquiline or a drug from the class of nitroimidazoles.

An extension of the intensive phase of treatment in any study arm does not constitute an unfavourable outcome, as long as the extension follows the protocol permitted algorithm for late smear conversion (Short regimen) or local policy (Long regimen).

Changes of treatment in participants allocated to Regimen A that result from a change in local guidelines not related in any way to any change in the participant's circumstances or condition will not be classified as unfavourable. A sensitivity analysis will be conducted where these changes are classified as unfavourable.

All re-infections with a different strain are classified as not assessable.

A participant who has a culture result within the Week 76 window or thereafter, but not within the Week 132 window, having not otherwise been classified as unfavourable (based on the definitions above) will be regarded as not assessable and will be excluded from the primary analysis provided their last two cultures, from specimens taken on separate occasions, are negative. Such participants that don't have a culture result within the Week 132 window because they were unable to produce sputum will be instead classified as favourable. Any participant who does not have a culture result within the Week 132 window and does not fulfil these criteria will be classified as unfavourable.

5.8 SAMPLE SIZE ASSUMPTIONS

Based on the experience in Bangladesh and given that the trial population would include HIV-infected participants, not all of whom would be receiving anti-retroviral treatment (ART), it was assumed that the cure rate would be less than 88% reported by Van Deun[18] and the Long regimen would perform better under trial conditions than the global mean of 48%.[19] It was assumed that the proportion of favourable outcomes in the Short regimen would be marginally higher than in the Long regimen, 75% and 70% respectively. A 10% margin of non-inferiority was considered an acceptable reduction in efficacy in broad discussion with the study investigators and external clinicians, given the considerably reduced pill burden and greater than 50% reduction treatment duration. This margin is slightly lower than margins being used in similar studies and ensures that a substantial proportion of the efficacy benefit of the control regimen is retained. Based on a 2:1 allocation ratio in favour of the Short regimen, allowing for 20% of participants being classified as not assessable in a per-protocol analysis, a one-sided level of significance of 2.5% and 80% power, 398 participants would be required to demonstrate non-inferiority.

5.9 REPORTING OF RESULTS

As the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects within subgroups.

5.10 BAYESIAN ANALYSIS OF NON-INFERIORITY

A Bayesian analysis of non-inferiority provides a more informative interpretation of the trial results by providing an estimate of the probability that the Short regimen has efficacy not much worse than the Long regimen for different thresholds of what might be considered ‘not much worse’. Following methods described previously[20], we used Bayesian binomial regression to estimate the distribution of the (unadjusted) difference in the proportion of favourable outcomes between the Long and Short regimens. Gaussian Normal priors were placed on the intercept term (mean = 0.0 and variance = 100) and on the difference in proportion between regimens (Flat: mean = 0.0 and variance = 100, Sceptical: mean = 0.1 and variance 0.05, and Expected: mean = -0.05 and variance 0.05). The Flat prior is an uninformative prior with very large variance centred around zero representing weak prior information, the Sceptical prior is centred around an absolute 10% increase in proportion of favourable in the Long regimen with a smaller variance, and the Expected prior represents the assumptions used in the sample size calculations representing an absolute 5% increase in the proportion of favourable outcomes in the Short regimen, see Figure S10. Initial values for the Markov Chain Monte Carlo algorithm came from estimates from the frequentist binomial regression model.

This Bayesian analysis was not pre-specified in the statistical analysis plan and is post hoc, nevertheless we believe it aids interpretation of the trial results.

6 SUPPLEMENTARY RESULTS

6.1 SUB-GROUP AND SENSITIVITY ANALYSES

Results of sub-group analyses are presented in Figure S2 and S3. In the mITT analysis population there were no significant interactions although there was a suggestion that the Long regimen may have been of greater benefit in some sub-groups that are often associated with a high risk of poor outcomes including low BMI, more advanced disease on chest x-ray and being a smoker. In the PP analysis population, the results were broadly similar, although there were some statistically significant interactions indicating greater benefit on the Long regimen for patients that were either younger or had lower weight. These results should be interpreted with caution since the PP analysis population resulted in considerably more exclusions on the Long regimen than on the Short regimen (see Figure 1). This is particularly seen where only 4 patients from Vietnam on the Long regimen remained in the PP analysis population.

Table S5 shows the results of several sensitivity analyses whereby different assumptions are made in the classification of the primary efficacy endpoint. All sensitivity analyses resulted in differences between regimens that were consistent with the primary analysis.

6.2 ACQUIRED DRUG RESISTANCE

Acquired drug resistance on the short and long regimens is shown in Table S6 for all participants in the mITT analysis population (excluding eight reinfections and one participant that withdrew in the first week for whom baseline phenotypic DSTs were not available).

Of note, there was no acquired resistance in the participants with ofloxacin or second-line injectable resistance at baseline.

In addition to this acquired resistance on the regimen, the following resistance developed after the end of allocated treatment during salvage regimens in participants on the short regimen:

- Resistance to second-line injectables developed in samples from four participants. In one of these participants, this was after ofloxacin and ethambutol resistance had been acquired while on allocated treatment.
- Resistance to second-line injectables and ethionamide developed in samples from two participants.
- Resistance to ofloxacin developed in samples from two participants.
- Resistance to ethionamide developed in samples from one participant.

In all these cases of acquired resistance after the end of treatment, phenotypic sensitivity to the drug was demonstrated at the end of treatment with the allocated short regimen, and there was no acquired resistance on allocated treatment unless otherwise stated.

There was no evidence of acquired resistance to pyrazinamide on either regimen

6.3 TIME TO SMEAR AND CULTURE CONVERSION

An analysis of time to sputum smear conversion, defined as the time from randomization to the first of two consecutive negative smear results, collected on separate days showed no difference between the regimens in either the mITT or PP population Figures S4 and S5. Time to sputum culture conversion, similarly defined, suggested some benefit to the study arm, Figures S6 and S7.

6.4 BAYESIAN ANALYSIS OF NON-INFERIORITY

Figure S11 shows the results of the Bayesian analysis of non-inferiority. The difference between the Flat, Sceptical and Expected priors is minimal (prior distributions shown in Figure S10). The probability that the difference in proportion favourable between the Long and Short regimens is less than 10% is 0.98 with the Flat prior, or 0.98 and 0.99 with the Sceptical and Expected priors. The probability that this difference is less than 5% is 0.83 with the Flat prior, or 0.81 and 0.84 with the Sceptical and Expected priors. The probability that the Short regimen has superior efficacy to the Long regimen (the difference in proportion favourable between the Long and Short regimens is less than 0%) is 0.42 with the Flat prior, or 0.39 and 0.44 with the Sceptical and Expected priors. The Bayesian mean estimate of the risk difference with 95% credible interval was 0.8% (-8.1%, 9.3%) with the Flat prior, 1.2% (-7.5%, 9.5%) with the Sceptical prior, or 0.6% (-8.1%, 9.0%) with the Expected prior.

7 SUPPLEMENTARY TABLES

Table S1. Total participants randomized by country and site in alphabetical order.

		Total screened	Total randomized
Ethiopia	Armauer Hansen Research Institute, Addis Ababa	80	55
	St. Peter's Tuberculosis Specialised Hospital, Addis Ababa	111	71
Mongolia	National Centre for Communicable Diseases, Ulaanbaatar	47	33
South Africa	Doris Goodwin Hospital, Pietermaritzburg	25	14
	King Dinuzulu Hospital, Durban	195	90
	Sizwe Tropical Diseases Hospital, Johannesburg,	129	61
Vietnam	Pham Ngoc Thach Hospital, Ho Chi Minh City	102	100
	Overall	**689**	**424**

Table S2. Baseline characteristics of modified intention to treat analysis population.

(Drug resistance is based on results from samples up to week 4 from central reference laboratory)

		Long	Short	Total
Total in MITT population		130	253	383
Gender	Male	83 (64%)	151 (60%)	234 (61%)
Age (years)	< 25	31 (24%)	56 (22%)	87 (23%)
	25 – 34	45 (35%)	88 (35%)	133 (35%)
	35 – 44	33 (25%)	58 (23%)	91 (24%)
	≥45	21 (16%)	51 (20%)	72 (19%)
Weight (kg)	< 33	0	1 (0%)	1 (0%)
	33- 50	59 (45%)	116 (46%)	175 (46%)
	≥ 50	71 (55%)	136 (54%)	207 (54%)
BMI (kg/m^2)	Median (IQR)	19 (17 - 21)	19 (17 - 21)	19 (17 - 21)
HIV status	Positive	40 (31%)	85 (34%)	125 (33%)
CD4 count (In HIV-infected)[1]	Median (IQR)	298 (166 - 532)	239 (139 - 394)	248 (143 - 429)
On ART at baseline (In HIV-infected)		24 (60%)	60 (71%)	84 (67%)
Smoking status	Never smoked	82 (63%)	164 (65%)	246 (64%)
	Ex-smoker	36 (28%)	59 (23%)	95 (25%)
	Current smoker	12 (9%)	30 (12%)	42 (11%)
Smear	Negative	3 (2%)	8 (3%)	11 (3%)
	Positive	127 (98%)	245 (97%)	372 (97%)
Previous TB treatment[2]	None	15 (12%)	18 (7%)	33 (9%)
	Drug susceptible-TB treatment	105 (81%)	220 (87%)	325 (85%)
	Second-line treatment	9 (7%)	15 (6%)	24 (6%)
Radiographic extent of disease[3]	None or minimal	14 (11%)	28 (12%)	42 (12%)
	Moderate	72 (58%)	126 (53%)	198 (54%)
	Advanced	39 (31%)	85 (36%)	124 (34%)
Radiographic extent of cavitation[3]	None	28 (22%)	55 (23%)	83 (23%)
	Single	13 (10%)	34 (14%)	47 (13%)
	Multiple	84 (67%)	150 (63%)	234 (64%)
Heart rate (bpm)	<75	21 (16%)	52 (21%)	73 (19%)
	75 – 99	70 (54%)	125 (49%)	195 (51%)
	≥100	39 (30%)	76 (30%)	115 (30%)
Fridericia corrected QTcF (ms)	< 400	58 (45%)	112 (44%)	170 (44%)
	400 – 449	71 (55%)	136 (54%)	207 (54%)
	450 - 499	1 (1%)	5 (2%)	6 (2%)
Drug resistance to:	Isoniazid[4]	118 (93%)	234 (94%)	352 (94%)
	Ofloxacin[5]	3 (3%)	2 (1%)	5 (1%)
	Kanamycin or capreomycin[5]	1 (1%)	3 (1%)	4 (1%)
	Pyrazinamide[6]	58 (59%)	131 (63%)	189 (62%)

There were no significant differences between the regimens.

[1] 52 HIV-infected participants were missing CD4 count (13 Long regimen, 39, Short regimen)

[2] 1 participant on the Short regimen had no previous treatment recorded

[3] 19 participants had no assessable chest x-ray readings (5 Long regimen, 14 Short regimen)

[4] Based on 127 on Long regimen and 248 on Short regimen with results available.

[5] Based on 120 on Long regimen and 237 on Short regimen with results available.

[6] Based on 99 on Long regimen and 207 on Short regimen with results available

Table S3. Retention by treatment regimen.

		Long	Short	Total
	Total randomised	**142**	**282**	**424**
	Total in mITT	**130**	**253**	**383**
Week 52	**Seen here or later**	120 (92%)	230 (91%)	350 (91%)
	Not seen here	1 (1%)	1 (<1%)	2 (1%)
	Died	5 (4%)	14 (6%)	19 (5%)
	After early discontinuation			
	Withdrawn (clinician request)	0	1 (<1%)	1 (<1%)
	Lost to follow-up	1 (1%)	1 (<1%)	2 (1%)
	Serious Adverse Event	0	1 (<1%)	1 (<1%)
	Withdrawal of consent	3 (2%)	5 (2%)	8 (2%)
Week 76	**Seen here or later**	118 (91%)	226 (89%)	344 (90%)
	Not seen here	1 (1%)	1 (<1%)	2 (1%)
	Died	5 (4%)	17 (7%)	22 (6%)
	After early discontinuation			
	Withdrawn (clinician request)	0	1 (<1%)	1 (<1%)
	Lost to follow-up	2 (2%)	1 (<1%)	3 (1%)
	Serious Adverse Event	0	1 (<1%)	1 (<1%)
	Withdrawal of consent	4 (3%)	6 (2%)	10 (3%)
Week 104	**Seen here or later**	113 (87%)	222 (88%)	335 (87%)
	Not seen here	1 (1%)	1 (<1%)	2 (1%)
	Died	6 (5%)	20 (8%)	26 (7%)
	After early discontinuation			
	Withdrawn (clinician request)	0	1 (<1%)	1 (<1%)
	Lost to follow-up	5 (4%)	1 (<1%)	6 (2%)
	Serious Adverse Event	0	1 (<1%)	1 (<1%)
	Withdrawal of consent	5 (4%)	7 (3%)	12 (3%)
Week 132	**Seen here or later**	110 (85%)	217 (86%)	327 (85%)
	Not seen here	0	1 (<1%)	1 (<1%)
	Died	7 (5%)	21 (8%)	28 (7%)
	After early discontinuation			
	Withdrawn (clinician request)	0	1 (<1%)	1 (<1%)
	Lost to follow-up	7 (5%)	3 (1%)	10 (3%)
	Serious Adverse Event	0	1 (<1%)	1 (<1%)
	Withdrawal of consent	5 (4%)	8 (3%)	13 (3%)
	Transferred to National Treatment Programme	1 (1%)	1 (<1%)	2 (1%)

Table S4. Primary efficacy outcome components by secondary classifications

Outcome	Modified ITT population			Per protocol population		
	Long	Short	Total	Long	Short	Total
Total randomised	142	282	424	142	282	424
Total in population	130	253	383	87	234	321
Not assessable (Reinfection)	1	7	8	1	6	7
Not assessable (Lost to follow-up after 76 weeks, culture converted when last seen)	5	1	6	3	1	4
Total assessable	124	245	369	83	227	310
Total favourable N (% of assessable)	99 (79.8%)	193 (78.8%)	292 (79.1%)	67 (80.7%)	186 (81.9%)	253 (81.6%)
Total unfavourable N (% of assessable)	25 (20.2%)	52 (21.2%)	77 (20.9%)	16 (19.3%)	41 (18.1%)	57 (18.4%)
Extended treatment beyond that allowed						
Unfavourable outcomes based on bacteriology						
Bacteriological reversion on treatment	0	1	1	0	0	0
Unfavourable outcomes not based on bacteriology						
Treatment extension after adverse event	0	3	3	0	2	2
Treatment extension after poor adherence or loss to follow-up	0	1	1	0	1	1
Started ≥2 additional drugs						
Unfavourable outcomes based on bacteriology						
Never achieved culture conversion	0	1	1	0	1	1
Bacteriological reversion on treatment	2	10	12	2	9	11
Reversion on treatment with limited bacteriology	1	0	1	1	0	1
Bacteriological relapse after treatment	0	6	6	0	6	6
Relapse after treatment with limited bacteriology	0	1	1	0	1	1
Unfavourable outcomes not based on bacteriology						
Investigator decision[1]	3	2	5	2	0	2
Participant withdrew consent for treatment	0	4	4	0	3	3
Treatment change after adverse event	3	1	4	2	1	3

Treatment change after poor adherence or loss to follow-up	0	1	1	0	0	0
Died during treatment or follow-up						
Unfavourable outcomes based on bacteriology						
Never achieved culture conversion	1	4	5	1	4	5
Bacteriological reversion on treatment	1	1	2	1	1	2
Culture positive when last seen	0	1	1	0	1	1
Unfavourable outcomes not based on bacteriology						
Culture negative when last seen	5	9	14	5	9	14
No culture at or after 76 weeks						
Unfavourable outcomes based on bacteriology						
Bacteriological reversion on treatment	0	1	1	0	1	1
Unfavourable outcomes not based on bacteriology						
Lost to follow-up prior to 76 weeks, culture converted when last seen	3	1	4	0	1	1
Participant withdrew consent for treatment	4	4	8	0	0	0
>1 of last 2 cultures is positive						
Unfavourable outcomes based on bacteriology						
Culture positive when last seen	2	0	2	2	0	2

[1] Investigator decision based on the following reasons: baseline drug susceptibility test results (three Long regimen participants), pregnancy (one Short regimen participant), switch to same regimen as her child (one Short regimen participant).

Table S5. Summary of sensitivity analyses of the primary efficacy outcome.

Sensitivity analysis are as follows:

A. Participants on the Long regimen with duration longer than 114 weeks are reclassified as unfavourable
B. Primary outcome adjusted for randomization stratification (HIV status and centre)
C. Primary outcome in additional analysis populations (ITT and safety)
D. Primary outcome reclassification - classification to include treatment changes due to changes in local guidelines as unfavourable.
E. Primary outcome reclassification - classification to include reinfections as unfavourable.

	Long regimen N(%) unfavourable / assessable	Short regimen N(%) unfavourable / assessable	Adjusted difference (95% CI)	Crude difference (95% CI)
Primary analysis (mITT population)	**25 (20.2%)/124**	**52 (21.2%) / 245**	**1.0% (-7.5%, 9.5%)**	**1.1% (-7.7%, 9.8%)**
Primary analysis (PP population)	**16 (19.3%)/83**	**41 (18.1%)/227**	**-0.7% (-10.5%, 9.1%)**	**-1.2% (-11.1%, 8.6%)**
Sensitivity analysis A. (mITT population)	26 (21.0%) / 124	52 (21.2%) / 245	0.2% (-8.4%, 8.8%)	0.3% (-8.5%, 9.1%)
Sensitivity analysis A. (PP population)	17 (20.5%) / 83	41 (18.1%) / 227	-1.9% (-11.8%, 8.1%)	-2.4% (-12.4%, 7.6%)
Sensitivity analysis B. (mITT population)	25 (20.2%)/124	52 (21.2%)/245	2.3% (-4.8%, 9.4%)	
Sensitivity analysis B. (PP population)	16 (19.3%)/83	41 (18.1%)/227	0.4% (-7.7%, 8.6%)	
Sensitivity analysis C. (ITT population)	28 (20.6%)/136	64 (23.4%)/274	2.9% (-5.3%, 11.2%)	2.8% (-5.7%, 11.2%)
Sensitivity analysis C. (Safety population)	27 (20.0%)/135	64 (23.4%)/274	3.6% (-4.6%, 11.8%)	3.4% (-5.0%, 11.8%)
Sensitivity analysis D. (mITT population)	27 (21.8%)/124	52 (21.2%)/245	-0.6% (-9.3%, 8.1%)	-0.5% (-9.4%, 8.3%)
Sensitivity analysis D. (PP population)	18 (21.7%)/83	41 (18.1%)/227	-3.2% (-13.3%, 7.0%)	-3.6% (-13.8%, 6.6%)
Sensitivity analysis E. (mITT population)	26 (20.8%)/125	59 (23.4%)/252	2.3% (-6.4%, 10.9%)	2.6% (-6.2%, 11.4%)
Sensitivity analysis E. (PP population)	17 (20.2%)/84	47 (20.2%)/233	0.3% (-9.7%, 10.2%)	-0.1% (-10.1%, 10.0%)

Table S6. Acquired resistance while on allocated regimen.

All participants from mITT analysis population are included with the exception of 8 participants that had a failure or relapse with a different *M. tuberculosis* strain (reinfections), and one participant that withdrew in the first week for whom baseline phenotypic DSTs were not available. Ofloxacin DST was used to evaluate fluoroquinolone resistance. All cases of acquired second-line injectable resistance were resistant to kanamycin. No other acquired drug resistance on allocated regimen was detected. Note that rows are not mutually exclusive.

	Long regimen	**Short regimen**	**Total**	**X^2 test**
Total in analysis	**128**	**246**	**374**	
No acquired resistance	**125 (97.7%)**	**238 (96.7%)**	**363 (97.1%)**	
Any acquired resistance	3 (2.3%)	8 (3.3%)	11 (2.9%)	**p = 0.622**
Any Fluoroquinolone resistance	2 (1.6%)	5 (2.0%)	7 (1.9%)	
Any Second-line injectable resistance	1 (0.8%)	4 (1.6%)	5 (1.3%)	
Resistance pattern				
- Fluoroquinolone, second-line injectable and ethambutol	0	1	1	
- Fluoroquinolone, ethionamide and ethambutol	0	1	1	
- Fluoroquinolone and ethionamide	1	0	1	
- Fluoroquinolone and ethambutol	1	1	2	
- Fluoroquinolone	0	2	2	
- Second-line injectable	1	3	4	
- Pyrazinamide	0	0	0	

Table S7. Deaths as classified by Independent Death Review Committee.

Time from randomization	Death Category	Long Regimen	Short Regimen	Total
	All deaths, N (% of safety population)	**9 (6.4%)**	**24 (8.5%)**	**33**
≤ 1 Year	TB related	0	4	4
	TB treatment-related	1[1]	1[2]	2
	HIV/HIV treatment-related	2	4	6
	Other/Uncertain - Hepato-biliary	1[3]	2[3]	3
	Other	1[4]	5[5]	6
	All ≤ 1 year, N (% of safety population)	**5(3.5%)**	**16 (5.7%)**	**21**
> 1 Year	TB related	2	3	5
	TB treatment-related	0	0	0
	HIV/HIV treatment-related	1	2	3
	Other/Uncertain	1[6]	3[7]	4
	All > 1 year, N (% of safety population)	**4 (2.8%)**	**8 (2.8%)**	**12**

1. Sudden death at home in a 40 year-old man (highest recorded QTcF 464ms)
2. Sudden death at home in a 46 year-old man (highest QTcF 500ms, but QT 518ms)
3. One on each regimen had liver failure associated with herbal medicine consumption
4. Renal, cardiac and respiratory failure
5. Two sudden deaths of uncertain cause at home(one 26 year-old woman on moxifloxacin 400mg with possible hypoglycaemic seizure related to alcoholic liver disease who was seen 2 days prior to death when blood glucose was 2.24mMol/L and QTcF readings were 525ms and 499ms;one 69 year-old man who collapsed at home and had no QT/QTcF readings over 450ms), and one sepsis, one diabetic ketoacidosis and one suicide
6. Violent death
7. One diabetic ketoacidosis, one cervical cancer and one cardio- and cerebrovascular

Table S8. Grade 3-5 AEs by system organ class and preferred term and treatment.

Specific Preferred Terms given when at least 5% of participants experienced AE in that particular System Organ Class. The preferred terms (Alanine aminotransferase increased, Haemoglobin decreased, International normalised ratio increased, Weight decreased) were recoded from the Investigations SOC to a clinically relevant class.

System Organ Class	Preferred term	Long regimen	Short regimen	Total
Any	Any	64 (45%)	136 (48%)	200 (47%)
Blood and lymphatic system disorders	Any	1 (1%)	15 (5%)	16 (4%)
Cardiac disorders	Cardiac failure	1 (1%)	1 (<1%)	2 (<1%)
	Cardiac failure congestive	1 (1%)	0	1 (<1%)
	Conduction disorder	7 (5%)	28 (10%)	35 (8%)
	Cor pulmonale	1 (1%)	1 (<1%)	2 (<1%)
	Palpitations	1 (1%)	0	1 (<1%)
	Pericarditis	0	1 (<1%)	1 (<1%)
	Any	10 (7%)	30 (11%)	40 (9%)
Ear and labyrinth disorders	Deafness	6 (4%)	13 (5%)	19 (4%)
	Ototoxicity	2 (1%)	6 (2%)	8 (2%)
	Vertigo	0	3 (1%)	3 (1%)
	Any	8 (6%)	21 (7%)	29 (7%)
Endocrine disorders	Any	4 (3%)	10 (4%)	14 (3%)
Eye disorders	Any	0	2 (1%)	2 (<1%)
Gastrointestinal disorders	Any	10 (7%)	7 (2%)	17 (4%)
General disorders and administration site conditions	Any	2 (1%)	8 (3%)	10 (2%)
Hepatobiliary disorders	Alanine aminotransferase increased	2 (1%)	2 (1%)	4 (1%)
	Drug-induced liver injury	2 (1%)	10 (4%)	12 (3%)
	Hepatic function abnormal	4 (3%)	6 (2%)	10 (2%)
	Hepatitis	1 (1%)	5 (2%)	6 (1%)
	Hepatitis C	0	1 (<1%)	1 (<1%)
	Hepatitis fulminant	0	1 (<1%)	1 (<1%)

	Jaundice	1 (1%)	2 (1%)	3 (1%)
	Any	8 (6%)	25 (9%)	33 (8%)
Immune system disorders	Any	0	1 (<1%)	1 (<1%)
Infections and infestations	Any	3 (2%)	4 (1%)	7 (2%)
Injury, poisoning and procedural complications	Any	2 (1%)	2 (1%)	4 (1%)
Metabolism and nutrition disorders	Hyperkalaemia	0	1 (<1%)	1 (<1%)
	Hyperuricaemia	0	1 (<1%)	1 (<1%)
	Hypoalbuminaemia	0	1 (<1%)	1 (<1%)
	Hypoglycaemia	1 (1%)	2 (1%)	3 (1%)
	Hypokalaemia	10 (7%)	3 (1%)	13 (3%)
	Hyponatraemia	0	2 (1%)	2 (<1%)
	Tetany	4 (3%)	1 (<1%)	5 (1%)
	Weight decreased	18 (13%)	33 (12%)	51 (12%)
	Any	28 (20%)	41 (15%)	69 (16%)
Musculoskeletal and connective tissue disorders	Any	4 (3%)	1 (<1%)	5 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Any	0	2 (1%)	2 (<1%)
Nervous system disorders	Any	4 (3%)	5 (2%)	9 (2%)
Pregnancy, puerperium and perinatal conditions	Any	1 (1%)	0	1 (<1%)
Psychiatric disorders	Any	8 (6%)	6 (2%)	14 (3%)
Renal and urinary disorders	Any	3 (2%)	11 (4%)	14 (3%)
Reproductive system and breast disorders	Any	1 (1%)	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders	Asthma	1 (1%)	0	1 (<1%)
	Chest pain	0	1 (<1%)	1 (<1%)
	Dyspnoea	1 (1%)	3 (1%)	4 (1%)
	Haemoptysis	0	2 (1%)	2 (<1%)
	Lower respiratory tract infection	0	1 (<1%)	1 (<1%)
	Pneumonia	1 (1%)	4 (1%)	5 (1%)
	Pneumothorax	1 (1%)	0	1 (<1%)
	Pulmonary embolism	1 (1%)	0	1 (<1%)
	Pulmonary hypertension	1 (1%)	0	1 (<1%)

	Pulmonary tuberculosis	0	4 (1%)	4 (1%)
	Respiratory distress	1 (1%)	1 (<1%)	2 (<1%)
	Respiratory failure	1 (1%)	1 (<1%)	2 (<1%)
	Any	6 (4%)	15 (5%)	21 (5%)
Skin and subcutaneous tissue disorders	Any	0	2 (1%)	2 (<1%)
Social circumstances	Any	1 (1%)	2 (1%)	3 (1%)
Surgical and medical procedures	Any	0	2 (1%)	2 (<1%)
Vascular disorders	Any	1 (1%)	4 (1%)	5 (1%)
Total		141	282	423

Table S9. Serious Adverse Events by system organ class and treatment. The preferred terms (Alanine aminotransferase increased, Haemoglobin decreased, International normalised ratio increased, Weight decreased) were recoded from the Investigations SOC to a clinically relevant class.

System organ class	Long regimen	Short regimen	Total
Blood and lymphatic system disorders	1 (1%)	5 (2%)	6 (1%)
Cardiac disorders	3 (2%)	4 (1%)	7 (2%)
Ear and labyrinth disorders	8 (6%)	16 (6%)	24 (6%)
Endocrine disorders	0	5 (2%)	5 (1%)
Eye disorders	0	1 (<1%)	1 (<1%)
Gastrointestinal disorders	9 (6%)	6 (2%)	15 (4%)
General disorders and administration site conditions	4 (3%)	11 (4%)	15 (4%)
Hepatobiliary disorders	5 (4%)	15 (5%)	20 (5%)
Infections and infestations	3 (2%)	7 (2%)	10 (2%)
Injury, poisoning and procedural complications	5 (4%)	5 (2%)	10 (2%)
Investigations	1 (1%)	0	1 (<1%)
Metabolism and nutrition disorders	12 (9%)	10 (4%)	22 (5%)
Musculoskeletal and connective tissue disorders	2 (1%)	0	2 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (1%)	2 (0%)
Nervous system disorders	4 (3%)	3 (1%)	7 (2%)
Pregnancy, puerperium and perinatal conditions	0	1 (<1%)	1 (<1%)
Psychiatric disorders	7 (5%)	4 (1%)	11 (3%)
Renal and urinary disorders	3 (2%)	6 (2%)	9 (2%)
Reproductive system and breast disorders	1 (1%)	0	1 (<1%)
Respiratory, thoracic and mediastinal disorders	7 (5%)	21 (7%)	28 (7%)
Skin and subcutaneous tissue disorders	0	1 (<1%)	1 (<1%)
Social circumstances	2 (1%)	6 (2%)	8 (2%)
Surgical and medical procedures	0	2 (1%)	2 (0%)
Vascular disorders	1 (1%)	1 (<1%)	2 (0%)
Any SAEs	53 (38%)	91 (32%)	144 (34%)
Total	141	282	423

Table S10. Participants whose maximum QT or QTcF was ≥500ms or ≥60ms higher than the baseline value by treatment.

		Long regimen			Short regimen		
Ever exceeding QT or QTcF threshold	Population	No	Yes	Total	No	Yes	Total
Maximum QT or QTcF ≥500ms[a]	**All**	**132 (94%)**	**9[a] (6%)**	**141**	**251 (89%)**	**31* (11%)**	**282**
Maximum QT or QTcF ≥500ms	Weight <33kg			.	1 (100%)	0	1
Maximum QT or QTcF ≥500ms	Weight 33-50kg[b]	58 (94%)	4 (6%)	62	114 (90%)	13 (10%)	127
Maximum QT or QTcF ≥500ms	Weight >50kg[c]	74 (94%)	5 (6%)	79	136 (88%)	18 (12%)	154
Change in Maximum QT or QTcF ≥60ms	**All**	**83 (59%)**	**58 (41%)**	**141**	**101 (36%)**	**181 (64%)**	**282**
Change in Maximum QT or QTcF ≥60ms	Weight <33kg			.	0	1 (100%)	1
Change in Maximum QT or QTcF ≥60ms	Weight 33-50kg[b]	34 (55%)	28 (45%)	62	43 (34%)	84 (66%)	127
Change in Maximum QT or QTcF ≥60ms	Weight >50kg[c]	49 (62%)	30 (38%)	79	58 (38%)	96 (62%)	154

[a] One participant on each regimen had an uncorroborated single reading over 500ms out of keeping with their other ECGs.
[b] Moxifloxacin dose 600mg daily on the Short regimen
[c] Moxifloxacin dose 800mg daily on the Short regimen

Table S11 Participants whose ALT or AST exceeded 5 times the upper limit of normal (ULN) post-baseline.

	Long regimen			Short regimen			Fisher's exact test
Ever exceeding ULN threshold	No	Yes	Total*	No	Yes	Total*	
ALT 5xULN	137 (99%)	2 (1%)	139	254 (93%)	18 (7%)	272	p = 0.027
ALT 10xULN	139 (100%)	0	139	268 (99%)	4 (1%)	272	p = 0.305
AST 5xULN	135 (97%)	4 (3%)	139	261 (96%)	11 (4%)	272	p = 0.782
AST 10xULN	138 (99%)	1 (1%)	139	270 (99%)	2 (1%)	272	p = 1.000

* Total in safety population, excluding those who were withdrawn from the study after baseline and with no post-baseline data.

Figure S1. Adherence to allocated treatment, mITT analysis population.

Number in each category and percentage of mITT population shown on figure.

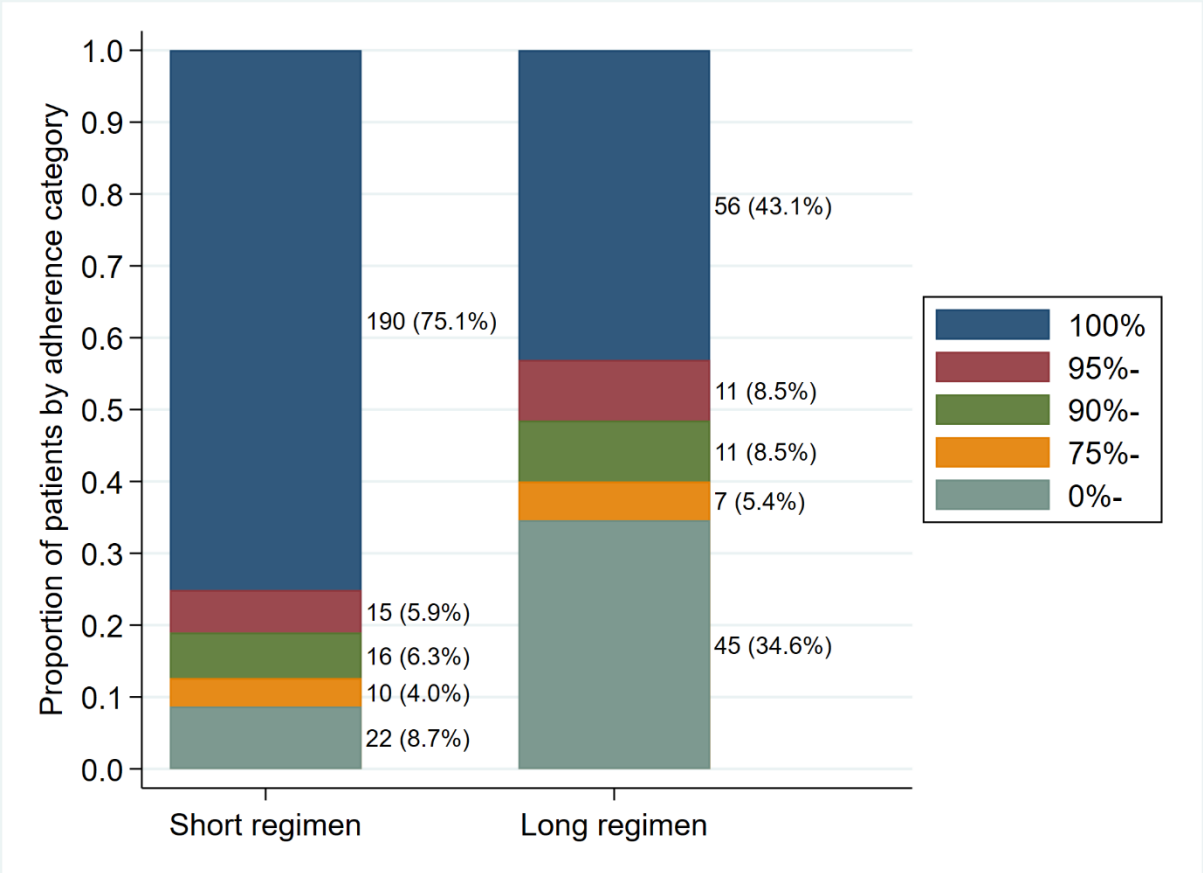
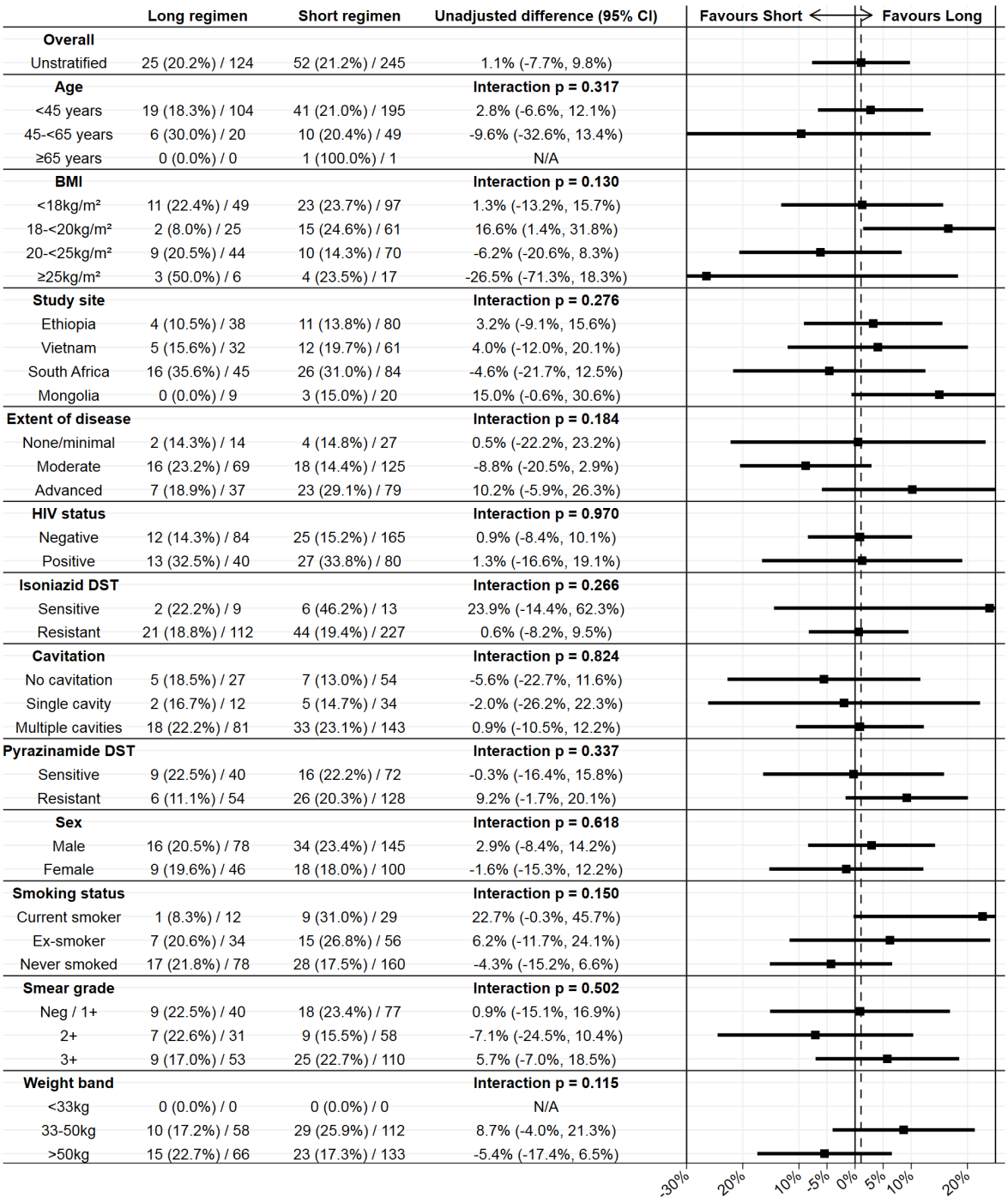


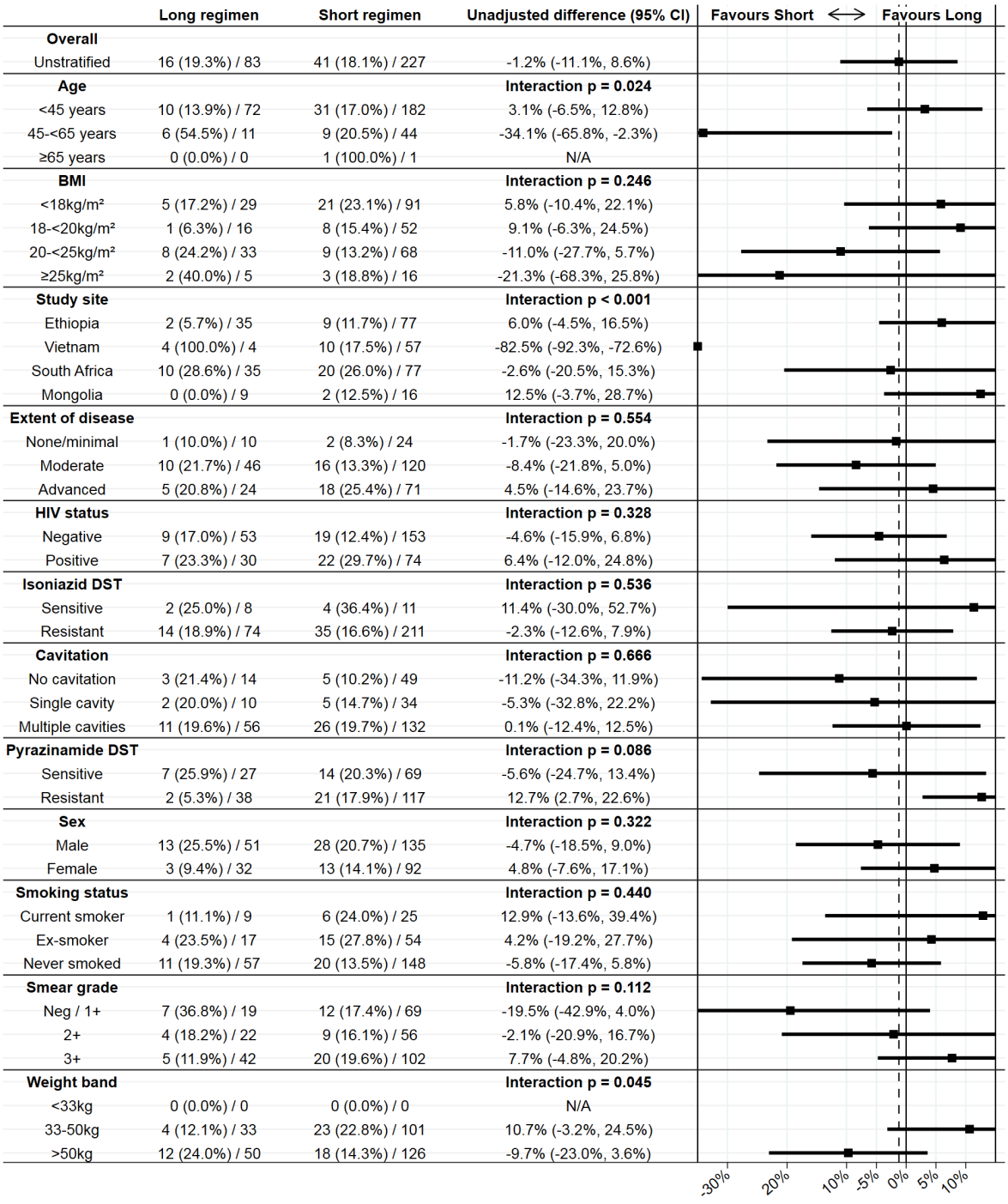
Figure S2. Forest plot of subgroup analyses, mITT analysis population.



	Long regimen	Short regimen	Unadjusted difference (95% CI)
Overall			
Unstratified	25 (20.2%) / 124	52 (21.2%) / 245	1.1% (-7.7%, 9.8%)
Age			**Interaction p = 0.317**
<45 years	19 (18.3%) / 104	41 (21.0%) / 195	2.8% (-6.6%, 12.1%)
45-<65 years	6 (30.0%) / 20	10 (20.4%) / 49	-9.6% (-32.6%, 13.4%)
≥65 years	0 (0.0%) / 0	1 (100.0%) / 1	N/A
BMI			**Interaction p = 0.130**
<18kg/m²	11 (22.4%) / 49	23 (23.7%) / 97	1.3% (-13.2%, 15.7%)
18-<20kg/m²	2 (8.0%) / 25	15 (24.6%) / 61	16.6% (1.4%, 31.8%)
20-<25kg/m²	9 (20.5%) / 44	10 (14.3%) / 70	-6.2% (-20.6%, 8.3%)
≥25kg/m²	3 (50.0%) / 6	4 (23.5%) / 17	-26.5% (-71.3%, 18.3%)
Study site			**Interaction p = 0.276**
Ethiopia	4 (10.5%) / 38	11 (13.8%) / 80	3.2% (-9.1%, 15.6%)
Vietnam	5 (15.6%) / 32	12 (19.7%) / 61	4.0% (-12.0%, 20.1%)
South Africa	16 (35.6%) / 45	26 (31.0%) / 84	-4.6% (-21.7%, 12.5%)
Mongolia	0 (0.0%) / 9	3 (15.0%) / 20	15.0% (-0.6%, 30.6%)
Extent of disease			**Interaction p = 0.184**
None/minimal	2 (14.3%) / 14	4 (14.8%) / 27	0.5% (-22.2%, 23.2%)
Moderate	16 (23.2%) / 69	18 (14.4%) / 125	-8.8% (-20.5%, 2.9%)
Advanced	7 (18.9%) / 37	23 (29.1%) / 79	10.2% (-5.9%, 26.3%)
HIV status			**Interaction p = 0.970**
Negative	12 (14.3%) / 84	25 (15.2%) / 165	0.9% (-8.4%, 10.1%)
Positive	13 (32.5%) / 40	27 (33.8%) / 80	1.3% (-16.6%, 19.1%)
Isoniazid DST			**Interaction p = 0.266**
Sensitive	2 (22.2%) / 9	6 (46.2%) / 13	23.9% (-14.4%, 62.3%)
Resistant	21 (18.8%) / 112	44 (19.4%) / 227	0.6% (-8.2%, 9.5%)
Cavitation			**Interaction p = 0.824**
No cavitation	5 (18.5%) / 27	7 (13.0%) / 54	-5.6% (-22.7%, 11.6%)
Single cavity	2 (16.7%) / 12	5 (14.7%) / 34	-2.0% (-26.2%, 22.3%)
Multiple cavities	18 (22.2%) / 81	33 (23.1%) / 143	0.9% (-10.5%, 12.2%)
Pyrazinamide DST			**Interaction p = 0.337**
Sensitive	9 (22.5%) / 40	16 (22.2%) / 72	-0.3% (-16.4%, 15.8%)
Resistant	6 (11.1%) / 54	26 (20.3%) / 128	9.2% (-1.7%, 20.1%)
Sex			**Interaction p = 0.618**
Male	16 (20.5%) / 78	34 (23.4%) / 145	2.9% (-8.4%, 14.2%)
Female	9 (19.6%) / 46	18 (18.0%) / 100	-1.6% (-15.3%, 12.2%)
Smoking status			**Interaction p = 0.150**
Current smoker	1 (8.3%) / 12	9 (31.0%) / 29	22.7% (-0.3%, 45.7%)
Ex-smoker	7 (20.6%) / 34	15 (26.8%) / 56	6.2% (-11.7%, 24.1%)
Never smoked	17 (21.8%) / 78	28 (17.5%) / 160	-4.3% (-15.2%, 6.6%)
Smear grade			**Interaction p = 0.502**
Neg / 1+	9 (22.5%) / 40	18 (23.4%) / 77	0.9% (-15.1%, 16.9%)
2+	7 (22.6%) / 31	9 (15.5%) / 58	-7.1% (-24.5%, 10.4%)
3+	9 (17.0%) / 53	25 (22.7%) / 110	5.7% (-7.0%, 18.5%)
Weight band			**Interaction p = 0.115**
<33kg	0 (0.0%) / 0	0 (0.0%) / 0	N/A
33-50kg	10 (17.2%) / 58	29 (25.9%) / 112	8.7% (-4.0%, 21.3%)
>50kg	15 (22.7%) / 66	23 (17.3%) / 133	-5.4% (-17.4%, 6.5%)

First two columns show number and percentage of unfavourable outcomes / assessable participants in MITT analysis population

Figure S3. Forest plot of subgroup analyses, PP analysis population.



	Long regimen	Short regimen	Unadjusted difference (95% CI)
Overall			
Unstratified	16 (19.3%) / 83	41 (18.1%) / 227	-1.2% (-11.1%, 8.6%)
Age			**Interaction p = 0.024**
<45 years	10 (13.9%) / 72	31 (17.0%) / 182	3.1% (-6.5%, 12.8%)
45-<65 years	6 (54.5%) / 11	9 (20.5%) / 44	-34.1% (-65.8%, -2.3%)
≥65 years	0 (0.0%) / 0	1 (100.0%) / 1	N/A
BMI			**Interaction p = 0.246**
<18kg/m²	5 (17.2%) / 29	21 (23.1%) / 91	5.8% (-10.4%, 22.1%)
18-<20kg/m²	1 (6.3%) / 16	8 (15.4%) / 52	9.1% (-6.3%, 24.5%)
20-<25kg/m²	8 (24.2%) / 33	9 (13.2%) / 68	-11.0% (-27.7%, 5.7%)
≥25kg/m²	2 (40.0%) / 5	3 (18.8%) / 16	-21.3% (-68.3%, 25.8%)
Study site			**Interaction p < 0.001**
Ethiopia	2 (5.7%) / 35	9 (11.7%) / 77	6.0% (-4.5%, 16.5%)
Vietnam	4 (100.0%) / 4	10 (17.5%) / 57	-82.5% (-92.3%, -72.6%)
South Africa	10 (28.6%) / 35	20 (26.0%) / 77	-2.6% (-20.5%, 15.3%)
Mongolia	0 (0.0%) / 9	2 (12.5%) / 16	12.5% (-3.7%, 28.7%)
Extent of disease			**Interaction p = 0.554**
None/minimal	1 (10.0%) / 10	2 (8.3%) / 24	-1.7% (-23.3%, 20.0%)
Moderate	10 (21.7%) / 46	16 (13.3%) / 120	-8.4% (-21.8%, 5.0%)
Advanced	5 (20.8%) / 24	18 (25.4%) / 71	4.5% (-14.6%, 23.7%)
HIV status			**Interaction p = 0.328**
Negative	9 (17.0%) / 53	19 (12.4%) / 153	-4.6% (-15.9%, 6.8%)
Positive	7 (23.3%) / 30	22 (29.7%) / 74	6.4% (-12.0%, 24.8%)
Isoniazid DST			**Interaction p = 0.536**
Sensitive	2 (25.0%) / 8	4 (36.4%) / 11	11.4% (-30.0%, 52.7%)
Resistant	14 (18.9%) / 74	35 (16.6%) / 211	-2.3% (-12.6%, 7.9%)
Cavitation			**Interaction p = 0.666**
No cavitation	3 (21.4%) / 14	5 (10.2%) / 49	-11.2% (-34.3%, 11.9%)
Single cavity	2 (20.0%) / 10	5 (14.7%) / 34	-5.3% (-32.8%, 22.2%)
Multiple cavities	11 (19.6%) / 56	26 (19.7%) / 132	0.1% (-12.4%, 12.5%)
Pyrazinamide DST			**Interaction p = 0.086**
Sensitive	7 (25.9%) / 27	14 (20.3%) / 69	-5.6% (-24.7%, 13.4%)
Resistant	2 (5.3%) / 38	21 (17.9%) / 117	12.7% (2.7%, 22.6%)
Sex			**Interaction p = 0.322**
Male	13 (25.5%) / 51	28 (20.7%) / 135	-4.7% (-18.5%, 9.0%)
Female	3 (9.4%) / 32	13 (14.1%) / 92	4.8% (-7.6%, 17.1%)
Smoking status			**Interaction p = 0.440**
Current smoker	1 (11.1%) / 9	6 (24.0%) / 25	12.9% (-13.6%, 39.4%)
Ex-smoker	4 (23.5%) / 17	15 (27.8%) / 54	4.2% (-19.2%, 27.7%)
Never smoked	11 (19.3%) / 57	20 (13.5%) / 148	-5.8% (-17.4%, 5.8%)
Smear grade			**Interaction p = 0.112**
Neg / 1+	7 (36.8%) / 19	12 (17.4%) / 69	-19.5% (-42.9%, 4.0%)
2+	4 (18.2%) / 22	9 (16.1%) / 56	-2.1% (-20.9%, 16.7%)
3+	5 (11.9%) / 42	20 (19.6%) / 102	7.7% (-4.8%, 20.2%)
Weight band			**Interaction p = 0.045**
<33kg	0 (0.0%) / 0	0 (0.0%) / 0	N/A
33-50kg	4 (12.1%) / 33	23 (22.8%) / 101	10.7% (-3.2%, 24.5%)
>50kg	12 (24.0%) / 50	18 (14.3%) / 126	-9.7% (-23.0%, 3.6%)

First two columns show number and percentage of unfavourable outcomes / assessable participants in PP analysis population

Figure S4. Kaplan-Meier plot of time to smear conversion in the mITT population.

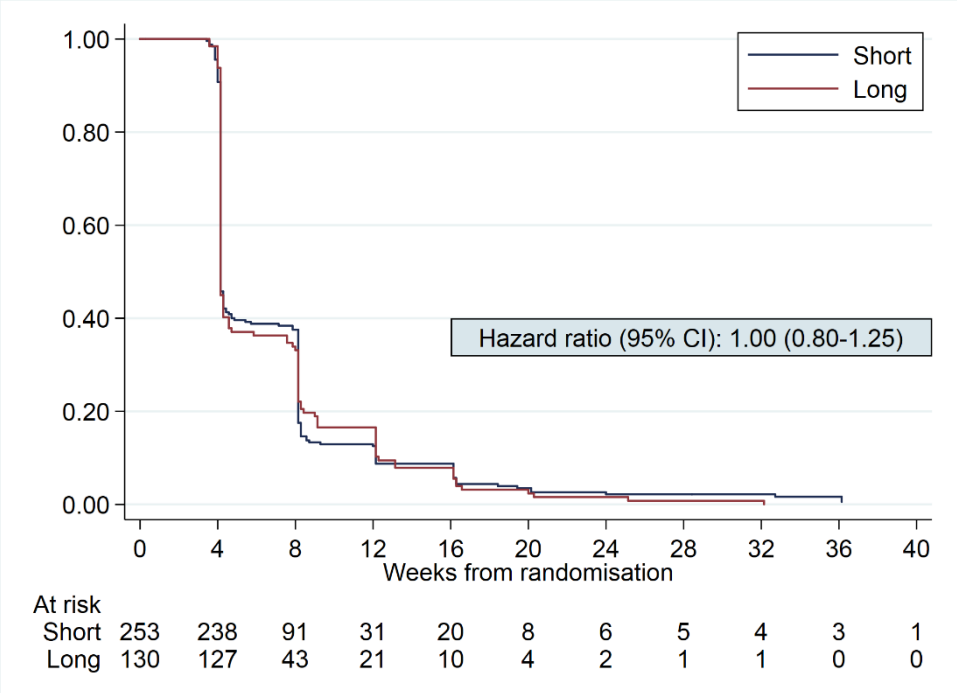


Figure S5. Kaplan-Meier plot of time to smear conversion in the PP population.

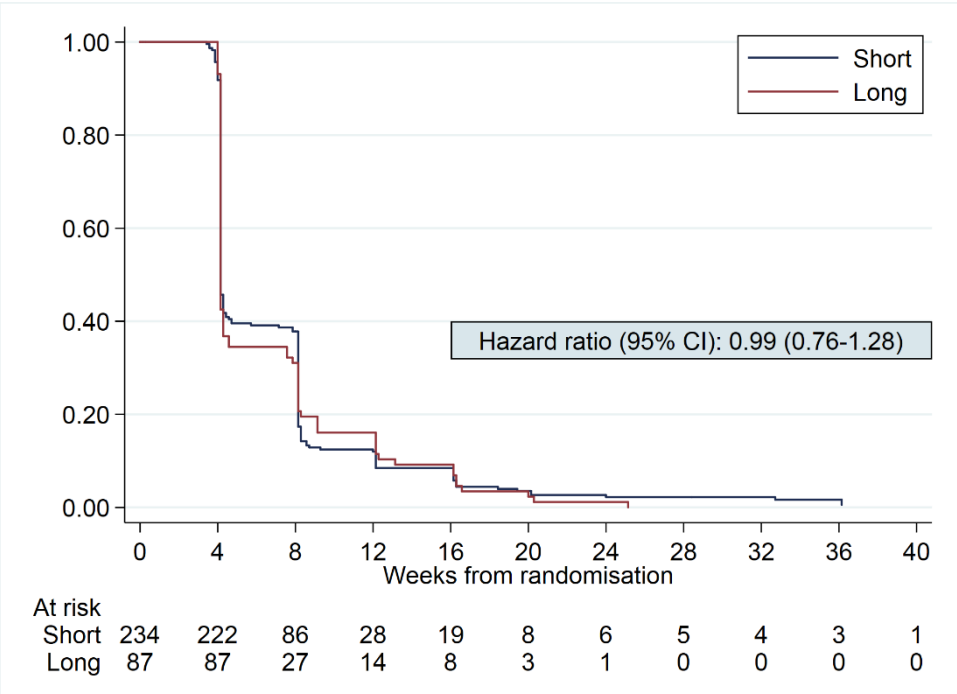


Figure S6. Kaplan-Meier plot of time to culture conversion in the mITT population.

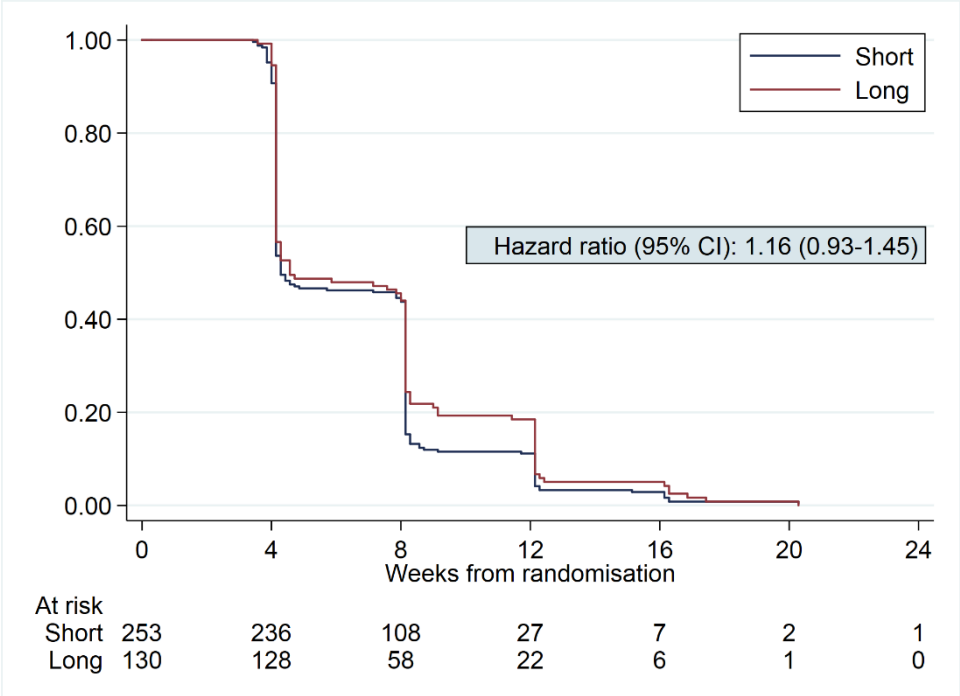


Figure S7. Kaplan-Meier plot of time to culture conversion in the PP population.

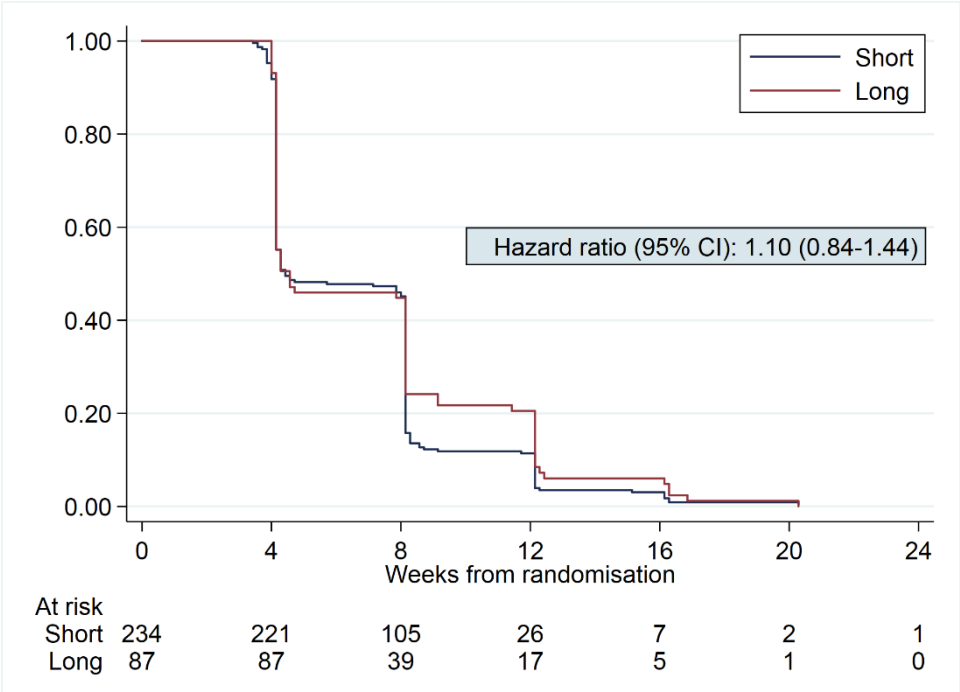
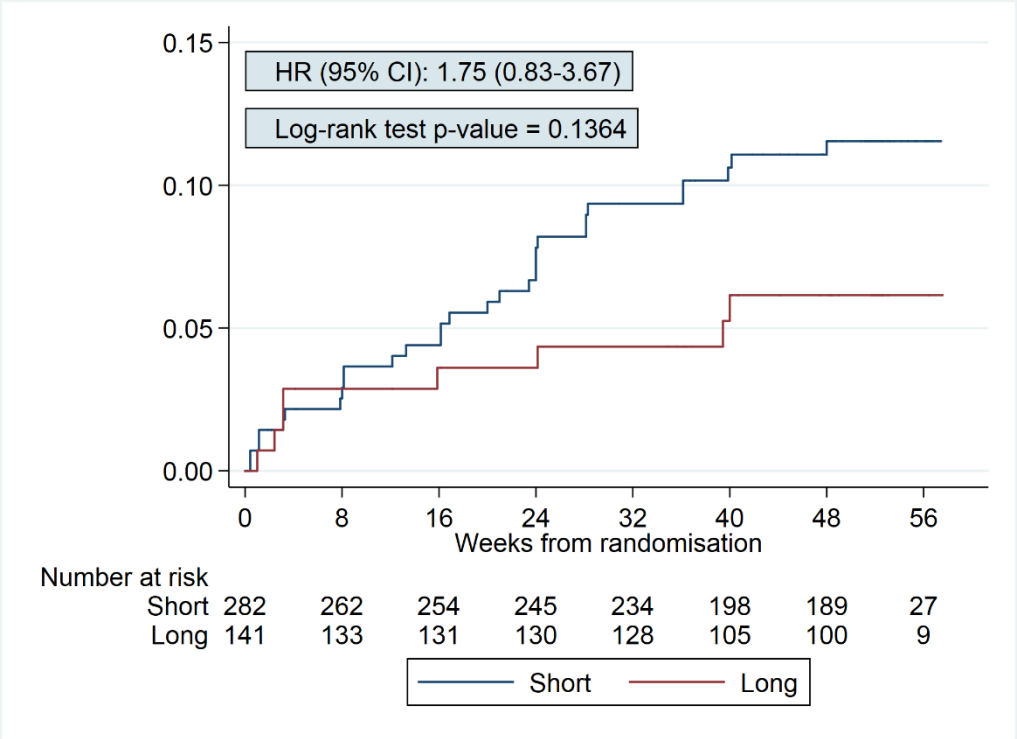


Figure S8. Kaplan-Meier plot of time to exceeding maximum in QT or QTcF to 500ms or above post baseline (safety analysis population).



Note: The maximum in QT or QTcF was used in this analysis.

Figure S9. Kaplan-Meier plot of time to ALT exceeding five times the upper limit of normal in the first 16 weeks of treatment (safety analysis population).

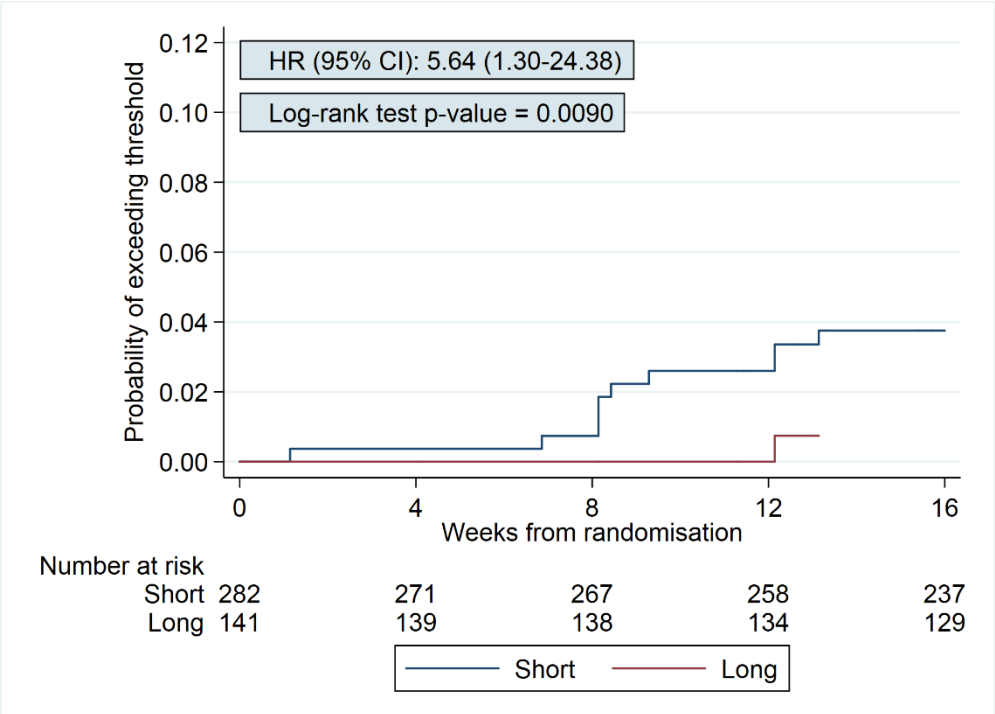


Figure S10. Flat, Sceptical and Expected priors for secondary Bayesian analysis.

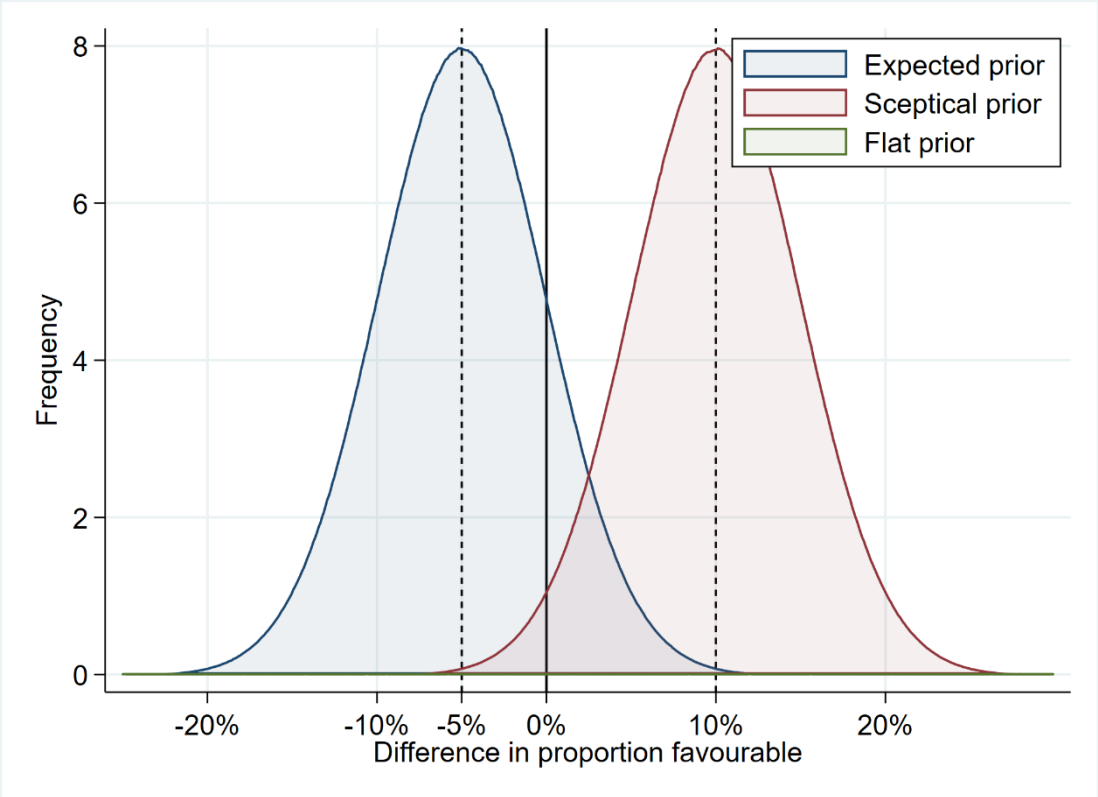
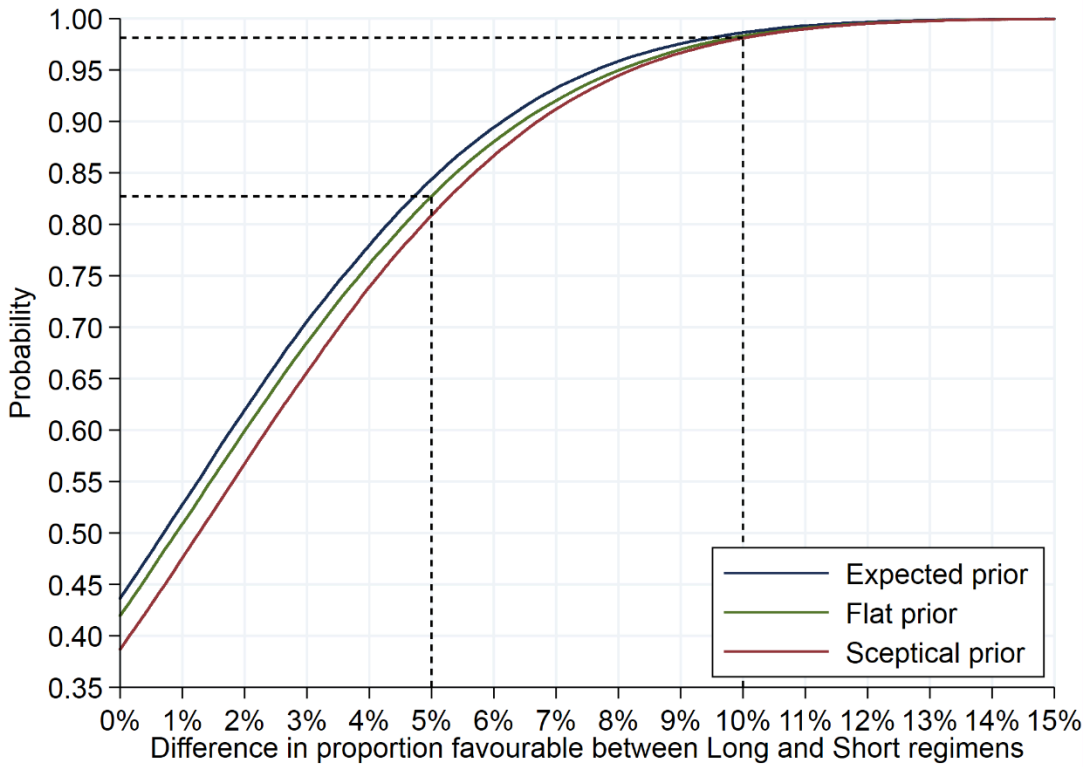


Figure S11. Results of Bayesian analysis of non-inferiority.



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