ISRCTN18148631 https://doi.org/10.1186/ISRCTN18148631

STREAM 2 - The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis

Submission date
26/01/2016

Registration date
10/02/2016

Last Edited
07/10/2024

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Tuberculosis (TB) is a common, infectious condition caused by a bacteria infection. It is generally spread by breathing in tiny droplets released into the air by an infected person coughing or sneezing. TB usually affects the lungs, but it can also affect other areas of the body such as the bones, brain and kidneys. Despite the availability and effectiveness of affordable six-month treatments for tuberculosis (TB), the worldwide control of this disease is currently being impacted by the emergence of multidrug resistant TB (MDR-TB). MDR-TB is where the powerful first-line drugs used to treat TB (at least isoniazid and rifampicin) are ineffective, leading to the spread of an infection that is much more difficult to treat. Currently the standard treatments for MDR-TB can last as long as 24 months with a success rate of no more than 50%. With an approximately 500,000 new cases every year there is an urgent need to develop shorter and more effective treatments. The aim of this study is to compare three different shorter drug regimens to the standard 18-month MDR-TB regimen, in order to find the most effective treatment.

Who can participate?
Adults who have multidrug resistant tuberculosis (TB).

What does the study involve?
The study involves four Regimens A-D. Those allocated to regimen A are given the standard MDR-TB regimen, which they take for 18 months. Those allocated to regimen B are given clofazimine, ethambutol, moxifloxacin or levofloxacin, and pyrazinamide given for 40 weeks, supplemented by isoniazid, kanamycin, and prothionamide in the first 16 weeks. Those allocated to regimen C begin a newly designed 40 week all-oral (by mouth) treatment programme which consists of the drugs bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks supplemented by isoniazid and prothionamide for the first 16 weeks. Those in

regimen D are given a newly designed 28-week regimen consisting of the drugs bedaquiline, clofazimine, levofloxacin, and pyrazinamide given for 28 weeks supplemented by isoniazid and kanamycin for the first 8 weeks.

Randomisation is currently mainly to Regimen B and C and in some sites to Regimen D. Participants are no longer randomised to Regimen A as countries are implementing the WHO 2016 short regimen or to Regimen D as the use of an injectable is seen as less attractive than a fully oral regimen for participants. However, participants already randomised to Regimens A and D will complete their course of treatment and continue in follow-up.

The effectiveness of regimen B and C are compared at 132 weeks using blood samples.

What are the possible benefits and risks of participating?
Participants benefit from receiving more information about their health from the results of the tests done and are able to talk to a study councilor about any concerns they may have. For patients that receive the shorter treatment regimes, they may also benefit from a quicker recovery. Risks of taking part involve the general risks of taking the study drugs, as well as the risk of pain and bruising when blood samples are taken.

Where is the study run from?
1. Vital Strategies (Formally The United States Agency for International Development, Sponsor) (USA)
2. Medical Research Council at University College London (UK)
3. Institute of Tropical Medicine (Belgium)

When is the study starting and how long is it expected to run for?
March 2016 to August 2022

Who is funding the study?
1. The United States Agency for International Development (USA)
2. Janssen Research and Development (USA)
3. Medical Research Council (UK)
4. Department of International Development (UK)

Who is the main contact?
Professor Andrew Nunn

Study website
https://www.mrcctu.ucl.ac.uk/studies/all-studies/s/stream-stage-2/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT02409290

Secondary identifying numbers
N/A

Study information

Scientific Title
The evaluation of a Standardised Treatment REgimen of Anti-tuberculosis drugs for patients with Multi-drug-resistant tuberculosis (MDR-TB): A multi-centre international parallel group randomised controlled trial

Acronym
STREAM 2

Study objectives
Current study hypothesis as of 18/02/2019:
Stage Two of the STREAM trial involves the investigation of an alternative regimen, a variation on Regimen B (the 9 month regimen evaluated in Stage 1 against the WHO recommended regimen), incorporating the newly available drug bedaquiline. This regimen, Regimen C, involves the removal of the injectable, kanamycin, which has known associated risks of ototoxicity and renal toxicity.

Study aim:
1. To assess whether Regimen C is non inferior to Regimen B
3Stage one of the study can be found via http://www.isrctn.com/ISRCTN78372190

Previous study hypothesis:
Stage Two of the STREAM trial involves the investigation of two alternative regimens, both variations on Regimen B (the 9 month regimen evaluated in Stage 1 against the WHO recommended regimen), incorporating the newly available drug bedaquiline. The first of these investigational regimens, Regimen C, involves the removal of the injectable, kanamycin, which has known associated risks of ototoxicity and renal toxicity. The second investigational regimen, Regimen D, investigates the possibility of treatment being further shortened to 28 weeks, with a shorter duration of the initial intensive phase containing kanamycin and isoniazid and the dropping of ethambutol, which is considered to be of limited efficacy, and prothionamide, which is commonly associated with severe gastric symptoms.

Study aims:
1. To assess the superiority of Regimen C over Regimen B; this is a US FDA requirement.
2. To assess whether Regimen C is not inferior to Regimen B
3. To assess whether Regimen D is non-inferior to Regimen B

Stage one of the study can be found via http://www.isrctn.com/ISRCTN78372190

Ethics approval required
Old ethics approval format

Ethics approval(s)
The International Union Against TB and Lung Disease's Ethics Advisory Group: 15/04/2015 ref: EAG number 97/14

Study design
Non-inferiority multi-centre international parallel-group open-label randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Multi-drug resistant pulmonary tuberculosis (MDR-TB)

Interventions
Current interventions as of 18/02/2019:
Patients consent to screening at their first visit at which stage they are assigned a unique study number. The patient is then evaluated for their eligibility according to the inclusion and exclusion criteria. If a patient is screened successfully and satisfies the criteria to participate in STREAM, the patient will then complete the randomisation consent and complete the Week 0 assessment prior to randomisation. Patients should be randomised no more than 4 weeks after screening consent.

Randomisation occurs using a web-based randomisation system at a ratio of 1:2:2:2 in favour of Regimen B, Regimen C, and Regimen D. Patients are then assessed at Week 1, Week 2, Week 3, Week 4, after which they will be seen 4-weekly until Week 52, after which they will be seen 8-weekly until Week 84, after which they will be seen 12-weekly until Week 132 post

randomisation.
In 2018, the study was modified and participants are no longer randomised to Regimen A and Regimen D. Randomisation to Regimen B and C is at a ratio of 1:1.

Regimen A - The locally-used World Health Organization (WHO) approved MDR-TB regimen, which should be given for a minimum of 18 months.

Regimen B - This is based on the regimen described by Van Deun 2010 consisting of clofazimine, ethambutol, moxifloxacin or levofloxacin, and pyrazinamide given for 40 weeks, supplemented by isoniazid, kanamycin, and prothionamide in the first 16 weeks).
Dose Schedule:
Kanamycin: 15 mg per kilogram body weight (maximum 1 g)
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Moxifloxacin: 400 mg (less than 33 kg), 600 mg (33 - 50 kg) or 800 mg (more than 50 kg)
Levofloxacin: 750 mg (less than 33 kg), 750 mg (33 - 50 kg) or 1000 mg (more than 50 kg)
Ethambutol: 800 mg (less than 33 kg), 800 mg (33 - 50 kg) or 1200 mg (more than 50kg)
Isoniazid: 300 mg (less than 33 kg), 400 mg (33 - 50 kg) or 600 mg (more than 50 kg)
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Prothionamide: 250 mg (less than 33 kg), 500 mg (33 - 50 kg) or 750 mg (more than 50 kg)

Regimen C - A 40-week all-oral regimen consisting of bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks supplemented by isoniazid and prothionamide for the first 16 weeks.
Dose schedule:
Bedaquiline 400 mg once daily for the first 14 days, then 200mg thrice weekly therefeafter
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Levofloxacin 750 mg (less than 33 kg), 750 mg (33 - 50 kg) or 1000 mg (more than 50 kg)
Ethambutol: 800 mg (less than 33 kg), 800 mg (33 - 50 kg) or 1200 mg (more than 50kg)
Isoniazid: 300 mg (less than 33 kg), 400 mg (33 - 50 kg) or 600 mg (more than 50 kg)
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Prothionamide: 250 mg (less than 33 kg), 500 mg (33 - 50 kg) or 750 mg (more than 50 kg)

Regimen D - A 28-week regimen consisting of bedaquiline, clofazimine, levofloxacin, and pyrazinamide given for 28 weeks supplemented by isoniazid and kanamycin for the first 8 weeks.
Dose schedule:
Bedaquiline 400 mg once daily for the first 14 days, then 200mg thrice weekly thereafter
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Levofloxacin 750 mg (less than 33 kg), 750 mg (33 - 50 kg) or 1000 mg (more than 50 kg)
Isoniazid: 400 mg (less than 33 kg), 500 mg (33 – less than 40 kg), 600 mg (40-50kg), 800mg (more than 50 kg – 60kg) or 900 mg (more than 60kg). Dose is taken once daily for first 14 days and thrice weekly thereafter.
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Kanamycin: 15 mg per kilogram body weight (maximum 1 g)

Previous interventions:
Patients consent to screening at their first visit at which stage they are assigned a unique study number. The patient is then evaluated for their eligibility according to the inclusion and exclusion criteria If a patient is screened successfully and satisfies the criteria to participate in STREAM, the patient will then complete the randomisation consent and complete the Week 0 assessment prior to randomisation. Patients should be randomised no more than 4 weeks after screening consent.

Randomisation occurs using a web-based randomisation system at a ratio of 1:2:2:2 in favour of Regimen B, Regimen C, and Regimen D. Patients are then assessed at Week 1, Week 2, Week 3, Week 4, after which they will be seen 4-weekly until Week 52, after which they will be seen 8-weekly until Week 84, after which they will be seen 12-weekly until Week 132 post-randomisation.

Regimen A - The locally-used World Health Organization (WHO) approved MDR-TB regimen, which should be given for a minimum of 18 months.

Regimen B - This is based on the regimen described by Van Deun 2010 consisting of clofazimine, ethambutol, moxifloxacin, and pyrazinamide given for 40 weeks, supplemented by isoniazid, kanamycin, and prothionamide in the first 16 weeks).
Dose Schedule:
Kanamycin: 15 mg per kilogram body weight (maximum 1 g)
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Moxifloxacin: 400 mg (less than 33 kg), 600 mg (33 - 50 kg) or 800 mg (more than 50 kg)
Ethambutol: 800 mg (less than 33 kg), 800 mg (33 - 50 kg) or 1200 mg (more than 50kg)
Isoniazid: 300 mg (less than 33 kg), 400 mg (33 - 50 kg) or 600 mg (more than 50 kg)
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Prothionamide: 250 mg (less than 33 kg), 500 mg (33 - 50 kg) or 750 mg (more than 50 kg)

Regimen C - A 40-week all-oral regimen consisting of bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks supplemented by isoniazid and prothionamide for the first 16 weeks.
Dose schedule:
Bedaquiline 400 mg once daily for the first 14 days, then 200mg thrice weekly therefeafter
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Levofloxacin 750 mg (less than 33 kg), 750 mg (33 - 50 kg) or 1000 mg (more than 50 kg)
Ethambutol: 800 mg (less than 33 kg), 800 mg (33 - 50 kg) or 1200 mg (more than 50kg)
Isoniazid: 300 mg (less than 33 kg), 400 mg (33 - 50 kg) or 600 mg (more than 50 kg)
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Prothionamide: 250 mg (less than 33 kg), 500 mg (33 - 50 kg) or 750 mg (more than 50 kg)

Regimen D - A 28-week regimen consisting of bedaquiline, clofazimine, levofloxacin, and pyrazinamide given for 28 weeks supplemented by isoniazid and kanamycin for the first 8 weeks.
Dose schedule:
Bedaquiline 400 mg once daily for the first 14 days, then 200mg thrice weekly thereafter
Clofazimine: 50 mg (less than 33 kg), 100 mg (33 - 50 kg) or 100 mg (more than 50 kg)
Levofloxacin 750 mg (less than 33 kg), 750 mg (33 - 50 kg) or 1000 mg (more than 50 kg)
Isoniazid: 400 mg (less than 33 kg), 500 mg (33 – less than 40 kg), 600 mg (40-50kg), 800mg (more than 50 kg – 60kg) or 900 mg (more than 60kg). Dose is taken once daily for first 14 days and thrice weekly there after.
Pyrazinamide: 1000 mg (less than 33 kg), 1500 mg (33 - 50 kg) or 2000 mg (more than 50 kg)
Kanamycin: 15 mg per kilogram body weight (maximum 1 g)

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)

Clofazimine, ethambutol, moxifloxacin, levofloxacin, pyrazinamide, isoniazid, kanamycin, prothionamide, bedaquiline

Primary outcome measure

Current primary outcome measures as of 18/02/2019:
The primary efficacy outcome is the proportion of patients with a favourable outcome at Week 76 defined as two negative cultures taken on separate visits, the latest of which being no more than six weeks earlier or later than week 76, provided the outcome has not previously been classified as unfavourable.

Unfavourable efficacy outcomes:
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
3. They are restarted on any MDR-TB treatment after the scheduled end of treatment, but before 76 weeks after randomisation.
4. They change their allocated study treatment for any reason other than the replacement of a single drug
5. Bedaquiline is started where the allocated regimen did not originally contain that drug (Regimen A or B).
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 for the Stage 2 comparison
10. The failure or recurrence specimen at or before the Week 76 window was a different strain to their randomisation specimen, i.e. re-infection

Previous primary outcome measures:
The primary efficacy outcome is the proportion of patients with a favourable outcome at Week 76 defined as two negative cultures taken on separate visits, the latest of which being no more than six weeks earlier or later than week 76, provided the outcome has not previously been classified as unfavourable.

Secondary outcome measures

Current secondary outcome measures as of 18/02/2019:
1.Time to sputum culture conversion is recorded during 132 weeks of follow-up
2. Time to sputum smear conversion is recorded during 132 weeks of follow-up
3. Efficacy status at end of follow-up, based on the same definition as the primary endpoint, but at week 132
5. All-cause mortality is recorded during 132 weeks of follow-up
6. Proportion of patients experiencing a grade 3 or greater adverse event, as defined by the DAIDS criteria is recorded during 132 weeks of follow-up
7. Change of regimen for adverse drug reactions are recorded throughout the study period
8. Number of adverse events occurring on treatment and during 132 weeks of follow-up
9. Pharmacokinetic outcomes are measured at selected visits using a validated and sensitive liquid chromatography-mass spectrometry method
10. Adherence to treatment during the treatment period is calculated from daily DOT (directly observed treatment) treatment cards

Previous secondary outcome measures:
1. Time to sputum culture conversion is recorded during 132 weeks of follow-up
2. Time to sputum smear conversion is recorded during 132 weeks of follow-up
3. Efficacy status at end of follow-up, based on the same definition as the primary endpoint, but at week 132
4. Time to unfavourable efficacy outcome* is recorded during 132 weeks of follow-up
5. The proportion of participants in each category who meet the WHO classification of outcome as applicable at the time of analysis is determined at Week 76 and Week 132
6. Time to cessation of clinical symptoms based on PI assessment is recorded during 132 weeks of follow-up
7. All-cause mortality is recorded during 132 weeks of follow-up
8. Proportion of patients experiencing a grade 3 or greater adverse event, as defined by the DAIDS criteria is recorded during 132 weeks of follow-up
9. Change of regimen for adverse drug reactions are recorded throughout the study period
10. Number of adverse events occurring on treatment and during 132 weeks of follow-up
11. Pharmacokinetic outcomes are measured at selected visits using a validated and sensitive liquid chromatography-mass spectrometry method
12. Adherence to treatment during the treatment period is calculated from daily DOT (directly observed treatment) treatment cards

*Unfavourable efficacy outcomes:
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
3. They are restarted on any MDR-TB treatment after the scheduled end of treatment, but before 76 weeks after randomisation.
4. They change their allocated study treatment for any reason other than the replacement of a single drug
5. Bedaquiline is started where the allocated regimen did not originally contain that drug (Regimen A or B).
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 for the Stage 2 comparison
10. The failure or recurrence specimen at or before the Week 76 window was a different strain to their randomisation specimen, i.e. re-infection

Overall study start date
01/03/2016

Completion date
09/08/2022

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 18/02/2019:
1. Is willing and able to give informed consent to participate in the trial treatment and follow-up

(signed or witnessed consent if the patient is illiterate). If the patient is below the age of consent (according to local regulations), the parent/caregiver should be able and willing to give consent, and the patient be informed about the study and asked to give positive assent, if feasible
2. Is aged 15 years or older
3. Has a positive AFB sputum smear result at screening (at least scanty), or a positive GeneXpert result (with a cycle threshold (Ct) value of 25 or lower) within four weeks prior to screening 4. Has evidence of resistance to rifampicin either by line probe assay (Hain Genotype), GeneXpert or culture-based drug susceptibility testing (DST), from a test performed at screening or from a test performed within the four weeks prior to screening
5. Is willing to have an HIV test and, if positive, is willing to be treated with ART in accordance with the national policies but excluding ART contraindicated for use with bedaquiline
6. Is willing to use effective contraception (men who have not had a vasectomy must agree to use condoms; pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilised must agree to use two methods of contraception, for example a hormonal method and a barrier method)
7. Resides in the area and expected to remain for the duration of the study
8. Has had a chest X-ray that is compatible with a diagnosis of pulmonary TB (if such a chest X-ray taken within 4 weeks of randomisation is available, a repeat X-ray is not required)
9. Has normal K+, Mg2+ and corrected Ca2+ at screening.

Previous participant inclusion criteria as of 29/10/2018:
1. Is willing and able to give informed consent to participate in the trial treatment and follow-up (signed or witnessed consent if the patient is illiterate). If the patient is below the age of consent (according to local regulations), the parent/caregiver should be able and willing to give consent, and the patient be informed about the study and asked to give positive assent, if feasible
2. Is aged 15 years or older
3. Has a positive AFB sputum smear result at screening (at least scanty), unless they are HIV positive in which case a positive GeneXpert result within four weeks prior to screening is sufficient
4. Has evidence of resistance to rifampicin either by line probe assay (Hain Genotype21), GeneXpert or culture-based drug susceptibility testing (DST), from a test performed at screening or from a test performed within the four weeks prior to screening
5. Is willing to have an HIV test and, if positive, is willing to be treated with ART in accordance with the national policies but excluding ART contraindicated for use with bedaquiline
6. Is willing to use effective contraception (men who have not had a vasectomy must agree to use condoms; pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilised must agree to use two methods of contraception, for example a hormonal method and a barrier method)
7. Resides in the area and expected to remain for the duration of the study
8. Has had a chest X-ray at that is compatible with a diagnosis of pulmonary TB (if such a chest X-ray taken within 4 weeks of randomisation is available, a repeat X-ray is not required)
9. Has normal K+, Mg2+ and corrected Ca2+ at screening.

Previous participant inclusion criteria:
1. Is willing and able to give informed consent to participate in the trial treatment and follow-up (signed or witnessed consent if the patient is illiterate)
2. Is aged 18 years or older
3. Has a positive AFB sputum smear result at screening (at least scanty), unless they are HIV positive in which case a positive GeneXpert result within four weeks prior to screening is sufficient

4. Has evidence of resistance to rifampicin either by line probe assay (Hain Genotype21), GeneXpert or culture-based drug susceptibility testing (DST), from a test performed at screening or from a test performed within the four weeks prior to screening
5. Is willing to have an HIV test and, if positive, is willing to be treated with ART in accordance with the national policies but excluding ART contraindicated for use with bedaquiline
6. Is willing to use effective contraception (men who have not had a vasectomy must agree to use condoms; pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilised must agree to use two methods of contraception, for example a hormonal method and a barrier method)
7. Resides in the area and expected to remain for the duration of the study
8. Has had a chest X-ray at that is compatible with a diagnosis of pulmonary TB (if such a chest X-ray taken within 4 weeks of randomisation is available, a repeat X-ray is not required)
9. Has normal K+, Mg2+ and corrected Ca2+ at screening.

Participant type(s)
Patient

Age group
Mixed

Lower age limit
15 Years

Sex
Both

Target number of participants
At least 530 participants

Total final enrolment
588

Key exclusion criteria
Participant exclusion criteria as of 29/10/2018:
1. Is infected with a strain of M. tuberculosis resistant to a second-line injectables by line probe assay (Hain Genotype) from a test performed at screening or from a test performed within the four weeks prior to screening
2. Is infected with a strain of M. tuberculosis resistant to a fluoroquinolone by line probeassay (Hain Genotype) from a test performed at screening or from a test performed within the four weeks prior to screening
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 or unwilling to comply with the treatment, assessment, or follow-up schedule
7. Is unable to take oral medication
8. Has AST or ALT more than 3 times the upper limit of normal for Stage 2
9. Has any condition (social or medical) which in the opinion of the investigator would make study participation unsafe
10. In the investigator’s opinion the patient is likely to be eligible for treatment with bedaquiline according to local guidelines due a pre-existing medical condition such as hearing loss or renal impairment

11. Is taking any medications contraindicated with the medicines in any trial regimen
12. Has a known allergy to any fluoroquinolone antibiotic
13. Is currently taking part in another trial of a medicinal product
14. Has a QT or QTcF interval at screening or immediately prior to randomisation of more than or equal to 450 ms for Stage 2.
15. Has experienced one or more of the following risk factors for QT prolongation:
15.1. confirmed prolongation of the QT or QTcF more than or equal to 450 ms in the screening ECG (retesting to reassess eligibility will be allowed once using an unscheduled visit during the screening phase)
15.2. Pathological Q-waves (defined as Q-wave more than 40 ms or depth more than 0.4-0.5 mV)
15.3. Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome)
15.4. Electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block
15.5. Evidence of second or third degree heart block
15.6. Intraventricular conduction delay with QRS duration more than 120 ms
15.7. Bradycardia as defined by sinus rate less than 50 bpm
15.8. Personal or family history of Long QT Syndrome
15.9. Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia
15.10. Syncope (i.e. cardiac syncope not including syncope due to vasovagal or epileptic causes)
15.11. Risk factors for Torsades de Pointes (e.g., heart failure, hypokalaemia, or hypomagnesemia)
16. Has received treatment for MDR-TB in the 12 weeks prior to screening
17. Has a history of cirrhosis and classified as Child's B or C at screening or a bilirubin more than 1.5 times upper limit of normal.
18. Has an estimated creatinine clearance (CrCl) less than 30 mL/min based on the Cockcraft-Gault equation
19. Is HIV positive and has a CD4 count less than 50 cells/mm3
20. Has pancreatic amylase elevation more than two times above the upper limit of normal
21. Has a history of alcohol and/or drug abuse
22. Has had previous treatment with bedaquiline
23. Has taken rifampicin in the seven days prior to randomisation
24. There has been a delay of more than four weeks between the screening consent and randomisation
25. Is an employee or family member of the investigator or study site staff with direct involvement in the proposed study

Previous participant exclusion criteria:
1. Is infected with a strain of M. tuberculosis resistant to a second-line injectables by line probe assay (Hain Genotype)
2. Is infected with a strain of M. tuberculosis resistant to a fluoroquinolone by line probeassay (Hain Genotype)
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 or unwilling to comply with the treatment, assessment, or follow-up schedule
7. Is unable to take oral medication
8. Has AST or ALT more than 3 times the upper limit of normal for Stage 2
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 any trial 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 QT or QTcF interval at screening or immediately prior to randomisation of more than or equal to 450 ms for Stage 2.
14. Has experienced one or more of the following risk factors for QT prolongation:
14.1. confirmed prolongation of the QT or QTcF more than or equal to 450 ms in the screening ECG (retesting to reassess eligibility will be allowed once using an unscheduled visit during the screening phase)
14.2. Pathological Q-waves (defined as Q-wave more than 40 ms or depth more than 0.4-0.5 mV)
14.3. Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome)
14.4. Electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block
14.5. Evidence of second or third degree heart block
14.6. Intraventricular conduction delay with QRS duration more than 120 ms
14.7. Bradycardia as defined by sinus rate less than 50 bpm
14.8. Personal or family history of Long QT Syndrome
14.9. Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia
14.10. Syncope (i.e. cardiac syncope not including syncope due to vasovagal or epileptic causes)
14.11. Risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, or hypomagnesemia)
15. Has received treatment for MDR-TB in the 12 weeks prior to screening
16. Has a history of cirrhosis and classified as Child's B or C at screening or a bilirubin more than 1.5 times upper limit of normal.
17. Has an estimated creatinine clearance (CrCl) less than 30 mL/min based on the Cockcraft-Gault equation
18. Is HIV positive and has a CD4 count less than 50 cells/mm3
19. Has amylase elevation more than two times above the upper limit of normal
20. Has a history of alcohol and/or drug abuse
21. Has had previous treatment with bedaquiline
22. Has taken rifampicin in the seven days prior to randomisation
23. There has been a delay of more than four weeks between the screening consent and randomisation
24. Is an employee or family member of the investigator or study site staff with direct involvement in the proposed study

Date of first enrolment
01/03/2016

Date of final enrolment
28/01/2020

Locations

Countries of recruitment
Ethiopia

Georgia

India

Moldova

Mongolia

South Africa

Uganda

Study participating centre
National Center of Infectious Diseases
Ulaanbaatar
Mongolia
13335

Study participating centre
St. Peter's TB Specialized Hospital
Addis Ababa
Ethiopia
N/A

Study participating centre
Armauer Hansen Research Institute (AHRI)
Addis Ababa
Ethiopia
N/A

Study participating centre
King Dinuzulu Hospital Complex
Durban
South Africa
N/A

Study participating centre
Doris Goodwin Hospital
Pietermaritzburg
South Africa
N/A

Study participating centre
Institute of Phthisiopneumology "Chiril Draganiuc"
Chisinau

Moldova
-

Study participating centre
Makerere University
Kampala
Uganda
-

Study participating centre
The National Center for TB and Lung Diseases
Tbilisi
Georgia
-

Study participating centre
The National Institute for Research in Tuberculosis
Chennai
India
-

Study participating centre
BJ Medical College Civil Hospital
Ahmedabad
India
-

Study participating centre
Empilweni TB Hospital
Port Elizabeth
South Africa
-

Study participating centre
Helen Joseph Hospital
Johannesburg
South Africa
-

Study participating centre
Rajan Babu TB Institute of Pulmonary Medicine and Tuberculosis
Kingsway Camp GTB Nagar
Delhi
India
110007

Sponsor information

Organisation
Vital Strategies (Formally International Union Against Tuberculosis and Lung Disease)

Sponsor details
61 Broadway
Suite 1720
New York
United States of America
10006

Sponsor type
Research organisation

Website
http://www.treattb.org/overview

ROR
https://ror.org/05mdyn772

Funder(s)

Funder type
Research organisation

Funder Name
United States Agency for International Development

Alternative Name(s)
U.S. Agency for International Development, Agency for International Development, USAID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Department for International Development, UK Government

Alternative Name(s)
Department for International Development, UK, DFID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Janssen Research and Development

Alternative Name(s)
Janssen R&D, Janssen Research & Development, Janssen Research & Development, LLC, Janssen Research & Development LLC, Janssen Pharmaceutical Companies of Johnson & Johnson, Research & Development at Janssen, JRD, J&J PRD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
1. Planned publication of results in a peer reviewed journal
2. Sharing of study results with participants through mechanisms and materials reviewed and approved by The Union's Ethics Advisory Group and other relevant stakeholders

Intention to publish date
31/12/2023

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from I.D. Rusen, STREAM@vitalstrategies.org

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	Economic evaluation protocol for bedaquiline-containing regimen	21/12/2020	08/03/2021	Yes	No
Other publications	Design changes	07/06/2022	08/06/2022	Yes	No
Statistical Analysis Plan	version 5.0	21/04/2022	01/09/2022	No	No
Results article		07/11/2022	14/11/2022	Yes	No
Results article	Economic evaluation of bedaquiline-containing regimens	21/12/2022	28/12/2022	Yes	No
Results article	Long-term outcomes	01/10/2024	07/10/2024	Yes	No