STREAM

The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB

ISRCTN 78372190 (Stage 1)

ISRCTN 18148631 (Stage 2)

PROTOCOL

VERSION 11.0

15 December 2020 **(Based on MRC CTU template protocol version 3.15)**

Authorised by:

Name:	Prof. Andrew Nunn
Role:	Co-Chief Investigator
Signature:	Date:

Name:	Prof. Sarah Meredith
Role:	Co-Chief Investigator
Signature:	Date:

SIGNATURE PAGE

Principal Investigator Signature:

The signature below confirms agreement by the individual at the clinical site responsible for signing the clinical trial agreement, that this is the trial protocol, STREAM (Version 11.0) dated 15 Dec 2020. The trial will be conducted in accordance with this protocol, with the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP), and the applicable regulatory requirements.

I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Any amendments to this protocol that have a direct influence on the participants in the trial will be approved by the relevant ethics committees, regulatory authorities and the sponsor before implementation.

Principal investigator's name: _____

Signature: _____

Date: _____

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GENERAL INFORMATION

This document describes the STREAM trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to site principal investigators in the trial by MRC Clinical Trials Unit at UCL (MRC CTU), London. Clinical problems relating to this trial should be referred to the co-Chief Investigator(s).

Compliance:

The trial will be conducted in accordance with this protocol, with the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP), and the applicable regulatory requirements.

Sponsor:

Vital Strategies, f/k/a The International Union Against Tuberculosis and Lung Disease, Inc.
100 Broadway, Fourth floor
New York, NY
10005 USA
Tel (main): +1 212 500 5720
Fax: +1 212 480 6040
Email: STREAM@vitalstrategies.org

Funders:

The United States Agency for International Development (USAID)

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Janssen Research & Development, LLC

Main Contacts:

Co-Chief Investigator
Prof. Andrew Nunn
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
90 High Holborn, 2nd Floor
London,WC1V 6LJ

Tel: +44 (0)20 7670 4703

Email: a.nunn@ucl.ac.uk

Co-Chief Investigator
Prof. Sarah Meredith
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
90 High Holborn, 2nd Floor
London,WC1V 6LJ

Tel: +44 (0)20 7670 4787

Email: s.meredith@ucl.ac.uk

Trial coordination

MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
90 High Holborn, 2nd Floor
London,WC1V 6LJ

Tel: +44 (0)20 7670 4738
Email: mrcctu.trial-stream@ucl.ac.uk

Reference laboratory

Institute of Tropical Medicine,
Nationalestraat 155,
B-2000 Antwerp, Belgium
Tel: +32 3 2476548
Fax: +32 3 2476333

Trial Statistician

Dr. Ruth Goodall
MRC Clinical Trials Unit at UCL
Institute of Clinical Trials and Methodology
90 High Holborn, 2nd Floor
London,WC1V 6LJ

Tel: +44 (0)20 7670 4728

Email: r.goodall@ucl.ac.uk

SAE/NE NOTIFICATION

Within one working day of becoming aware of an SAE/NE, please email a completed SAE/NE form to the MRC Clinical Trials Unit on:

Email: mrcctu.streamdata@ucl.ac.uk

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND GLOSSARY

AE	Adverse Event
AFB	Acid Fast Bacilli
AR	Adverse Reaction
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
BDQ	Bedaquiline
ICF	Informed Consent Form
CI	Chief Investigator
CFZ	Clofazimine
CRF	Case Report Form
CTA	Clinical Trials Authorisation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DCF	Data Clarification Form
DOT	Directly Observed Treatment
DST	Drug Susceptibility Test
ECG	Electrocardiogram
EMA	European Medicines Agency
EMB	Ethambutol
EQA	External Quality Assurance
FDA	Fluorescein diacetate staining
US FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLC	Green Light Committee
HE	Health Economics
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
ITM	Institute of Tropical Medicine
ITT	Intention To Treat
IUATLD	International Union Against Tuberculosis & Lung Disease
KM	Kanamycin
INH	Isoniazid
LFX	Levofloxacin
LPA	Line Probe Assay
LQAS	Lot Quality Assurance Sampling
M2	Metabolite 2
MDR	Multi-Drug Resistant
MFX	Moxifloxacin
Genotype MTBDRPlus	Rapid test for *M. tuberculosis* Complex and its resistance to Rifampicin and/or Isoniazid
Genotype MTBDR*sl*	Rapid test for *M. tuberculosis* Complex and its resistance to fluoroquinolones and/or second-line injectables/cyclic peptides and/or ethambutol
MIC	Minimal Inhibitory Concentration

MIRU-VNTR	Mycobacterial Interspersed Repetitive Units–Variable Number of Tandem Repeats
MRC CTU	Medical Research Council Clinical Trials Unit
NE	Notable Event
NTP	National Tuberculosis Programme
PK	Pharmacokinetics
PI	Principal Investigator
PIS	Patient Information Sheet
PTO	Prothionamide
PZA	Pyrazinamide
QA	Quality Assurance
QT Interval	A measure of time between the start of the Q wave and the end of the T wave in the ECG complex
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia correction
REC	Research Ethics Committee
RMP	Rifampicin
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedures
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SSG	Statistical Support Group
STREAM	The Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
The Union	International Union Against Tuberculosis & Lung Disease
TM	Trial Manager
TMG	Trial Management Group
TMT	Trial Management Team
TREAT TB	Technology, Research, Education, and Technical Assistance for Tuberculosis
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ULN	Upper limit of normal
USAID	United States Agency For International Development
WHO	World Health Organisation
XDR	Extensively Drug Resistant
ZN	Ziehl-Neelsen

Note. In this protocol time (in weeks) refers to the time from randomisation, e.g. Week 76 refers to 76 weeks from randomisation.

1 SUMMARY

1.1 Abstract and summary of trial design

1.1.1 Type of design

The STREAM study is an international, multi-centre, parallel-group, open-label, randomised, controlled trial.

1.1.2 Disease/patients studied

Patients with multi-drug resistance tuberculosis (MDR-TB) including patients with rifampicin-resistant and isoniazid-sensitive TB.

1.1.3 Trial interventions

Treatments that are evaluated within the STREAM trial include:

Regimen A

The locally-used MDR-TB regimen in accordance with 2011 WHO MDR-TB treatment guidelines.[1]

Regimen B

Regimen B is based on the regimen described by Van Deun 2010[2]. At the start of STREAM this consisted of clofazimine, ethambutol, moxifloxacin, and pyrazinamide given for 40 weeks, supplemented by isoniazid, kanamycin, and prothionamide in the first 16 weeks (intensive phase); this combination is referred to as Regimen B_{mox}. With Version 8.0 of the protocol Regimen B is modified by replacement of moxifloxacin with levofloxacin (referred to as Regimen B_{lev}). Regimen B without specification of which fluoroquinolone is in the regimen refers to either (B_{mox} or B_{lev}). With Version 10.0 of the protocol, Regimen B is further modified to replace kanamycin with amikacin in sites where:

- the national TB program has replaced kanamycin with amikacin in line with revised WHO guidance[14] and
- amikacin is available for the trial.

Kanamycin will continue to be used until the transition takes place within each country programme.

Regimen C

Regimen C is 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 (intensive phase).

Regimen D

Regimen D is 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 (intensive phase).

1.1.4 Trial Stages

The STREAM trial consists of 2 stages.

Stage 1

Stage 1 of the trial involves a comparison between two treatment arms: Regimen A and Regimen B (as described in section 1.1.3). During this stage Regimen A acts as the control arm to the investigational treatment arm, Regimen B.

Stage 2

Stage 2 of the trial involves the addition of two further treatment arms: Regimen C and Regimen D. During this stage Regimen B acts as the control arm for the primary comparison with the new investigational treatment arm, Regimen C and for secondary comparisons with Regimen D. With Version 8.0 of the protocol randomisation to Regimens A and D will end and patients will be randomised to Regimen B or Regimen C in a ratio 1:1.

The 2016 WHO MDR-TB treatment guidelines[3], including the short course regimen, have already been implemented in some participating countries and most of the remaining countries have plans to start during the course of 2018. Since patients eligible for the trial would be treated with a short regimen in routine practice outside the trial, continued randomisation to Regimen A (the long WHO regimen as recommended by the 2011 WHO MDR-TB guidelines) will not be feasible and therefore will be dropped from the randomisation options.

With version 8.0 of the protocol patients will no longer be randomised to Regimen D and comparisons involving Regimen D are no longer primary objectives. The rationale for this is two-fold. Firstly, there have been many important developments since the design of Stage 2 and fully oral 6-month regimens are being evaluated in ongoing Phase 3 trials. The elimination of the injectable from MDR-TB regimens, rather than just reducing the duration, has become a priority to clinicians and patients and as such, Regimen D is a less attractive treatment option and a less valuable research question. Even if Regimen D could be shown to be safe with non-inferior efficacy in STREAM, it is unlikely that it would ever be adopted as a treatment for MDR-TB. Secondly, enrolment to Stage 2 has been slower than expected and the continuation of recruitment to Regimen D will hamper the ability to make the primary comparison of Regimens B and C.

Patients already randomised to Regimens A and D will complete their course of treatment and continue in follow-up according to the protocol.

The start of Stage 2

Figure 1 presents an overview of the recruitment stages in the STREAM trial. However, sites may begin Stage 2 at different times, depending upon gaining country-specific approval. Additionally, some sites may only be participating in Stage 1 and others only in Stage 2.

Figure 1: Trial recruitment stages

1.1.5 Trial objectives

Primary trial objectives of Stage 1

The primary objectives of Stage 1 of the STREAM trial are:

1. To assess whether the proportion of participants with a favourable efficacy outcome at Week 132 on Regimen B is non-inferior to that on Regimen A (WHO 2011 long MDR-TB regimen)
2. To compare the proportion of participants who experience grade 3 or greater adverse events, during treatment or follow-up, on Regimen B as compared to Regimen A.

The secondary objectives of Stage 1 of the STREAM trial are listed in section 3.1.2.

Primary trial objective of Stage 2

The primary objective of Stage 2 of the STREAM trial is:
To assess whether the proportion of participants with a favourable efficacy outcome at Week 76 on Regimen C is non- inferior to that on Regimen B.

Secondary objectives, including safety objectives, of Stage 2 of the STREAM trial are listed in section 3.2.2.

1.1.6 Duration of follow-up

All patients in Stage 1 of the study will be followed up to Week 132. The primary analysis will be based on the data accrued to Week 132.

All patients in Stage 2 of the study will also be followed up to Week 132, 56 weeks beyond the primary analysis point at Week 76. The main purpose of this extended follow-up is to monitor safety outcomes, particularly deaths. Recruitment to Stage 2 was slower than initially expected, as several sites closed to recruitment early due to their NTP adopting a fully oral regimen in line with changing WHO Guidelines. Given the urgent need for evidence to contribute to global guidelines on all-oral treatment regimens, with Version 11 of the protocol the end of follow-up for efficacy has been brought forward, although follow-up for safety is unchanged; follow-up for efficacy will end when the last patient recruited is projected to have reached Week 96. This will allow microbiology results to be

complete by the end of the trial, facilitating rapid analysis and reporting of Stage 2 results. The impact of shortening the follow up period for efficacy is minimal, and outweighed by the benefits of earlier availability of long-term trial results. The majority of patients (approximately 75% on Regimens B and C) will still have efficacy outcomes at Week 132, but for a proportion of patients (those randomised towards the end of the recruitment phase) efficacy follow-up will be censored between 96 and 132 weeks. The reduction in the total person-years of follow-up for the efficacy analysis is small, only 3% in Regimens B & C.

In summary, in Stage 2 the primary analysis will be based on the data accrued to Week 76; the data accrued to the date when the last patient is projected to have reached Week 96 will be used for the secondary long-term efficacy analysis and all data to the end of trial at Week 132 will be used for the long-term safety analyses.

1.1.7 Primary outcome measures

Stage 1
The primary efficacy outcome of the Stage 1 comparison is status at the end of follow-up i.e. the proportion of patients with a favourable outcome at Week 132 (as defined in section 11).

The primary safety outcome is the proportion of patients experiencing a grade 3 or greater adverse event during treatment or follow-up.

Stage 2
The primary efficacy outcome of the Stage 2 comparison is status at Week 76 i.e. the proportion of patients with a favourable outcome at Week 76 (as defined in section 11).

1.1.8 Sample Size

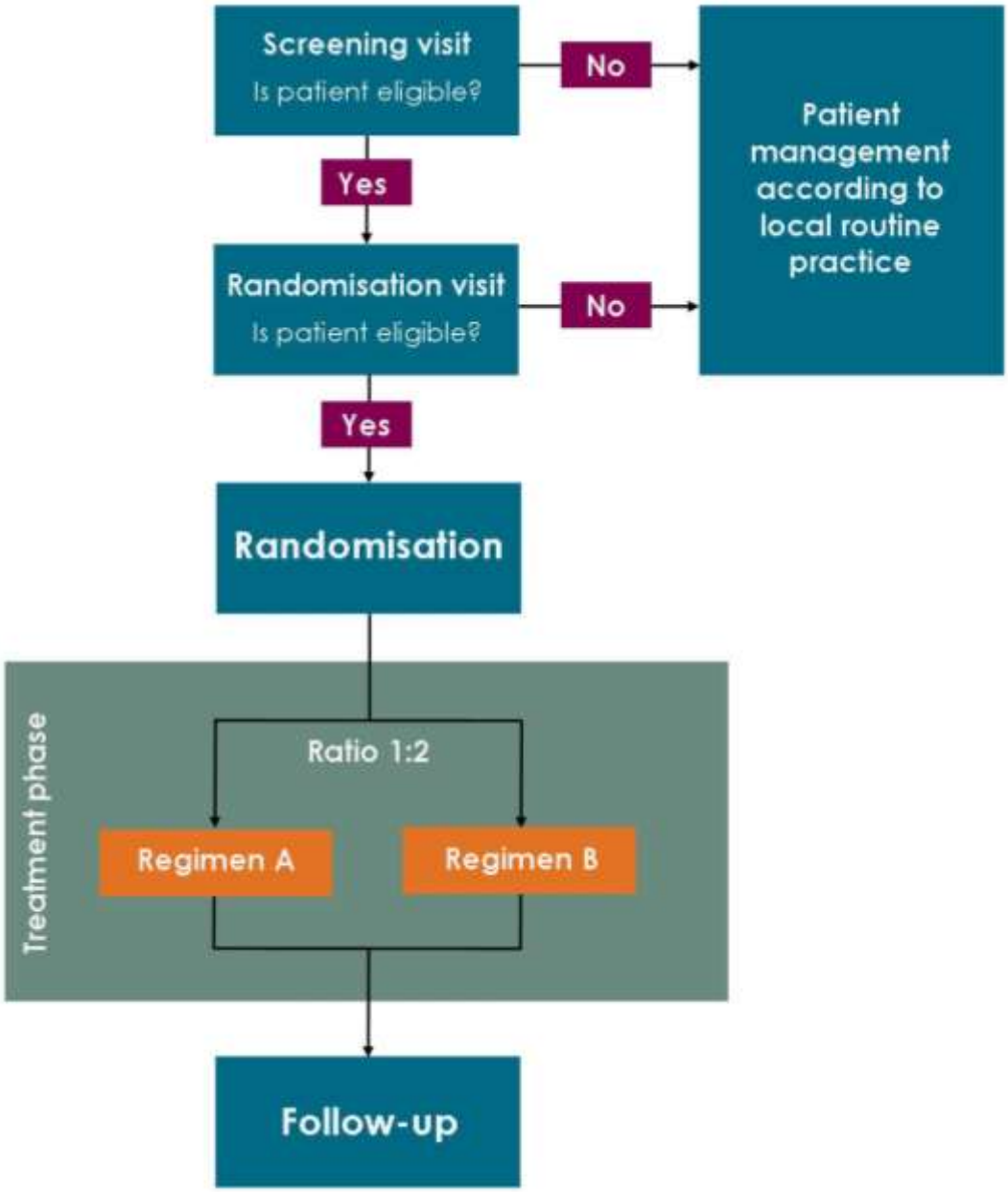
Stage 1
A minimum of 400 participants from sites in four or five countries will be randomised to either Regimen A or Regimen B in the ratio 1:2 (i.e. 133 allocated to Regimen A, and 267 allocated to Regimen B).

Stage 2
Stage 2 will aim to randomise at least 200 patients to each of Regimens B and C. This revised sample size was determined based on the assumption that the proportion of patients with a favourable efficacy outcome at Week 76 is 80% for Regimen B (estimated based on preliminary Stage 1 results) and 82% for Regimen C (based on an anticipated minimum benefit in efficacy of using 40 weeks treatment with bedaquiline compared to 16 weeks treatment with kanamycin). Using a non-inferiority margin of 10% and a one-sided significance level of 2.5%, 180 evaluable patients will be required in each of the two regimens to demonstrate non-inferiority of Regimen C to Regimen B with 82% power. To account for 10% of patients excluded from the primary efficacy analysis population, a total of 400 patients would be required across the 2 regimens.

An interim analysis will be performed for the purpose of determining the final sample size needed to achieve adequate power for testing the Stage 2 primary hypothesis of non-inferiority. The sample

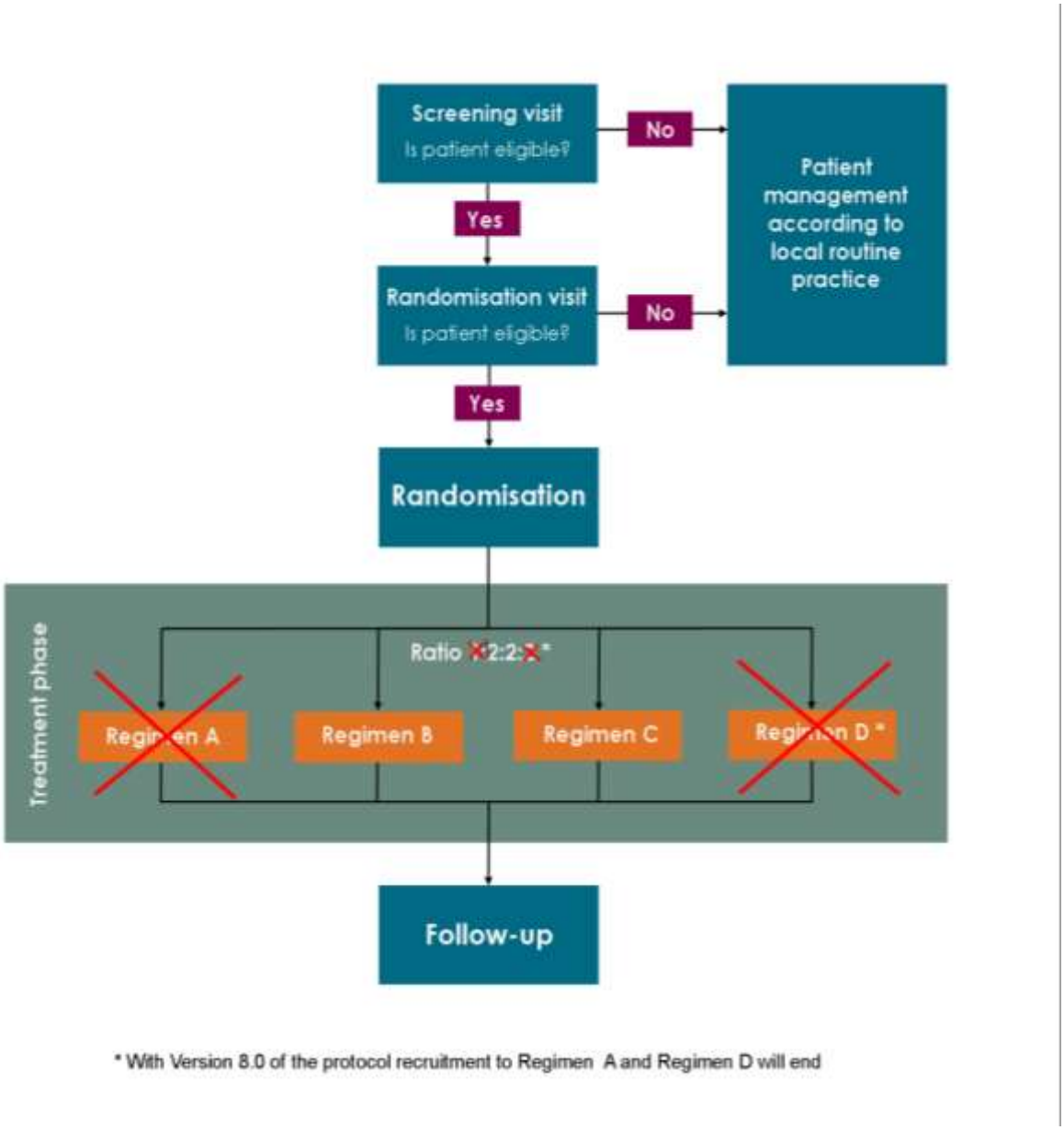
size re-estimation will be performed by an independent Statistical Support Group (SSG) and if necessary the sample size will be increased, to a maximum of 330 patients in each of regimens B and C (the original sample size).

Figure 2: Stage 1 Trial Design



Note. This figure applies to all sites during Stage 1 (i.e. before commencement of Stage 2), and to those sites only participating in Stage 1.

Figure 3: Stage 2 Trial Design



Note. **With Version 8.0 of the protocol recruitment to Regimens A and D will be terminated; this is indicated by the red cross over those regimens in the diagram.**

1.1.9 Blinding

Although the STREAM study is an open-label study, wherever possible it will be conducted masked to treatment allocation. The patient and treating clinician will be aware of treatment allocation, however, all laboratory assessments will be performed blind. See Section 10.1 for further details relating to blinding within the trial.

2 BACKGROUND

2.1 Introduction

Despite the availability of an efficacious and affordable six-month chemotherapy regimen for drug-sensitive TB and the definition of an efficient strategy to deliver treatment under direct observation to the majority of TB patients, TB control worldwide is impeded by two major issues: (i) the emergence of multidrug resistance (MDR) and (ii) co-existent HIV infection. The former hampers dramatically the efficacy of widely implemented standard short-course chemotherapy, thus limiting the success of efforts to fight against tuberculosis worldwide[3,4], and since 2002, at least one case of extensively drug-resistant tuberculosis (XDR-TB) has been reported from 45 countries[5].

2.1.1 Relevant studies/trials

In 2011, World Health Organisation (WHO) guidelines for the treatment for MDR-TB recommended an intensive phase of treatment based on at least four drugs known to be effective and given for a minimum of 20 months;[6] this is referred to below as the WHO 2011 long regimen. Outcomes with this approach are generally poor. In the most recent WHO TB surveillance report only 50% of MDR-TB patients were successfully treated.[7] and a recent meta-analysis reported on average 62% successful outcome and a mortality of 11%[8].

In 2010, Van Deun et al (2010)[2] reported excellent long-term outcomes in a cohort of over 200 patients in Bangladesh with MDR-TB who were treated with a regimen given for only nine to 11 months. Such a regimen, if successful, would represent a considerable advance over current practice. Evaluation of this regimen is the objective of Stage 1 of STREAM. In an updated analysis of over 500 patients in this cohort there was a relapse-free cure rate of 84.4% (95% confidence interval 81.3% - 87.6%).[9] These results were further supported by data from two West African cohorts with 89% cure rates seen in both the Niger and Cameroon cohorts of 65 and 150 patients respectively.[10,11] Both cohorts used a regimen similar to that studied in Bangladesh but of 12 months duration. Other prospective cohort studies of similar shortened regimens have also been implemented in Uzbekistan and several countries in West Africa.

In 2016, following review of the available data, the WHO MDR TB treatment guidelines were modified to recommend a 9-12 month shortened regimen under specific conditions similar to Regimen B used in STREAM Stage 1 (referred to below as the WHO 2016 short regimen).[12] This was a conditional recommendation based on very low certainty in the evidence. [12]

Final analysis of STREAM Stage 1, presented at the Union Conference in October 2018, found that 78.8% of participants on Regimen B, the short regimen, had a favourable outcome at 132 weeks from randomisation compared to 79.8% on Regimen A, the 20-24 month long regimen. After adjustment for the randomisation stratification factors of HIV status and centre, the difference in efficacy between the regimens was 1.0%, (95% CI -7.5 to 9.5%) meeting the pre-specified 10% non-inferiority margin. The primary safety outcome of the trial, the proportions of patients who experienced a Grade 3 or greater adverse event at any time during treatment and follow-up, was also similar on the two regimens (48.2% on the shorter regimen compared to 45.4% on the longer regimen).

Bedaquiline is a novel diarylquinoline antibiotic with bactericidal activity. In a phase II trial of patients with MDR-TB time to culture conversion was significantly less in patients receiving bedaquiline compared to those receiving an optimised background regimen only.[13] In December 2012 the US Food and Drug Administration (FDA) approved bedaquiline as part of the treatment regimen for MDR-TB when other agents are unavailable. Stage 2 of STREAM was designed to investigate ways in which Regimen B could be improved either by removing the second-line injectable, which is associated with severe drug toxicity, or by shortening the regimen to 6 months.

In December 2018, the WHO issued revised guidelines for treatment of MDR TB following review of a meta-analysis of available trial and observational data.[14] This included a re-classification of drugs for longer MDR-TB treatment regimens, with moxifloxacin or levofloxacin, bedaquiline and linezolid all listed in Group A (medicines that should be used in the regimen); it was also recommended that when an injectable agent is required, amikacin should be used rather than kanamycin or capreomycin.

2.1.2 Population

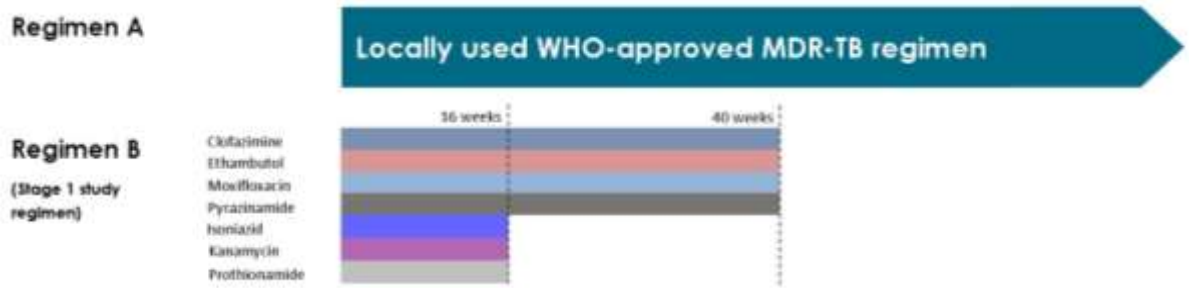
The STREAM study population consists of patients diagnosed with MDR-TB who fulfil the inclusion/exclusion criteria outlined in sections 5.1 and 5.2.

2.1.3 Investigational regimens

Stage 1

The investigational regimen in Stage 1 of the STREAM trial is Regimen B_{mox}. This regimen consists of clofazimine, ethambutol, moxifloxacin, and pyrazinamide given for 40 weeks, supplemented by isoniazid, kanamycin, and prothionamide in the first 16 weeks, as illustrated in Figure 4. This is compared with Regimen A, the locally-used WHO 2011 long regimen.

Figure 4: Regimen A* & Regimen B_{mox}



*WHO 2011 long regimen

The only change in Regimen B from the regimen described by Van Deun[2] is that gatifloxacin has been replaced by moxifloxacin because gatifloxacin was withdrawn by the original marketing authorisation holder and generic sources investigated did not meet WHO requirements for quality, safety and efficacy.

Stage 2

Stage 2 involves Regimen A and Regimen B as described in Stage 1 above, with the addition of two investigational regimens: Regimen C and Regimen D. These two regimens are modifications of Regimen B, both of which include the drug bedaquiline. In Stage 2 Regimen B is the control regimen for Regimen C and Regimen D.

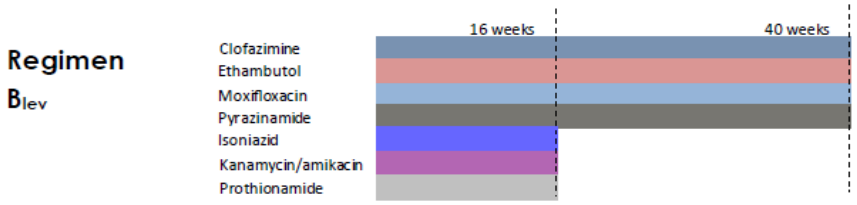
With Version 8.0 of the protocol, Regimen B is modified by replacement of moxifloxacin with levofloxacin. With Version 10.0 of the protocol, Regimen B is further modified to replace kanamycin with amikacin in sites where:

- the national TB programme is using amikacin as the preferred injectable in line with revised WHO guidance,[14]and
- amikacin is available for the trial.

Kanamycin will continue to be used until the transition takes place within each country programme.

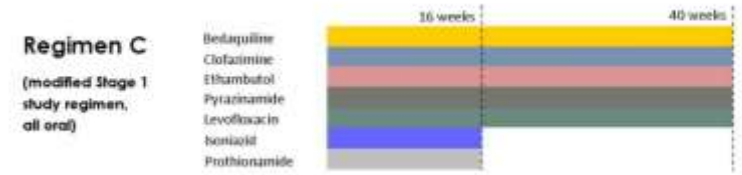
Participants randomised to Regimen B should be treated with the fluoroquinolone and injectable allocated at the start of treatment unless there is a clinical or operational reason to make a change.

Figure 5: Modified Regimen B - Regimen B_{lev} (Protocol Version 8.0 onwards)



Regimen C is a 40-week, fully-oral regimen consisting of bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks supplemented by isoniazid and prothionamide for the first 16 weeks (intensive phase). This is a modification of Regimen B, as illustrated in Figure 6, in which kanamycin is replaced with bedaquiline, and moxifloxacin is replaced with an alternative fluoroquinolone, levofloxacin, which has a better profile with respect to the potential for QT prolongation.

Figure 6: Regimen C (all oral)



Regimen D is 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 (intensive phase). This regimen is a modification of Regimen B, as illustrated in Figure 7, in which bedaquiline is given throughout, and moxifloxacin is replaced with an alternative fluoroquinolone, levofloxacin, and the total duration is reduced to 28 weeks.

Figure 7: Regimen D (28-week regimen)

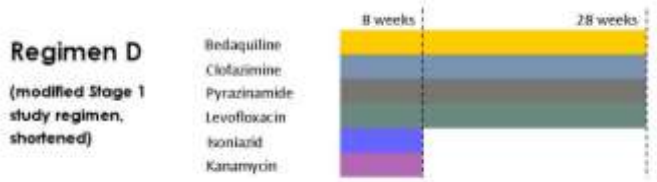
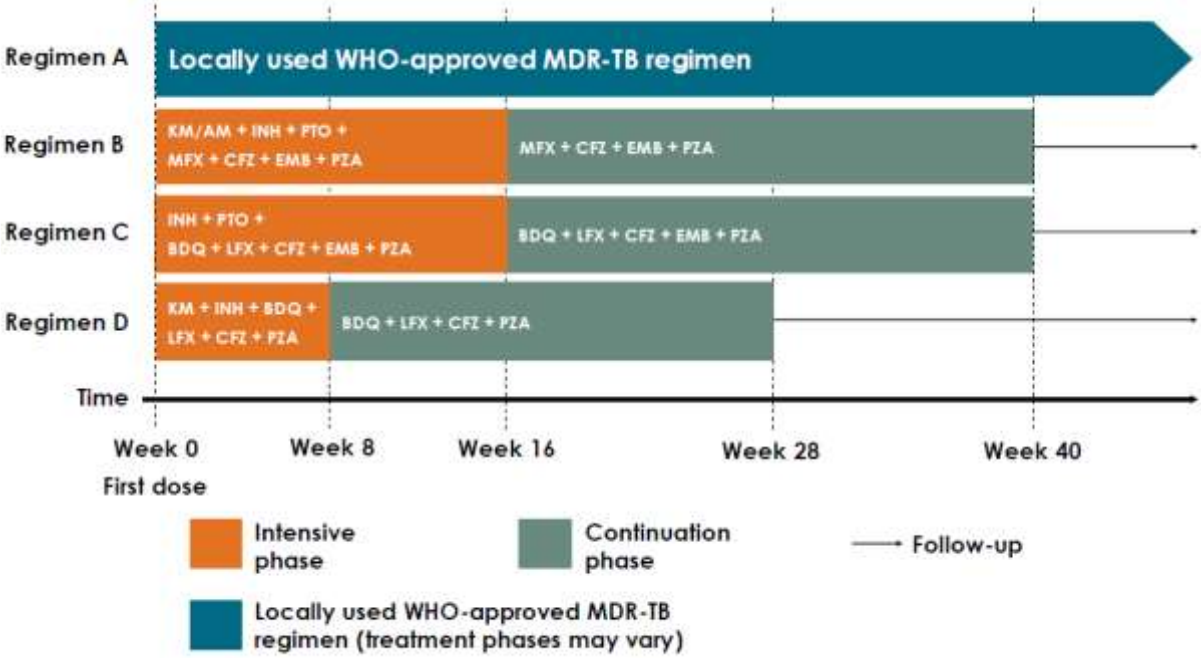


Figure 8 presents the phases of treatments across the four arms of the trial.

Figure 8: Treatment phases of investigational regimens



* Following implementation of protocol Version 8.0 recruitment to Regimen A and Regimen D was discontinued and in Regimen B moxifloxacin was replaced by levofloxacin.
Following implementation of protocol version 10.0, either kanamycin or amikacin will be used in Regimen B, depending on availability.

2.1.4 Ending randomisation to Regimen A

According to Version 7.0 of the Stage 2 protocol, patients may be randomised to Regimen A unless the participating country has adopted or has imminent plans to adopt a short MDR-TB regimen, in keeping with the WHO 2016 guidelines. This is because patients eligible for STREAM would also meet the WHO criteria for a shortened regimen and it is very unlikely that patients would accept the possibility of randomisation to a 20- to 24-month treatment regimen when under routine care they would be treated with a 9-month regimen. In addition, patients already enrolled in the trial and allocated to Regimen A would be more likely to subsequently withdraw from the trial, thus reducing the scientific value of the results.

With Version 8.0 of the protocol, randomisation to Regimen A will cease completely because several of the countries participating in STREAM have already implemented or have plans to implement a shortened regimen. As a result Regimen A would not have sufficient concurrently randomised patients for comparison and therefore continuation is considered futile. In addition, Stage 1 of

STREAM provides a good estimate of the performance of Regimen A under trial conditions. Patients already enrolled and allocated to Regimen A will continue on that treatment.

2.1.5 Ending randomisation to Regimen D

Patients will no longer be randomised to Regimen D from the point of implementation of Version 8.0 of the protocol and comparisons involving Regimen D will no longer be primary objectives. The rationale for this is two-fold. Firstly, there have been many important developments since the design of Stage 2 and fully oral 6-month regimens are being evaluated in several ongoing Phase 3 trials. The elimination of the injectable from MDR-TB regimens, rather than just reducing the duration, has become a priority to clinicians and patients and as such, Regimen D is a less attractive treatment option and a less valuable research question. Even if Regimen D was shown to be safe with non-inferior efficacy in STREAM, it is unlikely that it would be adopted as a treatment for MDR-TB. Secondly, enrolment to Stage 2 has been slower than expected and the continuation of recruitment to Regimen D will hamper the ability to make the primary comparison of Regimens B and C.

Patients already randomised to Regimen D will complete their course of treatment and continue in follow-up according to the protocol.

2.2 Rationale

Given the urgent need to increase access to treatment for MDR-TB, careful evaluation of treatment strategies is vital to ensure the most effective and feasible approaches are implemented, particularly in low-income settings where most cases of MDR-TB are found. New drugs with novel mechanisms of action for the treatment of MDR-TB are being evaluated. In addition, the optimisation of existing drugs is essential for the protection of new compounds for use in alternative regimens; clinical trials utilising these new compounds in treatment regimens are warranted.

The primary objective of Stage 1 of the STREAM trial is to assess whether Regimen B, which is based on the regimen used in Bangladesh,[2] is non-inferior to Regimen A, the locally-used WHO 2011 long MDR-TB regimen. Its practical, programme-based study design will also ensure that if the results are favourable, they will be generalisable to routine programme settings.

In addition, health system and patient costs associated with implementation will be documented. These will be analysed in association with the clinical outcomes of the trial using the TREAT TB Impact Assessment Framework[15] in order to provide as much information as possible for subsequent policy and practice decision-making.

It was necessary to substitute moxifloxacin for gatifloxacin in Regimen B because the original manufacturer of gatifloxacin withdrew their product from the market due to reports of associated dysglycaemia, and it was not possible to identify a generic source of gatifloxacin that met WHO manufacturing norms and standards for quality, safety and efficacy. If Regimen B was found to be inferior to Regimen A, one possible explanation could be that moxifloxacin is less effective than gatifloxacin. However, moxifloxacin and gatifloxacin have similar bactericidal activity[16] and the trial will therefore test the regimen closest to the standardised regimen developed by Van Deun[2] that is available in routine programme settings.

Stage 2 of the STREAM trial will involve the investigation of two alternative regimens, both variations on Regimen B, incorporating the drug bedaquiline. The first of these investigational regimens, Regimen C, involves the removal of the injectable, kanamycin, in order to avoid the 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 kanamycin and isoniazid and also whether ethambutol, which is of questionable efficacy, and prothionamide, commonly associated with severe gastric symptoms, can be removed.

The primary objective of Stage 2 is to assess whether Regimen C is non-inferior to Regimen B.

As the final results of STREAM Stage 1 would not be available until late in enrolment for Stage 2, and due to the urgent public health and clinical need to improve treatment of MDR-TB, Stage 2 was started without randomised controlled trial evidence that Regimen B is non-inferior to Regimen A. Regimen B was selected as the control arm for Stage 2 after careful consideration.

The final analysis of STREAM Stage 1 made public at The Union Conference in October 2018 found that 78.8% of participants on Regimen B had a favourable outcome at 132 weeks from randomisation compared to 79.8% on Regimen A. After adjustment for the randomisation stratification factors of HIV status and centre, the difference in efficacy between the regimens was 1.0%, 95% CI (-7.5 to 9.5%). The upper bound of the confidence interval met the pre-specified 10% non-inferiority margin. The proportions of patients who experienced a Grade 3 or greater adverse event at any time during treatment and follow-up, the primary safety outcome, was also similar on the two regimens (48.2% on the shorter regimen compared to 45.4% on the longer regimen).

From a preliminary review by the sponsor of the Stage 1 safety data it was apparent that regular ECG monitoring was of value throughout treatment. Although this is manageable in the context of a clinical trial, it would be a challenge for programmatic implementation, particularly in resource-limited settings. Because a key objective of STREAM is to evaluate effective and feasible approaches to MDR-TB treatment suitable for the settings in which the disease is most common, in Version 8.0 of the protocol Regimen B will be modified and moxifloxacin replaced by levofloxacin to assess whether this reduces the safety monitoring requirements of the regimen, given that the effect on the QT interval may be lower for levofloxacin than for moxifloxacin. The primary comparisons will be of Regimen C with Regimen B, whether it contains moxifloxacin or levofloxacin. Comparison of Regimen C with modified Regimen B (Regimen B_{lev}) alone will be added as secondary objectives of the trial.

In the light of the revised WHO recommendations for the treatment of MDR-TB in 2018, Regimen B was modified to allow either amikacin or kanamycin to be used in the intensive phase.

As described in sections 2.1.4 and 2.1.5, from the point of implementation of Version 8.0 of the protocol, patients will no longer be randomised to Regimens A or D. Comparisons involving Regimen D will no longer be primary objectives.

2.2.1 Risks and benefits

Regimens B, C and D are substantially shorter than regimens recommended by the 2011 WHO guidelines[6] and could therefore increase the risk of treatment failure or relapse, and the acquisition

of additional drug resistance. However, this has not been observed in settings where variations of Regimen B have been used.[9-11]

Additional data from Stage 2 will enable a more precise comparison of the true difference between Regimen B and A to be made.

Regimen D may carry greater risk of failure or relapse compared with Regimen B because it is shorter and because of the removal of prothionamide and ethambutol. Although unlikely, regimen C may also carry a risk of failure or relapse compared to regimen B. There may also be greater risk of acquisition of additional drug resistance in regimens C and D. However, this risk is believed to be small given that, in stage 2 of the bedaquiline C208 trial, no subject in the bedaquiline arm developed extensively drug-resistant (XDR) or pre-XDR infection with 24 weeks of dosing of bedaquiline compared to six participants in the control arm;[17] this is comparable with 9% reported from a recent follow-up of over 800 patients treated with the WHO 2011 long regimen.[18]

Restriction of the second-line injectables and prothionamide to the intensive phase may explain why no acquired resistance to these drugs was observed in the failure or relapse cases in the Van Deun[2] study. Although used with only one second-line drug in the continuation phase, acquired fluoroquinolone resistance did not occur, probably due to the relatively high fluoroquinolone dose used; baseline resistance to ofloxacin rarely resulted in an adverse bacteriological outcome. Moreover, study criteria limiting inclusion to cases with no LPA evidence of resistance to either fluoroquinolones or kanamycin is expected to almost certainly prevent amplification of resistance leading to extensively drug-resistant tuberculosis.

Most second-line drugs are associated with unpleasant and sometimes serious toxicities. The removal of prothionamide from Regimen D will avoid the gastric side effects which some patients find intolerable. The reduced duration of kanamycin in the 28-week regimen, Regimen D, and its removal from the fully oral 40-week regimen, Regimen C, will reduce the risk of kanamycin toxicity (renal damage and deafness).

Isoniazid is included in Regimen B, Regimen C, and Regimen D at higher doses than is usual. Similarly, the fluoroquinolone doses, moxifloxacin in Regimen B_{mox} and levofloxacin in regimens B_{lev}, C and D, for patients in the higher weight bands are greater than the standard doses. However, the regimen given in Bangladesh was well-tolerated and it is possible that the shorter duration of chemotherapy in Regimen B, Regimen C, and Regimen D may result in fewer severe adverse drug reactions than in Regimen A.

A summary of the safety information on the higher dose of moxifloxacin is provided in Appendix 1. The potential for QT prolongation is of particular concern and regular ECG monitoring is specified in the protocol (see Section 8.3.1).

Bedaquiline given in addition to a standardised background regimen has been shown to greatly reduce the time to culture conversion in MDR-TB (median 83 days compared to 125 days, HR 2.44, 95%CI (1.57 - 3.80)). However, there is less clinical experience with bedaquiline than with the other drugs in the study regimens, and although generally well tolerated, a number of potential risks have been identified from preclinical and clinical studies and the findings from the C208 trial; these are outlined below and will be carefully monitored in the course of this study.

Mortality
In Stage 2 of the bedaquiline C208 trial, a difference in the number of deaths was observed between the bedaquiline group (10/79, 12.7%) and the placebo group (3/81, 3.7%), despite better microbiological outcomes in the former. This imbalance remained in the pooled analysis of C208 Stage 1 and Stage 2. The reason for the increased overall mortality is as yet unclear; the causes of death were varied (the only cause of death reported more than once was death due to TB), and there was a wide range in time to death since last intake of bedaquiline/placebo (2-911 days). In addition, none of the deaths in the bedaquiline arm were considered related to study drug by the investigator. Mortality will be thoroughly evaluated in this study, which includes follow-up to 132 weeks for all participants.

Liver toxicity
In the bedaquiline C208 trial, the most frequently observed laboratory abnormalities that were more frequent in the bedaquiline than the placebo arm were increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). There were two cases (one in a subject in the bedaquiline arm in C208 and one in a subject in the bedaquiline arm in C209) where the transaminase increases were accompanied by increased total bilirubin such that both subjects met laboratory criteria for Hy's law. There were no cases of severe hepatotoxicity attributed to bedaquiline by the investigators in the clinical studies, however in view of the relatively small study populations and the combination with other potentially hepatotoxic drugs in the STREAM regimens, it will be important to monitor this closely.

Pancreatic toxicity
Pancreatic changes were observed in mice and dogs receiving bedaquiline that correlated with increases in pancreatic amylase and lipase, without trypsin-like immunoreactivity increase. Although there is no clear evidence of an increased risk in the clinical studies, patients with a pancreatic amylase more than twice the upper limit of normal will be excluded from Stage 2 of the trial and pancreatic function will be monitored closely.

Cardiac effects
Based on the observation of cardiac myocyte degeneration and QT prolongation in dogs that received exposures in excess of the clinical exposure in toxicology studies, cardiac muscle effects are monitored in the current study by creatine kinase-MB and safety ECGs. However, no increases in these laboratory tests suggesting bedaquiline cardiac toxicity were noted in either stage of the bedaquiline C208 trial. QT prolongation has been observed with bedaquiline:
1. The largest mean increase in QTcF in Janssen's C208 Stage 2 trial at a predose time point in the Any BDQ group during the first 24 weeks was 15.4 ms (at Week 24) and 7.7 ms in the Any placebo group (at Week 20).
2. In addition and pertinent to Stream Stage 2, in Janssen's C209 trial a maximal increase mean change from reference in QTcF at Week 24 was 12.2 ms over 24 months and in those patients also taking clofazimine (n=17) the mean increase change from reference was 32ms.[19]

In Stage 2 of STREAM, patients with a QTcF greater than or equal to 450 ms at screening will not be eligible and there will be regular ECG monitoring (see Section 8.3.1). As a consequence of the risk of QT prolongation with bedaquiline, moxifloxacin is contraindicated and has been replaced by

levofloxacin (see Appendix 2 for levofloxacin safety summary) in the two bedaquiline-containing experimental regimens: Regimen C and Regimen D.

Musculoskeletal effects
In some animal studies elevations of myoglobin and CK were observed, consistent with the known ability of cationic amphiphilic drugs to cause myopathies, which tend to occur only after prolonged dosing in humans or at high dose administration and are usually reversible after treatment cessation. No myopathies were reported in the clinical studies, but this will be kept under review in STREAM.

Reproduction
Since the effects of bedaquiline on foetal development are unknown, the use of effective contraception is required for both male and female participants (see Section 5.1).

2.2.2 Safety in the ongoing STREAM trial

The Independent Data Monitoring Committee (see Section 19.3) for STREAM have reviewed the safety data approximately 6-monthly since recruitment to Stage 1 started. The committee have not identified any safety concerns that required amendment of the protocol.

3 OBJECTIVES AND OUTCOMES

3.1 Stage 1 objectives

3.1.1 Stage 1 primary objectives

The primary objectives of the Stage 1 comparison of the STREAM trial are:

1. To assess whether the proportion of participants with a favourable efficacy outcome on Regimen B is non-inferior to that on Regimen A (WHO 2011 long MDR-TB regimen), the control regimen for Stage 1, at Week 132, using a 10% margin of non-inferiority.
2. To compare the proportion of participants who experience grade 3 or greater adverse events during treatment or follow-up in Regimen B as compared to Regimen A.

3.1.2 Stage 1 secondary objectives

The secondary objectives of the Stage 1 comparison of the STREAM trial are:

1. To determine the proportion of participants with a favourable efficacy outcome on Regimen B in each country setting
2. To compare the economic costs incurred by patients and by the health system during treatment on Regimen B as compared to Regimen A.

3.2 Stage 2 objectives

3.2.1 Stage 2 primary objective:

The primary objective of the Stage 2 comparisons of the STREAM trial is:

1. To assess whether the proportion of participants with a favourable efficacy outcome on Regimen C, the fully oral regimen, is non-inferior to that on Regimen B (with moxifloxacin or levofloxacin) at Week 76, using a 10% margin of non-inferiority

3.2.2 Stage 2 secondary objectives:

The secondary objectives of the Stage 2 comparison of the STREAM trial are:

1. To assess whether Regimen C is superior to Regimen B with regards to the proportion of participants with a favourable efficacy outcome at Week 76 and Week 132 (if non-inferiority is demonstrated at either time-point)
2. To assess whether Regimen C is non-inferior to Regimen B with regards to the proportion of participants with a favourable efficacy outcome at Week 132
3. To compare the efficacy of 40 weeks of bedaquiline in combination with the other drugs of Regimen C with Regimen B during treatment and follow-up
4. To compare the efficacy of 28 weeks of bedaquiline in combination with the other drugs of Regimen D with Regimen B during treatment and follow-up
5. To compare the safety, including the effect on mortality and tolerability, of 40 weeks of bedaquiline in combination with the other drugs of Regimen C with Regimen B during treatment and follow-up.

6. To compare the proportion of participants who experience grade 3 or greater adverse events during treatment or follow-up in Regimen C as compared to Regimen B
7. To estimate the difference between Regimen C and Regimen B_{mox} in the proportion of participants with a favourable efficacy outcome at Week 76 and Week 132
8. To estimate the difference between Regimen C and Regimen B_{lev} in the proportion of participants with a favourable efficacy outcome at Week 76 and Week 132
9. To estimate the difference between Regimen C and Regimen A in the proportion of participants with a favourable efficacy outcome at Week 132
10. To estimate the difference between Regimen B and Regimen A in the proportion of participants with a favourable efficacy outcome at Week 132
11. To estimate the difference between Regimen D and Regimen B in the proportion of participants with a favourable efficacy outcome at Week 76 and Week 132
12. To estimate the difference between Regimen D and Regimen A in the proportion of participants with a favourable efficacy outcome at Week 132
13. To investigate the safety, including the effect on mortality and tolerability of 28 weeks of bedaquiline in combination with the other drugs of Regimen D compared to Regimen B during treatment and follow-up.
14. To compare the proportion of participants who experience grade 3 or greater adverse events during treatment or follow-up in Regimen B as compared to Regimen A
15. To compare the proportion of participants who experience grade 3 or greater adverse events during treatment or follow-up in Regimen C as compared to Regimen B_{mox}
16. To compare the proportion of participants who experience grade 3 or greater adverse events during treatment or follow-up in Regimen C as compared to Regimen B_{lev}
17. To compare the proportion of participants who experience grade 3 or greater adverse events during treatment or follow-up in Regimen D as compared to Regimen B
18. To investigate the safety, including the effect on mortality and tolerability, of bedaquiline-containing regimens compared to Regimen B during treatment and follow-up.
19. To investigate the effect on mortality of bedaquiline-containing regimens compared to non-bedaquiline containing regimens.
20. To evaluate the pharmacokinetics of bedaquiline and M2 in all participants randomised to Regimen C or Regimen D at sites selected for the PK study and assess pharmacokinetic/pharmacodynamics relationships of bedaquiline for safety and efficacy
21. To evaluate the pharmacokinetics of bedaquiline and M2 in a subset of HIV co-infected participants on Regimen C or Regimen D receiving antiretroviral treatment
22. To evaluate the 4β-hydroxycholesterol/cholesterol ratio as a measure of cytochrome P450 3A (CYP3A) activity in Regimen C and Regimen D as compared to Regimen B.
23. To compare the economic costs incurred during treatment by patients (transport and food costs for attending DOTs and patient assessment visits, food supplements costs and income loss) and by the health system (inpatient stay, laboratory tests, medication, staff, consumables and serious adverse events costs) in Regimen B and C. To calculate economic costs associated with regimen D, and compare these with regimen B, for those sites where this is possible.
24. To compare the proportions of participants having undergone lung surgery (resection or pneumonectomy) by Week 76 and Week 132 in Regimen C and Regimen D as compared to Regimen B.

25. To compare the development of resistance to background drugs, especially resistance leading to the development of pre-XDR or XDR strains of TB in Regimen C and Regimen D as compared to Regimen B.
26. To investigate the development of increased MIC to bedaquiline in regimens C and D.

3.3 Outcome measures

3.3.1 Stage 1

The primary efficacy outcome measure of the Stage 1 comparison is the proportion of patients with a favourable outcome at Week 132 as defined in section 11, Statistical Considerations.

For the Stage 1 comparison, the primary safety outcome measure is the proportion of patients experiencing a grade 3 or greater adverse event, as defined by the DAIDS criteria[20], during treatment and follow-up.

Secondary outcome measures for the Stage 1 comparison include:

- Time to sputum smear conversion
- Time to sputum culture conversion
- All-cause mortality during treatment or follow-up
- Change of regimen for adverse drug reactions
- Number of serious adverse reactions occurring on treatment and during the follow-up period
- Adherence to treatment.

Additional exploratory outcome measures for the Stage 1 comparison include:

- Time to unfavourable efficacy outcome
- Time to cessation of clinical symptoms based on PI assessment

In selected sites, costs and acceptability of Regimens A and B to stakeholders will be analysed in terms of:

- Costs to the health system
- Household costs
- Patient treatment and support experiences
- Health worker experiences.

3.3.2 Stage 2

The primary efficacy outcome measure of the Stage 2 comparisons is the proportion of patients with a favourable outcome at Week 76 as defined in section 11, Statistical Considerations.

There will be two sensitivity analyses of the primary outcome:

- Proportion of patients with a favourable outcome at Week 76 as defined in section 11, Statistical Considerations, but ignoring substitutions of levofloxacin for moxifloxacin and vice versa as treatment changes.
- Proportion of patients with a favourable outcome at Week 76 as defined in section 11, Statistical Considerations of protocol v10.0 or earlier i.e. not counting starting linezolid alone as unfavourable.

Secondary outcome measures of the Stage 2 comparisons include:

- Time to failure or relapse
- Time to sputum culture conversion
- Time to sputum smear conversion
- Time to unfavourable efficacy outcome
- Efficacy status (unfavourable outcome) at week 132
- All-cause mortality during treatment or follow-up
- Proportion of patients experiencing a grade 3 or greater adverse event, as defined by the DAIDS criteria, during treatment and follow-up
- Change of regimen for adverse drug reactions
- Number of adverse events occurring on treatment and during the follow-up period
- Pharmacokinetic outcomes
- Adherence to treatment

Additional exploratory outcome measures of the Stage 2 comparisons include:

- The proportion of participants in each category who meet the WHO classification of outcome as applicable at the time of analysis
- Proportion of participants with a successful TB outcome at Week 132, irrespective of treatment changes
- Time to cessation of clinical symptoms based on PI assessment

In selected sites, the regimens will be analysed in terms of:

- Costs to the health system
- Patient direct and indirect costs

4 SELECTION OF SITES

Country selection is based on background disease burden of TB, MDR-TB, and TB-HIV co-infection. Sites within countries are selected to ensure sufficient numbers of MDR-TB cases to meet recruitment targets. Site suitability, based on the listed criteria in Section 4.1, will be evaluated during pre-trial and feasibility assessments.

4.1 Site inclusion criteria

Participating sites are required to meet the following criteria:

- Experience in treating MDR-TB patients
- Support from the Tuberculosis Control Programme at national or regional level
- A local Principal Investigator (PI) who is a TB specialist and experienced in the treatment of MDR-TB who will oversee the patients throughout the trial (there may be more than one PI per country)
- Suitable treatment site staff and facilities
- Treatment site staff willing to recruit all eligible patients into the trial (site would ideally function as a single coordinating/recruiting facility and work with satellite sites for treatment and follow-up)
- Acceptable plans for close supervision of patients in treatment and follow-up
- Willing to offer HIV testing to all patients wishing to participate in the trial and routinely available HIV clinical management services (including provision of antiretroviral therapy (ART)
- A network of well-functioning AFB smear microscopy laboratories and a reference laboratory already performing cultures, with a system of quality assurance
- Ability to export sputum culture for testing to ITM, Antwerp, if required
- Ability to get authorisation of importation for the medicines which will be procured and delivered by The Union/Vital Strategies.
- Agreement to use specified standardised bacteriological methods
- Availability of rapid genotypic line-probe drug susceptibility testing (LPA DST) for rifampicin, second-line injectables and fluoroquinolones of the required quality (or ability to quickly build capacity for this testing)
- Acceptable infection control procedures consistent with WHO guidance.

5 SELECTION OF PATIENTS

Patients will be recruited into the trial from tuberculosis clinics in the catchment area of the main site. The target population is patients with pulmonary TB and evidence of resistance to at least rifampicin[21] (including patients sensitive to isoniazid).

5.1 Patient inclusion criteria

A patient will be eligible for randomisation into the study (Stage 1 or Stage 2) if he/she:

1. Consent

1.1 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. Age

2.1 Is aged 18 years or older (Stage 1) or 15 years or older (Stage 2)

3. AFB or GeneXpert results

3.1 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) from a test performed at screening or from a test performed within the four weeks prior to screening

4. Has evidence of resistance to rifampicin either by line probe assay (Hain Genotype[22]), 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: pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilised must agree to use a barrier method or an intrauterine device unless their partner has had a vasectomy; men who have not had a vasectomy must agree to use condoms. In Stage 2 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.

In addition to the criteria above, for Stage 2 only, a patient will be eligible for randomisation to the study provided he/she:

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_{+}, Mg_{2+} and corrected Ca_{2+} at screening.

5.2 Patient exclusion criteria

A patient will not be eligible for randomisation into the study (Stage 1 or Stage 2) if he/she:

1. Is infected with a strain of *M. tuberculosis* resistant to second-line injectables by line probe assay (Hain Genotype[22]) 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 fluoroquinolones by line probe assay (Hain Genotype[22]) 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 5 times the upper limit of normal for Stage 1, and 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 to 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

12.1 Has previously experienced any serious adverse reaction when taking a quinolone or fluoroquinolone

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 500 ms for Stage 1, and more than or equal to 450 ms for Stage 2

In addition to the criteria above, for Stage 2 only, a patient will not be eligible for randomisation to the study if he/she:

15. Has experienced one or more of the following risk factors for QT prolongation:
    - A 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)
    - Pathological Q-waves (defined as Q-wave more than 40 ms or depth more than 0.4-0.5 mV)
    - Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome)
    - Electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block
    - Evidence of second- or third-degree heart block
    - Intraventricular conduction delay with QRS duration more than 120 ms
    - Bradycardia as defined by sinus rate less than 50 bpm
    - Personal or family history of Long QT Syndrome
    - Personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia
    - Syncope (i.e. cardiac syncope not including syncope due to vasovagal or epileptic causes)

- 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, other than the maximum permitted treatment specified in Section 5.2.1
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/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.

5.2.1 MDR-TB treatment prior to screening

Patients who are AFB smear positive who have received second-line treatment as part of an MDR-TB treatment regimen in the 12 weeks prior to screening are permitted to have had up to a maximum of four weeks treatment. However, if they have received more than seven days treatment they are only eligible for the trial if FDA vital staining of their sputum is positive.

5.2.2 MDR-TB treatment between screening and randomisation

MDR-TB treatment should not be initiated or continued between screening and randomisation unless clinically necessary or mandated by local policy, and if used may not exceed three weeks.

5.3 Number and source of patients

Stage 1

A minimum of 400 participants from sites in four to five countries will be randomised to either Regimen A or Regimen B in the ratio 1:2 (i.e. 133 allocated to Regimen A, and 267 allocated to Regimen B) in Stage 1.

Stage 2

At the start of Stage 2 randomisation was to Regimen A, Regimen B, Regimen C and Regimen D in a ratio of 1:2:2:2 to a maximum of 1155 patients from sites in a number of countries. From Version 8.0 of the protocol onwards, the aim is to randomise at least 200 patients to each of Regimens B and C. In addition, patients randomised to Regimen A or Regimen D prior to the implementation of Version 8.0 of the protocol will be part of the trial and therefore the overall sample size will be greater than 400 but is expected to be less than 800 patients.

5.4 Screening procedures

Written informed consent/assent **must** be obtained from the patient before any protocol-specific screening procedures are carried out. Each consenting/assenting patient will be assigned a study number which will be used to identify the patient throughout the study.

5.4.1 Screening visit

At the first (screening) visit, the study, including potential risks and benefits of joining the trial, will be explained to prospective participants. This will include a general overview of the trial purpose and procedures as well as the samples to be collected at this visit. Each patient will be asked to sign (or provide a thumb print in the presence of a witness if illiterate) for the screening procedures and will be given a copy of the signed informed consent form and a patient information sheet to take home.

After giving consent/assent for screening, patients will be assigned a unique study number by entering their name on to the next line of a screening register and evaluated for their eligibility according to the inclusion and exclusion criteria.

Patients who at the time of screening have documented results of second line drug (SLD) resistance tests that provide evidence of resistance to fluoroquinolones or second-line injectables are not eligible for the trial.

The following investigations will be undertaken:

- Sputum samples obtained for:
  - AFB smear
  - Culture
  - Rifampicin resistance testing by LPA or GeneXpert (unless there is a phenotypic result from another reliable source indicating rifampicin resistance from a sputum sample taken no longer than four weeks from date of screening)
  - Line probe assay (Hain Genotype[22]) for second-line injectable and fluoroquinolone, if rifampicin resistant, from a sputum sample taken no more than four weeks from date of screening)
- Blood samples obtained for:
  - HIV antibodies. In addition to the antibody test at the central lab, to minimise delays in randomisation local testing may be used (2 separate rapid tests plus a third test in the case of discordant results). Patients with a documented positive HIV result who are not receiving ART will need confirmation of this result by a single rapid test (plus a second rapid test in the case of discordance) prior to randomisation. Known HIV-positive patients who are receiving ART do not need further local rapid tests prior to randomisation. However, all patients, without exception, must have a sample for HIV antibodies sent to the central lab.
  - CD4 count and viral load (unless the patient is HIV negative)
  - Liver function tests (AST and ALT)
  - Pancreatic amylase
  - Serum potassium, calcium and magnesium
  - Creatinine clearance
  - TSH
  - Thyroxine or free thyroxine
- Urine sample for HCG pregnancy test
- 12 lead ECG
- Audiometry

5.4.2 Repeat testing and re-screening

Inconclusive LPA results at screening should be repeated on a second sample collected from the patient as soon as possible. Confirmation of rifampicin resistance is required before randomisation; patients with inconclusive LPA results for second-line drugs may be included if otherwise eligible (see Patient Management Guide for further details).

In the event that a patient is found to be ineligible based on laboratory abnormalities at screening, abnormal tests may be repeated if there is clinical suspicion that the laboratory abnormality may resolve (with or without intervention). Re-tests must be conducted (and results received) within four weeks of screening consent and before randomisation.

If the laboratory results remain abnormal on re-testing or if the re-tests cannot be done within four weeks of screening consent, the patients may still undergo a full re-screen in which the entire screening process must be repeated.

Patients found not to be eligible for the STREAM trial due to a potentially modifiable reason or timing of previous treatment may also be rescreened once. In addition, if a patient has not been randomised within four weeks of the start of screening, then they become ineligible for the trial but may be rescreened once.

A patient who fails a second screening is permanently excluded from trial participation. Patients who are rescreened should be reconsented/assented and given a new screening number for the second screening. All patients who are not eligible for the STREAM trial will be managed according to local routine practice.

If a patient is screened successfully and satisfies the criteria to participate in the STREAM trial, the patient should be randomised no more than 4 weeks after screening consent.

5.5 Late identification of drug-resistance or drug-sensitivity

5.5.1 Late identification of fluoroquinolone/injectable-resistance

In sites that currently undertake phenotypic second-line drug susceptibility resistance testing (DST), results from pre-treatment samples that provide evidence of fluoroquinolone, or second-line injectable resistance may become available after randomisation. In such cases, the patient's clinical progress should be taken into account before making any changes on the basis of the results, in consultation with the central clinical team. However, if patients are found to have XDR-TB (defined as resistance to fluoroquinolones **and** second-line injectables from phenotypic DST) these patients should be withdrawn from trial treatment and treated according to national guidelines.

5.5.2 Late identification of rifampicin-sensitivity

Any patients whose initial TB infection is found to be sensitive to rifampicin after they have been randomised, as confirmed by rpoB sequencing,[23] should have their treatment amended appropriately and be followed up according to the trial schedule.

6 RANDOMISATION PROCEDURE

6.1 Evaluations at the randomisation visit

Patients will need to be re-assessed for eligibility when returning after their screening visit. The time between the screening consent/assent and randomisation visits should be kept as short as logistically possible, but should be no more than four weeks; those returning after four weeks will have to be re-screened prior to randomisation. Patients who have been on MDR-TB treatment since screening and have had more than three weeks of treatment between the screening consent and randomisation are not eligible for trial participation (see section 5.2.1)

Patients attending the randomisation visit will be given further information about the trial and what would be expected of them in terms of follow-up visits and procedures. If they are still willing to take part, they will be asked to sign a participation informed consent form (or give a thumb print in the presence of a witness if illiterate) and will be given a signed copy to take home together with the Patient Information Sheet. Patients below the age of consent according to local regulations require the consent of a parent or caregiver and will be asked to give their assent to participation. Patients who are ineligible or do not wish to take part will be referred to the NTP for further management.

Once an eligible patient has given consent/assent to participate in the trial, the following will be done:

- Interview to obtain and confirm demographic details, medical history (prior diagnoses and treatment, concomitant disease and medication, smoking history, and current symptoms) and key information on asset ownership to document socio-economic status will be requested at sites participating in the health economic component of the study
- Record contact information
- Record alcohol use
- Clinical examination including height, weight and vital signs (temperature, systolic and diastolic blood pressure (BP) and pulse rate)
- Visual acuity test
- Collect at least two spot sputum samples with a third early morning sample if possible (for smear and culture)
- Urinalysis (dipstick in Stage 1; via urine sample to central laboratory in Stage 2)
- A urine pregnancy test (if pre-menopausal woman)
- Serum creatinine, serum potassium, blood glucose, haemoglobin,
- Posteroanterior (PA) chest X-ray, unless a good quality film is available that has been taken no longer than four weeks prior to randomisation; if possible this should be a digital x-ray
- 12-lead ECG immediately before randomisation and at 4 hours after the first dose of allocated trial treatment.

In addition to the above, in Stage 2 the following investigations will also be undertaken:

- Other tests listed in the serum chemistry panel in section 8.2
- Hepatitis A, B, and C

If any of the ECGs performed pre-randomisation show a QT or QTcF greater than or equal to 450 ms then the patient will be ineligible for the trial.

At sites participating in sample storage, all patients providing their consent/assent to participate in the study will also be asked to provide their consent/assent for the bio storage of additional specimens

for future investigation of potential predictors of disease outcome or effects of tuberculosis treatment. Those providing their consent/assent for bio storage of their specimens will be requested to give blood (at randomisation and at 16 weeks). If human genetic testing is to be performed, specific consent will be sought.

6.2 Allocation of treatment (following randomisation)

In each stage of the trial, patients will be randomised using a web-based randomisation system. Access to the web-based system will be controlled through an authorised username and password. Before treatment allocation the patient's eligibility will need to be confirmed, their site and HIV status, and CD4 count entered into the database. Local laboratory results can be used to determine a patient's HIV status and CD4 count for randomisation, unless central laboratory results are available at the time of randomisation.

Separate randomisation lists for each combination of strata will be prepared in advance, for each site according to whether they are participating in Stage 1 only, Stage 1 and 2, or Stage 2 only, by a statistician independent of the study, using varying block sizes. Should web access not be available at the time of randomisation, a manual alternative using sealed envelopes will be provided.

Stage 1 (before Stage 2 begins, or for sites only participating in Stage 1)

Patients will be randomised to Regimen A or Regimen B. Randomisation will be in a 1:2 ratio in favour of Regimen B to allow more data on efficacy and safety to be collected on this regimen. Randomisation will be stratified by (1) site, (2) HIV status for sites with high TB-HIV co-infection rates.

Stage 2

Prior to the implementation of Version 8.0 of the protocol, in countries where the local NTP has no imminent plans to adopt a short regimen, in keeping with the WHO 2016 MDR-TB guidelines, patients will be randomised to one of four regimens, Regimen A, Regimen B or Regimen C, or Regimen D in a ratio of 1:2:2:2. In countries where the local NTP has adopted or has imminent plans to adopt a short regimen in keeping with the WHO 2016 guidelines and it has been agreed with the STREAM Trial Management Group that randomisation to Regimen A will not be offered, patients will be randomised to one of three regimens (Regimen B, Regimen C or Regimen D) in a ratio of 1:1:1 (see Section 2.1.4). When Version 8.0 of the protocol has been implemented, randomisation to Regimen D will be discontinued as will Regimen A if it has not already been discontinued.

Randomisation will be stratified by (1) site, (2) HIV status & CD4 count status (i.e. three categories: HIV-negative, HIV-positive with low CD4 count of 50 to less than 350 cells/mm^3, or HIV-positive with high CD4 count of more than or equal to 350 cells/mm^3), for all sites.

7 TREATMENT OF PATIENTS

7.1 Introduction

During Stage 1 of the STREAM trial, all patients will be randomised to receive either Regimen A or Regimen B. In Stage 2 patients may be allocated one of four regimens (Regimen A, Regimen B, Regimen C, or Regimen D). However, with Version 8.0 of the protocol patients will no longer be randomised to Regimen A or Regimen D.

Some sites may recruit only to Stage 1, other sites may only participate in Stage 2 and some will participate in both.

7.2 Trial interventions

7.2.1 Stage 1

The control regimen for the Stage 1 comparison, Regimen A, is the locally-used WHO 2011 long MDR-TB regimen. Country- or site-specific regimens are described in the STREAM Patient Management Guide.

The investigative regimen for the Stage 1 comparison is Regimen B_{mox}, and consists of moxifloxacin, clofazimine, ethambutol and pyrazinamide given for 40 weeks, supplemented by kanamycin, isoniazid and prothionamide in the first 16 weeks.

All drugs are given daily (seven days a week), except for kanamycin which is initially given daily and then thrice-weekly from Week 12 onwards in Regimen B. After the first 4 weeks of treatment has been completed, in sites where it is not possible to administer kanamycin seven days a week to outpatients, the dose may be changed to six days a week. These sites may then administer kanamycin six days a week for weeks 5-12 of treatment and reduce the frequency to three days a week from week 12 onwards.

The intensive phase should be extended from 16 to 20 or 24 weeks for patients whose smear has not converted by 16 or 20 weeks, respectively, as described in section 7.3.2.

Table 1: Regimen B_{mox} doses (for patients randomised under versions of the protocol prior to Version 8.0)

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 kilogram body weight (maximum 1g)		

7.2.2 Stage 2

The control regimen for the primary comparison of Stage 2 is Regimen B. For all patients randomised according to versions of the protocol prior to Version 8.0, the details are given above in section 7.2.1. For patients randomised to Regimen B after Version 8.0 has been implemented, a modified version of the regimen will be used in which moxifloxacin is replaced by levofloxacin according to the doses in Table 2 below; all other details of the regimen and its administration are unaltered. This regimen is referred to as Regimen $B_{lev.}$

Patients randomised to Regimen B after Version 10.0 has been implemented will be treated with amikacin instead of kanamycin in all sites in which the national TB program is using amikacin for patients requiring an injectable agent, and amikacin is available for the trial. Kanamycin will continue to be used until the transition to amikacin takes place within each country programme.

Patients should be treated with the fluoroquinolone and injectable allocated at randomisation unless there is a clinical or operational reason to make a change.

Table 2: Regimen Blev doses (for patients randomised under Version 8.0 of the protocol onwards)

Product	**Weight group**		
	Less than 33 kg	**33 kg to 50 kg**	**More than 50 kg**
Levofloxacin	750 mg	750 mg	1000 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/amikacin*	15 mg per kilogram body weight (maximum 1g)		

*With Version 10.0 amikacin or kanamycin may be used

The investigative regimens for the Stage 2 comparisons are Regimen C and Regimen D.

Regimen C is an all-oral regimen that is a modification of Regimen B, and consists of bedaquiline, clofazimine, ethambutol, levofloxacin, and pyrazinamide given for 40 weeks, supplemented by isoniazid and prothionamide in the first 16 weeks (intensive phase). All drugs are given daily (seven days a week), except for bedaquiline which is given daily for the first two weeks and then thrice-weekly from Week 2 onwards. The intensive phase should be extended from 16 to 20 or 24 weeks for patients whose smear has not converted by 16 or 20 weeks, respectively, as described in section 7.3.2. If the intensive phase is extended beyond 16 weeks, then the overall treatment time will be extended except for bedaquiline, which will not be given for longer than 40 weeks in total.

Table 3: Regimen C doses, given daily unless otherwise stated

Product	Weight group		
	Less than 33 kg	**33 kg to 50 kg**	**More than 50 kg**
Bedaquiline	400 mg once daily for first 14 days/200 mg thrice weekly thereafter		
Levofloxacin	750 mg	750mg	1000 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

Regimen D is a six-month regimen that is a modification of Regimen B, and consists of bedaquiline, clofazimine, levofloxacin, and pyrazinamide given for 28 weeks, supplemented by kanamycin and isoniazid in the first eight weeks (intensive phase). All drugs are given daily (seven days a week) except for bedaquiline and isoniazid which are given daily for the first two weeks and then thrice-weekly from Week 2 onwards. After the first 4 weeks of treatment has been completed, in sites where it is not possible to administer kanamycin seven days a week to outpatients the dose may be changed to six days a week from weeks 5-8. The intensive phase should be extended from 8 to 12 weeks and 12 to 16 weeks for patients with a smear positive of 2+ or more at 8 or 12 weeks, respectively, as described in section 7.3.2. If the intensive phase is extended, kanamycin will be given then thrice-weekly from Week 8 onwards.

Table 4: Regimen D doses, given daily unless otherwise stated

Product	Weight group				
	Less than 33 kg	**33 kg to less than 40 kg**	**40 kg to 50 kg**	**More than 50 kg to 60 kg**	**More than 60 kg**
Bedaquiline	400 mg once daily for first 14 days/200 mg thrice weekly thereafter				
Levofloxacin	750 mg	750 mg		1000 mg	
Clofazimine	50 mg	100 mg		100 mg	
Pyrazinamide	1000 mg	1500 mg		2000 mg	
Isoniazid	400 mg	500 mg	600 mg	800 mg	900 mg
	Daily for the first 14 days, thrice-weekly thereafter for the duration of the intensive phase				
Kanamycin	15 mg per kilogram body weight (maximum 1g)				

*Note that in Regimen D isoniazid is administered daily for the first 14 days and then thrice weekly for the remainder of the intensive phase

Regimen D uses a higher dose of isoniazid than in the other treatment regimens in the trial. The dose of isoniazid has been kept to a maximum dose of 15 mg/kg (given daily for the first 14 days only and then reduced to thrice-weekly dosing). At this dose, isoniazid is unlikely to cause excessive adverse effects, the intention being to reach peak serum levels above the median resistance MIC of around 5 µg/ml, shown by the majority of strains with isoniazid resistance (i.e. the katG mutations) and not only the rarer strains with very low MICs due to inhA mutations

During Stage 2, patients allocated to Regimen B, Regimen C or Regimen D will be prescribed pyridoxine to help minimize the risk of isoniazid-related peripheral neuropathy.

All drugs should be given under directly observed treatment (DOT) by a treatment supervisor. Treatment supervisors may be clinic staff or family members or other members of the community, depending on local circumstances. At the end of the intensive phase of all the regimens, if the patient's weight has increased drug doses should be adjusted to allow for changes in patient's weight.

7.2.3 Medicines supplies

Supplies for Regimen A will be provided by the participating countries. The sponsor/funders will distribute the drug requirements for Regimen B, Regimen C, and Regimen D. Bedaquiline will be supplied as 100mg oral tablets from commercial stock manufactured for Janssen Products, LP. Details of drug supplies, storage and distribution are provided in the STREAM Pharmacy Plan.

7.2.4 Treatment cards

Following randomisation, the patient and/or a treatment supervisor will be given the relevant Treatment Card and a prescription to take to the pharmacy. The treatment supervisors will be instructed about observing the patient swallowing their oral medication according to intake schedule (directly observed treatment) and recording treatment taken on the treatment card. Treatment Cards should be returned at each visit and a new card issued.

7.3 Treatment procedures

7.3.1 Dispensing and supervision of medicines

Local policy will be followed as to whether the patient will be admitted to hospital during the intensive phase irrespective of the regimen allocated.

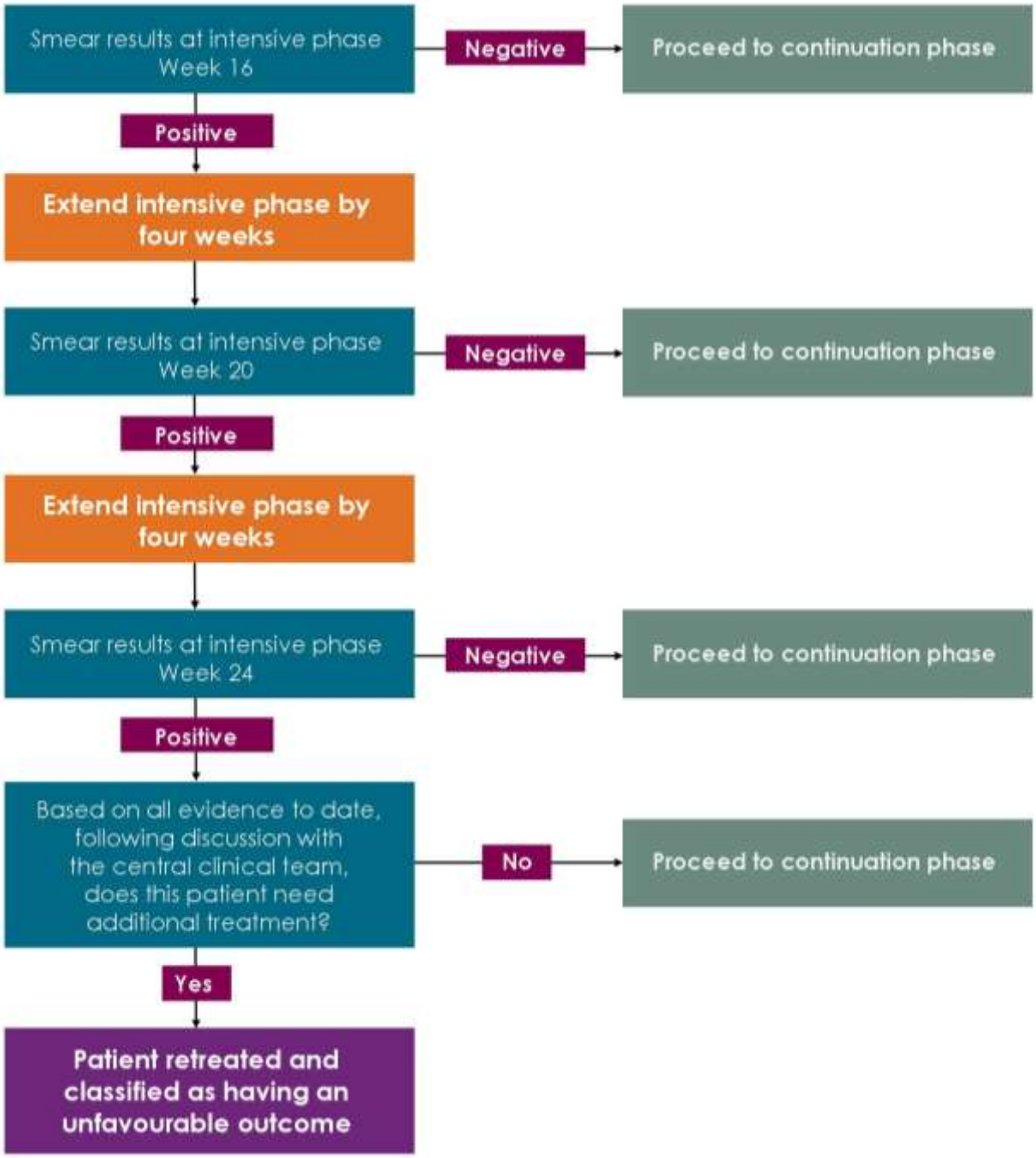
All medicines in Regimen B, Regimen C and Regimen D should be given according to the intake schedule under strict conditions of direct observation of treatment (seen to be swallowed) by a trained treatment supervisor for the whole treatment period. For Regimen A, sites will be strongly encouraged to follow the same standard. Full details of the medicines, regimen, including dosages, for each patient and of the procedure to be followed are also given on each Treatment Card.

The pharmacy staff will maintain drug accountability logs and provide, on a regular basis, a reconciliation report (between products delivered, in stock, dispensed and returned).

7.3.2 Transition from intensive to continuation phase in the regimens

For patients allocated to Regimen B, Regimen C, or Regimen D the following algorithm will be used in Stage 1 and Stage 2 to determine when a patient can proceed from the intensive to the continuation phase.

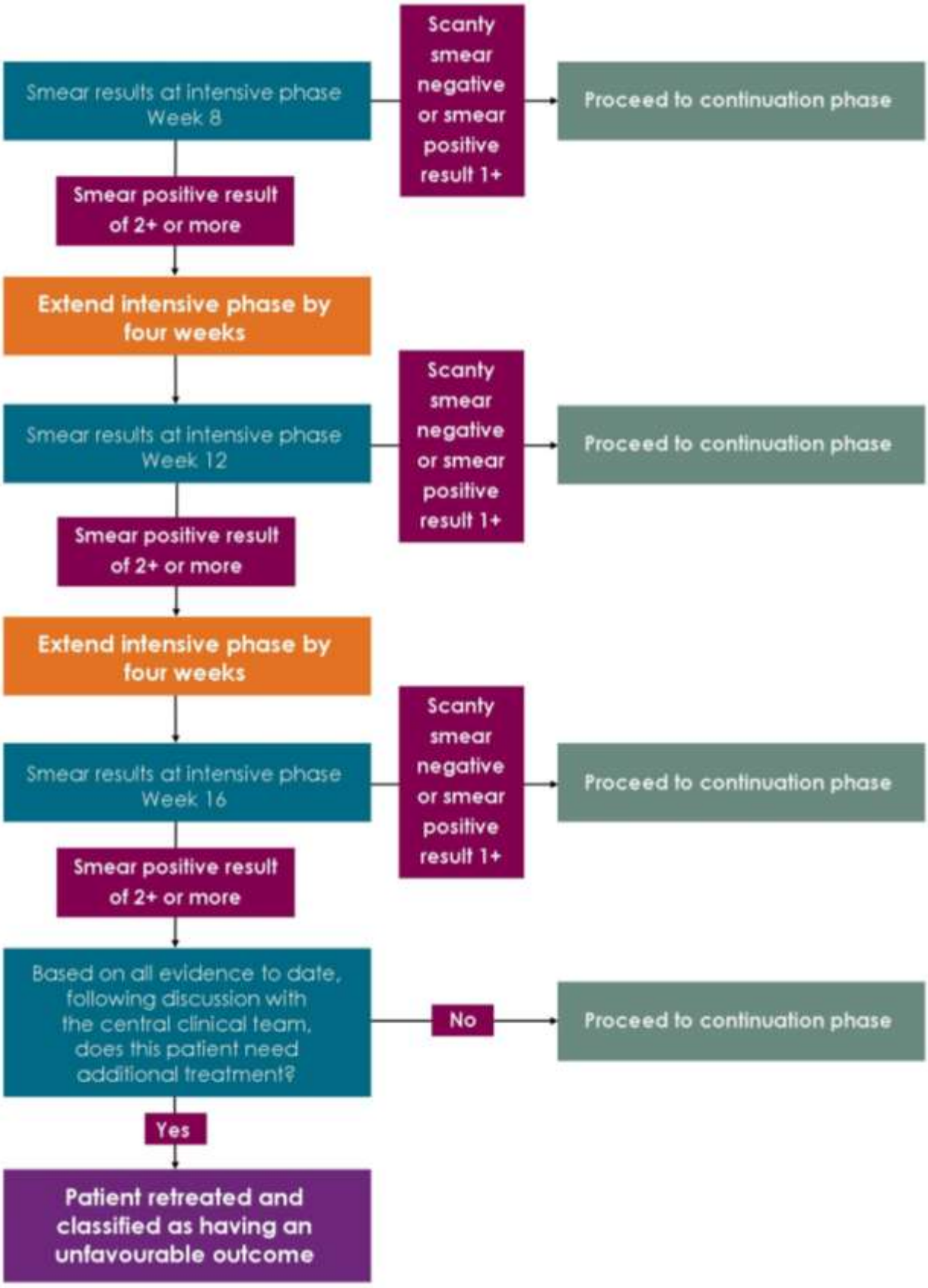
Figure 9: Transition from intensive to continuation phase for patients on Regimen B and Regimen C



Note: smear results based on regular AFB ZN or auramine staining and not FDA vital staining.

Patients randomised to Regimen B or Regimen C will receive 40 weeks of treatment (16 weeks intensive phase plus 24 weeks continuation phase). In the event of positive (at least "scanty" on the IUATLD/WHO scale) AFB smear at week 16, the drugs in the intensive phase of these regimens should be extended by 4 weeks. This extension of treatment by 4 weeks should be repeated at week 20 should the smear remain positive, allowing a maximum duration of the intensive phase of 24 weeks treatment and a maximum total duration of 48 weeks treatment (except for bedaquiline, which will be given for a maximum duration of 40 weeks regardless of whether the regimen is extended).

Figure 10: Transition from intensive to continuation phase for patients on Regimen D



Patients randomised to Regimen D will receive 28 weeks of treatment (eight weeks intensive phase plus 20 weeks continuation phase). As Regimen D has shorter intensive phase duration than the other treatment regimens, it is expected that more patients would have a smear positive result at

the end of the intensive phase than in the other regimens due to the shorter time that patients will have been on treatment to that point. Therefore, the less stringent criterion of a smear positive result of 2+ is sufficient for patients to require an extension of the intense period, i.e. patients can have a positive smear of 1+ and still advance on to the continuation phase, as opposed to Regimen B and Regimen C for which any positive smear result would result in an extension to the intensive phase. In the event of a 2+ or more positive smear at Week 8, the drugs in the intensive phase of the regimen should be extended by 4 weeks, and this extension should be repeated at Week 12 should the smear result remain 2+, allowing a maximum total duration of 36 weeks treatment.

The procedure for transition from the intensive to the continuation phase in Regimen A will be according to local policy.

7.3.3 Procedure following missed treatment

At the discretion of the investigator, any days missed in either the intensive or the continuation phase may be made up by extending this phase of the regimen by the number of days, with the exception of bedaquiline. Although small amounts of missed bedaquiline may be made up, any patient who has missed more than 30 days should not be given any further bedaquiline.

For managing patients who have had a treatment interruption, refer to Section 8.5.1.

7.3.4 Adherence assessment and counselling

At each visit, patients will be counselled about the importance of taking their medication and the dangers of developing further resistance if they fail to do so

7.3.5 Pregnancy & breastfeeding

It is possible that some of the drugs in the regimens, if given to a pregnant woman, will harm the unborn child. As pregnant women in this study population have alternative treatment options, they should not enrol in this trial; neither should women who plan to become pregnant during the trial. Women who could become pregnant must use appropriate contraception (as defined in the inclusion criteria in section 5) while on treatment. Women who are pre-menopausal, or whose last menstrual period was less than one year ago, will be asked to have a pregnancy test before taking part to ensure that they are not pregnant. Any woman who finds that she has become pregnant while taking part in the trial should immediately tell her study doctor who will contact a member of the STREAM clinical team to discuss management of the patient.

All pregnancies occurring in a patient or partner of a patient, in the trial, at any point during treatment or follow-up will be followed for outcome even if the pregnancy continues beyond 132 weeks from randomisation.

Women taking part in Stage 2 of the trial, and are recruited to Regimen C or Regimen D, should not breastfeed when taking bedaquiline, as the effects to their new-born child are unknown. Women who have a new-born child should consult their physician about the best way to feed their child.

7.4 HIV

Patients who are known to be HIV infected or who are found to be HIV infected at trial screening will be recruited into the study and follow the routine study procedures, provided they fulfil all other study eligibility criteria.

Newly-diagnosed HIV positive patients will be given appropriate counselling about the medical consequences of their diagnosis and about the need to take responsible precautions to reduce the risk of infecting others. They will be referred to appropriate medical and social HIV treatment services, and will be given the option of not proceeding to the randomisation stage of the STREAM trial if they wish to re-consider their options.

HIV co-infected patients in the STREAM trial will be managed or co-managed by clinicians with appropriate expertise in HIV medicine. It will be important therefore for the Principal Investigator at each participating site to establish links with the national AIDS programme and/or organisations that provide treatment in their country. Wherever possible, patients in the STREAM trial who are co-infected with HIV will be managed in a joint treatment clinic to ensure close co-ordination of management of the two conditions, and to ensure that appropriate decisions can be made concerning the management of drug interactions and side-effects.

Guidance on opportunistic infection prophylaxis, management of interactions between TB and HIV drugs, management of toxicity, and the timing of initiation of HIV and MDR-TB treatment are provided in the STREAM Patient Management Guide.

7.4.1 Permissible ART

All HIV co-infected patients who are taking ART during screening must be switched to one of the following permissible ART regimens during screening and at least one week prior to randomisation:

- Lopinavir/ritonavir based regimen consisting of lopinavir/ritonavir in combination with any two nucleoside reverse transcriptase inhibitors (NRTI)s
- Nevirapine (NVP) based regimen consisting of NVP in combination with any two NRTIs
- Integrase inhibitor based regimen consisting of an integrase inhibitor (either dolutegravir or raltegravir) in combination with any two NRTIs
- Triple NRTI based regimen, e.g. a regimen made up of zidovudine, lamivudine, and abacavir, or in accordance with local standard of care

The choice of regimen is dependent on local availability and preference of the treating clinician.

Patients randomised to Regimen C or Regimen D who start ART while on randomised treatment must take one of the permissible ART regimens listed above; they may start alternative ART on completion of their study regimen. Regimen A and B patients may start alternative ART at any time after randomisation at the discretion of the treating clinician.

The investigator must assess the risks and benefits of these antiretroviral regimens in the context of co-infection with MDR-TB, acknowledging the following caveats:
a) Triple NRTI is generally not considered optimal long-term ART;

b) Nevirapine based regimens are associated with higher ART failure in subjects having or known to have previously had a viral load more than or equal to 100,000 copies/mL

7.5 Other non-trial treatment

The following medications and foods are not allowed during administration of bedaquiline:

- The systemic use of moderate and strong CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, fluconazole, voriconazole, itraconazole; ketolides such as telithromycin; clarithromycin; integrase inhibitors containing cobicistat; or grapefruit juice) for more than 2 weeks
- The systemic use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort [*Hypericum perforatum*], rifamycins, and systemic, multiple dosing of dexamethasone).

The investigator should consult the label information, and if necessary contact the appropriate sponsor representative. A full list of CYP3A4 inhibitors and inducers may also be accessed via the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Unless part of the allocated regimen, drugs that are known to prolong the QT interval should not be used while the patient is on trial treatment. For patients whose allocated regimen includes bedaquiline (arms C and D), no drugs known to prolong the QT interval should be introduced until at least 4 weeks after the last dose of bedaquiline. The following list includes some examples of drugs known to prolong QT, but is not comprehensive:

- Antiarrhythmics Class IA, e.g. quinidine, hydroquinidine, disopyramide
- Antiarrhythmics Class III, e.g. amiodarone, sotalol, dofetilide, ibutilide
- Certain antifungals, e.g. fluconazole, ketoconazole
- Certain neuroleptics, e.g. phenothiazines, pimozide, sertinodole, haloperidol, sultopride
- Tricyclic antidepressive agents
- Certain antimicrobials, e.g. moxifloxacin, gatifloxacin, sparfloxacin, erythromycin IV, pentamidine
- Delamanid
- Certain antimalarials, e.g. halofantrine
- Certain antihistamines, e.g. terfenadine, astemizole, mizolastine
- Others: cisapride, vincamine IV, bepedril, diphemanil.

A more comprehensive list of QT-prolonging drugs may be accessed at www.crediblemeds.org

8. ASSESSMENTS AND FOLLOW-UP

8.1.1 Assessment schedule

See Table 5 in Section 8.1.1 for details of the assessments required for each visit for Stage 1, and Table 6 in Section 8.1.2 for details of the assessments required for each visit for Stage 2.

The intensive phase of treatment may be extended for late smear conversion or missed treatment (see sections 7.3.2 and 7.3.3). The continuation phase may also be extended for missed treatment.

For selected sites, at randomisation and every 12 weeks thereafter, patients will be interviewed to document the costs e.g. transport and hospitalisation costs, incurred by them in adhering to the regimen. System costs will also be estimated.

Stage 1

In Stage 1, patients will be assessed at screening, randomisation (Week 0), Week 1, Week 2, Week 3, Week 4, and at 4-weekly intervals throughout the study, until the end of follow-up, irrespective of whether on treatment or in the post-treatment follow-up phase.

Sputum for smear and culture will be collected at every visit, except at Week 1, Week 2, and Week 3, when no samples will be collected. At most visits this will be a single specimen during Stage 1, unless otherwise indicated in section 8.1.1. When two samples are required, if a patient does not bring an early morning sample, two spot samples will be collected at the visit.

Stage 2

In Stage 2, patients will be assessed at screening, randomisation (Week 0), Week 1, Week 2, Week 3, Week 4, after which they will be seen 4-weekly until Week 52, then 8-weekly until Week 84, and 12-weekly thereafter until end of trial follow-up.

A minimum of two sputum specimens should be collected at the screening and randomisation visit (with a third being an early morning sample if possible).

Two sputum specimens will be collected at every subsequent visit for smear and culture, except at Week 1, Week 2, and Week 3, when no samples will be collected. Because early morning samples are preferred, at the conclusion of each visit patients should be given a sputum container for sample collection to be presented at their next visit. The second sample will be taken as a spot sample at the time of clinic attendance. If a patient does not bring an early morning sample, two spot samples will be collected at the visit.

Routine sputum collection will end when the last patient is projected to have reached Week 96 (approximately end of November 2021). Thereafter sputum will be collected only if clinically indicated.

Table 5: Assessment schedule – for all patients recruited in Stage 1

Observation/ Investigation	Screening	Randomisation	Treatment Phase			Post-Treatment Phase
			Intensive Phase		Continuation Phase	Follow-up
			Weeks 1 – 3	Weeks 4 onwards		
Written informed consent	X	X				
Demographics	X	X				
Medical History	X	X				
Clinical Examination	X	X	X	X	X	X
Clinical assessment (including AEs and concomitant medication during treatment)	X	X	X	X	X	X
Height		X				
Weight		X	X	X	X	X
Simple hearing test		X	If clinically indicated			
HIV antibody test	X					
CD4 (in HIV positive patients)		X	According to national guidelines			
Haemoglobin		X				
AST and ALT	X		X	X		
Serum creatinine		X	X	X		
Serum potassium		X	X	X	If clinically indicated	
Blood glucose		X				
Urinalysis (dipstick)		X	X	X		
Urine: hCG Pregnancy test	X	X	If clinically indicated			
Chest X-ray		X				
ECG (12-Lead)	X	X[4]	X	Weeks 4 & 12	Weeks 24 & 36	
Sputum smear and culture[3]	X[1]	X[2]		X[1]	X[1]	X[1]
Sputum for drug resistance testing	X[6]					
Patient's costs (in selected sites)		X		X	X	X
Blood sample for storage (if patient consents)		X			X[5]	

X indicates assessments required at particular visits.

[1] At least one sample will be collected per visit, except at the final visit of each phase of treatment and at the Week 132 follow-up visit, when two samples will be collected.

[2] At least two samples will be collected at this visit.

[3] All positive strains post-randomisation onwards will be shipped to the reference laboratory for full drug susceptibility testing.

[4] One ECG will be done prior to randomisation and others at 4 hours after administering the first dose of treatment.

[5] One sample will be collected for storage at 16 weeks, for patients consenting to sample storage.

[6] Sputum will be collected for LPA sensitivity testing for resistance to rifampicin, fluoroquinolones and second-line injectables. If results for fluoroquinolones and second-line injectables sensitivity are inconclusive, then these tests need to be repeated on a new sputum sample before randomisation.

Table 6: Assessment schedule – for all patients recruited in Stage 2

The following assessment schedule applies to *all* treatment arms in the STREAM trial as soon as Stage 2 begins (for sites participating in Stage 2).

Observation/Investigation	Screening	Randomisation	Treatment Phase			Post-Treatment Phase
			Intensive Phase		Continuation Phase	Follow-up
			Weeks 1 – 3	Weeks 4 onwards		
Written informed consent	X	X				
Demographics	X	X				
Medical History	X	X				
Alcohol Use Questionnaire		X		Week 16	Week 32	Week 52
Clinical Examination	X	X	X	X	X	X
Clinical assessment (including AEs and concomitant medication during treatment)	X	X	X	X	X	X
Height		X				
Weight	X	X	X	X	X	X
Visual acuity and colour tests		X		Week 12 (and if symptoms)	Week 28 and 40 (and if symptoms)	
Hearing test	X		Week 1 (If clinically indicated)	Week 4, 8 and 16	At the start of the continuation phase[11], Week 28 and 40	Weeks 52, 76 and 132
Haemoglobin		X				
HIV antibody test	X					Week 76[15]
CD4 (in HIV positive patients)	X		According to national guidelines, at end of BDQ dosing and at week 132			
Viral load (in HIV positive patients)	X			X[13]	X[13]	X[13, 15]
Hepatitis A, B and C testing		X				
Urinalysis (sample sent to) central lab		X	X	X	X	X[17]
Urine: HCG Pregnancy test	X	X	If clinically indicated and at end of study			
Chest X-ray[14]	X					
ECG (12-Lead)[3]	X	X	X	X	X	X
Additional Post-Dose ECG (12 Lead) for sites in PK study[4]			Week 2	Week 12	Weeks 24 & 40	
Sputum smear and culture[2]	X[1]	X[1]		X[1]	X[1]	X[1]
Sputum for drug resistance testing	X[6]					
Patient's costs (in selected sites)		X		X[12]	X[12]	X[12]
Blood sample for storage (if consents)[5]		X[5]			X[5]	
PK samples[7,8,9,18]		X	Week 2	Weeks 4 & 12	Weeks 24 & 40	Weeks 76, 120 & 132

Laboratory safety tests[10]	X	X		X	X	X[16]
TSH & thyroxine of free thyroxine	X					Weeks 40 & 76

X indicates assessments required at particular visits

[1] At screening and randomisation two samples will be collected, with an additional third early morning sample if possible. Two samples will be collected at each subsequent visit, ideally one early morning and one spot sample, or two spot samples if the patient does not provide an early morning sample. Refer to the STREAM Microbiology Manual for details of the tests to be undertaken.

[2] Screening, randomisation, and all positive isolates of MTB post-randomisation from week 8 onwards will be shipped to the reference laboratory for full drug susceptibility testing.

[3] An ECG will be conducted prior to randomisation, a further ECG will then be conducted 4 hours after administering treatment at the randomisation visit. A 12-lead ECG will then be collected at each visit until Week 76. In participants who at Week 76 have a QTcF increase from baseline, a 12-lead ECG will be collected at each visit until the QTcF returns to either less than a 10ms increase above the baseline value or less than 450 ms. Single ECGs will be collected; however for QTcF prolongatons of more than or equal to 500 ms, two further ECGs must be collected.

[4] For patients on arms C and D, enrolled at sites that have been pre-selected for the PK sub-study, an additional 12-lead ECG will also be conducted 4 hours after administering treatment at the week 2, 12, 24 and 40 visits

[5] A blood sample will be collected for storage at randomisation and week 16 , for patients consenting/assenting to sample storage.

[6] Sputum will be collected for drug sensitivity testing for resistance to rifampicin, fluoroquinolones and second-line injectables. If LPA results for fluoroquinolones and second-line injectables sensitivity are inconclusive, then these tests need to be repeated on a new sputum sample before randomisation.

[7] The PK samples will be collected pre-dose and post-dose (sample from Week 2 visit). Details of PK sampling are specified in section 8.2.1.

[8] Samples for analysis of the plasma concentration of nevirapine (NVP) and lopinavir (LPV)/ritonavir(RTV) must be taken before intake of ARV and study drug. An additional pre-dose sample will be collected if the antiretroviral treatment regimen of a patient is changed, followed by sampling at time points indicated in the Assessment Schedule.

[9] Sample for analysis of the plasma concentration of nevirapine (NVP) and lopinavir (LPV)/ritonavir (RTV) and 4 β OH-cholesterol.

[10] See Section 8.2 for blood test details.

[11] Hearing test will be conducted at the first visit of the continuation phase.

[12] Patient costs collected every 12 weeks from after randomisation in selected sites.

[13] Viral load collected at Week 12, Week 24, Week 40, and Week 76.

[14] A chest X-ray is required at randomisation that is compatible with a diagnosis of pulmonary TB, however if a good quality X-ray is available that was taken in the 4 weeks prior to randomisation it does not need to be repeated

[15] HIV test at week 76 (for patients who were found to be HIV negative at screening). For patients found to be HIV positive at this visit a week 76 viral load measurement should also be taken.

[16] Laboratory safety tests should be undertaken at each visit to Week 76. After Week 76 only if clinically indicated.

[17] Urinalysis to central lab should be undertaken at each visit to Week 76. After Week 76 only if clinically indicated.

[18] Samples will not be taken after the projected Week 96 visit of the last patient randomised i.e. approximately end of November 2021.

8.2 Blood tests for Stage 2

For patients recruited in Stage 2, a blood sample for hepatitis A (IgM), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) and hepatitis C virus (HCV) antibody testing will be collected at the randomisation visit.

Blood samples for complete blood count (CBC) and serum chemistry will be measured at every scheduled evaluation (this excludes visits at weeks 1, 2, and 3) until the week 76 visit (as referred to as 'laboratory safety tests' in Table 6. After Week 76, blood tests will be undertaken if clinically indicated. All trial-specific samples taken at any time point will be processed and analysed centrally or at appropriately qualified local laboratories.

The CBC panel includes: RBC, WBC, platelets, Hb level, haematocrit, MCV and MHC.
The serum chemistry panel includes: sodium, serum bicarbonate, calcium (uncorrected), calcium (corrected for albumin), serum potassium, magnesium, chloride, blood glucose, blood urea nitrogen, serum creatinine, alkaline phosphatase, pancreatic amylase, human serum albumin, total protein, AST, ALT, total cholesterol, creatine phosphokinase, gamma-glutamyltransferase, creatine phosphokinase of muscle brain, total direct-indirect bilirubin, triglycerides, lipase, lactate dehydrogenase, uric acid.

8.2.1 Pharmacokinetic (PK) Evaluations

In Stage 2, the pharmacokinetics of bedaquiline will be assessed in all subjects from Regimen C and Regimen D enrolled at sites that have been pre-selected for the PK sub-study. It is important that patients on these regimens be informed to take their bedaquiline around the same time each day (as bedaquiline intake should ideally not vary by more than 2hours each day) and to take their study regimen with food.

To inform on drug-drug interactions of anti-tuberculosis drugs with ARTs, additional PK analysis will be performed in HIV positive patients who are enrolled into the PK sub-study; at least 20 patients who are receiving lopinavir/ritonavir and at least 20 patients who are receiving nevirapine as part of their ART will be included in the PK analysis. The history of ART intake up to one month prior to randomisation will be recorded in the CRF.

8.2.2 PK Blood Sampling

Venous blood samples for PK evaluation will be collected from all subjects at sites pre-selected for the PK sub-study at pre-specified time points outlined below. Samples will be collected, processed and shipped to the central laboratory as instructed in a laboratory manual provided separately.

All blood samples, with the exception of those taken at baseline, will be quantified for the determination of plasma concentrations of bedaquiline and M2. 4β-hydroxycholesterol and cholesterol will be quantified from PK samples collected at Baseline, and pre-dose samples of Week 4, 12, 24, and 40 for an assessment of the 4β-hydroxycholesterol/cholesterol ratio. Pre-dose blood samples from HIV positive patients will also be quantified for lopinavir/ritonavir and nevirapine.

8.2.3. Timing of PK blood samples and ECGs

A pre-bedaquiline dose blood sample must be taken within 1 hour of the next scheduled bedaquiline dose. A pre-ART blood sample should also be taken at this time in HIV co-infected patients on lopinavir/ritonavir and nevirapine.

A 12-lead ECG, which is in addition to the 12-lead ECG performed at each study visit as per the Stage 2 assessment schedule (Table 6) above), must be done 4 hours after the bedaquiline dose. A post-bedaquiline dose blood sample must then be taken 4-5 hours after bedaquiline intake and within 20 minutes of the post-dose ECG. The schedule for collection of PK blood samples and post-dose ECGs is outlined in Table 7 below.

Table 7: PK Sample Collection Timings

Visit	Pre-bedaquiline dose PK blood sample	Pre-ART dose blood sample	Post-bedaquiline dose PK blood sample	Additional post-bedaquiline dose 12-lead ECG
Randomisation	√	√		
2	√	√	√	√
4	√			
12	√	√	√	√
24	√		√	√
40	√		√ (Arm C only)	√ (Arm C only)
76	√			
120[1]	√			
132[1]	√			

[1] PK samples will not be taken after the projected Week 96 visit of the last patient randomised i.e. approximately end of November 2021.

8.2.4 Additional PK investigations for toxicity or change of ART

An additional blood sample should be collected at any visit when BDQ is withheld for suspected toxicity. If the antiretroviral treatment regimen of a patient is changed during the 40-week treatment period for Regimen C or the 28-week treatment period for Regimen D, a pre-dose sample should be collected, followed by collections as described above.

The exact date and time of each PK blood sample and the respective previous 2 doses of bedaquiline will be recorded in the CRF. For participants receiving lopinavir/ritonavir or nevirapine, the last three doses and dates of the ART prior to each PK sample time-point will be recorded in the CRF.

8.2.5 Bioanalysis

The bioanalysis will be performed by a contract research organization (CRO), under the supervision of the Sponsor and/or Janssen. Samples will be analysed using a validated and sensitive liquid chromatography-mass spectrometry/mass spectrometry method

8.3 Procedures for assessing safety

Throughout this study, patients will be closely monitored for signs and symptoms of drug toxicity. All toxicities leading to the study therapy being temporarily or permanently discontinued and all Grade 3 or greater toxicity effects will require thorough investigation with relevant clinical and laboratory tests, as clinically indicated.

These should be repeated as needed until final resolution or stabilisation of the toxicity; if this is after the end of the trial, follow-up will be the responsibility of the treating clinician. All symptoms and laboratory findings will be graded according to severity using DAIDS criteria. Laboratory events will be reported as adverse events only if clinically significant. If the patient has a medical diagnosis at randomisation whose signs or symptoms worsen during the study to a Grade 3 or greater, this is a notable event (NE) that must be reported. Other notable events and SAEs will be reported as they occur to the MRC CTU, as well as to other bodies required to be notified in each country. For details of safety reporting see Section 13.

8.3.1 ECG Monitoring

Several of the drugs used in the STREAM regimens have the potential to prolong QT, therefore ECG monitoring is used in both Stage 1 and Stage 2 to identify and manage patients who are at risk.

In Stage 1, all patients will have a 12-lead ECG immediately prior to randomisation and will be ineligible if the QT or QTcF interval is more than or equal to 500ms. An ECG will be recorded 4 hours after the first dose of trial treatment. Further ECGs will be performed weekly for the first four weeks, and then every four weeks until 52 weeks after randomisation. If a patient has a QT or QTcF of 450ms or more, then a second ECG should be conducted at least 10 minutes after the first ECG.

In Stage 2, if there is a QT or QTcF measurement of 450 ms or more the patient will not be eligible for randomisation. ECG monitoring for Stage 2 involves 12-lead ECGs undertaken at baseline (pre and 4 hours post-dose at the randomisation visit), weekly for the first four weeks and at every visit until week 76. All patients whose QTcF at week 76 is higher than their baseline recordings will continue to have 12-lead ECG monitoring at every visit until the confirmed QTcF is either less than 10 ms above the baseline value or below 450 ms.

In addition, patients in arms C and D enrolled at sites that have been pre-selected for the PK sub-study, should also have an ECG 4 hours after administering treatment at the week 2, 12, 24and 40 visits (see Section 8.2.3).

Any QT or QTcF prolongation to more than or equal to 500 ms while on treatment is considered a notable event and should be reported immediately to MRC CTU (See Section 13).

Patients found to have a QT or QTcF more than or equal to 500 ms on a 12-lead ECG at any point during treatment will be further investigated. The ECG should be repeated and if confirmed, the investigator should attempt to identify the cause, including checking and correcting abnormal K^+,

Ca^{+2}, and Mg^{+2}. If the patient is taking any drugs suspected of causing QT prolongation they should be withheld and the tests repeated to try to identify the cause. Further details are provided in the STREAM Patient Management Guide.

8.4 Post-treatment schedule

After completion of treatment the patient will be reminded of the need for follow-up visits by the Principal Investigator, or recruiting clinician, and be informed of the date of their next visit.

During the follow-up visits, the following procedures will be undertaken:

- Clinical investigations (as outlined above) will be carried out
- Patients will be asked about any adverse events that may have occurred after their last visit and any concomitant medications they may have received.

There may be times when the PI requests additional tests for a patient depending on their disease progression at a particular visit.

8.5 Changes to treatment or follow-up

8.5.1 Interruptions to treatment

The treatment regimens or selected drugs may be interrupted at the discretion of the local PI or treating clinician:

- For a serious adverse event
- For a QT or QTcF measurement of more than or equal to 500ms
- If ALT/AST rise to more than or equal to 5 times ULN, or if AST/ALT rise to more than or equal to 3 times ULN in the presence of a total bilirubin rise to more than or equal to 2 times ULN
- If the investigator decides to withhold treatment in the interest of the safety and well-being of the participant.

If treatment is interrupted for a suspected serious drug reaction, attempts should be made to identify the drug concerned. Further guidance on expected toxicities is provided in the STREAM Patient Management Guide. After resolution of the suspected adverse reaction, treatment may be gradually re-introduced until the allocated regimen has been re-instituted.
If treatment with one of the core drugs other than bedaquiline (i.e. kanamycin or amikacin, isoniazid, moxifloxacin or levofloxacin, and clofazimine) is missed in either the intensive or continuation phase of one of the study regimens this can be made up by extending this phase of the regimen by the number of treatment days missed at the discretion of the treating physician and in the absence of ongoing toxicity.

Bedaquiline treatment interruptions will be handled separately to those involving the other core drugs, and are managed based on the phase of bedaquiline dosing:

- Treatment interruptions during the 14-day loading period:
    - All treatment interruptions during the loading phase of bedaquiline must be reported to the clinical team at the MRC CTU within one working day of the site becoming aware, and advice will be given on a case by case basis

- For interruptions of less than or equal to 14 days, bedaquiline loading should resume at the point of the last dose to complete the total doses required in the loading period with the doses previously received taken into account
- For interruptions of >14 days, treatment should be re-started at the beginning of the loading period. The full 14 days of loading should be completed with no accounting for doses taken already
- Only one treatment interruption is allowed during the loading phase and restarting treatment is not permitted after interruptions of >30 days

- Treatment interruptions during the thrice-weekly maintenance dosing period:
  - Bedaquiline can be resumed at maintenance dosing for interruptions of up to 30 days
  - More than one interruption of up to 14 days is allowed but only one interruption of between 15 and 30 days is permitted
  - Restarting bedaquiline after treatment interruptions of >30 days is not permitted
- A maximum of 40 weeks' of bedaquiline (measured by number of doses, not by time since first dose) can be administered to any patient

There is no requirement to change the dates of scheduled PK sampling visits in response to treatment extensions. Treatment adherence must be accurately recorded, and this data can be used to adjust calculated pharmacokinetics.

In the event that the local PI considers that treatment needs to be modified or changed, he or she should inform MRC CTU by submission of an SAE/NE form and discuss treatment plans with a member of the central clinical team.

8.5.2 Missed visits

For each patient, clinic staff will obtain or confirm contact information. In the event that a patient misses a scheduled appointment, a Home Visitor will try within the week following the missed appointment to establish communication with the patient and/or treatment supervisor through all possible means which they have approved and while protecting their confidentiality (e.g. by telephone if this is possible, writing to the patient and contacts, and/or visiting the patient's home or workplace). All attempts to locate a patient following each missed appointment should be documented in their records. The need to attend all scheduled follow-up visits will be emphasised to all study patients at every visit.

8.5.3 Visit after a missed appointment

Patients who miss their scheduled appointment will be contacted and arrangements made for a new appointment. If patients are not successfully reached by phone/text messaging, a home visit should be made and the outcome recorded on a home visit form.

Patients returning after missed appointments should undergo the scheduled assessments for the visit that is closest to the time from randomisation (e.g. if a patient returns to the clinic at or near to Week 16 after missing their visits for weeks 8 and 12, the visit for that day should be recorded as Week 16 and the Week 16 assessments undertaken). Subsequent visits will continue as scheduled. However, treatment to be prescribed should be determined by the actual number of days on which a patient has taken their medication and not by the length of time they have been in the study.

8.5.4 Loss to follow-up

If a patient does not return to the clinic before the study is closed, a Final Form will be completed at the time of study closeout, after reasonable effort to contact the patient has been made. The form should indicate that the patient was lost to follow-up. The "loss to follow-up" designation cannot be made for any patient until after the patient's scheduled Week 132 visit.

8.5.5 Follow-up of patients discontinued from treatment

Every effort should be made to follow up all patients for the full duration of the study, including those whose treatment is discontinued or whose treatment is changed. A reduced frequency of follow up may be appropriate, and if necessary, should be agreed with the MRC CTU. In this event, a final status form should be completed. For patients who have discontinued follow-up visits, but have not withdrawn consent, the vital status should be obtained at least every six months until Week 132, if necessary by telephone follow up.

If a patient can be contacted and declines further study participation, an investigation into their reasons will be conducted, and the reasons documented. An attempt will be made to have him/her come to the clinic for a final visit, or at least obtain a sputum sample for the assessment of the primary efficacy outcome.

8.6 Trial closure

The trial will be considered closed when the last patient has completed their final visit and all follow-up and laboratory reports have been received.

The trial may be terminated early by the Trial Steering Committee (TSC), on the advice of the Independent Data Monitoring Committee (IDMC) (see sections 19.2 and 19.3). In addition, MRC CTU and the Sponsor have the right to close this trial and/or a site, at any time, although this should occur only after consultation between involved parties and with the agreement of the TSC.

At trial closure, the local and central Research Ethics Committees/Institutional Review Boards and the regulatory authorities that approved the trial should be informed. It is the responsibility of the sponsor to inform the main REC within 90 days of the 'end of the trial' that the trial has closed.

Following trial closure remaining samples will be transferred to a biobank following approval from the TSC.

Should a site be closed prematurely, trial materials will be disposed of according to the site agreement with the Sponsor or MRC CTU. The Principal Investigator will retain all specified documents, for at least 15 (fifteen) years, until notification is given by MRC CTU for destruction. Patients currently on treatment will be transferred to another STREAM site where available, or referred to the National Tuberculosis Programme for completion of treatment and further management.

8.7 Bacteriology

The following bacteriological tests will be performed at the site microbiology laboratory: smear, culture, diagnostic line probe assays or GeneXpert. At each visit, except for Week 1, Week 2, and Week 3, sputum samples will be collected. At most visits during Stage 1 this will be a single specimen unless otherwise indicated in sections 8.1.1, and will be two specimens during Stage 2. All specimens will be tested for AFB smear and culture. Because early morning samples are preferred, at the conclusion of each visit patients should be given a sputum container for sample collection to be presented at their next visit. The second sample will be taken as a spot sample at the time of clinic attendance. When two samples are required, if the patient does not bring an early morning sample, two spot samples will be collected at the visit. If a patient is unable to produce sputum this should be documented on the CRF.

The selected methods and techniques for use by the sites may not be the most sensitive ones, but they are simple and applicable at any site with high reproducibility, thus allowing a high degree of standardisation. Long-term follow-up will compensate for imperfect sensitivity. These methods are:

- hot Ziehl-Neelsen (ZN) or auramine fluorescence technique for all study smears
- FDA vital staining for selected smears in some sites (see 5.2.1)
- decontamination without neutralisation centrifugation and direct inoculation on acidified Ogawa (Kudoh medium) for isolation of mycobacteria and subsequent identification of all positive study cultures using any locally available method (e.g. GeneXpert, Hain Genotype MTBDRplus, SD Bioline).
- Hain Genotype MTBDRPlus line probe assay (LPA) from smear-positive sputum or GeneXpert System (Cepheid automated diagnostic test to identify rifampicin resistant *Mycobacterium tuberculosis*) for screening of suspects. If one of these tests or other DST shows at least resistance to rifampicin, the Hain Genotype MTBDRsl LPA will be performed to exclude fluoroquinolone and second-line injectable resistance.

To increase the probability of having at least one good baseline isolate, the sites should also inoculate the remaining part of the randomization and screening samples using their preferred culture method and medium (e.g. MGIT after neutralization and centrifugation).

All positive isolates, except those of week 4, will be sent to the designated study reference laboratory, to confirm species identification and susceptibility status. This includes diagnostic strains and recurrence strains, in case of failure or relapse besides isolated positive cultures in-between successive negatives. Strains from recurrences will be tested for DST as well as fingerprinting, to confirm their identity and to compare their resistance pattern with the originally isolated strain. The reference laboratory will store all study strains at -80°C and local laboratories will store at -20°C.

The techniques to be used at the reference laboratory are:

- Slow phenotypic DST using the proportion method on Löwenstein-Jensen medium for first line drugs and agar-based Middlebrook 7H11 medium for second line drugs; for difficult strains, the minimum inhibitory concentration (MIC) and DNA sequencing can be used to arrive at the most correct result
- Fingerprinting; MIRU-VNTR analysis (mycobacterial interspersed repetitive units–variable number of tandem repeats).

A detailed description of the various laboratory tests is found in the STREAM Microbiology Manual.

Results of resistance tests undertaken by the reference laboratory are primarily for analysis purposes and will not be routinely provided to the sites. Treatment changes will not be suggested on the basis of these results unless a patient is not doing well and it is decided that a change of treatment is required.

However, if any patients are found to have XDR-TB (confirmed resistance to fluoroquinolones and second-line injectables from phenotypic DST) from samples collected at baseline, these results will be provided to sites, and the patients should be withdrawn from trial treatment and treated according to national guidelines.

8.8 Health economic assessment

In sites participating in the health economic component of STREAM, data relevant to the health economic assessments will be collected as explained below:

8.8.1 Health system costs

Health system costs will be obtained through:

- An analysis of health worker time involved in prescribing, monitoring, and supervising the regimens in each country, health worker salary and benefits data from the Ministry of Health and health facility records based on grade of staff rather than named individuals
- A full assessment of the health system costs of delivering the MDR-TB regimens, including tests performed, consumables used, in-patient stay costs, drugs administered and overheads
- Standard costs of supplies from hospitals' accounting records where possible. Other appropriate sources such as private healthcare facilities costs will be used if data not available in hospitals' records
- An analysis of the costs associated with the diagnosis and management of serious adverse events (SAEs) caused by MDR-TB or its treatment. This will include all tests performed, examinations, investigations, in-patient stays and medication received, as well as staff costs.
- Summing the costs of each resource used in delivering the MDR-TB regimens

Costs will be assessed as one-off costs required for establishing the regimens and as costs for recurrent costs for sustaining it.

8.8.2 Patient and household costs

Data on patient and household costs will be collected through patient interviews based on the STOP-TB questionnaire. Interviews will take place at intervals of 12 weeks after initiation of treatment. The interviews will include questions out-of-pocket costs on fees paid to the health system, such as drugs and laboratory test costs, transport, food and accommodation costs incurred as a result of the treatment process. In addition, there will be questions regarding quality of life as well as time lost from economic activities.

8.8.3 Socio-economic status

The socioeconomic status of patients will be assessed through asking patients about asset ownership. The assets will be determined based on existing poverty analyses or similar sources (demographic and Health Surveys, population income surveys or census data) for the country or region within the country. These questions about asset ownership will be included in the demographic assessment at randomisation and again every 12 weeks after the initiation of treatment.

9 DISCONTINUATION FROM TREATMENT

In consenting to trial participation, patients are consenting to study treatment, follow-up and data collection. If a patient wishes to discontinue their allocated study treatment they should not be withdrawn from follow-up unless they expressly request it. Patients should be told about the importance of remaining on follow-up, or failing this, of allowing routine follow-up data to be used for study purposes.

The treating clinician will be discouraged from changing or restarting treatment without evidence of treatment failure or recurrence of MDR-TB. As soon as the treating clinician has any indication of a treatment failure, recurrence, or serious toxicity, they should contact the STREAM central clinical team to discuss whether treatment should be modified. Guidelines for retreatment, in the STREAM Patient Management Guide, will be used to inform the decision, which will be made on a case-by-case basis using all the available bacteriological and clinical data. If the decision is made not to retreat, then the case should be reassessed as further data accumulates with further discussions with the STREAM central clinical team as necessary.

9.1 Discontinuation of allocated regimen

The Investigator must make every reasonable effort to keep each patient on their allocated regimen and in follow-up for the whole duration of the study. However, if it is necessary to discontinue or change a patient's allocated regimen, every reasonable effort will be made to ensure the patient continues to be followed-up.

The following are justifiable reasons for the Investigator to discontinue or modify a patient's allocated treatment:

1. Unacceptable toxicity
2. Patient refuses to take study drugs
3. Serious violation of the study protocol (including persistent patient attendance failure, non-adherence to treatment and persistent non-compliance)
4. The Investigator decides to discontinue a patient's treatment for clinical reasons not related to the regimens
5. Evidence of treatment failure based on consistently positive bacteriology usually accompanied by signs and symptoms of disease
6. Pregnancy; women who become pregnant will stop their allocated trial treatment, and be treated according to local practice
7. A confirmed QT or QTcF more than or equal to 500 ms on 12-lead ECG in patients for whom no other cause can be identified
8. Confirmed resistance to fluoroquinolones and second-line injectables from phenotypic DST.

If it is local practice to do so, results from local drug susceptibility tests showing a patient's isolate is resistant to trial medications may be used to justify a change of treatment for patients, although this is discouraged if the patient is doing well clinically. Drug susceptibility test results alone should not be used to justify a change or discontinuation of treatment for patients in the regimens, although patients found to have resistance to **both** fluoroquinolones **and** second-line injectables from phenotypic DST (confirmed XDR-TB) should be withdrawn from trial treatment and treated according

to national guidelines (see section 5.5.1). If these results are obtained from a local laboratory, a patient can remain on trial medication at the discretion of the treating clinician if the patient appears to be doing well on treatment. However, if results from the central laboratory confirm XDR-TB, then the patient should be removed from the trial and treated according to national guidelines.

Should drug unavailability occur, local supply of drug(s) through the National Tuberculosis Programme or local market will be considered (after ensuring acceptable quality) for all study drugs except bedaquiline while regular study supplies are replenished. In instances where drug(s) remain unavailable for any period of time the central clinical team will be consulted to advise on appropriate management.

Any change or discontinuation of treatment should be discussed with the STREAM central clinical team before a decision is made, unless in response to a medical emergency.

9.2 Salvage regimens

Salvage regimens will be provided for trial patients who require retreatment provided adequate follow up can be maintained. All patients who are treated with a salvage regimen should be appropriately monitored for any toxicity during their treatment, this monitoring may include ECG and laboratory monitoring, and the data recorded. The STREAM central clinical team should be contacted for guidance on the appropriate monitoring in such cases. Trial patients who initiate a salvage regimen close to the end of their trial follow-up period may require treatment and follow up beyond this time point. In addition, where appropriate the Sponsor may initiate salvage regimens for patients who have completed their 132 week Study period.

The composition of the salvage regimen will be based on treatment history and DST results and be selected by the site clinicians in consultation with the central clinical team. Salvage regimens will also take into account local guidelines and availability of medicines. Patients who are unwilling or unable to be followed during their salvage regimen treatment, including those whose planned intensive phase will not be completed prior to site closure, will be referred to the National Tuberculosis Programme for management. Upon site closure, patients still undergoing salvage regimen treatment will be referred to the National Tuberculosis Programme to ensure treatment follow up and completion.

Procurement and provision of the salvage regimen for trial patients will be supported by the Sponsor as needed and site-specific approaches to ensuring availability of medicines will be developed and documented. Bedaquiline provided as IMP for the trial will be limited to 24 weeks in a salvage regimen and only utilized where trial patients initiate their salvage regimen within their 132 week Study period. Outside of the Patient's 132 week Study period, and where available, the Sponsor may, at their discretion, use bedaquiline in a salvage regimen from an alternative source. The safety and appropriateness of the salvage regimen is the responsibility of the investigator, as well as the reporting of Adverse Events.

9.3 Patient transfers

For patients moving out of the area, every effort should be made to continue to follow them if at all possible; this could include follow-up at another participating site.

9.4 Early stopping of follow-up

If patients explicitly state that they do not wish to contribute further data to the study, MRC CTU should be informed in writing of the patient's decision and a final form should be completed. Such patients who discontinue the study may not be re-randomised and will not be replaced.

10 DATA MANAGEMENT

Data will be recorded on paper case report forms (CRFs) and entered into a database either at each local site or at a central location. At each visit, details of clinical findings, procedures, tests and results will be recorded in the patient's case notes and on the appropriate CRF. The CRF top copy will be sent for data entry, and the duplicate retained in the patient's Trial Folder. Entries made in the CRF must be either verifiable against source documents or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. Instances where data may be entered directly in a CRF will be agreed by the Sponsor and documented. The Investigator Site File and all source data should be retained until notification is given by the sponsor for destruction.

Instructions on data capture, cleaning and subsequent storage can be found in the STREAM Data Management Plan.

10.1 Blinding of data

The co-chief investigators will be kept masked to allocation where possible, except in instances where the knowledge is needed for the review of adverse events. However, one of the co-chief investigators, Professor Andrew Nunn, will be kept entirely blinded to treatment allocation throughout the trial. The trial statisticians and data manager in the central team will not be blinded to the allocation. However, before database lock the only data summarised by treatment allocation will be within reports to the IDMC, which will not be distributed outside of the IDMC. The Trial Statisticians will be responsible for preparing the IDMC reports, and will be the only persons outside the IDMC who will have access to these reports. Should any modifications to the trial design be required, the unblinded statisticians will be excluded from the discussion.

11 STATISTICAL CONSIDERATIONS

11.1 Analysis population definitions

Only patients randomised in Stage 1 of the STREAM trial will be included in the Stage 1 analysis population.

The analysis populations for Stage 2 only include patients that are randomised after the start of Stage 2. Recruitment to Stage 2 may not begin simultaneously at all sites. Therefore, all patients randomised on or after the site-specific start date at that site will be included in the Stage 2 analysis.

Intention-to-treat (ITT)
All randomised patients will be included in the ITT analysis population.

Safety population
All randomised patients who have taken at least one dose of trial treatment will be included in the safety analysis population.

Modified intention-to-treat (mITT)
The mITT population is defined as all randomised patients that have a positive culture for *M. tuberculosis* at screening or randomisation, with the exception of patients with isolates taken before randomisation that are subsequently found to be susceptible to rifampicin, and patients with isolates taken before randomisation 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. Rifampicin susceptible phenotypic DST results will be confirmed by rpoB sequencing.

Per protocol (PP)
The PP population will be the same as the mITT population with the exclusion of patients not completing a protocol-adherent course of treatment (see Section 11.2.3), other than for treatment failure, change of treatment for an adverse event or death. Treatment failure is defined as failure to attain and maintain culture negativity until the end of allocated treatment.

11.2 Outcome measures

Culture results obtained using acidified Ogawa (Kudoh medium) will be used in the primary analysis, although results from other culture media will be used if the Ogawa result is missing. Any culture result that is missing because the patient is no longer able to produce sputum will be treated as a negative result, providing their last 2 available culture results (from sputum samples taken at separate visits) are negative.

11.2.1 Primary efficacy outcome

The primary outcome for the Stage 1 comparison between Regimen B and Regimen A is efficacy status at 132 weeks after randomisation.

The primary outcome for the Stage 2 comparison is efficacy status at 76 weeks after randomisation.

The status for all efficacy study comparisons is determined as follows:

Favourable

A patient's outcome will be classified as **favourable** if their last two sputum culture results are negative, unless they have previously been classified as unfavourable. These two sputum samples must be taken on separate visits, the latest of which being no more than six weeks earlier than Week 132 (for the Stage 1 comparison) or Week 76 (for the Stage 2 comparison), the time-points of interest for primary outcomes in the Stage 1 comparison and Stage 2 comparisons, respectively.

For the purpose of the analysis of primary outcome measures in Stage 1 and Stage 2, the visit windows for the Week 132 (for Stage 1) and Week 76 (for Stage 2) are defined as no more than six weeks prior to, or six weeks after 132 or 76 weeks, respectively, from randomisation.

The end dates in the above windows will be extended for any Stage 2 patients whose Week 76 appointment is scheduled to occur during the COVID-19 pandemic and did not occur due to restrictions on movement, unacceptable risk of exposure to COVID-19 in connection with the scheduled visit, or any other reason related to the pandemic. For those patients, the Week 76 sputum samples must be taken in a window beginning six weeks prior to the scheduled visit date and ending within the Week 84 visit window.

Unfavourable

A patient'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 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.
3. They are restarted on any MDR-TB treatment after the scheduled end of treatment, but before 132 weeks after randomisation for Stage 1 and before 76 weeks after randomisation for Stage 2.
4. They change their allocated study treatment for any reason other than (1) the replacement of a single drug* or (2) for patients allocated to Regimen A when the change is as a result of changes in local guidelines and not related to any change in the patient's circumstances or condition.
5. Bedaquiline is started where the allocated regimen did not originally contain that drug (Regimen A or B)
6. A second line injectable agent is started in Regimen C.
7. A drug from the class of nitroimidazoles or linezolid is started.
8. They die at any point during treatment or follow-up.
9. At least one of their last two culture results, from specimens taken on separate occasions, is positive.
10. They do not have a culture result at Week 76 or thereafter for the Stage 1 comparison, or within the Week 76 window for the Stage 2 comparison.

11. The failure or recurrence specimen at or before the Week 76 window was a different strain to their randomisation specimen, i.e. re-infection (the Stage 2 comparison only).

* Excluding changes from kanamycin to amikacin

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 (in Regimen A or B), a second-line injectable in Regimen C or a drug from the class of nitroimidazoles or linezolid (in any regimen).

Following publication of the revised WHO guidelines in 2018 it became more likely that a salvage regimen following bedaquiline use would contain linezolid rather than an injectable agent. To reflect the resulting imbalance in the likelihood of point 5 and 6 occurring based on drug choice, starting linezolid alone was added as an unfavourable outcome (point 7 above) in version 11.0.

For analysis of the Stage 1 comparison, re-infections with a different strain are classified as not assessable.

Only data before or within the Week 76 window will be used for the determination of the primary efficacy outcome for Stage 2, even though patient follow-up continues to end of trial. Participants with no sputum sample available at Week 76 due to Covid-19 who are not otherwise classified as unfavourable will be considered unfavourable in line with the above definition. Sensitivity analyses will reclassify these participants as i) **non-assessable** and excluded from the primary efficacy analysis, and ii) unfavourable/favourable if their culture result at their Week 68 visit is positive/negative respectively.

An extension of the intensive phase of treatment in any study arm does not constitute an unfavourable outcome, as long as the extension is in accordance with either the algorithms described in Figures 9 and 10 (section 7.3.2) for patients on Regimen B, Regimen C, or Regimen D, or the locally-used WHO 2011 long MDR-TB regimen for patients on Regimen A. Similarly, the discontinuation of drugs that are not replaced does not constitute an unfavourable outcome.

During Stage 1, a patient who has a culture result within the Week 76, 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; one of these cultures should be from a sample taken at week 76. Any patient who does not have a culture result within the Week 132 window and does not fulfil these criteria will be classified as **unfavourable**. These definitions apply to both Regimen A and Regimen B in Stage 1 of the trial.

11.2.2 Secondary efficacy outcome at Week 132 in Stage 2

Secondary efficacy analyses will be based on data from all visits occurring on or before the projected Week 96 visit of the last patient randomised i.e. approximately end of November 2021. A participant's scheduled last efficacy visit will be their latest scheduled trial visit on or before this date.

For purposes of analysis of the secondary efficacy outcome measures at Week 132 in Stage 2, a patient's outcome will be classified as **favourable** if their last two sputum culture results are

negative, unless they have previously been classified as unfavourable. These two sputum results must be from samples taken at separate visits; the latest must be no more than six weeks before their scheduled last efficacy visit.

The visit window for the scheduled last efficacy visit is defined as no more than six weeks prior to and up to six weeks after (or on 30 Nov 2021 if this is earlier) the scheduled last efficacy visit. The end dates of the window will be extended for any Stage 2 patients whose scheduled last efficacy visit was due during the COVID-19 pandemic and did not occur due to restrictions on movement, unacceptable risk of exposure to COVID-19 in connection with the scheduled visit, or any other reason related to the pandemic. For such patients, sputum samples must be taken in a window between six weeks prior to and twelve weeks after the last scheduled visit date (or on 30 Nov 2021 if this is earlier).

A patient's outcome at their scheduled last efficacy visit will be classified as unfavourable if:

- They are unfavourable at Week 76
- They start any MDR-TB treatment between their Week 76 and scheduled last efficacy visits
- They die between their Week 76 and scheduled last efficacy visits
- At least one of their last two culture results, from specimens taken on separate occasions, is positive.

A patient who does not have a culture result within the window for their scheduled last efficacy visit, having not otherwise been classified as unfavourable, will be regarded as **not assessable** and excluded from the analysis provided their last two cultures, from specimens taken on separate occasions, are negative.

11.2.3 Definition of a protocol-adherent course of treatment

Patients will be excluded from the per-protocol analysis if they do not complete a protocol-adherent course of treatment, other than for treatment failure, change of treatment for an adverse event or death.

A patient will have completed a protocol-adherent course of treatment when 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.

Stage 1

For Regimen B, **with or** without an extension of the intensive phase, a patient will have 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 will apply for Regimen A, the control regimen for Stage 1, and the exact number of doses and days depends on the duration of the intensive and continuation phases of Regimen A.

Stage 2

For Regimen B and Regimen C, with or without an extension of the intensive phase, a patient will have 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.

For Regimen D, with or without an extension of the intensive phase, a patient will have completed a protocol-adherent course of treatment if they have taken:

- 45 doses (80% of 8 weeks) within 67 days (120% of 8 weeks) in the intensive phase, and
- 157 doses (80% of 28 weeks) within 235 days (120% of 28 weeks) over the whole treatment period (i.e. the combined intensive and continuation phases) regardless of treatment extensions.

11.3 Sample size: Stage 1

A meta-analysis of treatment outcome in patients with MDR-TB found an overall favourable outcome of 64% (95% CI 59-68) in patients given individualised treatment and 54% (95% CI 43-68) in patients given standardised treatment[8]. A reasonable estimate of the efficacy of Regimen A in the STREAM trial would therefore be 70%.

Based on the experience with Regimen B, a reasonable estimate of its efficacy in the STREAM trial would be between 75% and 85%. The lower estimate is used for the sample size calculations below.

11.3.1 Power to demonstrate non-inferiority in the primary efficacy outcome

Based on a 2:1 allocation ratio in favour of Regimen B to Regimen A, Table 8 gives the total number of patients required to demonstrate non-inferiority under the specified scenarios using a margin of non-inferiority of 10%, assuming that Regimen B is actually 5% better. These totals allow for 20% of patients being classified as not assessable in a per protocol analysis and are based on a one-sided level of significance of 2.5%.

Table 8: Power to demonstrate non-inferiority in the primary efficacy outcome

Power	Percentage favourable outcomes in Regimen A	Difference in percentage favourable outcomes in Regimen B compared to Regimen A		
		0%	5%	10%
80%	60%	1060	464	255
	65%	1005	435	238
	70%	928	398	214
90%	60%	1419	620	340
	65%	1345	583	318
	70%	1242	533	287

Therefore, 398 patients would be required (rounding to 400 gives: 267 on Regimen B and 133 on Regimen A) to demonstrate non-inferiority with 80% power assuming 70% favourable outcomes in Regimen A and 75% in Regimen B and 20% not assessable. A larger difference in response rates of 10% would require fewer patients and could also be demonstrated with greater than 90% power with a total recruitment of approximately 400 patients.

A 10% margin of non-inferiority is considered an acceptable reduction in efficacy given the considerably reduced pill burden and duration and the expected increase in adherence in reducing a treatment regimen from 104 weeks (as with Regimen A), to 40 weeks (as with Regimen B).

If the difference in response rates in favour of Regimen B is more than 10% it may be possible to demonstrate superiority of that regimen over the control for the Stage 1 comparison, Regimen A.

A minimum of 400 patients will need to be recruited across all countries to give sufficient power to demonstrate non-inferiority. Patients will be randomised to Regimen B and Regimen A in the ratio 2:1.

11.3.2 Power to demonstrate non-inferiority in the primary safety outcome

Assuming a sample size of 400 on a 2:1 allocation ratio in favour of Regimen B to Regimen A, Table 9 gives the power available to demonstrate non-inferiority in the primary safety outcome under different proportions of grade 3 or 4 events on Regimen A and Regimen B. These calculations assume a margin of non-inferiority of 10% and a one-sided level of significance of 2.5%. All randomised patients who have received at least one dose of study medication will be included in the safety analysis.

Table 9: Power to demonstrate non-inferiority in the primary safety outcome

Proportion grade 3 or 4 on Regimen A	Assuming same proportion in Regimen A and Regimen B	Assuming an absolute 5% lower proportion on Regimen B than Regimen A
10%	88%	99%
15%	75%	99%
20%	65%	96%
25%	58%	93%
30%	53%	89%
35%	50%	86%
40%	48%	83%

11.4 Sample size: Stage 2

11.4.1 Power to demonstrate non-inferiority in the primary efficacy outcome (primary objective relating to Regimens B and C)

Stage 2 will aim to randomise at least 200 patients to each of Regimen B (B_{mox} or B_{lev}) and Regimen C. This revised sample size was determined based on the assumption that the proportion of patients with a favourable efficacy outcome at Week 76 is 80% for Regimen B (estimated based on preliminary Stage 1 results) and 82% for Regimen C (based on an anticipated minimum benefit in efficacy of using 40 weeks treatment with bedaquiline compared to 16 weeks treatment with kanamycin). Using a non-inferiority margin of 10% and a one-sided significance level of 2.5%, 172 evaluable patients will be required in each of the two regimens to demonstrate non-inferiority of Regimen C to Regimen B with 80% power. To account for 14% of patients excluded from the primary per protocol efficacy analysis population, a total of 400 patients will need to be enrolled across the 2 regimens. A sample size of 400 patients enrolled to the comparison of Regimens B and C is necessary to rule out an 8% increased mortality in Regimen C compared to the 8% observed on Regimen B in the preliminary analysis of STREAM Stage 1. This will provide 80% power with a one-sided 0.025 type I error.

An interim analysis will be performed for the purpose of determining the final sample size needed to achieve adequate power for testing the Stage 2 primary hypothesis of non-inferiority. The interim analysis will be performed when at least 40% of the 400 patients on Regimen B and C complete 24 weeks of treatment and at least 10% of the 400 patients complete Week 76. Based on data from the interim sample, the number of additional patients needed to achieve 80% conditional power will be determined and, if necessary, the sample size will be increased. The maximum sample size will be capped at 330 patients per regimen (ie, the initial sample size). The sample size re-estimation will be performed by an independent Statistical Support Group (SSG). Details on methodology, type I error control, decision rules of the sample size re-estimation will be provided in the statistical analysis plan to be completed prior to the interim analysis.

Table 10: Power to demonstrate non-inferiority in the primary efficacy outcome (Regimens B and C only)

Proportion favourable outcomes		80% power		90% power	
Regimen B	Regimen C	Total evaluable patients	Total sample size accounting for 14% exclusions.	Total evaluable patients	Total sample size accounting for 14% exclusions
75%	76%	484	562	646	750
75%	77%	402	466	536	624
78%	79%	444	516	592	688
78%	80%	368	428	490	570
80%	81%	414	482	554	644
80%	**82%**	**344**	**398**	**458**	**532**

Assuming a favourable efficacy outcome at week 76 in Regimen B (B_{mox} and B_{lev} combined) of 80% (consistent with the status of Regimen B at 76 weeks in Stage 1) and an increased favourable response of 82% in Regimen C, using a non-inferiority margin of 10% and a one-sided significance level of 2.5%, a total of 344 patients will be required to demonstrate non-inferiority of Regimen C with 80% power. To account for the 14% of patients being excluded from the per protocol population a total of 400 patients will be required across the two arms: Regimen B (B_{mox} or B_{lev}) and Regimen C.

The number of patients excluded from the mITT analysis population will be less than the per protocol population and, therefore, this sample size will be adequate for this analysis.

As only the comparison between Regimen C and Regimen B (B_{mox} and B_{lev} combined) is primary, no adjustment is made for multiplicity.

11.4.3 Secondary efficacy analyses involving Regimen A in Stage 2

Secondary objectives of Stage 2 include to estimate the difference in the proportion of patients with a favourable response at 132 weeks between Regimens B, C, D and A. With version 8.0 of the protocol it is now anticipated that approximately 100 patients will be randomised to Regimen D and no more than 50 patients to Regimen A.

11.4.4 Sample size

Stage 1

A minimum of 400 participants from sites in four or five countries will be randomised to either Regimen A or Regimen B in the ratio 1:2 (i.e. 133 allocated to Regimen A, and 267 allocated to Regimen B).

Stage 2

At the start of Stage 2, randomisation was to Regimen A, Regimen B, Regimen C and Regimen D in a ratio of 1:2:2:2 to a maximum of 1155 patients from sites in a number of countries. With Version 8.0 of the protocol at least 200 patients will be randomised to each of Regimens B and C. In addition, patients randomised to Regimen A and Regimen D prior to the implementation of Version 8.0 of the protocol will be part of the trial and therefore the overall sample size will be greater than 400 but is expected to be less than 800 patients.

11.5 Interim monitoring and analyses

There will be no formal interim analyses of the data (with the exception of that mentioned in Section 11.7), but the Independent Data Monitoring Committee (IDMC) will review efficacy and safety data every six months after commencement of recruitment or as required, including an early assessment of QT data after three months from the start of Stage 1, and an early assessment of safety data after three months from the start of Stage 2 (unless recruitment is low at three months, in which case this initial assessment would be delayed). The IDMC will give particular attention to the QT and QTcF data at these times and at other times as necessary, with technical assistance provided by a cardiologist to enable them to interpret the results and their implication on the study. The IDMC will also consider failure rates, and give attention to mortality data; reviewing numbers and cause of failure/death by treatment arm.

Following the interim analysis to be performed by the SSG for the purpose of determining the final sample size needed to achieve adequate power for testing the Stage 2 primary hypothesis of non-inferiority of Regimen C to Regimen B, the results will be given to the IDMC who will make recommendation to the Trial Steering Committee on the numbers of patients required (see section 11.4.1).

It is not the intention to stop the trial in Stage 2 based on differences in efficacy between any of the treatment arms unless this is regarded as a safety issue. Recommendations to stop the trial prematurely will be based only on safety considerations; therefore no type I error correction will be done for the primary analysis.

Further details of the role and function of the IDMC is given in Section 19 and in the STREAM IDMC charter.

Interim plasma concentration data (including an evaluation of patients receiving bedaquiline and LPV/rtv) will be reviewed during the first 3 IDMC meetings of Stage 2 (where PK data are available) and on an ad-hoc basis thereafter if deemed necessary by the IDMC/Sponsor.

11.6 Preliminary analysis plan

Sites participating only in Stage 1 will only contribute data to the analysis of that stage.

All patients included in the analysis will be analysed in the treatment group to which they were originally assigned.

Detailed analysis plans for the primary and/or final analyses of Stage 1 and Stage 2 will be developed and approved prior to database lock for the relevant analysis of the respective stages. These will include details of a number of sensitivity analyses.

Results concerning time to sputum conversion will be shared with the TREAT-TB transmission modelling team in order that the longer-term impacts of reducing treatment times may be assessed.

In Stage 2, data from patients on Regimen A will be included in the efficacy and safety analyses at 132 weeks, but not the primary Week 76 efficacy analyses. The Week 132 analyses comparing Regimens C and D with Regimen B will mirror the Stage 1 analyses described above and will be described fully in the statistical analysis plan.

Stage 1

In general, the primary efficacy analysis will be based on both per protocol and modified intention-to-treat (mITT) populations.

For the primary analysis, the difference in proportion of favourable outcomes between Regimen A and Regimen B with 95% confidence intervals will be estimated. The analysis will be stratified by the randomisation stratification factors. For the non-inferiority comparisons, the analyses will be repeated on a per protocol sub-population. Non-inferiority will be shown if the upper bound of the 95% confidence interval of the difference in proportion of favourable outcomes between Regimen A and B is less than the 10% margin of non-inferiority; this must be shown in both the mITT and the PP populations.

The proportion of unfavourable outcomes with 95% confidence intervals will be estimated for each country. The primary safety outcome is the occurrence of a Grade 3 or greater adverse events. This analysis will be repeated in subgroups according to HIV infection status and drug resistance patterns.

Stage 2

For the primary analysis of Stage 2, the difference in favourable outcome rate between Regimen B (B_{mox} and B_{lev} combined) and Regimen C with corresponding two-sided 95% confidence interval and p-value will be estimated using a stratified analysis of the risk difference from each stratum using Cochran-Mantel-Haenszel weights.[24] For Regimen C, non-inferiority will be shown if the upper bound of the 95% confidence interval of the difference in proportion of favourable outcomes is less than the 10% margin of non-inferiority; this must be shown in both the mITT and PP populations. The analysis will be stratified by HIV status with three strata: HIV negative, HIV positive with CD4 count between 50 cells/mm^3 and less than 350 cells/mm^3, and HIV positive with CD4 count more than or equal to 350 cells/mm^3.

The secondary non-inferiority outcome at Week 132 for Regimen B compared to Regimen C will be analysed using time to unfavourable outcome, thereby using information on all participants. Data from participants whose scheduled last efficacy visit is before Week 132 will be censored at the time of their last visit, unless they have already become unfavourable. Non-inferiority must be shown in both the mITT and the PP populations. A sensitivity analysis will estimate the proportion unfavourable at Week 132 on the subset of participants randomised at least 132 weeks on or before 30 November

2021. For the superiority comparisons e.g. of Regimen C compared to Regimen B, at Week 76 and Week 132 only the mITT analysis will be considered.

Mortality rates will be calculated for the individual treatment arms and treatment group differences in mortality rates will be calculated together with a 95% confidence interval. In addition, the number of deaths, per-patient years of exposure will be calculated by treatment arm.

Differences in proportions with Grade 3 or greater adverse events will be compared and 95% confidence intervals calculated for overall comparisons, and repeated in subgroups according to HIV infection status and drug resistance patterns.
ECG data for safety analyses for Stage 2 will be from the central cardiology reading facility for the study.

Analyses will only include concurrently randomised patients. For example, analyses involving comparisons with Regimen A will only include data from patients who were part of the four-arm randomisation. Data from sites that only recruited to three regimens will be excluded from these comparisons, as will data from patients randomised after the change from four to three regimens in sites where this change was made. Details are provided in the Statistical Analysis Plan.

11.7 IDMC review of Stage 1 results

An additional IDMC meeting will be scheduled to occur immediately after the results of Stage 1 are available. The IDMC will be asked to review the entirety of the results from Stage 1 including all efficacy and safety endpoints as well as available data from Regimen A and Regimen B from Stage 2 and data from other relevant studies and external sources. The IDMC will be asked to consider recommending to the TSC termination of recruitment to Regimen A if there is sufficient evidence to show that Regimen B is safe and non-inferior to Regimen A.

If Regimen B is shown to have inferior efficacy to Regimen A or has an inferior safety profile that is considered clinically significant, the IDMC will be asked to consider making an appropriate recommendation for Stage 2 based on all available data and external evidence as appropriate.

11.8 IDMC review of recruitment to Regimen A in Stage 2

The IDMC will also be asked to review at their regular meetings recruitment to Regimen A, and subsequent withdrawals. If there are predicted to be insufficient numbers of patients to provide useful data on the regimen they may recommend to the TSC that all recruitment to Regimen A should be discontinued.

11.9 Pharmacokinetic Analysis

Individual plasma concentrations will be listed and descriptive statistics will be generated for all quantified drugs, metabolites, cholesterol and 4β-hydroxycholesterol at each respective sampling time. Pharmacokinetic parameters will be derived based on the individual plasma concentration-time data, including AUC24h (week 2) and AUC168h (week 12 and week 24). A population PK model will be used to provide individual estimates of PK parameters. .

The drug-drug interaction between bedaquiline and ARTs will be assessed by descriptive statistics and graphical analysis of plasma concentration-time data and pharmacokinetic parameters.

Pharmacokinetic/pharmacodynamic relationships between bedaquiline concentrations and efficacy and safety parameters will be investigated.

12 TRIAL MONITORING

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the sites. MRC CTU must be informed immediately of any change in the personnel involved in the conduct of the study.

The purposes of trial monitoring are to verify that:

- The rights and well-being of human participants are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with the principles of GCP, and with the applicable regulatory requirement

12.1 Risk assessment

A risk assessment was carried out during the feasibility assessment for this trial and is updated and reviewed approximately annually as the trial progresses and ahead of Stage 2 of the trial. The outcome of this assessment and its components are detailed in a separate document; the STREAM Monitoring Plan, which reflects issues identified in the study risk assessment and periodic reviews.

12.2 Monitoring plan

A detailed monitoring plan has been developed to reflect specific needs of the trial as determined by the risk assessment. This plan specifies the responsibilities and qualifications of monitors, central monitoring procedures, and the site monitoring visit procedures. Site visits by MRC CTU (or delegated collaborators) will be made in accordance with MRC CTU SOPs to assure the quality and accuracy of data collected and entered in the database, to determine that the applicable regulatory requirements are met and that rights and well-being of trial participants are protected.

On-site monitoring visits will be made at a frequency determined by the risk assessment and pre-defined triggers, including 'for-cause' monitoring as detailed in the monitoring plan. These visits will be made by the Trial Manager, Data Manager and/or other members of MRC CTU Trial Team, and/or delegated collaborators.

12.3 Clinical site monitoring

12.3.1 Direct access to data

Participating investigators must agree to allow trial-related monitoring and audits, ethics committee review and regulatory inspections by providing direct access to source data/documents, including electronic records, as required. Patients' consent/assent for this is obtained as part of the trial consent process.

During the trial the MRC CTU TM is responsible for monitoring data quality in accordance with MRC CTU SOPs. Before the study start, the Local Trial Coordinator will be advised of the anticipated frequency of the monitoring visits and will receive reasonable notification before each monitoring visit. Responsibilities of the monitors are outlined in the Monitoring plan.

During the course of this trial, the TM will maintain contact with the study sites on a regular basis. This will include a training/initiation visit prior to participant randomisation; a monitoring visit soon

after screening/randomisation begins and further visits as detailed in the monitoring plan. The monitor will meet with the investigators on a regular basis during the study to provide feedback on study conduct. Closeout visits will be conducted after trial participation is completed. The sites will be contacted in advance to schedule each visit. All participant records, CRFs, and other source documents for the patients recruited in this study will, where possible, be made available for review by the monitor(s). A site-visit log will be maintained at each study site to record all STREAM-related site visits made by authorised individuals.

12.3.2 Quality assurance (QA) procedures

QA procedures at MRC CTU include a systematic review of the trial protocol by the Protocol Review Committee (PRC), the preparation of a Risk Assessment and Quality Management documents. A review of these documents is undertaken by the MRC CTU Research Governance Committee (RGC) and Quality Management Advisory Group (QMAG) which form the QA function of MRC CTU. Internal audits of the Trial Master File will be conducted as directed by the RGC. Audits of sites may be conducted by or on behalf of the sponsor. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Participant privacy, must however, be respected. The Investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance programme or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

Good Clinical Practice (GCP) training, and where appropriate Good Laboratory Practice (GLP)[25] training will be provided for all staff involved in the trial. This will form part of the capacity strengthening component of the trial.

12.3.3 Microbiology laboratory quality control

Details of the arrangements for laboratory quality control (QC) are found in the STREAM Laboratory Manual.

ITM Antwerp will assess and prepare all laboratories before start of the trial, and assure quality of the sites' microscopy and cultures throughout the trial and GeneXpert MTB/RIF and/or LPA during the screening. Test performance will be periodically monitored and reported.

The following QC procedures will be used:

- Microscopy: internal control of newly prepared lots of staining solutions at the sites, together with random checking of smears performed at the presumed end of the intensive phase.
- Cultures: monitoring of false negative and contamination rates.
- LPA DST: a water blank in each run, to check for cross-contamination; strip-inbuilt controls for QC of amplification and colour reaction. EQA will be performed by sending panels composed of bacilli suspensions with known resistance patterns (Proficiency Testing).
- GeneXpert MTB/RIF: monitoring of errors plus proficiency testing panels will be used for the sites. There will be QC of phenotypic DST, DNA sequencing of resistance-conferring mutations performed at the central laboratory in Antwerp.

Details of QC will be provided in the laboratory manual.

12.4 Central monitoring

Central monitoring of data at MRC CTU will be conducted by CRF review, with appropriate and range and consistency checks programmed into the database. MRC CTU will raise any concerns they may have about the data captured by use of query forms sent to the site, as detailed in the Data Management Plan.

The Trial Master File will be stored at MRC CTU and at Vital Strategies and will be maintained by the TM throughout the trial. All trial specific documents will be centrally tracked and copies obtained from the sites for all communication with regulatory bodies. Details about maintaining trial files and any other monitoring that will be carried out centrally are in the Monitoring Plan, other study documentation and plans as appropriate.

13 SAFETY REPORTING

GCP requires that both investigators and sponsor follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol. Section 13.1 lists definitions, section 13.2 gives details of the institution/investigator responsibilities and section 13.3 provides information on MRC CTU responsibilities.

AEs are collected from the time the informed consent form is signed at screening until follow-up is completed or the participant withdraws from the trial. If a patient is found to be ineligible for the trial at screening, or chooses not to be randomised, no further AE data should be collected from that point.

13.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on GCP apply in this protocol. These definitions are given in Table 11.

Table 11: Safety reporting definitions

Term	Definition
Adverse Event (AE)*	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (or Investigator brochure) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) (see 13.2.1 (d) for causality definition)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening** • Requires hospitalisation or prolongation of existing hospitalisation*** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition, including suspected transmission of any infectious agent via administration of a medicinal product; • Is a combination of the above (to be specified).

13.1.1 Clarifications and exceptions

*In addition, events from the point that the participant gives informed consent/assent to screening until randomisation are also defined as AEs for patients in stage 2.

**The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition that has not worsened (including elective procedures) do not constitute an SAE; nor do hospital admissions for social and not medical reasons. Due to the seriousness of the disease in this study, some patients may be admitted to hospital for the initial phase of their trial treatment. This would not qualify as an SAE, although if that hospitalisation had to be prolonged beyond the normal length of admission, then it would be an SAE.

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

13.1.2 Trial specific exceptions to expedited SAE notification and reporting

Data on disease relapse or progression are collected as part of the primary outcome of the trial and are not considered to be SAEs, unless fatal or in stage 2, requires hospitalisation. QT prolongation does not require grading since the actual QT and QTcF values are collected as part of routine monitoring, but QT or QTcF prolongation to more than or equal to 500 ms should be recorded as a notable event as specified in 13.1.3. Planned hospitalisations for the initial phase of trial treatment are also not considered as SAEs as noted in section 13.1.1 above.

In Stage 2, adverse events which are not serious should be reported on the Stage 2 AE log. However, abnormal laboratory results that are not deemed by the PI to be clinically significant or do not result in change in therapy are exempt from event reporting i.e. they do not need to be added to the AE log. A clinically significant lab value is one that indicates a new disease process, an exacerbation or worsening of an existing condition, or requires further action(s) to be taken.

13.1.3 Additional notable events

The following notable events should also be identified and reported to the MRC CTU within the same time frame as an SAE (unless they also meet the criteria for an SAE, in which case they should be reported as such):

- Pregnancy in a patient or partner of a patient during protocol treatment or follow-up
- QT or QTcF measurement more than or equal to 500 ms while on treatment
- ALT/AST more than or equal to ten times ULN, or ALT/AST more than or equal to three times ULN in the presence of total bilirubin more than or equal to 2 times ULN
- Creatinine kinase more than or equal to 10 times ULN
- Pancreatic amylase more than or equal to 2 times ULN
- The occurrence of any grade 3 or higher adverse event
- Any toxicity that leads to withholding or stopping of allocated treatment for more than 24 hours
- A clinically significant dysrhythmia, such as an episode of ventricular tachycardia, with three or more irregular beats in a row.
- An overdose of trial medication.

13.2 Institution/investigator responsibilities

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) in this trial should be graded using the DAIDS criteria except for hearing loss, which will be graded using Brock's Criteria.

13.2.1 Investigator assessment

(a) Seriousness

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definition given in Table 11. If the event is serious and not exempt from expedited reporting, then an SAE/NE form must be completed and the MRC CTU notified.

(b) Causality

The Investigator must assess the causality of all serious events/reactions in relation to each trial drug that the patient has received using the definitions in Table 12. There are 5 categories: unrelated, unlikely, possibly, probably and definitely related to trial treatment. If the causality assessment is "unrelated" or "unlikely to be related" to trial treatment the event is classified as an unrelated SAE. If the causality is assessed as possible, probable or definitely related then the event is classified as a Serious Adverse Reaction (SAR).

(c) Expectedness

If the event is a SAR the Investigator must assess the expectedness of the event, with the exception of events thought to be caused by bedaquiline, which will be assessed for expectedness at MRC CTU. The definition of an unexpected adverse reaction (UAR) is given in Table 11. A list of expected toxicities associated with the drugs being used in this trial is provided in the STREAM Patient Management Guide. If a SAR is assessed as being unexpected it is a Suspected Unexpected Serious Adverse Reaction, or SUSAR.

(d) Notification

Investigators should notify the MRC CTU of all SAEs and other notable events as defined above, within one working day of them becoming aware of the event.

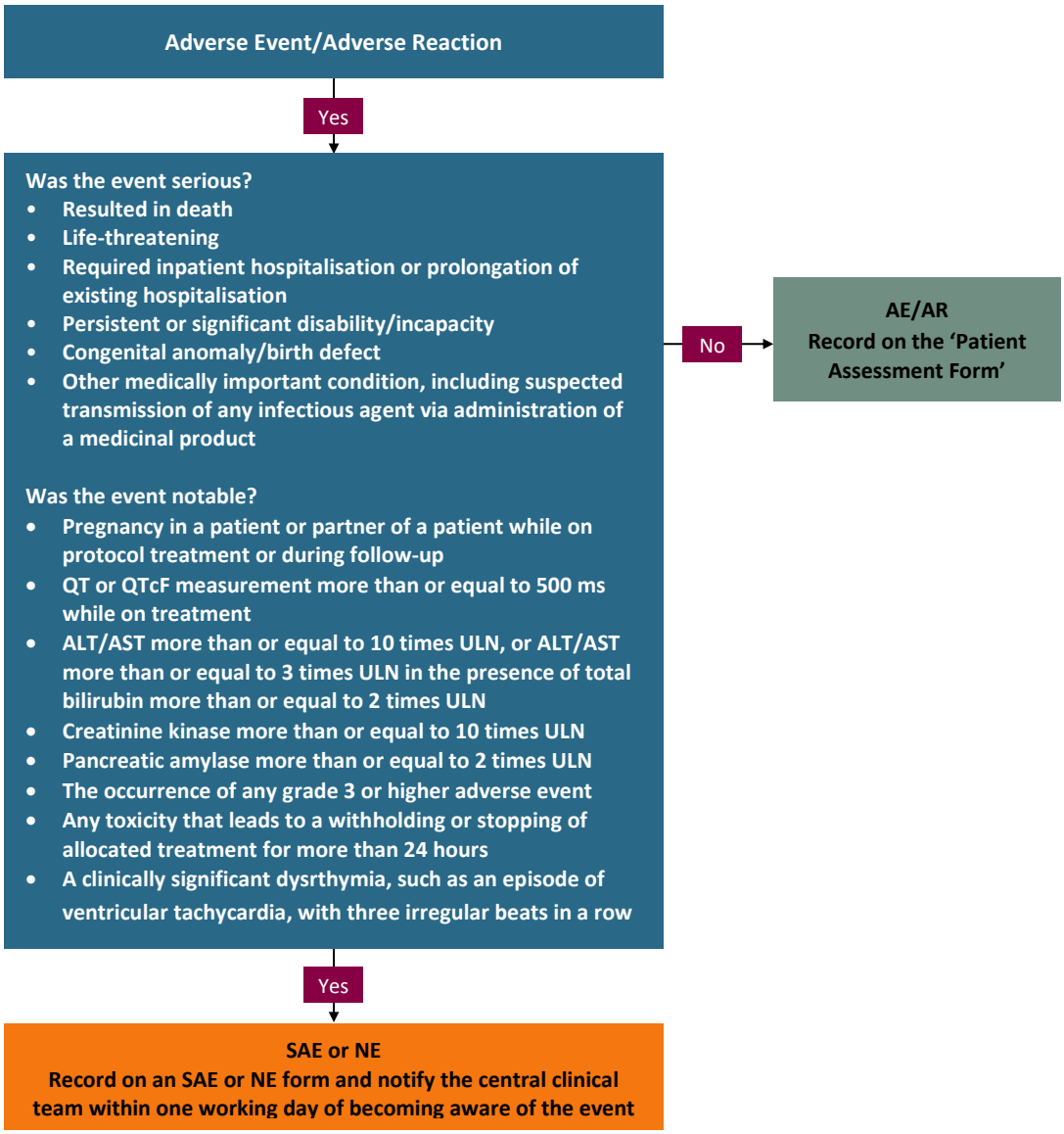
Table 12: Definitions of causality

Relationship	Description	Event Type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

Notification procedure:

1. The SAE/NE form must be completed by the Investigator (consultant named on the signature list and delegation of responsibilities log who is responsible for the patient's care), with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator the form should be completed and signed by a member of the site trial team delegated to do so. The responsible investigator should subsequently check the form, make changes as appropriate, sign and then re-send to the MRC CTU as soon as possible. The initial report shall be followed by detailed, written reports as appropriate
2. Send the SAE/NE form by email to the MRC CTU within one working day.
   Email: mrcctu.streamdata@ucl.ac.uk.
3. Follow-up: Patients must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. Follow-up information should be noted on a further SAE/NE form by ticking the box marked 'follow-up' and emailing it to the MRC CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by study number, date of birth and initials only. The patient's name should not be used on any correspondence
4. Staff at the investigator site must notify the research ethics committee and local Regulatory Authority of the event (as per the institutions standard local procedure).

Figure 11: Safety reporting flowchart



13.3 MRC CTU responsibilities

Medically qualified staff at the MRC CTU or the Co-CI's medically qualified delegate will review all SAE reports received. This may involve discussions with the STREAM central clinical team as outlined in the Patient Management Guide. The causality assessment given by the local clinical investigator cannot be overruled and in the case of disagreement, both opinions will be provided in any subsequent reports. The investigator's assessment of expectedness may be modified by the medical reviewer.

The MRC CTU is undertaking the duties of trial management and is responsible for providing the Sponsor's research ethics committee and the regulatory authorities that have approved the trial with the safety reports that they require.

The MRC CTU will provide the Independent Data Monitoring Committee (see section 19) with aggregated reports of SAEs for their review and will keep all investigators informed of any safety issues that arise during the course of the trial. After receipt and review of these reports, MRC CTU will also notify the trial sponsor.

SAE/NE NOTIFICATION

Within one working day of becoming aware of an SAE/NE,
please email a completed SAE/NE form to the MRC CTU on:

Email: mrcctu.streamdata@ucl.ac.uk

13.4 Product quality complaint handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labelling, or packaging, i.e. any dissatisfaction relative to the identity, quality, durability, and reliability of a product, including its labelling or package integrity. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

13.4.1 Procedures

All initial PQCs must be reported to the MRC CTU and the Sponsor by the site staff as soon as possible after being made aware of the event.

If the defect is combined with an SAE, the site staff must report the PQC to the MRC CTU according to the SAE reporting timelines (see Section 13.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

14 ETHICAL CONSIDERATIONS AND APPROVAL

14.1 Ethical considerations

The study will abide by the principles of the Declaration of Helsinki.

14.1.1 Research Ethics Committee (REC) review and approval

Before initiating the study at any given site, the study must be approved in writing by the local REC and/or Institutional Review Board (IRB), where appropriate, as well as the Ethics Advisory Group of The Union. The study will be conducted in accordance with all conditions of approval by the REC. The local Principal Investigator will forward the approval letter to MRC CTU.

Before starting the trial, the protocol, patient information sheet, informed consent and assent forms, study specific patient cards and any local advertising materials must be reviewed by the MRC CTU Protocol Review Committee; and be approved by the Trial Steering Committee (TSC) and the appropriate Ethics Committee in all participating countries.

It is the local Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information becomes available that might affect the patient's willingness to continue in the trial. The Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented/assented, where appropriate.

The sponsor and Investigators must ensure that the study is carried out in accordance with the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP), the Declaration of Helsinki and applicable regulations in each country.

14.1.2 Informed consent/assent

No patient may be screened for or randomised into this study until the investigator has obtained his/her informed consent/assent. Informed consent/assent encompasses all oral or written information given to the participant about the study and the study materials. All such information will be in a language which is understandable to him/her. The information will not include any language in which the participant is made to waive any of their rights or which releases (or appears to release) the investigator, the investigator's institution or the MRC CTU, from liability for negligence.

Consent/assent for study participation will be based on a template Patient Information Sheet (PIS), which will be provided to all participating sites. The information contained in the PIS will be translated into the relevant local languages and verified to ensure consistency of content. Literate patients will be asked to read the form and illiterate patients will have the contents explained to them by a counsellor, in the presence of a witness who will be present during the whole consent/assent process. Patients will have the opportunity to discuss the PIS with the medical officer/treatment supervisor. They will be assured that their decision to participate in the trial or not will not affect the quality of care they will receive. Once this person is satisfied that the patient has understood the PIS and the informed consent/assent form, the patient will be asked to give consent/assent.

The patient will sign (or thumbprint) and the investigator or designee will also sign the informed consent/assent form. If the patient is illiterate, their witness will also sign the form. One copy of the

signed informed consent/assent form will be offered to the participant, a second copy will be filed in the patient's medical notes (where available) and the original signed informed consent form will be kept in his/her study file. The investigator is also responsible for developing tools that may help in explaining the study to patients, these materials will also be submitted to MRC CTU at least one week before submission to the local REC.

14.1.3 Randomisation

Prior to the start of any trial procedures, the randomisation process will be explained as part of the patient information sheet at the patient's randomisation visit. Patients will be given a chance to ask any questions they may have before they consent to taking part in the trial.

14.1.4 Patient confidentiality

The confidentiality of all patients participating in this study will be protected to the fullest extent possible. All patient information will be kept secure and will be available only to the treatment staff and representatives of the sponsors, regulators, and ethics committees.

Study patients should not be identified by name on any case report form, email or on any other documentation sent to MRC CTU and will not be reported by name in any report, presentation or publication resulting from data collected in this study. Patients' data/specimens will be identified by study number or hospital number only.

The trial will comply with the principles of the UK Data Protection Act and the equivalent regulation/legislation of the country of the participating site.

14.1.5 Additional trial requirements

Patients may be required to provide additional samples or may be required to come to the clinic for more visits if clinically indicated.

14.1.6 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified.

All essential documents (according to GCP and MRC CTU SOPs) required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the local Regulatory Agency, the sponsor, or for US FDA or EMA inspection, for the minimum period required by national legislation or for longer if needed by MRC CTU. Records must not be destroyed without prior written approval from MRC CTU.

The medical files of trial participants shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

At the end of the trial, photocopies of pertinent study documentation (such as REC correspondence, etc.) will be kept by MRC CTU. CRFs will remain in the patient's study file at the participating sites. The signed original informed consent/assent documents for each participant and originals of other

study documentation (e.g. drug inventory forms, participant clinic records, original laboratory reports, etc.) will be retained by the local PI for a minimum of 15 years (as specified in MRC CTU working instructions on archiving). If those years have passed with no request for the data, the sites may request permission in writing from MRC CTU to destroy the records. No records may be destroyed without written permission from MRC CTU.

14.1.7 Audit

The investigator may be subject to a field audit by Vital Strategies, MRC CTU, or a health authority inspection to validate the participation of study patients, to verify the data reported on the Case Report Forms and to confirm the compliance of the conduct of the trial with applicable regulations and requirements and the protocol. This audit could occur while the study is in progress, several years after the study is completed, or when the data are under review. All of the patients' records and other study documentation must be filed and accessible on short notice (3-5 days) during the study and subsequent retention period.

14.2 Protocol deviations

No waivers will be given by MRC CTU on behalf of the sponsor for patients who do not fulfil the eligibility criteria for this trial. No deviations from, or changes to, the protocol should be initiated without prior written REC/IRB, regulatory authority approval/favourable opinion and approval from MRC CTU on behalf of the sponsor.

The reporting procedures and how to handle deviations are detailed in the MRC CTU SOPs and trial-specific Working Practice Documents for protocol deviations.

14.3 Ethical approval

The Union's Ethics Advisory Group has given a favourable opinion for the trial and protocol and has indicated in broad terms that the trial concept is consistent with ethical requirements. Each participating site will submit the protocol to their relevant Ethical Review Committees and/or Institutional Review Boards. All substantial amendments to this protocol will have to be submitted for approval.

A copy of local REC/IRB approval of the protocol and of the participant information sheet (PIS) and informed consent/assent form (ICF) on local headed paper and any other written information given to the participant should be forwarded to MRC CTU before patients are randomised into the trial. Each patient's consent/assent to participate in the trial should be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any Stage, after discussions with the STREAM central clinical team, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient must

remain free to withdraw at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing his/her further treatment.

15 REGULATORY ISSUES

All Investigators will be expected to obtain, in writing, approval to participate from their local Regulatory Authority. Copies of the approval (or non-approval) must be submitted to MRC CTU no later than 5 working days from receipt of the same.

A special authorisation of importation for the medicines to be used in the study should be obtained, by the responsible person at each site, from the National Drug Regulatory Authorities (NDRA) and provided to Vital Strategies.

16 INDEMNITY

The sponsor of the trial is Vital Strategies. Global insurance coverage for the trial was obtained by Vital Strategies. Country-specific insurance policies for the trial were also obtained by the Sponsor where required.

The local Principal Investigator/Investigator's institution is liable for negligent harm, for each of the participating sites unless alternative provisions have been made by the Sponsor. All personnel involved in the trial will be expected to be indemnified by their employing authority; in exceptional circumstances, the country-specific policies may also cover local investigator/practitioner liability.

17 ANCILLARY STUDIES

Ancillary studies may be conducted at selected sites participating in STREAM provided they have been approved by the Trial Steering Committee to ensure no negative impact on the main STREAM trial. Each ancillary study will have its own protocol and informed consent/assent forms and be approved by the relevant ethical and regulatory committees.

18 FINANCE

The trial is sponsored by Vital Strategies. The primary funder of the trial is the United States Agency for International Development (USAID), with additional funding from the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement and Janssen Research & Development, LLC. This trial will be managed and coordinated by the Medical Research Council Clinical Trials Unit at UCL (MRC CTU).

Each participating site will be supported according to the submissions of their budgetary requirements.

Reimbursements will be made according to sub-agreements signed between the the Sponsor and the participating sites.

19 TRIAL COMMITTEES

19.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will consist of representatives from different disciplines involved in the day to day running and management of the trial. It will include the Co-Chief Investigators, a member with clinical expertise in MDR-TB, members of the MRC CTU involved in the running of STREAM, namely the Trial Manager, the Data Manager, Project Manager and Trial Statistician. The group will also include representatives from Vital Strategies, including the Trial Pharmacist and others involved in the trial operations. Trial staff from ITM in Antwerp the Impact Assessment team from the Liverpool School of Tropical Medicine and the MRC CTU Data Management Systems will attend TMG meetings periodically upon request. The TMG will have access to clinical expertise in cardiac arrhythmias and hepatology for review of safety. Input to the TMG from relevant operational staff of Janssen Pharmaceuticals may be requested intermittently, on an as needed basis. The TMG will convene approximately monthly and it will report to the TSC on progress and issues.

19.2 Trial Steering Committee (TSC)

A TSC with an independent chair and a majority of independent voting members will be responsible for the oversight of the trial and provide advice to the investigators. No important decision should be made in the absence of a Co-Chief Investigator. Additional observers, including other investigators, a sponsor representative, and funder representatives, may be in attendance at the TSC meetings; they may provide additional input as requested. A STREAM TSC charter describes the membership and responsibilities of the TSC which include:

- providing expert oversight of the trial
- making decisions as to the future continuation (or otherwise) of the trial
- monitoring recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems
- reviewing regular reports of the trial from the trials unit (sent on behalf of the Trial Management Group (TMG))
- assessing the impact and relevance of any accumulating external evidence
- approving any amendments to the protocol, where appropriate
- approving any proposals by the TMG concerning any change to the design of the trial, including additional sub-studies
- overseeing the timely reporting of trial results
- approving the statistical analysis plan
- approving the publication policy
- approving the main trial manuscript
- approving any abstracts and presentations of any results *during* the running of the trial
- Approving external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples.

19.3 Independent Data Monitoring Committee (IDMC)

The IDMC will review safety and efficacy data regularly. The list of members and their responsibilities is included in the STREAM IDMC charter. The IDMC could, in exceptional circumstances, recommend termination of the study or termination of one of the treatment

regimens due to unacceptable levels of drug toxicity, or mortality; the trial should not be modified on account of differences in efficacy between treatment arms unless there is a concern for patient safety (except the possibility of the IDMC recommendation of termination of recruitment to Regimen A, see section 11.7). The IDMC will be asked to give advice to the TSC on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. They may recommend modification or closure of the study in a country or sub-group of patients, such as those who are HIV-infected.

The IDMC will convene approximately 6-monthly but may meet more frequently if it becomes necessary to do so. A charter describes in full the responsibilities of the IDMC and the format of their meetings and members will be required to sign this before the first meeting.

20 PUBLICATION

20.1 Publication

The definition of publication for this purpose is any public representation of the data emerging from this trial. Results of this study will be submitted for publication in a peer reviewed journal. This will be the analysis of the primary objectives of the study and this manuscript, together with subsequent manuscripts, including any single site data, will require the review and agreement of the TSC prior to submission.

Details for producing manuscripts, abstracts, press releases and any other publications including guidelines for authorship are outlined in the STREAM Publication Policy.

20.2 Dissemination of results to trial participants

Study results will be shared with participants through mechanisms and materials reviewed and approved by The Union's Ethics Advisory Group and other relevant stakeholders.

21 APPENDICES

Appendix 1: High-dose moxifloxacin safety summary

1. Rationale

Gatifloxacin (400mg daily for patients less than 33kg, 600mg for those 33-50kg, and 800mg if more than 50kg) was considered to be a critical component of the success of the regimen developed by van Deun et al; the ofloxacin-containing regimens tested were associated with inferior outcomes[2] . Because an internationally acceptable, quality-assured supply of gatifloxacin is not available, it was necessary to substitute a different fluoroquinolone, and moxifloxacin was judged to be the best alternative. Gatifloxacin and moxifloxacin have similar bactericidal activity at the same dose[1] and based on pharmacokinetic modelling there is reason to believe that the higher than standard doses are needed to prevent secondary fluoroquinolone resistance[26].

The standard dose of moxifloxacin is 400mg daily without any weight adjustment. In the STREAM study, as in the regimen developed by van Deun et al, 400mg will be used for patients less than 33kg, 600mg for those 33-50kg, and 800mg if more than 50kg. The main concern about the substitution of moxifloxacin for gatifloxacin is the potential for cardiac toxicity.

2. Cardiac safety of moxifloxacin at the standard dose

Moxifloxacin is an 8-methoxy quinolone, a member of the widely used fluoroquinolone family of anti-bacterial agents, which are some of the most frequently prescribed antibiotics in the world. Fluoroquinolones, in particular moxifloxacin, are known to prolong the QT interval, which occurs when drugs prevent the outward flow of potassium through cardiac voltage-gated potassium channels[27]. This causes a delay in cardiac repolarisation and may increase the risk of Torsades de pointes (TdP), a life threatening ventricular tachycardia. However, despite this propensity and its extensive use, there are very few reported cases of TdP induced by moxifloxacin[28].

QT prolongation is defined as a QT interval above the upper limit of normal: 450 ms for men and 470 ms for women[29,30]. However, the best indicator that a drug has the potential to induce arrhythmias is if it causes QTc (QT interval corrected for heart rate) prolongation to greater than 500ms[30].

The QTc increase following moxifloxacin has been well documented. Florian et al. reported an average increase of 10-14 ms following a single 400 mg dose across several investigations[31]. Tsikouris et al. acquired similar results after conducting an open label cross-over study in 13 healthy participants, including moxifloxacin at 400 mg, revealing an average QTc increase of 11 ms at 2-hours post dose[32].

Based on all the clinical trial data for moxifloxacin at the standard dose, ventricular tachyarrythmias are estimated to occur in less than 1/1,000 and Torsades de pointes and cardiac arrest in less than 1/10,000[33]. The case reports of TdP potentially related to moxifloxacin have occurred in elderly patients with pre-existing heart conditions[34,35,36].

Rubinstein's 2002 review reported that there were no cases of cardiovascular morbidity attributable to QTc prolongation recorded in 6000 patients involved in moxifloxacin phase II-IV clinical trials,

though there were four cases of arrhythmias (three non-specified) and one case of TdP in one elderly female patient with pre-existing risk factors including hypokalaemia, coronary artery disease, digoxin treatment and a pacemaker. They concluded that the fluoroquinolones in question (including moxifloxacin) were safe but should be closely monitored in patients with pre-existing conditions or those taking concomitant medication[36].

The trial data includes a randomised trial comparing the cardiac safety of moxifloxacin 400mg and levofloxacin 500mg in 387 elderly patients with community acquired pneumonia over 70% of whom had pre-existing cardiac disease; no difference in cardiac safety was detected[37].

3. Higher doses of moxifloxacin

Investigations using higher doses of moxifloxacin have been conducted although there is considerably less experience than with the standard dose. Démolis et al. conducted a placebo-controlled crossover study in 18 healthy volunteers in which both 400mg and 800mg prolonged the QT interval compared to placebo, but there was little difference between the two doses: the 400mg and 800mg doses increased QTc by 4.0% ± 5.1% and 4.5% ± 3.8%, respectively[38]. At two hours post dose, mean QTc intervals were recorded as 394 ±33 ms (400mg) and 396 ±28 ms (800mg) compared with the placebo mean of 379 ± 24ms. 800mg doses of moxifloxacin were also used in a 4-sequence cross-over study in 48 healthy patients across a spectrum of ages was conducted by Noel et al.[39]. Mean corrected QTc (Bazett) was recorded at 425-430 ms post-dose, with the peak between 2-4 hours; 6/47 patients (12.8%) had QTc intervals above the normal limits. All adverse events (six following moxifloxacin treatment) were described as mild, brief and spontaneously resolving.

In a trial of moxifloxacin-based treatments for *H. pylori* a total of 94 patients with a mean age of 50 received 800 mg moxifloxacin daily in conjunction with amoxicillin and esomeprazole for 10 days, 102 for 7 days and 98 for 5 days (294 in total) without any cardiac adverse events[40]; no ECG monitoring was undertaken.

Stass et al. conducted a study of moxifloxacin at doses ranging from 50mg – 600 mg in 7 healthy participants[41]. The study drug was well tolerated at all doses, with no clinically relevant changes in electrocardiogram data and only mild adverse events with no deaths or drop-outs.

In addition, there is one case report of a patient with miliary TB whose treatment included 800 mg moxifloxacin[42]. Results confirmed that the peak plasma concentration was between 2-4 hours with a mean QTc of 442.

4. Safety monitoring in STREAM

The available literature suggests that the difference in the effects of moxifloxacin on the QT interval at doses between 400 and 800mg are unlikely to be substantial, while the benefits in relation to prevention of acquired resistance are likely to be integral to the regimen.
The safety measures to be undertaken in STREAM are robust and designed to monitor the possible effects of moxifloxacin at peak concentration and to detect any possible cumulative effects. In Stage

1 any patient with a QT or QTc above 500 ms prior to treatment will be excluded from the trial. In Stage 2 any patient with a QT or QTc above 450 ms prior to treatment will be excluded from the trial.

In Stage 1, all patients will be monitored with a 12-lead ECG at 4 hours post the initial dose to capture the peak QTc increase, with further ECGs at weeks 1-4, and then every 4 weeks until Week 52. In Stage 2, the 4-weekly 12-lead ECGs will continue until Week 76;

As described in Section 8.31, patients found to have a QT or QTc more than or equal to 500 ms on a 12-lead ECG at any point during treatment will be further investigated to confirm the finding and identify the cause. If moxifloxacin is found to be the cause, and no other cause can be identified and eliminated, moxifloxacin at the standard dose (400 mg) should be tried. If standard dose moxifloxacin also causes persistent QT or QTc more than 500 ms moxifloxacin will be discontinued and levofloxacin tried instead. Concomitant medications will be closely monitored throughout the trial, in particular anti-retroviral therapy; however, the recent findings from the SMART trial would suggest that their effects are likely to be small[43].

Although ECG monitoring of this intensity would not be feasible in routine practice, it is being implemented here both to protect the patients in the trial and to determine the safety of the regimen. The current data suggests that TdP with moxifloxacin is a rare event. The STREAM protocol is designed to closely monitor patients and those at greatest risk of cardiac toxicity will be excluded. The potential risks of the regimens, Regimen B, Regimen C and Regimen D, should be balanced against both the risks of MDR-TB for which outcomes are poor and mortality is high (11% of patients in a systematic review of 33 studies of MDR-TB treatment died during treatment)[8], as well as the widely documented and serious adverse effects related to alternative MDR-TB treatment regimens.

Appendix 2: Levofloxacin Safety Summary

Stage 1 of STREAM (The evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with MDR-TB is an ongoing trial to evaluate the "Bangladesh regimen" compared to the WHO standard of care. In Stage 1 patients receive moxifloxacin (MFX) adjusted for weight instead of gatifloxacin which was used in the observational trial in Bangladesh.[2] This change was necessitated by the withdrawal of gatifloxacin by the marketing authorization holder. The weight adjusted MFX dosing in Stage 1 of STREAM was used to provide maximal fluoroquinolone activity which was felt by many experts to be critical to the reported success of the "Bangladesh regimen". In Stage 2 of STREAM, levofloxacin will be used in the bedaquiline containing arms (C and D) instead of MFX to minimize the QT prolongation associated with bedaquiline. Levofloxacin (LFX) will be dosed at 750mg/day in subjects weighing $\leq$ 50 kg and 1,000 mg in subjects weighing > 50kg. In Arm B MFX will be dosed at 400mg/day in subjects weighing < 33 kg, 600 mg/day in subjects weighing $\geq$ 33 kg to $\leq$ 50 kg, and 800 mg in subjects weighing > 50kg. This document summarizes information about the relative in vitro potencies against *Mycobacteria tuberculosis* of each fluoroquinolone. In addition, pertinent articles from the limited clinical literature that directly compares the use of both agents for the treatment of MDR TB is discussed.

Error! Reference source not found. shows the MIC values obtained by Dr. Ji's group for ofloxacin (OFX), LFX, clinafloxacin (CFX) and MFX against banked clinical isolates of MTB. The MIC_{50} and MIC_{90} were 0.50 and 1.0 ug/ml, respectively, for both LFX and MFX. Other investigators have reported that MFX was more potent in vitro than LFX.[44] However, lower MICs for MFX in comparison to LFX were not predictive of superior efficacy based upon pharmacokinetics/pharmacodynamics principles.

Table 13: MIC values for fluoroquinolones

Compound	MIC range	MIC_{50}	MIC_{90}	Reference
OFX	0.50-2.0	1.0	1.0	Ji et al. 1995[45]
LFX	0.25-1.0	0.50	1.0	Ji et al. 1995[45]
MFX	0.12-0.50	0.50	1.0	Ji et al. 1998[46]
CFX	0.12-1.0	0.50	1.0	Ji et al, 1998[46]

A recent evaluation of MDR-TB like treatment regimens given for 6 or 7 months in the mouse model of infection (see **Error! Reference source not found.**4) reported similar relapses at 5 months, but fewer relapses with MFX compared to LFX at months 6 and 7.

Table 14: Relapse* after Treatment Completion [45]

	% (Proportion) of Mice Relapsing after Treatment for:		
Regimen	**5 mo**	**6 mo**	**7 mo**
2 mo RHZ + RH	23 (7/30)	0 (0/30)	not done
2 mo MEtZA + MEtZ	97 (28/29)	59 (17/29)	20 (6/30)
2 mo LEtZA + LEtZ	100 (26/26)	79 (23/29)	38 (11/29)

Definition of abbreviations: A = amikacin; Et = ethionamide; H = isoniazid; L = levofloxacin; M = moxiflocacin; R = rifampin; Z = pyrazinamide.

* Relapse was defined by a positive culture upon plating the entire lung homogenate harvested 3 mo after completing the indicated duration of treatment.

- Using an extended Early Bactericidal Activity study design (eEBA)[16] described the early and extended bactericidal activity (eEBA) of LFX, gatifloxacin and MFX in patients with drug sensitive pulmonary tuberculosis. In this randomised, open-label trial, 40 adults with newly diagnosed smear-positive DS TB (10 subjects/arm) were assigned to receive: isoniazid (INH) 300 mg, LFX 1000 mg, gatifloxacin 400 mg, or MFX 400 mg daily for 7 days. Sputum for quantitative culture was collected for 2 days before and daily during 7 days of monotherapy. Bactericidal activity was estimated by measuring the decline in bacilli during the first 2 days (EBA 0–2) and last 5 days of monotherapy (extended EBA, EBA 2–7). The EBA 0–2 days of INH (0.67 log10 cfu/ml/day) was significantly greater than that of MFX and gatifloxacin (0.33 and 0.35 log10 cfu/ml/day, respectively), but was not significantly greater than LFX 1000 mg daily (0.45 log10 cfu/ml/day) (P=0.14). Bactericidal activity between days 2 and 7 was similar for all three fluoroquinolones. The authors concluded that MFX, gatifloxacin, and high-dose LFX have excellent EBA, only slightly less than for INH, and greater extended EBA and that these drugs warrant further study in the treatment of drug-susceptible TB.

- In a recent retrospective analysis from China, the efficacy of MFX and LFX was explored in the treatment of multidrug-resistant tuberculosis (MDR-TB).[47] 158 patients with MDR-TB receiving either MFX- or levofloxacin-containing regimens were described. Clinical data from patients were subjected to univariate analysis, stratification and multiple logistic regression to compare the roles of moxifloxacin and levofloxacin in multidrug regimens. In total, *72 patients received 400 mg of moxifloxacin once daily* and *86 patients received 509.9 ± 79.4 mg (mean ± standard deviation) of levofloxacin once daily* together with similar active agents for similar durations. The time to sputum culture conversion were similar. Adverse reactions occurred at comparable rates. *The success rates for the MFX group were 65.3% (overall), 77.1% (ofloxacin-susceptible cases) and 54.1% (ofloxacin-resistant cases) in comparison with 55.8%, 60.4% and 50.0%, respectively, for the LFX group.* No demographic, clinical, bacteriological or treatment characteristics were independent predictors of favourable outcome. Fourteen patients from the MFX group and twelve patients from the levofloxacin group had bacteriological relapse after treatment cessation. The authors concluded that compared with levofloxacin, MFX did not show superior efficacy when incorporated into multidrug regimens used for the treatment of MDR-TB.

- Koh et al.[48] described the effectiveness of LFX and MFX compared in terms of culture conversion after 3 months of treatment for MDR-TB. In this prospective multicentre randomised open label trial, 182 patients with MDR-TB (sensitive to LFX and MXF) received

either LFX (750 mg/day; 90 patients) or MXF (400 mg/day; 92 patients) with a background drug regimen. The primary outcome was the proportion of patients who achieved sputum culture conversion at 3 months of treatment. Secondary outcomes were the proportions of adverse drug reactions. At 3 months of treatment, 68 (88.3%) of the 77 patients in the LFX group and 67 (90.5%) of the 74 in the MXF group showed conversion to negative sputum cultures (odds ratio for LFX compared with MXF, 0.78; 95% confidence interval, 0.27-2.20). Adverse drug reactions were reported in six patients (7.7%) in the LFX group and four (5.2%) in the MXF group (P = 0.75). The authors concluded that the choice of LFX or MXF for treatment of patients with MDR-TB did not affect sputum culture conversion at 3 months of treatment.

Another group of investigators from Korea reported results from a retrospective review of the use of LFX and MFX in the treatment of MDR TB.[49] The outcomes of 171 patients are described. Detailed information on dosing and duration are not provided. One hundred and twenty-three of the 171 received LFX and 97 (78.9%) were classified as treatment successes compared to 40 treatment successes (83.3%) in the 48 who received MFX.

In conclusion, many authorities believe that MFX is more potent than LFX in vitro but that superior potency does translate into a better efficacy either in animal models or the treatment of MDR-TB in patients. In the mouse, there is a trend for fewer relapses when MFX is used as part of an MDR TB like regimen compared to LFX. However, an EBA study and several recent small clinical reports describe acceptable and generally similar clinical outcomes when either LFX or MFX was used as part of an MDR TB regimen. This data supports the use of levofloxacin adjusted for weight in Arms C and D of the STREAM trial.

Based the necessity of using LFX with bedaquiline and the design of the ongoing STREAM trial which utilizes weight based dosing for MFX we assert that the weight based dosing of LFX proposed in Stage 2 of STREAM is justified. This is supported by the limited clinical data and expert opinion.[50]

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