**Appendix 1. Eligibility Criteria for Randomization**

1. A patient will be eligible for randomization if s/he:
2. Has documented pulmonary tuberculosis due to strains of *M. tuberculosis* resistant to rifampin (RIF) and either susceptible to fluoroquinolones for endTB or not susceptible to fluoroquinolones for endTB-Q, diagnosed by validated rapid molecular test;
   * + *For both studies: one rifampicin-resistant from the designated study lab is required.*
     + *For endTB: in addition, one fluoroquinolone-susceptible result from the designated study lab is required;*
     + *For endTB-Q:* 
       - *In trial sites in Peru, Lesotho, South Africa, and Vietnam, an additional FQ-resistant result from the designated study lab is required.*
       - *In trial sites in India, Kazakhstan, and Pakistan, an additional FQ-resistant or FQ-indeterminate result from the designated study lab is required.*
     + *If patients have any molecular or phenotypic drug-susceptibility testing results (from tests performed at quality-assured/quality-controlled study-designated laboratories) from sputum specimens collected in the 3 weeks prior to screening, it is not necessary to repeat those tests at screening.*
3. Is ≥ 15 (or 18, depending on site) years of age;
   * + *Age is assessed on the date of the screening visit, or at pre-screening if this information is available.*

* **Criteria applicable for Protocol up to version 3.3 (endTB) and version 3.0 (endTB-Q)**

Is willing to use effective contraception: pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilized must agree to use two methods of contraception (e.g., a hormonal method and a barrier method) unless their partner has had a vasectomy; men who have not had a vasectomy must agree to use condoms;

* + - * *Female participants do not need to specify which contraceptive methods they plan to use. They simply need to affirm they will comply with the requirement. And, the study team should offer to facilitate access to the chosen methods, again, without needing to know what they are.*
      * *All contraception methods are allowed, as long as they are used according to manufacturer recommendations: long-acting reversible contraception methods, hormonal methods (short-acting or combined, including injectable and topical methods), and barrier methods;*
      * *Natural methods of contraception (such as rhythm method, based on abstention in specific periods of the ovulation cycle as determined by days of the menstruation cycle, body temperature, and other elements), when accompanied by proper counselling and follow-up during trial participation, are acceptable as one method for female participants, when used-together with one of the other methods specified above;*
      * *Contraception should be used, as described above, as long as the participant takes the study treatment and up to: a) two weeks after the last intake of study treatment, if the regimen did not include either clofazimine or bedaquiline (drugs with prolonged elimination half-life); or b) three months after the last intake of study treatment, if the regimen included clofazimine or bedaquiline.*
* **Criteria applicable from Protocol version 3.5 (endTB) and version 4.1 (endTB-Q)**

Is willing to use contraception: pre-menopausal women or women whose last menstrual period was within the preceding year, who have not been sterilized must agree to use contraception unless their partner has had a vasectomy; men who have not had a vasectomy must agree to use condoms;

* + - * *Menopausal woman who have not had a menstrual period for the past 12 months or more, or who had any well-documented method of surgical sterilization will not need to have a pregnancy test and are not considered able to become pregnant. Methods of surgical sterilization include having had a hysterectomy, bilateral oophorectomy, a tubal ligation, and transvaginal occlusion.*
      * *Participants who are sexually active and able to become pregnant or father a child must agree to abstain from sex or use acceptable birth control (methods listed below) while taking study drugs. Acceptable birth control may be achieved by using a single “highly effective” method or by using a combination of other methods.*

*Acceptable “highly effective” single birth control methods for use in this study are:*

* + - * *Hormonal method: birth control pills, patches, injections, vaginal rings, or implants.*
      * *Intrauterine device (IUD).*

*An acceptable combination birth control method is:*

* + - * *Condom (male or female) used with or without a spermicide AND one of the following used with a spermicide: diaphragm, cap, or sponge.*

*These options are also summarized in the table below:*

|  |  |
| --- | --- |
| ***Method*** | ***Use alone or in combination.*** |
| *Hormonal method: birth control pills, patches, injections, vaginal rings, or implants.* | *Highly effective alone; needs no combination.* |
| *Intrauterine device (IUD).* | *Highly effective alone; needs no combination.* |
| *Condom (male) used with or without a spermicide.* | *To be used in combination with one of the following: diaphragm, cap, or sponge AND spermicide.* |
| *Condom (female) used with or without a spermicide.* | *To be used in combination with one of the following: diaphragm, cap, or sponge AND spermicide.* |
| *Diaphragm, cap, or sponge used with a spermicide.* | *To be used in combination with male or female condom, with or without spermicide.* |

* + - * *Female participants do not need to specify which contraceptive methods they plan to use. They simply need to affirm they will comply with the requirement. And, the study team should offer to facilitate access to the chosen methods, again, without needing to know what they are.*
      * *All contraception methods are allowed, as long as they are used according to manufacturer recommendation.*
      * *Withdrawal (coitus interruptus), and natural methods of contraception (such as rhythm method, based on abstention in specific periods of the ovulation cycle as determined by days of the menstruation cycle, body temperature, and other elements), when accompanied by proper counselling and follow-up during trial participation, are unacceptable on their own but may be used in combination with any highly effective method or acceptable combination.*
      * *Contraception should be used, as described above, as long as the participant takes the study treatment and up to: a) two weeks after the last intake of study treatment, if the regimen did not include either clofazimine or bedaquiline (drugs with prolonged elimination half-life); or b) three months after the last intake of study treatment, if the regimen included clofazimine or bedaquiline.*

1. Provides informed consent for study participation; additionally one legal representative of patients considered minor per local laws should also provide consent;
2. Lives in a dwelling that can be located by study staff and expects to remain in the area for the duration of the study.
3. A patient will not be eligible for randomization if s/he:
4. Has known allergies or hypersensitivity to any of the investigational drugs;
   * + - * *Allergy or hypersensitivity can be documented in medical files or reported by the patient. In case they are reported by the patient, clinical judgement is required to assess whether the reported adverse reaction is compatible with allergy or hypersensitivity.*
5. Is known to be pregnant or is unwilling or unable to stop breast-feeding an infant;
6. Is unable to attend or comply with treatment or follow-up schedule;
7. Has any condition (social or medical) which, in the opinion of the site principal investigator, would make study participant unsafe;
8. a. Has had exposure (intake of the drug for 30 days or more) in the past five years to bedaquiline, delamanid, linezolid, or clofazimine, or has proven or likely resistance to bedaquiline, delamanid, linezolid, or clofazimine (e.g., household contact of a DR-TB index case who died or experienced treatment failure after treatment containing bedaquiline, delamanid, linezolid, or clofazimine or had resistance to one of the listed drugs); exposure to other anti-TB drugs is not a reason for exclusion.

b. Has received second-line drugs for 15 days or more prior to screening visit date in the current MDR/RR-TB treatment episode. Exceptions include: (1) patients whose treatment has failed according to the WHO definition1 and who are being considered for a new treatment regimen; (2) patients starting a new treatment regimen after having been “lost to follow-up” according to the WHO definition[[1]](#footnote-2) and, (3) patients in whom treatment failure is suspected (but not confirmed according to WHO definition), who are being considered for a new treatment regimen, and for whom the Clinical Advisory Committee (CAC) consultation establishes eligibility.

1. Has one or more of the following:

* Hemoglobin ≤ 7.9 g/dL;
* Uncorrectable electrolytes disorders:
  + Total Calcium < 7.0 mg/dL (1.75 mmol/L);
  + Potassium < 3.0 mEq/L (3.0 mmol/L) or ≥ 6.0 mEq/L (6.0 mmol/L);
  + Magnesium < 0.9 mEq/L (0.45 mmol/L);
* Serum creatinine > 3 x ULN;
* Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 x ULN;
* Total bilirubin ≥ 3 x ULN;
* Albumin < 2.8 g/dL [criteria applicable protocol up to version 3.3 (endTB) and version 3.0 (endTB-Q)];
* Unless otherwise specified, Grade 4 result as defined by the MSF Severity Scale on any of the screening laboratory tests.
  + *Total calcium values can refer to either “albumin-corrected” or “albumin-uncorrected” total values. If albumin values are available from samples taken in the last 3 weeks, it is advised to use albumin-corrected total calcium values. Please refer to* ***SOP SP-O18-CT Management of Specific Adverse Events*** *for guidance on how to perform the correction;*
  + *In case of laboratory abnormalities leading to ineligibility, laboratory tests can be repeated during the screening window.*

1. Has cardiac risk factors defined as:

* An arithmetic average of the two ECGs with highest QTcF intervals of greater than or equal to 450 ms. Retesting to reassess eligibility will be allowed using an unscheduled visit during the screening phase;
* Evidence of ventricular pre-excitation (e.g., Wolff Parkinson White syndrome);
* Electrocardiographic evidence of either:
  + Complete left bundle branch block or right bundle branch block; OR
  + Incomplete left bundle branch block or right bundle branch block and QRS complex duration greater than or equal to 120 msec on at least one ECG.
* Having a pacemaker implant;
* Congestive heart failure;
* Evidence of second or third-degree heart block;
* Bradycardia as defined by sinus rate less than 50 bpm;
* Personal or family history of Long QT Syndrome;
* Personal history of arrhythmic cardiac disease, with the exception of sinus arrhythmia;
* Personal history of syncope (i.e. cardiac syncope not including syncope due to vasovagal or epileptic causes).
  + *Congestive heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood, whose diagnosis is largely clinical, based on careful assessment of patient history and physical examination. Congestive heart failure should be diagnosed according to the clinical judgement of the* ***Site CI****, with the support of the* ***Site PI*** *as needed. As a reference, the New York Heart Association (NYHA) functional classification is a useful tool[[2]](#footnote-3). A patient with NYHA class III or IV heart failure could be considered as ineligible for inclusion.*
* **Criteria applicable Protocol up to version 3.3 (endTB) and version 3.0 (endTB-Q)**

Is currently taking part in another trial of a medicinal product;

* **Criteria applicable from Protocol version 3.5 (endTB) and version 4.1 (endTB-Q)**

Concurrent participation in another trial of any medication used or being studied for TB treatment, as defined in cited documents.

* + - * *List of medications used or being studied for TB treatment: ethambutol, isoniazid, pyrazinamide, rifabutin, rifampicin, rifapentine, ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, bedaquiline, linezolid, clofazimine, cycloserine, terizidone, delamanid, imipenem–cilastatin, meropenem, amikacin, capreomycin, kanamycin, streptomycin, ethionamide, prothionamide, P-aminosalicylic acid, pretomanid, SQ109, delpazolid, sutezolid, tedizolid, macozinone, telacebec.*

1. Is taking any medication that is contraindicated with the medicines in the trial regimen which cannot be stopped (with or without replacement) or requires a wash-out period longer than 2 weeks.
   * + - * *Please refer to* ***SOP SP-019-CT for Concomitant Medications*** *for the list of medications which should be stopped with observation of a wash-out period, and those medications which are disallowed and confer ineligibility for inclusion.*

1. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014). Geneva: WHO, 2014. pp. 1–47. Report No.: WHO/HTM/TB/2013.2. Retrieved from: <http://www.who.int/tb/publications/definitions/en/> [↑](#footnote-ref-2)
2. Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th ed.). Boston: Little, Brown & Co. pp. 253–256. [↑](#footnote-ref-3)