

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

<b>Submission date</b> 26/01/2016	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 10/02/2016	<b>Overall study status</b> Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 07/10/2024	<b>Condition category</b> Infections and Infestations	<input type="checkbox"/> 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

### **Contact name**

Prof Andrew Nunn

### **Contact details**

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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 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)

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 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)

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<sup>+</sup>, Mg<sup>2+</sup> and corrected Ca<sup>2+</sup> 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 Genotype<sup>21</sup>), 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<sup>+</sup>, Mg<sup>2+</sup> and corrected Ca<sup>2+</sup> 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<sup>+</sup>, Mg<sup>2+</sup> and corrected Ca<sup>2+</sup> 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 probe assay (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 hypomagnesaemia)
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 Cockcroft-Gault equation
19. Is HIV positive and has a CD4 count less than 50 cells/mm<sup>3</sup>
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 probe assay (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 Cockcroft-Gault equation
18. Is HIV positive and has a CD4 count less than 50 cells/mm<sup>3</sup>
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?
<a href="#">Protocol article</a>	Economic evaluation protocol for bedaquiline-containing regimen	21/12/2020	08/03/2021	Yes	No
<a href="#">Other publications</a>	Design changes	07/06/2022	08/06/2022	Yes	No
<a href="#">Statistical Analysis Plan</a>	version 5.0	21/04/2022	01/09/2022	No	No
<a href="#">Results article</a>		07/11/2022	14/11/2022	Yes	No
<a href="#">Results article</a>	Economic evaluation of bedaquiline-containing regimens	21/12/2022	28/12/2022	Yes	No
<a href="#">Results article</a>	Long-term outcomes	01/10/2024	07/10/2024	Yes	No